Cost-effectiveness of atypical antipsychotics for the treatment of dementia in Thailand

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Abstract

Dementia is a significant global health problem and has become a leading cause of morbidity and a functional decline in elderly people. This syndrome comes together with the behavioural and psychological symptoms of dementia, (BPSD), which more than half of people with dementia tend to encounter behavioural disturbances at any one point during the course of the disease, leading to several problems for those patients, caregivers, family members as well as healthcare systems. Due to a controversy of the management of BPSD at this time, it results in a variety of treatment options for BPSD sufferers. Currently, an economic evaluation of atypical antipsychotic drug use for behaviourally disturbed patients with dementia is not well explored. As a result, it is important to address this lack of knowledge as well as the paucity of economic evaluation studies associated with the cost-utility of atypical antipsychotics for the treatment of dementia patients.

This thesis aims to use the cost-utility analysis to assess the economic impact of olanzapine compared with risperidone, for patients with BPSD in Thailand.

The main stages applied for this analysis are as follows: firstly, the scope of the health economic evaluation was defined. Secondly, the models were developed in different schemes and justified the most appropriate model to apply for evaluating the treatment with olanzapine in comparison to risperidone, for patients with BPSD within a Thai setting. Then, the estimated monthly costs and utility weights of patients with BPSD and receiving olanzapine or risperidone were calculated from the primary data collected from two hospitals in Thailand. Finally, the cost-utility analysis of atypical antipsychotics for the treatment of patients with BPSD in Thailand was conducted from a societal perspective, over a five-year time horizon using a one-month cycle length.

The results suggest olanzapine is more cost-effective than risperidone, in the treatment of a patient with BPSD from a societal perspective (ICER< THB 160,000).

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List of Abbreviations

AAs	atypical antipsychotics
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive Function
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living
ADCS-CGIC	Alzheimer's Disease Cooperative Study-Activities of Daily Living - Clinical Global Impression of Change
ADL	Activity of Daily Living
ADRQOL	Alzheimer Disease Related Quality of Life
AHEAD	Assessment of Health Economics in Alzheimer's Disease
AIMS	Abnormal Involuntary Movement Scale
BEHAVE-AD	Behavioural Pathology in Alzheimer's disease Rating Scale
BPRS	Brief Psychiatric Rating Scale
BPSD	Behavioural and Psychological Symptoms of Dementia
CATIE-AD	Clinical Antipsychotic Trials of Intervention Effectiveness- Alzheimer's Disease
CBA	Cost-benefit analysis
CBS	Cornell-Brown Scale for Quality of Life in Dementia
CDR	Clinical Dementia Rating
CE plane	cost-effectiveness plane
CEA	Cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CERAD	Consortium to Establish a Registry in Alzheimer's Disease
CGI	Clinical Global Impression scale
CGI-C	Clinical Global Impression-Change scale
CGI-S	Clinical Global Impression-Severity scale
ChEIs	Cholinesterase inhibitors
CMA	Cost-minimisation analysis
CMAI	Cohen-Mansfield Agitation Inventory
CPI	Consumer Price Index
CSMBS	Civil Servants Medical Benefit Scheme

CUA	Cost-utility analysis
D-QOL	Dementia Quality of Life Instrument
DAD	Disability Assessment for dementia Scale
DALYs	Disability Adjusted Life Years
DEMQOL	Dementia Quality of Life
DES	Discrete Event Simulation
DMSIC	Drugs and Medical Supplies Information Centre
DQI	Dementia Quality of life Instrument
ED	Essential drug
EPSs	Extrapyramidal symptoms
EQ-5D-5L	Quality of life Measure on 5 Domains-5 Levels
FTC	Full-time care
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GNI	Gross National Income
HITAP	Health Intervention and Technology Assessment Program
HRQoL	Health-related quality of life
HUI	Health Utilities Index
HUI-2	Health Utilities Index Mark 2
HUI-3	Health Utilities Index Mark 3
IADL	Instrumental activities of daily living
ICD-10	International Classification of Disease and related health problem 10th revision
ICER	Incremental cost-effectiveness ratio
LASER	London and the South-East region
LOCF	Last Observation Carried Forward
LoS	Length of stay
LYG	Life-years gained
mMMS	modified Mini-Mental State examination
MMSE	Mini-Mental State Examination
MMSE-Thai	Mini-Mental State Examination: Thai version
MOCA	Montreal cognitive assessment

NCD	Non-communicable diseases
NED	Non-essential drug
NHB	Net Health Benefit
NHP	Nottingham Health Profile
NICE	National Institute for Health and Care Excellence
NLED	the National List of Essential Drugs
NMB	Net Monetary Benefit
NPI	Neuropsychiatric Inventory
NPS	Neuropsychiatric symptoms
NSW Health	New South Wales Ministry of Health
PANSS	Positive and Negative Syndrome Scale
PDS	Progressive Deterioration Scale
POMA	Performance-Oriented Mobility Assessment
Pre-FTC	Not requiring full-time care
PSY	Psychotic symptoms
QALYs	Quality-adjusted life years
QoL	Quality of life
QoL-AD	Quality of Life in Alzheimer's Disease
QoL-AD	Quality of Life in Late-Stage Dementia scale
QUALID	Quality of Life in Late-stage Dementia scale
QWB	Quality of Well-Being
RCTs	Randomized controlled trials
RR	Relative risk
SAS	Simpson-Angus Scale
SF-12	Short Form health survey-12
SF-36	Short Form health survey-36
SF-6D	Short-Form Six-Dimension
SG	Standard Gamble
SIB	Severe Impairment Battery
SIP	Sickness Impact Profile
THB	Thai Baht
TMSE	Thai Mental State Examination

TTO	Time Trade-Off
UC	Universal Coverage scheme
US-FDA	US Food and Drug Administration
VAS	Visual Analog Scale
WHO	World Health Organisation
WHOQOL-BREF	World Health Organization Quality of Life
WTP	Willingness to pay

Chapter 1: Introduction

The introductory chapter outlines the following:

- The background information associated with the situation of ageing populations both worldwide and in Thailand;
- The situation of dementia, including cost-associated dementia, both worldwide and in Thailand;
- Origins of the study;
- The rationale of the study, research questions and research contributions; and
- An overview of the structure of the thesis.

1.1 Overview

1.1.1 Ageing in Thailand and Worldwide

Today the growth of ageing populations continues rapidly in many parts of the world. In 2015, the prevalence of elderly people aged 65 and over was more than 8.5% of the world's population. The percentage gender mix of these populations was predominately female compared with male and were associated with 9.5% and 7.5% of the world's population respectively. By 2050, the forecast population of global elderly people will be more than 21% in 94 countries (He, Goodkind and Kowal 2016). The number of elderly people is estimated to be 1.56 billion, equivalent to 16.7% of the total population worldwide, (18.5% females and 14.9% males), by 2050 (U.S. Census Bureau 2013).

In Asia, there were approximately 341 million people aged 65 and over in 2015 and the numbers of elderly people is expected to be 634 million by 2050 (He, Goodkind and Kowal 2016). This is a significant region having a major impact on the total number of elderly people worldwide (U.S. Census Bureau 2013, He, Goodkind and Kowal 2016).

The current situation in Thailand shows the elderly population aged 60 and above has rapidly increased from 6.8% in 1994 to 14.9% in 2014 (National Statistical Office of Thailand 2014). In 2010, the percentage of people aged 60 years and over was 13.18% of

the total of the Thai population. This group is expected to increase by approximately 5.94% by 2020, 13.38% by 2030 and 18.95% by 2040. It is especially noticeable that a greater proportion of the elderly people are female rather than male. In 2010 the gender mix was 55.1% females compared to 44.9% being males and these percentages are likely to remain the same over the next 10 years. Looking at the age ranges by 2040, elderly people aged 70-79 years and 80 years and older are predicted to rise, whereas the reverse is expected in people aged 60-69 years (Office of the National Economic and Social Development Board of Thailand 2013). Between 2010 and 2040, the trend of living habits, (way of life), of elderly Thai people is also changing from living in rural areas to urban areas and is expected to increase by nearly 20% by 2040 when compared to 2010 (Office of the National Economic and Social Development Board of Thailand 2013, National Statistical Office of Thailand 2014). Furthermore, the National Statistical Office of Thailand (2014) reported that 18.8% of elderly people were living with their spouse, followed by 8.7% living alone in 2014. The major income sources of this group of people were 36.7% from their children, 33.9% from their earnings and 14.8% from the elderly allowance from the government. The increasing dependence in activities of daily living (ADL) of elderly people had progressively increased from 10.7% in 1994 to 22.3% in 2014 and those were classified by ADL, into 79.5% of well status, 19.9% of home-bound status and 1.5% of bed-bound status (National Statistical Office of Thailand 2014). In addition, the estimated percentage of dependency in ADL of Thai older individuals will tend to increase from 26.23% in 2017 to 54.95% in 2037 (Bureau of Policy and Strategy of the Ministry of Public Health of Thailand 2016). Interestingly, the demographic transition of Thailand's population is highlighted as being a completely aged society in 2021 and a super-aged society within the next 20 years (Office of the National Economic and Social Development Board 2002, Office of the National Economic and Social Development Board 2011, National Statistical Office of Thailand 2014).

1.1.2 Dementia

Currently, several components, such as health care services, medical technologies, pharmaceuticals, and other factors have been developed to enhance the longevity of the global population, leading to an increase in the numbers of ageing populations. In spite of that, the Non-Communicable Disease (NCDs) has increased and became a significant burden and has a substantial impact on several countries worldwide. Several studies reported that almost 42% of deaths in the global population are associated with NCD conditions (Lozano et al. 2012, GBD 2015 Mortality and Causes of Death Collaborators 2016). Additionally, the Global Burden of Disease 2015 suggested approximately 72%, (39.2 to 40.5 million), of all global deaths, had been caused by NCDs since 2005 (GBD 2015 Mortality and Causes of Death Collaborators 2016).

Dementia is one of the significant NCDs in elderly people and it is devastating in many countries worldwide. This is a syndrome or a set of related symptoms associated with a decline of cognitive abilities or brain functioning. Alzheimer's disease is classified as the most common form of dementia, but unfortunately the cause of this disease cannot be explained with any certainty (Chertkow et al. 2013, Alzheimer's Association 2019, Alzheimer's society 2019, NHS 2019). Vascular dementia, dementia with Lewy bodies and frontotemporal dementia are other examples of types of dementia, while mixed pathologies of dementia are more common than just one type (Jellinger 2006, World Health Organization 2012, Alzheimer's Association 2019). However, all types of dementia are associated with loss of memory, a deficit in cognition and behavioural disturbances as the disease progresses. Thus, this means people with dementia are likely to develop more severe symptoms over time, according to the disease progression (Lawlor 2002, Knapp and Prince 2007).

Based on the UN population statistics in 2001, experts estimated that more than 24 million people aged 60 years and over had dementia (Ferri et al. 2005). In 2010, WHO reported that there were about 35.6 million patients with dementia, and the number of people with this disorder globally will double every 20 years, suggesting that there will be

65.7 million and 115.4 million by 2030 and 2050, respectively. A new case of people with dementia was recorded to occur on average every 4 seconds worldwide and globally new cases were predicted to be nearly 8 million on average each year (World Health Organization 2012). The figures for people with dementia in low and middle-income countries, (LMIC), were higher compared with their counterparts who live in the high-income countries (Ferri et al. 2005, World Health Organization 2012). However, the increase in people with dementia was driven by the population growth and the population age of each country. The Global Burden of Disease 2015 also suggested that the neurological disorder situation had been rising to over 35% of all global deaths since 2005. Notably, Alzheimer's disease and other dementias were found to account for approximately 38.2% of global deaths between 2005 and 2015 (GBD 2015 Mortality and Causes of Death Collaborators 2016). Furthermore, an estimated survival time from onset was calculated at 4.6 years for people with dementia, whereas people with Alzheimer's disease were predicted at 7.1 years (Fitzpatrick et al. 2005, World Health Organization 2012).

In Thailand, the prevalence of Thai people with dementia was 2.4% of people aged 45 and over (Wangtongkum et al. 2008) and 3.3%- 8.1% of people aged 60 years and over (Jitapunkul et al. 2001, Jitapunkul, Chansirikanjana and Thamarpirat 2009, Aekphakorn et al. 2016). Alzheimer's disease and vascular dementia were also reported as the two commonest sub-types of dementia in Thailand, accounting for 75% and 12.5% respectively, in adults aged 45 and over in Chiang Mai province (Wangtongkum et al. 2008). In addition, based on Alzheimer's disease and Related Disorder Association (ARDA), the number of people with dementia was estimated at 0.6 million in 2015 and this tendency will double by 2030. Then the number of people living with dementia in Thailand are projected to be 1.12 million in 2030 and 2.1 million in 2050 (Alzheimer's Disease International and Alzheimer's Australia 2014). Focusing on age groups, the highest percentage of elderly adults with dementia in Thailand was found in people aged 80 years and over, accounting for 22.6%, followed by 8.0% in people aged between 70

and 79 years old and 4.8% in people aged 60-69 years (Aekphakorn et al. 2016). There is a tendency of levels of dementia to be higher in females than males (Aekphakorn et al. 2009, Aekphakorn et al. 2016). However, the prevalence of undiagnosed dementia in Thailand was nearly 3-times as high when compared with Canada (Sternberg, Wolfson and Baumgarten 2000, Jitapunkul, Chansirikanjana and Thamarpirat 2009). In 2013, a retrospective study at Srinagarind Medical School, at the Srinagarind University hospital in Thailand, reported that 53.85% of atypical presentation and 46.15% of typical presentation of elderly patients with dementia attended the emergency department (ED). Thus, a significant factor of ED visits by the elderly are associated with the atypical presentation of dementia (Limpawatana et al. 2016). Based on a diagnosis by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, (ICD-10), in 2010, the rate of illness of inpatients with dementia in Thailand was 14.65 per 100,000 population, (9,403 people), (Strategy and Planning Division of the Ministry of Public Health 2011). In 2015, the rate of inpatients with dementia increased to 16.41 per 100,000 population, (10,671 people). The predominance of inpatients having dementia also showed more females than males, (1.27 to 1 ratio), (Strategy and Planning Division of the Ministry of Public Health 2016). Additionally, dementia has increased as a cause in the death rate in the Thai population year on year. During the period 2012-2016, the mortality rates of mental and behavioural disorders, including dementia, had continued to grow and accounted for 1.3 per 100,000 population in 2012, 1.4 per 100,000 population in 2013, 1.6 per 100,000 population in 2014, 1.9 per 100,000 population in 2015 and 2.1 per 100,000 population in 2016 (Strategy and Planning Division of the Ministry of Public Health 2016). Considering the outpatient identified with dementia in Thailand, the rate of diagnosis of people with mental and behavioural disorders, excluding Bangkok, was 37.64 per 1,000 of the population in 2005. However, the figure had almost doubled to 72.09 per 1,000 population in 2015 (Strategy and Planning Division of the Ministry of Public Health 2011, Strategy and Planning Division of the Ministry of Public Health 2016). In fact, the current situation regarding dementia in the Thai population is

likely to increase continuously, along with Thai society becoming an aged society (Senanarong et al. 2013). This will lead to a variety of problems for the healthcare systems in Thailand.

1.1.3 The burden of Dementia in Thailand and Worldwide

From a socioeconomic perspective, dementia is a significant factor affecting elderly people. Global costs were approximately $605 billion to society in 2010 (World Health Organization 2012). Based on the Global Burden of Disease, dementia was classed as ninth in the top ten rankings leading to disability-adjusted life year (DALY) burden in 2010, accounting for 10 million DALYs (Prince et al. 2015). In 2010, the worldwide costs of dementia were the highest category in the social costs, followed by informal care costs and then direct medical costs. The total global informal care costs had increased from $252 billion in 2010 to $331 billion in 2015. Medical costs also showed significant changes, increasing by 3.5% from 2010 to 2015 (Prince et al. 2015).

In Thailand, the major cost for persons with dementia was informal care, estimated at $854 million in 2015. There were $721 million of non-medical costs and $89 million of medical costs for this group of people. These costs were estimated from the 600,000 people with dementia in 2015 (Alzheimer's Disease International and Alzheimer's Australia 2014).

In conclusion, the situation of people with dementia globally along with those in Thailand is on an upward trend leading to several serious problems, such as substantially greater costs and caregiver burden, which significantly affects the patients, caregivers and families as well as healthcare systems.

1.1.4 Origins of the study

In people with dementia, behavioural and psychological symptoms of dementia (BPSD), behavioural disturbances or neuropsychiatric symptoms (NPS) are the most common conditions occurring as the disease progresses. Some studies also reported that the prevalence of behavioural disturbances in people with dementia was nearly four times

higher than people without dementia (Lyketsos et al. 2000, Lyketsos et al. 2002). However, comparing between the sub-types of dementia, there were modest noticeable differences in behavioural disturbances in people with Alzheimer's disease and people with vascular dementia (Lyketsos et al. 2002). In addition, BPSD can be characterised into four main groups: mood disorders, sleep disorders, psychotic symptoms and agitation (Desai, Schwartz and Grossberg 2012), and those symptoms may also manifest in wandering, aggression, agitation, anxiety, depression, sleep disturbance, hallucinations and delusions (Finkel et al. 1996, Olin et al. 2002 and Feast et al. 2016). From the onset of cognitive symptoms, approximately 50-90% of people with dementia presented at least one symptom of behavioural disturbances at any one point in time (Lawlor 2002, Lyketsos et al. 2002, Angelini et al. 2007, Haibo et al. 2013, NSW 2013, Feast et al. 2016). Furthermore, there were several studies which reported that apathy, agitation, depression, and anxiety were the commonest symptoms in people with dementia (Mega et al. 1996, Lyketsos et al. 2000, Lyketsos et al. 2002).

In Thailand, a study showed 97.5% of Alzheimer-type dementia patients presenting neuropsychiatric symptoms (Phanasathit et al. 2010). The most frequent BPSD traits in Thai dementia patients were apathy, (71.0 %), aberrant motor behaviour, (61.3 %), sleep disturbances, (56.5 %), eating abnormalities, (51.6 %), and agitation/aggression, (45.2 %) (Charernboon and Phanasatit 2014).

For the management of BPSD, both non-pharmacological and pharmacological interventions are currently applied. In general, non-pharmacological treatments are recommended as being the first-line approach for treating patients with BPSD. The pharmacological approach is only initiated when the first-line approach is not successful. However, an integrated treatment of both approaches is suggested for better management of BPSD (Azermai et al. 2012, Cerejeira, Lagarto and Mukaetova-Ladinska 2012).

At present, there are various types of medications used for the management of complicated BPSD. The most common pharmacological treatments are antipsychotics,

antidepressants, mood stabilizers, benzodiazepines, as well as cognitive enhancers (Andrade and Radhakrishnan 2009, Tampi et al. 2011, Cerejeira, Lagarto and Mukaetova-Ladinska 2012 and Azermai et al. 2012). Nevertheless, in general, antipsychotic drugs have been routinely prescribed for BPSD patients more than any other drug class (Andrade and Radhakrishnan 2009).

In 2005, the U.S. Food and Drug Administration (US-FDA) launched an awareness programme for atypical antipsychotics[1], (AAs), use among the elderly, due to a 1.7 increase in the incidence of all-cause mortality risk (U.S. Food and Drug Administration 2005). In 2008, the FDA also increased the warning to typical antipsychotics[2] (U.S. Food and Drug Administration 2008).

Accordingly, the trend of prescribing antipsychotics for the elderly dropped from 2.3% in 2003 to 1.8% in 2011; however, the rate of prescribing atypical antipsychotics is reversing, with an escalation from 0.37% to 0.64% over the same period (Gallini et al. 2014). Although there are the safety warnings of atypical antipsychotic use, these drugs are still commonly administrated to patients with BPSD (Chiabrando et al. 2010).

To date, there are no available treatments approved by the US-FDA for people with BPSD, leading to controversial recommendations for the treatment of patients with BPSD in each country (Desai, Schwartz and Grossberg 2012). In general practice, physicians tend to prescribe antipsychotic drugs as the first-choice therapy for people with BPSD, albeit these drugs are off-label use to those patients. Generally, even if the newer

[1] Atypical antipsychotics are also called second-generation antipsychotics, and neuroleptic drugs such as clozapine, amisulpride, aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, and risperidone (Meltzer, Matsubara and Lee 1989, Meltzer 2013, The Government of the United Kingdom (2005).

[2] Typical antipsychotics are also known as conventional, classical or first-generation antipsychotics such as chlorpromazine, haloperidol, flupentixol, prochlorperazine, sulpiride and trifluoperazine (Meltzer, Matsubara and Lee 1989, Meltzer 2013, The Government of the United Kingdom (2005).

antipsychotics, (atypical antipsychotics), are costlier than the older antipsychotic drugs, (typical antipsychotics), atypical antipsychotic drugs are likely to be more frequently used for the treatment of BPSD relative to the other ones. The reason is that atypical antipsychotics account for superior efficacy and with inferior adverse effects, especially to extrapyramidal symptoms, (EPSs), namely acute dyskinesia or dystonic reactions, tardive dyskinesia, Parkinsonism, neuroleptic malignant syndrome, akinesia, and akathisia, in the geriatric population (Blair and Dauner 1992, Lawlor 2002, Andrade and Radhakrishnan 2009).

While a variety of atypical antipsychotic options for patients with BPSD are available in clinical practice, differences amongst these drugs are not well defined. Consequently, the cost-effectiveness of atypical antipsychotics for the treatment of those patients is a significantly critical issue that needs to be researched. The exploration of which drug is more cost-effective will indicate the best possible effective intervention for the treatment of BPSD patients and decrease the caregiver burden in providing care to those patients, as well as providing data to support policy-makers and healthcare system managers, and improving the QoLs of both patients and their caregivers.

1.2 The rationale of the study

It is estimated that 80% of the world's elderly population by 2050 will live in less-developed countries. Most middle-income countries are predicted to have double the numbers of older people by 2050 (United Nations 2017). Similarly, the characteristic of the Thai population had turned into an ageing society since 2005 and within the next 20 years is predicted to be a super-aged society. Thus, ailments in the elderly, particularly dementia, will grow significantly, leading to problems across both the formal and informal health care systems in Thailand as well as worldwide.

Behavioural and psychological symptoms of dementia are significantly coincident conditions, occurring in people with dementia. These symptoms are overwhelming not

only for the people who suffer from it, but also for their caregivers and families. They are also major causes of disability, mortality, long-term hospital stays, caregiver's distress, productivity losses of their families or caregivers for patient care, and the quality of life of both patients and caregivers (Fauth and Gibbons 2014, Feast et al. 2016).

Again, the guidelines of the management of BPSD have currently been under debate, leading to difficulties in developing clinical practices. Under the controversy of pharmacological approaches, atypical antipsychotics are frequently prescribed for BPSD patients, although the adverse effects and safety issues have been raised as genuine concerns.

There are several reasons for undertaking this study as follows: firstly, there are several studies focusing on health economic evaluations for other dementia drug groups, namely cholinesterase inhibitors and memantine, for the treatment of dementia. There are also several studies of the cost-effectiveness analysis on atypical antipsychotics for treating schizophrenia. However, there is a paucity of studies focusing on atypical antipsychotics for patients with BPSD. A pharmacoeconomic study on this topic is then a significant necessity. To the researcher's best knowledge, this will be the first study to explore and evaluate the cost-effectiveness of atypical antipsychotics in the comparison between olanzapine and risperidone, for the treatment of patients with BPSD, specifically in Thailand or Asia in general. Secondly, the increase in people with dementia year on year leads to a growth in the financial burden, (medical care costs, informal care costs, and societal costs), mainly affecting patients, caregivers, as well as healthcare systems. The study by Prince at el. (2015) reported that the average dementia-associated cost was higher than other chronic conditions, including depression, hypertension, diabetes, ischemic heart disease, stroke, and chronic obstructive pulmonary disease. Consequently, the burden of dementia, including BPSD, is inevitably a significant issue to healthcare systems across many countries, along with Thailand. Thirdly, there are variations in the prescription of atypical antipsychotics found in people with behavioural disturbances in Thailand. Risperidone is one of the atypical antipsychotics which is frequently prescribed

for those people because the drug is accommodated in the National List of Essential Drugs, (NLED), in Thailand as a reimbursable medicine (Rapeepatchai and Promma 2015). On the other hand, olanzapine is a newer atypical antipsychotic drug compared with risperidone and is also commonly used in people with BPSD (Chanthawong et al. 2012). However, olanzapine is more costly and is not provided in the NLED of Thailand. Thus, patients with BPSD have to pay for that drug treatment as out-of-pocket expenses, leading to restricted patient access to the treatment and their ability to receive the most suitable medication. Accordingly, the medical cost is a significant factor threatening the cost burden and decision making of the treatment to patients with BPSD, their caregivers, staff, and healthcare systems.

1.3 Research Question and Objectives

1.3.1 Research Question

The main research question sets out to address:

What is the cost-effectiveness of olanzapine relative to risperidone for the treatment of behavioural and psychological symptoms in patients with dementia in Thailand?

1.3.2 Aim and objectives

The overall aim of this study is to apply a cost-utility analysis to assess the economic impact of olanzapine in comparison to risperidone, for the treatment of behavioural and psychological symptoms in patients with dementia in Thailand.

The specific objectives of the research focus on three main sections as follows:

1. To use a decision-analytical model for assessing the costs and outcomes of interventions for the treatment of patients with BPSD
2. To explore the costs and health utilities, (or utility weights), of interventions for the treatment of patients with BPSD; and
3. To calculate the incremental cost-effectiveness ratio, (ICER, as presented in terms of cost per QALY), of the intervention of interest and the comparator.

1.4 Original Contribution

The current controversial management associated with safety and efficacy of atypical antipsychotic drug use for BPSD and the lack of pharmacoeconomic research on atypical antipsychotics for BPSD pose an immense challenge for current clinical practices in treating dementia patients. To the researcher's best knowledge, this will be the first study to evaluate the cost-effectiveness of atypical antipsychotics, (olanzapine versus risperidone), for the treatment of BPSD in the context of Thailand. The findings of this study will indicate the recommended effective treatment intervention for patients with BPSD and intentionally contribute to the decision making of physicians, patients, and caregivers, in planning and selecting the relevant treatment for BPSD sufferers. This study also considered the side effects and relapse rates of both drugs which allow the results to be as realistic as they could possibly be. Therefore, this data will be useful and may be replicated in other settings with similar circumstances.

In addition, this study integrated pharmacological, epidemiological and health economic evaluation techniques. A decision-analytical framework has been conducted to evaluate the cost-effectiveness of olanzapine compared with risperidone in patients with BPSD in Thailand, based on a societal perspective.

Aside from that, the study has identified a number of benefits that would accrue for patients, their caregivers, health professionals and health care providers in Thailand, in a philosophical sense. The obvious benefit for the patients is a more effective treatment of their condition, resulting in greater wellbeing. If the patient's overall health condition improves, this would also be reflected in the wellbeing of the caregivers, who would see an improvement in the condition of their charge, leading to better quality of life of both the patients and their caregivers. This also has a bearing on the treatment of those patients by health professionals, who may possibly benefit from lower stress levels as a direct improvement of their patients' health. Additionally, there may well be a significant impact on the wider healthcare systems in Thailand, if there is a significant improvement in patient wellbeing which could result in an overall reduction in the true costs of care for

these patients, even if there was a direct increase in pharmaceutical costs in using a different drug in the treatment of these cases. Less pressure on the health system for related treatments for these patients may well result in an overall reduction in treatment costs which would be beneficial for the wider Thai population.

1.5 The structure of the thesis

In this chapter, the background information associated with an ageing population, dementia situations, BPSD situations, and dementia associated costs, both worldwide and in Thailand has been provided. In terms of the structure, the thesis will focus on the following points.

Chapter 2: The literature review introduces the definition of dementia and BPSD, the management of BPSD, health economic evaluations, the model-based health economic evaluations in dementia, and the conceptual framework of this study.

Chapter 3: Philosophical underpinnings are addressed. This chapter also describes the design and methodology of this study, including sample size, target population, data settings, data collection processes, data requirements and data sources as well as data analyses. In addition, the ethical considerations of the study are presented here.

Chapter 4: The model development is based on data from literature reviews of model-based economic evaluations in dementia. This chapter provides the stages of developing the different models and the use of data from a Thai setting, for application in these developed models. The most appropriate model has been selected to be adopted for the cost-utility analysis of olanzapine compared with risperidone, in the treatment of patients with BPSD in Thailand in Chapter 7.

Chapter 5: Costs of the treatment of patients with BPSD in Thailand with atypical antipsychotics, (olanzapine or risperidone), are presented in this chapter. Based on the primary data collection from within a Thai setting, the findings initially present an

overview of patient and caregiver characteristics. Then, the characteristics of both patients and caregivers are displayed following the classification of patients by cognitive function and dependence. Also, the cost analyses are performed based on two different distributions as previously stated.

Chapter 6: This chapter is associated with the measure of the health-related quality of life of patients with BPSD and treatment with olanzapine or risperidone using the EQ-5D-5L. The responses to questionnaires are translated into utility weights, (or utility values). The utility analyses are then presented by classifying patients by cognitive function and dependence.

Chapter 7: This chapter presents the application of the cost-utility analysis of atypical antipsychotics for the treatment of BPSD in Thailand. The selected model is used to predict the expected costs and outcomes associated with olanzapine and risperidone treatment in Thai patients with BPSD aged 60 years and above, over a 5-year time period from a societal perspective. The data analyses display in terms of the incremental cost-effectiveness ratio, (ICER), calculated by incremental costs and incremental quality-adjusted life year gained (QALYs). Furthermore, the uncertainty analyses are presented here.

Chapter 8: This part is associated with the conclusion of an overview of this thesis, the summary of the findings, a contribution to knowledge, policy implements, the strengths and limitations of this thesis and the post-research evaluation. Moreover, further research opportunities and publications are presented in this chapter.

Chapter 2: Literature Review

Abstract

Introduction: Rapid growth of the elderly worldwide has led to several problems, particularly health, economic, social, mental, and family problems. The most common health issue facing the elderly is dementia which is a chronic health condition. Behavioural and psychological symptoms of dementia are closely associated with patients and are unavoidable in this progressive disease. These symptoms have a significant impact on distressing and burdening caregivers. Antipsychotics are one group of medications which are widely used in practice for the treatment of BPSD. However, there is currently limited data on the health economic evaluation of antipsychotics in patients with BPSD.

Aim: The objective of this chapter is to review issues associated with definitions of dementia and BPSD, the prevalence and economic impact of dementia, management of BPSD, efficacy of atypical antipsychotics for the treatment of BPSD, heath economic evaluations of atypical antipsychotics for dementia, and the modelling-based economic evaluations in dementia.

Methods: Relevant published studies of dementia from several sources were identified to review the definitions, prevalence and economic impact, as well as management of the disease. On the efficacy data of atypical antipsychotics (focused on risperidone, olanzapine, quetiapine, and aripiprazole) those published in the English language were identified by searching of MEDLINE, PsycINFO, and the Cochrane Library of randomised controlled trial, placebo-controlled, double-blind, parallel-group trials comparing drugs with placebo, from 1994 through to July 2015. Regarding the models of health economic evaluations, MEDLINE and CRD database were searched from January 1975 through to March 2018, written in English, on cost-minimisation analysis, cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis, of pharmacological treatments in dementia.

Results: Dementia is a progressive brain disease associated with cognitive impairment. At any one point, people with dementia had experienced BPSD accounting for 50-90% within the disease progression, leading to a significant caregiver burden. Due to clinicians having limited treatment alternatives, antipsychotics are widely used in treating BPSD, although these drugs are marginally useful in the treatment of these people. A total of 2,190 articles were reviewed on atypical antipsychotics for dementia. However, only 13 studies were identified for an in-depth review. The evidence supported the efficacy of atypical antipsychotics in patients with BPSD, although the adverse events might offset their efficacy. Regarding model-based economic evaluations in dementia, of 1,118 citations identified, 40 studies contributed data for the modelling used in the economic evaluations of dementia. Different model structures were found to apply in health economic evaluations in dementia. The grouping of models according to the disease progression, found that there were 16 model approaches. A Markov model was most commonly used for evaluation. The FTC conceptual framework and CERAD conceptual framework were the most used model structures applied to economic evaluation in dementia.

Conclusions: Despite the concerns with the adverse events of atypical antipsychotics for dementia, these drugs remain beneficial to patients with BPSD. The patients need to be monitored when they are prescribed antipsychotic drugs for dementia. There was a paucity of studies using model-based health economic evaluations in dementia on patients with BPSD and being treated with antipsychotic medications.

2.1 Dementia and Behavioural and Psychological Symptoms of Dementia (BPSD)

2.1.1 Definition of Dementia

Dementia can be defined as a progressive brain disease associated with the impairment of brain function. The dysfunction involves cognition, personality, and a person's intellect, for example: memory, thinking, language, learning ability, calculation, comprehension, judgement, and orientation. Thus, the deterioration of the brain in this way can have a significant impact on people living with the condition, as well as on society as a whole (World Health Organization 2012, Butler and Radhakrishnan 2011, Holmes 2012, National Institute for Health and Care Excellence 2006). Alzheimer's disease (AD) is the most common type of dementia, accounting for 50-70% of cases. Vascular dementia (VaD), dementia with Lewy bodies, and frontotemporal dementia (FTD) are also substantial categories of the disorder accounting for 20%, 10% and 2% cases, respectively (Butler and Radhakrishnan, 2011, Holmes 2012, NSW Health 2013). According to the World Health Organisation (2012), dementia can be classified into three stages:

•Stage 1 - the early dementia stage occurs in the first or second year of the condition;

•Stage 2 - the middle dementia stage occurs from the second to fourth or fifth year; and finally

•Stage 3 - the late dementia occurring in the fifth year and beyond.

2.1.2 Definition of Behavioural and Psychological Symptoms of Dementia (BPSD)

Behavioural and psychological symptoms of dementia (BPSD) are common symptoms of the disease, including neuropsychiatric symptoms, non-cognitive symptoms and behavioural disturbance (NSW Health 2013, Byrne, 2005). Diagnosis of BPSD has no formally specified approach; therefore, clinical magnitude is more subjective than objective in patients with dementia. The clinical symptoms of BPSD present themselves as: agitation, apathy, anxiety, depression, delusion, hallucination, disinhibition, aberrant motor behaviour, elation, irritability, and sleep and appetite changes (Cerejeira, Lagarto

and Mukaetova-Ladinska 2012, NSW Health 2013, Byrne 2005). At any one point in time, 50-90% people with dementia are likely to experience at least one symptom of disorder (Lawlor 2002, Angelini et al. 2007, NSW Health 2013). Additionally, BPSD tends to be more prevalent in the last stage of the disorder. As a result, these problems directly affect patients, caregivers and their families. These include, but are not limited to, distress among carers and patients, long term hospitalisation, drug abuse, and other health care costs (Cerejeira, Lagarto and Mukaetova-Ladinska 2012). The decline in patients' and caregivers' quality of life is the more troublesome aspect of BPSD management rather than cognitive impairment.

2.2 Prevalence and Economic Impact of Dementia

Dementia is a worldwide problem resulting from the rapid increase in populations aged 60 or above. The worldwide size of the over 60 years old population is estimated to be 2 billion in 2050 (World Health Organization 2012). It is predicted that 6.7% of this older population are expected to have dementia which would equate to 135 million people (See Figure 2.1) (Alzheimer's Disease International 2013). It can be seen that the condition has the potential to impact significantly on social and economic welfare worldwide. There are three different aspects of dementia costs namely: informal care costs, direct social costs, and direct medical costs (See Figure 2.2). These tend to vary in proportion according to each nation's wealth (World Health Organization 2012).

In Thailand, the number of the population over 60 years old was approximately 10 million in 2014 (National Statistical Office of Thailand 2014). The prevalence of dementia amongst Thai people aged 60 and above was 3.3-8.1% (Jitapunkul et al. 2001, Kalaria 2008, Aekphakorn et al. 2016). The projection for 2050 suggests that there will be more than 1.2 million Thai people with dementia (Uddin Akter et al. 2012). It is clear that the demographic characteristics of the Thai population have changed and it is entering into an

ageing society. The increased numbers of people with dementia will therefore lead to various demands and problems on the healthcare systems and communities in Thailand.

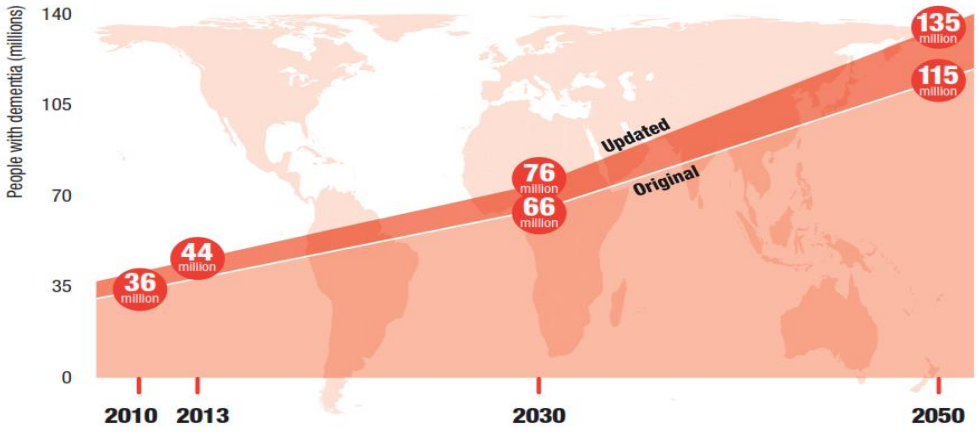


Figure 2.1: Increase in the number of people with dementia worldwide (2010-2050), showing original and updated estimates (Alzheimer's Disease International 2013)

Figure 2.2: Distribution of total societal costs (%) by World Bank Income level (World Health Organization 2012)

2.3 Management of behavioural and psychological symptoms of dementia

Generally, people with dementia may experience BPSD at any point during the progression of the illness, associated with poor outcomes for patients and caregivers. Also, the disorder is significantly troublesome in clinical practice. The guidelines for

management of BPSD, classified into non-pharmacological and pharmacological approaches are listed below:

2.3.1 Non-pharmacological approaches

Non-pharmacological approach was recommended as the first-line management for BPSD (NSW Health 2013, Scottish Intercollegiate Guidelines Network 2006, Tampi et al. 2011, Sadowsky and Galvin 2012, Azermai et al. 2012, The American Geriatrics Society 2011). The treatments were applied for behavioural disorders following the characteristics of symptoms. The most common approaches are environmental design, music therapy, light therapy, and carer education for behavioural disturbances (NSW Health 2013, Scottish Intercollegiate Guidelines Network 2006). For example, the stimulation/activities and simple tasks were introduced for apathy (Segal-Gidan et al. 2011, Opie, Rosewarne and O'Cornor 1999). Furthermore, Fujii et al. (2010) suggested that behavioural and psychological symptoms of caregivers (BPSC) resulted from BPSD, namely, the behaviour of caregivers was an important factor that would affect a relationship and the emotions of a patient.

2.3.2 Pharmacological approaches

Pharmacological methods will be necessary when non-pharmacological interventions are unsuccessful or there is no response to the BPSD treatment (NSW Health 2013, Scottish Intercollegiate Guidelines Network 2006). There are several classes of drugs that have been utilised for the management of BPSD. The categories are listed below:

2.3.2.1 Anticonvulsants

There are studies associated with carbamazepine, sodium valproate, and gabapentin for the treatment of behavioural symptoms related to patients with dementia. Of these the evidence showed that valproate was insufficient for the treatment of BPSD (Lonergan and Luxenberg 2009, Scottish Intercollegiate Guidelines Network 2006). Carbamazepine revealed short- term effectiveness for agitated behaviour (Tariot et al. 1998, Scottish Intercollegiate Guidelines Network 2006). Gabapentin alone and also combined with psychotropic drugs showed efficacy for the treatment BPSD, however more evidence is

required (Scottish Intercollegiate Guidelines Network 2006, Tempi, Ozkan and Williamson 2012, Yeh and Ouyyang 2012). On the basis of the data, anticonvulsant drugs were not recommended for the treatment BPSD associated with dementia (Konovalov et al. 2008, Scottish Intercollegiate Guidelines Network 2006).

2.3.2.2 Cholinesterase inhibitors (ChEIs)

At present, there is evidence accounting for the benefits of ChEIs. Rodda et al. (2009) showed a limitation of effectiveness data, but ChEIs can be used for BPSD in Alzheimer's disease (National Institute for Health and Care Excellence 2015). The US-FDA has approved donepezil, galantamine, and rivastigmine for treatment of symptoms of Alzheimer's disease; however, the recommendations of ChEIs are inconsistent in guidelines (Azermai et al. 2012). If behavioural symptoms still persist during ChEIs use, alternative drug classes may be considered as therapeutic options (Sadowsky and Galvin 2012).

2.3.2.3 Antidepressants

Depression symptoms are common in patients with dementia. Selective serotonin reuptake inhibitors (SSRI) were observed for efficacy on depression (Gauthier et al. 2010). Citalopram and sertraline had commensurate efficacy on agitated behaviour relative to risperidone or haloperidol. However, there were several controversial guidelines to support antidepressants for behaviour disturbances, excepting comorbid depression in patient associated with dementia (Scottish Intercollegiate Guidelines Network 2006, Sink, Holden and Yaffe 2005, Azermai et al. 2012).

2.3.2.4 Memantine or NMDA (N-methyl-D-aspartate)

Memantine is currently the US-FDA approved drug for treatment of moderate to severe stages of Alzheimer's disease (Sink, Holden and Yaffe 2005). Nevertheless, the recommendation for BPSD is disputed in guidelines. The SIGN guidelines addressed the insufficient evidence of memantine for management of patients with BPSD (Scottish Intercollegiate Guidelines Network 2006). In contrast, the NICE guidelines recommended memantine for non-cognitive symptoms in cases of moderate to severe stages and the

ineffectiveness of ChEIs and antipsychotics (National Institute for Health and Care Excellence 2015).

2.3.2.5 Antipsychotics

The classification of antipsychotics is divided into two classes: typical antipsychotics and atypical antipsychotics. All guidelines have consistency for introducing antipsychotics for treatment of patients with BPSD, in particular agitation, aggression, and psychosis (Azermai et al. 2012, National Institute for Health and Care Excellence 2015). Due to adverse effects, the NSW guidelines did not recommend conventional antipsychotics as a first-line drug (NSW Health 2013). Atypical antipsychotic drugs are commonly prescribed for BPSD rather than typical antipsychotics. Drouillard, Mithani and Chan (2013) noted that atypical antipsychotics were useful for managing BPSD in relation to agitation and aggression. However, before applying medications, patients should be investigated. Tampi et al. (2011) recommended that risperidone, aripiprazole and olanzapine should be considered as the first-line of the treatment of patients with BPSD. Aripiprazole, olanzapine, and risperidone showed statistically significant effects in the reduction of psychosis, agitation, and global behavioural symptoms in dementia (Maher et al. 2011).

In conclusion, the management of BPSD should integrate both non-pharmacological treatments and pharmacological treatments. Non-pharmacological approaches should be introduced as initial strategies. When non-pharmacological interventions have no response, starting medication was appropriate. Notwithstanding, atypical antipsychotic drugs have a significant performance. These are considered to be first-line drugs for the treatment of psychotic disorders in elderly people with dementia due to their more effectiveness and having less adverse effects. Currently, although these are controversial for use concerning drug safety, the goal of pharmacological therapy is the reduction in the problematic disorders and not in eliminating symptoms. The concept of antipsychotic drugs is “start slow, go slow”. Thus, caregivers should take part in the decision-making of

the care map for patients with dementia. Also, pharmacological treatment should scrutinize the risk-benefits to patients and be considered on a case by case assessment. Since there are an extensive variety of antipsychotics prescribed for the treatment of patients associated with BPSD, in this proposed research, the researcher will focus exclusively on atypical antipsychotic drugs.

2.4 Efficacy of Atypical Antipsychotic Drugs for Dementia

A comprehensive literature search was undertaken in electronic databases. The literature search was focusing on efficacy of atypical antipsychotics for dementia. In this procedure, there were four main steps. Firstly, the key search terms were developed on the basis of the relevant topic. Secondly, titles were considered for screening using the inclusion and exclusion criteria (see below). If they met the criteria, they were then exported to RefWorks for further evaluation. Thirdly, the abstracts were scrutinised for inclusion and exclusion criteria, to confirm whether they met an engagement. Finally, an assessment and in-depth review identified whether they were for inclusion or exclusion. If they fulfilled the criteria, they were then included into the final stage. Studies in non-English language were excluded from the literature review.

2.4.1 Literature Search for Efficacy of Atypical Antipsychotics for Dementia

A literature search for efficacy of second-generation antipsychotic drugs for the treatment of dementia, in particular risperidone, olanzapine, quetiapine and aripiprazole was undertaken in electronic databases, including MEDLINE, PsycINFO, and the Cochrane Library. The literature search covered the period from 1994 up to July 2015. The search terms were broken down into the relevant topics following these criteria:

a) Dementia and Alzheimer's disease;
b) Behavioural and psychological symptoms of dementia, BPSD and neuropsychiatric symptoms;

c) Atypical antipsychotics, Risperidone, Olanzapine, Aripiprazole and Quetiapine.

The database search for the efficacy of atypical antipsychotic (risperidone, olanzapine, quetiapine and aripiprazole) drugs for dementia retrieved 2,190 articles from MEDLINE, PsycINFO, and the Cochrane Library. Of these 1,075 articles were retrieved from MEDLINE, 754 articles retrieved from PsycINFO and 361 articles from the Cochrane Library. The titles were screened using the inclusion and exclusion criteria. Of the original 2,190 articles, 2,063 were excluded due to their title. The remaining 127 articles were identified for further scrutiny. A further 81 articles were excluded after screening the abstracts. 46 articles still remained to undergo the next step. From the remaining 46 articles, a further 26 were excluded due to duplication. 20 articles remained to undergo the next step which was screening the full paper. Six articles were excluded due to not meeting the outline criteria. Another one paper was excluded due to having no access to full-text paper. 13 articles then remained which were potentially relevant on which to undertake a full review. Finally, these articles were reviewed to synthesise the results on the efficacy of newer antipsychotic agents for the treatment of patients with dementia.

Inclusion criteria:

- Participants: people with dementia, people with behavioural and psychological symptoms of dementia;
- Interventions: atypical antipsychotic, risperidone, olanzapine, quetiapine and aripiprazole for the treatment of dementia, Alzheimer's disease, behavioural and psychological symptoms of dementia and neuropsychiatric symptoms;
- Study designs: randomised controlled trial, placebo-controlled, double-blind, parallel-group trials comparing drugs with placebo;
- Outcomes: Behavioural Pathology in Alzheimer's disease Rating Scale (BEHAVE-AD), Clinical Global Impression (CGI) scale, Neuropsychiatric Inventory (NPI), Cohen-Mansfield Agitation Inventory (CMAI), Brief Psychiatric

Rating Scale (BPRS), Severe Impairment Battery (SIB), time for initial treatment to the discontinuation, and Mini-Mental State Examination (MMSE).

Table 2.1 shows the summary of studies for the efficacy of atypical antipsychotics for dementia.

Table 2.1: **The summary of studies for the efficacy of atypical antipsychotics for dementia**

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
De Deyn et al. (1999)	-n=344 -Patient with dementia -Mean age 81 years -Flexible dosage regimen of risperidone or haloperidol was 0.25-2 mg twice daily	Risperidone, haloperidol, or placebo	-BEHAVE-AD total score -CMAI -CGI-S -Tolerability (including EPS rating scale) -Functional Assessment -MMSE -Adverse events	-At the end point and week 12, the mean dose of risperidone (1.1 mg/day) showed improvement on BEHAVE-AD total score (the score reduction was equal to or greater than 30% from baseline), but not significant when compared with placebo (*p=0.19*) -BEHAVE-AD aggression and CMAI aggression, CGI-S score showed significant reduction at 12-week and the endpoint outcome -Patient with vascular dementia demonstrated statistically significant improvements on BEHAVE-AD aggression and CMAI aggression both the end point and 12-week	Risperidone showed efficacy for the treatment of patient with AD associated with aggression (mean dosage 1.1 mg/day)

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
				-No significant difference on EPS between risperidone and placebo	
Brodaty et al. (2003)	n=345 -Patients diagnosed AD, Vascular dementia, mixed dementia, and aggressive behaviour	Risperidone vs Placebo	-CMAI -BEHAVE-AD rating scale -CGI-S and CGI-C	Primary efficacy outcomes: -Significant result for CMAI total aggression score *(p<0.001)* of risperidone compared with placebo Secondary efficacy outcomes: -Improvement on CMAI subscale (total non-aggression, *p<0.002)* in risperidone vs placebo -Significant results on BEHAVE-AD total *(p<0.001)* and psychotic symptoms subscale *(p=0.004)* -Risperidone showed no significant reduction in BEHAVE-AD activity disturbance and diurnal rhythm disturbances (*p=0.067, p=0.098,* respectively*)*	Risperidone showed efficacy for treating of patients with dementia with psychosis, aggression and agitation (mean dosage 0.95 mg/day)

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
				At the endpoint, risperidone improved CGI-S and CGI-C scale *(p<0.001)* -Risperidone and placebo showed no significant in ESRS at the endpoint *(p=0.407*)	
Street et al. (2000)	n=206 -the elderly with AD with psychosis and/or behavioural symptoms in nursing home -6-week -Fixed-dose olanzapine 5.0, 10.0, and 15.0 mg/day	Olanzapine vs placebo	Primary efficacy outcome: -NPI-NH Core Total (agitation/aggression, hallucinations, and delusions items) Secondary outcomes: -NPI/NH Total score -NPI-NH Psychosis total (Hallucinations and Delusions) -NPI-NH Occupational Disruptiveness score -BPRS total and subscale -MMSE -EPS	Primary outcome: -Significant results on olanzapine 5 and 10 mg/day improving in NPI-NH Core Total *(p<0.001* and *p<0.006,* respectively) compared with placebo Secondary outcomes: -Olanzapine 5 mg/day showed significant results for NPI/NH Total score (*p=0.005*), NPI-NH Occupational Disruptiveness score (*p=0.008*), BPRS total (*p=0.005*), BPRS positive subscale (*p=0.05*)	Olanzapine 5 and 10 mg daily resulted in effectiveness for the treatment of patients with AD with agitation, aggression, and psychosis

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
				-NPI-NH psychosis scale, NPI-NH agitation/aggression, BPRS anxiety/depression subscale were significant in both dosage 5 and 10 mg/day of olanzapine -NPI-NH depression/dysphoria, MMSE, and EPS not significant in all treatment groups	
De Deyn et al. (2004)	-n=652 -Patients with AD with psychosis symptoms -10-week -Fixed dose olanzapine 1.0, 2.5, 5.0, and 7.5 mg/day	Olanzapine vs placebo	Primary Outcomes: -NPI-NH psychosis total score (sum of delusion, hallucination items) -CGI-C -CGI-S Secondary outcomes: -BPRS score -Occupational Disruptiveness Psychosis total score -MMSE -SIB	-No significant results for primary efficacy outcomes between olanzapine and placebo -Repeated-measure analysis showed improvement in NPI-NH psychosis total score (sum of delusion, hallucination items, $p<0.001$) in all treated olanzapine relative to placebo -Repeated-measure showed significant effect for olanzapine 2.5 and 7.5 mg/day relative to placebo ($p=0.049$ and $p=0.030$, respectively)	-Olanzapine 2.5 and 7.5 mg daily showed significant effectiveness in treating of patients with AD with psychosis

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
			-SAS -AIMS -POMA	-Olanzapine 2.5 mg/day improved on CGI-C score (*p=0.030*) relative to placebo -Occupational Disruptiveness Psychosis total and overall Occupational Disruptiveness favoured olanzapine 7.5 mg daily (*p=0.021* and *p=0.007, respectively*) -BPRS score showed improvement in all treatment groups but not significant differences. -MMSE showed significant increase in use of olanzapine 2.5 mg/day (*p=0.019*) -Treatment groups resulted in no significant differences in SAS, AIMS, and POMA compared with baseline in each group	
Zhong et al. (2007)	-n=333	Quetiapine vs placebo	-PANSS -CGI-C	Primary efficacy outcomes:	-Quetiapine 200 mg/day showed a

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
	-Patients with dementia and agitation -Fixed-dose quetiapine 100, 200 mg/day or placebo -10-week -Mean age 83 years		-NPI-NH -CMAI -Incidence of adverse events -MMSE	-Quetiapine at dose 100 mg/day showed no difference compared with placebo -Quetiapine 200 mg/day changed in PANSS (LOCF, *p=0.017* and OC, *p=0.002*) Secondary outcomes: -Significant results for CGI-C (LOCF, *p=0.017* and OC, *p=0.002*), CGI-C response rate (LOCF, *p=0.002* and OC, *p<0.001*) in all treatment groups relative to placebo -No significances in NPH-NH total score, agitation, psychosis score, and occupational disruptiveness, and CMAI in treated group compared with placebo -MMSE was not change compared with baseline	significance impact in patients with dementia related to agitation

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
				-CVE showed no significant changes among treatment groups	
Tariot et al. (2006)	-n=284 -Patients with AD with probable psychoses -Mean age 83.2 years -10-week	-Quetiapine, haloperidol, and placebo	Primary outcomes: -BPRS total score -CGI-S Secondary outcomes: -BPRS agitation factors subscale -NPI-NH agitation scores -MMSE -MOSEC -PSMS -SAS -AIMS	Primary outcomes: No statistical significance in BPRS total score (quetiapine vs placebo, *p=0.217*, quetiapine vs haloperidol, *p=0.354*) and CGI-S (quetiapine vs placebo, *p=0.577* quetiapine vs haloperidol, *p=0.887*) Secondary outcomes: -Significant results for BPRS agitation factors subscale (quetiapine vs placebo, *p=0.023*) No significant differences in NPI-NH agitation scores, MMSE in all treatment groups, except MOSEC ,PSMS, and SAS not significant in quetiapine vs placebo (*p=0.612, p=0.198* and *p=0.974* respectively)	-No significant differences of all treatment groups for patients with AD with psychosis

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
Paleacu et al. (2008)	n=40 -Patients with AD associated with BPSD -6-week	Quetiapine vs placebo	Primary efficacy outcomes: -NPI total score -CGI-C Secondary efficacy outcomes: -MMSE -SAS -AIMS	-No significant reduction in NPI total score in quetiapine vs placebo compared with baseline -Significant change in CGI-C score at 6-week in quetiapine (*p=0.009*) - Placebo showed no significance (*p=0.048*) relative to baseline -No significant differences in secondary outcomes between quetiapine and placebo	-Quetiapine showed no significance difference for treating AD patient with psychosis compared with placebo
Kurlan et al. (2007)	n=40 -Patient with dementia and parkinsonism -10-week	Quetiapine vs placebo	Primary outcome: -BPRS Secondary outcomes: -NPI Psychosis and agitation -MMSE -ADSC-CGIC -ADCS Activities of Daily Living Questionnaire	-No significant results for the primary and secondary outcomes between quetiapine and placebo -No worsening of parkinsonism showed in quetiapine	-Quetiapine had no efficacy for psychosis or agitation in patients with dementia and parkinsonism

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
De Deyn et al. (2005)	-n=208 -AD patients with psychosis -10-week -Mean age 81.5 years	Aripiprazole vs placebo	Primary outcome: -NPI psychosis subscale Secondary outcomes: -NPI total -BPRS -CGI-S -CGI-I -MMSE -Adverse events report -EPS rating scale -Body weight	Primary outcome: -No significance of aripiprazole on NPI psychosis subscale compared with placebo (*p=0.0169*) Secondary Outcomes: -Aripiprazole showed significant improvement on BPRS psychosis and BPRS core subscale compared with placebo (*p=0.029* and *p=0.042*, respectively) No significant differences in NPI total, BPRS total, CGI-I, CGI-S, ASA, AIMS, and BAS -Aripiprazole and placebo were no significant differences in EPS rating Scale	-Aripiprazole and placebo showed no significant improvements in NPI psychosis subscale -Aripiprazole showed improvement in BPRS psychosis core subscale relative to placebo
Streim et al. (2008)	-n=256 -AD patients with psychotic symptoms	Aripiprazole vs placebo	Primary endpoints: -NPI-NH psychosis score (sums of Hallucinations and Delusions) -CGI-S	Primary efficacy outcomes: -No significant differences in primary outcomes, NPI-NH psychosis score (*p=0.883*)	Aripiprazole was efficacious for agitation, anxiety, and

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
	-10-week		Secondary endpoints: -NPI-NH total score -BPRS total -BPRS psychosis -CMAI -Cornell scale -NPI-NH Psychosis Caregiver distress -NPI-NH Total Caregiver distress ADCS-ADL-SEV	and CGI-S (*p=0.198*) Secondary efficacy outcomes: -Significant results for NPI-NH total score (*p=0.009*), BPRS total (*p=0.031*), CMAI (*p=0.030*), Cornell scale (*p=0.006*), and NPI-NH Total Caregiver distress (*p=0.003*)	depression but not psychosis
Mintzer et al. (2007)	n=487 -AD patients with psychosis -Aripiprazole 2.0, 5.0, and 10 mg/day -Mean age 82.5 years	Aripiprazole vs placebo	Primary outcomes at 10-week: -NPI-NH psychosis subscale score Secondary outcomes: -NPI-NH total score -CGI-S score -BPRS psychosis, core and total score -CMAI total score -MMSE score -CGI-I	At 10-week primary endpoint: -Aripiprazole 10 mg/day was significant improvement in NPI-NH psychosis subscale (*p=0.013*) relative to placebo Secondary efficacy outcomes: -NPI-NH total score, aripiprazole 10 mg/day showed statistically significant improvement in the aggression/agitation, anxiety, and	-Aripiprazole 10 mg/day showed significant efficacy for treatment of AD patients with psychosis, agitation, and aggression

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
				irritability, as well as 5 mg/day resulted in reduced aggression/agitation and anxiety compared with placebo -No significant improvement on aripiprazole 2 mg/day vs placebo -Aripiprazole 10 mg/day also showed significant differences on CGI-S (*p=0.031*), BPRS total score (*p=0.030*), BPRS core score (*p=0.007*), and CMAI (*p=0.023*) compared with placebo -Aripiprazole 5 mg/day was significant in BPRS and CMAI score compared with placebo -On dose 2 mg/day showed no significant differences of aripiprazole relative to placebo	

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
				-The dose-dependent was significant leading to increase in cerebrovascular events (*p=0.03)*	
Schneider et al. (2006)	-n=421 -AD patients with psychosis, aggression or agitation -Mean dose olanzapine 5.5 mg/day -Mean dose quetiapine 56.5 mg/day -Mean dose risperidone 1.0 mg/day	Olanzapine, risperidone, quetiapine vs placebo	Primary outcome: -Time for initial treatment to the discontinuation Secondary outcomes: -CGI-C scale -Time to the discontinuation of treatment due to lack of efficacy -Time to the discontinuation of treatment due to adverse events, intolerability, or death	- All treatments showed no significant differences in time to the discontinuation of treatment -Lack of efficacy with regard to time to the discontinuation of treatment was greater in olanzapine (22.1 weeks) and risperidone (26.7 weeks) than quetiapine (9.1 weeks), and placebo (9.0 weeks) (*p=0.002)* -CGI-C scale showed no difference against all treatments (*p=0.22*) -Olanzapine and risperidone had a greater effect on Parkinsonism or extrapyramidal signs than quetiapine or placebo -Sedation effect favoured placebo more than drug groups	-Atypical antipsychotics showed adverse events outweighed benefits for AD patients with psychosis, aggression or agitation

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
				-Olanzapine group showed higher cognitive disturbance and psychotic symptoms than the three-remaining treatment groups	
Deberdt et al. (2005)	-n=494 -Patients with moderate to severe psychotic symptoms with dementia -Mean dose risperidone 1.0 mg/day -Mean dose olanzapine 5.2 mg/day	Olanzapine, risperidone vs placebo	Primary outcomes: -NPI Psychosis Total -CGI-severity of psychosis scale Secondary outcomes: NPI Total -BPRS -CMAI aggression -PDS -Cornell Scale	Primary outcome: -All treatment groups showed no significant difference in NPI Psychosis Total Secondary outcomes: NPI Total, CGI-S Psychosis, BPRS Total, CGI-S dementia, Cornell Total, PDS, and CMAI aggression showed no significant differences of both olanzapine and risperidone compared with placebo -Overall discontinuation favoured in placebo -Incidence of discontinuation due to adverse effects was the greater in olanzapine	Olanzapine, risperidone, and placebo were showed no significant differences for treating of patients with moderate to severe psychotic symptoms with dementia

Trials	Populations	Interventions	Outcome assessment	Result	Conclusion
				-Somnolence, urinary incontinence and hostility significantly presented in risperidone and olanzapine compared with placebo	

Abbreviations: Behavioural Pathology in Alzheimer's disease Rating Scale (BEHAVE-AD), Clinical Global Impression (CGI) scale, Clinical Global Impression-Change scale (CGI-C) scale, Clinical Global Impression-Severity scale (CGI-S) scale Neuropsychiatric Inventory (NPI), Cohen-Mansfield Agitation Inventory (CMAI), Brief Psychiatric Rating Scale (BPRS), Severe Impairment Battery (SIB), time for initial treatment to the discontinuation, and Mini-Mental State Examination (MMSE), the Simpson-Angus Scale (SAS), the Abnormal Involuntary Movement Scale (AIMS), the Modified Performance-Oriented Mobility Assessment (POMA), the Progressive Deterioration Scale (PDS), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL-SEV), Extrapyramidal Symptoms Rating scale (EPS rating scale), the ADCS Clinical Global Impression of Change (ADSC-CGIC), Positive and Negative Syndrome Scale (PANSS), Last Observation Carried Forward (LOCF), Observed Cases (OC)

From the literature review, the published evidence has supported the efficacy of atypical antipsychotics for the treatment of patients with dementia associated with behavioural and psychological symptoms.

However, the adverse events associated with atypical antipsychotics may offset efficacy for the treatment of BPSD. The serious side effects in senile dementia accounted for cerebrovascular events, extrapyramidal symptom, falls, somnolence, sedation, disinhibition, depression, incontinence, Parkinsonism, weight gain, orthostatic hypotension, dyskinesia and cognitive function impairment (Schneider et al. 2006, Tan et al. 2015).

To sum up, despite, the US-FDA warning of using atypical antipsychotics due to increased incidence in cerebrovascular mortality of 1.5 -1.7 times in the elderly with dementia in 2005, the trend of prescribing atypical antipsychotic for patients with dementia was paradoxical. Atypical antipsychotics were significantly prescribed for the treatment of BPSD (Schulze et al. 2013, Mcllroy, Thomas and Coleman 2015). Additionally, several published articles showed that second-generation antipsychotic drugs had modest efficacy for the treatment of behavioural and psychological symptoms, namely agitation, aggression, psychosis, depression, anxiety. However, the limited and conflicting evidence for efficacy of atypical antipsychotic drugs were debatable for introducing them to manage BPSD in patients with dementia. The efficacy of certain drugs may be offset by adverse events.
Although this still needs to be a debate about atypical antipsychotics on their effectiveness and adverse events, these drugs are widely used for the treatment of behavioural disturbance related to geriatric dementia. This is because the severity of behavioural disturbance worsens following disease progression. This then has potential impacts on morbidity, caregiver's general health, the burden of care, patient and caregiver distress, and risk of harm to patients and carers. Consequently, it is important to weigh the risks and benefits before making judgments regarding the treatment of behavioural problems in people with dementia. The

pharmacological approaches are important and these are recommended after non-pharmacological methods fail, for the better management of the disease. Finally, despite the modest efficacy for the reduction of behavioural symptoms, the potential improvement of the condition has considerable impact on the quality of life for patients and caregivers.

2.5 Health Economic Evaluations

Economic evaluations of health care involve a comparative analysis of the costs involved and the relevant options implemented. The purpose of this type of analysis is mainly to allocate scarce resources rationally for optimal decision making (Drummond et al. 2005). Cost-effectiveness analysis (CEA), which is in widespread use in economic evaluations of health, compares the costs and the outcomes of one intervention against alternative interventions. The effect in this type of analysis is measured in terms of life-years gained (LYG). By contrast cost-utility analysis (CUA) is a type of health economic evaluation adapted from CEA. The outcome of this analysis is reported on the basis of life-years gained adjusted by the utility value (QALYs). These quality adjusted life years (QALYs) reflect both the quality and the quantity of life gains (Drummond et al. 2005).

The cost-effectiveness plane (See Figure 2.3) is a diagram that can be applied to economic evaluations when comparing new technologies with current technologies. The horizontal and the vertical axes represent the differences in effectiveness and cost of both the new treatment and the current treatment respectively. The four scenarios can be illustrated as follows: in quadrant II, the new treatment dominates the comparator, which means the new treatment is more effective and cheaper than the comparator. Conversely, the new intervention is more expensive and less effective in quadrant IV and the new treatment is dominated by the current treatment. In quadrant I, is the scenario generally found in health economic evaluation, whereby the new treatment is more effective and also more expensive than the current

treatment. The same applies in quadrant III, but the justification is consistent with the previous quadrant (Drummond et al. 2005).

The comparison of two heath care programmes can be demonstrated in terms of the incremental cost-effectiveness ratio (ICER). This ratio represents the incremental cost over the incremental outcome, which identifies how much it is worth paying for additional health gains (Drummond et al. 2005). Conventionally, the lowest ratio is held to be the optimal decision.

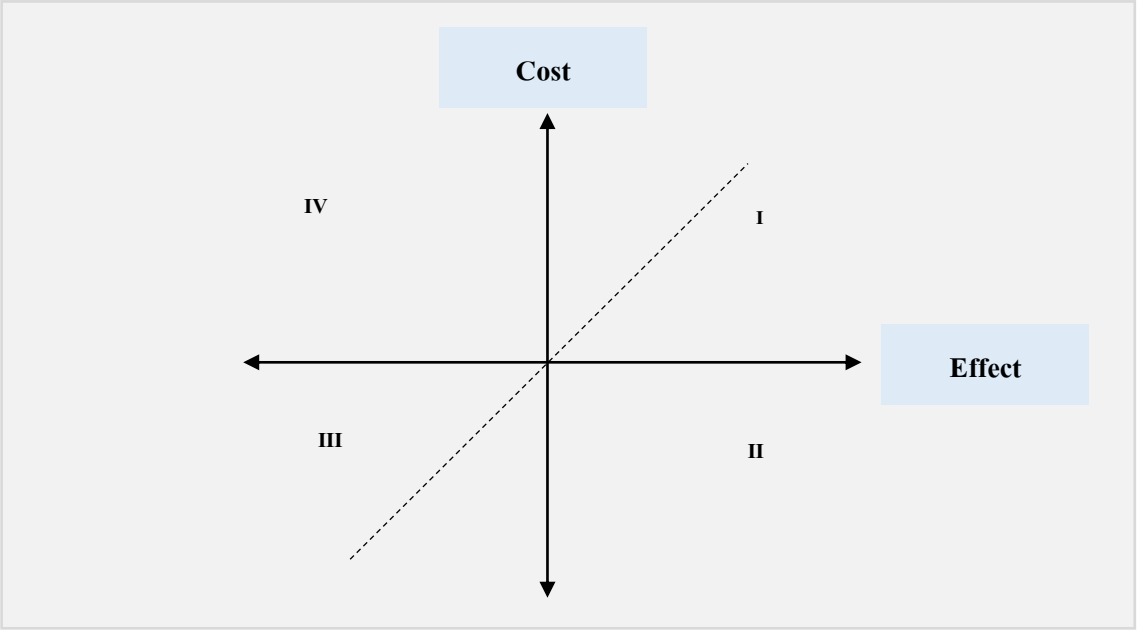


Figure 2.3: The cost-effectiveness plane

2.5.1 Literature Search for Heath Economic Evaluations of Atypical Antipsychotics for Dementia

A comprehensive literature search was undertaken in electronic databases. The literature search was focusing on health economic evaluation of atypical antipsychotics for dementia. The procedure was similar to the literature search for efficacy of atypical antipsychotics for dementia.

A literature search was undertaken in the electronic databases MEDLINE, the Centre for Reviews and Dissemination (CRD), and the National Health System Economic Evaluation Database (NHS EED). The literature search covered the period between 1995 and June 2015. Search terms were as follows:

a) Cost-effectiveness, cost-analysis, cost-benefit, cost-utility;
b) Dementia, Alzheimer's disease;
c) Risperidone, Olanzapine, Aripiprazole, Quetiapine.

The database search for cost-effectiveness of atypical antipsychotics, including risperidone, olanzapine, quetiapine and aripiprazole for dementia, resulted in a total of 14 articles retrieved from MEDLINE, NHS EED, and CRD. The titles were screened for inclusion and exclusion criteria.

The result found only two studies associated with the cost-effectiveness. One study focused on olanzapine for agitation and psychosis in Alzheimer's disease, based on a Markov state-transition model to estimate the cost-effective treatment. The conclusion showed olanzapine was cost-effective compared with an untreated group, for agitation and psychosis in AD in a community dwelling in the United States, using the perspective of the US health system. However, the limitation of this study was the variables to enter into the model derived from other studies. Another factor to consider is the estimation of health utilities which was deduced from schizophrenia studies (Kirbach et al. 2008).

On the contrary, another study is the cost-benefit analysis in a randomized controlled trial of second-generation antipsychotics and placebo for treating psychosis, agitation, or aggression in AD, followed-up over 9 months. The finding demonstrated that risperidone, olanzapine and quetiapine showed no differences in effectiveness compared to placebo, in a community dwelling in United States (Rosenheck et al. 2007).

2.5.2 The extended literature search for health economic evaluations of atypical antipsychotics for dementia

A comprehensive literature search of electronic databases was conducted on 16th September, 2015. MEDLINE, the Centre for Reviews and Dissemination (CRD) (containing the National Health System Economic Database (NHS EED), the Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment database were searched. Search terms were as follows:

a) Costing, costs, finance, "economic evaluation", pharmacoeconomic;
b) Dementia, Alzheimer's disease;
c) Risperidone, Risperdal, Olanzapine, Zyprexa, Aripiprazole, Abilify, Quetiapine, Seroquel.

Inclusion criteria:

- Population: people with dementia, people with Alzheimer's disease;
- Interventions: risperidone, risperdal, olanzapine, zyprexa, aripiprazole, abilify, quetiapine, and seroquel;
- Study designs: comparison in terms of cost, and cost and health outcome, costs;
- Outcomes: QALYs, monetary costs, health benefits, health outcomes.

A total of 25 articles were retrieved. Twenty articles were retrieved from MEDLINE. Three articles were retrieved from NHS EED, two retrieved from HTA and DARE. The titles were screened for inclusion and exclusion criteria. After screening the titles, 15 articles were excluded. A further seven articles were excluded after screening the abstracts, while another one was excluded due to being non-English language which left two articles remaining. However, these articles had already been identified from a former literature search for health economic evaluations of atypical antipsychotics for dementia.

2.5.3 Review for Modelling in Dementia

Green (2007) reviewed the modelling method for cost-effectiveness analysis of Alzheimer's disease. The results focused on four drugs which were most commonly used for the treatment of AD: donepezil, rivastigmine, galantamine, and memantine. Most of the models for evaluating the cost-effectiveness of donepezil used the Markov model. The models for rivastigmine used the Hazard model, introducing individual data of patients from clinical trials. Whereas, galantamine applied the Assessment of Health Economics in Alzheimer's Disease (AHEAD) model for tracking the progression of disease. Most of the modelling for the economic evaluation of memantine used the Markov model.

Green et al. (2011), a review of model-based economic evaluation in AD, findings showed a state-transition modelling, a Markov model, used in most studies for economic evaluation of disease progression in AD. The author also summarised the models of AD as follows: the McDonnell model, the Kinosian model, the Consortium to Establish a Registry in Alzheimer's Disease-Clinical Dementia Rating (CERAD-CDR model-refer to Markov model), the CERAD-MMSE model, the Assessment of Health Economics in Alzheimer's Disease model (AHEAD model), the memantine model, the Fenn and Gray model, the Kungsholmen-MMSE model, the CERAD-Severe Impairment Battery model (CERAD-SIB model, and the Predictors Alzheimer's Disease Assessment Scale-Cognitive Function (ADAS-cog model).

Pouryamout et al. (2012) studied a systematic review of cost-effectiveness analysis in patients with AD. The study demonstrated four main models used for economic evaluation. The models were the Markov model, microsimulation model, AHEAD model, and discrete-event simulations.

As a result of the lack of pharmacoeconomic research of atypical antipsychotics on dementia, it is recommended to explore this significant problem. Although the atypical

antipsychotics for treatment in BPSD are still controversial in practical guidelines due to the efficacy and safety related to adverse events, they currently remain in general use in clinical practices and have a relatively adverse impact on the burden of care, and quality of life of patients and caregivers. There were several studies using a decision-analytic model to evaluate the cost-effectiveness on the use of atypical antipsychotics for schizophrenia. However, there were very few focusing on dementia. Additionally, there were other health economic evaluations for other classifications of drug groups for dementia, namely Cholinesterase Inhibitors, memantine, based on decision-analytic models. This study will be the first to explore and evaluate the cost-effectiveness of atypical antipsychotics drugs between olanzapine relative to risperidone, for treatment of behavioural and psychological symptoms, in patients with dementia in Thailand.

2.6 Modelling-based economic evaluation in dementia

The purpose of this review is to explore the existing decision-analytic models, which have been used to undertake economic evaluations in dementia. The results from a literature review identify the further development of the most appropriate model to apply with the cost-effectiveness of atypical antipsychotics, for the treatment of behavioural and psychological symptoms of dementia in Thailand.

2.6.1 Literature search for model-based economic evaluation in dementia

A comprehensive literature search was undertaken in electronic databases. The literature search was performed using the following parameter: modelling in dementia. In this procedure, there were four main steps. Firstly, the key search terms were developed on the basis of the relevant topic. Secondly, titles were considered for screening using the inclusion and exclusion criteria. If they met the criteria, they were then exported to RefWorks for further evaluation. Thirdly, the abstracts were scrutinised for inclusion and exclusion criteria

to confirm whether they met the inclusion criteria. Finally, an assessment and in-depth review were conducted to identify whether the literature was for inclusion or exclusion. If they fulfilled the criteria, they were then included into the final stage.

The literature search for model-based economic evaluation in dementia was undertaken in electronic databases, including MEDLINE, the Centre for Reviews and Dissemination of the University of York (CRD), the Database of Abstracts of Reviews of Effects (DARE), the NHS Economic Evaluation Database (NHS EED) and the HTA database (HTA). The literature search covered January 1975 up to March 2018. The search terms were broken down into the relevant topics as follows:

a) Dementia or Alzheimer's disease;
b) Modelling or models or economic models;
c) Assessment of health economics, economic evaluations (cost-minimisation analysis, cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis).

The inclusion for the literature search was critically appraised using a PICO framework. The inclusion and exclusion criteria are listed below:

Inclusion criteria:

- Participants: people with dementia, people with Alzheimer's disease;
- Interventions and Comparators: interventions for people with dementia and people with Alzheimer's disease which focused on the treatment of disease progression;
- Study designs: decision-analytic models, statistical models;
- Outcomes: economic evaluations (cost-minimization analysis, cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis).

Exclusion criteria:

Articles were excluded when they did not match the inclusion criteria; and in particular if they were:

- Abstracts, letters or commentaries;
- Studies of cost of illness;
- No access to full-text papers;
- Non-English-language articles;
- Review of articles.

2.6.2 Data Extraction Strategy

Initially, the database search retrieved in total 1,118 articles both from MEDLINE and the CRD database, respectively. The search resulted in 755 articles retrieved from MEDLINE and 363 articles from CRD.

The initial total of 755 articles from the MEDLINE database underwent screening of the title against the inclusion and exclusion criteria. Of these, 616 articles were removed due to their title not meeting the inclusion criteria. The remaining 139 articles were identified for conducting further scrutiny. A further 101 articles were excluded after the abstract screening. The remaining of 38 articles progressed to a full review of the texts.

From the CRD database, 363 articles were identified based on their titles. After a further scrutiny, 299 irrelevant articles based on their titles were removed, and the remaining 64 articles abstracts were scrutinised. The result of abstract screening was that a further 28 articles were excluded. The remaining 36 articles were identified to progress to the next step in the review process. However, 33 articles were excluded due to duplication, 3 articles remained which were potentially relevant and progressed to a full-text review.

As a result of scrutinising the two databases, 41 articles were identified as meeting the inclusion criteria and were retrieved for full-text reviews. After the articles had been identified for full text reviews, a paper was judged to be excluded if access to the full text of the paper was not available. Finally, a total of 40 articles were potentially identified to be reviewed in-depth, for the model in the treatment of patients with dementia. A literature review flowchart is presented in Figure 2.4.

2.6.3 Results of the literature review

The screening of the 1,118 article titles identified from MEDLINE and the CRD resulted in 203 articles being retrieved for abstract consideration. After considering the exclusion criteria, a total of 40 were judged to meet the inclusion criteria for an in-depth review. Following a more detailed review of those articles, the main findings focused on the model for economic evaluation in dementia.

Following on from the literature search, 40 articles modelled the disease progression in dementia. The majority of studies were based on Alzheimer's disease (n = 39 out of 40). There was only one paper identified which was associated with vascular dementia. The Markov model was the most commonly used as the decision-analytic model to be employed for the disease progression of economic evaluations in dementia, in particular Alzheimer's disease (n = 30 out of 40).

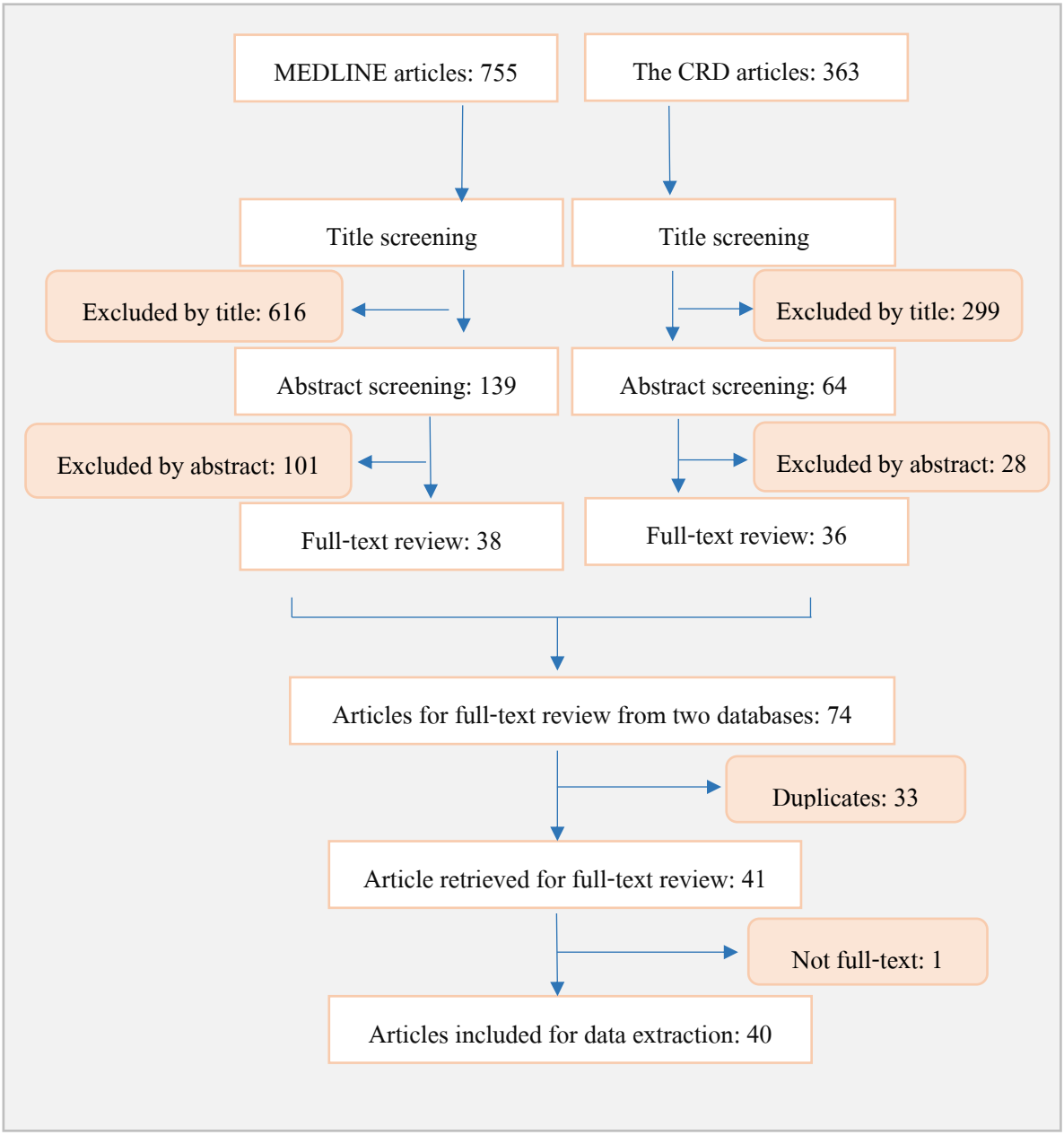


Figure 2.4: A comprehensive literature search for model-based economic evaluation in dementia

Most model-based economic evaluation in dementia included data analyses carried out in different time periods and these were classified into five different model structures: the Markov model, the Discrete Event Simulation (DES) model, the microsimulation, the decision tree, and the statistic model. The findings from the literature search are presented as follows: the overall analytical approaches are categorised model structures presented in Table 2.2. The economic evaluation based on modelling is classified by year and by region presented in Table 2.3 and 2.4, respectively.

Table 2.2: **Summary of the decision-analytic models based on model structures used in the disease progression of dementia**

Model structure	Reference
1. Markov model	Stewart, Phillips and Dempsey (1998), Jonsson et al. (1999), Neumann et al. (1999), O' Brien et al. (1999), Getsios et al. (2001), Caro et al. (2002), Garfield et al. (2002), Ikeda, Yamada and Ikegami (2002), Migliaccio-Walle et al. (2003), Ward et al. (2003), Caro et al. (2004), Francois et al. (2004), Jones, McCrone and Guilhaume (2004), Green et al. (2005), Jonsson et al. (2005), Antonanzas et al. (2006), Gagnon et al. (2007), Teipel et al. (2007), Fuh and Wang (2008), Kirbach et al. (2008), Lopes-Bastida et al. (2009), Suh (2009), Rive et al. (2010), Hoogveldt et al. (2011), Lachaine et al. (2011), Pfeil, Kressig and Szucs (2012), Rive et al. (2012), Touchon et al. (2014), Hu et al. (2015), Zala, Chan and McCrone (2017)
2.The Discrete Event Simulation (DES)	Getsios et al. (2010), Guo et al. (2010), Hartz et al. (2012), Thibault et al. (2015)
3. Microsimulation	Weycker et al. (2007)
4. Decision tree	Henke and Burchmore (1997), Wong et al. (2009)
5. Statistical model	Fenn and Gray (1999), McDonnell et al. (2001), Nagy et al. (2010)

Table 2.3: **Summary of the model types used to model the disease progression of dementia by year**

Model Type	1996-2000	2001-2005	2006-2010	2011-2015	2016-present
	No. Referenced	No. Referenced	No. Referenced	No. Referenced	No. Referenced
1. FTC framework -AHEAD model based on Caro and colleague (2001)		7	1		
2. FTC framework-model structure based on Rive and colleague (2010)			1	1	1
3. CERAD-CDR model structure	1	1	3		
4. CERAD-SIB model			1		
5. Model developed to evaluate memantine drug		3	2	1	
6. DES model			2	2	
7. Model based on Lachaine et al. (2011)				3	
8. McDonnell et al. (2001)		1			
9. Fenn and Gray (1999)	1				
10. Model based on the data from Kungsholmen project	1		1		
11. Henke and Burchmore (1997)	1				
12. Nagy et al. (2010) based on the MMSE- and ADL- based model			1		
13. Wong et al. (2009)			1		
14. Stewart, Phillips and Dempsey (1998)	1				
15. Hu et al. (2015)				1	

Model Type	1996-2000	2001-2005	2006-2010	2011-2015	2016-present
	No. Referenced	No. Referenced	No. Referenced	No. Referenced	No. Referenced
16. O' Brien et al. (1999)	1				

The modelling based on the Markov model

The model based on the FTC conceptual framework using the predictive equation of time to FTC developed by Caro and colleagues (2001) was widely used and modified in studies between 2001 and 2009. The model based on the FTC conceptual framework using the predictive equation of time to FTC developed by Rive et al. (2010) was applied in several studies conducted in 2010 to 2017. In addition, modelling based on the CERAD data using the CDR scale to assess the cognitive function of patients was applied in various studies of the economic evaluation of dementia during 1999 to 2009. The modelling used to evaluate the cost-effectiveness of memantine based on the Markov model was conducted in six studies between 2004 and 2011. There were also three studies based on Lachaine et al. (2011) conducted between 2011 and 2014. The project of Kungsholmen was adopted to Jonsson et al. (1999) and Teipel et al. (2007). Other models were the studies by O' Brien et al. (1999) and Hu et al. (2015).

The modelling based on the Discrete Event Simulation (DES) model, *the decision tree model, the statistic model, and the microsimulation model*

Most studies associated with DES models were applied in 2010 to 2015. The decision tree model was adopted by two studies those of Henke and Burchmore (1997) and Wong et al. (2009), respectively. Fenn and Gray (1999), McDonnell et al. (2001) and Nagy et al. (2010) applied the statistic model in their studies. Only one model based on the CERAD study using

the SIB scale to measure the cognitive function was applied in the microsimulation model (Weycker et al. 2007).

Table 2.4: **Summary of the model types used to model the disease progression of dementia by regions**

Model Type	Worldwide	USA/Canada	Europe	Asia	Multinational
	Referenced (%)	Referenced (%)	Referenced (%)	Referenced (%)	Referenced (%)
1. FTC framework -AHEAD model based on Caro and colleague (2001)	8 (20)	2 (25)	4 (50)	1 (12.5)	1 (12.5)
2. FTC framework-model structure based on Rive and colleague (2010)	3 (7.5)		3 (100)		
3. CERAD-CDR scale model	5 (12.5)	2 (40)	1 (20)	2 (40)	
4. CERAD-SIB model	1 (2.5)	1 (100)			
5. Model developed to evaluate memantine drug	6 (15)	1 (20)	5 (80)		
6. DES model	4 (10)	1 (25)	3 (75)		
7. Model based on Lachaine et al. (2011)	3 (7.5)	1 (33.3)	2 (66.7)		
8. McDonnell et al. (2001)	1 (2.5)		1 (100)		
9. Fenn and Gray (1999)	1 (2.5)		1 (100)		
10. Model based on the data from Kungsholmen project	2 (5.0)		2 (100)		
11. Henke and Burchmore (1997)	1 (2.5)	1 (100)			
12. Nagy et al. (2010) based on the MMSE- and ADL- based model	1 (2.5)		1 (100)		
13. Wong et al. (2009)	1 (2.5)	1 (100)			
14. Stewart, Phillips and Dempsey (1998)	1 (2.5)		1 (100)		
15. Hu et al. (2015)	1 (2.5)			1 (100)	

Model Type	Worldwide	USA/Canada	Europe	Asia	Multinational
	Referenced (%)	Referenced (%)	Referenced (%)	Referenced (%)	Referenced (%)
16. O' Brien et al. (1999)	1 (2.5)	1 (100)			

Based on the classification by region as seen in Table 2.4, the most often used was the model based on the FTC conceptual framework using the predictive equation of time to FTC developed by Caro and colleagues (2001) accounting for 20% out of all studies. Approximately 50% of the studies were conducted in Europe, followed by the US or Canada. The model based on the FTC conceptual framework using the predictive equation of time to FTC developed by Rive et al. (2010), was used to evaluate all the studies in Europe. 40% of the studies in the US and Asia employed the CERAD-CDR scale, whereas there was only one study that applied this model in Europe. The memantine and the Lachaine models were also used in studies in Europe accounting for 80% and 66.7%, respectively. There were only two studies based on the Kungsholmen project and these were conducted exclusively in Europe. 75% of the studies based on the DES model were conducted in Europe. The remaining studies were undertaken in Europe and the USA or Canada (Henke and Burchmore 1997, Stewart, Phillips and Dempsey 1998, O' Brien et al. 1999, Fenn and Gray 1999, McDonnell et al. 2001, Wong et al. 2009, Nagy et al. 2010), with one exception which was employed in Asia (Hu et al. 2015).

The major interventions applied to the model-based economic evaluations in dementia were categorised as follows:

1. Donepezil
2. Galantamine
3. Rivastigmine

4. Memantine
5. Olanzapine
6. Tacrine

Additionally, the target groups of patients identified in the model-based economic evaluations in dementia are summarised as listed below:

1. Mild to moderate Alzheimer's disease patients;
2. Mild to moderate Vascular dementia patients;
3. Mild to moderately severe Alzheimer's disease patients;
4. Mild to moderate and moderate to severe Alzheimer's disease patients;
5. Mild to moderately severe and moderate to moderately severe Alzheimer's disease patients;
6. Moderate to severe Alzheimer's disease patients;
7. Moderately severe to severe Alzheimer's disease patients;
8. Moderate and severe Alzheimer's disease patients;
9. Agitation and psychosis Alzheimer's disease patients;
10. Moderate Alzheimer's disease patients;
11. Alzheimer's disease patients not specified severity.

2.6.4 A summary of the model-based economic evaluation in dementia

Most studies of modelling in economic evaluations in dementia are focused on Alzheimer's disease. There is only one study identified related to vascular dementia. The literature search shows that the modelling used in classifying dementia progression follows one of these models:

1. Model based on the FTC conceptual framework;

   1.1 AHEAD-based model developed by Caro et al. (2001); the predictive equation of time to FTC was based on data from the study by Stern et al. (1997);

1.2 model structure developed by Rive et al. (2010); the predictive equation of time to FTC was based on Rive et al. (2010);

2. Model based on the Consortium to Establish a Registry for Alzheimer's disease (CERAD);
   2.1 Cognitive function was measured based on the Clinical Dementia Rating (CDR) scale: CERAD-CDR model;
   2.2 Cognitive function was measured based on the Severe Impairment Battery: CERAD-SIB model;
3. Model developed to evaluate memantine drugs;
4. The Discrete Event Simulation (DES) model;
5. Model developed by Lachaine et al. (2011);
6. Model developed by McDonnell et al. (2001);
7. Model developed by Fenn and Gray (1999);
8. Model based on the data from Kungsholmen project;
9. Model developed by Henke and Burchmore (1997);
10. Model developed by Nagy et al. (2010) based on the MMSE- and ADL- based model;
11. Model developed by Wong et al. (2009);
12. Model developed by Stewart, Phillips and Dempsey (1998);
13. Model developed by Hu et al. (2015);
14. Model developed by O' Brien et al. (1999).

The next section goes on to the findings of the model-based economic evaluation in dementia from the literature review.

2.6.4.1 Findings of the model-based economic evaluation in dementia from the literature review

Most studies of modelling in economic evaluations in dementia focused on Alzheimer's disease, with one exception related to vascular dementia. The findings from the

comprehensive literature search are presented in Table 2.5 which is classified by model types and chronological order.

2.6.4.1.1 Concept of model-based economic evaluations in dementia and model applications from the literature review

According to the comprehensive literature review, the concept of modelling applied to economic evaluations in dementia are outlined below.

2.6.4.1.1.1 Model based on the FTC conceptual framework

The model-based the FTC conceptual framework according to the literature review in this thesis was classified into two main types as subsequently described.

2.6.4.1.1.1.1 The Assessment of Health Economics in Alzheimer's disease (AHEAD)-AHEAD model using the predictive equation of time to FTC developed by Caro and colleagues (2001)

The original model of the Assessment of Health Economics in Alzheimer's disease (AHEAD) based on the need for full-time care (FTC) was initially developed by Caro et al. (2001). The model was used to estimate the disease progression of patients to the FTC requirement. FTC was the requirement that patients need a significant amount for care and supervision almost every day, regardless of the locus of care or who provided it. Further, the prediction to death was also estimated. The health states in the model consisted of not requiring FTC, FTC and death. Basically, the time spent in the different stages of AD was measured. The transition probabilities of requiring FTC were computed by the hazard function, based on the patient characteristics. Similarly, the Gompertz hazard functions were used to calculate the transition probabilities for patients moving from one state to death were based on the patient characteristics. The average delay to FTC was the difference in the expected time spent in the given state. The mean time of patients, based on different characteristics, was computed by the subtraction between both values. In addition, the

equation to predict the need for FTC was developed from data from the study by Stern and colleagues (1997), which was undertaken in USA, and modelled in 236 Alzheimer's disease patients. The patients were followed-up for 7 years and the mean age of the patients was 73 years, (this marked age was brought about to determine younger and older groups which were computed in the regression equations for needing FTC). The endpoints of follow-up of patients were the need of health related facility, (HRF), care and death. The set of patient characteristics were important to the predictive equation to estimate disease progression over time, which correlates to the time to reach FTC. The presence of extrapyramidal symptoms (EPS), presence of psychotic symptoms, aged at the onset of disease, cognitive function, and duration of illness were found to be the significant factors of the equation. The coefficient of predictors were the EPS = -0.9419, psychotic symptoms = -0.4027, at young age of the onset of disease = -0.4848, cognitive function = 0.0724, and duration of illness = 0.0617, respectively. The cognitive function was measured in terms of the modified Mini-Mental State examination (mMMS), whereas the significant predictors of death were based on female gender, EPS, cognitive function, and duration of illness. The coefficient of the predictors of death were the female gender = 0.7046, EPS = -1.2825, cognitive function = 0.0310, and duration of illness = 0.1052, respectively. To calculate the time to FTC need, the following two steps were undertaken (Caro et al. 2001). The first step was a calculation around the average hazards for reaching FTC and death. The equation was:

$$\lambda = \frac{-\ln(1-F)}{(t_i - t_{i-1})}$$

where λ was the average hazard over the period,

F was the cumulative of proportion of patients with failure over period,

t_i was the time at failure (i) and

t_{i-1} was the previous time $(i-1)$.

In accordance with the index derived from the hazard model, the baseline hazard for index (λ_0) was computed by:

$$\lambda_0^t = \frac{\lambda_{index}^t}{e^{-index}}$$

The next step was to calculate the relationship between the baseline hazard and time. The equations were separated by aged group, defined into younger and older, the cut-off point being aged 73-year. The coefficients applied in the equation to calculate for risk over time were A = 0.0231, B = -1.8117, C = 0.0373, D = 0.1532, and E = -4.7903 for patients aged 73 years and younger. Whereas the coefficients for the patient aged more than 73 years were A = 0, B = -0.6846, C = -6.4172, D = 0.0112, and E = 0.1413. Thus, the relation for risk over time was calculated by the equation:

$$\lambda_{FTC} = e^{(At+B+C\sinh(Dt+E))}$$

where sinh was the hyperbolic sine,

t was the time and

A, B, C, D and E were coefficients as presented above.

Then the regression equation was applied to estimate the hazard for other index values based on the Cox proportional hazard equation. The hazard for risk over time for any index scores was calculated for the time to FTC need using the equation below.

$$\lambda_{index}^t = \frac{\lambda_0^t}{e^{index}}$$

In conclusion, the concepts of the AHEAD model, which was developed by Caro et al (2001), used the patient characteristics at a given point to predict the disease progression to a

level of requiring FTC. The health states in the model consisted of pre-FTC, FTC and death. The Cox proportional hazard models were used to predict the risk of FTC need and death of patients as a function of time as well as index scores that incorporated the various patient characteristics. The significant covariates to predict those requiring FTC were the presence of EPS, presence of psychotic symptoms, age at onset of disease, duration of illness, and cognitive score (mMMS). The prediction to death was based on EPS, duration of illness, female gender, and mMMS score. The mMMS was the modified Mini-Mental State examination.

In addition, eight studies used the AHEAD model developed by Caro et al. (2001). Concepts of these models were the course of disease progression in terms of health states defined by the time until patients requiring FTC (Getsios et al. 2001, Caro et al. 2002, Garfield et al. 2002, Migliaccio-Walle et al. 2003, Ward et al. 2003, Caro et al. 2004, Green et al. 2005, Suh 2009).

● *Model type:*	All eight studies applied Markov models (Getsios et al. 2001, Caro et al. 2002, Garfield et al. 2002, Migliaccio-Walle et al. 2003, Ward et al. 2003, Caro et al. 2004, Green et al. 2005, Suh 2009).
● *The definition of disease severity*:	The need to FTC was used to define the disease severity in the model of all eight studies (Getsios et al. 2001, Caro et al. 2002, Garfield et al. 2002, Migliaccio-Walle et al. 2003, Ward et al. 2003, Caro et al. 2004, Green et al. 2005, Suh 2009).
● *The study population*:	Most studies conducted in the mild to moderate Alzheimer's patients (Getsios et al. 2001, Caro et al. 2002, Garfield et al. 2002, Migliaccio-Walle et al. 2003, Ward et al. 2003, Caro et al. 2004). Two studies conducted in mild to moderately severe Alzheimer's disease (Green et al. 2005, Suh 2009).
● *Interventions*:	The majority of studies conducted the treatment of galantamine compared with no pharmacological treatment (Getsios et al. 2001, Caro

	et al. 2002, Garfield et al. 2002, Migliaccio-Walle et al. 2003, Caro et al. 2004). However, the differences of dosage regimen of galantamine were applied. A comparison between galantamine (not identified dosage regimen) and no pharmacological treatment was found in studies by Caro et al. (2002) and Caro et al. (2004). Getsios et al. (2001) examined galantamine 24 mg/day versus no pharmacological treatment. Between galantamine 12 mg given twice daily in Alzheimer's patient and no pharmacological treatment were compared in the study by Garfield et al. (2002). Migliaccio-Walle et al. (2003) conducted the comparison of galantamine 16 mg/day and 24 mg/day versus no pharmacological treatment. Galantamine 16 mg/day and 24 mg/day compared with no cholinesterase treatment were employed in the study by Ward et al. (2003). Between galantamine 24 mg/day plus usual care versus usual care were examined by Suh (2009). Green et al. (2005) studied donepezil, galantamine and rivastigmine compared with usual care.
● *The disease progression*:	The predictive equation was needed to predict time to FTC over time. The significant covariates to predict the need to FTC were presence of EPS, presence of psychotic symptoms, age at onset of disease, duration of illness, and cognitive score (mMMS).
● *Model structure*:	The health states in all models comprised three states: not requiring FTC (Pre-FTC), requiring FTC, as well as death (Getsios et al. 2001, Caro et al. 2002, Garfield et al. 2002, Migliaccio-Walle et al. 2003, Ward et al. 2003, Caro et al. 2004, Green et al. 2005, Suh 2009).
● *Data sources*:	Seven studies used the predictive equation based on the longitudinal study, undertaken in USA, in 236 Alzheimer's disease patients by Stern et al. (1997), to predict the time until patients needed FTC (Getsios et al. 2001, Caro et al. 2002, Garfield et al. 2002, Migliaccio-Walle et al. 2003, Ward et al. 2003, Caro et al. 2004, Green et al. 2005). The other applied the longitudinal studies in South Korea (Suh 2009).

	For mortality probabilities, six out of eight studies used data from a longitudinal study, as mentioned above, to predict the transition probabilities of death, with two exceptions which used data from the prospective study (Green et al. 2005) and a longitudinal study in South Korea (Suh 2009). There were six studies using the RCT data for the treatment effect (Getsios et al. 2001, Caro et al. 2002, Garfield et al. 2002, Migliaccio-Walle et al. 2003, Ward et al. 2003, Caro et al. 2004), while one study used the meta-analysis on RCT study (Green et al. 2005) and another study adopted data from longitudinal studies in South Korea (Suh 2009).
● *Time horizon and cycle length*:	Six studies conducted over a 10-year period modelled using a monthly Markov cycle (Getsios et al. 2001, Caro et al. 2002, Garfield et al. 2002, Migliaccio-Walle et al. 2003, Ward et al. 2003, Caro et al. 2004). Two studies modelled a 5-year time horizon performing with a one month cycle length (Green et al. 2005, Suh 2009).
● *Healthcare Perspective of model*:	Caro et al. (2002) used the broad perspective and formal care in their studies, whereas Caro et al. (2004) applied the broad perspectives including social services. The public health payer was used in Garfield et al. (2002). A third party approach was employed in the studies by Migliaccio-Walle et al. (2003) and Suh (2009). The studies by Ward et al. (2003) and Green et al. (2005) were conducted from the perspectives of the National Health Service and Personal Social Service.
● *Costs data and Utilities*:	All eight studies included direct costs for cost data (Getsios et al. 2001, Caro et al. 2002, Garfield et al. 2002, Migliaccio-Walle et al. 2003, Ward et al. 2003, Caro et al. 2004, Green et al. 2005, Suh 2009). However, one study considered the additional out-of-pocket expenses for the patients' assistant or paid caregiver, caregiver time-related costs, and caregiver's lost productivity (Suh 2009). Costs associated with visiting patients were encompassed in the study by Green et al. (2005).

	Six studies used the Health Utilities Index Mark 2 (HUI:2) based on the cross-sectional study (Getsios et al. 2001, Caro et al. 2002, Ward et al. 2003, Caro et al. 2004, Green et al. 2005, Suh 2009). Two studies were not identified (Garfield et al. 2002, Migliaccio-Walle et al. 2003).
● *Discount rates*:	The discount rates for costs and benefits varied in the studies. A 3% discount rate in both costs and outcomes was conducted in three studies (Getsios et al. 2001, Migliaccio-Walle et al. 2003, Caro et al. 2004). One study used the discount rate for only costs at 3% (Garfield et al. 2002). Three studies applied a 6% and 1.5% for the discount rate, respectively, for costs and outcomes per annum (Ward et al. 2003, Green et al. 2005, Suh 2009). A discount rate at 5% in both costs and outcomes was employed in Caro et al. (2002).

In conclusion, the AHEAD model, which was developed by Caro and colleagues (2001), was wildly used to apply to the assessment of health economics between 2001 and 2009. The Markov model was used to predict the time until patients reached FTC. The predictive equation developed based on data from the study by Stern et al. (1997) was used in most studies. The three main health states in the model were Pre-FTC, FTC, as well as death. Approximately 75% of all studies were conducted in patients with mild to moderate Alzheimer' disease. Most studies examined the treatment of galantamine relative to no pharmacological treatment (62.5%). The randomized controlled trials were used as data sources for the effectiveness data. Varieties were found in perspectives, the discounted rates of costs and outcomes, as well as the time horizon of the model. Most studies applied the data from the study by Neumann et al. (1999) for the utilities, and was the most commonly applied in the models, being associated with 62.5% of the studies, (5 out of the 8 studies).

2.6.4.1.1.1.2 Model structure based on the FTC framework using the predictive equation of time to FTC development by Rive and colleague (2010)

In 2010, Rive and colleagues attempted to develop a new predictive equation of time to FTC applying to the model based on the FTC conceptual framework. The model consisted of the three health states: pre-FTC, FTC and death. The core concept of the model was to predict the disease progression of the patient until requiring FTC. The baseline patient characteristics were derived from London and the South-East region, (LASER), which was a longitudinal epidemiological study conducted in 224 people with Alzheimer's disease and their caregivers (Livingston et al. 2004). The new predictive equations were used to compute the transition probabilities from pre-FTC to FTC deriving from the LASER-AD cohort of 117 pre-FTC patients with a 54-month follow-up period. Also, the predictive equations of disease progression were correlated to the key features of Alzheimer's disease; including cognitive function, functional ability, and behaviour, which predicted the time to FTC based on patient's three core elements at baseline. The cognitive function was measured using the Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog). The functional ability was defined by the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL). The behavioural aspect was assessed using the Neuropsychiatric Inventory (NPI). The predictive equations which were developed by Rive and colleagues are presented below:

- To predict the time to FTC in patients with Alzheimer's disease, the predictive equation was calculated by:

$$P_j = 1 - \exp(-\exp(-11.1343 + 0.0330 \times ADAS - cog_{total\ score}^{baseline} - 0.0877 \times ADCS - ADL_{total\ score}^{baseline} + 0.0377 \times NPI_{total\ score}^{baseline} + 0.8122 \times ADAS - cog_{total\ score}^{slope}(j) - 2.4072 \times ADCS - ADL_{total\ score}^{slope}(j)) \times \exp(3.3195 \times \ln(interval_j)))$$

where the coefficient of baseline parameters were logarithms of time = 3.320, baseline ADAS-cog total score = 0.033, baseline ADCS-ADL total score = -0.088, baseline NPI total score = 0.038, ADAS-cog slope = 0.812, ADCS-ADL slope = -2.407, and intercept = -11.134, j was time interval, and P was hazard function.

- To estimate the monthly transition probability to FTC state was calculated by:

$$p_{ji}^{FTC} = 1 - \sqrt[length(j)]{(1 - Pj)}$$

where p_{ji}^{FTC} was monthly probability

p_j was probability for the time interval j.

- The equation to estimate monthly death probability:

$$S_i = \exp(-\exp(-13.615) \times time^{\exp(0.568)})$$

where S_i was monthly probability of death

$time$ was in days from the model start.

- Then, the probabilities of dying between two cycles were estimated from

$$P_i^{death} = 1 - S_{(i+1)}/S_i$$

where P_i^{death} was death probability for the time interval i.

Based on the equations as presented above, the disease progression over time of time to FTC was predicted by the rate of changes in cognition and functional ability (Rive et al. 2010).

Additionally, three studies used the model based on the FTC framework using the predictive equation of time to FTC development by Rive and colleague (2010). The model concepts were the course of disease progression in terms of health states defined by patients needing FTC (Rive et al. 2010, Rive et al. 2012, Zala, Chan and McCrone 2017).

● *Model type:*	All studies used the Markov model (Rive et al. 2010, Rive et al. 2012, Zala, Chan and McCrone 2017).
● *The definition of disease severity*:	The need to FTC was used to define the disease severity in the model (Rive et al. 2010, Rive et al. 2012, Zala, Chan and McCrone 2017).
● *The study population*:	Two studies examined patients with moderate to severe Alzheimer's disease (Rive et al. 2010, Rive et al. 2012). Only one study was conducted using moderate to severe and mild to moderate in Alzheimer's patients (Zala, Chan and McCrone 2017).
● *Interventions*:	The comparison of memantine to no pharmacological treatment or background therapy with cholinesterase inhibitors (ChEIs) was examined by the studies of Rive et al. (2010) and Rive et al. (2012). Comparisons of memantine versus ChEIs or no treatment, in moderate to severe Alzheimer's in patients and ChEIs versus no treatment in mild to moderate in Alzheimer's patients were examined by Zala, Chan and McCrone (2017).
● *The disease progression*:	The predictive equation was needed to predict time to FTC over time. The significant covariates to predict those requiring FTC were cognitive function, (as measured by ADAS-cog), functional ability (as assessed by ADCS-ADL), and behaviour (as defined by NPI) (Rive et al. 2010, Rive et al. 2012, Zala, Chan and McCrone 2017).
● *Model structure*:	The health states in the models were pre-FTC, FTC and death (Rive et al. 2010, Rive et al. 2012, Zala, Chan and McCrone 2017).
● *Data sources*:	Two studies used data from longitudinal studies for the course of disease progression (Rive et al. 2010, Rive et al. 2012). One study

	obtained data from a longitudinal study and RCTs (Zala, Chan and McCrone 2017). The probabilities of death were derived from longitudinal studies which were applied to all these studies and a meta-analysis on RCTs was also employed for the treatment effect in these studies (Rive et al. 2010, Rive et al. 2012, Zala, Chan and McCrone 2017).
● *Time horizon and cycle length*:	The model conducted over a 5-year period with a 1-month cycle length in all models (Rive et al. 2010, Rive et al. 2012, Zala, Chan and McCrone 2017).
● *Healthcare Perspective of model*:	There were differences in the perspective of the models. Rive et al. (2010) employed the model based on the National Health Service and Personal Social Services. The societal and healthcare system was used as viewpoints in the study by Rive et al. (2012). The National Health Service and Social care perspectives were applied by Zala, Chan and McCrone (2017).
● *Costs data and Utilities*:	All three studies included direct costs in the models (Rive et al. 2010, Rive et al. 2012, Zala, Chan and McCrone 2017). Only one study encompassed informal care, including caregiver lost productivity, in the cost data (Rive et al. 2012). Regarding utilities, one study used QoL-AD, HSQ-12 and Ferm' D-test mapped to EQ-5D for the utility in the Pre-FTC state, whilst the utility on the FTC state was derived from the LASER-AD study (Rive et al. 2010). One study was conducted in a similar fashion to the study by Rive et al. (2010) for the utility in the Pre-FTC state. For the utilities in the FTC state were based on the published studies by Rive et al. (2010) and Caro et al. (2002) (Zala, Chan and McCrone 2017). Another study was not clear (Rive et al. 2012).
● *Discount rates*:	Costs and health outcomes were discounted using an annual rate of 3.5% in two studies (Rive et al. 2010, Zala, Chan and McCrone 2017).

	A discount rate of 3% was applied in both costs and benefits in the remaining study (Rive et al. 2012).

To conclude, the model based on the FTC framework using the predictive equation of time to FTC development by Rive and colleague (2010), was used to apply to the assessment of health economics of dementia during 2010 and 2017. This model concept was used to predict the disease progression of patients until requiring FTC. The health states were defined as Pre-FTC, FTC and death. Most studies were conducted in patients with moderate to severe Alzheimer's disease and memantine was a substantial treatment that was evaluated in three different studies using this model. The transition probability of the pre-FTC to the FTC state was applied with a predictive equation based on the study by Rive et al. (2010), along with the transition probability of dying which was based on the LASER-AD cohort (Rive et al. 2010, Rive et al. 2012, Zala, Chan and McCrone 2017). Cognition, function, and behaviour were the significant components to predict the time to FTC. In addition, the healthcare perspectives used in the models varied as stated above. The application of the discount rate of costs and outcomes ranged between 3% and 3.5%.

2.6.4.1.1.2 Model based on the Consortium to Establish a Registry for Alzheimer's disease (CERAD)

In this thesis, the concept of modelling based on the CERAD framework following the literature review are classified into two approaches as described below.

2.6.4.1.1.2.1 Cognitive function was measured based on the Clinical Dementia Rating (CDR) scale: CERAD-CDR model

The study of the cost-effectiveness analysis was conducted on donepezil in comparison to no treatment in mild to moderate Alzheimer's disease patients in the US (Neumann et al. 1999). A Markov model was used to simulate patients' progression through the disease severity

stages and residential settings. Patients were classified into disease severities based on the Clinical Dementia Rating (CDR) scale, measured memory, orientation, judgement and problem-solving, community affairs, home and hobbies, and personal care, as follows: mild (CDR = 0.5 or 1), moderate (CDR = 2), and severe (CDR = 3). Also, these patients were assigned to two settings (community or nursing home) at each disease stage, however, the transition amongst the disease severity stages of patients were not conditional on their settings. The CERAD database was compiled from 1986 to 1995 by clinicians from 22 medical centres in the US, who had investigated 1,145 patients with dementia. The database was used to estimate the state-to-state transition probabilities in which the modified survival analysis was applied. The transition probability from mild state to moderate state was computed by the number of the annual transitions or events divided by the total number of years spent in a mild stage. Similarly, the transition probability from the community to the nursing home was predicted by the identical method using the data from CERAD. The effect of donepezil was derived from a clinical trial. To calculate the effectiveness of the drug, patients were initially identified as being in a mild state, then using the Cox proportional hazards regression model, comparing the hazard ratio between the drug and placebo, to estimate the transition probabilities to the moderate state.

The CERAD-CDR model has been widely used in the economic evaluation in dementia. Five studies applied the CERAD-CDR concept. The course of disease progression was mainly defined by the disease severity levels associated with cognitive function (Neumann et al. 1999, Ikeda, Yamada and Ikegami 2002, Fuh and Wang 2008, Kirbach et al. 2008, Lopes-Bastida et al. 2009).

● *Model type:*	All studies developed the Markov approach to characterise the progression of disease (Neumann et al. 1999, Ikeda, Yamada and Ikegami 2002, Fuh and Wang 2008, Kirbach et al. 2008, Lopes-Bastida et al. 2009).

● *The definition of disease severity*:	All five studies used the CDR scale to determine the levels of disease severity (Neumann et al. 1999, Ikeda, Yamada and Ikegami 2002, Fuh and Wang 2008, Kirbach et al. 2008, Lopes-Bastida et al. 2009).
● *The study population*:	Four out of five studies conducted in mild to moderate Alzheimer's patients (Neumann et al. 1999, Ikeda, Yamada and Ikegami 2002, Fuh and Wang 2008, Lopes-Bastida et al. 2009). Only one study examined patients with agitation and psychosis in Alzheimer's disease (Kirbach et al. 2008).
● *Interventions*:	Four out of five studies conducted donepezil compared with usual care or no pharmacological treatment (Neumann et al. 1999, Ikeda, Yamada and Ikegami 2002, Fuh and Wang 2008, Lopes-Bastida et al. 2009). One study examined olanzapine versus no drug treatment (Kirbach et al. 2008).
● *The disease progression*:	Three studies showed that the transition probabilities from stage-to-stage, used levels of disease severity to simulate the disease progression (Ikeda, Yamada and Ikegami 2002, Fuh and Wang 2008, Lopes-Bastida et al. 2009). Two studies used the disease severity probabilities and institutionalisation probabilities to estimate the patients' progress through the different states (Neumann et al. 1999, Kirbach et al. 2008).
● *Model structure*:	The health states in the models of three studies associated with the levels of disease severity were mild, moderate, severe, as well as death (Ikeda, Yamada and Ikegami 2002, Fuh and Wang 2008, Lopes-Bastida et al. 2009). Two studies included the severity levels of the cognitive function (mild, moderate and severe), institutionalisation and death as health states in the model (Neumann et al. 1999, Kirbach et al. 2008).

● *Data sources*:	Based on 1,145 dementia patients from the CERAD study, a longitudinal study was used to estimate the transition probabilities of the disease progression (Neumann et al. 1999, Ikeda, Yamada and Ikegami 2002, Kirbach et al. 2008, Lopes-Bastida et al. 2009). One study applied data from an observational study in Taiwan (Fuh and Wang 2008). For mortality probabilities, four studies also obtained data from the CERAD studies (Neumann et al. 1999, Ikeda, Yamada and Ikegami 2002, Kirbach et al. 2008, Lopes-Bastida et al. 2009). Another study applied data from an observational study in Taiwan (Fuh and Wang 2008). Four studies took the treatment effect data from RCTs (Neumann et al. 1999, Ikeda, Yamada and Ikegami 2002, Kirbach et al. 2008, Lopes-Bastida et al. 2009), with one study which used a longitudinal study in Taiwan (Fuh and Wang 2008).
● *Time horizon and cycle length*:	Two studies conducted a 2-year period with a 1-month Markov cycle (Ikeda, Yamada and Ikegami 2002, Lopes-Bastida et al. 2009). One study examined over a 5-year period with 1-year cycle length (Fuh and Wang 2008). One study employed an 18-month time horizon and a 6-week cycle length for the model (Neumann et al. 1999). Another study used the lifetime period with a 6-month cycle length (Kirbach et al. 2008).
● *Healthcare Perspective of model*:	Three studies used the societal perspective as the viewpoint (Neumann et al. 1999, Fuh and Wang 2008, Lopes-Bastida et al. 2009). One study was performed for the US health system (Kirbach et al. 2008). Another model was conducted from the payer perspective (Ikeda, Yamada and Ikegami 2002).
● *Costs data and Utilities*:	All studies encompassed direct costs (Neumann et al. 1999, Ikeda, Yamada and Ikegami 2002, Fuh and Wang 2008, Kirbach et al.

	2008, Lopes-Bastida et al. 2009). However, one study included unpaid caregiving cost data (Neumann et al. 1999). Another study covered unpaid informal care (Fuh and Wang 2008). Regarding health utilities, two studies used HUI:2 instrument to describe the health states (Neumann et al. 1999, Fuh and Wang 2008). One study applied HUI:3 in the Japanese version from a survey (Ikeda, Yamada and Ikegami 2002). One study adopted EQ-5D based on the survey (Lopes-Bastida et al. 2009). Another study took utilities from a schizophrenia study and the study by Murman and Colenda (2005) (Kirbach et al. 2008).
● *Discount rates*:	All studies discounted costs at 3% and quality of life benefits at 3% per annum (Neumann et al. 1999, Ikeda, Yamada and Ikegami 2002, Fuh and Wang 2008, Kirbach, et al. 2008, Lopes-Bastida et al. 2009).

In brief, the CERAD-CDR model used the Markov model to simulate the disease progression through the disease severity. Four out of five studies were conducted in mild to moderate Alzheimer's patients to compare donepezil to usual care or no pharmacological treatment. Only one study was associated with olanzapine versus no drug treatment which examined patients with agitation and psychosis in Alzheimer's disease. The main health states were classified to mild, moderate, severe, and death as defined by the CDR scale. However, the residential settings which were the community and the nursing home were also considered in the Markov model by Neumann et al. (2001) and Kirbach et al. (2008). The studies based on CERAD-CDR had differences in the perspective of study (i.e. the health system, payer, societal perspectives) and the time horizon of study (i.e. a 2-year period and lifetime). However, all studies were similar in the use of their discounting rate of costs and outcomes at 3%. Regarding the health utilities, studies applied the values based on HUI, HUI:2, HUI:3, and EQ-5D instrument.

2.6.4.1.1.2.2 Cognitive function was measured based on the Severe Impairment Battery: CERAD-SIB model

Weycker et al. (2007) developed a microsimulation to evaluate the cost-effectiveness of memantine and donepezil compared with donepezil only, in moderate to severe Alzheimer's disease patients, on a monthly cycle over a lifetime horizon from a societal perspective. The model was constructed to predict the changes in disease progression in terms of the cognitive function, as measured by SIB score. However, based on the data applied in the model, several studies used MMSE or CDR scale for measuring the disease severity. Thus mapping between MMSE or CDR and SIB were needed to allow comparisons between the data. The transition probability was obtained from data from a longitudinal study. The impacts of memantine and donepezil treatments were taken from data from clinical trials. The transition probabilities to institutionalisation were captured based on a longitudinal study by Neumann et al. (1999). The probability of dying was based on the life table of the general US population, adjusted by age and gender. Then the relative risk of death of Alzheimer's patients was employed to compute the mortality probabilities. The utility weights were derived from the Health Utilities Index Mark 3 (HUI:3) and CDR (disease severity). The CDR was mapped to MMSE and the result was finally transformed to SIB. The costs considerations were both formal and informal care services. The discount rate of the analysis was at 3% for both costs and outcomes per annum.

2.6.4.1.1.3 Model developed to evaluate memantine drug

Jones, McCrone and Guilhaume (2004) studied the cost-effectiveness of memantine compared with no pharmacological treatment, in moderately severe to severe Alzheimer's disease patients in the UK. A Markov model was used to predict the outcomes from treating with memantine over a 2-year time horizon. The outcomes were time to dependency (as a primary outcome), time to institutionalisation, and quality-adjusted life years (QALYs) (as

secondary outcomes). The Markov states were based on the three domains: cognitive function, physical dependency, and residential setting. The cognitive function was measured using Mini-Mental State Examination (MMSE). The MMSE defined the severities of disease as moderate state (MMSE>14), moderately severe state (MMSE =10-14), and severe state (MMSE<10). The standardised tool, Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), was used to assess the abilities to perform daily activities. The physical dependency was divided into dependence and independence. The residential settings were defined into community or institutionalisation. Therefore, the health states in the model totalled 13 states based on multiplying the 3 states of the disease severity, 2 states of physical dependency, 2 states of residential setting plus the state of death. The transitions in the model calculated the severity, dependency, institutionalisation, and mortality transitions. The severity transition probabilities were based on the disease severity at the initiate cycle and on the treatment. The disease severity and the dependency at the initiate cycle and on the treatment were the significant parameters used to calculate the dependence transition probability. The transition probability of institutionalisation was dependent on the disease severity at the initiate cycle and on the treatment. The death probabilities were derived from the UK epidemiological study and were assumed to be similar values in both no treatment and treatment.

In addition, six studies examined the treatment with memantine in patients with dementia. The concepts of this model were the course of the disease defined on the basis of disease severity, patients' dependency, and with/without residential setting (Jones, McCrone and Guilhaume 2004, Francois et al. 2004, Jonsson 2005, Antonanzas et al. 2006, Gagnon et al. 2007, Hoogveldt et al. 2011).

● *Model type:*	All studies used the Markov model (Jones, McCrone and Guilhaume 2004, Francois et al. 2004, Jonsson 2005, Antonanzas et al. 2006, Gagnon et al. 2007, Hoogveldt et al. 2011).

● *The definition of disease severity*:	Three studies used cognitive impairment, physical dependency, and care setting to predict the disease progression (Jones, McCrone and Guilhaume 2004, Francois et al. 2004, Jonsson 2005). The other studies relied on two domains: cognitive function and physical dependency (Antonanzas et al. 2006, Gagnon et al. 2007, Hoogveldt et al. 2011). The cognitive function was measured by MMSE scores in all studies (Jones, McCrone and Guilhaume 2004, Francois et al. 2004, Jonsson 2005, Antonanzas et al. 2006, Gagnon et al. 2007, Hoogveldt et al. 2011). MMSE scores were classified into moderate (MMSE>14), moderately severe (MMSE=10-14), and severe (MMSE<10) in four studies (Jones, McCrone and Guilhaume 2004, Francois et al. 2004, Jonsson 2005, Antonanzas et al. 2006). Two study defined the disease severity as moderate (MMSE=10-19) and severe (MMSE< 10) (Gagnon et al. 2007, Hoogveldt et al. 2011). The physical dependency was classified into dependent and independent as assessed by ADCS-ADL or ADL or IADL (Jones, McCrone and Guilhaume 2004, Francois et al. 2004, Jonsson 2005, Antonanzas et al. 2006, Gagnon et al. 2007, Hoogveldt et al. 2011). The place of residence was associated with living in the community and living in an institution (Jones, McCrone and Guilhaume 2004, Francois et al. 2004, Jonsson, 2005).
● *The study population*:	Four studies were conducted in patients with moderately severe to severe Alzheimer's disease (Jones, McCrone and Guilhaume 2004, Francois et al. 2004, Jonsson 2005, Antonanzas et al. 2006). While, two studies were conducted using moderate to severe Alzheimer's patients (Gagnon et al. 2007, Hoogveldt et al. 2011).
● *Interventions*:	All studies compared the memantine treatment with no pharmacological treatment or standard care (Jones, McCrone and

	Guilhaume 2004, Francois et al. 2004, Jonsson 2005, Antonanzas et al. 2006, Gagnon et al. 2007, Hoogveldt et al. 2011).
● *The disease progression*:	Severity transition probabilities were conditional upon patients' disease severity at the beginning of the cycle and on the treatment. Dependency transition probabilities depended on the patients' disease severity and levels of patients' dependency at the beginning of the cycle and on the treatment. Institutionalisation transitions were associated with patients' disease severity at the beginning of the cycle and on the treatment (Jones, McCrone and Guilhaume 2004, Francois et al. 2004, Jonsson 2005). Two studies were based on disease severity and dependency; severity transitions depended on the disease severity at the beginning of the cycle and on the treatment and dependency transitions relied on the disease severity and levels of dependency at the beginning of the cycle, and on the treatment (Antonanzas et al. 2006, Gagnon et al. 2007). Only one study showed that severity and dependency transitions were conditional on the levels of the patients' disease severity and levels of patients' dependency at the beginning of the cycle and on the treatment (Hoogveldt et al. 2011).
● *Model structure*:	In three studies, the health states in the model totalled 13 states based on multiplying three states of disease severity (moderate, moderately severe, and severe), two states of physical dependency (dependent and independent), two states of residential setting (community and institution) plus the state of death (Jones, McCrone and Guilhaume 2004, Francois et al. 2004, Jonsson 2005). Seven health states associated with three levels of cognitive function (moderate, moderately severe, and severe) and two dependency states (dependent and independent), including death, were applied in one study (Antonanzas et al. 2006). Two studies employed five health

	states accounting for two disease severity modes (moderate and severe), dependency (dependent and independent), and death (Gagnon et al. 2007, Hoogveldt et al. 2011).
● *Data sources*:	Regarding the severity transition probabilities, four studies used data from RCTs (Francois et al. 2004, Jones, McCrone and Guilhaume 2004, Antonanzas et al. 2006, Hoogveldt et al. 2011). One study applied RCT and a longitudinal study (Jonsson 2005). The other was obtained data from RCT and open-label extension study (Gagnon et al. 2007). For the dependence probabilities, four of six studies adopted data from RCT study (Francois et al. 2004, Jonsson 2005, Antonanzas et al. 2006, Hoogveldt et al. 2011). One study employed RCT and a longitudinal study (Jones, McCrone and Guilhaume 2004). The remaining study used RCT and open-label extension study (Gagnon et al. 2007). For institutionalisation probabilities, two studies applied data from longitudinal studies for no pharmacological treatment and RCTs for the treatment (Jones, McCrone and Guilhaume 2004, Francois et al. 2004). One study used data from a longitudinal study. The institutionalisation was not included in the models of three studies (Gagnon et al. 2007, Antonanzas et al. 2006, Hoogveldt et al. 2011). For the death probabilities, five studies adopted data from longitudinal studies (Francois et al. 2004, Jones, McCrone and Guilhaume 2004, Jonsson 2005, Gagnon et al. 2007, Hoogveldt et al. 2011). The other used data from a cross-sectional study (Antonanzas et al. 2006). According to the treatment effects of memantine, two studies applied the treatment effect data from RCTs (Jonsson 2005, Antonanzas et al. 2006). RCTs and an open-label extension study were used in three

	studies (Francois et al. 2004, Jones, McCrone and Guilhaume 2004, Gagnon et al. 2007). One study adopted data from an open-label extension study (Hoogveldt et al. 2011).
● *Time horizon and cycle length*:	The models conducted a 2-year period in three studies (Jones, McCrone and Guilhaume 2004, Antonanzas et al. 2006, Gagnon et al. 2007). The remaining studies covered a 5-year period (Francois et al. 2004, Jonsson 2005, Hoogveldt et al. 2011). All studies employed a 6-month cycle length to predict the disease progression of the model.
● *Healthcare Perspective of model*:	The National Health Service and Personal Services were the viewpoints (Jones, McCrone and Guilhaume 2004). In addition, the public's payer perspective was used in the study by Jonsson (2005). The other studies used a societal perspective in the model (Francois et al. 2004, Antonanzas et al. 2006, Gagnon et al. 2007, Hoogveldt et al. 2011).
● *Costs data and Utilities*:	Direct costs were included in all studies (Jones, McCrone and Guilhaume 2004, Francois et al. 2004, Jonsson 2005, Antonanzas et al. 2006, Gagnon et al. 2007, Hoogveldt et al. 2011). However, Francois et al. (2004) encompassed informal care in the model. Costs associated with the monitoring of patients were included in the study by Jones, McCrone and Guilhaume (2004). While, caregiver medication and indirect costs were considered in the study by Antonanzas et al. (2006). Gagnon et al. (2007), added caregiver time-related costs in the model. Pharmacist fees, family care, and informal care were incorporated in one study (Hoogveldt et al. 2011). The utility weights were taken from a cross-sectional study using EQ-5D instrument (Jonsson 2005). QoL-AD mapped to EQ-5D from a longitudinal study was applied in Gagnon et al. (2007) and Hoogveldt et al. (2011).

● *Discount rates*:	The discount rate for costs and outcomes varied in all studies. Costs and health outcomes were discounted at 3.5% per annum in the study by Jones, McCrone and Guilhaume (2004). Francois et al. (2004) applied a discount rate of 5% for both costs and benefits. An annual discount rate of 3% was applied for costs in one study (Jonsson 2005). Gagnon et al. (2007) also used a 5% discount rate for costs. Antonanzas et al. (2006) used a discount rate applied at 6% for both costs and benefits per annum. The last study employed a discount rate at 4% for costs and 1.5% for outcomes (Hoogveldt et al. 2011).

To conclude, the Markov model was used in all of the studies. 50% of all studies considered the three domains: cognition, dependency, and care setting, while the other 50% covered only two domains: cognition and dependency. The target populations in most studies were moderately severe to severe patients. 60% of all studies used the societal perspective. The range of time horizons was 2-5 years. The discount rate for costs ranged from 3-6%. Also the discount rates of outcomes ranged from 1.5-6%. The utilities were based on EQ-5D and QoL-AD mapped EQ-5D.

2.6.4.1.1.4 The Discrete Event Simulation (DES) model

A discrete event simulation was applied in the study of Getsios and colleagues in 2010 in the UK. To compare the costs and health outcomes of donepezil to no treatment, the study was conducted in mild to moderate Alzheimer's patients from a health care payer and societal perspective over a 10-year period. The technique used was patient-level modelling to capture the disease progression and outcomes. The concepts of the model were as follows: first, patients were categorised by their characteristics. These categorised patients were cloned and assigned to interventions, namely, donepezil and no treatment. Then the patients were simulated and the patient characteristics were updated over time. Before progressing to the next event, patient profiles were updated based on disease severity, treatment status,

physician visits, death, and end of model. Three domains, defined as cognitive function, functioning ability, and behavioural, were the significant predictors used to measure disease severity. The cognitive function was measured in terms of MMSE. The physical functioning was assessed using ADL and IADL. As part of behavioural assessment, NPI was used as the indicator. The developed integrated equations were applied to estimate the change in MMSE, NPI, ADL, and IADL consecutively. The changes in cognitive function affected to NPI, ADL, and IADL. Therefore, the changes in IADL were influenced from the changes of ADL. The various data sources were taken to predict the disease progression and effectiveness of the treatment. The baseline characteristics of patients were taken from data from the clinical trials of donepezil and a longitudinal study. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) data was used to develop the equation and estimate the change in MMSE. Therefore, the NPI, ADL, and IADL were computed from the changes based on those equations. The premature treatment discontinuation employed data from the UK study (Lyle et al. 2008).

Furthermore, four studies which were conducted using a discrete-event simulation (DES) approach were associated with the individual-patient characteristics. The model was conceptualised on the basis of correlations of disease severity, functional ability, and behavioural ability (Getsios et al. 2010, Guo et al. 2010, Hartz et al. 2012, Thibault et al. 2015).

● *Model type:*	The framework of all studies was the DES model (Getsios et al. 2010, Guo et al. 2010, Hartz et al. 2012, Thibault et al. 2015).
● *The definition of disease severity*:	Two studies simulated the disease progression of patients over time based on cognition (as measured by MMSE), behaviour (as measured by NPI scale), and function (as measured by ADLs and IADLs) (Getsios et al. 2010, Hartz et al. 2012). One study predicted the disease progression based on cognitive function (using ADAS-

	cog and MMSE), behavioural assessment (using NPI scale), and functional abilities (using the Disability Assessment of Dementia (DAD) scale) (Guo et al. 2010). The other study incorporated cognition (as assessed by SIB scale), behaviour (as assessed by NPI scale), and function (as assessed by ADLs and IADLs) in the model to predict the disease progression (Thibault et al. 2015).
● *The study population*:	Two studies conducted in patients with mild to moderate Alzheimer's disease (Getsios et al. 2010, Guo et al. 2010). One study applied in mild to moderately severe and moderate to moderately severe Alzheimer's patients (Hartz et al. 2012). The other study examined moderate to severe patients with Alzheimer's disease (Thibault et al. 2015).
● *Interventions*:	The varieties of interventions were engaged in studies. Getsios et al. (2010) examined donepezil compared with no treatment. A comparison amongst galantamine, no treatment, and ginkgo biloba was conducted by Guo et al. (2010). One study compared donepezil with memantine or no treatment (Hartz et al. 2012). While, memantine extended release plus cholinesterase inhibitor compared with cholinesterase inhibitor monotherapy was studied by Thibault et al. (2015).
● *The disease progression*:	Two studies used the regression models to predict the changes of disease progression through MMSE, NPI, ADLs, and IADLs over time (Getsios et al. 2010, Hartz et al. 2012). One study applied the regression model to estimate the changes of the disease progression over time based on the ADAS-cog score which was mapped to the MMSE score. In addition, the MMSE score had significant impacts on the NPI scale, DAD scale, and other outcomes (Guo et al. 2010). Another study considered the changes in SIB scale, NPI scale,

	ADLs, and IADLs over time in the progression of the disease (Thibault et al. 2015).
● *Model structure*:	The model functions were based on the following: at the beginning the patient's categorised characteristics were created. Then identical copies were created for individual patients. The interventions were also assigned. When the model was simulated, the patient characteristics were updated over time to predict the disease progression through correlated changes in cognitive function, behaviour, and functional performance (Getsios et al. 2010, Guo et al. 2010, Hartz et al. 2012, Thibault et al. 2015).
● *Data sources*:	Three studies used data from RCTs and longitudinal studies for the baseline patient characteristics (Getsios et al. 2010, Guo et al. 2010, Hartz et al. 2012). One study adopted data from the RCT for baseline population characteristics (Thibault et al. 2015). Three studies derived mortality rates from life tables (Guo et al. 2010, Hartz et al. 2012, Thibault et al. 2015), whereas one study was based on a longitudinal study (Getsios et al. 2010). For the treatment effect, two studies were based on data from RCTs (Getsios et al. 2010, Thibault et al. 2015). The other two studies applied data from RCTs and pooled data from clinical trials (Guo et al. 2010, Hartz et al. 2012)
● *Time horizon*	Three studies conducted the models over a 10-year time horizon (Getsios et al. 2010, Guo et al. 2010, Hartz et al. 2012). One study employed for a 3-year period (Thibault et al. 2015).
● *Healthcare Perspective of model*:	Three studies were performed based on the healthcare payer or care insurance and societal perspective (Getsios et al. 2010, Hartz et al. 2012, Thibault et al. 2015). One study only implemented from a healthcare insurance perspective (Guo et al. 2010).

● *Costs data and Utilities*:	All studies included direct costs and costs associated with caregiver time (Getsios et al. 2010, Guo et al. 2010, Hartz et al. 2012, Thibault et al. 2015). One study covered costs of antipsychotic changes from the beginning of the treatment (Thibault et al. 2015). Three studies also encompassed costs for monitoring patients (Getsios et al. 2010, Guo et al. 2010, Hartz et al. 2012). Regarding utilities, two studies used data from a cross-sectional study using EQ-5D (Getsios et al. 2010, Hartz et al. 2012). One study adopted HUI from a cross-sectional study for measuring quality of life (Thibault et al. 2015).
● *Discount rates*:	Two studies applied discount rates at 3% in both costs and benefits per annum (Hartz et al. 2012, Thibault et al. 2015). Costs and health outcomes were discounted using an annual rate of 3.5% in the study by Getsios et al. (2010). The other study used the discount rate at 5% of for both costs and outcomes per annum (Guo et al. 2010).

In brief, the models based on the DES used individual-patient data. The changes of disease progression were updated through MMSE, NPI, ADLs, IADLs, and DAD over time. There were differences in the target populations of all studies, however, a half of all studies were conducted in patients with mild to moderate Alzheimer' disease. A 10-year time horizon was most commonly applied in the models. Most studies adopted healthcare payer, healthcare insurance, and societal as the viewpoints of studies. The EQ-5D, and HUI instruments were the most applied to the utility weights. The discount rates ranged from 3-5% of both costs and outcomes.

2.6.4.1.1.5 Model based on Lachaine, et al. (2011)

In Canada, the first cost-utility analysis of memantine plus ChEI compared with ChEI and memantine versus ChEI was undertaken by Lachaine et al. (2011). A 7-year Markov model

was constructed to predict the impact on time to institutionalisation in patients with Alzheimer's disease. The model was developed on the basis of a study by Lopez and colleagues, who conducted an observational study in 943 probable Alzheimers' patients assigned interventions using memantine plus ChEI, ChEI only and no treatment, to predict time to nursing home admission and death (Lopez et al. 2009). Societal and the Canadian health care system was the viewpoint. The health states in the model consisted of non-institutionalisation, not admitted to the nursing home, institutionalisation, admitted to the nursing home, and death. The significant transition probabilities in the model were the probabilities of nursing home admission and dying. The transition probability of institutionalisation was taken from published studies (Lopez et al. 2009). The mortality probability was derived from the life table, adjusted for age and sex and specific-Alzheimer's disease-related mortality.

Additionally, three studies used models developed based on the study by Lachaine, et al. (2011). The model framework applied the patients' placement status as defined by noninstitutionalised and institutionalised as the health states of disease progression (Lachaine et al. 2011, Pfeil, Kressig and Szucs 2012, Touchon et al. 2014).

● *Model type:*	A Markov model was applied in all studies (Lachaine et al. 2011, Pfeil, Kressig and Szucs 2012, Touchon et al. 2014).
● *The definition of disease severity*:	The severity of disease was defined by requiring nursing home admission or institutionalised in all studies (Lachaine et al. 2011, Pfeil, Kressig and Szucs 2012, Touchon et al. 2014).
● *The study population*:	All studies conducted in patients with Alzheimer's disease (Lachaine et al. 2011, Pfeil, Kressig and Szucs 2012, Touchon et al. 2014).
● *Interventions*:	The comparison of memantine and cholinesterase inhibitors to cholinesterase inhibitors alone was employed in two studies (Pfeil, Kressig and Szucs 2012, Touchon et al. 2014). Another study examined memantine plus cholinesterase inhibitors compared with

	cholinesterase inhibitors and memantine versus cholinesterase inhibitors (Lachaine et al. 2011).
● *The disease progression*:	The transition probabilities of moving from one state to another state were used to predict the disease progression of the model (Lachaine, et al. 2011, Pfeil, Kressig and Szucs 2012, Touchon et al. 2014).
● *Model structure*:	The model consisted of three health states: noninstitutionalised, institutionalized, and deceased in all three studies (Lachaine et al. 2011, Pfeil, Kressig and Szucs 2012, Touchon et al. 2014).
● *Data sources*:	The probabilities of transition of disease progression between the non-institutionalised to the institutionalised state in all three studies were based on a longitudinal study by Lopez et al. (2009) (Lachaine et al. 2011, Pfeil, Kressig and Szucs 2012, Touchon et al. 2014). The probabilities of dying used data obtained from the life tables in two studies (Lachaine, et al. 2011, Touchon et al. 2014). One study used a longitudinal study to estimate the transition probability to death (Pfeil, Kressig and Szucs 2012). All studies adopted data from longitudinal studies for the treatment effect (Lachaine et al. 2011, Pfeil, Kressig and Szucs 2012, Touchon et al. 2014).
● *Time horizon and cycle length*:	Two studies were conducted over a 7-year period to predict time to institutionalisation and the cycle lengths of the model were defined as 1-year (Lachaine et al. 2011, Touchon et al. 2014). Another study was conducted over a 5-year time horizon with one year defined as the Markov cycle (Pfeil, Kressig and Szucs 2012).
● *Healthcare Perspective of model*:	The societal and healthcare system perspectives were applied to all models (Lachaine et al. 2011, Pfeil, Kressig and Szucs 2012, Touchon et al. 2014).
● *Costs data and Utilities*:	Direct costs were included in all three studies (Lachaine et al. 2011, Pfeil, Kressig and Szucs 2012, Touchon et al. 2014). One study

	considered the lost productivity of caregivers (Lachaine et al. 2011), whereas costs associated with informal care were encompassed in two studies (Pfeil, Kressig and Szucs 2012, Touchon et al. 2014). The health utility sources were taken from cross-sectional studies using HUI:2 as an instrument (Lachaine et al. 2011, Pfeil, Kressig and Szucs 2012, Touchon et al. 2014).
● *Discount rates*:	Two studies applied a discount rate at 3% for both costs and outcomes (Pfeil, Kressig and Szucs 2012, Touchon et al. 2014), while one study used a 5% discounted rate of both costs and outcomes per annum (Lachaine et al. 2011).

To sum up, the model applications based on the Lachine model used the Markov structure to predict the disease progression. The main health states were noninstitutionalised, institutionalised and deceased. Comparison of memantine and cholinesterase inhibitors to cholinesterase inhibitors alone were applied in most studies. The societal and healthcare system perspectives were used in all studies. Time horizon of models employed a 5-7 year period with cycle length of one year. Utility data based on HUI:2 was applied in all models. The range of the discount rate was at 3-5% per annum in both costs and outcomes.

2.6.4.1.1.6 Model developed by McDonnell et al. (2001)

McDonnell et al. (2001) investigated the impact of treatment in Alzheimer's patients based on the regression-based simulation model. The model was developed to estimate the disease progression through the decline in cognitive function, as measured by the MMSE score, during the treatment. The Rotterdam study, in the Netherlands, was used as a data source associated with the patient's demographic and disease history data. The analyses were conducted through the MMSE model and the institutionalisation model. The MMSE model, a random-effect, linear regression incorporating several parameters based on the Rotterdam study, was used to predict the change in MMSE score over time and MMSE at baseline. The

institutionalisation used the multinomial logistic regression to predict the movement amongst the residence states or death. In the institutionalisation model, the presence of caregivers, the place of residence at the initial time, and the probability of hospitalisation were included. The simulations were functioned as follows: at the beginning, the patient's baseline distribution and regression functions were created based on the Rotterdam study. Then the patient's profiles were copied and defined the patients groups as treated or untreated. The next event was the movement of patients between states based on the disease progression. When the disease progressed, the cognitive function was expected to decrease. Patients also moved from one state to another state of residence or death. The costs data were accumulated within the cycle lengths of the cohorts until a 10-year period or death occurring. In addition, the cohort was simulated 10,000 times to calculate the median results. The data sources of costs included direct costs derived from Netherlands, but informal care was not included. The discount rate was at 5% for costs and benefits.

2.6.4.1.1.7 Model developed by Fenn and Gray (1999)

Fenn and Gray (1999) conducted a model to evaluate the cost saving from rivastigmine compared to a placebo, in mild to moderate Alzheimer's patients, in the UK over a 3-year time horizon. The concept of the model was the time in which patients moved to the more severe stages of the disease severity. The more severe states of the disease were correlated to the increase in costs, such as caregiver care costs as well as the risk to nursing home admission. Thus the survival analysis was applied to assess the benefits from the treatment for delaying the disease progression to the more severe stages. The disease progressing was defined by the disease severity using a MMSE score. The model health states consisted of mild (MMSE=30-21), moderate (MMSE=20-11), and severe (MMSE=10-1) with the MMSE score classification being based on expert opinion. The Weibull distribution for the hazard function was used to calculate the transition probabilities. Only costs of formal care were employed in the study, using the UK price index for hospital and community health services.

2.6.4.1.1.8 Model based on the data from Kungsholmen project

Jonsson et al. (1999) was an original model conducting a Markov model to evaluate the cost-effectiveness of donepezil and no treatment, in mild to moderate probable Alzheimer's patients over a 5-year period. The model applied the cognitive function to defined states of disease using the MMSE score. The health states in model consisted of MMSE=30-27, MMSE=26-21, MMSE=20-15, MMSE=14-10, MMSE=9-0, as well as death. The baseline transition probabilities were derived from the observational study, Kungsholmen project, in Sweden (Jonsson et al. 1999). A total of 206 elderly patients diagnosed with dementia in the Kungsholmen study, were adopted to compute the probabilities. The effectiveness data of donepezil was taken from the clinical trial. The cost data were also obtained from the Kungsholmen study, including home help, accommodation, and medications.

Furthermore, two studies adopted data from the Kungsholmen project to develop their model. The concept of this model was similar to the CERAD-CDR model which defined health states of the disease progression by levels of disease severity (Jonsson et al. 1999, Teipel et al. 2007).

● *Model type:*	Both studies conducted the cost-effectiveness analysis based on a Markov model framework (Jonsson et al. 1999, Teipel et al. 2007).
● *The definition of disease severity*:	The levels of disease severity were defined by cognitive function as measured by MMSE scores (Jonsson et al. 1999, Teipel et al. 2007).
● *The study population*:	Jonsson et al. (1999) conducted the study in people aged 75 years and over. Teipel et al. (2007) studied in patients with mild to moderate Alzheimer's disease.
● *Interventions*:	Both studies examined the comparison of donepezil versus no treatment or placebo (Jonsson et al. 1999, Teipel et al. 2007).
● *The disease progression*:	The movement from one state to another in the model relied on the transition probabilities (Jonsson et al. 1999, Teipel et al. 2007).

● *Model structure*:	The six health states were classified into MMSE 30-27, MMSE 26-21, MMSE 20-15, MMSE 14-10, MMSE 9-0, as well as death (Jonsson et al. 1999). The other study applied mild, mild to moderate, moderate, severe and death as the Markov states in the model (Teipel et al. 2007).
● *Data sources*:	Without treatment, the transitions between the health states of the disease progression were based on longitudinal studies (Jonsson et al. 1999, Teipel et al. 2007). The probabilities of mortality in both studies were taken from longitudinal studies (Jonsson et al. 1999, Teipel et al. 2007). The treatment effect data used data from RCTs in both studies (Jonsson et al. 1999, Teipel et al. 2007).
● *Time horizon and cycle length*:	One study was conducted over a 5-year period with 10 Markov cycles (Jonsson et al. 1999), while the other study was conducted over a 5-year time horizon with cycle length of one year (Teipel et al. 2007).
● *Healthcare Perspective of model*:	The health insurance and nursing care insurance company perspectives were adopted in Teipel et al. (2007), while the model perspective was not identified in the study by Jonsson et al. (1999).
● *Costs data and Utilities*:	Both studies included direct costs (Jonsson et al. 1999, Teipel et al. 2007). Costs associated with caregiver time were encompassed only in the study by Teipel et al. (2007). One study used utility data taken from a cross-sectional study as measured by HUI:2 (Teipel et al. 2007). Another study was not clear regarding health outcomes (Jonsson et al. 1999).
● *Discount rates*:	The discount rate for costs was 3% in the study by Jonsson et al. (1999). The costs and outcomes were discounted at 5% per annum in the study by Teipel et al. (2007).

In conclusion, both studies were modelled based on the data from the Kungsholmen project. A Markov model was constructed to predict costs and outcomes. The cognitive function as measured by MMSE was used to define levels of disease severity. Also, the Markov states consisted of disease severity levels and death. Both studies compared donepezil with no treatment or a placebo and covered a 5-year period with different cycle lengths. The discount rate of costs ranged from 3-5%, while the outcome was discounted at 5%, but only identified in one study.

2.6.4.1.1.9 Model developed by Henke and Burchmore (1997)

Henke and Burchmore (1997) applied a decision tree model to evaluate the cost-effectiveness of tacrine in treating mild to moderate Alzheimer's disease over the patient's lifetime. The health states of the model were: the need for nursing home care and the no requirement for nursing home care. The assumption of this study was that the increase in functional dependency leads to an increase in the nursing home care. The data sources were derived from various studies. The probability of no treatment to nursing home care was taken from cohort studies. The transition probabilities of tacrine treatment were derived from RCT study. Also, the mortality was obtained from RCT. The cost data included the medical care, paid social services, and costs for monitoring patients. The perspective was from the public and private payers. The discount rate was at 5% per annum for costs and outcomes.

2.6.4.1.1.10 Model developed by Nagy et al. (2010) based on the MMSE- and ADL- based model

Nagy et al. (2010) investigated the cost-effectiveness of a rivastigmine patch and capsule in comparison to basic support care from the UK health and social care costs. This study was conducted over a 5-year period. This study used the MMSE score and the MMSE-ADL model to predict the disease progression. The discontinuation rates used data from an open-label study. Data from a prospective study was applied for the mortality rate. According to

the MMSE-based model, this model employed data from the study by Stewart (1997) in a UK context, to develop the linear regression equation of the institutionalisation probability. Another model was constructed to incorporate ADL into the traditional MMSE-based model. However, there were no studies associated with the correlation between ADCS-ADL and the institutionalisation probability. Based on the study by McNamee et al. (2001), the MMSE and Townsend-ADL were used to estimate the probabilities of institutionalisation. Consequently, the mapping between ADCS-ADL and Townsend-ADL was applied. The utility weights were based on the Health Utilities Index version III (HUI:3) which were mapped by the clinical data, to compute the utility weights of the MMSE and MMES-ADL models. The regression function was then used to calculate utility values based on the MMSE score. Health and social care costs of institutionalisation from the UK were included in the model. Costs and outcomes were discounted using an annual discount rate of 3.5%.

2.6.4.1.1.11 Model developed by Wong et al. (2009)

According to Wong et al. (2009), a decision tree model was conducted to evaluate the cost-effectiveness of ChEI (donepezil, galantamine, and rivastigmine) and memantine compared with a placebo, in vascular dementia cases, from a societal perspective. The ICER was calculated from the incremental cost per the decline in the ADAS-cog scale. A published systematic review was used as the probabilities of adverse events of each drug. The model timeframe was conducted over 24-28 months. The cost data were taken from the drug costs using the drug prescriptions and physician visits.

2.6.4.1.1.12 Model developed by Stewart, Phillips and Dempsey (1998)

In 1998, Stewart, Phillips and Dempsey conducted a Markov model to evaluate the treatment of donepezil over 5 years in the UK using 6-month cycles. The health states were classified into minimal, mild, moderate, severe, as well as death which correlated to the disease severity. This study adopted existing data from previously published studies. The transition

probabilities for people with no treatment were derived from a cohort study. The treatment effectiveness of donepezil was acquired from the RCT. The data from a cohort study and a historic prospective study were applied to calculate the mortality probability. The cost data were taken from cost packages of elderly people with cognitive impairment in the UK. Costs were discounted using an annual rate of 6% in this study.

2.6.4.1.1.13 Model developed by Hu et al. (2015)

The study by Hu and colleagues in 2015 constructed 6-monthly Markov cycles over a 5-year period to predict the clinical benefits of memantine which patients were starting at a moderate level compared with starting at a severe level in Alzheimer's disease in urban China. The health states were based on dependency (independent and dependent) and agitation/aggression (non-agitated/aggression and agitation/aggression). Then a total of nine possible health states, including four health states in moderate stage, four health states in severe stage, as well as death were applied in the model. The dimensions of the disease progression were cognitive function (as measured by MMSE or ADAS-cog or SIB), dependency (as assessed by ADL), and agitation/aggression (as defined by NPI). Expert panels were used to determine the data sources for the dependency, agitation/aggression, and resource utilisation. Transition probabilities were taken from pooled data of clinical trials of memantine. The discontinuation rate was derived data from the RCT study of memantine in Alzheimer's patients in China. The mortality rate was based on data from the general Chinese population and mortality risk was taken from data of the elderly with dementia in Shanghai. Hospitalisation, caregiver time-associated costs, and nursing homes were included in the cost data of the model. The discount rate of the analysis was at 3% per annum for both costs and outcomes.

2.6.4.1.1.14 Model developed by O' Brien el al. (1999)

O' Brien et al. (1999) studied the cost-effectiveness of donepezil in comparison to usual care, in mild to moderate Alzheimer's patients in Canada, over a 5-year period. The perspective in this study was the government payer and society. A Markov model was constructed to estimate the decrease in MMSE score over time. The levels of disease severity were defined by the MMSE score. Data from the Alzheimer' disease cohort study in Alberta was used to classify people with probable AD into three subgroups at baseline as follows: MMSE=10-14, MMSE=15-20, and MMSE=21-26. Six health states were employed in the model, consisting of MMSE<10, MMSE=10-14, MMSE=15-20, MMSE=21-26, MMSE=27-30, as well as death. The transition probabilities of patients moving amongst the health states were taken from the clinical trial. The discontinuation rate was considered when the MMSE score was less than 10. The cost data were encompassed medications, dispensing fee, community services (i.e. homemaking, home-help, and in-home meals), and caregiver time-associated costs. This analysis applied a discount rate at 5% for costs and outcomes.

Table 2.5: **Summary of the modelling approaches used to model the disease progression in economic evaluations in dementia**

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
Henke and Burchmore	1997	USA	Cost analysis	Decision-tree model	Specific model	-Loss of functional independence of people with AD associated with increasing in nursing home placement	Mild-to-moderate AD	Tacrine vs no treatment	Health states: nursing home placement and non-nursing home placement
Stewart, Phillips, and Dempsey	1998	UK	CEA	Markov model	Specific model	-Time in lower disease severity stages (as defined by MMSE score)	AD patients aged 75 years and over	Donepezil 5 mg and 10 mg vs placebo	Health states: minimal, mild, moderate, severe, and dead
Fenn and Gray	1999	UK	Cost analysis	Statistical model-based survival analysis	Specific model	-Time in stages of disease severity (as measured by MMSE score) -Survival analysis, using the accelerated	Mild to moderate AD	Rivastigmine vs placebo	Health states in the model: mild (MMSE=21-30), moderate (MMSE=11-20),

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
						failure-time model with the Weibull distribution for the hazard function			and severe (MMSE=1-10)
Jonsson et al.	1999	Sweden	CEA	Markov model	Specific model based on the project of Kungsholmen	-Time in the stages of disease severity (as defined by MMSE score)	Mild to moderate probable AD	Donepezil vs no treatment	Health states: MMSE=30-27, MMSE=26-21, MMSE=20-15, MMSE=14-10, MMSE=9-0 and death
Neumann et al.	1999	USA	CEA	Markov model	CERAD based on CDR scale (cognitive function measured as CDR)	-Time in the stages of disease severity (as defined by CDR score) -CERAD cohort was used to estimate the state-to-state transition probabilities using a	Mild to moderate AD	Donepezil vs no treatment	Health states: mild(comm/ NH), moderate(comm/ NH), severe(comm/ NH), and death

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
						Cox proportional hazards regression model			
O' Brien et al.	1999	Canada	CEA	Markov model	Specific model	-Time in stages of disease severity (as defined by MMSE)	Mild to moderate AD	Donepezil 5 mg vs usual care	Health states: MMSE <10, MMSE=10-14, MMSE=15-20, MMSE=21-26, MMSE=27-30, and death
Getsios et al.	2001	Canada	CEA	Markov model	FTC framework (AHEAD)	-Time to need of FTC -The Cox proportional hazard function used to predict time to require FTC	Mild to moderate AD	Galantamine 24 mg/day vs no pharmacological treatment	Health states in the model: Pre-FTC, FTC, and death
McDonnell et al.	2001	Nether-lands	CEA	Statistical model-based	Specific model	-Changes in MMSE, resident, and mortality	Patient with dementia	Treatment vs non-treatment	-Four aspects: patient characteristics,

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
				regression analysis		-Two models used for analyses: one model based on MMSE score and the other model based on the institutionalisation and patients' vital status			clinical characteristics of disease, place of residence (living in community, home for the elderly, nursing home), and vital status of patients
Caro et al.	2002	Nether-lands	CEA	Markov model	FTC framework (AHEAD)	-Time to need of FTC -The Cox proportional hazard model used to predict time to require FTC	Mild to moderate AD	Galantamine vs no pharmacological treatment	Health states in the model: Pre-FTC, FTC, and death
Garfield et al.	2002	Sweden	CEA	Markov model	FTC framework (AHEAD)	-Time to need of FTC -The Cox proportional hazard model used to	Mild to moderate AD	Galantamine 12 mg twice daily vs no treatment	Health states in the model: Pre-FTC, FTC, and death

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
						predict time to require FTC			
Ikeda, Yamada and Ikegami	2002	Japan	CUA	Markov model	CERAD based on CDR scale (cognitive function measured as CDR)	-Time in the stages of disease severity (as defined by CDR score) -CERAD cohort was used to estimate the state-to-state transition probabilities using a Cox proportional hazards regression model	Mild to moderate AD	Donepezil vs no treatment	Four-health states in the model structure: mild, moderate, severe, and death
Migliaccio-Walle et al.	2003	USA	CEA	Markov model	FTC framework (AHEAD)	-Time to need of FTC	Mild to moderate AD	Galantamine 16 mg/day and 24 mg/day vs no treatment	Health states in the model: Pre-FTC, FTC, and death

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
Ward et al.	2003	UK	CEA	Markov model	FTC framework (AHEAD)	-Time to need of FTC	Mild to moderate AD	Galantamine 16 mg/day and 24 mg/day vs no cholinesterase treatment	Health states in the model: Pre-FTC, FTC, and death
Caro et al.	2004	Multi-national	CEA	Markov model	FTC framework (AHEAD)	-Time to need of FTC	Mild to moderate AD	Galantamine vs no pharmacological treatment	Health states in the model: Pre-FTC, FTC, and death
Francois et al.	2004	Finland	CEA	Markov simulation model	Memantine model	-Time to dependency, institutionalisation/nursing home	Moderately severe to severe AD	Memantine vs no pharmacological treatment	Health states based on the multiplicity of three severity states, two physical dependencies, and two residence

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
									settings, and plus death
Jones, McCrone and Guilhaume	2004	UK	CEA	Markov simulation model	Memantine model	-Time to dependency, institutionalisation/nursing home	Moderately severe to severe AD	Memantine vs no pharmacological treatment	Health states based on multiplying: three severity states, two physical dependencies, and two residence settings, and plus death
Green et al.	2005	UK	CEA	Markov model	FTC framework (AHEAD)	-Time to need of FTC	Mild to moderately severe AD	Donepezil, galantamine, and rivastigmine vs usual care	Health states in the model: Pre-FTC, FTC, and death

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
Jonsson	2005	Sweden	CEA	Markov simulation model	Memantine model	-Time to dependency, institutionalisation/nursing home	Moderately severe to severe AD	Memantine vs no pharmacological treatment	Health states based on the multiplicity of three severity states, two physical dependencies, and two residence settings, plus death
Antonanzas et al.	2006	Spain	CEA	Markov simulation model	Memantine model	-Time to dependence	Moderately severe to severe AD	Memantine and standard care	Health states in the model: multiplying of three severities, two dependencies, plus death

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
Gagnon et al.	2007	Canada	CEA	Markov simulation model	Memantine model	-Time to dependence	Moderate to severe	Memantine vs standard care	Health states based on multiplying of two severities, two dependencies, and death
Teipel et al.	2007	Germany	CEA	Markov model	Specific model based on the Kungsholmen project	-Time in stages of disease severity (as defined by MMSE score)	Mild to moderate AD	Donepezil 10 mg vs placebo	Health states: mild, mild-moderate, moderate, severe and death
Weycker et al.	2007	USA	CEA	Microsimulation model	CERAD based on SIB (cognitive function measured as SIB)	-To predict the changes in cognitive function (as measured by SIB score) -Regression model was used to map SIB to MMSE	Moderate to severe AD	Memantine + donepezil vs donepezil alone	The states in the model defined into profound and terminal (MMSE=0-4), severe (MMSE=5-9),

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
									moderate (MMSE=10-14), and questionable/mild (MMSE=15-23) and living in community
Fuh and Wang	2008	Taiwan	CEA	Markov model	CERAD based on CDR scale (cognitive function measured as CDR)	-Time in the stages of disease severity (as defined by CDR score) -The hazard ratios were used to estimate the transition probabilities between one state to another state during the drug treatment	Mild to moderate A	Donepezil and usual care	Health states: mild, moderate, severe, and death

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
Kirbach et al.	2008	USA	CUA	Markov model	CERAD based on CDR scale (cognitive function measured as CDR)	-Time in the stages of disease severity (as defined by CDR score) -CERAD cohort was used to estimate the state-to-state transition probabilities using a Cox proportional hazards regression model	Patients with agitation and psychosis in AD	Olanzapine vs no treated with olanzapine	Heath states: mild, moderate, severe, institutionalized, and death -The institutionalised was classified separately as a health state
Lopes-Bastida et al.	2009	Spain	CEA	Markov model	CERAD based on CDR scale (cognitive function measured as CDR)	-Time in the stages of disease severity (as defined by CDR score) -CERAD cohort was used to estimate the state-to-state transition probabilities using a	Mild and moderate AD	Donepezil vs no drug treatment	The model states classified into mild, moderate, severe, and death

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
						Cox proportional hazards regression model			
Suh	2009	Korea	CUA	Markov model	FTC framework (AHEAD)	-Time to FTC require	Mild to moderately severe AD	Galantamine 24 mg/day + usual care vs usual care	Health states in the model: Pre-FTC, FTC, and death
Wong et al.	2009	Canada	CEA	Decision tree	Specific model	-The decision model included the effectiveness and the probabilities of adverse events of each medication	Mild to moderate vascular dementia	Cholinesterase Inhibitors or memantine vs standard care	Two states were defined into no adverse events and adverse events
Getsios et al.	2010	UK	CEA	Discrete-Event Simulation (DES)	Patient-level data	-The individual-level data -The simulation based on the inter-relationship of cognitive function	Mild to moderate AD	Donepezil vs no treatment	Update of disease severity, treatment status, physician visit, death, and end of model

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
						(MMSE), behavioural ability (NPI), and functional abilities (ADLs and IADL)			
Guo et al.	2010	Germany	CBA	Discrete-Event Simulation (DES)	Individual patient simulation	-The individual-level data -The simulation based on the inter-relationship of disease severities (ADAS-cog and MMSE), behavioural abilities (NPI), and functional abilities (DAD)	Mild to moderate AD	Galantamine vs no treatment vs ginkgo biloba	Update of disease severity, treatment status, physician visit, death, and end of model
Nagy et al.	2010	UK	CEA	Statistical model-based regression analysis	MMSE-ADL model	-Regression analysis used to calculate probability of institutionalisation	Patients with probable Alzheimer's disease	Rivastigmine patch and capsule treatment vs best supportive care	-MMSE model based on MMSE -MMSE-ADL model based on MMSE and ADL

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
						-Two models: MMSE model and MMSE-ADL model			
Rive et al.	2010	UK	CUA	Markov model	FTC framework	-Time to FTC required	Moderate to severe AD	Memantine vs no pharmacological treatment or background therapy with cholinesterase inhibitors (ChEIs)	The model health states based on: Pre-FTC, FTC and death
Hoogveldt et al.	2011	Nether-lands	CEA	Markov simulation model	Memantine model	-Time to dependence	Moderate to severe AD	Memantine vs standard care	Health states based on the multiple of two severities and two dependence states, plus death

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
Lachaine et al.	2011	Canada	CUA	Markov model	Specific model bases on data from Lopez et al.	-Time to nursing home	Patients with AD	Memantine + Cholinesterase inhibitor vs Cholinesterase inhibitor alone	Health states: noninstitutionalised, institutionalized, and death
Hartz et al.	2012	Germany	CEA	Discrete-Event Simulation (DES)	Individual-patient simulation	-The individual-level data -The simulation of disease progression based on the correlated changes in disease severities (MMSE), behavioural abilities (NPI), and functional abilities (ADLs and IADL)	Mild to moderately severe and moderate to moderately severe AD	Donepezil vs memantine or no tratment	Update of disease severity, treatment status, physician visit, death, and end of model

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
Pfeil, Kressig and Szucs	2012	Switzer-land	CUA	Markov model	Model based on the developed model by Lachaine et al.	-Time to nursing home	Patients with AD	Memantine + Cholinesterase inhibitor vs Cholinesterase inhibitor alone	Health states: home, nursing home, and decease
Rive et al.	2012	Norway	CUA	Markov model	FTC framework	-Time to need of FTC	Patients with moderate and severe AD	Memantine vs no pharmacological treatment or background therapy with cholinesterase inhibitors (ChEIs)	The model based on three health states: Pre-FTC, FTC and death
Touchon et al.	2014	France	CEA	Markov model	Based on the model of Lachaine and colleague	-Time to nursing home admission	Patients with AD	Memantine + cholinesterase inhibitor vs cholinesterase inhibitor alone	The health states: non-institutionalised, institutionalized, and deceased

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
Hu et al.	2015	China	Cost analysis	Markov model	Specific model	-Time in health states of disease progression based on two disease severities (moderate and severe as measured by MMSE score or ADAS-cog or SIB), functional abilities (dependence and independence as measured by ADL), presence of agitation/aggression (agitation/aggression and non-agitation/aggression as measured by NPI)	Moderate and severe patient with AD	Initiated memantine in moderate vs initiated memantine in severe	Health states based on the multiplicity of two severities, two functional abilities, two the presence of agitation/aggression, plus death

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
Thibault et al.	2015	USA	CUA	Discrete-Event Simulation (DES)	Individual-patient simulation	-The individual-level modelling -The simulation of the disease progression based on SIB, NPI, B-ADL, and I-ADL over time	Moderate to severe AD	Memantine extended release + Cholinesterase inhibitor vs Cholinesterase inhibitor monotherapy	Update of disease severity, treatment status, physician visit, death, and end of model
Zala, Chan and McCrone	2017	UK	CUA	Markov model	FTC framework	-Time to need of FTC	Mild to moderate and moderate to severe AD	-Moderate to severe: memantine vs Cholinesterase inhibitor (ChEIs) alone or no treatment -Mild to moderate: cholinesterase	The model based on three health states: Pre-FTC, FTC and death

Study	Year published	Country	Study type	Model type	Model Framework	Health outcomes	Target populations	Comparators	Health States
								inhibitor (ChEIs) vs no treatment	

Based on model-based economic evaluation in dementia, the comparison of strengths and limitations of each model is presented in Table 2.6.

Table 2.6: **Comparison of strengths and limitations of model-based economic evaluation in dementia**

Model Type	Strength	Limitation
FTC framework -AHEAD model using a predictive equation to predict the time to FTC developed by Caro et al. (2001)	1. Predict time to need of FTC required which is the significant factor affecting the costs of Alzheimer's disease 2. Consider several factors influencing the progression of disease, namely EPS, Psychotic symptoms, duration of illness, cognitive function (as measured by mMMS), and age at disease onset 3. Feasible to apply both individual-patient data or cohort data 4. Feasible to compare outcomes of specific patients or disease conditions 5. The model has been widely used in health economic evaluations of dementia	1. The predictive equation uses mMMS score 2. Differences in the cognitive assessment (MMSE or ADAS-cog) need to be translated to mMMS, leading to concerns about the accuracy of cognitive score 3. Functional performance is not captured in the equation 4. According to the development of the predictive equations based on data from the study by Stern et al. (1997) in the US patients, there is a concern that the application of these equations in different contexts leads to unreliable data
FTC framework- model using a predictive equation to predict the time to FTC developed by Rive et al. (2010)	1. To predict time to need of FTC 2. Incorporate the significant domains associated with Alzheimer's disease to the predictive equation, including	1. The equations were developed based on the LASER-AD cohort study in the UK, there is a concern that the application of

Model Type	Strength	Limitation
	cognitive function (ADAS-cog), functioning (ADCS-ADL), and behavioural (NPI)	these equations in different contexts leads to unreliable data
CERAD-CDR scale model	1. To predict time in stages of disease severity as measured by the CDR scale 2. The state-to-state transition probabilities were derived data from CERAD cohort using a Cox proportional hazards regression model 3. Feasible to adjust the transition probabilities by age, gender, and behavioural symptoms 4. The model has been widely used in health economic evaluations	1. CDR scale is a significant predictor in the model 2. The rating on CDR scale is mainly based on the cognitive ability 3. The transition probabilities were based on the CERAD database in the US, there is a concern that the application of these equations in different contexts may not be accurate with regards to patient characteristics
CERAD-SIB model	1. To predict time in stages of disease severity as measured by the SIB scale 2. Apply the regression analysis for mapping MMSE score, CDR scale and SIB score	1. The mapping of MMSE score, CDR scale, and SIB score may raise an issue concerning the accuracy of the process
Model developed to evaluate memantine drug	1. To predict the delay institutionalisation and time to dependence 2. The model categorises health states into disease severity,	1. Data associated with treatment and no pharmacological treatment were obtained from RCT, use for the transition probabilities

Model Type	Strength	Limitation
	dependency, and with/without residential setting 3. Transition probabilities between states are based on severity, dependency and care setting 4. The model is applied to evaluate the treatment of patients in more severe states of disease	2. The cognitive score is the important factor in the model, inasmuch as the severity transition, dependency transition and with/without institutionalisation transition were influenced by cognitive score at the beginning of the cycle
DES model	1. The model simulates based on the patient-level information 2. Incorporates important factors associated with the disease progression, including MMSE, NPI, ADL, IADL, and DAD 3. The analysis is a much finer gradient and much more realistic over time	1. Requires the patient-level data sets related to the availability of data 2. May be concerns over the complexity of the model
Model developed by Lachaine et al. (2011)	1. To predict time to nursing home admission, leading to the most significant predictor affecting the costs of Alzheimer's disease 2. The development of model and parameters are based on observational studies in particular the study by Lopes et al. (2009) in the US	1. The model is based on data from the study by Lopes et al. (2009) in the US, the application in different contexts needs to be a concern regarding patient characteristics

Model Type	Strength	Limitation
Model developed by McDonnell et al. (2001)	1. Apply statistical model-based regression analysis 2. The model applies the patient characteristics, clinical characteristics, care settings, and mortality	1. The model is based on data from the Rotterdam study in the Netherlands, the application in different contexts needs to be a concern regarding patient characteristics
Model developed by Fenn and Gray (1999)	1. To predict time in delaying the onset of more severe disease stages 2. Apply the survival analysis as accelerated failure time model based on the Weibull distribution for the hazard	1. The model is reliant on the cognitive score 2. Specific patients due to patient data taken from the clinical trials of rivastigmine
Model based on the data from Kungsholmen project	1. To predict Time in stages of disease severity (as defined by MMSE score) 2. The transition probabilities and mortality rate are based on the Kungsholmen project	1. Cognitive function is a significant predictor in the model 2. The model is based on data from Kungsholmen project in Sweden, the application in different contexts needs to be a concern
Model developed by Henke and Burchmore (1997)	1. The model is not complex due to using the decision tree 2. The model is used to predict the reduction of costs from the institutionalised care	1. A specific model for the tacrine treatment
MMSE- and ADL- based model	1. The model is used to predict the probability of requiring institutionalisation	1. May be concerns over the accuracy of the mapping between the ADCS-ADL scale and the Townsend-ADL scale for

Model Type	Strength	Limitation
	2. The ADL is incorporated into the MMSE model to predict health outcomes and costs	calculating the transition probability of institutionalisation
Model developed by Wong et al. (2009)	1. The model is not complex due to using the decision tree 2. The model is applied in vascular dementia 3. The effectiveness and clinical probabilities of adverse events of medications are applied in the model	1. The model is undertaken over a short period of time (24-28 weeks) 2. Only ADAS-cog is used for effectiveness data, leading to an underestimation in the capture of the executive function of patients with vascular dementia
Model developed by Stewart, Phillips and Dempsey (1998)	1. To predict time in stages of disease severity as measured by the MMSE scale	1. Cognitive function is the only factor used to estimate the disease progression 2. Model is specific for donepezil (Aricept®) treatment
Model developed by Hu et al. (2015)	1. To predict time in health states of disease progression 2. The cognitive function (as measured by MMSE, ADAS-cog and SIB score), functional abilities (as defined by ADL) and presence of agitation/aggression (as defined using NPI) are incorporated in health states of the model	1. The clinical management in the model is based on Delphi panel meetings by clinical experts in China 2. The model focuses on an urban population in China
Model developed by O' Brien et al. (1999)	1. To predict time in stages of disease severity (as assessed by MMSE score)	1. Cognitive score is a significant factor to measure the improvement

Model Type	Strength	Limitation
	2. The model combined data from RCT and a cross-sectional study	2. MMSE score is mapped into cost data

2.7 Conclusion

In summary, based on the literature review, Alzheimer's disease is the most common type of dementia studied in the health economic evaluation area. There is only one study identified that is associated with vascular dementia. Based on the interventions, donepezil forms the majority of health economic studies in dementia being 25.5% from the total studies in this literature review. The other interventions used in studies on dementia are galantamine and memantine which account for 20% in both instances. Considering the model-based economic evaluation, most studies apply the Markov model to predict the disease progression (75%). Based on the FTC frameworks, the AHEAD model, developed by Caro et al. (2001), is the most common method used to categorise the progression of disease. The model structure consists of pre-FTC, FTC, and death. The "requiring FTC" is employed to estimate the effectiveness of interventions from the disease progression. The FTC conceptual framework used to evaluate health economics in dementia is divided into two approaches, since there are differences in the approaches to calculate the time to FTC need. The conventional study using the predictive equation of time to FTC developed by Caro et al. (2001). That study used the data based on the study by Stern et al. (1997), to develop the predictive equations to calculate the patient's time to require FTC. From Stern and colleagues, the predictive equations to FTC incorporated various parameters, including the presence of EPS, presence of psychotic symptom, duration of illness, cognitive function, and age at disease onset. The mortality probability relied on the female gender, presence of EPS, cognitive function, and duration of illness. Furthermore, in the initial period, during 2001 to 2005, these equations were widely

used in the health economic evaluation. In the recent period from 2010 onwards, new predictive equations were developed to be used for computing the disease progression of the time of patients to requiring FTC (Rive et al. 2010). The model structure remained similar to the model structure from the study by Caro et al. (2001). Further, the new predictive equation integrated the three main characteristics of the Alzheimer's disease progression to predict the time to FTC, as categorised into cognitive, functional, and behavioural assessment. The details of each method are as previously stated.

In addition, another model framework, generally used in health economic evaluation in Alzheimer's disease studies, is the CERAD model structure. This model was constructed based on the CERAD database. The health states in the model structure are the severities in the cognitive function predicting the disease progression as composed of mild, moderate, and severe. Further, the health state also included the absorbing state, as defined death, in the model. The cognitive function was assessed by the CDR scale. The transition probabilities of patient's moving from one state to another state used the modified survival analysis to calculate based on the data from the CERAD database (Neumann et al. 1999). In the early period, most studies based on CERAD adopted the same fashion of the study by Neumann et al. (1999), in terms of applying the transition probabilities in their studies (Yamada and Ikegami 2002, Kirbach et al. 2008, Lopes-Bastida et al. 2009). On the basis of the model structure, another study applied data from the epidemiological cohort study to compute the transition probabilities (Fuh and Wang 2008). Another study used different instruments, namely SIB, to measure the level of cognitive function (Weycker et al. 2007).

Other types of models used in health economic evaluations in dementia are: the discrete event simulation (DES), statistical analysis model, regression-based analysis model, decision tree, and microsimulation. The finding showed that DES has been adopted during the latter period since 2010. However, the decision-analytical model based on the Markov model stands out as

the one to use when compared against the other models in the health economic evaluation in dementia area.

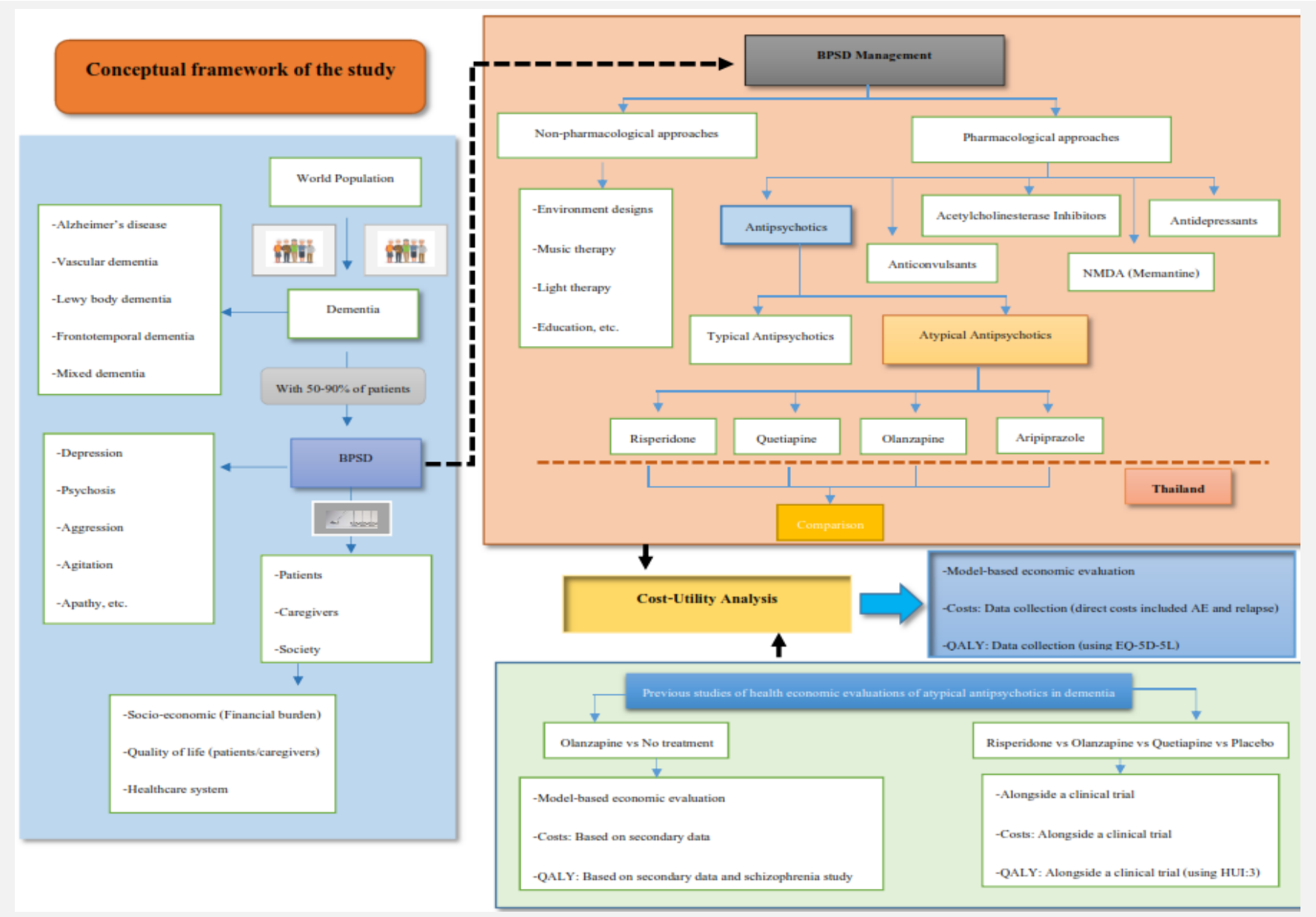
For interventions, the major studies of model-based economic evaluations in dementia were associated with anti-dementia medications, including acetylcholinesterase inhibitors, (donepezil, galantamine, and risvastigmine), and NMDA receptor antagonist (memantine). Based on data from the U.S. Food and Drug Administration (FDA), donepezil was the first drug approved in 1996 followed by rivastigmine in 2000. Galantamine and memantine were then approved in 2001 and 2003, respectively. The combination of donepezil and memantine was recently approved in 2014. The US-FDA data also indicated that there are delays in developing new anti-dementia treatments (Alzheimer's Association 2017). Consequently, the tendency of economic evaluations in dementia is currently focusing on the diagnostic or the early detection of dementia.

Considering the behavioural and psychological symptoms of dementia (BPSD), these symptoms are significant problems and have vital impacts on patients and caregivers experiencing this disorder. Non-pharmacological approaches are recommended for these BPSD patients. However, the pharmacological approaches are important to patients who have persistent symptoms. Although, antipsychotic drugs are widely used for patients with BPSD, in the real practice, these drugs are off-label use for those patients. Currently, there is only one model-based study which takes into account BPSD, in particular agitation, aggression, and psychosis, in an economic evaluation in dementia (Kirbach et al. 2008). This implies a shortage of studies in this field. Thus, further health economic evaluation studies of dementia should take into consideration patients with BPSD and their treatment.

To conclude, the model-based economic evaluation in dementia from the literature review highlighted the strengths and weaknesses of the models identified, including the model conception, leading to further implementation and development of a suitable model to apply

for the economic evaluation in dementia. The conceptual framework of this thesis is displayed in Figure 2.5.

Figure 2.5: Conceptual framework of the thesis



Chapter 3: Methods

Abstract

Introduction: Behavioural and psychological symptoms of dementia (BPSD) are the most common problems of patients with dementia. These symptoms lead them to be a danger to themselves and their caregivers and a complication for the management of the disease. In addition, there are currently no US-FDA approved drugs for the treatment of those symptoms. This results in a wide range of treatment options that are available to behaviourally disturbed patients with dementia. In Thailand, the atypical antipsychotic group is one type of medication which has been widely used for the treatment of BPSD. However, there is a paucity of data on the health economic evaluations of these drugs. Thus, atypical antipsychotic use for the treatment of BPSD sufferers needs to be evaluated to provide useful information to decision-makers, namely, patients themselves, caregivers, patient's families, physicians and health policy-makers.

Aim: The objective of this chapter is to address the research methodology of the cost-effectiveness of olanzapine in comparison to risperidone, for the treatment of patients with BPSD in Thailand.

Methods: An analysis of the cost-effectiveness was constructed following these stages: firstly, the scope of the health economic evaluation was defined. Secondly, different models were developed for applying to the evaluations. Thirdly, the estimated monthly costs of patients with BPSD were calculated from the primary data collection in a Thai setting. Then, the utility weights were also measured from those patients and/or their caregivers. Finally, the analysis, reporting, presenting as well as a sensitivity analysis were conducted.

Results: The five main stages that were applied for this study of olanzapine in comparison to risperidone of patients with BPSD in Thailand were: the defining scope of the evaluation;

developing models and selecting the most appropriate model to adopt in following stage of the cost-utility analysis of the atypical antipsychotic use for BPSD in Thailand; monthly costs and utility weights, using the cost and the EQ-5D-5L questionnaires, are then estimated; lastly, results of the cost-utility analysis together with sensitivity analyses are reported.

Conclusions: By comparing olanzapine with risperidone, the cost-utility analysis will indicate the more cost-effective drug for the treatment of patients with BPSD in Thailand. The findings also have benefits to patients, caregivers and physicians in managing and planning the appropriate treatment for sufferers. Furthermore, policy-makers are able to use the data in deciding on the allocation of healthcare resources efficiently for these patients.

3.1 Introduction

Currently, a rapid rise in the elderly population is a major cause of a substantial number of people with dementia. By 2050, people aged over 60 years were estimated to be two billion globally and approximately 116 million of these will be people with dementia (World Health Organisation 2012). Behavioural and psychological symptoms of dementia (BPSD) are significantly relevant to people with dementia and these symptoms are the most common that occur during the progression of the disease, consequently leading to serious problems. Patients with a presence of BPSD have potential impacts on the burden of care, caregiver's distress, and quality of life of both themselves and their caregivers. The presence of problematic behavioural symptoms in people with dementia is more difficult to cope with than cognitive changes (Kar 2009).

In clinical practice, the management of BPSD is now complicated and troublesome. However, atypical antipsychotics are widely used for the management of these symptoms in BPSD patients, although there is a concern over the adverse effects that these drugs have. Whilst a variation of atypical antipsychotic use for treatment of patients with BPSD are available, they are not well defined. A difference in drug prices of those atypical antipsychotics might also influence the decision making of individual patients, caregivers as well as physicians, leading to a limitation in the prescribing of those drugs for patient care. Consequently, the exploration of the treatment BPSD with atypical antipsychotics is significantly important.

To our knowledge, this is the first study to conduct a cost-utility analysis in comparison of atypical antipsychotics for the treatment of patients with BPSD, based on the decision-analytic model from the societal perspective in Thailand. Cost and utility data is based on the data collected from BPSD patients in a Thai setting, using face-to-face interviews by cost and the EQ-5D-5L questionnaires. This study also takes into account adverse event-related costs and relapse-related costs of atypical antipsychotic use in those patients for the cost analysis.

The results of the study indicate the most cost-effective treatment in comparing between olanzapine to risperidone, for those patients with BPSD. In addition, this study also estimates the cost and health utility data of BPSD patients treated with olanzapine and risperidone. These useful data also help to support the relevant person in all matters relating to the planning and the management of the effective treatment option to BPSD patients. Consequently, the purpose of this chapter addresses the research methodology of the cost-utility analysis in assessing the economic evaluation of olanzapine in comparison to risperidone, of behaviourally disturbed patients with dementia in Thailand.

3.2 Philosophical underpinnings of the research

Philosophical underpinnings are significant to all researches exposing the ontological, epistemological, theoretical perspective, methodological approach and methods which the researchers choose to adopt in their researches.

Ontology is the study of existence. Ontological assumptions are concerned with the nature of reality. The key ontological question is what is real (Saunders, Lewis and Thornhill 2006, Scotland 2012). When the researcher takes a position on an ontological perspective, it means that the researcher begins to choose the methodological decision-making which is based on beliefs, values, independent social reality, dependent social reality, or reality constructed by the social environment. The approach, (quantitative, qualitative or mixed methods), of the research will often be influenced by such ontological perspectives. In this thesis, the ontological perspectives are categorised into realism and idealism. Realism is the view that the reality is objective and it exists independently of the human mind. The idealism is contrasted, it is the view that the reality is subjective and it is constructed by the mental awareness of individuals.

Epistemology is the theory of knowledge. Epistemological assumptions are concerned with the way of knowing (Saunders, Lewis and Thornhill 2006, Scotland 2012). In seeking new knowledge, the epistemological perspective is an aid in informing the methodology of the research in terms of purposes and goals (Snap and Spencer 2003). Objectivism, constructivism and subjectivism are elements of epistemological terms in this thesis as subsequently outlined.

The objectivists hold the view that the discovery of knowledge is based on an objective reality which is separately formed in the consciousness of the human (Scotland 2012). Objectivist epistemology also stands alongside the realism of the ontological position. Subjectivists believe that the reality is only based on the individual's perceptions. Also, the subjectivists do not pursue the reality that exits out there in the world. Thus, the conclusions from subjectivism are drawn from the individual's perceptions and the perspective of the subjectivists is consistent with the ontological position of idealism. Considering the constructivists, they attempt to reach a balance between objectivists and subjectivists. The constructivists hold the view that truths and meanings are their concepts. The meanings engage objects and subject meanings are developed based on individuals' experiences (Creswell 2014).

As indicated above, a relationship between ontology and epistemology is that the ontological perspective is about what is true of the world and epistemological perspective is about methods of figuring out those truths.

According to ontological and epistemological assumptions, there are different theoretical perspectives which could be applied in research in general. Within realism and objectivism, *the positivist approach* emphasis is to establish universal laws or generalisations. The positivism focus more on a quantitative research, (observations and measurements of empirical data), than a qualitative research. Thus, positivism is also known as the scientific

method for undertaking research in science. Moreover, the positivists tend to belief in empiricism and do not try to explain or interpret the correlation of phenomena which have been observed. The statements of the positivists are descriptive and factual. The conclusion of those positivists has been produced through a deductive approach. The key strategies of the positivists approach are therefore found in experiments.

The post-positivist approach has similar theme to the ontological and epistemological perspectives as in the positivist approach. However, post-positivists believe that the reality exists, but this reality cannot explain by an observation alone. They also accept that theories, backgrounds, knowledge and values of researchers can affect what is observed. From the post-positivists view, the most important is developing various measurements for observations and studying the behaviours and actions of humans. The laws or theories in the world need to be tested and refined in order to achieve a greater understanding of the world. Thus, the post-positivists begin with a theory and then collect data associated with such theory. Finally, they produce the revisions or additional investigations of tests (Creswell 2014). This implies that the post-positivists do not pursue absolute truths of knowledge, whilst they do consider more on the impacts of biases associated with objectivity. Based on the post-positivists, the conclusions are derived through a deductive approach.

Considering the critical realist approach, the critical realist holds the view that all observation is fallible and has some errors and that all truths are revisable. The human action could be changeable in reality. Additionally, both a description and an explanation of social phenomena are required for the critical realists and they focus on exploring the method to explain the regularities. Critical realism starts with an observation of relations from within social phenomena and then constructs the hypothetical relations of phenomena. Finally, exploration to demonstrate the real existence of those hypothesised relations is conducted. Due to all observation being fallible, it is important that critical realists attempt to apply

various measurements and observations in their research. A combination of quantitative and qualitative methodology is frequently conducted in this critical realist approach. Thus, inductive and deductive approaches, as combined in terms of a retroductive approach, are also applied for the understanding of both socially constructed and the impacts of such structures, leading to knowledge gained based on the critical realist approach (Henry et al. 2005).

The pragmatist approach focuses on tasks, activities, situations and consequences rather than preceding abstract theory. Pragmatism is conducted on the basis of what works and its usefulness, (solutions to problems). Further, the pragmatists seek to perceive the problems, they then attempt to apply all approaches available to obtain knowledge from those problems. The methods generally applied in the pragmatic approach are mixed methods.

Regarding the interpretive approach, it is constructed to describe the social phenomena through the interaction between human consciousness and their world. The knowledge gained from this approach is likely to understand the differences in individuals as social actors. The importance of the interpretive approach is to enter into the social actors' world to understand their world from their view points and then develop a theory from the social actor's activities and transfer data to a social context. However, this knowledge is limited to the viewpoints of the individuals who participated in the study. Typically, the methods of open-ended interviews, focus groups, open-ended questionnaires and role-playing are applied to the interpretivists. It provides qualitative data and analyses are based on the researcher's interpretations. Then the conclusions are obtained through an abductive approach.

The aim of this thesis is to apply a cost-utility analysis to assess the economic impact of atypical antipsychotics for the treatment of patients with BPSD in Thailand using a decision-analytic model. Thus, the theoretical underpinning of this thesis based on the cost-utility analysis is posed on a basis of the extra-welfarist approach whereby it incorporates utility

units in its outcomes, (as measured in terms of QALYs, a combination of years and quality of life gained through an intervention). Further, the extra-welfarist approach is based on the concept of the maximisation of the overall health behaviours (Edwards et al. 2013).

To position the research and its philosophical underpinnings, the ontology perspective of this thesis explicitly highlights realism. Also, the epistemological perspective clearly focuses on the objectivism approach based on a post-positivist perspective, an empirical method as well as a deductive approach. The methods are consistently used in objectivism which mainly focus on the quantitative method.

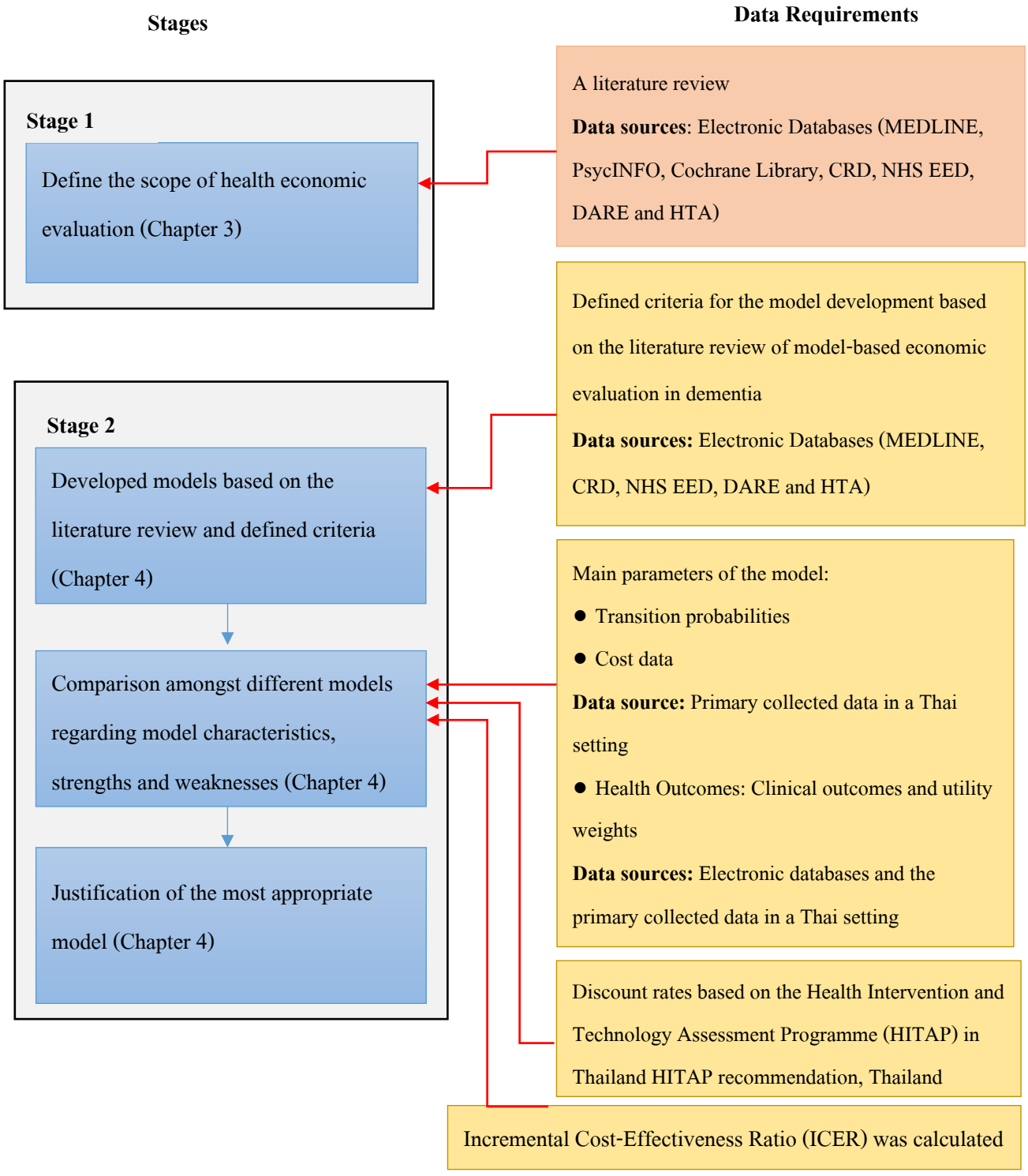
This positioning represents an appropriate approach in the thesis because it has benefits to identify:

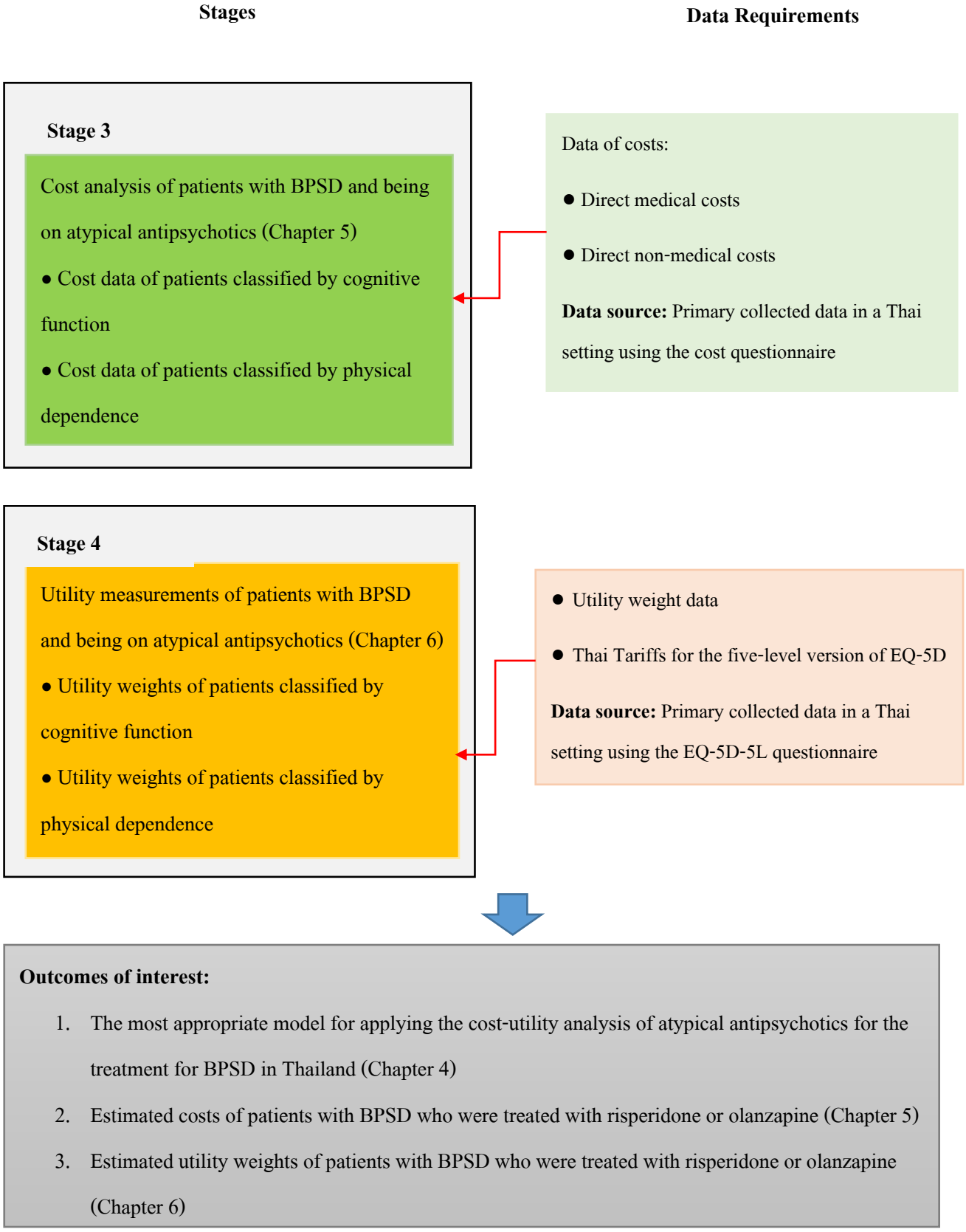
- a dominant effective treatment for patients with BPSD in a comparison of olanzapine to risperidone based on the cost-utility analysis using the decision-analytic model; and
- how to assess the economic impact of atypical antipsychotics, (olanzapine and risperidone), for the treatment of patients with BPSD in Thailand.

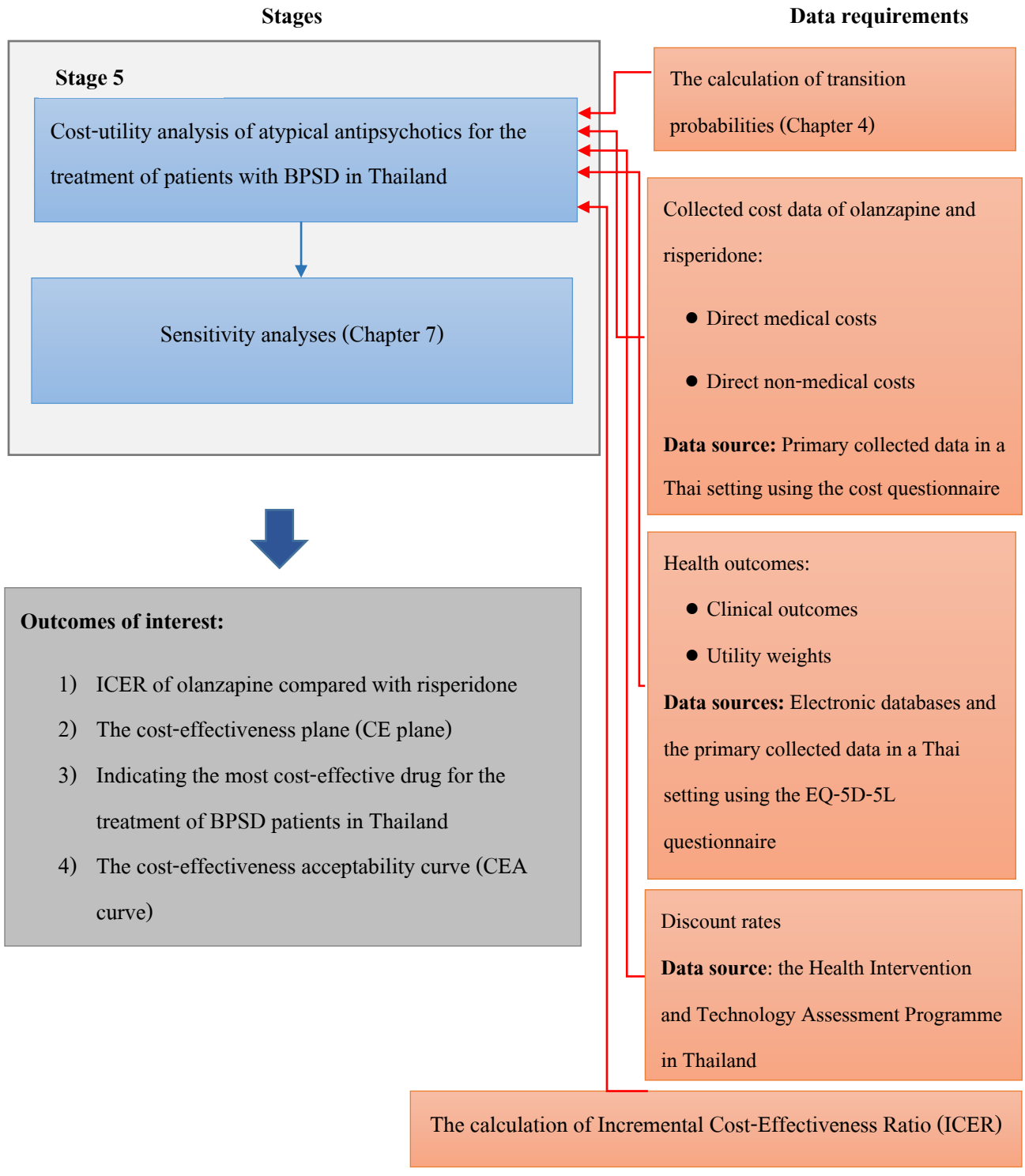
3.3 Research methods

As Flowchart 3.1 shows, the five main stages were performed for undertaking an economic evaluation in this thesis. More details of each stage are presented below.

Flowchart 3.1: **Stages of the cost-utility analysis to assess the economic evaluation of olanzapine in comparison to risperidone for the treatment of behavioural and psychological symptoms of dementia in Thailand**




Stages
Data Requirements
Stage 3
Cost analysis of patients with BPSD and being on atypical antipsychotics (Chapter 5)
● Cost data of patients classified by cognitive function
● Cost data of patients classified by physical dependence
Data of costs:
● Direct medical costs
● Direct non-medical costs
Data source: Primary collected data in a Thai setting using the cost questionnaire
Stage 4
Utility measurements of patients with BPSD and being on atypical antipsychotics (Chapter 6)
● Utility weights of patients classified by cognitive function
● Utility weights of patients classified by physical dependence
● Utility weight data
● Thai Tariffs for the five-level version of EQ-5D
Data source: Primary collected data in a Thai setting using the EQ-5D-5L questionnaire
Outcomes of interest:
1. The most appropriate model for applying the cost-utility analysis of atypical antipsychotics for the treatment for BPSD in Thailand (Chapter 4)
2. Estimated costs of patients with BPSD who were treated with risperidone or olanzapine (Chapter 5)
3. Estimated utility weights of patients with BPSD who were treated with risperidone or olanzapine (Chapter 6)


Stages
Data requirements
Stage 5
Cost-utility analysis of atypical antipsychotics for the treatment of patients with BPSD in Thailand
Sensitivity analyses (Chapter 7)
The calculation of transition probabilities (Chapter 4)
Collected cost data of olanzapine and risperidone:
Direct medical costs
Direct non-medical costs
Data source: Primary collected data in a Thai setting using the cost questionnaire
Health outcomes:
Clinical outcomes
Utility weights
Data sources: Electronic databases and the primary collected data in a Thai setting using the EQ-5D-5L questionnaire
Discount rates
Data source: the Health Intervention and Technology Assessment Programme in Thailand
Outcomes of interest:
1) ICER of olanzapine compared with risperidone
2) The cost-effectiveness plane (CE plane)
3) Indicating the most cost-effective drug for the treatment of BPSD patients in Thailand
4) The cost-effectiveness acceptability curve (CEA curve)
The calculation of Incremental Cost-Effectiveness Ratio (ICER)

3.3.1 Stage 1: Defining the scope of the health economic evaluation

The principal objective of the study was to examine the value for money of the treatment of BPSD patients with atypical antipsychotics. A cost-utility analysis was used to predict the expected costs and outcomes of atypical antipsychotics for the treatment of those patients with BPSD. Based on the current treatments of BPSD patients in Thailand, atypical antipsychotics are widely used, even though these drugs have no US-FDA approvals for their use in the treatment of patients with dementia. Consequently, this leads to a variety of atypical antipsychotic treatment options for patients with BPSD in a routine clinical setting. It was therefore necessary to conduct a cost-effectiveness of the atypical antipsychotic drugs, to explore the most cost-effective drug for the treatment of BPSD within a real setting in Thailand.

Further, the scope of the evaluation of this study was defined based on a comprehensive literature search on the use of atypical antipsychotic drugs for the treatment of dementia (see Chapter 2). The finding found 13 studies which have been summarised in the following Table 3.1.

Table 3.1: **Summary of the effectiveness of atypical antipsychotics for the treatment of patients with dementia**

Study	Intervention	Risperidone	Olanzapine	Quetiapine	Aripiprazole
De Deyn et al. (1999)	Risperidone, haloperidol, or placebo	/			
Brodaty et al. (2003)	Risperidone vs Placebo	/			
Street et al. (2000)	Olanzapine vs placebo		/		
De Deyn et al. (2004)	Olanzapine vs placebo		/		
Zhong et al. (2007)	Quetiapine vs placebo			/	
Tariot et al. (2006)	Quetiapine, haloperidol, and placebo			x	
Paleacu et al. (2008)	Quetiapine vs placebo			x	
Kurlan et al. (2007)	Quetiapine vs placebo			x	
De Deyn et al. (2005)	Aripiprazole vs placebo				/
Streim et al. (2008)	Aripiprazole vs placebo				/
Mintzer et al. (2007)	Aripiprazole vs placebo				/
Schneider et al. (2006)	Olanzapine, risperidone, quetiapine vs placebo	/	/		
Deberdt et al. (2005)	Olanzapine, risperidone vs placebo	x	x		

* (/) refers to effectiveness when compared between/amongst interventions and (x) refers to no significant differences between/amongst interventions

As the data shows above, olanzapine, risperidone and aripiprazole showed the most significant beneficial effects on the treatment of patients with BPSD.

Considering the treatment of BPSD in Thailand, amongst those atypical antipsychotic drugs (olanzapine, risperidone, quetiapine and aripiprazole), olanzapine and risperidone were the most widely used for the treatment of those patients. According to retrospective studies, just over 50% patients with dementia at Srithanya Hospital have been prescribed risperidone and nearly 18% patients were assigned olanzapine to treat BPSD in Alzheimer's and other types of dementia at Srinagarind Hospital (Chanthawong et al. 2012, Rapeepatchai and Promma 2015).

Moreover, only drugs approved in the National List of Essential Drugs (NLED) in Thailand are covered by the Universal Coverage scheme (UC), which is a foundation healthcare system or entitlement, for all patients within the Thai population.

For risperidone, this drug was classed as an essential drug (ED) in NLED for the treatment of patients with BPSD. The expenditure on this medicine was then reimbursed under the UC scheme in Thailand.

Olanzapine was the alternative drug that was compared with the current drug (risperidone) in the context of the treatment of BPSD in Thailand. This drug was chosen for evaluation in this study due to recommendations from the guidelines and its efficacy data from clinical trials for the management of behavioural problems in dementia, especially Alzheimer's disease (Schneider et al. 2006, Scottish Intercollegiate Guidelines Network 2006, The American Geriatrics Society 2011, Azermi et al. 2012, Sadowsky and Galvin 2012, British Columbia 2012, Prasat Neurological Institute 2014). However, olanzapine was provided as a non-essential drug (non-ED) based on Thai NLED. Consequently, olanzapine-associated expenses for the treatment of BPSD patients were the patients' responsibility as out-of-pocket expenses (Ministry of Public Health in Thailand 2013).

Accordingly, the comparators of this study were defined as follows:

1) The alternative treatment of patients with BPSD used olanzapine;

2) The current treatment of patients with BPSD used risperidone;

The dosage regimens that were recommended by guidelines are presented below:

Drugs	Dosage Regimen
Risperidone (Risperdal®)	● Initial dosage: 0.25 mg/day ● Maximum dosage: 0.5-2 mg/day
Olanzapine (Zyprexa®)	● Initial dosage: 2.5 mg/day ● Maximum dosage: 5 mg/day

3.3.2 Stage 2: Model development and application to health economic evaluation of the treatment with antipsychotics for behavioural and psychological symptoms of dementia in Thailand (Chapter 4)

At this stage, there were several steps that were undertaken. Firstly, models were developed in different structures, reflecting the progression of the disease based on the comprehensive literature review (Chapter 2). The criteria for developing models were defined in Chapter 4. Secondly, a comparison amongst different developed models was conducted to identify the characteristics, strengths as well as weaknesses of each model. At step 2, the parameters of each model function for each developed model needed to be explicitly identified. Whilst the main parameters required for each model were transition probabilities, drug effectiveness, cost data and utility weights. The transition probabilities were the chance of patients changing from one health state to another as the disease progressed which was conditional on the model framework of each model. These might be derived from the calculations by the equations or available data from published studies. The effectiveness of the drugs was obtained from a literature review of published studies searched from 1994 up to July 2015. However, this data needed to be reviewed, considered and appraised to determine the quality of the evidence that was presented in the studies. For cost data and utility weights, these were received from the primary

collected data from patients with BPSD in Thailand (Chapter 5 and 6). The health outcome of each model was presented in terms of quality-adjusted life years (QALYs). Thus, the main outcome of this analysis was the cost per QALY gained or the incremental cost-effectiveness ratio (ICER) which was calculated as outlined below:

$$\text{ICER} = \frac{\text{Cost of Olanzapine - Cost of Risperidone}}{\text{QALY of Olanzapine - QALY of Risperidone}}$$

where: ICER was an incremental cost-effectiveness ratio

QALY was the quality-adjusted life year

In addition, the time horizon and discount rates for all developed models were conducted over a 5-year time period with a one-month cycle length. The discounted rate was calculated at 3% per annum of both costs and outcomes for all those models. These rates were recommended by the Health Intervention and Technology Assessment Programme (HITAP) in Thailand (The Health Intervention and Technology Assessment Program 2014).

After conducting the two steps as stated above, the last step of Stage 2 was that the different models would be justified based on model characteristics and the advantages and disadvantages of each model, (in Chapter 4), in order to select the most appropriate one to apply for further analysis (Chapter 7).

The outcome of interest from this stage was:

The selected model to adopt for the cost-utility analysis of olanzapine and risperidone, for the treatment of patients with BPSD in Thailand.

3.3.3 Stage 3: Estimation of costs based on the primary data collection in Thailand (Chapter 5)

From a societal perspective, data on direct medical and non-medical costs were collected for economic evaluation and this was adjusted to take into account the Thai setting.

3.3.3.1 Direct medical costs consisted of the medication costs of olanzapine and risperidone, hospitalised costs, additional payments beyond the patient's healthcare insurance coverage and comorbidity-related costs. Medication costs were referenced to data from the Drugs and Medical Supplies Information Centre (DMSIC), using the database of drug prices of the Ministry of Public Health in Thailand.

Additionally, this study considered the safety of atypical antipsychotic drugs because a variety of atypical antipsychotic treatment options for BPSD were available. Although their efficacy was available for scrutiny, safety was just as significant a factor as the efficacy that should be considered in the treatment of patients. Generally, the adverse effects of atypical antipsychotics are often associated with extrapyramidal symptoms, somnolence, injury by falling, gait disturbance, oedema, urinary tract infection, weight gain, sedation, prolactin increase, and cerebrovascular events (Deberdt et al. 2005, Schneider et al. 2006, Tan et al. 2015). The impact of these adverse events had to be taken into account when considering the use of atypical antipsychotics for the treatment of patients with BPSD. Thus, costs of the potential adverse events of these drugs were also encompassed in the economic evaluations, to cover the aspect of the costs of care, the drug effectiveness and the quality of life for patients and caregivers, namely drug-related adverse events, additional medication use for the treatment of drug-induced adverse events, and adverse event-associated emergency department visits.

Relapses are also a common event occurring during a course of treatment of patients with atypical antipsychotic drugs. Thus, relapse risk was also included to calculate the direct medical costs of drug-related relapse in the economic evaluation of BPSD patients in this study.

3.3.3.2 Direct non-medical costs were applied to the patients' out-of-pocket expenses, the cost of informal care, paid caregiver time, the cost of transportation, the cost of accommodation, and the cost of extra food for patients.

All patients' costs, such as direct medical and non-medical costs, were collected at face-to-face interviews, using the cost questionnaire completed by patients and/or caregivers. The processes of data collection of the costs data and cost analysis are presented in section 3.4. The cost questionnaire can be seen in Appendix 4.

The outcome of interest from this stage is:

The estimated costs of patients with BPSD who were treated with risperidone or olanzapine in Thailand.

3.3.4 Stage 4: Estimation of health-related quality of life weights based on the data collection in Thailand (Chapter 6)

In this study, quality-adjusted of life years (QALYs) used as a health outcome which were mainly based on utilities. These values were collected during the face-to-face interviews with the patients or caregivers conducted in Thailand, using a preference-based health measure questionnaire (see Appendix 4). The data collection process of the health-related quality of life and utility analysis are shown in section 3.4.

The outcome of interest from this stage is:

The estimated utility weights of patients with BPSD who were treated with risperidone or olanzapine in Thailand.

3.3.5 Stage 5: Cost-utility analysis of atypical antipsychotics for the treatment of patients with behavioural and psychological symptoms of dementia and sensitivity analysis (Chapter 7)

This study was a full economic evaluation, which compared both costs and outcomes of two interventions, (olanzapine or risperidone), for the treatment of BPSD. A decision-analytic model was used to assess the costs and outcomes of treatments associated with the management of BPSD patients aged 60 years or above, over a 5-year time period with a cycle length of one month. In addition, both costs and outcomes were discounted at 3% per annum in this analysis.

As this stage focused on the application of the most appropriate model derived from Stage 2. The ICER and the net benefit approach were also applied. Sensitivity analyses were also performed to handle the uncertainty of the parameters in the model. The cost-utility analysis is shown in section 3.5.

The outcomes of interest from this stage are:

1) ICER of olanzapine compared with risperidone;
2) The cost-effectiveness plane (CE plane);
3) An indication of the most cost-effective drug in comparison of olanzapine and risperidone, for the treatment of BPSD patients in Thailand; and
4) The cost-effectiveness acceptability curve (CEAC).

3.4 Data collection for cost and utility analyses of patients with behavioural and psychological of dementia in Thailand

3.4.1 Study design

The research question of this thesis is "What is the cost-effectiveness of olanzapine versus risperidone for the treatment of behaviourally disturbed patients with dementia in Thailand". A justification of the study design in this thesis was then based on the criteria as follows:

- Aims of research
- Inclusion criteria of patients
- Data settings
- Time and budget management

An observational study using a cross-sectional study

The study aimed to undertake a comparison on the cost-effectiveness of existing drugs, (risperidone and olanzapine), used in patients with BPSD in Thailand, during the time period 2017. Costing and utility data in this study were based on the actual routine clinical practices.

This study explored the associated factors with dementia patients suffering from BPSD who are on atypical antipsychotic drugs, including the costs and utility during some point in 2017. Thus, the data were collected based on one interview with each patient during this time period and was not aimed at any follow up of the participants. Consequently, a cross-sectional study was then considered to be the most appropriate and was designed to undertake data collection of cost and utility data, at only one point in time by face-to-face interviews based on the routine clinical practices. This also relates to potentially providing actual data to inform patients, caregivers and physicians in designing, managing and choosing the relevant treatment for BPSD sufferers, as well as policy-makers for a drug-reimbursement decision-making process. Further, to the researcher's best knowledge, this was also the first study to survey the costs and the utility weights of the treatments with atypical antipsychotics for Thai patients with BPSD.

3.4.2 Sample size

There were about 160 patients attending the neurological outpatient clinic weekly. As it was a cross-sectional study, the plan was to recruit between 40 and 50 patients in each group to detect the changes in their quality-adjusted life years (QALYs). For the purposes of this study, the researcher considered a 20% non-response. Thus, 44 patients per group were recruited at the baseline; using the power of 0.8 with a significance level of 0.05 to detect a one point difference between the two groups with SD of 1.5. However, this study expected to have at least 36 patients per category to detect one unit change in QALY between the two categories.

3.4.3 Data settings

Based on the aims of this study as previously mentioned, the selected data settings were justified from the criteria as listed below:

- Hospitals where risperidone and olanzapine were used for the treatment of behaviourally disturbed patients with dementia aged 60 years and over;
- A local supervisor; and

- Management of time and budget.

Accordingly, Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital were chosen for the data collection of costing and utility weights as they met all the above criteria. The details of the hospitals are described below.

3.4.3.1 *Thammasat University Hospital* is a centre of excellence in health care, situated in Pathum Thani province in the central region of Thailand. This hospital has over 600 beds and serves an average of 2,000-3,000 outpatients per day. Patients with dementia or Alzheimer's disease typically attend two main outpatient clinics, including the internal medicine and the psychiatric clinic, which provides an integrated service from multiple discipline staff, for follow-up on the progression of the disease in each patient. The internal medicine clinic opened on Mondays, Thursdays, and Saturdays. The clinic delivered a service between 8.30 am and 4.30 pm on Mondays and Thursdays and from 9.00 am to 5.00 pm on Saturdays. The psychiatric clinic was open on Wednesdays and Thursdays between 8.30 am and 4.30 pm. In addition, the patients' symptoms were the significant factors of the frequency of doctors' appointments; namely 2-week, 1-month, 1.5-month, 2-month, 3-month, or 6-month intervals. In this setting, Assoc. Prof. Dr Sombat Muengtaweepongsa, who was a specialist in neurology, (nerve), was the local supervisor (see Appendix 2).

3.4.3.2 *Khon Kaen Rajanagarindra Psychiatric Hospital* is a tertiary care unit, situated in Khon Kaen province in the North Eastern region of Thailand. The hospital has 372 beds and provides care for an average of 400 outpatients per day, covering patients from 4-province areas (Khon Kaen, Kalasin, Roi Et and Maha Sarakham). The outpatient department opened 8 hours per day between 8.30 am and 4.30 pm. The frequency of patient hospital visits was similar to those at Thammasat University Hospital.

3.4.4 Target population and data collection process

Ethics approval was secured before data collection took place. A formal letter and research proposal were submitted to the data setting steering committee of Thammasat

University Hospital (Human Research Ethics Committee of Thammasat University, Faculty of Medicine) and Khon Kaen Rajanagarindra Psychiatric Hospital, as well as the Faculty Research Ethics Committee of the Centre for Health and Social Care Research of Sheffield Hallam University, for their approval of the agreement (see Appendix 3). The patient information sheet and the consent form were also submitted for approval by the ethical committees (see Appendix 4).

Patients with behavioural and psychological symptoms of dementia were recruited from the outpatient departments in the excellence centre, (Thammasat University Hospital) and the tertiary care centre, (Khon Kaen Rajanagarindra Psychiatric Hospital). At each site, the local supervisor or healthcare providers were the gatekeepers in reviewing the medical records of patients diagnosed with dementia or Alzheimer's disease and who contacted patients and their caregivers to make appointments for interviews for this study. Patients and their primary caregivers were contacted if they met the criteria set out to participate in the study. The inclusion criteria comprised patients aged 60 years and over (Aekphakorn et al. 2009) and having been diagnosed with dementia or Alzheimer's disease and being on olanzapine or risperidone for at least the last two months, (during December 2016 to January 2017 and August 2017 to September 2017), before the interview.

If patients with BPSD had some difficulties in making a decision to participate due to their disease conditions, primary caregivers were approached to be the informants instead of the patients for practical reasons. A primary caregiver was defined as the person who had lived with patients or visited to provide care to patients for at least eight hours per day and over three days per week for at least two months. Also, the caregiver should be a knowledgeable informant who could contribute to the assessment associated with the patient's health and other patient information. In this study, dementia and Alzheimer's disease and BPSD were defined according to the International Statistical Classification of diseases and related health problems (ICD-10: 10^{th} revision, fifth edition, 2016) (World Health Organization 2015). Dementia and Alzheimer's disease had been classified by the ICD-10 codes of which F00-F03 referred to dementia and disorders related to dementia

(including BPSD) and G30 referred to Alzheimer's disease (World Health Organisation 2015). In addition, the Thai Mental State Examination (TMSE) test was used to assess patients' cognitive status. If patients had their cognitive states assessed during the last six months, (August 2016 to January 2017 and April 2017 to September 2017 before the interview), the cognitive assessment was not required to be tested again. The scores from the assessment test during the last six months would be used as the patients' cognitive status to classify their levels of disease severity (see Appendix 5). In addition, patients and caregivers were excluded if they did not meet criteria or were unable to answer the questionnaire. The data collection processes are presented in the flow diagram in Flowchart 3.2A, Flowchart 3.2B-1 Flowchart 3.2B-2, and Flowchart 3.2C.

Flowchart 3.2: **Flow diagram of the data collection process in this study: planning process, participant recruitment and data gathering**

1) Ethical consideration:
    - 1.1 Ethical reviews
        - 1.1.1 University ethics committee
        - 1.1.2 Hospital ethics committees
    - 1.2 Documentation
        - 1.2.1 Information Sheet
        - 1.2.2 Consent form
        - 1.2.3 Research protocol
2) Instrument/Questionnaires:
    - 2.1 TMSE: Thai Mental State Examination
    - 2.2 EQ-5D-5L (Thai version): EuroQol Group
    - 2.3 Costing Questionnaire: developed by researcher
3) Sample size calculation: a cross-sectional survey

Flowchart 3.2A: Planning process

Inclusion Criteria:

Patients

1) Patients aged 60 years and above* diagnosed with Dementia (ICD-10: F00-F03) or Alzheimer's disease (ICD-10: G30) and being on olanzapine or risperidone for at least the last 2 months.

Partners or caregivers

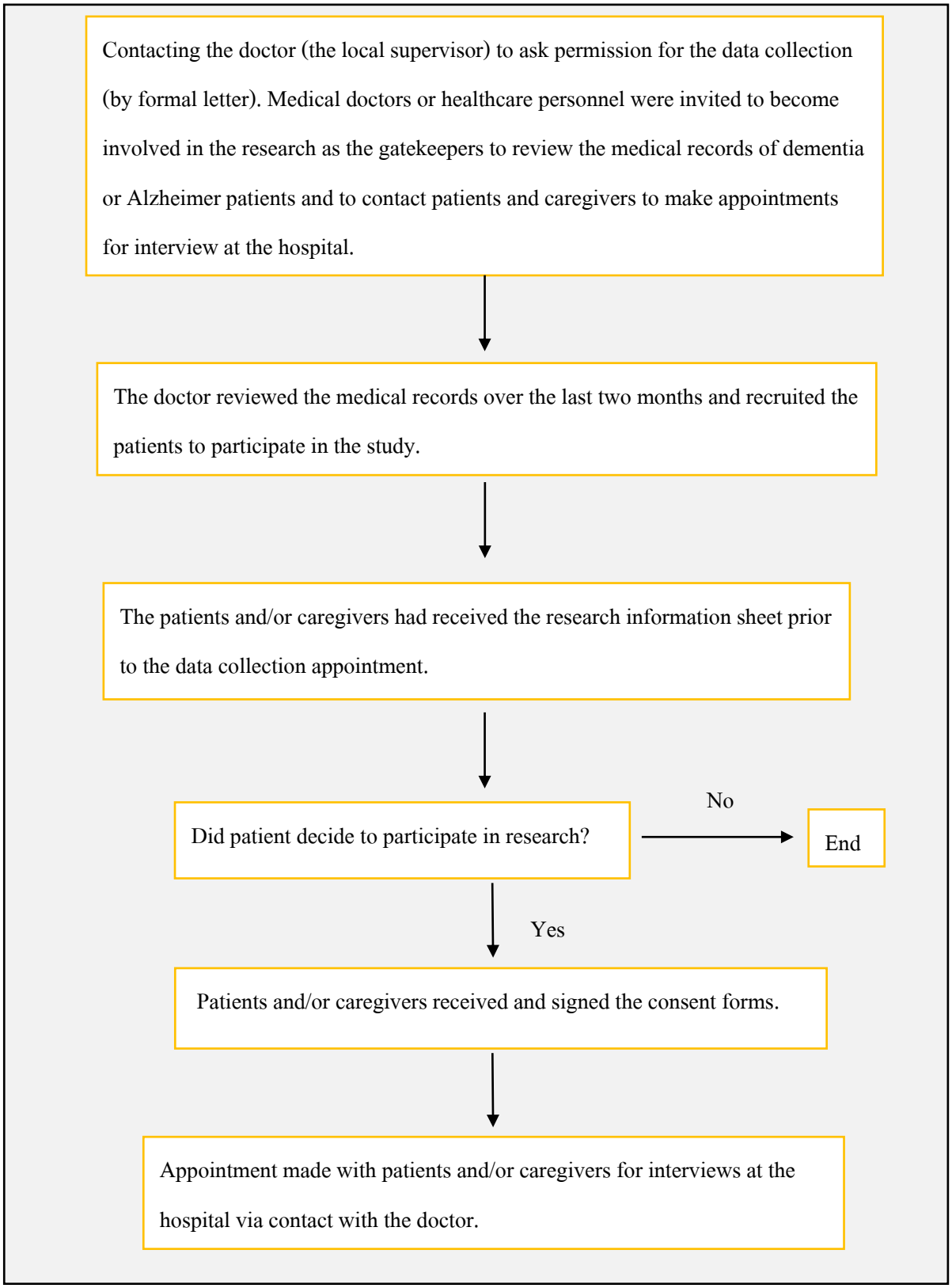
1) A person who lived with or visited the patient for at least 8 hours per week over 3 days or more per week for the last 2 months, were encouraged to contribute to the assessment.

Exclusion criteria*:*

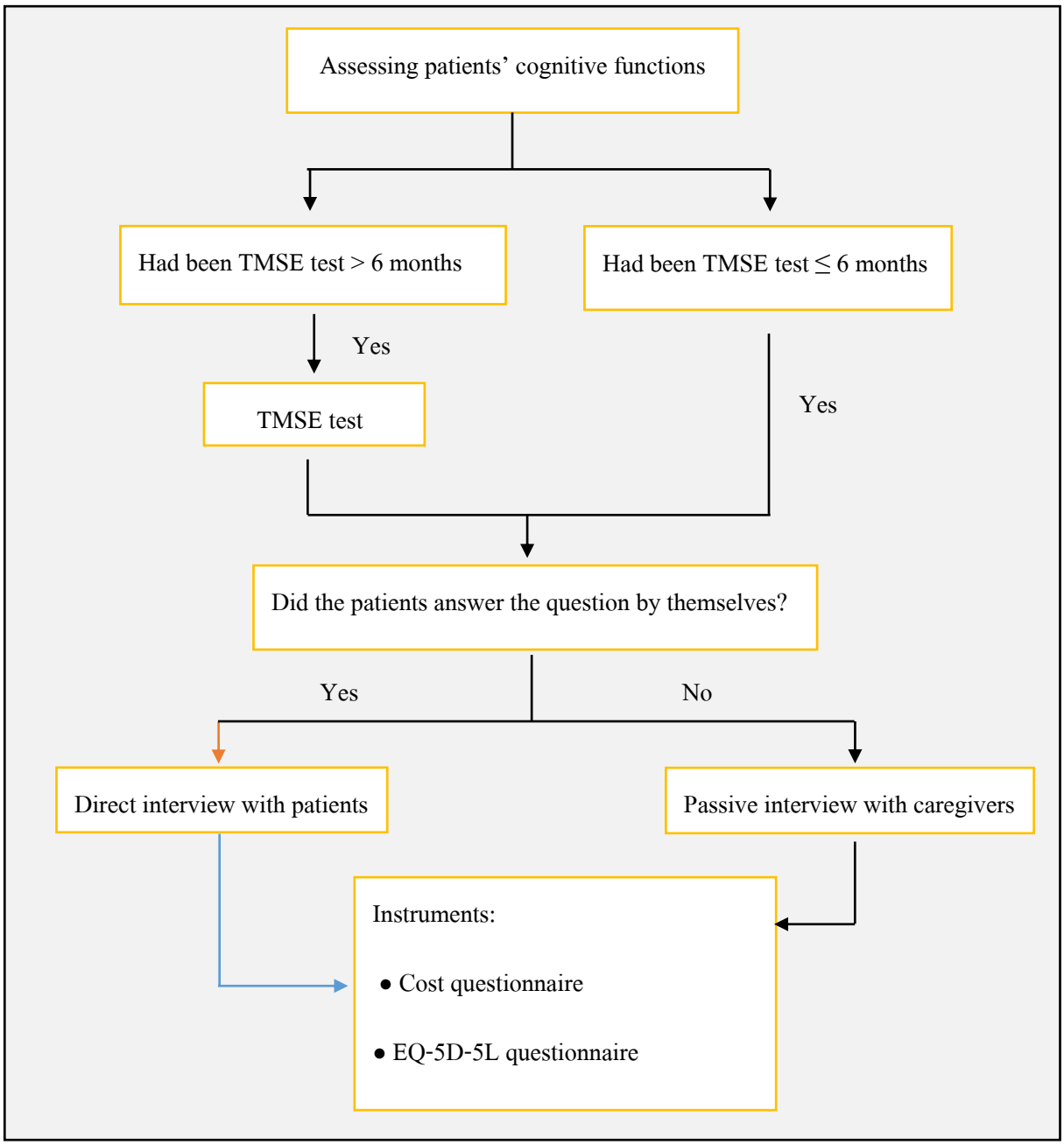
1) Patients, who had no partners or caregiver support and were unable to answer the questionnaire on their own.

***** The definition of an elderly person in Thailand is a person aged 60 and above (the Ministry of Social Development and Human Security 2003, Aekphakorn et al. 2009, Aekphakorn et al. 2016)

Flowchart 3.2B-1: Step I - Process of participant recruitment



Flowchart 3.2B-2: Step I - Process of participant recruitment



Flowchart 3.2C: Step II - Process of data gathering

3.4.5 Cost and quality of life questionnaires

Two questionnaires were used in this study, namely a costing questionnaire and quality of life questionnaire, both of which aimed to collect data associated with costs and utilities in BPSD patients being treated with risperidone and olanzapine in Thailand. More details are outlined below.

3.4.5.1 Costing questionnaire

The costing questionnaire was designed for study purposes to collect data regarding the costs of patients with BPSD and being treated with atypical antipsychotics, (olanzapine or risperidone), in Thailand.

In designing the questionnaire in this study, firstly, the literature review was used to identify examples of the cost measurements associated with dementia and/or BPSD and healthcare resource utilisation. In addition, examples of those cost questionnaires were used to design the cost assessment in this study, especially studies associated with cost-utility analyses in Thailand (Murman et al. 2002, Beard et al. 2006, Kirbach et al. 2008, Turongkavee et al. 2011, Rive et al 2010, Mohara, 2012, Thongsri et al. 2012, Lachaine et al. 2014). Secondly, question items were produced by reviewing existing guidelines, existing health economic evaluation studies as well as information from an education expert, a medical specialist and a dementia caregiver. Finally, the researcher developed the cost questionnaire based on all the available data from the processes as previously stated.

The costing questionnaire consisted of three main parts as listed below:

- Part 1: This part was associated with the general data of patients, including demographic data (gender, age, marital status, religion, education, current occupation, prior occupation, income sources, living area, residence, living arrangement, (a status of living), time since diagnoses with dementia, TMSE scores, comorbidity conditions, drug-related adverse events, patients' health insurance system and patients' activities of daily living.

- Part 2: This part focused on cost data, including outpatient- and inpatient-associated costs, costs of other treatments, paid caregiver costs and informal care costs.

  For outpatient-associated costs, these comprised of the number of visits to the outpatient department, additional payments associated with outpatient visits, costs associated with drug-induced adverse events, (falls, constipation and extrapyramidal symptoms), comorbidity condition-associated costs, and additional costs for travel, extra accommodation and extra food due to outpatient visits in excess of their normal routine daily expenditure.

  For inpatient-associated costs, these encompassed the number of hospital admissions with dementia or symptom-related dementia events, average length of stay at hospital (days), additional payments associated with the hospital admissions and additional costs for travelling, extra accommodation and extra food due to the hospital admissions, but again only those in excess of their normal daily living expenses were included.

  Other costs such as having new equipment, including wheelchairs, walkers and patient beds, food and dietary supplements, (e.g. liquid diets for patients, ginseng, grape seed extract, spirulina, dietary fibre, Moringa capsules and extracted mangosteen juice), herbs, vitamins, other nutritional sources (e.g. Anlene®, sterilised milk, yoghurt milk, UHT milk, Lactasoy®, Milo® and Ovaltine®) and disposable adult diapers were also included.

  Paid caregiver costs were associated with out-of-pocket expenses or paying for the hire of caregivers or home helpers whose time was solely for providing care to patients with BPSD.

  For informal care costs, these were related to family members, relatives or friends who spent time in providing care to patients but were not paid for their provision of care to these patients. However, informal care costs were calculated as the same as for paid workers based on an opportunity cost method (Berg, Brouwer and

Koopmanschap 2004) (see more details in Chapter 5). This was also consistent with the cost estimation of informal care of people with dementia according to World Health Organization (2012).

- Part 3: This part focused on the general data of caregivers as follows: gender, age, marital status, religion, education, current occupation, prior occupation, stopping work due to providing patients' care, duration of stopping work to care for their patients, relationship with patients, hours spent caregiving for patients and the impacts of the patient's illness on the caregivers due to providing care, classified into physical health conditions, (e.g. low back pain, knee pain, shoulder pain, muscle pain and quality of sleep) and mental health problems, (e.g. distress, anxiety, stress and depression).

In addition, the instruments used to measure patients' cognitive status, (if patients had no cognitive assessment during the last six months), and patients' physical dependency in this study are explained below.

3.4.5.1.1 Measuring patients' cognitive status

To measure a person's cognitive status in Thailand, there are several instruments, including Thai Mental State Examination (TMSE), Mini-Mental State Examination: Thai version (MMSE-Thai 2002), the 7-minute test and Montreal cognitive assessment (MOCA) (Prasat Neurological Institute 2014). However, the Institute of Geriatric Medicine, Ministry of Public Health in Thailand, suggested that the TMSE and MMSE-Thai 2002 could help for diagnosis, indicating the levels of disease severity of dementia and indicating the disease progression over time (Institute of Geriatric Medicine 2008). The MMSE-Thai 2002 was developed by the Thai Cognitive Test Development Committee (1999). This test was developed for one-to-one matching based on the MMSE test established by Folstein, Folstein and McHugh (1975). The MMSE-Thai 2002 composed of 11 main items as follows: orientation for time (5 points), orientation for place (5 points), registration (3 points), attention/calculation (5 points), recall (3 points), naming (2 points), repetition (1 point), verbal command (3 points), written command (1

point), writing (1 point) and visuoconstruction (1 point). Eventually, the MMSE-Thai 2002 yielded a maximum score of 30 (Institute of Geriatric Medicine 2008, Prasat Neurological Institute 2014).

Alternatively, in 1993 the TMSE test was formed by the Train the Brain Forum Committee in Thailand and this test was also adapted from the MMSE test established by Folstein, Folstein and McHugh (1975). However, the TMSE test consisted of six main items as follows: orientation (6 points), registration (3 points), attention (5 points), calculation (3 points), language (10 points) and recall (3 points). The TMSE also contributed a maximum score of 30 (Institute of Geriatric Medicine 2008, Prasat Neurological Institute 2014).

Both the TMSE and the MMSE-Thai 2002 instruments could be grouped into six domains as follows: complex attention, executive function, learning and memory, language, visuoconstructional-perceptual ability and social cognition (Prasat Neurological Institute 2014). Both of the instruments are compared in the following Table 3.2.

Table 3.2: **Differences between the TMSE and MMSE-Thai 2002**

	TMSE		**MMSE-Thai 2002**	
	Presented	**Point**	**Presented**	**Point**
Social cognition				
Orientation of time	●	4	●	5
Orientation of place	●	1	●	5
The orientation of the person	●	1		
Learning and memory				
Registration	●	3	●	3
Recall	●	3	●	3
Complex attention and executive function				
Attention and calculation	●	8	●	5

	TMSE		MMSE-Thai 2002	
	Presented	**Point**	**Presented**	**Point**
Language				
Naming	●	2	●	2
Repetition	●	1	●	1
Verbal command	●	3	●	3
Written command	●	1	●	1
Writing			●	1
Comparison of things	●	1		
Visuoconstructional perceptual ability				
Visuoconstruction	●	2	●	1
Total score		30		30

* (●) refers to the presence of items to measure cognition when compared between the TMSE and MMSE-Thai 2002

When comparing between the two instruments, scores from both tests studied in people aged 60 and over in Thailand showed in the same direction and it also found that the Pearson correlation coefficient of both tests was 0.904 ($p<0.000$) (Institute of Geriatric Medicine 2008). Further, 84.2% of medical staff reported that the MMSE-Thai 2002 was easy to administer, compared to the TMSE which only 38.5% found easy. Time spent to complete the tests in less than 10 minutes accounted for 23.1% for the MMSE-Thai 2002 and 9.6% for the TMSE. Therefore, it was clear that the MMSE-Thai 2002 was quicker to complete when compared with the TMSE (Institute of Geriatric Medicine 2008).

To measure patients' cognitive states, the TMSE was chosen in this study. The reason was that the TMSE was the recommended cognitive assessment tool from both the clinical practice guidelines for dementia in Thailand and the Institute of Geriatric Medicine, as mentioned above. The test was also commonly used for screenings patients' cognitive states in Thailand. In essence, the selection of a cognitive test also relied on clinical practices or policy at each hospital or setting.

Moreover, the classification of disease severity by TMSE scores in this study was based on MMSE scores from previous studies, (Perneczky et al. 2006, Bond et al. 2012), which were TMSE: 21-26 (mild dementia), TMSE: 10-20 (moderate dementia), and TMSE: <10 (severe dementia).

3.4.5.1.2 Measuring patients' physical dependency based on Activities of Daily Living (ADL)

Dementia is a leading cause of illness affecting elderly patients where each patient has a difference in levels of disease severity following the disease progression. The cognitive deterioration of patients is not only problematic to themselves but also impacts on caregivers who provide care to those patients.

To measure the basic activities of daily living (bADL), there were various approaches used to assess the ability to perform ADL. However, Barthel Index and Katz Index of ADL were instruments which were widely used measurement tools providing useful information to differentiate between levels of dependence in Thailand (Table 3.3).

The Barthel Index in the Thai version was developed by Jittapunkul et al. (1994) based on the original Barthel Index established by Mahoney and Barthel (1965). This instrument comprises 10 items, including feeding, grooming, transfer, toilet use, mobility, dressing, stairs, bathing, bowels and bladder. In addition, definitions of scoring the Barthel index (Thai version) are described as follows:

- Feeding

  0 = Patient was unable to feed by himself/herself.

  1 = Patient needed some help such as cutting up the food and preparing devices such as a spoon and a fork.

  2 = Independent.
- Grooming (e.g. washing face, combing hair, cleaning teeth and shaving within last 24-48 hours)

  0 = Patients needed the help.

1 = Patient was able to do these activities as stated above by himself/herself, including preparing equipment.

- Transfer (e.g. transferring in the same level floor, transferring to a bed, lying down on the bed, getting on and off the bed, changing their position to sit on the bed, transferring to sit a chair)

  0 = Patient was unable to transfer by himself/herself or needed to be lifted by two people.

  1 = Patient needed a great deal of help from an assistant to change position to sitting.

  2 = Patient needed minimal help from an assistant. For example, the patient needed to be supervised for safety or reminded of what to do.

  3 = Patient was able to transfer without help or supervision.

- Toilet use

  0 = Patient was unable to use the toilet by himself/herself.

  1 = Patient needed some help in some steps of this activity.

  2 = Independent. For example, the patient could get on and off the toilet and clean themselves.

- Mobility (moving within a room or home)

  0 = Patient was unable to move by himself/herself.

  1 = Patient used a wheelchair independently and was able to go around a room corner and through a door.

  2 = Patient needed some help to walk and move or needed to be supervised for safety or reminded of what to do.

  3 = Patient could independently move by himself/herself without help or supervision.

- Dressing

  0 = Patient was able to put on and remove his/her clothing.

1 = Patient could dress by himself/herself accounting for 50% of dressing. The rest of the activity they needed some help to complete.

2 = Independent.

- Stairs (ascending and descending stairs)

  0 = Patient was unable to go up and down stairs.

  1 = Patient needed some help to do these activities.

  2 = Patient could ascend or descend himself/herself without help or supervision. If they used a walker or canes, they had to carry them going up or downstairs.

- Bathing

  0 = Patient needed supervision to do this activity.

  1 = Patient was able to do all steps of bathing by himself/herself.

- Bowels (continence of bowels over the last week)

  0 = Patient was uncontrollable his/her bowel movement. Some patients often need a suppository or an enema.

  1 = Patient was sometimes unable to control his/her bowels; however, this was less than once a week.

  2 = Patient was normally able to control his/her bowels.

- Bladder (controlling bladder over the last week)

  0 = Patient was uncontrollable with his/her bladder.

  1 = Sometimes the patient was unable to control his/her bladder; however, this was less than once a week.

  2 = Patient was normally able to control his/her bladder.

Based on the Katz Index of ADL, this consisted of six activities as follows: feeding, transferring, toileting, dressing, bathing and continence. The definitions of scoring were slightly adapted from Katz et al. (1970) and are presented below:

- Feeding

  0 = needed partial or total help with feeding or required parenteral feeding.

1 = got food from the plate into the mouth without help, preparation of food might be done by another person.

- Transferring

  0 = needed help in moving from bed to chair or required a complete transfer.

  1 = moved in and out bed or chair unassisted. Mechanical transferring aides were acceptable.

- Toileting

  0 = needed help transferring to the toilet, cleaning self, or used bedpan or commode.

  1 = went to the toilet, got on and off, arranged clothes and cleaned genital area without help.

- Dressing

  0 = needed help with dressing or needed to be completely dressed.

  1 = got clothes from closets and drawers and put on clothes and outer garments complete with fasteners. Might have help trying shoes.

- Bathing

  0 = needed help with bathing more than one part of the body, getting in or out of bathtub or shower. Required total bathing.

  1 = bathed self completely or needed help in bathing only a single part of the body such as the back, genital area, or disabled extremity.

- Continence

  0 = was partially or totally incontinent of bowel or bladder.

  1 = exercised complete self-control over urination and defecation.

Table 3.3: **Differences between the Barthel Index-Thai and the Katz Index of ADL**

	Barthel Index-Thai	Katz Index of ADL
Feeding	●	●
Grooming	●	
Transferring	●	●

	Barthel Index-Thai	Katz Index of ADL
Toileting	●	●
Mobility	●	
Dressing	●	●
Stairs	●	
Bathing	●	●
Bowels	●	●
Bladder	●	●
Total score	20	6

* (●) refers to the presence of activities when compared between the Barthel Index-Thai and Katz Index of ADL

For an interpretation of scores, the Barthel Index-Thai scores contributed four levels as follows: 0-4 points (a total dependence), 5-8 points (a severe dependence), 9-11 points (a moderate dependence), and more than 12 points (a mild dependence). The Katz Index of ADL scores were 6 points (independence), 4 points (a moderate dependence) and less than 2 points (a severe dependence) (Prasat Neurological Institute 2014).

To measure patients' functional ability, the Barthel Index-Thai and the Katz Index of ADL were widely used and recommended to assess ADL; however, the Barthel Index-Thai was designed specifically as a Thai version. This scale was also applied to assess ADL in the elderly that provide helpful information regarding long-term care (LTC) conditions to a LTC management policy for older Thai people (National Health Security Office 2016). Thus, the Barthel Index-Thai was chosen as the tool to assess ADL of patients with BPSD in this study.

3.4.5.2 Quality of life questionnaire

As previously stated, this study used the QALYs as health outcomes in an evaluation. The concept of QALYs is a measure of outcome which captures both quality of life and quantity of life (Drummond et al. 2005, Gray et al. 2012). For more clarification, this is that individuals have experienced various health states over time where each health state

is weighted, correlating to a health utility score during that time. Consequently, the multiplication of the time spent in each health state by the health-related quality of life weight (HRQoL weight) associated with that health state is the calculation of the QALY (Drummond et al. 2005, Whitehead and Ali 2010, Gray et al. 2012). Based on this assumption, this indicates that HRQoL weights or utility values or utility weights are significantly substantial factors in producing QALYs.

For technology appraisals, the QALY is frequently used in a cost-utility analysis. This is also recommended by several agencies, such as NICE in the UK, the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, the Pharmaceutical Management Agency (PHARMAC) in New Zealand, The Pharmaceutical Benefit Advisory Committee (PBAC) in Australia and the Health Intervention and Technology Assessment Program (HITAP) in Thailand (National Institute for Health and Care Excellence 2013, The Health Intervention and Technology Assessment Program 2014, The Pharmaceutical Benefit Advisory Committee 2016, The Pharmaceutical Management Agency 2017, Canadian Agency for Drugs and Technologies in Health 2017).

In addition, health-related quality of life was measured by several instruments including generic instruments and disease-specific instruments (Guyatt et al. 1989, Guyatt, Feeny and Patrick 1993, O' Brien 1994, Drummond et al. 2005).

Generic instruments were designed to use a wide range of treatments, populations and interventions. The measures of HRQoL by these scales are classified into two main techniques as follows: health profiles and utility measures (preference-based measures). Sickness Impact Profile (SIP), Nottingham Health Profile (NHP), Short Form health survey-36 (SF-36) as well as World Health Organization Quality of Life (WHOQOL-BREF) were examples used to measure the health profiles of people. For utility weights, this could be scaled by direct and indirect methods for measurements of the preferences of individuals for their health outcomes. Standard Gamble (SG), Time Trade-Off (TTO), and Visual Analog Scale (VAS) were patterns which were the most commonly used in the

direct approaches. For indirect methods or multi-attribute health status classification systems with preference scores, there were SF-6D, Quality of Well-Being (QWB), Health Utilities Index (HUI), and EuroQOL (EQ-5D) which were favourable tools of this method. Disease-specific instruments were applied to specific diseases and sub-populations. Thus, instruments used in this method were focused on particular uses in diseases or conditions (Guyatt et al. 1989, Guyatt, Feeny and Patrick 1993, O' Brien, 1994, Drummond et al. 2005).

To measure the utility weights of BPSD patients being treating with risperidone or olanzapine in this study, the EQ-5D-5L instrument was chosen. The reasons for this were that the results from this tool provided utility weights which could be adopted for the aim of this study as a cost-utility analysis. The tool was also widely used to measure the HRQoL and recommended by several agencies, especially the HITAP in Thailand. Although there were some doubts about using this scale in applying the EQ-5D-5L instrument for use in patients with dementia, there were several studies reporting that this scale was valid and able to use for an assessment of the HRQoL in people with dementia (Wolfs et al. 2007, Jones, Edwards and Hounsome 2012, Diaz-Redondo et al. 2014, Aquirre et al. 2015, Yang et al. 2017). The disease-specific measure, such as the Dementia Quality of life Instrument (DQI), the Quality of Life in Late-Stage Dementia scale (QoL-AD), and Dementia Quality of Life (DEMQOL), had been developed to identify HRQoL in patients with dementia, but these instruments still did not apply for the utility measurement which was used to calculate for the QALY (Hounsome, Orrell and Edwards 2011, Missotten, Dupuis, and Adam 2016). Lastly, dementia-specific instruments are still limited in Thailand.

Consequently, the quality of life questionnaire in this study used the EQ-5D-5L which was derived and permitted from the EuroQol Group. The EQ-5D-5L questionnaire was a Thai version. This instrument consisted of five domains, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and five levels of problems, including no problems, slight problems, moderate problems, severe problems and extreme

problems (EuroQol Group 2015). The conversion from EQ-5D-5L health states into index values was recommended to use data based on tariff or value sets of country-specific data. Thus, this thesis employed value sets based on the study in the Thai population (see more details in Chapter 6).

In addition, the utility weights in this thesis were measured by the EQ-5D-5L. This instrument was only used in the targeted patients based on calculated sample size as stated above (see section 3.4.2), to evaluate health-related quality of life, at only one point in time during some point in 2017. These values were then used in the evaluation of the cost-utility analysis of olanzapine and risperidone use in patients with BPSD in Thailand, (see more details in Chapter 6). Moreover, the additional assessment to evaluate the improvement of the treatment was also conducted after first interviewing patients and/or caregivers by using the EQ-5D-5L. This was undertaken based on asking those patients or their caregivers by face-to-face interviews or a telephone interview at any point of time, which was at least five months to six months from the initial interview, using a 5-point Likert scale. The scales are described as follows: 1 = not at all improved, 2 = slightly improved, 3 = moderately improved, 4 = much improved and 5 = extremely improved. Results associated with this evaluation are presented in Appendix 6.

3.4.5.3 Implement the questionnaire

After developing the costings questionnaire for the purpose of this study, it was then examined by an education expert, a medical specialist, (a local supervisor in Thailand), and a dementia caregiver, which aimed to evaluate and refine the relevance of the questions in cost questionnaire.

Owing to this being study a primary data collection tool in patients with BPSD and/or their caregivers an ethics approval was required before the process of data gathering could begin.

To apply the questionnaire with patients suffering from BPSD and being treated with either risperidone or olanzapine and/or their caregivers at an outpatient clinic of

Thammasat University Hospital, Thailand, using a face-to-face interview process, patients and/or caregivers were recruited based on the participant recruitment process, (as considered from inclusion criteria in Flowchart 3.2B). If patients and/or caregivers decided to participate in this study, information sheets and consent forms were distributed to those informants. Signed consent forms of informants were needed before being interviewed by the researcher. The process then carried on the data gathering of the study as previously mentioned (see Flowchart 3.2C).

There were two informants, one risperidone-treated patient with mild dementia and his caregiver and one moderate dementia patient's caregiver of an olanzapine-treated patient. These were interviewed to complete the questionnaire both for the costing and quality of life data. Based on an information sheet the total time to accomplish the questionnaire was determined to be around 30-45 minutes. Interviewing both of the informants completed the interview within a defined time. The time needed interviewing the patient was nearly 45 minutes, whereas the caregiver was approximately timed at about 28 minutes. Both informants could follow and respond to all of the items (the general data of the patient, costing and the general data of the caregiver). Interestingly, the patient with moderate dementia was unable to complete the questionnaire by himself, so his caregiver became the informant (as a proxy) instead of the patient. The major time-consuming aspect of the interviews was predominantly the part consisting of the costing questionnaire which was composed of more questions when compared with the other part. Whereas, a part of the EQ-5D-5L, (as measure health-related quality of life), was completed within a few minutes. In addition, all informants responded well to co-operate during the interviews.

3.4.6 Cost and utility analyses

For calculating cost data, descriptive statistics, including percentage, arithmetic mean and standard deviation (SD), were conducted for a cost analysis of each drug treatment (olanzapine and risperidone) using Microsoft® Excel version 2013. All cost data were

presented in Thai baht, (THB), at 2017 values, (1£ = THB 45). A societal perspective was used as a viewpoint of this study.

Furthermore, cost data analysis was also presented by the classifications of patients by cognitive function and physical dependence. The patients' cognitive states were classified into mild dementia, moderate dementia and severe dementia. Pre full-time care (Pre-FTC) and full-time care (FTC) were used to classify patients by their dependent status. The FTC state in this study was defined as a patient's requirement for care and supervision for the greater part of each day (Caro et al. 2001).

According to utility measurements, a utility analysis was conducted in a similar fashion to the cost analysis. The percentage, the arithmetic mean and the SD were also calculated for the utility analysis of olanzapine treated patients and risperidone treated patients using Microsoft® Excel version 2013. The analysis of utility data was also separately reported by patients' cognitive function and patients' physical dependence following the criteria outlined above.

3.5 Cost-utility analysis

Health economic evaluation methods are classified into four main techniques as presented below.

A cost-minimisation analysis (CMA) is conducted to compare interventions (two or more alternative treatments) in which those interventions are assumed to have equivalent outcomes. Thus, the core purpose of this method is to consider only the minimisation of costs (Drummond 1998, Drummond et al. 2005, Gray et al. 2012). However, the CMA technique is not characterised as a full health economic evaluation (Drummond et al. 2005). Briggs and O'Brien (2001) also suggested that using this technique does not frequently encounter the right conditions regarding the equivalence of costs or outcomes of the interventions due to having an uncertainty of costs and outcomes in real situations.

The CMA is not then appropriate to employ for healthcare evaluations which should test a hypothesis of differentiating between costs and outcomes.

A cost-effectiveness analysis (CEA) is one method which is widely used in health economic evaluations and is also under full health economic evaluation scheme. This method is based on the concept of an extra-welfare (Brouwer et al. 2008). The CEA undertakes a comparison between costs and outcomes, (effectiveness or efficacy) where these outcomes are measured as disease-specific outcomes or natural units of disease such as case detected, case prevented, a reduction of serum cholesterol (LDL-C), a reduction of blood pressure (mmHg), bone mineral density, disability avoided and life year gained (LYG). However, this approach is likely to be limited in comparing across different disease areas (Wanner and Hutton 1980, Drummond 1998, Drummond et al. 2005). Consequently, the CEA is classified as a technical efficiency measure (Shiell et al. 2002, National Information Center on Health Services Research and Health Care Technology 2016).

A cost-utility analysis (CUA) is based on the principal of extra-welfare (Brouwer et al. 2008). The CUA is a similar concept to the CEA, yet this method compares between costs and utility-based outcome measurement as quality-adjusted life years (QALYs). The QALY accommodates both life years (quantity gained) and a quality of life (quality gained) and is the life year gained yielded from the intervention, adjusted by preferences for health outcomes of individuals on different health states. This method is classified as a full health economic evaluation. Some studies suggest the CUA is a subdivision of the CEA. Due to the outcomes of the CUA, it is classed as a generic measure and this allows the studies based on this method to compare a wide range of different disease areas (Drummond 1998, Drummond et al. 2005, Gray et al. 2012). Thus, this method is classed as a technical efficiency measure and an allocative efficiency measure (Shiell et al. 2002, National Information Centre on Health Services Research and Health Care Technology 2016). However, a study by Jakubiak-Lasocka and Jakubczyk (2014) reported the CUA

method is more time and resource consuming when compared with using the CEA method.

A cost-benefit analysis (CBA) is a comparison of costs and outcomes approach in which the outcomes are defined in monetary terms. The principle of this method is based on social welfare (Brouwer et al. 2008) and also facilitates an allocative efficiency (Shiell et al. 2002, National Information Centre on Health Services Research and Health Care Technology 2016). This approach can then be used to compare a wide range of scopes, such as different programmes and different diseases and not focused only on healthcare aspects. A full health economic evaluation also covers the CBA method. However, the major restraint is that it is not simple to transform effects into monetary terms (Drummond 1998, Drummond et al. 2005).

The different methods of health economic evaluations and comparisons of the strengths and weaknesses of each method are presented in the following Table 3.4 and Table 3.5, respectively.

Table 3.4: **Methods of health economic evaluations**

	Costs	**Outcomes**
Cost-minimisation analysis (CMA)	Monetary units	Equivalent outcomes
Cost-effectiveness analysis (CEA)	Monetary units	Health outcomes in natural units (e.g. case prevented, mmHg blood pressure reduction, case successfully treated, case detected and LYG)
Cost-utility analysis (CUA)	Monetary units	Utility-based outcomes (e.g. QALYs and DALYs)
Cost-benefit analysis (CBA)	Monetary units	Monetary units

Table 3.5: **Comparison of the strengths and weaknesses of each method of health economic evaluation**

	Strength	Weakness
Cost-minimisation analysis (CMA)	● Outcomes of two or amongst treatments are equivalent ● The comparison is based on only different costs of different interventions ● Favouring in lower costs	● Rare circumstances of an assumption whether outcomes of interventions are equivalent ● Not a full health economic evaluation ● Not appropriate to study in health economic evaluations
Cost-effectiveness analysis (CEA)	● A full health economic evaluation ● Based on extra-welfare ● A technical efficiency measure ● The method is widely used in health economic evaluations ● Outcomes are measured as effectiveness/efficacy for clinical evaluations (disease-specific outcomes or natural units) ● Less resource- and time-consuming compared with the CUA ● An interpretation of the results is a cost-effectiveness ratio (CER) and an incremental cost-effectiveness ratio (ICER) which ICER is the most widely used	● Limits to compare across different disease areas.

	Strength	Weakness
	● A minimised ICER is favourable	
Cost-utility analysis (CUA)	● A full health economic evaluation ● Based on extra-welfare ● A technical efficiency and allocative efficiency ● The method is commonly used in health economic evaluations ● Outcomes are measured in terms of QALYs ● Allows comparison across different disease areas ● Interpreting the result in terms of CER and ICER which ICER is the most commonly uses ● A lower ICER is favourable	● More resource- and time-consuming ● The method is mainly based on a questionnaire for measuring utility which might have over- or under-estimate utility weights
Cost-benefit analysis (CBA)	● A full health economic evaluation ● Based on social welfare ● An allocative efficiency measure ● Allows comparison to a wide range of areas such as programmes, diseases ● Results are interpreted in terms of a cost to benefit ratio approach or a net benefit approach	● The difficulty for translating effects to monetary terms

In summary, to measure the most cost-effective treatment between risperidone-treated BPSD patients and olanzapine-treated BSPD patients, a cost-utility analysis was chosen for this study. The reasons were that an outcome of this study is measured in terms of the quality-adjusted life year (QALY) which was most frequently used in health economic evaluations and also allowed the comparison with a wide range of disease areas. In essence, the CUA was also recommended by the HITAP in Thailand for health economic evaluations (The Health Intervention and Technology Assessment Program 2009, The Health Intervention and Technology Assessment Program 2014).

Analysing the cost-effectiveness of a new treatment by comparison with a current treatment was based on an incremental analysis which uses differences in costs (incremental costs) and differences in outcomes (incremental outcomes) (Drummond et al. 2005, Gray et al. 2012). The result could possibly be in the four quadrants based on the cost-effectiveness plane (see Chapter 2, section 2.5).

Where the new treatment was more costly than the current treatment and the outcome of the new treatment was also better than the existing treatment, it was necessary to perform a trade-off which would provide valuable information associated with an incremental cost relative to an incremental outcome or an incremental-effectiveness ratio (ICER). This would help decision-makers in their judgement of those interventions, on the basis of a cost-effective threshold, (CE threshold), of a country-specific data. Indeed, if the ICER was greater than the CE threshold, the new treatment was not considered to be cost-effective when compared with the current treatment.

3.5.1 Base-case analysis

At a base case or reference case analysis, the result of the cost-utility analysis was 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) (see the equation in section 3.3.2).

Following conventions used in policy making in Thailand, the CE threshold was set at THB 160,000 per QALY as a cut-point to consider with regards to a cost-effectiveness strategy which was defined by the Sub-committee of the NLEM of Thailand (Teerawattananon 2018). Thus, this value was exercised in this thesis as the CE threshold.

3.5.2 Sensitivity analyses

Using the model-based on health economic evaluations, there was the uncertainty of the variables which were used in the model. Therefore, to consider the responsiveness of results to change in different parameters, sensitivity analyses needed to be conducted to test robustness of the results (see more details in Chapter 7). Both methods of a deterministic sensitivity analysis, using a one-way sensitivity analysis, and a probabilistic sensitivity analysis, (PSA), using a Monte Carlo simulation of simulating 1,000 times of parameters, were conducted in this study.

In this thesis, the results from the PSA were presented by the cost-effectiveness acceptability curve, (CEAC). The CEAC was constructed based on the net monetary benefit approach. A range of willingness to pay, (ceiling ratio), for an additional QALY gained, was used to draw the proportion of estimating the net benefit values at the given willingness to pay, (WTP), threshold. The willingness to pay was the valuation of health benefit in monetary terms. More explicitly, this was that the maximum price which a consumer will definitely pay for the health benefit (Bertram et al. 2016). For evaluating in this thesis, the willingness to pay was defined as a range between THB 0 - 500,000.

In addition, the CEAC was correlated between a range of cost-effectiveness thresholds or willingness to pay thresholds, (the horizontal axis, X), and the probability of the treatment being cost-effective at that threshold (the vertical axis, Y). The net monetary benefit, (NMB), method was calculated following the equation presents below (Drummond et al. 2005).

$$NMB = R_T * (E_A - E_B) - (C_A - C_B)$$

where: NMB was the net monetary benefit

R_T was a willingness to pay (WTP) per unit of increased effectiveness (QALY)

C_A was the cost of the intervention of interest

C_B was the cost of current treatment

E_A was the effectiveness of an intervention of interest

E_B was the effectiveness of current treatment

By interpreting if the net benefit values were greater than zero, these indicated if the treatment of interest was more cost-effective than the current treatment (Drummond et al. 2005). Further, a curve deriving from this approach would present the probability of the cost-effectiveness of the treatment of interest compared with the current treatment, by incorporating the uncertainty of sampling the variation of costs and outcomes and the uncertainty of an acceptable level of cost-effectiveness ratio for a decision maker (Fenwick, Claxton and Sculpher 2001, Briggs, O'Brien and Blackhouse 2002, Fenwick and Byford 2005).

Although the thesis was defined the CE threshold at THB 160,000 per QALY based on the Sub-committee of the NLEM of Thailand, the study by Thavorncharoensap et al. (2013) suggested a range of the willingness to pay for an additional QALY in Thailand was between THB 59,000-285,000 as reported in 2008. Hence, these values, adjusted to 2017 currencies by the Consumer Price Index, (CPI), of Thailand, would be applied in this thesis to consider by what price society would be willing to pay to gain an additional QALY.

From the sensitivity analyses, different assumptions of inputs used in an analysis were applied to test the sensitivity of the results and conclusions to such alterations. The sensitivity analyses also incorporated a wide range of plausible parameters for assessing, then these would be able to support more confidence of the results. Further, the sensitivity analyses had benefits to quantify parameters which had the potential impacts on the degree of accuracy of the results, leading to more appropriate decisions of the decision-makers.

3.6 Comparison of the research relative to the existing literature

According to the comprehensive literature search between 1995 to June 2015 (see Chapter 2, section 2.5.1), the findings found only two published studies conducting associated with health economic evaluations of atypical antipsychotics for dementia or Alzheimer's disease. To position this study relative to those two existing studies, the comparison has been summarised in the following Table 3.6. Whilst the strengths and limitations of each published studies are also outlined in Table 3.7.

Table 3.6: **Comparisons of this study relative to other published studies on the cost-effectiveness of atypical antipsychotics in the treatment of dementia or Alzheimer's disease**

	Rosenheck et al. (2007)	**Kirbach et al. (2008)**	**This study**
Type of economic evaluation	● Cost-benefit analysis	● Cost-utility analysis	● Cost-utility analysis
Economic evaluation approach	● Alongside a clinical trial	● Model-based economic evaluation (Markov model)	● Model-based economic evaluation
The study population	● Eligible patients with AD type of dementia, who were ambulatory outpatients living at home or in assisted living, with MMSE scores from 5-26 with hallucination, delusion, aggression, or agitation	● US adults aged 65 years and over with AD with psychosis and/or agitation	● Thai adults aged 60 years and over with BPSD

	Rosenheck et al. (2007)	Kirbach et al. (2008)	This study
Intervention and Comparator	● Risperidone vs olanzapine vs quetiapine vs placebo	● Olanzapine vs no treatment	● Olanzapine vs risperidone
Costing data	● Primary data: total health care and medication costs based on follow-up for 9 months ● Costs data were based on proxy reports from patients' caregivers	● Secondary data: total costs (direct and indirect costs) ● Direct costs for patients with AD with low and high levels of NPI were based on costing data from a cross-sectional study (Murman et al. 2002) multiplied by the proportions of expenditures from study by Jonsson et al. (2006) ● Indirect costs for patients with AD with low and high levels of NPI were based on a cross-sectional study by Murman et al. (2002)	● Primary data: direct medical and direct non-medical costs, including adverse event- and relapse-associated costs based on a cross-sectional study
Utility data	● Primary data: Health Utilities Index Mark 3 (HUI:3) instrument based on follow-up for 9 months	● Secondary data and using utility data from Murman and Colenda (2005) adjusted by the information of	● Primary data: EQ-5D-5L instrument based on a cross-sectional study

	Rosenheck et al. (2007)	Kirbach et al. (2008)	This study
	● Utility weights were based on proxy reports from patients' caregivers ● Analysis required a single measure of HRQoL which reflected both health gains and health losses	olanzapine treatment from the schizophrenia study to extrapolate for changes in the health utility weights for olanzapine ● Utility weights were derived from examining the relationship between the Health Utilities Index (HUI) in patients with probable AD based on a cross-sectional study by Neumann et al. (1999) and cognition, behaviour and functioning; however, they were unpublished data	
Outcome	● QALYs gained	● QALYs gained	● QALYs gained
Time horizon and cycle length	● The follow-up for 9 months	● Over a 13-year time period with a 6-month cycle length	● Over a 5-year time period with a one-month cycle length
Perspective	● Economic perspective	● The US health system perspective	● A societal perspective

	Rosenheck et al. (2007)	Kirbach et al. (2008)	This study
Discount rates	● N/A	● At 3% of both costs and QALYs per annum	● At 3% of both costs and QALYs per annum

Abbreviations: AD, Alzheimer's disease; BPSD, behavioural and psychological symptoms of dementia; NPI, the Neuropsychiatric Inventory; HRQoL, Health-related Quality of Life; N/A, not applicable

Table 3.7: **Comparison strengths and limitations of published studies on the cost-effectiveness of atypical antipsychotics in the treatment of dementia or Alzheimer's disease**

	Strength	Limitation
Rosenheck et al. (2007)	● Large sample size ● Based on primary analysis which was follow-up for 9 months ● Based on highly controlled conditions ● This cost-benefit analysis was conducted in accompany with the CATIE-AD study	● A placebo did not reflect to real-world clinical practice which it was not offered as a treatment ● The 9-month continued original treatment might raise an issue concerning the accurate of the treatment ● A statistical power of the study, specially Phase 1-only results, might need to be a concern ● 80% of patients discontinued initially assigned treatments before 9 months ● Cost data were reported by caregivers
Kirbach et al. (2008)	● The first cost-utility analysis of olanzapine compared with	● Health utilities were derived from schizophrenia studies

	Strength	Limitation
	no treatment for patients with AD with agitation and psychosis in the US using a decision-analytic method	● There was a limitation of quality of studies associated with parameters used in the model.

In summary, to the researcher's best knowledge, this study is the first cost-effectiveness of atypical antipsychotic medications, (olanzapine and risperidone), in the treatment of Thai patients aged 60 years and over with BPSD based on a societal perspective. A decision-analytic model is used to predict the costs and outcomes over a period of 5 years with a one-month of each cycle length. The main outcome measure used was the cost per QALY gained, (or ICER). Costs data are also expressed as direct medical costs and direct non-medical costs and reported in 2017 Thai Baht (THB). In addition, both costs and QALYs are discounted at 3% per annum.

However, cost and utility data in this thesis are based on a cross-sectional study design. This can be helpful to supply results to answer the cost-effectiveness question of real clinical settings in Thailand. However, this approach is from a hypothesis-generating study and also limited by randomised comparisons. Data from this method should therefore be applied for designing further studies, namely larger confirmation studies. In addition, the interpretation of the results from this study needs to be viewed cautiously.

3.7 Ethical Considerations

The study required ethics committee approval before any data collection could begin. A formal submission was made to the Centre for Health and Social Care Research of Sheffield Hallam University in the UK and both hospitals in Thailand. Ethics approval was granted by the Human Research Ethics Committee of Thammasat University (Faculty

of Medicine) in Thailand, in full compliance with international standards such as the Declaration of Helsinki, The Belmont Report, CIOMS Guidelines and the International Practice (ICH-GCH), the Human Research Ethics Committee of Khon Kaen Rajanagarindra Psychiatric Hospital in Thailand as well as the Faculty Research Ethics Committee of Centre for Health and Social Care Research of Sheffield Hallam University in the UK. The ethical issues considered are described below:

1) Recruitment -The primary data collection was based on a cross-sectional study of patients with BPSD in Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital in Thailand. In the case that patients with dementia had difficulties in providing informed consent due to cognitive impairment, then caregivers, who had contact with these dementia patients, were approached to be the respondents to the survey on behalf of the patients.
2) Confidentiality - All data were anonymised and kept confidential. The names and the identities of the individuals were concealed and kept in a separate file from the main dataset for analysis. The data were kept securely and only used by the researcher.
3) Consent - This study was associated with the data collected from the patients and caregivers, so a consent form was applicable. However, participants could withdraw from the study at any time as needed.
4) Risks and benefits - Information was sought from patients and their caregivers on their treatment. Therefore, there were no risks, harmful and/or discomforts to the individuals associated with this study.

3.8 Conclusion

This study focuses more on the post-positivist ontological and epistemological assumptions by generating a model for health economic evaluation. The study also carries through five main steps, namely the defined scope of the evaluation, the model development, the cost analyses, the utility analyses, and the cost-utility analysis along

with sensitivity analyses. In addition, the questionnaires is conducted to explore costs and utility weights of behaviourally disturbed patients with dementia being treated with olanzapine or risperidone based on routinely delivered care in the Thai setting. Consequently, the following chapters will demonstrate research steps undertaken within each chapter in more details and also deal with the findings attained from these studies.

Chapter 4: Model development and application to health economic evaluation of the treatment with atypical antipsychotics for behavioural and psychological symptoms of dementia in Thailand

Abstract

Introduction: Atypical antipsychotics are widely used as a first-line pharmacological approach to treat patients with behavioural and psychological symptoms of dementia, even though these drugs are off-label use for those patients due to safety concerns. Currently, there is a lack of studies conducting economic evaluations of atypical antipsychotics for the treatment of BPSD patients, particularly economic evaluations using models. Hence, it is important to explore the existing model-based economic evaluations in dementia to apply for the treatment with atypical antipsychotic drugs of such patients.

Aim: The objective of this chapter is to develop the models and identify the most appropriate model for the economic evaluation for olanzapine treatment compared with risperidone treatment of BPSD within the Thai circumstances.

Methods: Model development of the BPSD treatment were based on the existing model-based economic evaluations reviewed through the comprehensive literature search from electronic databases between January 1975 and March 2018. The selected models were defined based on the selection criteria, including common use in the health economic evaluation in dementia, applying to the disease progression of dementia, and their applicability and feasibility in a Thai context. Parameters were then incorporated into each model. These also included cost and utility data of patients with BPSD in Thailand which were assigned to health states that were relevant to the condition of interest. The characteristics of the different models were then compared in order to justify the selection of the most appropriate model within a Thai setting for adoption in further evaluations.

Results: Three different model structures, including the CERAD-based conceptual framework (Neumann et al. 1999), the full time care, (FTC), conceptual framework using the predictive equation for predicting the time to FTC developed by Caro et al. (2001), and the FTC conceptual framework using the predictive equation for predicting the time to FTC developed by Rive et al. (2010), were considered for assessment. Based on a comprehensive assessment, the FTC conceptual framework using the predictive equation developed by Rive et al. (2010) was favoured as the most suitable model to apply for an assessment of health economics in comparison of olanzapine to risperidone for BPSD treatment in Thailand.

Conclusions: The model using the predictive equation for predicting the time to FTC developed by Rive et al. (2010) took into account core domains of dementia, including cognitive function, functional abilities and behaviour, in the predictive equation. This model had more benefits for estimating the disease progression of patients with dementia when compared with the other two models. Hence, the selected model will be applied for further cost-utility analysis of olanzapine compared with risperidone for behaviourally disturbed patients with dementia in Thailand.

4.1 Introduction

Due to the rapid increase in the number of people with dementia globally over the past few decades, many countries are concerned about the consequential losses because of this disease; in particular costs of medical and formal care, informal care costs, and social care costs (World Health Organization 2012). Therefore, several segments, namely pharmaceutical companies, WHO and the Alzheimer's Association, have attempted to develop new interventions against the disease progression and highlight the main points of the current situation (World Health Organization 2012, Alzheimer's Association 2019, Alzheimer's Society 2019). Clinical trials, modelling and risk factor predictions are examples of the improvements being undertaken to cope with the progression of the disease. The modelling technique is one of the most important approaches to simulate the progression of the disease in patients. This is widely used in studies associated with economic evaluations in dementia to predict the disease progression and estimate the long-term outcomes of the treatments (Hernandez et al. 2016). Consequently, model-based analyses have been continuously developed to provide more accurate information regarding costs and effectiveness of the treatments or technologies used in this disorder. This also assists the decision making for patients, caregivers as well as policy-makers in developing a response to dementia within their particular healthcare systems.

Behavioural and psychological symptoms of dementia are one of the most debilitating problems in people with dementia and have a significant economic impact to themselves, family members, caregivers, and healthcare systems. Currently, no treatments are approved by the US-FDA (Desai, Schwartz and Grossberg 2012, Zdanys et al. 2016). This leads to a wide range of drug options for the BPSD management. However, antipsychotic drugs, particularly atypical antipsychotics, are frequently used to treat these symptoms (Andrade and Radhakrishnan 2009, Chiabrando et al. 2010). Although these drugs are off-label treatment in dementia at this time, use of atypical antipsychotic drugs in patients with BPSD can be offered to control the symptoms, improve the quality of life

of both patients and caregivers and reduce the caregiver burden (Maher et al. 2011, Maglione, et al. 2011).

To date, health economic evaluation of atypical antipsychotics for the treatment of BPSD, especially using a model-based techniques, is not well examined. There was only one study that applied the decision-analytic model, (Markov model), to evaluate the cost-effectiveness of antipsychotic drugs for the treatment of agitation and psychosis in patients with Alzheimer's disease (Kirbach et al. 2008). That solitary study investigated the comparison of olanzapine versus no treatment. The health states of the model comprised mild, moderate, severe symptoms of Alzheimer's disease, nursing home as well as death. (Kirbach et al. 2008).

Due to a lack of model-based economic evaluation of atypical antipsychotic use in patients with BPSD, it is necessary to explore a range of model developments. As a result, the main purpose of this chapter is to develop the modelling in different schemes and identify the most appropriate model to apply for evaluating the treatment with olanzapine in comparison to risperidone, for patients with BPSD within a Thai context.

4.2 Methods

In this chapter, the model development to indicate the most suitable model for adopting in an economic evaluation of olanzapine compared with risperidone for the treatment of patients with BPSD in Thailand were conducted in the following three main steps as outlined below.

4.2.1 Step 1: Model development for health economic evaluation of the BPSD treatment in comparison of olanzapine to risperidone based on the literature review

To begin with the existing model-based economic evaluation of dementia was critically reviewed through the comprehensive literature search from electronic databases, including the MEDLINE and the Centre for Reviews and Dissemination of University of

York (CRD) - the Database of Abstracts of Reviews of Effects (DARE), the NHS Economic Evaluation Database (NHS EED), and the HTA database (HTA). The literature search covered the period from January 1975 up to March 2018 (see Chapter 2, section 2.6).

Based on the literature review, critical data was taken to develop models. Then the criteria for the model development was defined to consider the suitability and feasibility within a Thai setting as outlined below.

Inclusion criteria:

a) The model types are widely used in the health economic evaluation in dementia;
b) The model frameworks are generally applied for the disease progression of dementia; and
c) The development of the model is applicable and feasible to be employed within a Thai context.

Exclusion criteria:

a) The model is used to simulate patient-level data;
b) The model is used to estimate the events occurring over a short time period, (one year);
c) The model is used for specific purposed study or specific data sets;
d) Health states of the model included institutionalisation or nursing home.

To develop models in this thesis, the model frameworks that met the inclusion criteria were adopted to build the different models in the cost-utility analysis of olanzapine versus risperidone for the treatment of patients with BPSD in Thailand. In addition, for those models to functions, parameters were needed and these are outlined below.

a) Transition probabilities: The transition of patients to move from one state to another state of each model relied on probabilities which were derived from a literature review. If the probabilities were available from the published studies, these could be applied for the models. If the probabilities of transitioning were driven by the equations,

the factors used in calculating those equations were firstly considered from data of the Thai population or data collection in a Thai setting, in order to more closely reflect the actual circumstances of the routine clinical practice in Thailand. However, if data were not available from the Thai populations or Thai setting, data from published literature which were applicable and feasible to be used in the model were alternatively proposed.

b) Clinical effectiveness data of treatments: The effectiveness data of drug treatments, (olanzapine or risperidone), were also obtained from data based on a comprehensive literature search of published studies covered from 1994 up to July 2015 (see Chapter 2, section 2.4). If clinical data being assigned to the models were not provided by those reviewed studies, other studies relevant to the reviewed studies given clinical data be assigned to the models would be considered instead, such as Phase 1 outcomes from the clinical trials.

c) Cost data: The costing data of patients with BPSD and being treated with olanzapine or risperidone used in the developed models were direct medical costs and direct non-medical costs. These costs data were collected from patients and/or patients' caregivers from Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital in Thailand, at only one point in time during some point in 2017 by face-to-face interviews using a cost questionnaire. However, indirect costs, namely costs of productivity losses, were not included for cost data purposes because all patients were either not working or retired. In addition, this thesis also took into account adverse event-associated costs and relapse-associated costs due to atypical antipsychotic use for treating patients with BPSD. More details of cost analyses are presented in Chapter 5.

d) Utility values: The utility weights applied in the developed models were also derived from the data collection of patients with BPSD and treated with olanzapine or risperidone and/or the patients' caregivers from the two hospitals as indicated above. The data were also captured at only one point in time during some point in 2017 by face-to-face interviews using the EQ-5D-5L questionnaire. Furthermore, the individual responses to the questionnaire were then translated into the utility weights, (EQ-5D index utilities),

using the Thai value sets available for Thailand. More details of the utility analyses are presented in Chapter 6.

e) Perspective of the model: All developed models in this thesis were conducted from a societal viewpoint.

f) Time horizon and cycle length: A five-year time horizon was chosen for all developed models. This was because dementia is a chronically progressive disease and this also reflects the natural history of the disease. Additionally, a one month cycle length was also applied for all those models.

g) Discount rates: Both costs and health outcomes for all developed models were discounted using an annual rate at 3%. These rates were based on the recommendation of the guideline of health technology assessment in Thailand (The Health Intervention and Technology Assessment Program 2014).

From this step, the next steps were a comparison and a justification amongst those models to select the most appropriate model to apply for further analysis of an economic evaluation (in Chapter 7).

4.2.2 Step 2: Comparing the distinctive developed models

This step, the developed models were compared to find out the most advantageous model based on the following points:

a) Characteristics of the model structure of each model, (health states in the model);

b) Characteristics of the progression of the disease of each model, (the transition probabilities of changing health states of patients from one state to another state);

c) The clinical effectiveness data of the treatments which were applied in each model; and

d) The results of an economic evaluation of the treatment of patients with BPSD with olanzapine compared with risperidone based on the different models.

In addition, the findings from this step were used in the following step which was associated with a justification and decision of the most appropriate model.

4.2.3 Step 3: Justification and selecting the most suitable model for applying in the cost-utility analysis within a Thai setting

In this step, the considerations for making the decision to select the most appropriate model are outlined below:

a) The model was constructed to reflect the natural disease progression of dementia;

b) The model was commonly used in an economic evaluation in dementia;

c) Clinical effectiveness data used in the model was deemed to cover an assessment on all core domains relevant to the clinical course of dementia; and

d) The model was recently developed for the economic evaluation in dementia.

Finally, the most appropriate model was chosen based on all the previous steps as stated above in order to be adopted for further analysis of the cost-utility analysis of atypical antipsychotics for the treatment of patients with BPSD in Thailand.

4.3 Results

4.3.1 The model development for health economic evaluation of the BPSD treatment in comparison of olanzapine to risperidone based on the literature review

Based on a comprehensive literature search on model-based economic evaluation in dementia, (see Chapter 2, section 2.6.1), the findings of model frameworks and type of models from 40 articles have been summarised in the following Table 4.1.

Table 4.1: **Summary of the type of models and the model frameworks of model-based economic evaluation in dementia based on the comprehensive literature search**

Study	Markov model	The Discrete Event	Decision tree	Micro simulation	Statistical model	Model framework	Health States
Henke and Burchmore (1977)			/			Specific model	Nursing home placement and non-nursing home placement
Stewart, Phillips, and Dempsey (1998)	/					Specific model	Minimal, mild, moderate, severe, and dead
Fenn and Gray (1999)					/	Specific model	Mild, moderate and severe
Jonsson et al. (1999)	/					Specific model (based on Kungsholmen project)	MMSE=30-27, MMSE=26-21, MMSE=20-15, MMSE=14-10, MMSE=9-0 and death

Study	Markov model	The Discrete Event	Decision tree	Micro simulation	Statistical model	Model framework	Health States
Neumann et al. (1999)	/					CERAD	Mild (comm/NH), moderate (comm/NH), severe (comm/NH), and death
O' Brien et al. (1999)	/					Specific model	MMSE <10, MMSE=10-14, MMSE=15-20, MMSE=21-26, MMSE=27-30, and death
Getsios et al. (2001)	/					FTC framework (AHEAD)	Health states in the model: Pre-FTC, FTC, and death
McDonnell et al. (2001)					/	Specific model	Patient characteristics, clinical characteristics of disease, place of residence (living in community,

Study	Markov model	The Discrete Event	Decision tree	Micro simulation	Statistical model	Model framework	Health States
							home for the elderly, nursing home), and vital status of patients
Caro et al. (2002)	/					FTC framework (AHEAD)	Pre-FTC, FTC, and death
Garfield et al. (2002)	/					FTC framework (AHEAD)	Pre-FTC, FTC, and death
Ikeda, Yamada and Ikegami (2002)	/					CERAD	Mild, moderate, severe, and death
Migliaccio-Walle et al. (2003)	/					FTC framework (AHEAD)	Pre-FTC, FTC, and death
Ward et al. (2003)	/					FTC framework (AHEAD)	Pre-FTC, FTC, and death
Caro et al. (2004)	/					FTC framework	Pre-FTC, FTC, and death

Study	Markov model	The Discrete Event	Decision tree	Micro simulation	Statistical model	Model framework	Health States
						(AHEAD)	
Francois et al. (2004)	/					Memantine model	The multiplicity of three severity states, two physical dependencies, and two residence settings, and plus death
Jones, McCrone and Guilhaume (2004)	/					Memantine model	The multiplying of three severity states, two physical dependencies, and two residence settings, and plus death
Green et al. (2005)	/					FTC framework (AHEAD)	Pre-FTC, FTC, and death

Study	Markov model	The Discrete Event	Decision tree	Micro simulation	Statistical model	Model framework	Health States
Jonsson (2005)	/					Memantine model	The multiplicity of three severity states, two physical dependencies, and two residence settings, plus death
Antonanzas et al. (2006)	/					Memantine model	The multiplying of three severities, two dependencies, plus death
Gagnon et al. (2007)	/					Memantine model	The multiplying of two severities, two dependencies, and death
Teipel et al. (2007)	/					Specific model	Mild, mild-moderate, moderate, severe and death

Study	Markov model	The Discrete Event	Decision tree	Micro simulation	Statistical model	Model framework	Health States
						(based on Kungsholmen project)	
Weycker et al. (2007)				/		CERAD-SIB	Profound and terminal (MMSE=0-4), severe (MMSE=5-9), moderate (MMSE=10-14), and questionable/ mild (MMSE=15-23) and living in community
Fuh and Wang (2008)	/					CERAD	Mild, moderate, severe, and death
Kirbach et al. (2008)	/					CERAD	Mild, moderate, severe, institutionalized, and death

Study	Markov model	The Discrete Event	Decision tree	Micro simulation	Statistical model	Model framework	Health States
							(The institutionalised was classified separately as a health state)
Lopes-Bastida et al. (2009)	/					CERAD	Mild, moderate, severe, and death
Suh (2009)	/					FTC framework (AHEAD)	Pre-FTC, FTC, and death
Wong et al. (2009)			/			Specific model	No adverse events and adverse events
Getsios et al. (2010)		/				Patient-level data	Update of disease severity, treatment status, physician visit, death, and end of model

Study	Markov model	The Discrete Event	Decision tree	Micro simulation	Statistical model	Model framework	Health States
Guo et al. (2010)		/				Patient-level data	Update of disease severity, treatment status, physician visit, death, and end of model
Nagy et al. (2010)					/	MMSE-ADL model	-MMSE model based on MMSE -MMSE-ADL model based on MMSE and ADL
Rive et al. (2010)	/					FTC framework (based on a new predictive equation)	Pre-FTC, FTC and death
Hoogveldt et al. (2011)	/					Memantine model	The multiple of two severities and two

Study	Markov model	The Discrete Event	Decision tree	Micro simulation	Statistical model	Model framework	Health States
							dependence states, plus death
Lachaine et al. (2011)	/					Specific model (based on Lopez et al.)	Non-institutionalised, institutionalized, and death
Hartz et al. (2012)		/				Patient-level data	Update of disease severity, treatment status, physician visit, death, and end of model
Pfeil, Kressig and Szucs (2012)	/					Specific model (based on Lachaine et al.)	Home, nursing home, and decease
Rive et al. (2012)	/					FTC framework	Pre-FTC, FTC and death

Study	Markov model	The Discrete Event	Decision tree	Micro simulation	Statistical model	Model framework	Health States
						(based on a new predictive equation)	
Touchon et al. (2014)	/					Specific model (based on Lachaine et al.)	Non-institutionalised, institutionalised, and deceased
Hu et al. (2015)	/					Specific model	The multiplicity of two severities, two functional abilities, two the presence of agitation/aggression, plus death
Thibault et al. (2015)		/				Patient-level data	Update of disease severity, treatment status, physician

Study	Markov model	The Discrete Event	Decision tree	Micro simulation	Statistical model	Model framework	Health States
							visit, death, and end of model
Zala, Chan and McCrone (2017)	/					FTC framework (based on a new predictive equation)	Pre-FTC, FTC and death
Total	**30**	**4**	**2**	**1**	**3**		

* (/) refers to the type of the model-based economic evaluation of each study

Abbreviation: Activity of Daily Living (ADL), Assessment of Health Economics in Alzheimer's Disease (AHEAD), Consortium to Establish a Registry in Alzheimer's Disease (CERAD), Community (Comm), Full-time care (FTC), Mini-Mental State Examination (MMSE), Nursing home (NH), Severe Impairment Battery (SIB)

As the data shows above, a Markov model was the commonest model type which had been used in the health economic evaluations in dementia, particularly Alzheimer's disease, accounting for 75% of all studies. Most model structures built to predict the disease progression were based on the FTC and the CERAD conceptual frameworks accounting for 11 (27.5%), and 5 (12.5%) studies, respectively.

According to the defined inclusion criteria as introduced above, (see section 4.2.1), and the literature review, the FTC conceptual framework and the CERAD conceptual framework using the Markov-based type were then identified to build the models in this thesis. There were three possible models, which met the inclusion criteria which were selected and developed for simulating the disease progression and applying the cost-utility analysis of olanzapine compared with risperidone in the treatment of patients with BPSD in Thailand. These models are outlined below.

- The first model was based on the Consortium to Establish a Registry in Alzheimer's Disease database, (CERAD-based model framework), (Neumann et al. 1999). The CERAD-based model used severity levels of cognitive function to define the health status of the model and predict the disease progression of patients. The Clinical Dementia Rating, (CDR), scale was used to assess the levels of disease severity. Thus, the health states of this CERAD-based model consisted of mild, moderate, severe, as well as death. The transition probabilities were also derived data from the CERAD database (Neumann et al. 1999).

- The second model was constructed based on the full-time care, (FTC), conceptual framework which was used to predict the patient's disease progression until requiring FTC. This model was constructed on the basis of an Assessment of Health Economics in Alzheimer's Disease, (AHEAD), using the predictive equation developed by Caro et al. (2001). The health states of the model consisted of not requiring FTC (Pre-FTC), FTC and

death. The FTC state was defined as the patient's dependency status when care and supervision was required for the greater part of each day, regardless of the location of care (Caro et al. 2001). The transition from the Pre-FTC to FTC state was driven by a predictive equation from data obtained from the published study by Stern et al. (1997). The patient's characteristics, including the presence of extrapyramidal symptoms (EPSs), the presence of psychotic symptoms, age at onset of disease, duration of illness and cognitive score, (as measured by modified Mini-Mental State examination, mMMS), were significant factors to predict the need for FTC of the predictive equation. Estimating the transition to death was dependent on female sex, the presence of EPS, cognitive function and the duration of illness (Stern et al. 1997, Caro et al. 2001).

- The third model was conceptualised based on the FTC conceptual framework using a new predictive equation for predicting the time to FTC which was developed by Rive et al. (2010). The health sates comprised of Pre-FTC, FTC and death. The significant factors needed to predict the time to FTC are as follows: cognitive function, (as measure by ADAS-cog), functional ability, (as measured by ADCS-ADL), and behaviour, (as measured by NPI).

Table 4.2 shows the summary of possible models classified by model frameworks which have been used to develop the models for health economic evaluation of BPSD treatment in comparison of olanzapine to risperidone in this thesis.

Table 4.2: **The possible models used for developing models for an economic evaluation of BPSD treatment in comparison of olanzapine to risperidone based on the inclusion criteria of the thesis, classified by model frameworks**

	CERAD framework (Neumann et al. 1999)	**FTC framework using the equation for predicting the time to FTC developed by Caro et al. (2001)**	**FTC framework using the equation for predicting the time to FTC developed by Rive et al. (2010)**
Model type	Markov model	Markov model	Markov model
Health states	Mild, moderate, severe and death	Pre-FTC, FTC and death	Pre-FTC, FTC and death
Model concept	The course of disease progression through stages of the disease severity	The need for FTC	The need for FTC
Disease progression	Transition probabilities between health states were estimated from the CERAD database, in the US (Neumann et al. 1999)	A predictive equation for predicting the time to FTC developed by Caro et al. (2001)	A predictive equation for predicting the time to FTC developed by Rive et al. (2010)
Risk factors of progression to FTC	N/A	The presence of EPS, the presence of psychotic symptoms, age at onset of disease, duration of illness and cognitive score (as measured by mMMS)	ADAS-cog, ADCS-ADL and NPI

Abbreviation: Assessment of Health Economics in Alzheimer's Disease (AHEAD), Alzheimer's Disease Assessment Scale-Cognitive Function (ADAS-cog), Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), Clinical Dementia Rating (CDR), Consortium to Establish a Registry in Alzheimer's Disease (CERAD), Extrapyramidal symptoms (EPS), Full-time care (FTC), Not applicable (N/A)

Although there were other studies that used the Markov model for health economic evaluation in dementia, the model frameworks were constructed by incorporating nursing home or institutionalisation as the health states of the model (Francois et al. 2004, Jones, McCrone and Guilhaume 2004, Lachaine et al. 2011, Pfeil, Kressig and Szucs 2012, Touchoun et al. 2014). These might be inappropriate in a Thai context because the institutionalised setting or nursing home provision are not generally provided for the care process of people with dementia in Thailand. Thus, model frameworks, including nursing home or institutionalisation, were not considered in developing the models in this thesis.

In addition, the developed models based on the defined inclusion criteria are displayed in the following sections.

4.3.2 Characteristics of the developed models based on the inclusion criteria in this thesis

According to the inclusion criteria, three different models were developed in this thesis, including the CERAD-based framework (Neumann et al. 1999), the FTC conceptual framework using the predictive equation for predicting the time to FTC developed by Caro et al. (2001) and the FTC conceptual framework using the predictive equation for predicting the time to FTC developed by Rive et al. (2010). The next section then goes on to more details of each developed model.

4.3.2.1 Model 1: The model based on the Consortium to Establish a Registry in Alzheimer's Disease, (CERAD), conceptual framework

The structure and concept of the model which were developed on the basis of the CERAD framework from the study by Neumann et al. (1999), data inputs of this model type, (including transition probabilities, clinical effectiveness data of drug treatments, costs and utility weights), results of the cost-utility analysis and limitation of the model type are subsequently outlined.

4.3.2.1.1 Model structure and model concept of the CERAD-based model

According to the CERAD-based framework, the structure and model concept of the developed model in this thesis are displayed below.

4.3.2.1.1.1 The model structure of the CERAD-based model

The model was constructed to simulate the natural history of Alzheimer's patients across the different progressive disease states, in the form of a Markov model. The health states were developed to characterise the progress of the disease and were classified into mild, moderate, and severe states, according to the Clinical Dementia Rating scales, (CDR). These were a mild stage (CDR = 0.5 or 1), moderate stage (CDR =2), severe stage (CDR = 3), as well as the health state of death (Neumann et al. 1999).

However, in this thesis the Thai version of the Mini-mental State Examination (TMSE) was used as a measure of cognitive function. The test was developed from the standard Mini Mental State Examination (MMSE) and was more appropriate to the Thai population. The study by the Institute of geriatric medicine of the Ministry of Public Health in Thailand (2008) reported that either the TMSE test or the MMSE test did not show a significant difference in the scores of a cognitive test (Institute of Geriatric Medicine 2008). Then, the different levels of the disease severity of cognitive function as measured by the TMSE scores were implied to be the same value as the MMSE scores. These scores classified the severity

levels as follows: a score of 21-26 was associated with a mild stage, a score of 10-20 with a moderate stage, and a score of <10 with a severe stage. For the purpose of this thesis, the mapping between MMSE score and CDR scale was also conducted to define the severity levels of the patient's cognitive function following these parameters: MMSE=21-26 for mild (CDR scales of 0.5 or 1.0), MMSE=10-20 for moderate (a CDR scale of 2.0) and MMSE<10 for severe stages (a CDR scale of 3.0) (Perneczky et al. 2006, Bond et al. 2012). In addition, the original model structure was initially developed by Neumann et al. (1999). Thereafter, the structure of such models was adapted to several studies in undertaking economic evaluations of Alzheimer's disease (Ikeda, Yamada and Ikegami 2002, Fuh and Wang 2008, Lopez-Bastida et al. 2009).

However, the treatment of patients with BPSD was the focus of this thesis. Therefore, BPSD associated with patients requiring atypical antipsychotic drugs for their treatment were also incorporated into the health states of the model. The model structure outline is depicted in the following Figure 4.1.

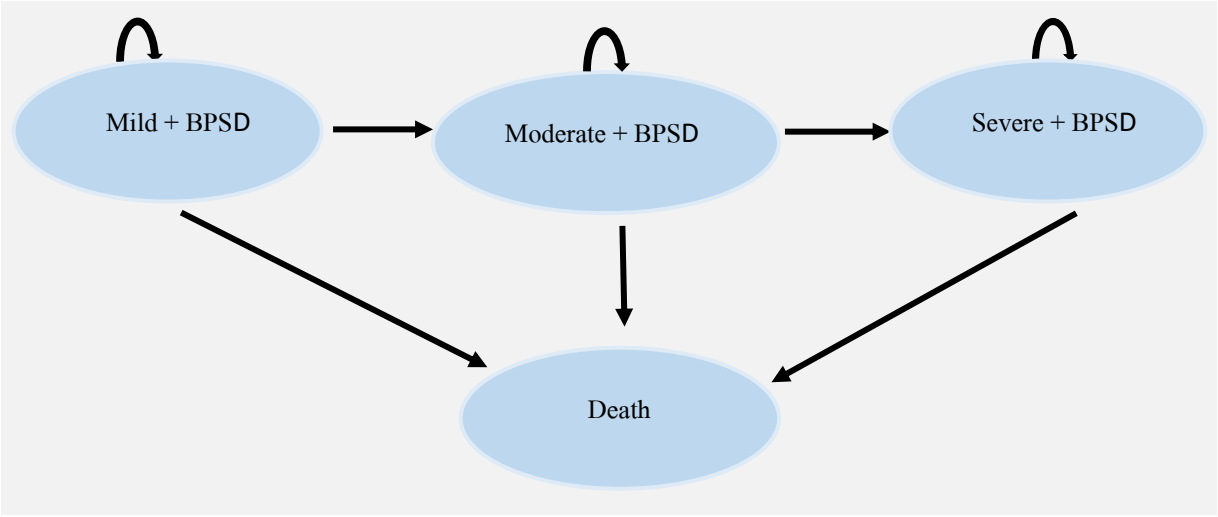


Figure 4.1: **Outline view of the model structure based on the CERAD framework**

4.3.2.1.1.2 The model concept and flow of the CERAD-based model

At the beginning of the decision node, patients faced the possibility of treatment with one of the two available choices of drugs, either olanzapine or risperidone. Initially, the patient began using only one of the two drug therapies. As patients receiving treatments, there were four possible health states which the patients could be in mild, moderate, severe, or death. In this decision-analytic model, all patients were assumed to start at time zero. Consequently, the initial probabilities for the Markov states were 1, 0, 0 and 0 for the four health states associated with mild, moderate and severe, as well as death, respectively. In each cycle length of the model, patients could have a movement between these possible health states and this process occurred repeatedly. The transition of patients' moving from one state to another depended upon the probabilities to simulate the progression of the disease through health states in the model over time. Thus, any change to another state was determined by the transition probabilities based on the effects of drug treatments.

The concept behind the model structure was demonstrated as follows:

- From the mild with BPSD state, there were four possible transition states of the severity of the disease, these being mild with BPSD, moderate with BPSD, severe with BPSD, and death. Some patients remained in the mild with BPSD state, whereas the rest moved through the other three possible pathway combinations of moderate with BPSD, severe with BPSD, and death as the disease progressed;
- From the moderate with BPSD state, some patients moved from this to severe with BPSD and death, whereas others remained in the moderate with BPSD state;
- From the severe with BPSD state, some patients remained in this state whilst others progressed to the death state; and

- Death state was the absorbing state.

Further, the transition from the more severe disease stages back to the less severe stages was not allowed for in the model in this thesis. The Markov model was constructed to simulate patients' progression through the levels of severity of cognitive function and to predict the costs and outcomes of the disease progression over time. As the cohorts cycle through the Markov model until the time horizon was reached, the costs and outcomes were accumulated for each cycle which then used to compute the incremental costs per quality-adjusted life year gained over a five-year time horizon, covering disease progression and reflecting the natural history of the disease. A societal perspective was the viewpoint of this model. Both costs and outcomes were discounted at 3% per annum.

4.3.2.1.2 Data inputs of the model based on the CERAD framework

In this thesis, the main parameters required for the developed model based on the CERAD framework are demonstrated below.

4.3.2.1.2.1 Transition probabilities of the model based on the CERAD framework

The transition probabilities for this model were retrieved from the published study conducted by Neumann et al. (2001) based on data from a Consortium to Establish a Registry for Alzheimer's Disease, (CERAD), cohort, the longitudinal cohort study in 1,145 patients from 22 medical centres in the US between 1986 and 1995 (Morris et al. 1989).
The Markov cycle of this study was defined as one month. However, the existing transition probabilities based on the CERAD database were expressed in the annual probabilities. Thus, the annual probabilities were converted to one-month transition probabilities according to the cycle length of the model.

Based on the longitudinal study, the Cache County Dementia Progression Study examined 335 cases of possible or probable Alzheimer's disease and found that the correlation of the neuropsychiatric symptoms, (NPS), were associated with the progression to severe

Alzheimer's disease and death (Peters et al. 2015). Thus, the transition probabilities between health states in this model were adjusted by the hazard ratios of behavioural disturbances, as assessed by the Behavioural Rating Scale for Dementia score, (BRSD), based on the data from the previous literature (Neumann et al. 2001).

As the hazard ratios were the ratio of the rate it was not possible to apply these values directly for the transition probabilities or risks. On the basis of definitions, rates were the instantaneous potential for the occurrence of an event, indicated per the number of patients at risk. The value of rates varies from zero to infinity. As part of the probabilities, these were the values, describing the tendency of an event occurring over the given time period. The possible value was as between 0 and 1 (Briggs, Claxton and Sculpher 2011, Gray et al. 2012).

For this reason, the functions used to convert between rates and probabilities were needed. Hence, the annual probabilities were initially transformed to the rates and adjusted by the behavioural symptoms-related hazard ratio. The rates were ultimately converted back to the monthly probabilities. The relation between rate and probability and the conversion from rate to probability and vice versa were provided below (Sonnenberg and Beck 1993).

The conversion from rate to probability was calculated by:

$$p = 1\text{- } \exp^{(-rt)}$$

where p was the probability,

r was the rate,

and t was the time period of interest.

Alternately, the conversion from probability to rate was produced by:

$$r = \frac{-[\ln(1-p)]}{t}$$

where r was the rate,

p was the probability,

and t was the time period of interest.

The estimated monthly transition probabilities, adjusted by the hazard ratios for behavioural symptoms, used to simulate the disease progression in the model is presented in Table 4.3.

Table 4.3: **Estimated monthly transition probabilities adjusted by the hazard ratios for behavioural symptoms from the CERAD cohort (Neumann et al. 2001)**

Monthly transition probabilities (stage to stage)	Value
Mild + BPSD to Mild + BPSD	# *
Mild + BPSD to Moderate + BPSD	0.04216
Mild + BPSD to Severe + BPSD	0.00610
Mild + BPSD to Dead	0.00090
Moderate + BPSD to Moderate + BPSD	# *
Moderate + BPSD to Severe + BPSD	0.03691
Moderate + BPSD to Dead	0.00421
Severe + BPSD to Severe + BPSD	# *
Severe + BPSD to Dead	0.01837

* The residual (#) refers to the remaining probability

In this decision-analytic model, all patients were assumed to start at time zero in a mild state. The probabilities were used to define the transitions amongst the possible events during a cycle. For example, the transition probabilities of moving within a severe state and moving from a severe state to death were # and 0.01837 respectively.

4.3.2.1.2.2 Clinical effectiveness data of olanzapine and risperidone treatments

To date, no drugs have US-FDA approval for the treatment of behavioural and psychological symptoms of dementia or non-cognitive symptoms. Generally, antipsychotics are widely used to treat Alzheimer's patients with agitation, aggression or psychosis (Leeuwen E et al. 2018). These drugs are also recommended for individuals with persistent symptoms. Several

previous studies indicated that the patients with neuropsychiatric symptoms had a shorter survival time from mild dementia to severe dementia than those without symptoms (Cohen-Mansfield et al. 1999, Peters et al. 2015). Thus, the assumption of this study was that decreasing the neuropsychiatric symptoms was associated with delaying the more severe states of patients with dementia.

The effectiveness data of this thesis were adopted from the large clinical trial- the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease, (CATIE-AD), study. This trial examined the effectiveness of atypical antipsychotics in outpatients with Alzheimer's disease between 2001 and 2004, a double-blind, placebo-controlled trial comprising 421 outpatients with agitation, aggression, or psychosis, across 42 sites in the US and follow-up to 36 weeks. The primary outcome was the time to the discontinuation of treatment for any reason, whereas the improvement on the Clinical Global Impression of Change (CGI-C) score at 12 weeks was the main secondary outcome. The average medication doses of olanzapine and risperidone in this study were 5.5 mg and 1 mg per day, respectively.

The CGI-C score at 12 weeks showed that at least minimal progress with continued use of olanzapine was an 11.00% increase in score compared with the placebo. Also, this was found to be 8.00% of risperidone relative to the placebo (Schneider et al. 2006). As a result, this study used the change in the CGI-C score as the clinical effectiveness of medications, to predict the long-term outcomes from the treatments with each drug (olanzapine or risperidone).

The neuropsychiatric symptoms also had an association with the mortality in patients with Alzheimer's disease (Cohen-Mansfield et al. 1999, Peters et al. 2015). As Kales et al. (2012) suggested, a retrospective study in 33,604 patients with dementia based on the national data of Veterans Affairs between 1999 and 2008, olanzapine treated patients had lower mortality

rates than risperidone treated patients (RR 0.99, 95% CI 0.89–1.10), but it was not statistically significant. Then, the mortality rates between the two drugs were not included in the model.

Further, the tendency of patients with Alzheimer's disease with more severe neuropsychiatric symptoms, in particular, agitation, aggression, or psychosis, respond well to long-term antipsychotic treatment (Leeuwen E et al. 2018). Consequently, the assumption of this thesis was that drug effects were assumed to be constant over a five-year time horizon. The effectiveness data of olanzapine and risperidone used in the model is as described in Table 4.4.

Table 4.4: **The clinical effectiveness data of olanzapine and risperidone for the CERAD-based model**

Effectiveness data (CGI-C score change compared with placebo)	Value	Reference
Risperidone (mean dose 1.0 mg per day)	8.00%	Schneider et al. (2006)
Olanzapine (mean dose 5.5 mg per day)	11.00%	Schneider et al. (2006)

4.3.2.1.2.3 Costs of patients with behavioural and psychological symptoms of dementia and being treated with atypical antipsychotics (olanzapine and risperidone) based on the data collected in Thailand

A societal perspective was used in the study. The cost data were retrieved from two hospitals in Thailand: Thammasat University Hospital, which is located in Pathum Thani province and is an Excellence care centre, and Khon Kaen Rajanagarindra Psychiatric Hospital, a psychiatric hospital which is located in Khon Kaen province, is a tertiary care centre providing patient care covering four provinces in the Northeast region of Thailand.

For this thesis the cost data of patients with BPSD and receiving olanzapine or risperidone took into account only direct costs, including direct medical costs and direct non-medical costs, were used as the cost parameters in the model. The indirect costs, indicating the cost of illness and loss of productivity, were not included in this study because all patients were either not working or retired. During the course of treatment, patients with BPSD were expected to consume different levels of costs. The data of medical costs included the drug prices, (risperidone and olanzapine), for the treatment of BPSD, hospitalisation-associated costs, costs of treating drug-induced adverse events, costs of drug-associated relapse, additional costs for the treatments associated with this illness, and costs of comorbidity conditions. The direct non-medical care costs covered travel, additional food, accommodation, costs due to other treatment resources, paid caregivers, and costs of informal care.

Cost data were obtained from patients and/or caregivers participating in the two phases: Phase I (from February to March 2017) and Phase II (between October and November 2017). Briefly, the inclusion criteria of patients who were recruited in this thesis are described below:

1) Patients who had been diagnosed with Dementia or Alzheimer's disease and being on olanzapine or risperidone for at least the last two months, and aged 60 years and above;
2) Caregivers or partners defined as the person who had lived with or visited for caregiving for at least eight hours per week over three days or more per week for the last two months, were requested to contribute the assessment. Patients who did not have a partner or caregivers and were unable to answer the questionnaire on their own were excluded.

Cross-sectional data were collected on a sample of 82 patients and/or caregivers in a Thai setting, from the two hospitals as stated above, using face-to-face interviews to complete a dataset questionnaire. There were 41 patients of each of the risperidone and olanzapine groups. In addition, a total of 98.78% of the part of the questionnaire which focused on cost data were completed by the primary caregivers as proxy respondents in this study, (see more details in Chapter 5, in section 5.3.1).

All costs in this study were expressed in Thai Baht at 2017 values, (1£ =THB 45). The estimated costs before 2017 were adjusted by using the Thailand Consumer Price Index based on the health components, (Bureau of Trade and Economic Indices of the Ministry of Commerce Thailand, 2018). The monthly cost parameters for the model are presented in Table 4.5.

Table 4.5: **Monthly cost parameters for the model, calculated based on data from Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital, Thailand, in Thai Baht (THB) at 2017 values**

Cost Assumptions	Value [mean (SD)]	Reference
By health state		
Risperidone:		
Mild + BPSD	41,444.22 (17,037.35)	Primary collected data
Moderate + BPSD	46,470.29 (11,607.73)	Primary collected data
Severe + BPSD	53,038.90 (11,918.14)	Primary collected data
Olanzapine:		
Mild + BPSD	41,901.85 (16,879.63)	Primary collected data
Moderate + BPSD	48,368.34 (16,228.88)	Primary collected data
Severe + BPSD	52,901.64 (18,029.26)	Primary collected data

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

4.3.2.1.2.4 Utility weights of patients with behavioural and psychological symptoms of dementia and being treated with atypical antipsychotics, (olanzapine and risperidone), based on the data collected in Thailand

The quality-adjusted life year (QALY), a measure of quantity and quality of life (QoL), were used as the outcome measurement in this thesis. Then utility weights of an individual's preference-based specific health states were required for estimating QALYs (Drummond et al. 2005).

For this thesis, utility weights were derived from the data collection of patients and/or caregivers. The face-to-face interviews were conducted at the outpatient departments of both hospitals at only one point in time during some point in 2017. The patient recruitment and data collection process followed the cost data as previously stated above. Most of the EQ-5D-5L questionnaires were completed by the primary caregivers as proxy respondents. The utility weights be assigned to health states that were relevant to the health states in the CERAD-based model were 0.59 for mild, 0.27 for moderate, and 0.26 for severe stages of dementia, of risperidone prescribed patients. As for the utilities of olanzapine treated patients, these were 0.62 for mild, 0.53 for moderate, and 0.39 for severe stages (see more information in Chapter 6).

4.3.2.1.3 Results of the cost-utility analysis of the CERAD-based model

Over a five-year time horizon prediction, olanzapine treatment for BPSD patients was predicted to result in a gain of 6.42 QALYs when compared with risperidone. The incremental cost was THB 36,311.41 from a societal perspective. Thus, the incremental cost-effectiveness ratio (ICER) was estimated to be THB 5,656/QALY (Table 4.6).
Using this result, olanzapine was considered to be a considerably more cost-effective treatment in comparison to risperidone, for the treatment of patients with BPSD. The

olanzapine treatment group had an increase of cost less than THB 160,000 per an increase of one QALY for patients with BPSD, based on the cost-effective threshold in Thailand.

Table 4.6: **Cost-utility analysis results of olanzapine relative to risperidone for the treatment patients with BPSD, (THB at 2017 values), from the model based on the CERAD framework**

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	ICER
Risperidone	2,268,254.00		19.66		
Olanzapine	2,304,565.41	36,311.41	26.08	6.42	5,655.98

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

4.3.2.1.4 Limitation

The CERAD-based model focused on the impact of treatment on the change in cognitive functions. The assumption was that neuropsychiatric symptoms, (NPS), related to the more severe dementia cases (as a predictor); therefore, the decrease in NPS from the drug effectiveness might delay patients moving to the more severe health states and/or death. This might not directly affect the cognitive function which defined the health states of the model. Another consideration was that the transition probabilities applying in this model were based on data from the CERAD database in the US. This might be of concern over the generalisability of the patient data. In addition, this thesis included only the adverse events which often occurred in the elderly due to the use of atypical antipsychotic drugs such as EPSs, constipation and falls. Any other events, namely somnolence, cardiovascular events, cerebrovascular events and death were not encompassed in costs of drug-induced adverse events in this thesis. Due to the lack of studies for relapse rates of atypical antipsychotic drugs for dementia treatment, this data was adopted from a schizophrenia study. Lastly,

utility weights were mainly based on caregiver ratings, leading to a concern over the interpretation of the data.

4.3.2.2 Model 2: The model based on the FTC conceptual framework: the Assessment of Health Economics in Alzheimer's Disease (AHEAD)-based model using a predictive equation for predicting the time to FTC developed by Caro et al. (2001)

The structure and concept of the model on the basis of the AHEAD framework using the predictive equation to predict the time until patients required for FTC developed by Caro et al. (2001), data inputs of this model, (including transition probabilities, clinical effectiveness data of drug treatments, costs and utility weights), results of the cost-utility analysis and limitation of the model type are subsequently outlined.

4.3.2.2.1 Model structure and model concept of the AHEAD-based model using the predictive equation for predicting the time to FTC developed by Caro et al. (2001)

According to the AHEAD-based model, the structure and model concept of the developed model in this thesis are described below.

4.3.2.2.1.1 The model structure of the AHEAD-based model using the predictive equation for predicting the time to FTC developed by Caro et al. (2001)

This decision-analytic model based on the AHEAD model conducted on three possible health states of Pre-FTC, FTC and death, to predict the health and economic impact of the treatment in patients with Alzheimer's disease. FTC was defined as the patient's dependency status when care and supervision was required for the greater part of each day (Caro et al. 2001). The significant concept of this model was the disease progression until patients needed for FTC.

In this thesis, the dependence of patients was measured by physicians and the Activities of Daily Living rating, (ADL). The Barthel Index-Thai was applied in the assessment. The

scores were categorised as follows: a score of 0-4 was associated with total dependence, a severe dependence was associated with a score of 5-8, a moderate dependence was associated with a score of 9-11, and a mild dependence was associated with a score of 12 and above (Prasat Neurological Institute 2014). Consequently, the FTC and Pre-FTC states were defined by a score of 0-8 and 9 and over, respectively. The model structure is depicted in Figure 4.2 which was also adopted from several previous studies (Getsios et al. 2001, Caro et al. 2002, Garfield et al. 2002, Ward et al. 2003, Caro et al. 2004, Green et al. 2005, Suh 2009).

However, this thesis focused on the treatment of patients with BPSD. Therefore, BPSD associated with patients requiring atypical antipsychotic drugs for their treatment were also incorporated into the health states of the model.

4.3.2.2.1.2 The model concept and flow of the AHEAD-based model using the predictive equation for predicting the time to FTC developed by Caro et al. (2001)

At the beginning of the model, the baseline patient distributions were assigned characteristics, (age, the presence of psychotic symptoms, the presence of EPS, cognitive level assessed by MMSE, and duration of disease).

The concepts of the AHEAD-based model incorporated the patient characteristics at a given point to predict the disease progression to require FTC. The status of patients with Alzheimer's disease was classified into three possible health states: Pre-FTC, FTC, as well as death. The following transitions were possible:

- At Pre-FTC, some patients remained at the same state; some groups changed from Pre-FTC to FTC, and others moved from Pre-FTC to death;
- At FTC state, there was a possibility of patients remaining in FTC, but there were also those who moved to death; and
- Death was defined as an absorbing state.

The predictive equations based on the Cox proportional hazard models developed from a longitudinal study in the USA by Stern et al. (1997), were adopted to predict the risk of requiring FTC in the model (Caro et al. 2001). The significant covariates incorporated into the equations to estimate the time until requiring FTC, were the presence of EPS, the presence of psychotic symptoms, age at onset of disease, duration of illness, and cognitive score (defined as modified Mini-Mental State examination-mMMS).

The probabilities of dying were obtained data from the epidemiological data of the Thai population and the relative risk of mortality in Alzheimer's disease (Gambassi et al. 1999, The Thai working group on the burden of disease and injuries 2002). For this model, the Markov process was undertaken in one-month cycle lengths over a five-year time horizon, to cover disease progression and to reflect the natural history of the disease. This model was also conducted from a societal perspective. The discount rates applied were at 3% per annum for both costs and outcomes.

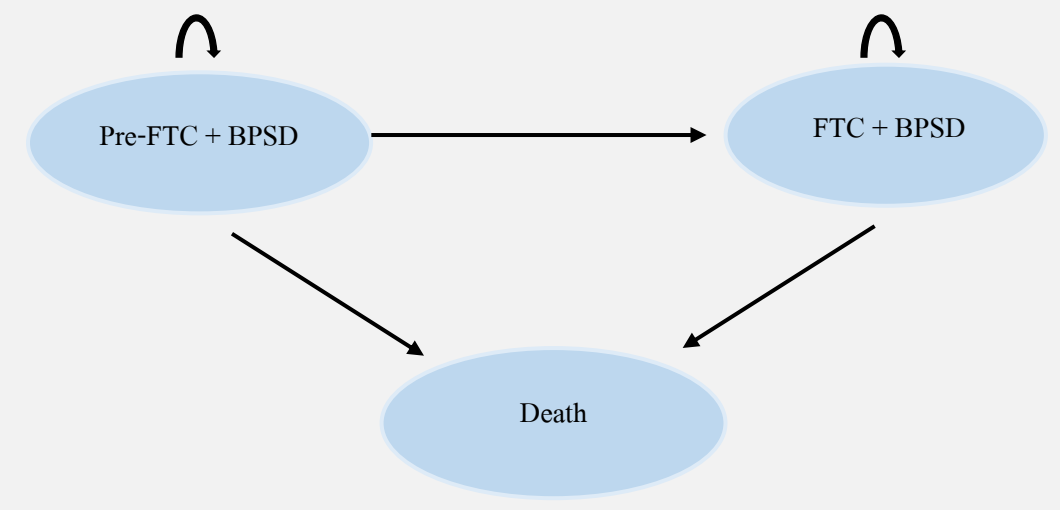


Figure 4.2: **Outline view of the model structure based on the AHEAD framework using the predictive equation developed by Caro et al. (2001)**

4.3.2.2.2 Data inputs of the AHEAD-based model using the predictive equation for predicting the time to FTC developed by Caro et al. (2001)

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

4.3.2.2.2.1 Transition probabilities of the AHEAD-based model using the predictive equation for predicting the time to FTC developed by Caro et al. (2001)

A predictive risk equation was developed based on longitudinal epidemiological data. The AHEAD model allowed for a risk index (Stern et al. 1997) and regression equations (Caro et al. 2001) to be incorporated in the model.

As Caro et al. (2001) suggested, predictor indices were employed, based on the Cox proportional hazard analysis of disease progression, to judge the significant characteristics of those patients who might need FTC. Such characteristics include the presence of extrapyramidal symptoms (EPS), the presence of psychotic symptoms, young age at onset (≤ 65 years), a modified Mini-Mental State Examination (mMMS) score, and the duration of illness. These coefficients were employed to calculate the risk index once patients had entered the model. Additionally, the regression equations distinguished between two groups of patients: those aged 73 years old and younger, and those over 73 years old. These age factors were considered in calculating the baseline risk over time. The predictor indices and the coefficients of the regression equations are also illustrated in Table 4.7.

Table 4.7: **Predictive risk equation to calculate the transition probabilities from the Pre-FTC state to FTC state based on Caro et al. (2001)**

	Variables	EPS	PSY	Age at Onset	mMMS	Duration of illness
Risk index	Coefficient	-0.9419	-0.4027	-0.4848	0.0724	0.0617

	Variables	EPS	PSY	Age at Onset	mMMS	Duration of illness
Risk over time	Coefficient	**A**	**B**	**C**	**D**	**E**
	$\leq$ 73 years	0.0231	-1.8117	0.0373	0.1532	-4.7903
	> 73 years	0	-0.6846	-6.4172	0.0112	0.1413

The equations to predict time to FTC: The transition probabilities from the Pre-FTC state to FTC state were calculated as follows:

- *The equation used to calculate the baseline risk over time:*

$$\lambda_0^t = e^{(At+B+Csinh(Dt+E))}$$

where λ_0^t was the baseline risk over time

$sinh$ was the hyperbolic sine

A, B, C, D and E were coefficients of the regression equation separately for patient aged 73 years old and younger and those over 73 years old

- *To compute the hazard over time using the equation:*

$$\lambda_{index}^{t} = \frac{\lambda_0^t}{e^{riskindex}}$$

where λ_{index}^{t} was the hazard over time (the transition probability from Pre-FTC to FTC)

λ_0^t was the baseline risk over time

the risk index was the coefficient of predictor indices

The baseline characteristics of patients in this model are presented in Table 4.8. These values were then used to calculate the risk index of the model. However, the presence of EPS, the presence of psychotic symptoms, and an age of onset were assessed by the present (value=1)

or not present (value= 0), these predictors were limited to measure the difference in changes of their scores.

Table 4.8: **Characteristics of patients with BPSD and being treated with olanzapine or risperidone from the data collected in the Thai setting**

Model Inputs	Value	References
Baseline characteristics of patients		
Age (yr) [Mean (SD)]	78.35 (8.80)	Primary collected data
Presence of EPS [n (%)]	11 (13.41)	Primary collected data
Presence of psychotic symptoms [n (%)]	82 (100.00)	Primary collected data
MMSE [Mean (SD)]	15.50 (7.52)	Primary collected data
Duration of illness (yr) [Mean (SD)]	2.44 (1.76)	Primary collected data

The probabilities of death in this model: The probabilities for transitioning to death were calculated by multiplying the relative risk (RR) of the mortality associated with each health state (Pre-FTC or FTC) and the probability of dying of the general Thai population as classified by age (The Thai working group on burden of disease and injuries 2002). The relative risks of mortality in patients with Alzheimer's disease were taken from a previous study accounting for 1.45 in Pre-FTC and 3.03 in FTC, respectively (Gambassi et al. 1999). The estimated monthly probabilities of the mortality in the Thai population are presented in Table 4.9. In addition, the assumptions in this model are as follows: 1) drugs, (olanzapine and risperidone), had no impact on the mortality; and 2) drug benefits were constant over the defined time period of this model.

Table 4.9: **Monthly probabilities of mortality in the elderly Thai population classified by age group**

Age group (years)	Probability	Reference
60-64	0.00119	The Thai working group on the burden of disease and injuries (2002)
65-69	0.00175	
70-74	0.00267	
75-79	0.00423	
80-84	0.00667	
> 85	0.01000	

4.3.2.2.2.2 Clinical effectiveness data of olanzapine and risperidone treatments

Due to off-label antipsychotic treatment of dementia, the effectiveness data of drugs are controversial. There were only two studies comparing olanzapine and risperidone treatment in dementia based on the comprehensive literature review (see Chapter 2, section 2.4). However, the outcomes of both studies were not assessed regarding cognitive function (as measured by MMSE, ADAS-cog or mMMS). Thus, the clinical effectiveness data for olanzapine and risperidone applying in this model were derived from the study by Sultzer et al. (2008), in which the outcomes of atypical antipsychotics drugs of that study were based on a study of Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD). The CATIE-AD cohort study examined 421 outpatients with Alzheimer's disease and with psychosis, aggression, or agitation, randomly assigned under double-blind conditions to treatment with olanzapine, risperidone, quetiapine and a placebo, in 42 locations in the US (Schneider et al. 2006). Both olanzapine and risperidone altered cognition levels at 12 weeks in Phase 1 of the CATIE-AD study. The changes in the cognitive score, as measured by the Mini-Mental State Examination (MMSE), were -0.10 for the olanzapine-treated group and -0.80 for the risperidone-treated group, however, there were no significant

differences among patients receiving the active drug or placebo (Sultzer et al. 2008). Table 4.10 shows the effectiveness data on the difference in MMSE for olanzapine and risperidone which were applied in the model.

Table 4.10: **Model inputs for the clinical effectiveness data of olanzapine and risperidone**

Effectiveness Data (change in MMSE score compared with placebo)	Value	References
Olanzapine (mean dose 5.5 mg/day)	0.60	Sultzer et al. (2008)
Risperidone (mean dose 1.0 mg/day)	-0.10	Sultzer et al. (2008)

In addition, the MMSE score from the effectiveness data had to be converted to mMMS because the predictive equation incorporated mMMS as a variable for calculating the transition probability to FTC. The relationship between the MMSE and mMMS was depicted as presented below (Stern et al. 1997):

$$mMMS = 1.73\ MMSE + 2.81$$

where $mMMS$ was the modified Mini-Mental State Examination

$MMSE$ was the Mini-Mental State examination

4.3.2.2.2.3 Costs of patients with behavioural and psychological symptoms of dementia and being treated with atypical antipsychotics, (olanzapine and risperidone), based on the data collected in Thailand

As table 4.11 shows, the cost data of each type of care were obtained from the collected data from two hospitals in Thailand. Patients and/or caregivers were asked to provide the cost data that patients had expended during their treatment course. Face-to-face interviews were

conducted in this thesis. The gathering of data processes, including the inclusion and exclusion criteria are as presented in Chapter 5 (sections 5.2.1 and 5.2.2).

The cost data of this model also included the direct medical costs and direct non-medical costs which were similar to the costing data in the CERAD-based model. All costs used in the model were reported in 2017 financial year values (see more information in Chapter 5).

Table 4.11: **Monthly cost parameters for the model, calculated based on data from Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital, Thailand, Thai Baht (THB) at 2017 values**

Cost Assumptions	Value [Mean (SD)]	Reference
By health state		
Risperidone:		
Pre-FTC	44,717.09 (14,573.74)	Primary collected data
FTC	53,167.03 (11,251.27)	Primary collected data
Olanzapine:		
Pre-FTC	44,347.28 (16,071.51)	Primary collected data
FTC	58,294.20 (19,227.41)	Primary collected data

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

4.3.2.2.2.4 Utility weights of patients with behavioural and psychological symptoms of dementia and being treated with atypical antipsychotics, (olanzapine and risperidone), based on the data collected in Thailand

The utility weights applied in the AHEAD-based model using the predictive equation to estimate the need of FTC developed by Caro et al. (2001) were derived from a cross-sectional study in Thailand. The face-to-face interviews were conducted at the outpatient departments of both hospitals as previously stated at only one point in time during some point in 2017 using the EQ-5D-5L. For patients receiving risperidone, the utility weights were 0.46 of the

Pre-FTC state and 0.12 of the FTC state, whereas the utility weights of patients treated with olanzapine were 0.63 and 0.23 of the Pre-FTC state and the FTC state, respectively (see more information in Chapter 6).

4.3.2.2.3 Results of the cost-utility analysis of the AHEAD-based model using the predictive equation for predicting the time to FTC developed by Caro et al. (2001)

In a comparison of olanzapine to risperidone, the incremental cost and effectiveness were THB 26,171.15 and 0.22 higher, respectively, in favour of olanzapine treatment. Based on a societal perspective over a five-year time horizon, the ICER at the base case scenario was THB 118,959.77 per QALY gained. (Table 4.12). This indicated that olanzapine was more cost-effective compared with risperidone for the treatment of patients with BPSD at the ceiling cost-effective threshold in Thailand (THB 160,000).

Table 4.12: **Cost-utility analysis results of olanzapine relative to risperidone for the treatment patients with BPSD, (THB at 2017 values), from the AHEAD-based model using the predictive equation for predicting the time to FTC developed by Caro et al. (2001)**

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	ICER
Risperidone	1,901,735.35		41.23		
Olanzapine	1,927,906.50	26,171.15	41.45	0.22	118,959.77

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

4.3.2.2.4 Limitation

There are several points to be concerned with regarding the model developed based on the AHEAD-based model using the predictive equation to predict the time to FTC developed by Caro et al. (2001). Firstly, this model might raise concerns over the generalisability of the data used in the predictive equations which were developed based on an observational study of US patients. Secondly, cognitive function, as measured by mMMS score, used to apply in

the predictive equation to predict time to FTC need, thus error may have arisen in the conversion from the differences in cognitive scale (as measured by MMSE and ADAS-cog) to mMMS. Although the predictive equation incorporated several factors to estimate time to requiring FTC, the functional ability was not included. Further, the definition of FTC might be different in each setting. Also, the treatment effect applied to the equation was focused only on the cognitive function, whereas other aspects associated with the progression of the disease, namely behaviour and functional ability, were not considered. Further, the presence of psychotic symptoms in the equation was assessed in terms of yes or no, thus this did not differentiate between the effectiveness of antipsychotics. Next, this model adopted data from a schizophrenia study to calculate costs associated with relapses. Finally, the caregivers were the main respondents for completing the questionnaire, thus there should be concerns over the interpretation of the utility weights.

4.3.2.3 Model 3: The model based on the FTC conceptual framework using a new predictive equation for predicting the time to FTC developed by Rive et al. (2010)

The structure and concept of the model on the basis of the FTC conceptual framework using the predictive equation to predict the time until patients required for FTC developed by Rive et al. (2010), data inputs of this model, (including transition probabilities, clinical effectiveness data of drug treatments, costs and utility weights), results of the cost-utility analysis and limitation of the model type in this thesis are presented in the subsequent sections.

4.3.2.3.1 Model structure and model concept based on the FTC framework using a new predictive equation for predicting the time to FTC developed by Rive et al. (2010)

According to the FTC-based framework using the predictive equation to predict the time until patients required for the FTC state, the structure and model concept of the developed model in this thesis are described below.

4.3.2.3.1.1 The model structure of the model based on the FTC framework using the predictive equation for predicting the time to FTC developed by Rive et al. (2010)

The model structure consisted of three possible health states: Pre-FTC, FTC and death. The FTC state was considered based on either the dependency status or locus of care of the patients. Both physical and functional abilities were used for assessing the patients' dependence status. In this study, the physician's assessment and the Activities of Daily Living rating (ADL) score were used to evaluate the dependence of patients as previously stated in the model using the predictive equation to estimate the need of FTC developed by Caro et al. (2001). The model structure is presented in Figure 4.3.

However, this thesis focused on the treatment of patients with BPSD. Therefore, BPSD associated with patients requiring atypical antipsychotic drugs for their treatment were also incorporated into the health states of the model.

4.3.2.3.1.2 The model concept and flow of the model based on the FTC framework using the predictive equation for predicting the time to FTC developed by Rive et al. (2010)

The model concept was the patient's need for FTC. The time to FTC was estimated by the predictive equation.

A new predictive equation to predict time for requiring FTC was developed by Rive et al. (2010). The baseline characteristics of the patients were taken from a longitudinal epidemiological study-the London and the South-East region (LASER-AD), which investigated 224 people with Alzheimer's disease and their caregivers (Livingston et al

2004). Based on the LASER-AD cohort, 117 pre-FTC patients were followed-up over a 54-month period which was used to construct the equations in computing the transition probabilities from pre-FTC to FTC and the probabilities of death. Also, the three main dimensions of Alzheimer's disease, including cognitive, functional, and behavioural performances, were incorporated into the equations to predict time to FTC. In addition, the cognitive function, functional ability, and behavioural performance were assessed by the Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog), the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL), and the Neuropsychiatric Inventory (NPI), respectively.

A Markov model was used to predict the progression of a patient with Alzheimer's disease with three possible health states: Pre-FTC, FTC, as well as death. The following transitions were possible:

- At the Pre-FTC state, some patients had the possibility of moving to the FTC or death, while others remained in the same health state;
- At the FTC state, some patients remained in the FTC state, but there was also the possibility that some could move to death; and
- Death was an absorbing state.

The Markov process was undertaken using a one-month cycle length over a five-year time period, covering disease progression and reflecting the natural history of the disease.

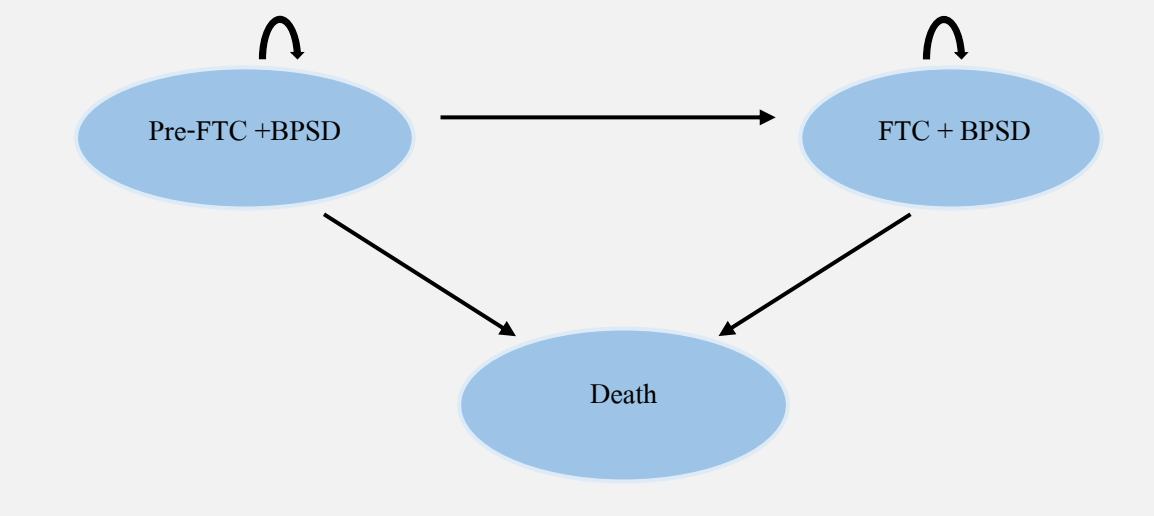


Figure 4.3: **Outline view of the model structure based on the FTC conceptual framework using the predictive equation for predicting the time to FTC developed by Rive et al. (2010)**

4.3.2.3.2 Data inputs of the model based on the FTC framework using the predictive equation for predicting the time to FTC developed by Rive et al. (2010)

In the thesis, 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.

4.3.2.3.2.1 Transition probabilities of the model based on the FTC framework using the predictive equation for predicting the time to FTC developed by Rive et al. (2010)

A predictive risk equation was used to calculate the time to FTC. The main variables were ADAS-cog, ADCS-ADL, and NPI scores which reflected the three domains, cognition, functioning and behaviour, in Alzheimer's disease (AD) (Rive et al. 2010). To compute the interval probabilities of reaching the FTC state, the predictive equation parameters at baseline were based on data from the LASER-AD cohort study (Table 4.13). The estimated length of time to FTC in patients with Alzheimer's disease was based on the equations as follows:

- *The hazard function equation used to predict the length of time to FTC*

$$p_j = 1 - \exp(-\exp\left(-11.1343 + 0.0330 \times ADAS - cog_{total-score}^{baseline} - 0.0877 \times ADCS - ADL_{total-score}^{baseline} + 0.0377 \times NPI_{total-score}^{baseline} + 0.8122 \times ADAS - cog_{total-score}^{slope}(j) - 2.4072 \times ADCS - ADL_{total-score}^{slope}(j)\right) \times \exp(3.3195 \times \ln(interval_j)))$$

where p_j was probability for the time interval *j*

$ADAS - cog_{total-score}^{baseline}$ was the Alzheimer's Disease Assessment Scale-Cognitive Subscale at baseline

$ADCS - ADL_{total-score}^{baseline}$ was the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale at baseline

$NPI_{total-score}^{baseline}$ was the Neuropsychiatric Inventory total score at baseline

$ADAS - cog_{total-score}^{slope}(j)$ was the Alzheimer's Disease Assessment Scale-Cognitive Subscale for the time interval *j*

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

- *The estimation of the monthly transition probability to the FTC state was calculated by*

$$p_{ji}^{FTC} = 1 - \sqrt[length(j)]{(1 - Pj)}$$

where p_{ji}^{FTC} was the monthly probability

p_j was the probability for the time interval *j*

Table 4.13: **Parameters at baseline deriving from the LASER-AD cohort study (Livingston et al. 2004)**

Characteristics	Value
ADAS-cog baseline	36.30
ADCS-ADL baseline	45.00
NPI baseline	18.54
ADAS-cog slope	0.6116
ADCS-ADL slope	-0.7503

The transition probabilities of death: The probabilities for transitioning to death in this model were estimated from the mortality rates of the epidemiological data of the general Thai population, multiplied with the relative risk (RR). The study by Gambassi et al. (1999) reported, the relative risks of patients dying from Alzheimer's disease were 1.45 in the Pre-FTC state and 3.03 in the FTC state. The monthly probabilities of dying for the general Thai population, classified by age group that were derived from the epidemiological data of the Thai working group on burden of disease and injuries (2002), were similar to the AHEAD-based model using the predictive equation for predicting the time to FTC developed by Caro et al. (2001) (see in Table 4.9).

4.3.2.3.2.2 Clinical effectiveness data of olanzapine and risperidone treatments

Due to the controversial use of antipsychotics for the treatment of BPSD, the effectiveness data applied to the model using the predictive equation to predict the need of FTC developed by Rive et al. (2010) were derived from two studies. The effectiveness of treatments associated with the functional ability and the cognitive function were obtained from the Phase 1 outcomes of the CATIE-AD study, a double-blind randomly masked study (Sultzer et al. 2008). At 12 weeks in Phase 1 of the CATIE-AD study, the changes in the cognition scores, as measured by the Alzheimer's Disease Assessment Scale-cognitive subscale

(ADAS-cog), was 0.70 for olanzapine, 1.70 for risperidone and 1.30 for the placebo. However, these scores were not significantly different. The changes in the Alzheimer's Disease Cooperate Study-Activities of Daily Living Scale total (ADCS-ADL) found -6.1 in patients treated with olanzapine, -1.10 of patient's receiving risperidone and 0.50 of the placebo group. In addition, neuropsychiatric inventory total (NPI-total) scores were derived from a double-blind randomised controlled trial (RCT) by Deberdt et al. (2005). This study reported that the changes of NPI-total scores compared with placebo were 0.50 and 2.60 for olanzapine and risperidone, respectively. Table 4.14 provides the summary of drug effectiveness that used to calculate in the model.

Table 4.14: **Summary of the clinical effectiveness data of olanzapine and risperidone**

Variable	Olanzapine	Risperidone	Reference
Behavioural (NPI-total)	0.50	2.60	Deberdt et al. (2005)
Functioning (ADCS-ADL)	-6.60	-1.60	Sultzer et al. (2008)
Cognition (ADAS-cog)	-0.60	0.40	Sultzer et al. (2008)

According to the LASER-AD cohort, the assessment was conducted at baseline, at 6-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 to the FTC state was constant in each time interval (Table 4.15). The monthly probabilities of the need of the FTC state were then calculated using the equation presented above. The estimated monthly probabilities time to the FTC state of olanzapine and risperidone are shown in Table 4.16.

Table 4.15: **Interval transition probabilities of reaching the FTC state of olanzapine treatment and risperidone treatment**

	Interval	Olanzapine	Risperidone
P_1	0-6 months	0.01275	0.00922
P_2	7-18 months	0.38880	0.29900
P_3	19-30 months	0.93167	0.85575
P_4	31-42 months	0.99973	0.99730
P_5	43-54 months	1.00000	0.99999
P_6	55-60 months	1.00000	1.00000

Table 4.16: **Monthly transition probabilities time to the FTC state of olanzapine treatment and risperidone treatment**

	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

4.3.2.3.2.3 Costs of patients with behavioural and psychological symptoms of dementia and being treated with atypical antipsychotics (olanzapine or risperidone) based on the data collected in Thailand

Cost data were derived from the directly gathered data of two hospitals in Thailand. The face-to-face interviews were conducted using the cost questionnaire. Further, the processes of data collection and calculating costs were given previously (see more details in Chapter 5). Cost

data included direct medical costs and direct non-medical costs. In addition, both health states of the AHEAD-based model using the predictive equation for predicting the time to FTC developed by Caro et al. (2001) and the model using the predictive equation to predict time to FTC developed by Rive et al. (2010) had similarities, (Pre-FTC and FTC). Then, the costing data of the AHEAD-based model using the predictive equation developed by Caro et al. (2001) were also used in this model (see Table 4.11).

For patients receiving risperidone, the monthly costs were THB 44,717.09 for the Pre-FTC state and THB 53,167.03 for the FTC state, whereas the monthly cost of patient treated with olanzapine were THB 44,347.28 and THB 58,294.20 for the Pre-FTC and FTC states, respectively. All costs used in this model were reported in 2017 financial year values (1£ = THB 45) (see more information in Chapter 5).

4.3.2.3.2.4 Utility weights of patients with behavioural and psychological symptoms of dementia and treated with atypical antipsychotics (olanzapine or risperidone) based on the data collected in Thailand

Again, the health states of the model using the predictive equation to predict the time to FTC developed by Rive et al. (2010) comprised of Pre-FTC, FTC and death. Thus, the utility weights used here were similar to the AHEAD-based model using the predictive equation to predict the time to FTC developed by Caro et al. (2001) as follows: 0.46 for the Pre-FTC state and 0.12 for the FTC state of patients receiving risperidone treatment and 0.63 for the Pre-FTC state and 0.23 for the FTC state of patients receiving olanzapine treatment. More details of the utility analyses are presented in Chapter 6.

4.3.2.3.3 Results of the cost-utility analysis of the model based on the FTC framework using the predictive equation to predict the time to FTC developed by Rive et al. (2010)

The total five-year cost for a patient with BPSD receiving treatment with risperidone was estimated at THB 1,918,257, while the cost for a patient with BPSD receiving treatment with

olanzapine was THB 2,015,958. The incremental cost was THB 97,701.31. The estimated QALYs were 10.81 and 15.45 for the risperidone and the olanzapine treatment groups respectively. The incremental QALYs between the two drugs was 4.64. Consideration of the cost-utility analysis of the model, the ICER yielded THB 21,039.45/QALY under the base case scenario (Table 4.17).

Using this result, olanzapine was considered to be the most cost-effective treatment when compared with risperidone, in the treatment of patients with BPSD from a societal perspective, following the ceiling threshold of the cost-effectiveness in Thailand as previously stated.

Table 4.17: **Cost-utility analysis results of olanzapine relative to risperidone for the treatment patients with BPSD, (THB at 2017 values), from the model based on the FTC framework using the predictive equation to predict the time to FTC developed by Rive et al. (2010)**

Strategy	Cost	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

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

4.3.2.3.4 Limitation

The applied the model based on the FTC framework using the predictive equation to predict the time to FTC developed by Rive et al. (2010) for the health economic evaluation study in dementia has limitations. Firstly, the patient baseline characteristics used data from the LASER-AD cohort, a longitudinal epidemiological study in the UK. Secondly, predictive equations were also based on the same cohort. Thus, this model might raise some concerns over the generalisability of the data used in the new predictive equations. Thirdly, the drug

effects on the cognitive function used the MMSE score, thus the conversion from MMSE to ADAS-cog score might introduce some errors. Finally, caregivers were the major respondents providing a rating for the utilities, therefore the results need to be interpreted with caution.

4.3.3 The comparisons of the three developed models

By comparing amongst developed models, the finding are presented following the defined points, (see section 4.2.2), as outlined below.

4.3.3.1 Disease severity and health states of the models

According to the CERAD-based model, the health states of the model comprised of mild, moderate, severe as well as death. The disease severity was defined by severity levels of the cognitive function as measured by TMSE scores.

The dependency status of patients was used to define the disease severity of the two other models of the FTC conceptual framework which was measured by activities of daily living (ADL) together with an assessment by physicians. Therefore, the health states of the models using the predictive equation to predict the need of FTC developed by Caro et al. (2001) and developed by Rive et al. (2010) were Pre-FTC, FTC and death.

4.3.3.2 The disease progression and transition probabilities of the models

In the CERAD-based model, the course of the disease according to severity levels was used as a concept of this model type. The stage-to-stage transition probabilities of this model used data from the CERAD cohort, a longitudinal database of 1,145 patients with dementia in the US between 1986 and 1995 (Morris et al. 1989).

Regarding the model based on the FTC frameworks, the need for FTC was used as a concept of the disease progression of this model type. The FTC state was a requirement for a significant amount of time for care and supervision, regardless of the locus of care or who

provided the patients' care. To estimate the time until patients needed FTC, the predictive equation developed by Caro et al. (2001) used data of patient characteristics undertaken in 236 Alzheimer's disease patients followed-up over 7-years in the US by Stern et al. (1997). This equation incorporated multiple characteristics, including the presence of EPS, presence of psychotic symptoms, duration of illness, age at the onset of disease, and cognitive function. The probability of dying was based on the mortality rates of the general Thai population.

The predictive equation developed by Rive et al. (2010) used data obtained from the LASER-AD cohort, a longitudinal epidemiological study conducted in 117 pre-FTC patients with Alzheimer's disease with a 54-month follow-up period in the UK to estimate the time until patients needed of FTC. The predictive equation included the cognitive function (as measured by ADAS-cog scale), the functional performance (as assessed by the ADCS-ADL) and behavioural ability (as measured by NPI). The probabilities of death in the model used the mortality rates of the general Thai population.

4.3.3.3 The clinical effectiveness data of the treatments applied to the model

The CERAD-based model used the change in the Clinical Global Impression of Change (CGI-C) scale as the effectiveness of drug treatment.

Although the model based on the FTC framework using the predictive equation to predict the time to FTC developed by Caro et al. (2001) incorporated multiple characteristics of patients in the predictive equation to predict time until patients needed for the state of FTC, the effectiveness data of treatments mainly depended upon the alteration of the cognitive function, particularly mMMS score.

The model using the predictive equation for predicting the time to FTC developed by Rive et al. (2010) considered several aspects of the clinical effectiveness of drug treatments, including cognition, (ADAS-cog scale), behaviour, (NPI), and functioning, (ADCS-ADL).

4.3.3.4 The results of an economic evaluation of the treatment of patients with BPSD with olanzapine compared with risperidone based on the different models

All three developed models suggested olanzapine was a domonant treatment option for patients with behavioural and psychological symptoms of dementia in Thailand when compared with risperidone. However, the incremental cost-effectiveness ratio, (ICER as measured an incremental of costs and an incremental of QALYs), of each model had provided different results which the model using the predictive equation for predicting the time to FTC developed by Caro et al. (2001) had the highest ICER.

Furthermore, the significant characteristics of each model are summarised in Table 4.18. A comparison of strengths and limitations of each model are also presented in Table 4.19.

Table 4.18: **Summary of the characteristics of each developed model**

Description	**CERAD framework (Neumann et al. 1999)**	**FTC framework using the equation developed by Caro et al. (2001)**	**FTC framework using the equation developed by Rive et al. (2010)**
Disease severity characteristics			
CDR scale	●		
Dependence-need for FTC		●	●
Disease progression of modelling			
Discrete states	●	●	●
TMSE scale	●		
Cognitive function		●	●
Functional performance			●
Behavioural characteristics		●	●
Presence of extrapyramidal symptoms		●	
Age at disease onset		●	

Description	CERAD framework (Neumann et al. 1999)	FTC framework using the equation developed by Caro et al. (2001)	FTC framework using the equation developed by Rive et al. (2010)
Duration of illness		●	
The effectiveness data			
CGI-C	●		
Cognitive assessment		●	●
Functional assessment			●
Behavioural assessment			●
Utility weights			
EQ-5D-5L (a cross-sectional survey)	●	●	●

* (●) refers to the presence of characteristics of each developed model when compared amongst developed models

Table 4.19: **Comparison of strengths and limitations of each developed model**

Model	Strength	Limitation
The CERAD-based model	● Health states were based on the CDR scale. ● Mild, moderate, severe and death were the health states in the model. ● Transition probabilities were based on the CERAD cohort. ● CGI-C used as effectiveness data of treatments. ● Cost data included adverse event-associated costs and relapse-associated costs	● Health states were discrete states, there is a concern regarding a limitation to represent how changes occur over time. ● Transition probabilities were based on the CERAD database in the US, leading to a concern over the application in different contexts.

Model	Strength	Limitation
	● QALY was a measure of outcome.	● Effectiveness data of treatment mainly depended on cognitive assessment. ● Data of costing and utility weights in the model were based on a cross-sectional study, leading to a concern associated with a limitation in representing how costing and utility changes influence the disease progression of patients and the treatment.
The AHEAD-based model using the predictive equation developed by Caro et al. (2001)	● Health states were based on Pre-FTC, FTC and death. ● Transition probabilities were based on the equation which included various characteristics of the patients. ● Effectiveness data relied on the mMMS score. ● Cost data included adverse event-associated costs and relapse-associated costs ● QALY was a measure of outcome.	● Health states were discrete states, there is a concern regarding a limitation in representing how changes occur over time. ● Transition probabilities were based on the equation by Caro et al. (2001) using patient characteristics from the study by Stern et al. (1997), in the US, there is a concern over the application in different contexts. ● Effectiveness data of treatment mainly relied upon cognitive assessment, particularly mMMS. The

Model	Strength	Limitation
		difference in the cognitive measurement needed to be changed to mMMS, leading to a concern over accuracy. ● Functional performance was not considered in the predictive equation to predict time to FTC. ● Data of costing and utility weights in the model were derived from a cross-sectional study. There is a concern over a limitation to perform how costing and utility changes influence the disease progression and the treatment.
The model using the predictive equation developed by Rive et al. (2010)	● Health states of the model were Pre-FTC, FTC and death. ● Transition probabilities were based on the equation which included cognition, functioning and behavioural performances. These were reflected a multi-dimension associated with the natural disease progression of dementia. ● Several factors, including ADAS-cog scale, NPI score and	● Health states were discrete states, there is a concern regarding a limitation to represent how changes over time occur. ● Transition probabilities were based on the equation by Rive et al. (2010) which used data from the LASER-AD cohort in the UK, there is a concern over the application in different contexts.

Model	Strength	Limitation
	ADCS-ADL, were taken into account as effectiveness data. ● Cost data included adverse event-associated costs and relapse-associated costs ● QALY was a measure of outcome. ● The most recently used model compared with the model-based CERAD framework and FTC framework using the equation developed by Caro et al. (2001)	● Data of costing and utility weights in the model were based on a cross-sectional study. This might be associated with a limitation in producing how costing and utility changes affect the disease progression and the treatment.

4.3.4 Justification of the most suitable model for applying to the cost-utility analysis of antipsychotics (olanzapine compared with risperidone) for the treatment patients with BPSD in Thailand

According to the defined considerations criteria for making the decision to select the most appropriate model, (see section 4.2.3), the model using the predictive equation to predict the need of FTC developed by Rive et al. (2010) was selected as being the most suitable model to be applied to the economic evaluation of the treatment BPSD in the comparison of olanzapine to risperidone for the Thai population. There were several reasons as follows: firstly, the model had taken into account all significant dimensions, (cognitive, functional and behavioural abilities), which were more consistent with the natural disease progression of dementia to predict the progression of disease.

Secondly, the model structure based on the FTC conceptual framework was widely used in studies of economic evaluation of dementia.

Thirdly, the clinical effectiveness of drug treatments to use in the model also considered all core components of the disease progression of dementia, including cognition, functioning and behaviour.

Finally, the model using the predictive equation developed by Rive et al. (2010) is the most recently developed when compared with the CERAD-based model and the AHEAD-based model using the predictive equation to predict the time to FTC developed by Caro et al. (2001).

4.4 Discussion

Based on the literature review, most studies of model-based economic evaluation in dementia were associated with Alzheimer's disease. The majority of models for economic evaluations in dementia used the Markov model to predict the outcomes and estimate the most cost-effective treatment. Also, it can be seen from the review that the two most common model structures in order of frequency used in several studies were based on the CERAD conceptual framework and the FTC conceptual framework (Neumann et al. 1999, Ikeda, Yamada and Ikegami 2002, Fuh and Wang 2008, Kirbach et al. 2008, Lopes-Bastida et al. 2009, Getsios et al. 2001, Caro et al. 2002, Garfield et al. 2002, Migliaccio-Walle et al. 2003, Ward et al. 2003, Caro et al. 2004, Green et al. 2005, Suh 2009). However, there were some studies which were conducted using the DES model, the microsimulation model, the decision tree model, and statistical model (Henke and Burchmore 1997, Fenn and Gray 1999, McDonnell et al. 2001, Weyker et al. 2007, Wong et al. 2009, Getsios et al. 2010, Guo et al. 2010, Nagy et al. 2010, Hartz et al. 2012, Thaibault et al. 2015).

Following the review and the defined criteria to develop models, (see the methods section 4.2.1), three different models are selected to predict the cost-utility analysis of the use of atypical antipsychotics in the treatment of BPSD patients. Three decision-analytic models are

developed based on the different concepts of the model-based economic evaluations in dementia, especially Alzheimer's disease. One is adopted from the CERAD-based structure and two models use the FTC conceptual framework.

Although two models based on the FTC conceptual framework, including the models using the predictive equation for predicting the need of FTC developed by Caro et al. (2001) and developed by Rive et al. (2010), have similarities regarding the health states, (Pre-FTC, FTC and death), the predictive equations to predict the time to FTC are significantly different between the two models. Based on Caro et al. (2001), the predictive equation for predicting the time to FTC takes into account two domains of patient's cognition and behavioural symptoms, whereas the predictive equation for predicting the time to FTC developed by Rive et al. (2001) includes three domains associated with patient's cognition, behavioural symptoms as well as functioning.

Moreover, all three models adopt data from different longitudinal epidemiology cohorts to use as sources for the calculation of state-to-state transition probabilities. Two models of the CERAD-based model and the model using the predictive equation to predict the time to FTC developed by Caro et al. (2001) obtain data from studies conducted in the US, whereas the other model using the predictive equation to predict the time to FTC developed by Rive et al. (2010) uses data from a study in the UK.

There are different clinical effectiveness data of the treatments use in each model which these affect the transitioning between health states of the model. One model uses CGI-C, another model uses mMMS score and the other model considers ADAS-Cog, ADCS-ADL and NPI.

Although the three developed models use different approaches, the results of cost-utility analyses of all models are similar, in that olanzapine is a cost-effective treatment for patients with BPSD in Thailand, when compared with risperidone. This is consistent with the study by Kirbach et al. (2008) in the US, conducted using the CERAD model as the model

structure. That study reported that olanzapine was a favourable treatment in Alzheimer's patients with agitation and psychosis, compared with no treatment. However, it should be noted that there are concerns about the differences in methods, data inputs and healthcare provision for each country between the Kirbach's study and this thesis.

According to the comparison amongst the three models, the model using the predictive equation to predict the time to FTC developed by Rive et al. (2010) is chosen as the most suitable model. This is associated with the model having met all defined points for the considerations of this thesis, (see section 4.2.3). Moreover, it is important to note that the model using the predictive equation to predict the time to FTC developed by Rive et al. (2010) included assessments of the core domains of Alzheimer's disease, (cognition, behaviour and functioning), to estimate the transition from the Pre-FTC state to the FTC state. This implies that the model using the predictive equation to predict the time to FTC developed by Rive et al. (2010) is more consistent with the natural history of the disease progression of dementia, in particular Alzheimer's disease.

However, the developed models in this chapter also have several limitations. Firstly, they are associated with the generalisability of data used in the transition probabilities for the health states of the models.

Secondly, all three models are conducted using discrete states. This might limit their ability to represent how changes over time influence the disease progression for patients and their treatments.

Thirdly, the costing data and utility weights of all models are conducted in a cross-sectional study, and this might limit their ability to represent how costing and utility changes influence the disease progression for patients and their treatments. Thus, the application of the selected model to the economic evaluation in dementia should be carried out and interpreted with caution.

To the researcher's best knowledge, this is the first study to explore the model-based economic evaluations in a comparison between olanzapine and risperidone, for the treatment of patients with behavioural and psychological symptoms of dementia, based on existing and available data. This thesis also highlights the model using the predictive equation to predict the time to FTC developed by Rive et al. (2010) as the most suitable model to apply for an economic evaluation of the BPSD treatment with atypical antipsychotic drugs in Thailand. Therefore, this model was adopted for further cost-utility analysis of olanzapine compared with risperidone for the treatment of BPSD patients in Thailand (in the Chapter 7).

Chapter 5: Cost analyses of patients with behavioural and psychological symptoms of dementia in Thailand

Abstract

Introduction: Dementia is a progressive illness and has become the leading cause of morbidity and functional decline in elderly people. This illness involves with cognitive and non-cognitive symptoms. Whilst the non-cognitive symptoms or behavioural and psychological symptoms of dementia (BPSD) are a serious complication of people with dementia and these symptoms occur at some point during the patient's illness. The mental or behavioural disturbances are substantial predictors associated with the burden to patients, their families, their caregivers, and healthcare systems and also profoundly affect the quality of life of relevant individuals. However, there is a lack of data on costings, especially in patients with BPSD and being treated with atypical antipsychotics.

Aim: The objective of this chapter is to analyse the costs of patients with behavioural and psychological symptoms of dementia using different atypical antipsychotic drugs, (risperidone and olanzapine), in Thailand.

Methods: A cross-sectional study was conducted, with face-to-face interviews and using questionnaires, from patients with BPSD and being treated with atypical antipsychotics, (olanzapine or risperidone), and/or patients' caregivers to estimate costs associated with these patients. The data collections were undertaken in two phases: Phase I, (from February 2017 to March 2017), and Phase II, (from October 2017 to November 2017), at Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital in Thailand. Cost analyses included direct medical costs and direct non-medical costs of risperidone and olanzapine prescribed patients, classified by their cognitive function and dependence.

Results: Average monthly costs in THB at 2017 values, (1£ = THB 45), per patient classified by cognitive function, were THB 41,444.22 for mild, THB 46,470.29 for moderate, and THB

53,038.90 for severe stages for those treated with risperidone and THB 41,901.85 for mild, THB 48,368.34 for moderate, and THB 52,901.64 for severe stages for those prescribed olanzapine. The severity of cognitive impairment was associated with the costs of those patients with the greater severity predicted at higher costs. Classifying patients by their dependence on care, the average monthly costs of risperidone treatment in 2017 THB were THB 44,717.09 and THB 53,167.03 per patient for not requiring full-time care, (Pre-FTC), and full-time care, (FTC), states respectively. For olanzapine treatment, the monthly costs per patient were THB 44,347.28 for the Pre-FTC and THB 58,294.20 for the FTC state. The higher costs correlated with the higher dependence of care for those patients. Co-morbidity conditions had a substantial impact on total direct medical costs per month of both classifications of patients by cognitive function and dependence, accounting for 9.1%-10.0%. Informal care was also a significant burden of both groups of classified patients, leading to a major proportion of direct non-medical costs for these patients and their caregivers, (62.4% - 66.4%). Although the medication costs per month showed significant differences between patients treated with risperidone and those treated with olanzapine, the average monthly costs between two drug treatments of both different methods of categorised patients were not significantly different.

Conclusions: The costs of patients with BPSD relate to the high burden of patients and their caregivers, especially in the later stages of dementia in which patients experience a progressive decline in cognitive function and performing activity of daily living, (ADL), tasks. Behavioural disturbances are also correlated with the higher costs of BPSD patients, causing significantly high costs due to the patients' care. Thus, a reduction of disturbances of BPSD patients has a potential to decrease the burden on those patients, their families, their caregivers and healthcare systems.

5.1 Introduction

Dementia is a chronic illness in relation to cognitive decline which intensives as the population ages. Cognitive deterioration not only affects patients with dementia, but also influences the care providers as well as society in general. Behavioural and psychological symptoms of dementia (BPSD), known as neuropsychiatric symptoms (NPS), or non-cognitive symptoms, are common and frequently arise at any point of the disease progression in these patients. The symptoms are classified into different characteristics according to Neuropsychiatric Inventory (NPI) items as follows: psychotic (delusions or hallucinations); affective disorders (depression, agitation, anxiety, and irritability); and behavioural disturbances (apathy, disinhibition, aberrant motor behaviour, and euphoria). These symptoms are able to occur concurrently in people with dementia (Canevelli et al 2013). Some studies however used behavioural disturbances referring to symptoms associated with BPSD as previously stated (Mangone et al. 1993, Lyketsos 2000, Lyketsos et al. 2002, Kirbach et al. 2008, Mesterton et al. 2010, Bergvall et al. 2011). As previously stated, 50-90% of patients with dementia tend to experience BPSD during the course of their illness (Lyketsos 2000, Lawlor 2002, Lyketsos et al. 2002, Cerejeira, Lagarto and Mukaetova-Ladinska 2012, Torrisi et al 2016). The symptoms also increase according to the higher stages of disease severity. A study in rural Tanzania found a total of 88% of patients with dementia having at least one symptom of BPSD and 51% of those patients suffered from three or more symptoms of BPSD (Paddick et al. 2015). In Thailand, at least one current BPSD was reported by 90-100% of patients with Alzheimer's disease (Charernboon and Phanasathit 2014, Taemeeyapradit, Udomittipong and Tepparak 2014). Although most patients with dementia manifested symptoms related to BPSD at some point in their illness, these disturbances vary in frequency and severity. Apathy, depression, and agitation/aggression were generally reported as the main behavioural disturbances occurring in those patients (Levy et al 1996, Lyketsos et al. 2000, Lyketsos 2001, Lyketsos et al. 2002,

Fauth and Gibbons 2014, Paddick et al. 2015, Zhao et al. 2016, Sousa et al. 2016). Whilst, the most problematic symptoms reported in Thailand were apathy, aberrant motor behaviour, irritability, sleep disorders and depression (Pinidbunjerdkool, Saengwanitch and Sithinamsuwan 2014, Charernboon and Phanasathit 2014, Taemeeyapradit, Udomittipong and Tepparak 2014). In addition, several studies suggested behavioural disturbances were significant problems in patients with dementia. These disturbances correlated to cognitive decline in patients with advanced stage and functional decline, leading to worse prognosis, increased caregiver distress, increased burden on caregivers, greater care costs, earlier institutionalization and decreased quality of life of both patients and their caregivers (Mangone et al. 1993, Lyketsos et al. 2000, Getsios et al. 2002, Allegri et al. 2006, Shaji et al. 2009, Mohamed et al. 2010, Pinidbunjerdkool, Saengwanitch and Sithinamsuwan 2014, Torrisi et al. 2016, Lanctot et al. 2017, Cheng 2017, Shikimoto et al. 2018).

Due to the rapid growth of the number of people with dementia worldwide, care costs of these people, including people with BPSD are overwhelming, not only for the people who have it, but also for their families, their caregivers and healthcare systems (Canevelli et al 2013). According to the Alzheimer's Association (2015), there were nearly 15.7 million family caregivers in the US providing care for people with Alzheimer's disease or other types of dementia. WHO reported the total societal cost of dementia was $604 billion globally in 2010, consisting of direct medical costs, direct social costs, and costs of informal care; whilst a major part of these costs fell into the informal care (World Health Organisation 2012). In Sweden, the annual costs of patients with dementia, especially Alzheimer's disease, were $23,400, $56,800 and $71,400 for mild, moderate and severe stages, respectively (Mesterton et al. 2010). In the Scandinavian, (Sweden, Denmark, Finland and Norway), Jonsson et al. (2006) showed that the costs for patients with dementia were 172,000 SEK per annum ($1 = 8.09 SEK in 2003). Further, a range of costs per annual were 60,730 SEK to 374,962 SEK for mild to severe dementia. In addition, the costs of community care per annum were 26,662

SEK for other community care and 61, 222 SEK for special accommodation. Informal care costs were 6,338 SEK and 39,733 SEK per annual for lost production and lost leisure time, respectively. According to Ferretti et al. (2018), costs of patients with dementia per month in a cross-sectional study in Brazil, classified by the severity of disease, were $1,012.35 for mild, $1,683.18 for moderate and $1,372.20 for severe dementia. Ferretti, Nitrini and Brucki (2015) also reported the estimated monthly indirect costs of patients with dementia in Brazil, were $1,122, $1,508, and $1,644 for mild, moderate, and severe dementia, respectively. In Germany, a total cost of €38,165 per patient per annum was spent on informal care, which covered 81% of the societal costs for patients with mild and moderate dementia in a community setting (Schwarzkopf et al. 2011). Morris et al. (2015) reported that a patient diagnosed with Alzheimer's disease and suffering from agitation in the UK had excess costs of more than £4,000 per annum which accounted for 12% of the health and social care costs. In Spain, the costs of informal care for patients with dementia were approximately €1,214 per month (Farre et al. 2016). A study by Akerborg et al. (2016) reported the average cost of patients who were diagnosed with dementia in Sweden was estimated to be €43,200 per year. Cognitive function, functional ability, and NPS were significant predictors affecting the total annual cost of those patients (Akerborg et al. 2016). The study by Ku, Pai and Shih (2016) described informal care costs being estimated at 42% and 43% of the total costs in patients with mild and severe dementia, respectively. Whilst the monthly cost of informal care in Thailand was in a range of THB 4,814-25,872 for a patient with Alzheimer's disease (Turongkaravee 2008).

As previously stated, the behavioural disturbances add substantially to people with the illness and to the burden on caregivers, therefore it is necessary to give attention to this problem to help tackle the difficulties they experience. Levy et al. (2012) suggested that a decrease in the caregiver burden was attributable to the management of BPSD. Thus, the costs of care for patients with BPSD are a significant burden on household expenditures for patients

themselves and their caregivers since these symptoms relate to their quality of life and well-being. These costs also have a great impact on policy makers in deciding and improving the distribution of resources properly for those patients. Consequently, the main objective of this chapter is to indicate the costs of patients with behavioural and psychological symptoms of dementia and being treated with atypical antipsychotics, (risperidone or olanzapine), in Thailand.

5.2 Methods

5.2.1 Target population

Outpatients with BPSD at Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital meeting the following criteria were recruited:

- Aged 60 years and over (National Health Examination Survey in Thailand criteria, 2008-2009)
- Diagnosed with dementia (ICD-10: F00-F03) or Alzheimer's disease (ICD-10: G30) according to the International Statistical Classification of diseases and related health problems, (ICD-10: 10th revision, fifth edition, 2016), (World Health Organization 2015) and receiving olanzapine or risperidone for the treatment BPSD for at least the last two months, (during December 2016 to January 2017 and August 2017 to September 2017), before the interview.

In cases where patients with dementia had difficulties in their decision making due to cognitive impairment or patients having difficulties and were unable to answer the cost questionnaire by themselves, caregivers were then approached and encouraged to participate as being the respondents to the survey on behalf of all those patients. However, the caregivers had to meet the following defined criteria to be included in the study which included:

- Primary caregivers who lived with the patients; or
- Caregivers who visited to provide patient care for at least eight hours per day and had to provide the care for a minimum of three days per week for at least the last two months before the interview.

For more information regarding the inclusion and exclusion criteria of the patients and respondents see Chapter 3 (section 3.4.4).

5.2.2 Data settings and data collection process

A cross-sectional study and face-to-face interviews were undertaken in the outpatient departments at these hospitals: Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital in Thailand in 2017 during February to March 2017 and October to November 2017.

As previously mentioned in Chapter 3 (section 3.4.4), patients and/or their caregivers, who met the criteria and had received the information sheet were asked to decide whether to participate in the study. Consent forms were then administered to those who had agreed and a signed consent form was needed before beginning the interview. The interview process took approximately 30-45 minutes to collect sociodemographic factors of the patients, information about the caregivers, clinical status of patients, impact of caregiving on physical and mental health, and costs related to the treatment of BPSD.

The data gathering process in all patients with dementia and/or their caregivers who consented to participate in this thesis was divided into two phases as follows:

5.2.2.1 Phase I: The initial data collection was conducted between February and March 2017 focusing on Thammasat University Hospital. Based on this phase, a total of 49 cases were included in the study. There were 31 cases of risperidone-treated patients in one group and 18 cases of the olanzapine-treated patients in another group. However, in this thesis, the targeted subjects were calculated to be at least 36 patients per group as mentioned

in Chapter 3 (section 3.4.2). Consequently, the number of patients in the study needed to be increased in each group for the following reasons:

a) To have enough subgroups (in each arm) in the suggested models;

b) To allow the development of an appropriate model and have precise outcomes;

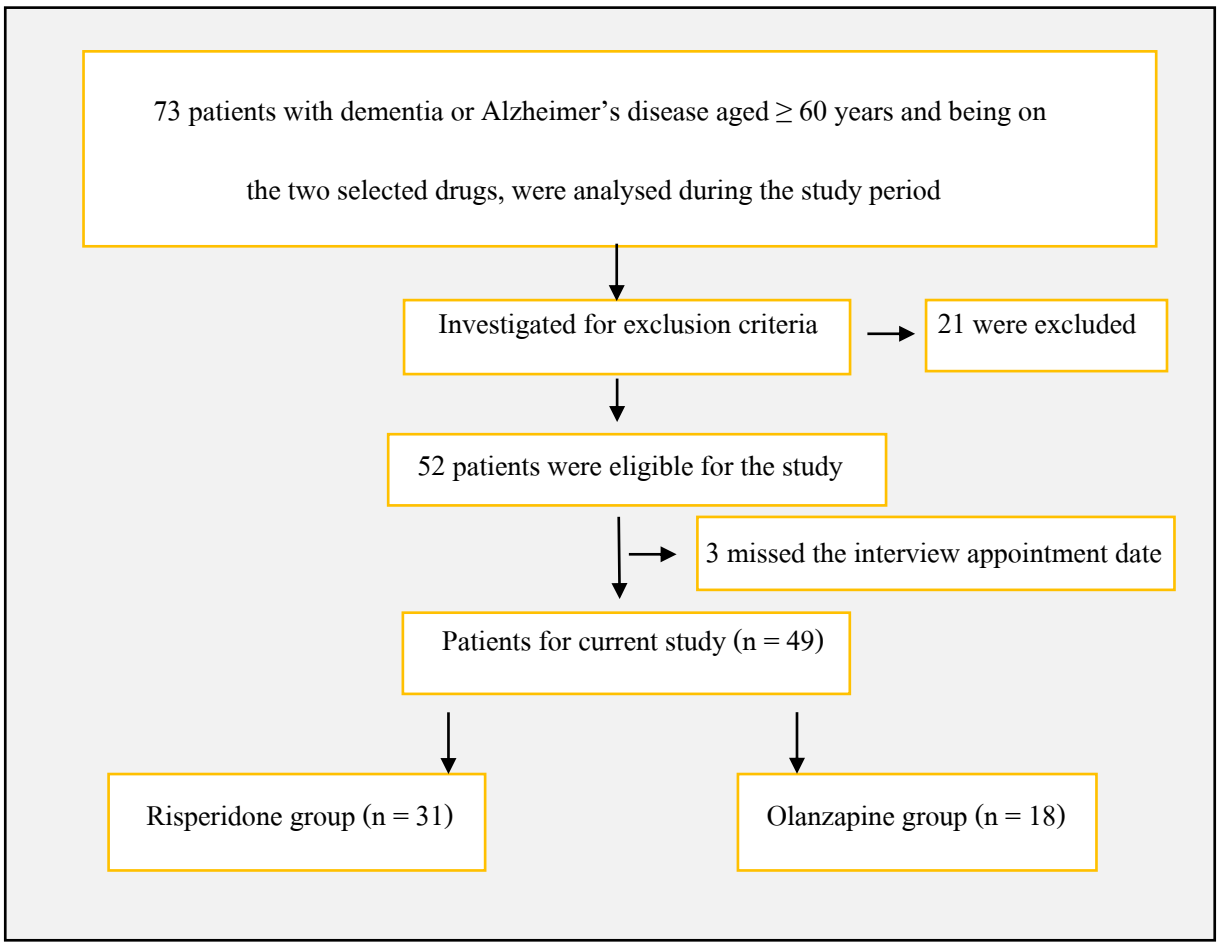
c) To provide population characteristics in a precise way; and

d) To identify transition probabilities, risk factors and developing predictions accurately.

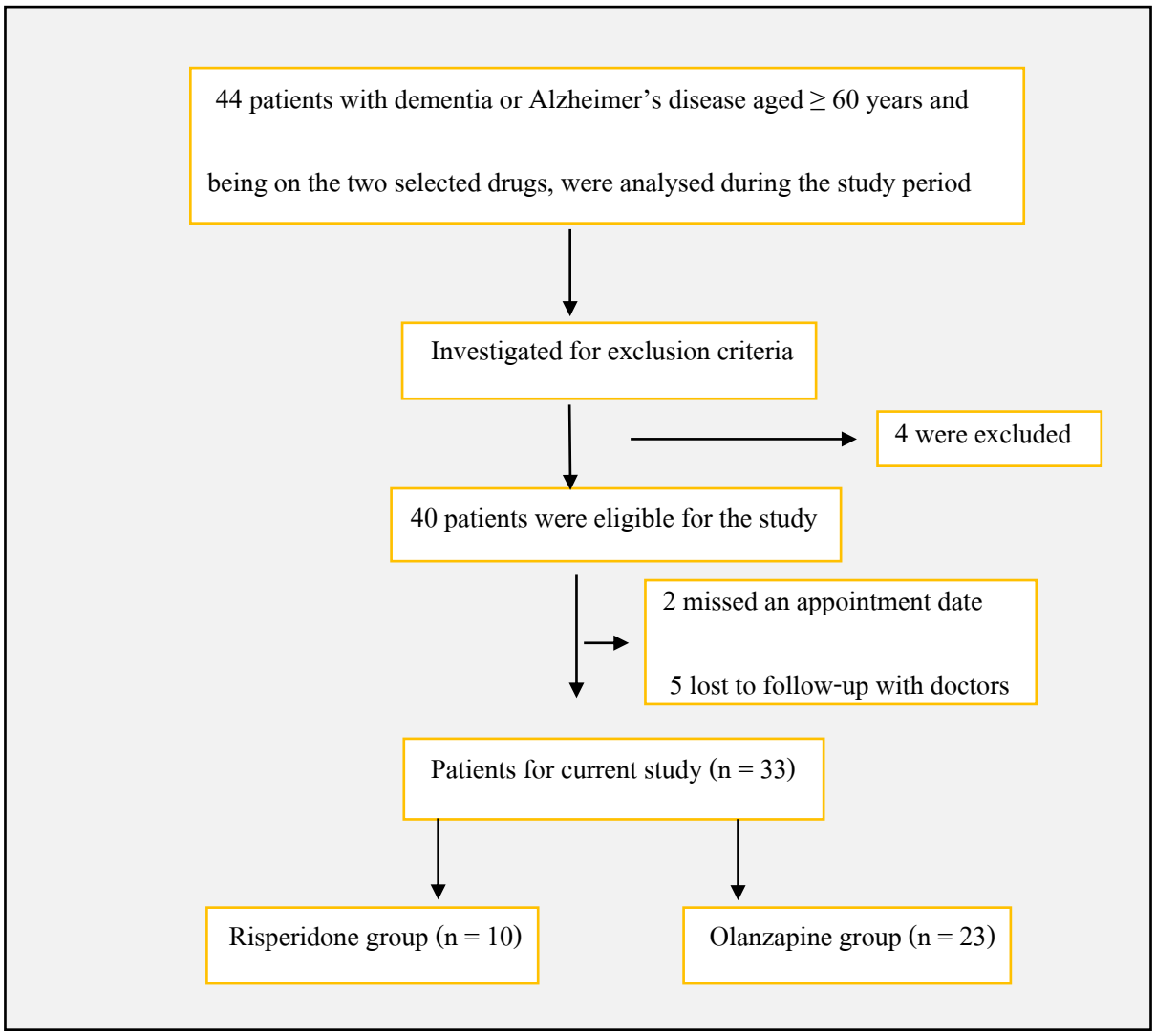
5.2.2.2 Phase II: The additional data collection was undertaken between October and November 2017. The data settings in this phase were at Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital. From this phase, a further 23 cases of patients using olanzapine treatment and a further 10 cases of risperidone treatment were included in this stage.

Based on the data as stated above, a total of 82 patients and/or caregivers were the respondents from the data collections in Phase I and Phase II from the two hospitals. These were evenly divided into 41 patients of each group. The respondents consisted of 33 cases from Thammasat University Hospital and 8 cases from Khon Kaen Rajanagarindra Psychiatric Hospital for both drug-treated groups. Flowchart 5.1A-5.1C show the flow diagram of the data collection process.

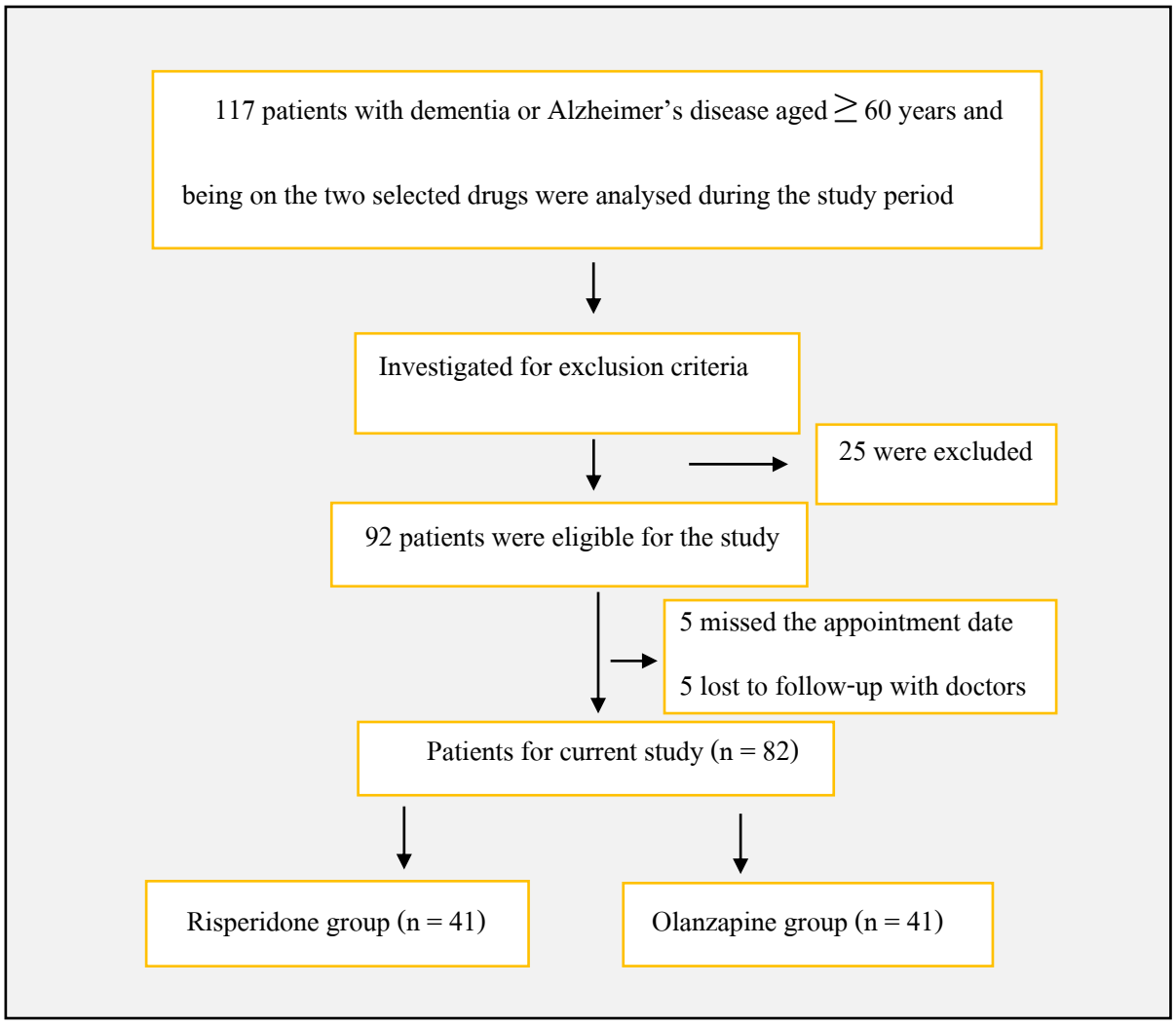
Flowchart 5.1A-5.1C: Flow diagram of data collection from Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital in Thailand



Flowchart 5.1A: Phase I- The data collection conducting between February and March 2017



Flowchart 5.1B: Phase II- The additional data collection conducted between October and November 2017



Flowchart 5.1C: An overall view of the data collection process of this study

5.2.3 Cost evaluation and analysis

5.2.3.1 Sociodemographic characteristics of patients and caregivers

Sociodemographic characteristics of patients were extracted, including gender, age, marital status, religion, education, current occupation, previous occupation, income, geographical area, residence, living arrangements, status of living, and health insurance coverage, were collected using a questionnaire. Regarding caregiver characteristics, these were collected using the same approach to that of patients. Thus, data included gender, age, marital status, religion, education, current occupation, previous occupation, patients' relationship, duration of providing care, caregiving time per day, the status of caregivers' living, and health problems due to providing care to those patients (see Appendix 4).

5.2.3.2 Classification of costs

Costs of patients with BPSD and receiving atypical antipsychotics (olanzapine or risperidone) were classified into two domains: patients' cognitive function and patients' dependence.

5.2.3.2.1 Patients' cognitive function

Cognitive function was assessed using the Thai Mental State Examination (TMSE). Due to the TMSE being developed based on the Mini-Mental State Examination (MMSE) (Folstein, Folstein and McHugh 1975), the cognitive severity was then classified as follows: mild (TMSE 21-26), moderate (TMSE 10-20), and severe stages (TMSE <10), respectively (Perneczky et al. 2006, Bond et al. 2012).

5.2.3.2.2 Classification by patients' dependence

The dependence of patients was assessed by activities of daily living (ADL) using the Barthel Index-Thai version. In the study, the scores were defined according to the Prasat Neurological Institute in Thailand (2014): 0-4 points = a total dependence, 5-8 points = a

severe dependence, 9-11 points = a moderate dependence and more than 12 points = a mild dependence (Prasat Neurological Institute 2014).

Caro et al. (2001) suggested health states were classified into pre-full time care (Pre-FTC) and full-time care (FTC). FTC was defined as a patient's dependency status when care provision or supervision was required for the greater part of each of the patient's day, regardless of the location of care.

To classify the patient's dependence into Pre-FTC and FTC states, this thesis used the ADL together with the physicians' assessments, based on the following scores: 0-8 points = the FTC state and more than 8 points = the Pre-FTC state.

5.2.3.3 Types of cost estimations

To estimate the costs of patients with BPSD and being treated with atypical antipsychotics from a societal perspective, cost definitions in this study were in line with the suggestions by Kobelt (2002) and the guideline of the health intervention and technology assessment in Thailand (The Health Intervention and Technology Assessment Program 2014).

The direct costs were then categorised into direct medical costs and direct non-medical costs. The indirect costs associated with the loss of productivity were excluded because all patients aged 60 years and above were retirees and therefore there were no productivity costs to assess. Furthermore, patients with BPSD were expected to consume different levels of costs during the course of treatment. The costs were then classified as follows:

5.2.3.3.1 Evaluation of direct medical costs

The costs included in the analyses were those associated with the medication, (risperidone or olanzapine), for the treatment of BPSD, additional care costs due to outpatient visits, additional care costs due to hospitalisation, costs for treating drug-induced adverse events or side effect-related costs, relapse-related costs, and costs for treating comorbidities or comorbidity-associated costs. The multiplication of the quantified utilisation of types of care

by cost for each type was used to estimate direct medical costs. In addition, a unit cost referring to an average charge for health care services, including the outpatient department and the inpatient department, was derived from both hospitals as mentioned above. The details of the direct medical costs are outlined below:

5.2.3.3.1.1 Medications for the treatment BPSD

The medications were based on a daily treatment cost of risperidone (0.25-2 mg daily) and olanzapine (2.5-5 mg daily), considering the average dosage regimen from several studies (Schneider et al. 2006, Scottish Intercollegiate Guidelines Network 2006, the American Geriatrics Society 2011, Sittironnarit 2011, Azermai et al. 2012, Sadowsky and Galvin 2012, British Columbia 2012). For each patient, the mean medical cost per month was calculated by the multiplication of the drug price, (risperidone or olanzapine), and the total quantity used during a one month period. The drug price was obtained from the Drug and Medical Supplies Information Centre (DMSIC), which was supplied by the Ministry of Public Health in Thailand, (Ministry of Public Health in Thailand 2017). To estimate the mean total medication cost of each drug per month, the calculation was the sum of the total monthly costs of drug used divided by the total number of patients receiving such drugs.

5.2.3.3.1.2 Costs associated with outpatient visits and hospital admissions

The frequency of outpatient visits and length of stay at the hospital (LoS) related to dementia per month were quantified. Estimating the monthly cost of outpatient visits of each patient was calculated by multiplying the frequency of visits to the outpatient department per month and the unit cost of the outpatient for each hospital. The unit costs of Thammasat University Hospital were THB 2,737.29 as reported in 2012, (THB 2,874.15 as adjusted to 2017 values), for the internal medicine clinic and THB 6,761.20, (THB 7,099.26 as adjusted to 2017 values), for the psychiatric clinic, respectively (Lapsuwansakul and Kunkum 2012). A unit cost of the outpatient clinic of Khon Kaen Rajanagarindra Psychiatric Hospital was

approximately THB 478 as reported in 2005, (THB 563 as adjusted to 2017 values), (Tangseree et al. 2005).

For costs of hospital admissions, the monthly hospitalised cost per patient was calculated by multiplying the frequency of hospital admissions, length of stay (LoS) and the unit cost of inpatients. The cost of an overnight hospital stay per diem was obtained from the data of each hospital, accounting for THB 13,292.26 as reported in 2012, (THB 13,956.87 as reported in 2017 values) at Thammasat University Hospital, and THB 17,956.00 as reported in 2005 (THB 21,134.21 as reported in 2017 values) at Khon Kaen Rajanagarindra Psychiatric Hospital, respectively (Tangseree et al. 2005, Lapsuwansakul and Kunkum 2012). However, the costs, especially unit costs of both hospitals, were calculated in different time periods. These costs then needed to be adjusted to a 2017 value using the consumer price index (CPI). The CPI is a common tool used as a measure of inflation. Whereby, the inflation is used as an indicator of the changes in prices which were paid by consumers for goods or services over a set period of time (Gray et al. 2012). For instance, the unit cost of Thammasat University Hospital was compiled in the fiscal year 2012, therefore this was adjusted to the present value in 2017, as all costs of the thesis were being reported in year 2017 in Thai currency (Baht, 1£ = THB 45). The costs were then inflated to reflect a 2017 value based on the CPI of Thailand, reported in the healthcare section (Bureau of Trade and Economic Indices of the Ministry of Commerce Thailand 2018). For the conversion to a present value, the equations were outlined below:

$$PV = price * IAF$$

or

$$PV = Price * \frac{CPI_{present}}{CPI_{past}}$$

where PV was a present value

IAF was an inflation adjustment factor (the CPI in a given year divided by the CPI in the baseline year)

CPI present was the Consumer Price Index of the present year

CPI past was the Consumer Price Index of the past year.

5.2.3.3.1.3 Additional payments

Costs, including additional costs from the patient healthcare insurance of both outpatient visits and hospital admissions and the dementia-associated comorbidity, were included. The frequencies of outpatient visits and length of stay at the hospital (LoS) per month were quantified for calculating the additional costs or self-pay patients due to non-covered services by their healthcare insurance coverage. These costs were counted by multiplying additional payments and the frequency of outpatient visits or hospitalised per month of each drug.
In addition, the cost of dementia-associated comorbidities, such as gout, osteoarthritis, hypertension, diabetes mellitus, hyperlipidaemia and stroke, was calculated based on the current medication used to treat comorbid conditions of each patient per month.

5.2.3.3.1.4 Costs for treating drug-induced adverse events

The adverse events from using olanzapine and risperidone were considered to calculate the costs for treating these events from such drugs. Antipsychotics-associated serious adverse events reported from published studies were anticholinergic events, (such as falls and constipation), weight gain, and extrapyramidal symptoms (EPSs) (Schneider et al. 2006, Maher et al. 2011, Riggs 2013, Ma et al. 2014, Tampi et al. 2016). Maglione et al. (2011) and Riggs (2013), reported the incidence of weight gain due to atypical antipsychotic use in the elderly was less than younger patients; thereby drug-induced weight gain was excluded in this analysis. Consequently, adverse event-associated costs in the study focused only on falls, constipation and EPS and these were calculated as follows:

I. Falls: The costs of managing drug-associated falls were estimated by the multiplication of three variables: the percentage of falling in elderly due to olanzapine or risperidone use, fall-required treatment in the elderly, and the costs of treatment due to falls. According to the study by Deberdt et al. (2005), that investigated a comparison of olanzapine and risperidone for the treatment of patients with BPSD, a double-blind, flexible-dose treatment in 494 patients with dementia and having moderate to severe psychotic symptoms, followed-up for 10-week periods from 64 sites across the US, the risk of falling was estimated to be 11.3% for patients treated with olanzapine, 9.2% for patients treated with risperidone, compared to 6.4% of those treated with a placebo. However, data from that study was not adopted in this thesis because the risk of falls was calculated from fall-associated costs deriving from primary collected data in a Thai setting. In this thesis, the fall-required treatment and costs of treating due to falls were taken from data from previous literatures which was in line with a previous study of a cost-benefit analysis of alternative and antipsychotic drug use for dementia in the UK (NHS Institute for Innovation and Improvement 2011). Rubenstein (2002) reported the fall-required treatment in the elderly people was estimated at 7.5%. An average cost of treatment due to falls in the elderly was approximately £2,264 per year as reported in 2010 by NHS Institute for Innovation and Improvement (2011). Thus, the cost of treating falls in this analysis was calculated to a monthly cost and then adjusted to a 2017 value using the GDP inflator (National Statistics of HM Government 2018). Purchasing Power Parity (PPP) was used to adjust for Thai Baht (THB) based on the data from the World Bank (World Bank Organisation 2018).

II. Constipation: Constipation management was based on laxative use according to the study by Martin et al. (2003) who investigated the adverse events of oral risperidone and oral olanzapine in long-term care patients with BPSD. That study found the increased percent for laxative use accounted for 1.8% of patients treated with risperidone and 10.2% for patients treated with olanzapine. According to the study by Pekmezaris et al.

(2002), it reported that the cost for the treatment of constipation was $2.11 per day. Additionally, 49% of treatments were fleet enema and milk of magnesia (MOM) from a total of 31 elderly patients with chronic constipation. Thus, this thesis assumed that the management of constipation focused only on the milk of magnesia owing to this being the only drug approved in the National List of Essential Medicines (NLEM) of Thailand. The dosage regimen of milk of magnesia (MOM) for constipation treatment in the elderly was assumed to be 15-30 mg per day up to twice daily (Gandell et al. 2013, Sethi 2012). This is consistent with the clinical practice guideline for treating constipation in Thailand (Kittinouvarat, 2009 and Thai Neurogastroenterology and Motility Society, 2018). Consequently, the estimated cost for treating drug-induced constipation per month was calculated by multiplying the increased per cent for laxative use due to patients treated with olanzapine or risperidone, the mean days of laxative administration, and the medication cost for the laxative drug. Furthermore, the medical cost was obtained from the DMSIC in Thailand (Ministry of Public Health in Thailand 2018).

III. Extrapyramidal symptoms (EPSs): Costs for managing drug-induced EPS events were computed by multiplying the incidence of the treatment-emergent EPSs of each drug by costs of emergency room visits. According to a comparison of olanzapine to risperidone in the treatment of BPSD patients by Deberdt et al. (2005), this showed that the incidence of treatment-emergency EPSs was 49.6% for risperidone-treated patients, 35.6% for olanzapine-treated patients, and 29.5% for the placebo group. However, the incidence of drug-induced EPSs in this thesis's analysis was based on primary collected data in a Thai setting. As the Canadian Psychiatric Association (2005) suggested, drug-induced EPS events tended to be managed by a physician's visit either for reducing drug dosage or switching to other medications. This is similar to the clinical practice guideline of dementia in Thailand for management the adverse events of patients (Prasat Neurological Institute in Thailand 2014). Thus, one extra physician visit per year was assumed in calculating the costs for

management of EPSs. In addition, this thesis assumed that the treatment-emergent EPSs would occur at the emergency service point. The unit cost of the emergency department from Thammasat University Hospital, adjusted to a 2017 value, was used to calculate this cost (Lapsuwansakul and Kunkum 2012).

5.2.3.3.1.5 Costs of drug-associated relapse

A frequency of behavioural and psychological symptoms in patients with dementia was more likely to increase mortality and morbidity in these patients (Peters et al. 2015). The treatment of patients with those symptoms should be concerned over the potential response to drugs. The consequence of the failure of the treatment was serious, leading to a greater risk of relapse of those patients. As a result, the relapse risks were taken into account to compute the cost analyses in this thesis. Although several guidelines recommended the short-term use of antipsychotic drugs to treat patients with BPSD, the management of these symptoms, including agitation, aggression, and psychosis, showed benefits in the long-term treatment, for those patients who had more severe BPSD or persistent symptoms according to the systematic review by Leeuwen E et al. (2018) and a retrospective, population-based cohort study in Ontario, Canada between 2009 and 2012 by Mast et al. (2016). For this reason, the relapses due to using olanzapine or risperidone were included in the cost analyses. The relapse-associated costs of patients were classified into those requiring hospitalisation and not requiring hospitalisation.

I. The relapse-associated costs requiring hospitalisation: To estimate relapse-associated costs, these were calculated by multiplying the relapse rate of each drug, (hospitalisation rates associated with atypical antipsychotic adherence and hospitalisation risk ratios), the length of stay spent in hospital due to such relapses, relapse frequency and costs of admission.

The study by Schneider et al. (2006), a large double-blind, placebo-controlled trial in 421 outpatients with Alzheimer's disease with psychosis, aggression or agitation to compare effectiveness of risperidone, olanzapine, quetiapine and placebo in the US, suggested the number of patients discontinuing the treatment because of the lack of efficacy was found to be 39% of Alzheimer's patients treated with olanzapine, 44% of Alzheimer's patients treated with risperidone, and 70% of those Alzheimer's patients using a placebo. However, antipsychotics are currently off-label use in dementia, leading to a lack of information with regard to the relapse risks of these patients. Thus, the relapse rates and lengths of stay at the hospital due to relapses adopted data from a schizophrenia study.

For the treatment with atypical antipsychotics, adherence to the treatment was a significant factor, leading to increased hospital admissions and poor conditions of patients regarding the relapse of these patients (Haddad, Brain and Scott 2014). Thus, this thesis made the assumption that all patients were fully adherent to their treatments. For the annual rate of admission associated with patients with atypical antipsychotic being fully adherent to their treatment, data in this analysis were derived from the previous study of adherence to treatment with antipsychotic drugs for schizophrenia. Gilmer et al. (2004), who conducted data from 2,801 person-years of Medicaid Beneficiaries with schizophrenia during 1998 and 2000 in San Diego County, USA, reported that the annual rate of admission associated with patients' fully adherent to atypical antipsychotic treatment was estimated at 7.0%.

In addition, data of the hospitalisation risk ratios were taken from the literature for effectiveness of antipsychotic drugs for patients with chronic schizophrenia. According to Lieberman et al. (2005), the large randomised, double-blind study in a total 1,493 patients with schizophrenia who were assigned to receive olanzapine, risperidone, perphenazine, quetiapine and ziprasidone conducted in 57 sites in the US or Clinical Antipsychotic Trials of Intervention Effectiveness study, (CATIE): Phase 1, the hospitalisation risk ratios of the two

medications of interest were 0.29-fold of olanzapine-treated patients and 0.45-fold of risperidone-treated patients, respectively. Thus, the relapse rates requiring hospitalisation of patients due to olanzapine or risperidone treatment in this thesis were 2% of olanzapine and 3.2% of risperidone based on the multiplication of the adherence to treatment of patients and hospitalisation risk ratio of the drugs. This is in line with the cost-effectiveness study of oral olanzapine and other oral atypical antipsychotics in the treatment of patients with schizophrenia in the US (Furiak, et al. 2009).

Moreover, the mean number of days spent in hospital per year used in this thesis obtained data from previous literature of olanzapine and risperidone use on the risk of psychiatric hospitalization of patients with schizophrenia in the US. Ascher-Svanum et al. (2004) reported the mean number of days spent in hospital per year was 9.9 days for patients receiving olanzapine and 14.5 days for patients receiving risperidone. Then these values were applied in calculating the mean number of days spent in hospital per year in this thesis. This is also in line with a cost analysis in a comparison of olanzapine, risperidone, quetiapine, ziprasidone and haloperidol, of the treatment of patients with schizophrenia in Thailand Kongsakorn et al. (2005).

According to Kongsakorn et al. (2005), it was suggested patients with schizophrenia were assumed to have only one relapse per patient per year due to antipsychotic drug use for their treatment. This thesis used the same assumption regarding the number of relapses per patients per year as in Kongsakorn's study.

Furthermore, costs associated with hospital admission were obtained from data from Thammasat University Hospital, adjusted to 2017 values (Lapsuwansakul and Kunkum, 2012).

II. The relapse-associated costs not requiring hospitalisation: The proportion of inpatient-to-outpatient rates of relapse and physician's visits were taken into account in the

calculation of relapse-associated costs not requiring hospitalisation. The assumption of the relapses requiring hospitalisation whether all patients were fully adherent with their treatments was also adopted for the relapses not requiring hospitalisation.

According to Furiak et al. (2009), the cost-effectiveness study of olanzapine and other oral atypical antipsychotics for treating schizophrenia in the US, assumed that the proportion of relapse rates of inpatient-to-outpatient was assumed to be 1.0 for patients who were fully adherent to their treatment. Similarly, the study by Edwards et al. (2005) reported relapse rates for requiring hospital to not requiring hospital were 1.0 in patients with full adherence to their treatment. Therefore, this thesis has taken that value for calculating the proportion of inpatient-to-outpatient rates of relapse of patients using olanzapine or risperidone treatment. Subsequently, the relapse rates not requiring hospitalisation in this analysis were 2.0% and 3.2% of olanzapine and risperidone, respectively, based on multiplying the relapse rates requiring hospitalisation of patients due to olanzapine or risperidone treatment and the proportion of inpatient-to-outpatient rates of relapse.

Based on the clinical practice in Thailand, the management of patient's relapses not requiring hospitalisation depended upon the physician's visits for making a decision regarding the patient's treatment. Thus, this thesis assumed that patients with BPSD and being treated with olanzapine or risperidone would require one extra physician's visit per year according to the assumption of the schizophrenia study in Thailand, where patients with schizophrenia and treated with antipsychotics had one relapse per patient per year (Kongsakorn et al. 2005). Further, the cost for the physicians' visit at a psychiatric department was obtained from Thammasat University Hospital, adjusted to 2017 values (Lapsuwansakul and Kunkum 2012).

Due to a lack of data associated with adverse events and relapses which were categorised according to the disease severity, (mild, moderate and severe stages), and patients'

dependency, (Pre-FTC and FTC), of olanzapine and risperidone in the treatment of dementia, this thesis made the assumption that costs for treating adverse effects and costs for relapses due to olanzapine and risperidone treatments had the same values amongst patients with mild, moderate and severe stages and between those patients in the Pre-FTC and FTC stages.

5.2.3.3.2 Evaluation of direct non-medical costs

By estimating the direct non-medical costs, these covered patients' out-of-pocket expenses, travel, additional food, accommodation, paid caregivers, and informal care.

5.2.3.3.2.1 Costs of travel, accommodation and food

These costs were quantified by multiplying the patients' expenses for travel, accommodation and extra food, and the frequency of hospital visits of both outpatient visits and hospital admissions.

5.2.3.3.2.2 Costs of other treatments

Other treatments, namely vitamins, food supplements, milk, liquid diet, equipment for patients with dementia and disposable diapers, were also included for the cost analyses.
In addition, caregiving time-associated costs in this thesis were classified into paid caregiver time and unpaid caregiver time, following the study by Clipp and Moore (1995).

5.2.3.3.2.3 Costs of paid caregiving

These costs were associated with out-of-pocket expenses for the hiring of caregivers or home helpers whose time was solely for providing care to patients.

5.2.3.3.2.4 Costs of informal care or unpaid caregiving

An opportunity cost method was used to estimate the value of unpaid caregiving for providing care to patients, based on the principle on whether the time spent in providing care could be earned as same as paid workers, using market wage rates (Berg, Brouwer and Koopmanschap 2004). Accordingly, costs of informal care were calculated using time spent

in patients' care per day multiplied by the wage per hour. The respondents were asked to estimate the number of hours spent in care provision for patients per day. However, the number of hours counted toward caring for patients was maximised to 16 hours a day, excluding sleeping time. The hourly wage was calculated by the average Gross National Income (GNI) per capita per year, divided by working hours, at 52 weeks a year and 48 hours a week (Department of Labour Protection and Welfare 2018, The Health Intervention and Technology Assessment Program 2014). The GNI was used in this analysis as following the recommendation by the HITAP guideline in Thailand and the World Health Organisation (The Department of Immunization, Vaccines and Biologicals 2008, The Health Intervention and Technology Assessment Program 2014). The GNI per capita in Thailand was reported at THB 205,339.00 per year, based on data from the National Economic and Social Development Board, the Government of Thailand (Office of the National Economic and Social Development Board 2018).

5.2.4 Data analyses

Data on patients' and caregivers' sociodemographic and health characteristics, clinical assessments of patients, direct medical costs and direct non-medical costs due to dementia, were analysed by descriptive statistics, categorised according to the classification of patients, including cognitive function and dependence. The analysis produced the results in percent, mean and standard deviation which had been performed using Microsoft® Excel version 2013.

5.3 Results

5.3.1 Patient and caregiver characteristics

A total of 82 patients and/or patients' caregivers from the outpatient departments of the two hospitals in Thailand were interviewed, with 41 patients receiving risperidone, and the remaining patients receiving olanzapine. Regarding the completed questionnaires, the section

on the characteristics of patients was completed by the primary caregivers, as proxy respondents, accounting for 97.56%, while the remaining percentage relates to one patient receiving risperidone with mild dementia and another one receiving olanzapine with mild dementia who completed the questionnaire in this section by themselves (2.44%). The section of cost data was completed by caregivers (98.78%) and one patient receiving olanzapine with mild dementia (1.22%). For the section of characteristics of caregivers, a total of 81 caregivers had completed by themselves (100%), however one patient receiving olanzapine with mild dementia had no caregiver for providing care.

5.3.1.1 Overall patient characteristics

Table 5.1 shows the patient characteristics. Patients receiving risperidone were predominantly female gender (65.85%) and a mean age of 80.37 (± 1.28) years. For the olanzapine treated group, 73.17% of these patients were of the female gender with a mean age of 76.34 (± 1.41) years.

The largest proportion of the patients' educational level was primary school accounting for 65.85% of the risperidone treated group and 58.54% of the olanzapine treated group.

All patients in both treatment groups were retired. The main sources of income of both groups were supported by public funds and their children. Most patients receiving risperidone lived in the Bangkok metropolitan areas (56.10%), such as Pathum Thani and Nonthaburi. Conversely, a total of 56.10% of the olanzapine treated group lived in provincial areas, namely Phra Nakhon Si Ayutthaya, Khon Kaen and Maha Sarakham.

None of the patients in both drug groups lived alone. As the risperidone treated group illustrated, most patients were living with their children (85.37%), followed by living with their spouse (31.71%). Similarly, the patients receiving olanzapine were 70.73% living with their children and 43.90% with their spouse. Most patients were diagnosed Alzheimer's disease accounting for 87.8% of risperidone treated patients and 85.37% of olanzapine

treated patients. The diagnosis of unspecified dementia was 9.76% of the risperidone group, whilst it was found to be 12.2% in the olanzapine group. Mixed dementia had the lowest percentage of diagnosis in those patients accounting for 2.44% of both risperidone and olanzapine treated groups.

The meantime of patients diagnosed with dementia was lower in the risperidone treated patients (2.34 years) compared with the olanzapine treated patients (2.63 years). Mean TMSE score was also lower in the risperidone treated group than the olanzapine treated group 14.2 (±1.21) for the risperidone and 16.37 (± 1.17) for the olanzapine. These indicated that most patients of both treatment groups were suffering from moderate dementia.

Main comorbidity conditions of patients of both treatment groups were hypertension, (56.10% of olanzapine treated patients and 51.22% of risperidone treated patients), followed by hyperlipidaemia, (34.15% of olanzapine treated patients and 24.39% of risperidone treated patients), and diabetes mellitus, (19.51% of olanzapine treated patients and 29.27% of risperidone treated patients). The percentage of patients with osteoarthritis in the risperidone treated group was nearly twice as high as the olanzapine treated group, accounting for 14.63% and 7.32%, respectively. Other comorbidities, namely heart disease, liver disease, thyroid, arrhythmia, thalassemia, anaemia, pulmonary embolism, and gastrointestinal tract disease, showed a higher incidence in the olanzapine treated group than in the risperidone treated group, by 4.88%.

The percentage of non-adverse events was 46.34% of risperidone treated patients and 19.51% of olanzapine treated patients. Sedation or drowsiness was the most frequent adverse event occurring in both treatment groups, accounting for 36.59% of the olanzapine group and 31.71% of the risperidone group. Drug-induced EPSs, (dystonia, akathisia, and tardive dyskinesia), were found to be higher risks in the risperidone prescribed patients (19.50%) than those olanzapine prescribed patients (7.32%). The risk of falls in patients receiving

risperidone was twice as higher than in the olanzapine treated patients, accounting for 4.88% and 2.44%, respectively.

The Civil Servants Medical Benefits Scheme (CSMBS) was the main health insurance coverage scheme of both drug groups. However, this was a lower percentage in the risperidone treated group (60.98%) compared with the olanzapine treated group (80.49%). Conversely, the Universal Coverage (UC) scheme had a higher proportion in the patients receiving risperidone accounted for almost 32% compared with only 4.88% in the olanzapine treated group. The out-of-pocket payments were predominantly in the olanzapine treated group compared with the risperidone group accounting for 14.63% and 7.32%, respectively.

Table 5.1: **Characteristics of patients from the data collection based on Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital, in Thailand**

Characteristics	Risperidone (N = 41)	Olanzapine (N = 41)
Patient		
Sex [n (%)]		
Male	14 (34.15)	11 (26.83)
Female	27 (65.85)	30 (73.17)
Age, year [mean (SD)]	80.37 (8.22)	76.34 (9.00)
Marital status [n (%)]		
Married	18 (43.90)	22 (53.66)
Widowed	21 (51.22)	18 (43.90)
Divorced/Separated	2 (4.88)	1 (2.44)
Religion [n (%)]		
Buddhism	41 (100.00)	39 (95.12)
Islam	-	1 (2.44)
Christian	-	1 (2.44)
Education [n (%)]		
Never attend school/lower primary education	6 (14.63)	2 (4.88)

Characteristics	Risperidone (N = 41)	Olanzapine (N = 41)
Primary education	27 (65.85)	24 (58.54)
Lower-secondary education	1 (2.44)	3 (7.32)
Upper-secondary education	1 (2.44)	4 (9.76)
Certificate/diploma	2 (4.88)	2 (4.88)
Bachelor's degree	4 (9.76)	6 (14.63)
Current occupation [n (%)]		
Retired	41 (100.00)	41 (100.00)
Income sources [n (%)]		
Pension	7 (17.07)	8 (19.51)
Deposit/interest	1 (2.44)	1 (2.44)
Public fund	23 (56.10)	25 (60.98)
Spouse's	-	6 (14.63)
Child's	26 (63.41)	23 (56.10)
Other income	7 (17.07)	6 (14.63)
Living area [n (%)]		
Bangkok	3 (7.32)	6 (14.63)
Bangkok metropolitan	23 (56.10)	12 (29.27)
Countryside/Province	15 (36.59)	23 (56.10)
Residence [n (%)]		
Detached house	34 (82.93)	33 (80.49)
Townhouse, Town home	7 (17.07)	5 (12.20)
Shop house/Row house	-	2 (4.88)
Other	-	1 (2.44)
Living arrangement [n (%)]		
House owner	16 (39.02)	20 (48.78)
Rental	1 (2.44)	-
Resident	24 (58.54)	21 (51.22)
Status of living [n (%)]		

Characteristics	Risperidone (N = 41)	Olanzapine (N = 41)
Living with spouse	13 (31.71)	18 (43.90)
Living with child	35 (85.37)	29 (70.73)
Living with the third generation	5 (12.20)	15 (36.69)
Living with relatives	1 (2.44)	3 (7.32)
Others	-	4 (9.76)
Diagnosis [n (%)]		
Alzheimer's disease	36 (87.80)	35 (85.37)
Unspecified dementia	4 (9.76)	5 (12.20)
Mixed dementia	1 (2.44)	1 (2.44)
Time since diagnosed with dementia, year [mean (SD)]	2.34 (1.71)	2.63 (1.82)
Mean TMSE score [mean (SD)]	14.17 (7.75)	16.37 (7.46)
Cognitive impairment [n (%)]		
Mild	10 (24.39)	12 (29.27)
Moderate	15 (36.59)	19 (46.34)
Severe	16 (39.02)	10 (24.39)
Non-comorbidity conditions [n (%)]	7 (17.07)	4 (9.76)
Comorbidity conditions [n (%)]		
Gout	2 (4.88)	2 (4.88)
Osteoarthritis	6 (14.63)	3 (7.32)
Asthma	-	1 (2.44)
Chronic renal failure	1 (2.44)	2 (4.88)
Hypertension	21 (51.22)	23 (56.10)
Diabetes Mellitus	12 (29.27)	8 (19.51)
Hyperlipidaemia	10 (24.39)	14 (34.15)
Stroke	4 (9.76)	3 (7.32)
Cancer	2 (4.88)	1 (2.44)
Other comorbidities	8 (19.51)	10 (24.39)

Characteristics	Risperidone (N = 41)	Olanzapine (N = 41)
Non adverse events [n (%)]	19 (46.34)	8 (19.51)
Adverse events [n (%)]		
Dystonia	4 (9.76)	2 (4.88)
Falls	2 (4.88)	1 (2.44)
Edema	3 (7.32)	3 (7.32)
Weight gained	1 (2.44)	9 (21.95)
Sedation/drowsiness	13 (31.71)	15 (36.59)
Other adverse events	6 (14.63)	1 (2.44)
Health insurance coverage [n (%)]		
Universal Healthcare scheme (UC)	13 (31.71)	2 (4.88)
Civil Servants Medical Benefits (CSMBS)	25 (60.98)	33 (80.49)
Out-of-pocket expense	3 (7.32)	6 (14.63)

5.3.1.2 Overall Caregiver Characteristics

As Table 5.2 shows, a total of 81 primary caregivers were investigated from 2 hospitals, with 41 caregivers of patients receiving risperidone being the respondents and 40 caregivers of patients receiving olanzapine being the respondents. For the olanzapine group, there was one patient who had no caregiver in providing care to him.

Regarding the caregiver characteristics, most caregivers were female, accounting for 75.61% of the risperidone group and 80.00% of the olanzapine group. The mean age of the caregivers showed no significant differences in accounting for 54.93 years in the risperidone group and 53.03 years in the olanzapine group.

The educational levels of caregivers of the risperidone group were 39.02% graduated with a bachelor's degree, followed by 29.27% to primary education. Similarly, caregivers of the

olanzapine group were 32.5% achieving a bachelor's degree level, followed by 27.50% achieving primary education level.

For the current occupation, there were differences in both groups of caregivers. Caregivers of the risperidone group showed that 56.10% were unemployed. Conversely, 57.50% of caregivers of the olanzapine group were employed. However, the majority of caregivers were housewives, accounting for 41.46% of the risperidone treated group and 17.50% of the olanzapine treated group. It seems that almost 20% of caregivers in each group were the spouse, while at least 50% were daughters providing care to the patients in each group.

In comparison to the olanzapine treatment, caregivers of the risperidone treated patients showed a significantly higher percentage of stopping work to provide care for the patients (20%). The mean duration time of stopping work to provide care to patients was 8.24 months in the risperidone group and 6.15 months in the olanzapine group. The mean time spent in patients' care was not significantly different in both drug groups, accounting for 12.51 hours a day in the risperidone group and 12.87 hours a day to the olanzapine group.

In addition, the impacts of the patient's illness on caregivers due to patients' care were classified into physical health conditions, (such as low back pain, knee pain, shoulder pain, muscle pain, and quality of sleep), and mental health problems, (such as distress, anxiety, stress, and depression). The physical health conditions in the risperidone group showed that nearly half of total caregivers had no problems due to providing care, accounting for 48.78%. Other physical health conditions in the risperidone group were found to be 7.32% with slight problem levels, 24.39% at moderate problem levels, 17.07% at severe problem levels and 2.44% at extreme problem levels. Similarly, caregivers of the olanzapine group experiencing physical health conditions were associated with 52.50% having no problems, 15.00% having slight problems, 22.50% having moderate problems, and 10% having severe problems, but none were found in extreme problem levels. Regarding mental health problems, this found

that the percentage of no problems was similar to that of severe problems, accounting for 29.27% in caregivers of the risperidone group. There were 10% of caregivers in the risperidone treated group having extreme problems. In caregivers of the olanzapine group, the highest proportion of mental health problems had similar percentages in both "no problems" and "slight problems" being 25%. There were approximately 10% of caregivers in the olanzapine treated group having extreme mental health problems. Furthermore, stress and sleep quality were significant impacts on caregivers in the risperidone treated group due to patients' care, accounting for 68.29% and 53.66%, respectively. The remaining problems of caregivers in the risperidone treated group associated with caregiving were associated with musculoskeletal disorders (43.90%), distress (34.15%), depression (7.32%), and other health problems (2.44%). For caregiver in the olanzapine treated group, 65% of caregivers experienced stress and caregiver distress was found to be approximately 33.00%. The remaining problems of caregivers in the olanzapine treated group due to providing care were musculoskeletal disorders (30.00%), sleep quality (27.50%), depression (15.00%) and other health problems (7.50%).

Table 5.2: **Characteristics of caregivers from the data collection based on Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital, in Thailand**

Characteristics	Risperidone (N = 41)	Olanzapine (N = 40)
Caregiver		
Sex [n (%)]		
Male	10 (24.39)	8 (20.00)
Female	31 (75.61)	32 (80.00)
Age, year [mean (SD)]	54.93 (11.83)	53.03 (11.84)
Marital status [n (%)]		
Single	10 (24.39)	6 (15.00)
Married	27 (65.85)	30 (75.00)

Characteristics	Risperidone (N = 41)	Olanzapine (N = 40)
Widowed	1 (2.44)	4 (10.00)
Divorced/Separated	3 (7.32)	-
Religion [n (%)]		
Buddhism	40 (97.56)	40 (100)
Islam	-	-
Christian	1 (2.44)	-
Education [n (%)]		
Never attend school/lower primary education	-	-
Primary education	12 (29.27)	11 (27.50)
Lower-secondary education	3 (7.32)	2 (5.00)
Upper-secondary education	3 (7.32)	10 (25.00)
Certificate/diploma	3 (7.32)	-
Bachelor's degree	16 (39.02)	13 (32.50)
Higher bachelor's degree	4 (9.76)	4 (10.00)
Others	-	
Current occupation [n (%)]		
Unemployment	23 (56.10)	17 (42.50)
Employment	18 (43.90)	23 (57.50)
Type of current occupation [n (%)]		
Housewife/Househusband	17 (41.46)	7 (17.50)
Wage-earner	4 (9.76)	4 (10.00)
Farmer/Fisherman	-	1 (2.50)
Self-employed/Owner	3 (7.32)	7 (17.50)
Government officer	3 (7.32)	6 (15.00)
State enterprise employee	1 (2.44)	2 (5.00)
Company employee	2 (4.88)	1 (2.50)
Retiree	7 (17.07)	9 (22.50)

Characteristics	Risperidone (N = 41)	Olanzapine (N = 40)
Others	4 (9.76)	3 (7.50)
Previous occupation [n (%)]		
Unemployment	24 (58.54)	26 (65.00)
Employment	17 (41.46)	14 (35.00)
Stop work due to provide patient's care [n (%)]	8 (19.51)	5 (12.50)
Duration of stopping work due to provide care, month [mean (SD)]	8.24 (20.38)	6.15 (21.19)
Relationship with patient [n (%)]		
Spouse	8 (19.51)	8 (20.00)
Son	1 (2.44)	3 (7.50)
Daughter	25 (60.98)	20 (50.00)
Relatives/Cousin	-	1 (2.50)
Niece/Nephew	1 (2.44)	1 (2.50)
Friend/Neighbour	-	-
Maid/Paid caregiver	3 (7.32)	6 (15.00)
Others	3 (7.32)	1 (2.50)
Hours spent for caregiving patients [mean (SD)]	12.51 (3.95)	12.87 (5.69)
Physical problem [n (%)]		
No problems	20 (48.78)	21 (52.50)
Slight problems	3 (7.32)	6 (15.00)
Moderate problems	10 (24.39)	9 (22.50)
Severe problems	7 (17.07)	4 (10.00)
Extreme problems	1 (2.44)	-
Mental problem [n (%)]		
No problems	12 (29.27)	10 (25.00)
Slight problems	6 (14.63)	10 (25.00)

Characteristics	Risperidone (N = 41)	Olanzapine (N = 40)
Moderate problems	7 (17.07)	8 (20.00)
Severe problems	12 (29.27)	8 (20.00)
Extreme problems	4 (9.76)	4 (10.00)
Overall health problems from providing care to patients [n (%)]		
Depression	3 (7.32)	6 (15.00)
Stress	28 (68.29)	26 (65.00)
Distress	14 (34.15)	13 (32.50)
Quality of sleep	22 (53.66)	11 (27.50)
Musculoskeletal disorders	18 (43.90)	12 (30.00)
Others	1 (2.44)	3 (7.50)

5.3.1.3 Patient and caregiver characteristics classified by cognitive function

According to a classification of patients by cognitive function in this thesis, the disease severity was measured by TMSE scores which were categorised as follows: mild (TMSE=21-26), moderate (TMSE=10-20), severe stages (TMSE<10). The profile of patients receiving risperidone were categorised according to severity being mild (24.39%), moderate (36.59%), and severe stages (39.02%) of the disease. The profile of patients receiving olanzapine were mild (29.27%), moderate (46.34%), and severe stages (24.39%).

Table 5.3 shows that most risperidone treated patients were female, being 70%, 53.33%, and 75% of those with mild, moderate and severe stages. Similarly, most patients treated with olanzapine were female accounting for 41.67%, 94.74%, and 70% of those with mild, moderate and severe stages, respectively.

The range of mean ages of patients was 77.80-83.44 years for the risperidone treatment and 73.58-78.94 years for the olanzapine treatment. The highest of the mean age of patients was

found in the risperidone group within the severe stage (83.44 years). Primary education was the predominant educational level in both treatment groups (61.68%). The highest percentage of educational levels of the risperidone treated patients showed 75.00% achieving a primary level of those within the severe stage. Similarly, achieving the primary level was the highest proportion of the educational level of the olanzapine treated patients within the severe stage (70.00%).

The main source of income of the olanzapine treated patients within the severe stage was public funds (90%). In the risperidone treated group, the highest percentage of the source of income was from their children in the mild stage (80%).

Patients living with their children were the highest percentage of all severity levels of both treatment groups, followed by those living with their spouse. All risperidone treated patients within the severe stage were living with their children. The highest percentage in the olanzapine group showed that 83.33% of patients within the mild stage of the disease lived with their children. In both the two treatment groups, none of the patients of all severity levels were living alone.

Patients diagnosed with Alzheimer's disease were the highest percentage within both treatment groups of which the risperidone treated patients were 36.59% within the severe stage, followed by 34.15% within moderate stage and 17.07% within mild stage. For the olanzapine group, patients diagnosed with Alzheimer's disease accounted for 21.95% within the mild stage, 43.90% within the moderate stage and 19.52% within the severe stage. The diagnosis regarding unspecified dementia was 7.31% with mild and 2.44%with moderate stages of the risperidone treated patients, whilst the olanzapine treated patients showed 7.32% within the mild stage, 2.44% within the moderate stage and 2.44% within the severe stage. Mixed dementia was found at only 2.44% in the severe stage of both risperidone and olanzapine treatments.

For patients treated with risperidone, time from the first diagnosis ranged between 2.06 – 2.67 years with the longest time being found in cases at the moderate stage. In the olanzapine group, the range of time from the first diagnosis was 2.08-3.06 years and the longest time was found in patients within the moderate stage. Mean TMSE scores were 22.8 for the mild stage, 17.6 for the moderate stage, and 5.56 for the severe stage of the risperidone treated patients. Similarly, in the olanzapine group, there were 24.58 for mild, 16.78 for moderate and 5.7 for severe stages as measured by TMSE.

The main comorbidity conditions were hypertension, hyperlipidaemia, and diabetes mellitus of all severity levels in both patient groups. In addition, hypertension was the highest percentage in the risperidone treated patients within the mild stage and in the olanzapine treated patients within the severe stage, accounting for 70%. Diabetes showed the highest percentage in patients within the moderate stage and receiving risperidone (33.33%). The dominance of hyperlipidaemia was shown in patients within a mild stage and being treated with olanzapine (41.67%). In the risperidone treatment group, stroke was found only in patients with a mild stage (26.67%). Whereas patients receiving olanzapine in the mild and moderate stages, incidences of having stroke were 16.67% and 5.26%, respectively.

Most adverse events were sedation/drowsiness in both groups, with 50% of the risperidone treated patients within the severe stage and 42.11% of the olanzapine treated patients within the moderate stage. Extrapyramidal symptoms were found in 10% of mild, 13.33% of moderate, and 31.25% of severe stages in risperidone prescribed patients. There were also ESPs occurring in the olanzapine prescribed patients with 5.26% and 20% in moderate and severe stages, respectively. The highest percentage of drug-induced EPSs was found in the severe stage of both treatments. The incidence of falls was the highest risk at 13.33% of the moderate stage in patients receiving risperidone and 8.33% of the mild stage in the patients receiving olanzapine.

In terms of health insurance coverage, patients in the risperidone group within the moderate stage were covered by the UC scheme (53.33%), followed by patients within the mild stage (40.00%). Conversely, only two patients in the olanzapine group with mild and severe stages were covered under the UC scheme. The CSMBS was the greatest proportion of healthcare insurance schemes in both groups across all severity levels at 59.03% of the risperidone treatment group and 76.58% of the olanzapine treatment group. Most out-of-pocket expenses were in the olanzapine-treated patients with the severe stage (30.00%).

Table 5.3: **Characteristics of patients from the data collection based on Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital, in Thailand, classified by cognitive function**

Characteristics	Risperidone (N=41)			Olanzapine (N=41)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Patient *[n (%)]*	10 (24.39)	15 (36.59)	16 (39.02)	12 (29.27)	19 (46.34)	10 (24.39)
Sex [n (%)]						
Male	3 (30.00)	7 (46.67)	4 (25.00)	7 (58.33)	1 (5.26)	3 (30.00)
Female	7 (70.00)	8 (53.33)	12 (75.00)	5 (41.67)	18 (94.74)	7 (70.00)
Age, year [mean (SD)]	79.30 (6.34)	77.80 (9.68)	83.44 (7.14)	73.58 (8.85)	78.94 (8.57)	74.70 (9.48)
Marital status [n (%)]						
Married	2 (20.00)	9 (60.00)	7 (43.75)	11 (91.67)	7 (36.84)	4 (40.00)
Widowed	7 (70.00)	5 (33.33)	9 (56.25)	1 (8.33)	11 (57.89)	6 (60.00)
Divorced/Separated	1 (10.00)	1 (6.67)	-	-	1 (5.26)	-
Religion [n (%)]						
Buddhism	10 (100.00)	15 (100.00)	16 (100.00)	12 (100.00)	18 (94.74)	9 (90.00)
Islam	-	-	-	-	1 (5.26)	-
Christian	-	-	-	-	-	1 (10.00)
Education [n (%)]						

Characteristics	Risperidone (N=41)			Olanzapine (N=41)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Never attend school/lower primary education	1 (10.00)	3 (20.00)	2 (12.5)	-	1 (5.26)	1 (10.00)
Primary education	7 (70.00)	8 (53.33)	12 (75.00)	4 (33.33)	13 (68.42)	7 (70.00)
Lower-secondary education	-	1 (6.67)	-	1 (8.33)	-	2 (20.00)
Upper-secondary education	-	1 (6.67)	-	3 (25.00)	1 (5.26)	-
Certificate/diploma	-	1 (6.67)	1 (6.25)	1 (8.33)	1 (5.26)	-
Bachelor's degree	2 (20.00)	1 (6.67)	1 (6.25)	3 (25.00)	3 (15.79)	-
Current occupation [n (%)]						
Retired	10 (100.00)	15 (100.00)	16 (100.00)	12 (100.00)	19 (100.00)	10 (100.00)
Income sources [n (%)]						
Pension	1 (10.00)	3 (20.00)	3 (18.75)	5 (41.67)	3 (15.79)	-
Deposit/interest	-	-	1 (6.25)	1 (8.33)	-	-
Public fund	7 (70.00)	8 (53.33)	8 (50.00)	5 (41.67)	11 (57.89)	9 (90.00)
Spouse's	-	-	-	3 (25.00)	3 (15.79)	-

Characteristics	Risperidone (N=41)			Olanzapine (N=41)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Child's	8 (80.00)	8 (53.33)	10 (62.50)	5 (41.67)	11 (57.89)	7 (70.00)
Other income	1 (10.00)	3 (20.00)	3 (18.75)	1 (8.33)	2 (10.53)	4 (40.00)
Living area [n (%)]						
Bangkok	-	1 (6.67)	2 (12.50)	2 (16.67)	1 (5.26)	3 (30.00)
Bangkok metropolitan	6 (60.00)	9 (60.00)	8 (50.00)	4 (33.33)	6 (31.58)	2 (20.00)
Countryside/ Province	4 (40.00)	5 (33.33)	6 (37.50)	6 (50.00)	12 (63.16)	5 (50.00)
Residence [n (%)]						
Detached house	9 (90.00)	12 (80.00)	13 (81.25)	10 (83.33)	16 (84.21)	7 (70.00)
Townhouse, Town home	1 (10.00)	3 (20.00)	3 (18.75)	1 (8.33)	3 (15.79)	1 (10.00)
Shop house/Row house	-	-	-	1 (8.33)	-	1 (10.00)
Other	-	-	-	-	-	1 (10.00)
Living arrangement [n (%)]						
House owner	2 (20.00)	7 (46.67)	7 (43.75)	5 (41.67)	11 (57.89)	4 (40.00)

Characteristics	Risperidone (N=41)			Olanzapine (N=41)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Rental	-	-	1 (6.25)	-	-	-
Resident	8 (80.00)	8 (53.33)	8 (50.00)	7 (58.33)	8 (42.11)	6 (60.00)
Status of living [n (%)]						
Living with spouse	1 (10.00)	9 (60.00)	3 (18.75)	9 (75.00)	6 (31.58)	3 (30.00)
Living with child	8 (80.00)	11 (73.33)	16 (100.00)	10 (83.33)	12 (63.16)	7 (70.00)
Living with the third generations	1 (10.00)	1 (6.67)	3 (18.75)	5 (41.67)	7 (36.84)	3 (30.00)
Living with relatives	1 (10.00)	-	-	-	1 (5.26)	2 (20.00)
Others	-	-	-	1 (8.33)	2 (10.53)	1 (10.00)
Diagnosis [n (%)]						
Alzheimer's disease	7 (17.07)	14 (34.15)	15 (36.59)	9 (21.95)	18 (43.90)	8 (19.52)
Unspecified dementia	3 (7.31)	1 (2.44)	-	3 (7.32)	1 (2.44)	1 (2.44)
Mixed dementia	-	-	1 (2.44)	-	-	1 (2.44)
Time since diagnosed with dementia, year [mean (SD)]	2.29 (1.88)	2.67 (2.26)	2.06 (0.85)	2.08 (1.24)	3.06 (2.13)	2.50 (1.72)
Mean TMSE score [mean (SD)]	22.80 (1.04)	17.6 (2.75)	5.56 (3.48)	24.58 (1.66)	16.78 (2.66)	5.7 (3.64)

Characteristics	Risperidone (N=41)			Olanzapine (N=41)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Non-comorbidity conditions [n (%)]	-	3 (20.00)	4 (25.00)	1 (8.33)	2 (10.53)	1 (10.00)
Comorbidity conditions [n (%)]						
Gout	2 (20.00)	-	-	1 (8.33)	1 (5.26)	-
Osteoarthritis	2 (20.00)	1 (6.67)	3 (18.75)	-	3 (15.79)	-
Asthma	-	-	-	-	1 (5.26)	-
Chronic renal failure	-	1 (6.67)	-	1 (8.33)	-	1 (10.00)
Hypertension	7 (70.00)	6 (40.00)	8 (50.00)	7 (58.33)	9 (47.37)	7 (70.00)
Diabetes Mellitus	2 (20.00)	5 (33.33)	5 (31.25)	2 (16.67)	3 (15.79)	3 (30.00)
Hyperlipidaemia	3 (30.00)	3 (20.00)	4 (25.00)	5 (41.67)	7 (36.84)	2 (20.00)
Stroke	-	4 (26.67)	-	2 (16.67)	1 (5.26)	-
Cancer	2 (20.00)	-	-	-	1 (5.26)	-
Other comorbidities	1 (10.00)	3 (20.00)	4 (25.00)	4 (33.33)	5 (26.32)	1 (10.00)
Non adverse events [n (%)]	5 (50.00)	7 (46.67)	7 (43.75)	2 (16.67)	3 (15.79)	3 (30.00)
Adverse events [n (%)]						
Dystonia	-	2 (13.33)	2 (12.5)	-	1 (5.26)	1 (10.00)

Characteristics	Risperidone (N=41)			Olanzapine (N=41)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Falls	-	2 (13.33)	-	1 (8.33)	-	-
Edema	-	1 (6.67)	2 (12.5)	3 (25.00)	-	-
Weight gained		1 (6.67)	-	3 (25.00)	5 (26.32)	1 (10.00)
Sedation/ drowsiness	1 (10.00)	4 (26.67)	8 (50.00)	4 (33.33)	8 (42.11)	3 (30.00)
Other adverse events	1 (10.00)	1 (6.67)	4 (25.00)	-	-	1 (10.00)
Health insurance coverage [n (%)]						
Universal Healthcare scheme (UC)	4 (40.00)	8 (53.33)	1 (6.25)	1 (8.33)	-	1 (10.00)
Civil Servants Medical Benefits scheme (CSMBS)	5 (50.00)	5 (33.33)	15 (93.75)	9 (75.00)	18 (94.74)	6 (60.00)
Out-of-pocket expense	1 (10.00)	2 (13.33)	-	2 (16.67)	1 (5.26)	3 (30.00)

According to Table 5.4, caregivers of the risperidone treated patients accounted for 24.39% of mild, 36.59% of moderate, and 39.02% of severe stages. In the olanzapine treated patient group, the caregiver percentages were 27.50% of mild, 47.50% of moderate, and 25.00% of severe stages. The range of mean ages of caregivers was 50.5-58.67 years in the risperidone group and 47.8-54.82 years in the olanzapine group.

A total of 43.75% caregivers of the risperidone treated patients within the severe stage had achieved bachelor's degree level, followed by 40% achieving a primary education of those caregivers of patients in the moderate stage and 40% achieving bachelor's degree of those caregivers of patients in the mild stage. A bachelor's degree was the greatest educational level of caregivers in the olanzapine treatment group caring for patients in the moderate stage, associated with 42.11%, followed by 40% achieving upper-secondary education of those caregivers of patients in the severe stage.

A total of 70% caregivers of the risperidone group of patients within the mild stage were unemployment and 25% of those caregivers of this group of patients within the severe stage were retired. In the olanzapine group, 45.45% of caregivers of patients within the mild stage were unemployed. It was also found that 27.27% of those caregivers of the olanzapine treated patients within the mild stage had retired.

Caregivers of the risperidone group of patients within the severe stage showed that they stopped working to provide care at 10.25 months since last paid employment. Patients' daughters were the main caregivers in all levels of disease severity of both drug groups, accounting for 70% of the risperidone group and 54.55% of the olanzapine group within the mild stage. Time spent in providing care to patients showed no significant differences across all disease severity levels of both drug treatment groups. Time spent in patients' care was mostly found in the severe stage of both the risperidone and olanzapine groups.

For both treatments, the care of patients within the severe stage had a significant impact on both the physical and mental health of their caregivers. Stress was the main problem for caregivers due to patients' care accounting for 81.25% and 80% of the severe and mild stages of the patients receiving risperidone and 73.68% and 70% of the moderate and severe stages in the olanzapine group.

Table 5.4: **Characteristics of caregivers from the data collection based on Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital, in Thailand, classified by cognitive function**

Characteristics	Risperidone (N=41)			Olanzapine (N=40)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Caregiver *[n (%)]*	10 (24.39)	15 (36.59)	16 (39.02)	11 (27.50)	19 (47.50)	10 (25.00)
Sex [n (%)]						
Male	1 (10.00)	5 (33.33)	4 (25.00)	2 (18.18)	5 (26.32)	1 (10.00)
Female	9 (90.00)	10 (66.67)	12 (75.00)	9 (81.82)	14 (73.68)	9 (90.00)
Age, year [mean (SD)]	56.40 (9.79)	58.67 (14.41)	50.50 (9.25)	54.82 (12.41)	54.73 (11.93)	47.80 (10.53)
Marital status [n (%)]						
Single	3 (30.00)	2 (13.33)	5 (31.25)	2 (18.18)	2 (10.53)	2 (20.00)
Married	6 (60.00)	10 (66.67)	11 (68.75)	9 (81.82)	15 (78.95)	6 (60.00)
Widowed	-	1 (6.67)	-	-	2 (10.53)	2 (20.00)
Divorced/Separated	1 (10.00)	2 (13.33)	-	-	-	-
Religion [n (%)]						
Buddhism	9 (90.00)	15 (100.00)	16 (100.00)	11 (100.00)	19 (100.00)	10 (100.00)
Islam	-	-	-	-	-	-
Christian	1 (10.00)	-	-	-	-	-
Education [n (%)]						

Characteristics	Risperidone (N=41)			Olanzapine (N=40)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Never school	-	-	-	-	-	-
Primary education	3 (30.00)	6 (40.00)	3 (18.75)	3 (27.27)	5 (26.32)	3 (30.00)
Lower-secondary education	2 (20.00)	-	1 (6.25)	-	-	2 (20.00)
Upper-secondary education	1 (10.00)	1 (6.67)	1 (6.25)	3 (27.27)	3 (15.79)	4 (40.00)
Certificate/diploma	-	2 (13.33)	1 (6.25)	-	-	-
Bachelor's degree	4 (40.00)	5 (33.33)	7 (43.75)	4 (36.36)	8 (42.11)	1 (10.00)
Higher bachelor's degree	-	1 (6.67)	3 (18.75)	1 (9.09)	3 (15.79)	-
Others	-	-	-	-	-	-
Current occupation [n (%)]						
Unemployment	7 (70.00)	9 (60.00)	7 (43.75)	5 (45.45)	8 (42.11)	4 (40.00)
Employment	3 (30.00)	6 (40.00)	9 (56.25)	6 (54.55)	11 (57.89)	6 (60.00)
Type of current occupation [n (%)]						
Housewife/	5 (50.00)	9 (60.00)	3 (18.75)	2 (18.18)	2 (10.53)	3 (30.00)

Characteristics	Risperidone (N=41)			Olanzapine (N=40)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Househusband						
Wage-earner	3 (30.00)	2 (13.33)	-	1 (9.09)	3 (15.79)	-
Farmer/Fisherman	-	-	-	1 (9.09)	-	-
Self-employed/Owner	-	1 (6.67)	2 (12.50)	2 (18.18)	1 (5.26)	4 (40.00)
Government officer	-	1 (6.67)	2 (12.50)	2 (18.18)	4 (21.05)	-
State enterprise employee	-	-	1 (6.25)	-	2 (10.53)	-
Company employee	-	1 (6.67)	1 (6.25)	-	1 (5.26)	-
Retiree	2 (20.00)	1 (6.67)	4 (25.00)	3 (27.27)	4 (21.05)	2 (20.00)
Others	-	1 (6.67)	3 (18.75)	-	2 (10.53)	1 (10.00)
Previous occupation [n (%)]						
Unemployment	5 (50.00)	9 (60.00)	10 (62.50)	6 (54.55)	13 (68.42)	7 (70.00)
Employment	5 (50.00)	6 (40.00)	6 (37.50)	5 (45.45)	6 (31.58)	3 (30.00)
Stop work due to provide patient's care [n (%)]	1 (10.00)	3 (20.00)	4 (25.00)	1 (9.09)	2 (10.53)	2 (20.00)

Characteristics	Risperidone (N=41)						Olanzapine (N=40)					
	Mild		Moderate		Severe		Mild		Moderate		Severe	
Duration of stopping work due to provide care, month [mean (SD)]	7.20	(22.77)	6.80	(16.50)	10.25	(23.12)	5.45	(18.09)	2.05	(6.64)	15.30	(38.22)
Relationship with patient [n (%)]												
Spouse	1	(10.00)	7	(46.67)	-		4	(36.36)	3	(15.79)	1	(10.00)
Son	-		1	(6.67)	-		-		2	(10.53)	1	(10.00)
Daughter	7	(70.00)	7	(46.67)	11	(68.75)	6	(54.55)	9	(47.37)	5	(50.00)
Relatives/Cousin	-		-		-		-		-		1	(10.00)
Niece/Nephew	-		-		1	(6.25)	1	(9.09)	-		-	
Friend/Neighbour	-		-		-		-		-			
Maid/Paid caregiver	-		-		3	(18.75)	-		4	(21.05)	2	(20.00)
Others	2	(20.00)	-		1	(6.25)	-		1	(5.26)	-	
Hours spent for caregiving patients [mean (SD)]	11.40	(4.88)	12.20	(3.63)	13.50	(3.61)	11.33	(5.97)	13.37	(4.75)	13.80	(7.15)
The physical problem [n (%)]												

Characteristics	Risperidone (N=41)			Olanzapine (N=40)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
No problems	7 (70.00)	7 (46.67)	6 (37.50)	7 (63.64)	9 (47.37)	5 (50.00)
Slight problems	-	1 (6.67)	2 (12.50)	2 (18.18)	3 (15.79)	1 (10.00)
Moderate problems	1 (10.00)	5 (33.33)	4 (25.00)	2 (18.18)	6 (31.58)	1 (10.00)
Severe problems	2 (20.00)	2 (13.33)	3 (18.75)	-	1 (5.26)	3 (30.00)
Extreme problems	-	-	1 (6.25)	-	-	-
The mental problem [n (%)]						
No problems	3 (30.00)	8 (53.33)	1 (6.25)	4 (36.36)	4 (21.05)	2 (20.00)
Slight problems	2 (20.00)	1 (6.67)	3 (18.75)	3 (27.27)	4 (21.05)	3 (30.00)
Moderate problems	1 (10.00)	2 (13.33)	4 (25.00)	2 (18.18)	4 (21.05)	2 (20.00)
Severe problems	4 (40.00)	2 (13.33)	6 (37.50)	2 (18.18)	5 (26.32)	1 (10.00)
Extreme problems	-	2 (13.33)	2 (12.50)	-	2 (10.53)	2 (20.00)
Overall health problems from providing care to patients [n (%)]	8 (80.00)	11 (73.33)	15 (93.75)	7 (63.64)	17 (89.47)	8 (80.00)
Depression	-	2 (13.33)	1 (6.25)	2 (18.18)	2 (10.53)	2 (20.00)
Stress	8 (80.00)	7 (46.67)	13 (81.25)	5 (45.45)	14 (73.68)	7 (70.00)
Distress	2 (20.00)	5 (33.33)	7 (43.75)	2 (18.18)	7 (36.84)	4 (40.00)

Characteristics	Risperidone (N=41)			Olanzapine (N=40)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Quality of sleep	4 (40.00)	7 (46.67)	11 (68.75)	2 (18.18)	6 (31.58)	3 (30.00)
Musculoskeletal disorders	2 (20.00)	7 (46.67)	9 (56.25)	1 (9.09)	5 (26.32)	6 (60.00)
Others	-	-	1 (6.25)	2 (18.18)	-	1 (10.00)

5.3.1.4 Patient and caregiver Characteristics classified by patients' dependency

The patients' physical dependency was defined by a physician's assessment along with the Activities of Daily Living (ADL) score as measured by the Barthel Index (Thai version). Scores were categorised as follows: total dependence (score=0-4), severe dependence (score =5-8), moderate dependence (score=9-11), and mild dependence (score ≥ 12) (Prasat Neurological Institute, 2014). To classify patients' dependence into Pre-FTC and FTC states, the Pre-FTC state (not requiring full-time care) was a score of 9 and over and the FTC state (requiring full-time care) was a score of 0-8. The FTC state was defined as patients requiring a significant amount of care and supervision almost every day, regardless of the location of the care or who provided it.

Table 5.5 shows patient characteristics by classifying patients with dependence status. The risperidone treated patients were 65.85% of the Pre-FTC state and 34.15% of the FTC state, whilst in the olanzapine treated patients there were 73.17% of the Pre-FTC state and 26.83% of the FTC state. Most patients were predominantly female in both dependence states of both treatment groups.

The risperidone treated patients had a mean age at 82.93 years in the FTC state and 79.04 years in the Pre-FTC state. In the olanzapine treatment, there were no differences in the mean age of the patients between the two dependence states, being 76.20 in the Pre-FTC state and 76.23 years in the FTC state.

Primary school was the greatest proportion of patient educational levels of both the Pre-FTC and the FTC states within each treatment group.

All patients in both dependency states of both treatments were retired. The main sources of income were from public funds and the patients' children in patients with the Pre-FTC and FTC states of both treatment groups. The highest percentage of income of those patients in each group was from their children, accounting for 64.29% of the Pre-FTC state of the

risperidone group and 72.73% of the FTC state of the olanzapine group. Most patients in both dependence states of both treatment groups were living with their children.

For risperidone treatment, patients who were diagnosed with Alzheimer's disease were 56.10% in the Pre-FTC state and 31.71% in the FTC state. For the olanzapine group, patients diagnosed with Alzheimer's disease accounted for 60.98% in the Pre-FTC state and 24.39% in the FTC state. Whilst the unspecified dementia was 9.76% of risperidone treated patients in the Pre-FTC state, 9.76% of olanzapine treated patients in the Pre-FTC and 2.44% of olanzapine treated patients in the FTC state. Mixed dementia was found at only 2.44% of both treatment groups in the FTC state of risperidone and the FTC state of olanzapine.

Mean time since the first diagnosis of dementia was 2.52 years in the Pre-FTC patients using risperidone treatment which was longer than patients in the FTC state by 0.52 years. For patients using olanzapine treatment, the mean time from the first diagnosis of dementia was 3.73 years in the FTC state which was longer than the Pre-FTC state by 1.49 years.

Hypertension was the main comorbidity in both dependence states of both patient groups. Diabetes and hyperlipidaemia had higher proportions in the risperidone treated patients within the FTC state compared with the Pre-FTC state. For the olanzapine treated patients, diabetes mellitus showed a higher percentage in the FTC state than the Pre-FTC state while hyperlipidaemia was lower in the FTC state than the Pre-FTC state.

For the adverse effects, most patients in the FTC state of the olanzapine group had weight gain and sedation/drowsiness (36.36%). In the risperidone treated patients it was found that 37.04% in the Pre-FTC state presented sedation/drowsiness. The risk of EPSs also occurred in the risperidone treated patients being 14.81% and 28.57% of the Pre-FTC and the FTC states respectively. In the olanzapine group, the EPSs were only found in the FTC state (27.27%). The risk of falls was 7.41% of the Pre-FTC state of patients treated with risperidone and 3.33% of the Pre-FTC state of olanzapine treated patients.

Civil Servants Medical Benefits was the prominent healthcare insurance of both the Pre-FTC and the FTC states in patients of both drug groups. Importantly, both dependence states of the olanzapine treated patients had a greater portion of out-of-pocket expenses compared with risperidone treated patients.

Table 5.5: **Characteristics of patients from the data collection based on Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital, in Thailand, classified by dependence**

Characteristics	Risperidone (41)		Olanzapine (41)	
	Pre-FTC	FTC	Pre-FTC	FTC
Patient *[n (%)]*	27 (65.85)	14 (34.15)	30 (73.17)	11 (26.83)
Sex [n (%)]				
Male	10 (37.04)	4 (28.57)	8 (26.67)	3 (27.27)
Female	17 (62.96)	10 (71.43)	22 (73.33)	8 (72.73)
Age, year [mean (SD)]	79.04 (8.59)	82.93 (7.02)	76.20 (8.53)	76.23 (10.61)
Marital status [n (%)]				
Married	10 (37.04)	8 (57.14)	18 (60.00)	4 (36.36)
Widowed	16 (59.26)	5 (35.71)	11 (36.67)	7 (63.64)
Divorced/Separated	1 (3.70)	1 (7.14)	1 (3.33)	-
Religion [n (%)]				
Buddhism	27 (100.00)	14 (100.00)	29 (96.67)	10 (90.91)
Islam	-	-	1 (3.33)	-
Christian	-	-	-	1 (9.09)
Education [n (%)]				

Characteristics	Risperidone (41)				Olanzapine (41)			
	Pre-FTC		FTC		Pre-FTC		FTC	
Never attend school/lower primary education	3	(11.11)	3	(21.43)	-		2	(18.18)
Primary education	18	(66.67)	9	(64.29)	17	(56.67)	7	(63.64)
Lower-secondary education	1	(3.70)	-		2	(6.67)	1	(9.09)
Upper-secondary education	-		1	(7.14)	3	(10.00)	1	(9.09)
Certificate/diploma	1	(3.70)	1	(7.14)	2	(6.67)	-	
Bachelor's degree	4	(14.81)	-		6	(20.00)	-	
Current occupation [n (%)]								
Retired	27	(100.00)	14	(100.00)	30	(100.00)	11	(100.00)
Income sources [n (%)]								
Pension	5	(18.52)	2	(14.29)	7	(23.33)	1	(9.09)
Deposit/interest	1	(3.70)	-		1	(3.33)	-	
Public fund	15	(55.56)	8	(57.14)	19	(63.33)	7	(63.64)
Spouse's	-		-		4	(13.33)	3	(27.27)
Child's	17	(62.96)	9	(64.29)	15	(50.00)	8	(72.73)
Other income	4	(14.81)	3	(21.43)	4	(13.33)	2	(18.18)

Characteristics	Risperidone (41)				Olanzapine (41)			
	Pre-FTC		FTC		Pre-FTC		FTC	
Living area [n (%)]								
Bangkok	1	(3.70)	2	(14.29)	4	(13.33)	2	(18.18)
Bangkok metropolitan	17	(62.96)	6	(42.86)	9	(30.00)	3	(27.27)
Countryside/Province	9	(33.33)	6	(42.86)	17	(56.67)	6	(54.55)
Residence [n (%)]								
Detached house	24	(88.89)	10	(71.43)	24	(80.00)	9	(81.82)
Townhouse, Town home	3	(11.11)	4	(28.57)	5	(16.67)	-	
Shop house/Row house	-		-		1	(3.33)	1	(9.09)
Other	-		-		-		1	(9.09)
Living arrangement [n (%)]								
House owner	7	(25.93)	9	(64.29)	17	(56.67)	3	(27.27)
Rental	1	(3.70)	-		-		-	
Resident	19	(70.37)	5	(35.71)	13	(43.33)	8	(72.73)
Status of living [n (%)]								
Living with spouse	7	(25.93)	6	(42.86)	14	(46.67)	4	(36.36)
Living with child	21	(77.78)	14	(100.00)	22	(73.33)	7	(63.64)

Characteristics	Risperidone (41)				Olanzapine (41)			
	Pre-FTC		FTC		Pre-FTC		FTC	
Living with the third generations	3	(11.11)	2	(14.29)	11	(36.67)	4	(36.36)
Living with relatives	1	(3.70)	-		2	(6.67)	1	(9.09)
Others	-		-		2	(6.67)	2	(18.18)
Diagnosis [n (%)]								
Alzheimer's disease	23	(56.10)	13	(31.71)	25	(60.98)	10	(24.39)
Unspecified dementia	4	(9.76)	-		4	(9.76)	1	(2.44)
Mixed dementia	-		1	(2.44)	1	(2.44)	-	
Time since diagnosed with dementia, year [mean (SD)]	2.52	(2.03)	2.00	(0.78)	2.24	(1.69)	3.73	(1.79)
Mean TMSE score [mean (SD)]	17.19	(6.29)	8.36	(7.11)	17.6	(6.13)	13.00	(9.85)
Non-comorbidity conditions [n (%)]	5	(18.52)	2	(14.29)	4	(13.33)	-	
Comorbidity conditions [n (%)]								
Gout	2	(7.41)	-		1	(3.33)	1	(9.09)
Osteoarthritis	3	(11.11)	3	(21.43)	2	(6.67)	1	(9.09)
Asthma	-		-		1	(3.33)	-	
Chronic renal failure	-		1	(7.14)	1	(3.33)	1	(9.09)

Characteristics	Risperidone (41)				Olanzapine (41)			
	Pre-FTC		FTC		Pre-FTC		FTC	
Hypertension	14	(51.85)	7	(50.00)	15	(50.00)	8	(72.73)
Diabetes Mellitus	6	(22.22)	6	(42.86)	5	(16.67)	3	(27.27)
Hyperlipidaemia	6	(22.22)	4	(28.57)	12	(40.00)	2	(18.18)
Stroke	2	(7.41)	2	(14.29)	2	(6.67)	1	(9.09)
Cancer	2	(7.41)		-		-	1	(9.09)
Other comorbidities	5	(18.52)	3	(21.43)	8	(26.67)	2	(18.18)
Non adverse events [n (%)]	9	(33.33)	10	(71.43)	5	(16.67)	3	(27.27)
Adverse events [n (%)]								
Dystonia	2	(7.41)	2	(14.29)		-	2	(18.18)
Falls	2	(7.41)		-	1	(3.33)		-
Edema	2	(7.41)	1	(7.14)	3	(10.00)		-
Weight gained	1	(3.70)		-	5	(16.67)	4	(36.36)
Sedation/drowsiness	10	(37.04)	3	(21.43)	11	(36.67)	4	(36.36)
Other adverse events	4	(14.81)	2	(14.29)		-	1	(9.09)
Health insurance coverage [n (%)]								
Universal Healthcare scheme (UC)	9	(33.33)	4	(28.57)		-	2	(18.18)

Characteristics	Risperidone (41)				Olanzapine (41)			
	Pre-FTC		FTC		Pre-FTC		FTC	
Civil Servants Medical Benefits scheme (CSMBS)	15	(55.56)	10	(71.43)	26	(86.67)	7	(63.64)
Out-of-pocket expense	3	(11.11)	-		4	(13.33)	2	(18.18)

Table 5.6 shows the caregiver characteristics based on a classification of patients by dependence. Caregivers of the risperidone treated patients were 65.85% of the Pre-FTC state and 34.15% of the FTC state. For the olanzapine treated group, caregivers were 72.50% of the Pre-FTC state and 27.50% of the FTC state. Caregivers in both dependence states of each treatment group were predominantly female. The mean age of caregivers of the Pre-FTC and the FTC states of both drugs ranged from 48.45-55.74 years.

Most caregivers had a primary education level and some a bachelor's degree level in both dependence states and both drug groups. By comparing current occupation and previous occupation status, this showed that the increased unemployment of caregivers was only found in the Pre-FTC state of the risperidone group by 3.70%.

Caregivers in the FTC state of the risperidone group had the highest percentage of stopping work due to patients' care (21.43%). The main caregivers of both dependence states and both drug groups were their daughters.

The illness of patients in the Pre-FTC state of both treatment groups had less impact on the physical health problems of their caregivers accounting for 59% compared with the FTC state. Only patients in the FTC state of the risperidone treatment group showed that patients' illness had extreme problems affecting the physical health conditions of their caregivers. Examining the mental health problems, the risperidone treated group within the Pre-FTC state showed that the illness of patients had severe problems affecting their caregivers accounting for 37.04%. Conversely, more than half of caregivers of the olanzapine treatment within the FTC state showed that the patients' illness had no impact on their mental health. In addition, the extreme problems of caregiver's mental health due to providing care were found within the risperidone treatment (21.43% and 3.70% of the FTC and Pre-FTC states, respectively) and within the olanzapine group (18.18% and 6.90% of the FTC and the Pre-FTC states, respectively). Stress was a significant problem for most caregivers. The highest

percentage of caregiver stress was found in the Pre-FTC state of both the risperidone and the olanzapine treated patients, associated with 70.37% and 72.41%, respectively.

Table 5.6: **Characteristics of caregivers from the data collection based on Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital, in Thailand, classified by dependence**

Characteristics	Risperidone (41)				Olanzapine (40)			
	Pre-FTC		FTC		Pre-FTC		FTC	
Caregiver	27	(65.85)	14	(34.15)	29	(72.50)	11	(27.50)
Sex [n (%)]								
Male	7	(25.93)	3	(21.43)	7	(24.14)	1	(9.09)
Female	20	(74.07)	11	(78.57)	22	(75.86)	10	(90.91)
Age, year [mean (SD)]	55.74	(12.71)	53.35	(10.19)	54.76	(10.45)	48.45	(14.45)
Marital status [n (%)]								
Single	7	(25.93)	3	(21.43)	4	(13.79)	2	(18.18)
Married	17	(62.96)	10	(71.43)	22	(75.86)	8	(72.73)
Widowed	1	(3.70)		-	3	(10.34)	1	(9.09)
Divorced/Separated	2	(7.41)	1	(7.14)		-		-
Religion [n (%)]								
Buddhism	26	(96.30)	14	(100.00)	29	(100.00)	11	(100.00)
Islam		-		-		-		-

Characteristics	Risperidone (41)		Olanzapine (40)	
	Pre-FTC	FTC	Pre-FTC	FTC
Christian	1 (3.70)	-	-	-
Education [n (%)]				
Never attend school/lower primary education				
Primary education	9 (33.33)	3 (21.43)	7 (24.14)	4 (36.36)
Lower-secondary education	2 (7.41)	1 (7.14)	1 (3.45)	1 (9.09)
Upper-secondary education	2 (7.41)	1 (7.14)	6 (20.69)	4 (36.36)
Certificate/diploma	1 (3.70)	2 (14.29)	-	-
Bachelor's degree	11 (40.74)	5 (35.71)	12 (41.38)	1 (9.09)
Higher bachelor's degree	2 (7.41)	2 (14.29)	3 (10.34)	1 (9.09)
Others				
Current occupation [n (%)]				
Unemployment	16 (59.26)	7 (50.00)	13 (44.83)	4 (36.36)
Employment	11 (40.74)	7 (50.00)	16 (55.17)	7 (63.64)
Type of current occupation [n (%)]				

Characteristics	Risperidone (41)		Olanzapine (40)	
	Pre-FTC	FTC	Pre-FTC	FTC
Housewife/Househusband	12 (44.44)	5 (35.71)	4 (13.79)	3 (27.27)
Wage-earner	3 (11.11)	1 (7.14)	3 (10.34)	1 (9.09)
Farmer/Fisherman	-	-	1 (3.45)	-
Self-employed/Owner	1 (3.70)	2 (14.29)	5 (17.24)	2 (18.18)
Government officer	2 (7.41)	1 (7.14)	5 (17.24)	1 (9.09)
State enterprise employee	-	1 (7.14)	2 (6.90)	-
Company employee	1 (3.70)	1 (7.14)	1 (3.45)	-
Retiree	5 (18.52)	2 (14.29)	7 (24.14)	2 (18.18)
Others	3 (11.11)	1 (7.14)	1 (3.45)	2 (18.18)
Previous occupation [n (%)]				
Unemployment	15 (55.56)	9 (64.29)	19 (65.52)	7 (63.64)
Employment	12 (44.44)	5 (35.71)	10 (34.48)	4 (36.36)
Stop work due to provide patient's care [n (%)]	5 (18.52)	3 (21.43)	4 (13.79)	1 (9.09)

Characteristics	Risperidone (41)				Olanzapine (40)			
	Pre-FTC		FTC		Pre-FTC		FTC	
Duration of stopping work due to provide care, month [mean (SD)]	7.63	(21.15)	9.43	(19.51)	8.00	(24.45)	1.09	(3.62)
Relationship with patient [n (%)]								
Spouse	7	(25.93)	1	(7.14)	6	(20.69)	2	(18.18)
Son	1	(3.70)	-		3	(10.34)		
Daughter	14	(51.85)	11	(78.57)	15	(51.72)	5	(45.45)
Relatives/Cousin	-		-		1	(3.45)	-	
Niece/Nephew	1	(3.70)	-		-		1	(9.09)
Friend/Neighbour								
Maid/Paid caregiver	2	(7.41)	1	(7.14)	3	(10.34)	3	(27.27)
Others	2	(7.41)	1	(7.14)	1	(3.45)		
Hours spent for caregiving patients [mean (SD)]	12.04	(3.94)	13.42	(3.96)	13.21	(5.09)	13.18	(6.63)
The physical problem [n (%)]								
No problems	16	(59.26)	4	(28.57)	17	(58.62)	4	(36.36)

Characteristics	Risperidone (41)		Olanzapine (40)	
	Pre-FTC	FTC	Pre-FTC	FTC
Slight problems	1 (3.70)	2 (14.29)	5 (17.24)	1 (9.09)
Moderate problems	6 (22.22)	4 (28.57)	6 (20.69)	3 (27.27)
Severe problems	4 (14.81)	3 (21.43)	1 (3.45)	3 (27.27)
Extreme problems	-	1 (7.14)	-	-
The mental problem [n (%)]				
No problems	8 (29.63)	4 (28.57)	4 (13.79)	6 (54.55)
Slight problems	4 (14.81)	2 (14.29)	10 (34.48)	-
Moderate problems	4 (14.81)	3 (21.43)	6 (20.69)	2 (18.18)
Severe problems	10 (37.04)	2 (14.29)	7 (24.14)	1 (9.09)
Extreme problems	1 (3.70)	3 (21.43)	2 (6.90)	2 (18.18)
Overall health problems from providing care to patients [n (%)]	21 (77.78)	13 (92.86)	24 (82.76)	8 (72.73)
Depression	1 (3.70)	2 (14.29)	4 (13.79)	2 (18.18)
Stress	19 (70.37)	9 (64.29)	21 (72.41)	5 (45.45)
Distress	8 (29.63)	6 (42.86)	11 (37.93)	2 (18.18)

Characteristics	Risperidone (41)		Olanzapine (40)	
	Pre-FTC	FTC	Pre-FTC	FTC
Quality of sleep	14 (51.85)	8 (57.14)	7 (24.14)	4 (36.36)
Musculoskeletal disorders	7 (25.93)	11 (78.57)	5 (17.24)	7 (63.64)
Others	1 (3.70)	-	2 (6.90)	1 (9.09)

5.3.2 Costs

Cost data were classified into two different approaches based on patients' cognitive function and patients' dependence status as outlined below.

5.3.2.1 The distribution of costs by patients' cognitive function

In Table 5.7, TMSE scores were used as a measure of patient cognitive function, to classify patients according to severity into mild, moderate and severe stages of the disease. More details can be seen in section 5.3.1.3.

5.3.2.1.1 Direct medical costs

The medication cost per month was nearly15-fold higher of the olanzapine treated patients than those of risperidone treated patients. The highest cost of medications was associated with the patients with the severe stage of olanzapine and risperidone treated groups, being THB 1,076.30 and THB 76.31, respectively. Medications prescribed per month were THB 63.43 for mild and THB 74.41 for moderate stages of risperidone treated patients and THB 981.39 for mild and THB 1,033.66 for moderate stages of olanzapine treated patients. There were 0.44-0.50 physician visits per month for the risperidone treated patients, whereas the olanzapine patients showed fewer physician visits at 0.39-0.47 per month. The greatest proportions of additional payments due to outpatient visits were found in patients with the mild stage, (THB 2,419 for the risperidone treated group and THB 1,758.33 for the olanzapine treated group), when compared with those who had moderate, (THB 1,972.67 for the risperidone treated group and THB 1,359.47 for the olanzapine treated group), and severe stages, (THB 762.19 for the risperidone treated group and THB 1,360 for the olanzapine treated group), for both the risperidone and olanzapine groups.

Compared with the risperidone group, the olanzapine treated patients had a greater frequency of hospital admissions. Also, the patients with the moderate stage showed the highest lengths of stay in hospital, accounting for 3 days for the risperidone treated group and 2.53 days of

the olanzapine treated group. Further, the risperidone treated patients with a moderate stage incurred the highest cost of additional payments due to hospital admissions accounting for THB 5,366.67.

The highest comorbidity associated costs of both treatment groups were found in patients within the severe stage of the risperidone group (THB 5,746.20) and patients within the moderate stage of the olanzapine group (THB 4,955.63). When comparing amongst the levels of disease severity, patients within the moderate stage and treated with risperidone had the lowest cost due to comorbidity conditions (THB 2,958.33 per month). Conversely, the highest cost was found in the moderate stage of the olanzapine group, at THB 4,955.63 per month.

For the costs of drug induced adverse events, the olanzapine treated patients had a lower cost of falls compared with the risperidone treated patients by THB 7.05 per month of each cognitive severity stage. Conversely, the olanzapine treated patients showed a higher cost of treatment due to drug induced constipation compared with those risperidone treated patients. Costs of treatment associated with drug induced EPSs were lower in the olanzapine treated group than those in the risperidone treated group at approximately THB 8 per month.

The costs of relapses requiring the hospitalisation of patients being treated with risperidone and patients undergoing olanzapine treatment were THB 393.24 and THB 167.80, respectively. Also, costs of relapses not requiring hospitalisation showed that patients using olanzapine were approximately THB 7 lower than those patients using risperidone, (THB 18.93 for the risperidone group and THB 11.83 for the olanzapine group).

As presented above, costs associated with adverse events and relapses were higher for individuals receiving risperidone than those individuals using olanzapine by THB 246.49. The monthly direct medical costs of the patients using risperidone were THB 5,095.03 for the mild stage, THB 4,437.31 for the moderate stage, and THB 5,327.03 for the severe stage. For

the olanzapine users, the monthly direct medical costs were THB 6,044.10, THB 5,569.29, and THB 5,855.27 for patients with mild, moderate, and severe stages, respectively.

5.3.2.1.2 Direct non-medical costs

For direct non-medical costs, including travel, food and accommodation of both physician visits and hospital admissions, the mean cost was higher in the risperidone group than the olanzapine group accounting for THB 5,537.28 and THB 4,450.73, respectively. In addition, the highest cost of each treatment was found in patients within the moderate stage.

Other treatment costs were highest in the risperidone treated patients within the moderate (THB 2,892.00), followed by severe (THB 2,243.25) and mild stages (THB 2,109.00). Similarly, the olanzapine treated patients had the greatest cost for moderate (THB 1,852.63), followed by severe (THB 1,740.00) and mild stages (THB 1,445.83).

Paid caregiver-associated costs were correlated with the severity levels of cognitive impairment. Thus, patients within severe stage were found to have the highest expense per month when compared against other severity stages. For the risperidone group, the mean cost of paid caregivers per month of all severity was THB 7,981.43. According to severity, these were for severe (THB 10,985.63), moderate (THB 7,650.67), and mild stages (THB 5,308.00). Likewise, the mean cost of paid caregivers per month of the olanzapine treated patients was THB 7,674.68. These were for severe (THB 10,401.00), moderate (THB 7,000.53), and mild stages (THB 5,622.50).

The mean informal care cost per month was higher in the olanzapine treated group than the risperidone treated group, with costs of THB 31,647.33 and THB 30,522.17, respectively. Cognitive deterioration was a significant predictor relating to informal care costs. Less impaired cognitive functions had lower costs of informal care of patients.

Accordingly, a mean direct non-medical cost per month showed a higher proportion in the risperidone group, compared with the olanzapine group by THB 130.29. The total non-

medical costs per month were estimated at THB 42,031 for the risperidone treated group and THB 41,901 for the olanzapine treated group.

5.3.2.1.3 Monthly costs of patients, classified by the cognitive severity, associated with the treatment BPSD

The mean total cost of patients receiving risperidone was THB 46,984.87 per month. Based on cognitive severity, the monthly costs were THB 41,444.22 for mild, THB 46,470.29 for moderate, and THB 53,038.90 for severe stages of dementia for the risperidone treated patients. For patients receiving olanzapine, the mean total cost was THB 47,723.94 per month. The monthly costs for mild, moderate, and severe stages of the olanzapine treated patients were THB 41,901.85, THB 48,368.34, and THB 52,901.64, respectively.

Table 5.7: **Parameters of costs, classified by cognitive severity in patients with dementia based on the data collected from Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital, Thailand, in Thai Baht (THB) in 2017**

Type of costs	Mild Stage	Moderate Stage	Severe Stage
Direct medical costs			
Medication use (per month, THB) *[mean (SD)]*			
Risperidone treatment	63.43 (36.94)	74.41 (24.20)	76.31 (31.40)
Olanzapine treatment	981.39 (568.75)	1,033.66 (655.02)	1,076.30 (533.76)
Outpatient department (OPD)			
The frequency of physician visits of patient (per month) [mean (SD)]			
Risperidone treatment	0.50 (0.32)	0.44 (0.30)	0.50 (0.30)
Olanzapine treatment	0.47 (0.22)	0.39 (0.25)	0.47 (0.28)

Type of costs	Mild Stage	Moderate Stage	Severe Stage
Additional healthcare insurance coverage of OPD per visit, THB [mean (SD)]			
Risperidone treatment	2,419.00 (3,828.32)	1,972.67 (2,976.42)	762.19 (1,065.51)
Olanzapine treatment	1,758.33 (4,219.10)	1,359.47 (3,433.10)	1,360.00 (1,364.18)
Inpatient department (IPD)			
The frequency of hospital admission (per month) [mean (SD)]			
Risperidone treatment	0.01 (0.03)	0.04 (0.09)	-
Olanzapine treatment	0.04 (0.01)	0.04 (0.08)	0.01 (0.03)
Length of stay at the hospital, day (per admission) [mean (SD)]			
Risperidone treatment	0.70 (2.21)	3.00 (7.92)	-
Olanzapine treatment	1.67 (4.25)	2.53 (5.64)	2.20 (6.96)
Additional healthcare insurance coverage of IPD per admission, THB [mean (SD)]			
Risperidone treatment	2,100.00 (6,640.78)	5,366.67 (15,684.92)	-
Olanzapine treatment	2,500.00 (8,660.25)	463.16 (1,616.65)	880.00 (2,782.80)
Cost of comorbidity (per month, THB) *[mean (SD)]*			
Risperidone treatment	4,110.00 (3,047.52)	2,958.33 (3,380.31)	5,746.20 (4,456.06)
Olanzapine treatment	4,252.75 (6,231.32)	4,955.63 (4,637.72)	4,102.50 (3,818.37)
Adverse events (per month, THB)			

Type of costs	Mild Stage	Moderate Stage	Severe Stage
Falls [mean (SD)]			
Risperidone treatment	14.10 (0.00)	14.10 (0.00)	14.10 (0.00)
Olanzapine treatment	7.05 (0.00)	7.05 (0.00)	7.05 (0.00)
Constipation [mean (SD)]			
Risperidone treatment	0.24 (0.00)	0.24 (0.00)	0.24 (0.00)
Olanzapine treatment	1.68 (0.00)	1.68 (0.00)	1.68 (0.00)
Extrapyramidal symptoms (EPS) [mean (SD)]			
Risperidone treatment	13.35 (0.00)	13.35 (0.00)	13.35 (0.00)
Olanzapine treatment	5.01 (0.00)	5.01 (0.00)	5.01 (0.00)
Relapses (per month, THB)			
Relapse requiring hospitalisation [mean (SD)]			
Risperidone treatment	393.24 (0.00)	393.24 (0.00)	393.24 (0.00)
Olanzapine treatment	167.80 (0.00)	167.80 (0.00)	167.80 (0.00)
Relapse not requiring hospitalisation [mean (SD)]			
Risperidone treatment	18.93 (0.00)	18.93 (0.00)	18.93 (0.00)
Olanzapine treatment	11.83 (0.00)	11.83 (0.00)	11.83 (0.00)
Total direct medical cost (per month, THB) *[mean (SD)]*			
Risperidone treatment	5,095.03 (2,599.93)	4,437.31 (2,720.76)	5,327.03 (2,415.49)
Olanzapine treatment	6,044.10 (5,366.58)	5,569.29 (2,193.90)	5,855.27 (2,602.49)
Direct non-medical costs			
Non-medical costs (travel, food, accommodation) of OPD (per month, THB) [mean (SD)]			
Risperidone treatment	1,564.68 (473.54)	2,658.85 (2,534.71)	2,327.29 (1,172.77)

Type of costs	Mild Stage	Moderate Stage	Severe Stage
Olanzapine treatment	1,453.81 (551.57)	2,197.46 (1,052.39)	1,782.68 (798.54)
Non-medical costs (travel, food, accommodation) of IPD (per admission, THB) [mean (SD)]			
Risperidone treatment	1,621.42 (5,127.39)	5,085.93 (14,400.20)	-
Olanzapine treatment	3,168.86 (7,425.50)	2,971.42 (9,960.53)	1,777.95 (5,622.38)
Other treatment (per month, THB) [mean (SD)]			
Risperidone treatment	2,109.00 (3,454.16)	2,892.00 (2,874.04)	2,243.25 (2,150.14)
Olanzapine treatment	1,445.83 (1,462.79)	1,852.63 (2,250.52)	1,740.00 (1,938.61)
Paid caregiver (per month, THB) [mean (SD)]			
Risperidone treatment	5,308.00 (4,690.26)	7,650.67 (4,074.83)	10,985.63 (3,697.95)
Olanzapine treatment	5,622.50 (4,322.09)	7,000.53 (5,315.40)	10,401.00 (2,424.30)
Informal care (per month, THB) [mean (SD)]			
Risperidone treatment	28,136.34 (12,046.31)	30,110.82 (8,957.34)	33,319.35 (8,921.65)
Olanzapine treatment	27,970.86 (15,406.77)	32,993.49 (11,727.35)	34,058.63 (17,636.68)
Total direct non-medical cost (per month, THB) *[mean (SD)]*			
Risperidone treatment	36,349.19 (16,806.37)	42,032.98 (11,379.14)	47,711.87 (11,449.53)
Olanzapine treatment	35,857.75 (17,289.18)	42,799.05 (14,655.77)	47,046.37 (17,821.80)
Total costs (per month, THB) *[mean (SD)]*			
Risperidone treatment	41,444.22 (17,037.35)	46,470.29 (11,607.73)	53,038.90 (11,918.14)
Olanzapine treatment	41,901.85 (16,879.63)	48,368.34 (16,228.88)	52,901.64 (18,029.26)

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

Figures 5.1-5.3 show the distribution of total costs, costs of treatment with risperidone and costs of treatment with olanzapine according to a classification of patients by cognitive function. From the distribution of total costs, this showed that direct medical costs of olanzapine treated patients were higher than risperidone treated patients, accounting for 12.20% and 10.54%, respectively. Conversely, the olanzapine treated group had lower direct non-medical costs compared with the risperidone treated group, accounting for 87.80% and 89.46%, respectively. Focusing on the distribution of costs of patients using risperidone treatment, significant part of the costs attributable to dementia were costs relating to unpaid caregivers or informal care (64.96%), followed by paid caregiver costs (16.99%) and non-medical costs associated with transportation, extra food and extra accommodation (11.79%); whilst the lowest proportion was found in medication costs per month accounting for 0.15%. For patients using olanzapine treatment, the greatest proportion of costs was also in the informal care (66.37%), followed by paid caregiver costs (16.08%) and non-medical costs associated with transportation, extra food and extra accommodation (9.33%). However, in this olanzapine treated group, the lowest percentage was found in costs for treating adverse events (0.41%). The proportion of medication costs per month of olanzapine treated patients was 2.16%. Comparing the proportion of comorbidity conditions associated costs, risperidone treated patients had a slightly lower percentage compared with olanzapine treated patients, associated with 9.09% and 9.30%, respectively. Regarding other treatment costs, costs of additional healthcare insurance associated with outpatient visits and costs of additional healthcare insurance associated with hospital admissions, patients receiving olanzapine had lower percentages of these costs compared with patients receiving risperidone. Costs of additional healthcare insurance associated with outpatient visits were 3.66% and 3.13% of risperidone treated and olanzapine treated patients, respectively. Whilst costs of additional healthcare insurance associated with hospital admissions were 7.95% of the risperidone group and 2.68% of the olanzapine group. When considering costs associated

with other treatments, 5.14% was for patients receiving risperidone and 3.52% for those receiving olanzapine.

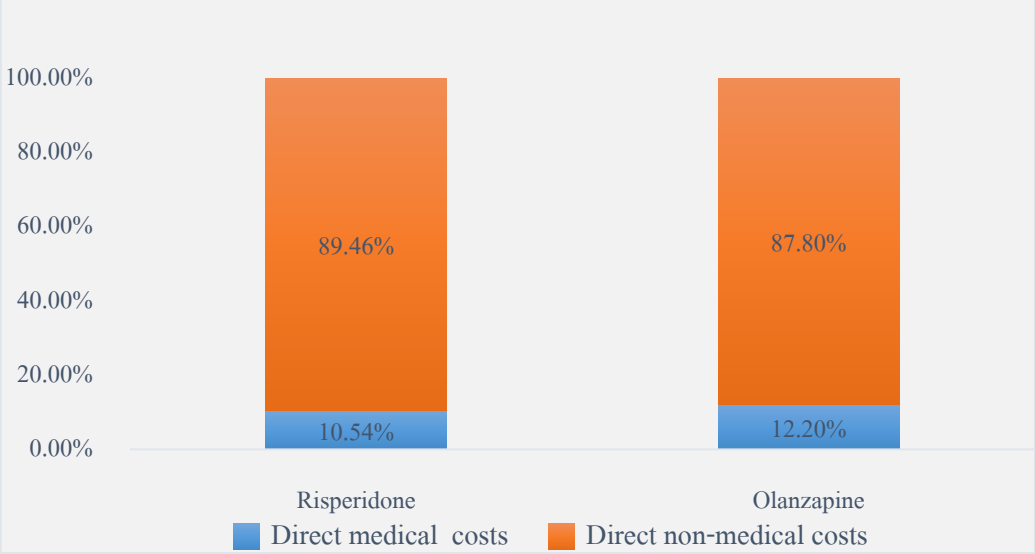


Figure 5.1: Distribution of total costs (%) classified by drugs and by patients' cognitive function

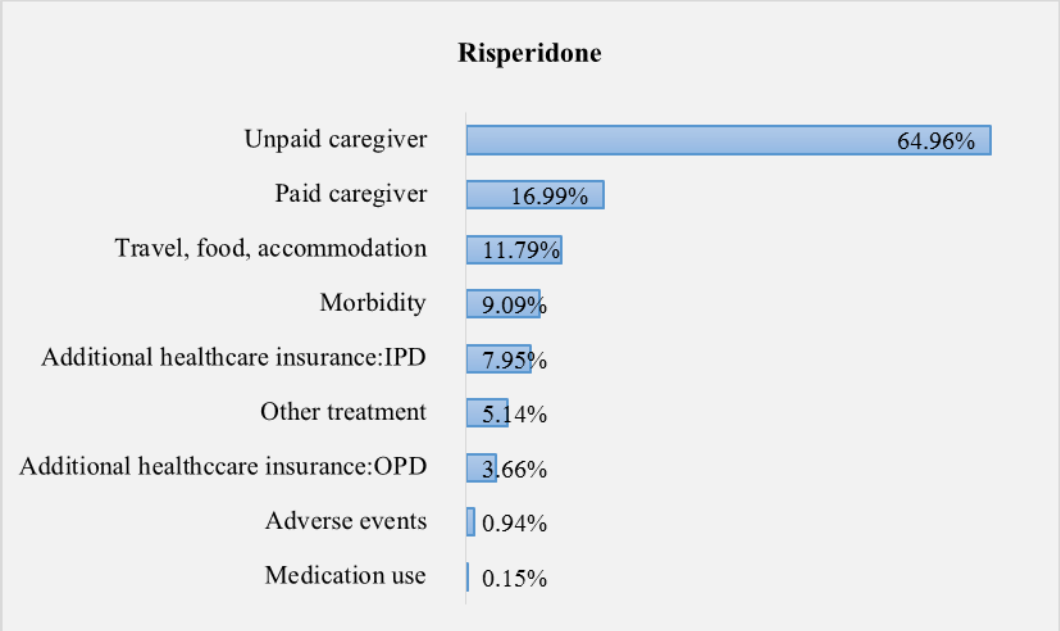


Figure 5.2: Distribution of type of costs (%) of risperidone classified by patients' cognitive function

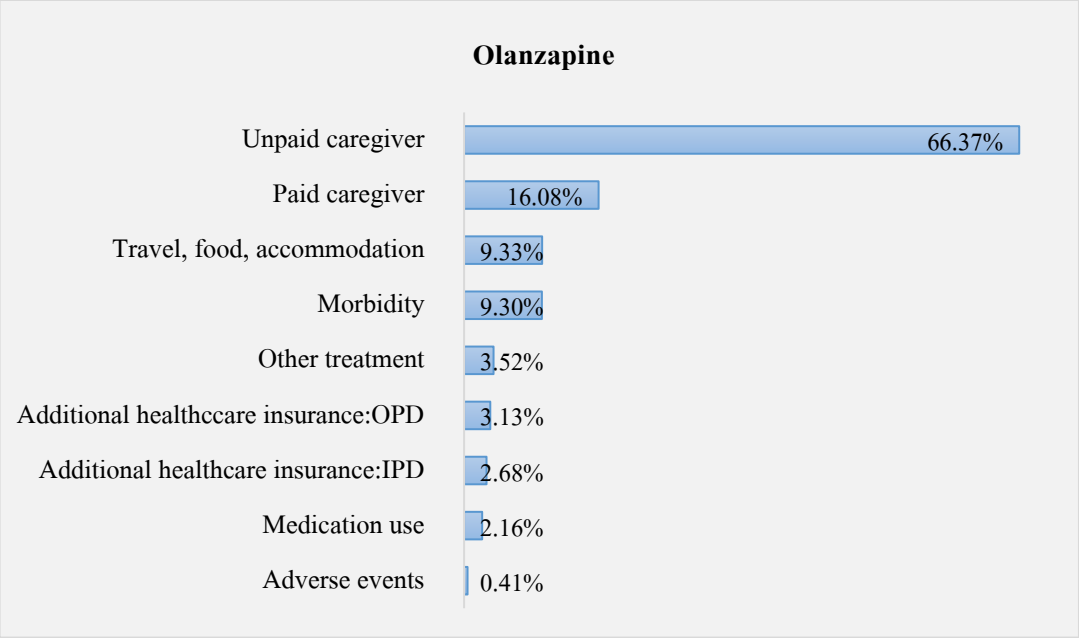


Figure 5.3: Distribution of type of costs (%) of olanzapine classified by patients' cognitive function

5.3.2.2 The distribution of costs by patients' dependence

The classification of patients by physical dependence used the patients' activities of daily living, (as measured by ADL scores), along with a physician's assessments. Thus, patients were classified into two different dependence states as follows: Pre-FTC state and FTC state. More details can be seen as previously stated (in section 5.3.1.4). As Table 5.8 shows, cost parameters are based on the dependence of patients.

5.3.2.2.1 Direct medical costs

The mean monthly medication cost was higher in olanzapine treated patients than those risperidone treated patients, accounting for THB 1,105.63 and THB 73.38, respectively. Patients within the FTC state of both the olanzapine and risperidone treated groups had more monthly medication costs compared with the patients within the Pre-FTC state.

The frequency of physician visits per month of patients was not different between the patients receiving risperidone and those patients receiving olanzapine. However, additional payments due to outpatient visits were different between the two states of each treatment group. In the

risperidone-treated patients, the costs were THB 2,002.96 for the Pre-FTC state and THB 849.64 for the FTC state. Conversely, patients with the olanzapine treatment in the FTC state had higher additional payments of physician visits than those Pre-FTC patients, being THB 2,190.91 and THB 1,214.33, respectively.

Regarding hospital admissions, approximately 1% of patients of both the olanzapine and risperidone treated groups with the Pre-FTC state tended to be admitted per month. These were found to be 4% of the patients receiving risperidone and 8% of those receiving olanzapine within the FTC state. The mean length of stay (LoS) was lower in the patients receiving risperidone than those patients receiving olanzapine, accounting for 1.22 days and 2.68 days, respectively. The longest LoS was found in the olanzapine treated patients within the FTC state (3.73 days). The mean additional payments associated with hospital admissions showed a higher cost in the risperidone group relative to the olanzapine group by THB 362.15.

Comorbidity associated costs related to the functional abilities of the patients within the FTC state who had more monthly costs of comorbidity conditions compared with the Pre-FTC state. For the risperidone treated patients, the difference of comorbidity associated costs for the Pre-FTC and the FTC states was approximately THB 702. Similarly, the olanzapine treated patients within the FTC state had THB 2,644.98 higher costs of comorbidities compared with those patients in the Pre-FTC state.

For adverse events, the risperidone treated patients had higher costs of falls compared with the olanzapine treated patients for both the Pre-FTC and the FTC states accounting for THB 14.10 and THB 7.05, respectively. The difference of mean monthly costs associated constipation was THB 1.44 between the Pre-FTC state and the FTC state of both treatments. Costs associated EPSs were predominantly in patients treated with risperidone compared with those patients treated with olanzapine. For the risperidone treated patients, costs of drug

induced EPSs were approximately THB 13.35 per month for both the Pre-FTC and the FTC states. The costs of the olanzapine treated group were THB 5.01 per month for both the Pre-FTC and the FTC states.

Regarding relapse associated costs, the mean monthly cost of relapses requiring hospitalisation was lower in the patients treated with olanzapine than those patients treated with risperidone for both the Pre-FTC and the FTC states by THB 225.44. Similarly, the olanzapine treated patients had lower costs of the relapse not requiring hospitalisation when compared with those risperidone treated patients by THB 7 per month for both the Pre-FTC and the FTC states.

Based on the data as stated above, total direct medical costs per month for the patients prescribed risperidone were THB 4,324.47 for the Pre-FTC state and THB 5,627.54 for the FTC state. For the patients receiving olanzapine, direct medical costs for both the Pre-FTC and the FTC states were THB 4,782.94 and THB 9,905.50 per month, respectively.

5.3.2.2.2 Direct non-medical costs

The mean monthly cost was THB 4,391.66 for patients treated with risperidone and THB 6,541.86 for the patients treated with olanzapine.

Costs of other treatments of patients receiving risperidone were THB 3,567.29 for the FTC state and THB 1,867.41 for the Pre-FTC state. Patients receiving olanzapine showed similar costs associated with other treatments as those patients receiving risperidone, being THB 3,190.91 for the FTC state and THB 1,161.67 for the Pre-FTC state. Additionally, the risperidone treated patients had a higher cost of other treatments compared with the olanzapine treated patients.

Regarding the costs of paid caregivers, these costs were relevant to the patient's functional abilities. Patients with more dependence were more likely to have higher costs of paid caregivers. For the risperidone treated patients, the monthly costs associated with paid

caregivers were THB 9,382.86 for the FTC state and THB 7,861.11 for the Pre-FTC state. The olanzapine group was THB 6,189.67 and THB 10,800.00 for the Pre-FTC and FTC states of paid caregiver-associated costs per month.

Costs of informal care showed that the patients in the olanzapine group had a higher mean cost compared with the patients in the risperidone group, where these costs differed by THB 594.82 per month. Informal care costs also related to the functional abilities of patients. The FTC state was noted for higher costs in comparison to the Pre-FTC state of both treatment groups.

As presented above, patients treated with olanzapine and those treated with risperidone showed slightly significant differences with regard to the mean direct non-medical costs per month, which were THB 43,966.06 of the risperidone group and THB 43,976.52 of the olanzapine group.

5.3.2.2.3 The monthly cost of patients, classified by patients' dependence, associated with the treatment of BPSD

Based on the classification of patients by dependence, a higher monthly cost was found in the patients receiving olanzapine compared with those patients receiving risperidone by THB 2,378.68. For patients using risperidone treatment, monthly costs for the Pre-FTC and the FTC states were THB 44,717.09 and THB 53,167.03, respectively. Whilst, THB 44,347.28 was the monthly cost for the Pre-FTC state and THB 58,294.20 for the FTC state of patients using the olanzapine treatment.

Table 5.8: **Parameters of costs, classified by dependence in patients with dementia based on the data collected from Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital, Thailand, in Thai Baht (THB) in 2017**

Type of costs	Pre-FTC State	FTC State
Direct medical costs		
Medication use (per month, THB) *[mean (SD)]*		
Risperidone treatment	70.51 (34.13)	76.24 (21.12)
Olanzapine treatment	939.29 (588.38)	1,271.97 (544.42)
Outpatient department (OPD)		
The frequency of physician visits of patient (per month) [mean (SD)]		
Risperidone treatment	0.43 (0.29)	0.57 (0.30)
Olanzapine treatment	0.39 (0.22)	0.55 (0.31)
Additional healthcare insurance coverage of OPD per visit, THB [mean (SD)]		
Risperidone treatment	2,002.96 (3,187.04)	849.64 (1,130.96)
Olanzapine treatment	1,214.33 (2,843.98)	2,190.91 (4,287.47)
Inpatient department (IPD)		
The frequency of hospital admission (per month) [mean (SD)]		
Risperidone treatment	0.01 (0.02)	0.04 (0.09)
Olanzapine treatment	0.01 (0.04)	0.08 (0.12)
Length of stay at the hospital, day (per admission) [mean (SD)]		
Risperidone treatment	1.37 (5.88)	1.07 (2.73)
Olanzapine treatment	1.63 (5.42)	3.73 (5.69)
Additional healthcare insurance coverage of IPD per admission, THB [mean (SD)]		

Type of costs	Pre-FTC State	FTC State
Risperidone treatment	3,000.00 (12,086.23)	1,464.29 (4,352.12)
Olanzapine treatment	340.00 (1,618.13)	3,400.00 (9,066.42)
Cost of comorbidity (per month, THB) *[mean (SD)]*		
Risperidone treatment	4,087.41 (3,222.32)	4,789.58 (5,020.62)
Olanzapine treatment	3,832.20 (3,667.20)	6,477.18 (7,108.94)
Adverse events (per month, THB)		
Falls [mean (SD)]		
Risperidone treatment	14.10 (0.00)	14.10 (0.00)
Olanzapine treatment	7.05 (0.00)	7.05 (0.00)
Constipation [mean (SD)]		
Risperidone treatment	0.24 (0.00)	0.24 (0.00)
Olanzapine treatment	1.68 (0.00)	1.68 (0.00)
Extrapyramidal symptoms (EPS) [mean (SD)]		
Risperidone treatment	13.35 (0.00)	13.35 (0.00)
Olanzapine treatment	5.01 (0.00)	5.01 (0.00)
Relapses (per month, THB)		
Relapse requiring hospitalisation [mean (SD)]		
Risperidone treatment	393.24 (0.00)	393.24 (0.00)
Olanzapine treatment	167.80 (0.00)	167.80 (0.00)
Relapse not requiring hospitalisation [mean (SD)]		
Risperidone treatment	18.93 (0.00)	18.93 (0.00)
Olanzapine treatment	11.83 (0.00)	11.83 (0.00)
Total direct medical cost (per month, THB) *[mean (SD)]*		
Risperidone treatment	4,324.47 (2,030.91)	5,627.54 (3,003.93)
Olanzapine treatment	4,782.94 (1,938.46)	9,905.50 (7,990.77)
Direct non-medical costs		

Type of costs	Pre-FTC State	FTC State
Non-medical costs (travel, food, accommodation) of OPD (per month, THB) [mean (SD)]		
Risperidone treatment	2,173.87 (1,992.12)	2,433.69 (1,112.33)
Olanzapine treatment	1,795.05 (738.14)	2,106.62 (1,289.50)
Non-medical cost (travel, food, accommodation) of IPD (per admission, THB) [mean (SD)]		
Risperidone treatment	2,618.66 (10,825.31)	1,557.10 (4,707.30)
Olanzapine treatment	592.65 (3,246.08)	8,589.39 (13,671.29)
Other treatment (per month, THB) [mean (SD)]		
Risperidone treatment	1,867.41 (2,466.27)	3,567.29 (2,939.93)
Olanzapine treatment	1,161.67 (1,248.56)	3,190.91 (2,672.25)
Paid caregiver (per month, THB) [mean (SD)]		
Risperidone treatment	7,861.11 (5,372.65)	9,382.86 (2,397.09)
Olanzapine treatment	6,189.67 (4,548.64)	10,800.00 (3,561.29)
Informal care (per month, THB) [mean (SD)]		
Risperidone treatment	29,708.61 (9,716.47)	33,143.06 (9,763.31)
Olanzapine treatment	31,508.35 (13,713.54)	32,532.95 (16,364.21)
Total direct non-medical cost (per month, THB) *[mean (SD)]*		
Risperidone treatment	40,392.62 (14,412.45)	47,539.49 (10,245.71)
Olanzapine treatment	39,564.34 (15,404.85)	48,388.70 (18,511.68)
Total costs (per month, THB) *[mean (SD)]*		
Risperidone treatment	44,717.09 (14,573.74)	53,167.03 (11,251.27)
Olanzapine treatment	44,347.28 (16,071.51)	58,294.20 (19,227.41)

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

Figures 5.4 to 5.6 show the distributions of total costs, costs of treatment with risperidone and costs of treatment with olanzapine according to a classification of patients by dependency.

For total costs, the percentages of direct medical costs and direct non-medical costs of patients using risperidone treatment were 10.17% and 89.83%. For patients using olanzapine treatment, there were 14.31% of direct medical costs and 85.69% of direct non-medical costs. Considered by drug treatment, the main proportion of risperidone treated patients was informal care (64.21%), followed by paid caregiver costs (17.62%) and comorbidity condition associated costs (9.07%). The non-medical costs associated with transportation, extra food and extra accommodation in the risperidone group was 8.97%. For olanzapine treated patients, the highest percentage was found in informal care (62.39%), followed by paid caregiver costs (16.55%) and non-medical costs associated with transportation, extra food and extra accommodation (12.75%). In the olanzapine group, costs associated with comorbidity conditions was 10.04%. When considering costs of other treatments and additional payments associated with hospital admissions, patients using the risperidone treatment had a higher percentage compared with those patients using the olanzapine treatment. These were 5.55% of costs for other treatments and 4.56% of additional payments associated with hospital admissions of patients receiving risperidone. For patients receiving olanzapine, there were 4.24% of costs for other treatments and 3.64% of additional payments due to hospital admissions. However, additional payments associated with outpatient visits were higher in the olanzapine treated group than the risperidone treated group, accounting for 3.32% and 2.91%, respectively. The percentage of medication costs per month was 0.15% of patients receiving risperidone and 2.15% of patients receiving olanzapine. For costs of treating adverse events, this showed that patients using the risperidone treatment had a higher percentage compared with patients treated with olanzapine, accounting for 0.90% and 0.38%, respectively.

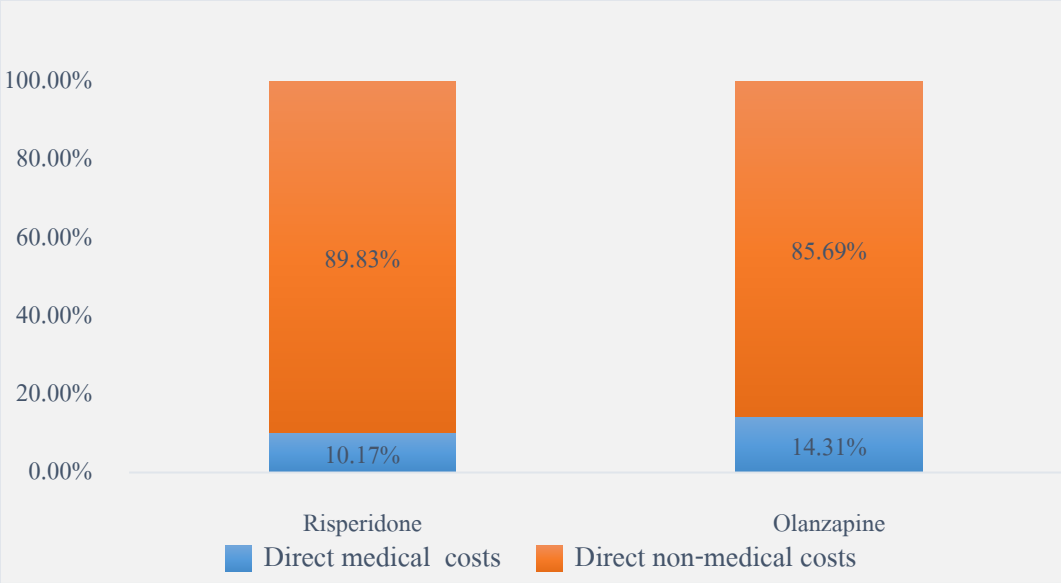


Figure 5.4: **Distribution of total costs (%) classified by drugs and by patients' dependence**

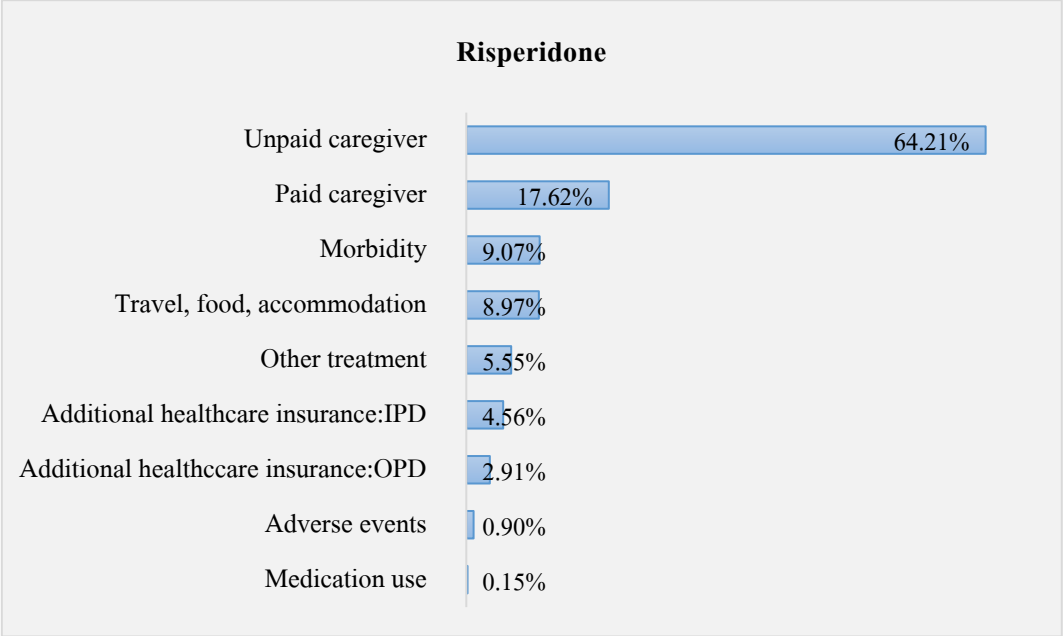


Figure 5.5: **Distribution of type of costs (%) of risperidone classified by patients' dependence**

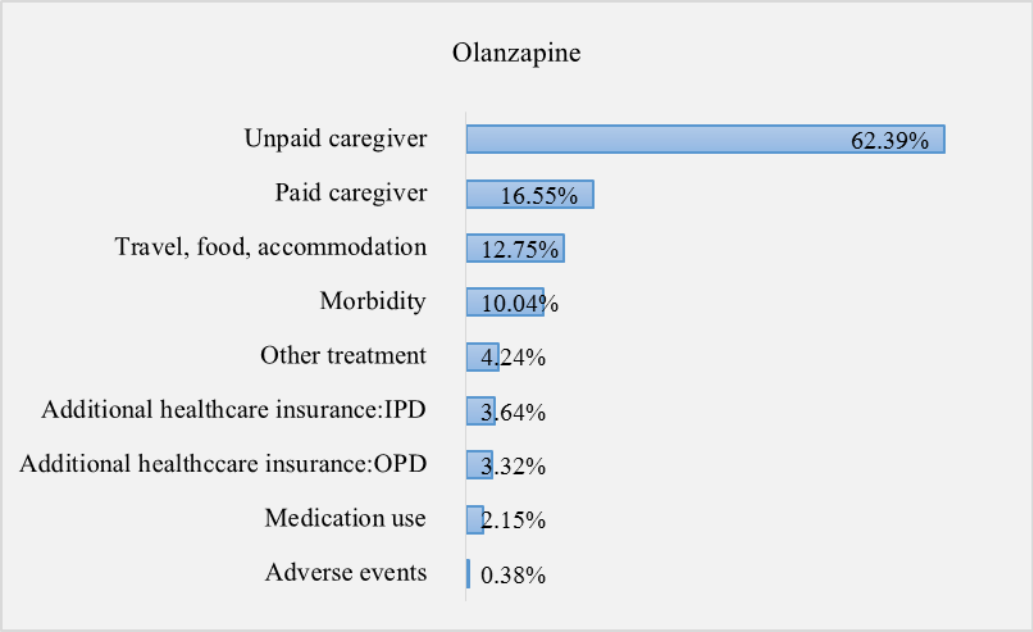


Figure 5.6: **Distribution of type of costs (%) of olanzapine classified by patients' dependence**

5.4 Discussion

This chapter has reported the costs of patients with behavioural and psychological symptoms of dementia in Thailand. Cost analyses are classified by patients' cognitive function and by patients' physical dependence.

When considering a classification of patients by their cognitive function, the findings show that costs of patients per month are increased following more severity stages of cognitive function of both treatment groups. Patients within the severe stage have the highest costs compared with the mild and moderate stages. Moreover, patients within severe stage have the highest direct non-medical costs, especially costs associated with paid caregivers and informal care, compared with the other stages of mild and moderate. Based on the findings (Table 5.7), the proportion of the direct medical cost of both treatment groups is only 11-12% of the total costs, whilst a significant part of the cost is the direct non-medical costs, being 88-89% of total costs. Moreover, informal care costs are a significant part, leading to a

greater cost to those patients, accounting for 65-66% of the total costs of the treatments. This is consistent with the study by Permsuwan, Niwatananun and Pimkrai (2013), that conducted the cost-utility analysis of donepezil for the treatment of Alzheimer's disease in Thailand, reported patients with the severe stage have the highest costs, (THB 13,896 per month), compared with the mild stage, (THB 6,254 per month), and the moderate stage, (THB 7,736 per month). However, the monthly costs in each severity state from Permsuwan, Niwatananun and Pimkrai (2013) are lower than this thesis. That is because the cost data from Premsuwan and colleagues did not included non-medical costs due to transportation, extra food and accommodation, costs associated with other treatments and costs due to paid caregivers, whereas this thesis includes all of these costs. Moreover, it should be highlighted that Permsuwan, Niwatananun and Pimkrai (2013) conducts an analysis in general Alzheimer's disease patients, whilst this thesis focuses on patients with BPSD and receiving olanzapine or risperidone.

For hospital admissions, none of the patients within the severe stage and receiving risperidone had a hospital admission. This might be because those patients had no exacerbation of BPSD such as aggressiveness, hallucinations, and delusions when compared with patients with mild and moderate stages. By contrast, several studies reported that BPSD are correlated with the level of the disease severity of dementia, especially in Alzheimer's disease. An increase in behavioural disturbances is frequently found in the late stage of the disease (Shimabukuro, Awata and Matsuoka 2005, Hashimoto et al. 2015).

Additionally, patients within the severe stage and using risperidone have the lowest cost of additional payments for physician visits in comparison to patients having mild and moderate stages. These might be associated with the difference in healthcare insurance scheme proportions of those patients. For the risperidone treated patients within the severe stage, the healthcare insurance is approximately 6% under the Universal Coverage scheme, (UC

scheme), and 94% under the Civil Servants Medical Benefit Scheme, (CSMBS), whereas the patients with mild and moderate stages are 40-53% under the UC scheme and 33-50% under the CSMBS and 10-13% out-of-pocket expenses, respectively. In general, the additional costs of patients are associated with medical procedures, doctor fees, and non-essential drugs, (the NEDs are not covered by the healthcare insurance schemes for the Thai population), where these costs might be not covered by patients' healthcare insurance scheme. Amongst healthcare insurance schemes in Thailand, the CSMBS tends to have more healthcare benefits relative to the UC scheme where the CSMBS is THB 12,767.06 per capita per year and the UC scheme is THB 2,592.89 per capita per year (The Comptroller General's Department of the Ministry of Finance in Thailand 2018, the National Health Security Office of the Ministry of Public Health in Thailand 2018, the Budget Bureau of the Office of the Prime Minister of Thailand 2018). Consequently, patients under the UC scheme are likely to have more additional payments compared with the CSMBS. Further, additional costs for admissions vary for both drug groups. These expenditures are associated with costs of special rooms, equipment and medical procedures which are relied on during the length of stay, (LoS), at hospital and patients' healthcare insurance schemes.

Regarding physician visits, based on both treatments, patients with mild and severe stages have a similar frequency of physician visits per month and these patients tend to have more physician visits when compared with patients within the moderate stage. This is consistent with Ferretti et al. (2018), who examined direct and indirect costs of dementia in Brazil, suggested that Alzheimer's patients with mild and severe stages have a similar frequency of specialised physician visits per month and these patients are likely to have more specialised physician visits when compared with patients within the moderate stage. However, it is in contrast with the study by Jonsson et al. (2006) which investigated costs of care for patients with Alzheimer's disease according to the level of cognitive impairment, as measured by MMSE, in Sweden, Denmark, Norway and Finland. Jonsson's study reported that patients

with the moderate stage have the highest mean specialist physician visits per year compared with the other stages.

When considering costs of additional payments due to physician visits, there are differences amongst studies because these costs are depended on several factors, such as the provisions of healthcare systems by the government, medication accommodated in NLED and other expenditures not covered by patients' healthcare insurance of each country.

Focusing on comorbidity conditions, the risperidone treated patients within the moderate stage show the lowest costs for the treatment of comorbidities compared to those patients within the mild and severe stages. This might be associated with those patients in the moderate stage in the risperidone group have fewer comorbidity conditions and lower rates of osteoarthritis, hyperlipidaemia and hypertension, leading to lower costs of comorbidity condition treatment than the other groups.

Further, the direct non-medication costs of hospital admissions vary across all cognitive severity levels of both drug groups. These might be associated with the differences in costs of transportation and food for their caregivers. Most caregivers spend more money on food and their transportation between home and the hospital, when patients are admitted into the hospital.

Compared with patients with mild and severe stages and treated with risperidone, the highest cost of other treatments is found in moderate dementia patients. These costs might be associated with the patients having new wheelchairs, dietary supplements, (e.g. nutritional liquid diets), other sources of nutrition, (e.g. sterilised dairy milk, UHT milk, UHT yoghurt milk, Anlene®, and Lactasoy®), vitamins, and disposable adult diapers.

To summarise, based on a classification of patients by cognitive function, the total direct medical cost of the risperidone treated patients is lower than those olanzapine treated patients by THB 870. When excluding costs associated with adverse events and relapses, this shows

that the olanzapine treated patients have higher total direct medical cost compared with the risperidone treated patients by THB 1,116. As a result, this implies adverse events and relapses are significant factors affecting the direct medical costs of patients. In addition, the severity levels of cognitive function have a substantial impact on direct non-medical costs and total costs for all patients. This indicates that an increase in costs of patients is directly correlated with more cognitive impairment of those patients. Consistently, several studies reported that neuropsychiatric symptoms (NPSs) in patients with dementia are correlated with declining cognitive function and an increase in the caregiver burden (Hux et al. 1998, Mohamed et al. 2010, Sansoni et al. 2013, Reed et al. 2014, Ku et al. 2016). Accordingly, it can be inferred that behavioural disturbances are significant predictors, leading to greater direct non-medical costs, especially for paid caregivers and informal care, in patients with dementia.

When considering a classification of patients by their dependence, the total mean monthly costs show no significant differences between patients treated with risperidone and those treated with olanzapine. The direct non-medical costs are associated with 86-90% of total costs. In addition, informal care is also highlighted at 62-64%, whereas the direct medical costs are approximately 10-14% of the total costs.

Patients receiving risperidone treatment within the Pre-FTC state have more additional costs for hospital admissions compared with those patients within the FTC state. This might be associated with the different proportions of healthcare insurance between two dependence states. The risperidone treated patients within the Pre-FTC state account for 33% under the UC scheme, 56% under the CSMBS, and 11% out-of-pocket expenses, whereas the patients with the FTC state are 29% under the UC scheme and 71% under the CSMBS. Regarding the UC scheme in Thailand, some costs are not covered by this healthcare scheme, such as special rooms and some medical procedures (National Health Security Office, the Ministry of

Public Health in Thailand 2018). Thus, the patients might have to pay those costs by themselves (as out-of-pocket expenses). These additional costs for the risperidone treated patients within the Pre-FTC state are approximately 15% higher than those FTC patients. For the olanzapine treatment, patients within the FTC state have higher additional costs associated hospitalisation than those patients within the Pre-FTC state. These might be associated with patients with the FTC state of the olanzapine treatment having more frequencies of hospital admissions and longer stays in hospital than those Pre-FTC patients. According to the frequency of hospital admissions of olanzapine treatment, this is in line with the findings from the study by Turongkaravee et al. (2011). Turongkaravee and colleagues, who conducted a cost-utility analysis of acetylcholine inhibitors in the treatment of Alzheimer's disease in Thailand, reported patients in the FTC state had a 53% higher frequency of admission compared with patients in the Pre-FTC state.

Comparing the direct non-medical costs for hospitalisation, risperidone treated patients within the Pre-FTC have a higher cost than those patients with the FTC state due to these patients having longer overnight stays in hospital than the other patient groups. Similarly, patients using olanzapine treatment within the FTC state have a higher hospitalisation associated cost compared with those patients within the Pre-FTC state because these FTC patients have a 2.3-fold higher LoS than the other state. Also, the FTC patients of the olanzapine treatment have more than an 8-fold frequency of hospital admissions compared with the patients within the Pre-FTC state.

In a comparison of the comorbidity-associated costs, both treatment groups show that increased costs are associated with the greater dependence state of patients. Thus, it implies that the patients within the FTC state of both the risperidone and olanzapine groups have higher percentages of comorbidities compared with those patients within the Pre-FTC state.

Regarding other treatment costs, paid caregivers and informal care, these costs also increase with the greater dependence of patients. Accordingly, this infers that the total direct medical costs and direct non-medical costs are dependent upon the functional dependence of the patients. The total costs show a similar fashion where these are likely to be higher in patients with greater dependence. This is consistent with the study by Turongkaravee et al. (2011) which reported that costs of paid caregivers and informal care in Thailand are higher in patients within the FTC state than those patients within the Pre-FTC state. However, Turongkaravee and colleagues conducted the study in the Thai elderly with dementia in a Thai University hospital and was not focused on patients with BPSD and being treated with atypical antipsychotics.

In brief, with regard to a classification of patients by their dependence, the total costs of patients show a THB 2,378.68 difference between the treatment groups. Medication costs, additional payments beyond patient healthcare coverage schemes, the frequency of hospital admissions, LoSs, comorbidity-associated costs, and costs associated with adverse events and relapses are important factors, leading to the cost discrepancy between the two treatment groups. Although direct non-medical costs are the greater part of the total costs of patients with BPSD, these costs are not significantly different between the risperidone treated and the olanzapine treated patients. Focusing on the total direct medical costs, the risperidone treated patients have lower costs than the olanzapine treated patients. The costs associated with adverse events and relapses are higher in the patients receiving risperidone than those patients receiving olanzapine. This indicates that the risperidone treated patients are associated with higher drug induced adverse effects and have more relapse rates than those olanzapine treated patients. However, the proportion of comorbidity conditions is higher in the patients receiving olanzapine than those patients receiving risperidone, leading to a greater cost of comorbidity treatment associated costs in the olanzapine group. When considering the total direct non-medical costs, these costs are directly associated with more impairment in

activities of daily living. Several studies consistently suggest patients with BPSD are correlated with increasing dependence and caregiver burden (Mangone et al. 1993, Getsios, et al. 2002, Allegri et al. 2006, Miyamoto, Tachimori and Ito 2010, Mohamed et al. 2010, Cerejeira, Lagarto and Mukaetova-Ladinska 2012, Pinidbunjerdkool, Saengwanitch and Sithinamsuwan 2014, Reed et al. 2014, Lanctot et al. 2017). Consequently, behavioural disturbances are the significant predictors affecting the direct non-medical costs, especially paid caregivers and informal care, in patients with dementia.

Using to two different approaches for classifying patients, (by cognitive status and physical dependence), the direct medical costs and the direct non-medical costs of the olanzapine and risperidone treated patients have similar results. The medication cost per month is a significant difference between patients treated with risperidone and those treated with olanzapine. The lower direct medical costs and direct non-medical costs are found in patients using risperidone compared with patients using olanzapine in both methods of classification. Also, informal care has highlighted an impact on socio-economic conditions of patients and their families. These are in line with reporting from WHO, that costs of informal care are associated with 40-65% in lower-middle-income countries and upper-middle-income countries, whilst the direct medical costs contribute only 23-32% in those countries (World Health Organisation 2012).

For adverse events and relapses, costs associated with falls, EPSs, relapses requiring hospitalisation, and relapses not requiring hospitalisation, they are higher in patients using the risperidone treatment than those patients treated with olanzapine, with the exception of constipation. This might be because the patients using risperidone treatment have a higher percentage in occurrence of EPSs, falls and relapses when compared with the olanzapine treatment. Consequently, these also imply that the risperidone treated patients are associated

with higher drug induced side effects and more relapse rates than those olanzapine-treated patients.

For adverse events associated with falls, the findings in this thesis are contrary with previous published studies which reported olanzapine treated patients had a higher incidence of falls compared with risperidone treated patients (Deberdt et al. 2005, Schneider, Dagerman and Insel 2006 and Schneider et al. 2006). The findings in this thesis shows a higher incidence of falls in risperidone treated patients compared with olanzapine treated patients. According to Derberdt, et al. 2005, the risk of falls was higher in olanzapine treated patients than risperidone treated patients where risk differences between active drugs and placebo accounted for 4.9% and 2.8%, respectively. Conversely, the findings based on the patient data collection in Thailand found that olanzapine treated patients were at lower risks of falls than risperidone treated patients, accounting for 2.44% and 4.88%, respectively.

Considering extrapyramidal symptoms, the findings from this thesis are consistent with several studies, including the RCT and a meta-analysis of the RCTs which reported that the EPSs are significantly higher in patients using risperidone treatment compared with those patients using the olanzapine treatment (Deberdt et al. 2005, Schneider, Dagerman and Insel 2006 and Ma et al. 2014). For drug induced EPSs, the differences in incidence of treatment-emergency EPSs between active drugs and placebo were 20.10% of risperidone treated patients and 6.10% of olanzapine treated patients (Derberdt et al. 2005). Consistently, the incidence of drug-induced ESPs from the data collected in the Thai setting were 19.50% of the risperidone treated patients and 7.32% of olanzapine treated patients. However, the CATIE-AD study by Schneider et al. (2006) suggested that extrapyramidal signs had the same percentage in both risperidone and olanzapine treated patients.

Interestingly, this thesis is the first study to investigate the costs of patients with BPSD using olanzapine or risperidone in a Thai setting which includes costs associated with relapses

requiring hospitalisation and relapses not requiring hospitalisation and the costs associated with adverse events, (falls, EPSs and constipation), due to atypical antipsychotic use for treating BPSD.

The cost analyses presented in this chapter have several limitations. Firstly, atypical antipsychotics are off-label use in dementia (Maglione et al. 2011). Thus, there are a lack of studies of atypical antipsychotics associated with drug induced adverse events within the different cognitive severity levels, dependence levels and drug-associated relapses, for the treatment of dementia patients. Consequently, costs of drug-induced adverse events and relapses are assumed to have similar values for all the patients' cognitive severity levels (mild, moderate, and severe stages) and all patients' dependence (Pre-FTC and FTC states). The relapse rates are associated with greater risks of the return of behavioural and psychological symptoms of patients, leading to an increase in costs of medication, outpatient services and inpatient services. Paid caregivers and informal care are associated with the NPS of patients, leading to caregiver burden and increasing costs of care (Torrisi et al. 2016, Cheng 2017, Lanctot et al. 2017, Shikimoto et al 2018). Thus, this study takes into account the relapses to estimate for costs. However, the relapse rate data are adopted from a study of schizophrenia. Therefore, these costs might be an over or underestimation of the actual costs of patients with BPSD being treated by atypical antipsychotics, (risperidone or olanzapine). Based on reporting in several previous studies, there are several adverse events that occur due to antipsychotic drug use in elderly people with dementia (Schneider et al. 2006, Maher et al. 2011, Riggs 2013, Ma et al. 2014, Tempi et al. 2016). However, only three significant adverse events (falls, constipation and EPSs) are included in this cost analysis. Thus, costs associated with adverse events are likely to be underestimated due to the hidden costs of other adverse events. In addition, the treatment of constipation in this thesis is focused on magnesium hydroxide, (Milk of Magnesia or MOM), because this drug is recommended as a suitable treatment for elderly people and also is provided in NLED of Thailand. Therefore,

constipation treatment-associated costs may result in an undervaluation of cost data due to drug-induced constipation.

Secondly, indirect costs of lost productivity have not been included due to all patients in this thesis have retired and/or are not working.

Another limitation is that this study was conducted as a cross-sectional study, thus the data are limited in its ability to represent how NPS changes, influencing the costs of providing care to patients over time.

To the researcher's best knowledge, this thesis is the first study to explore the costs of patients with BPSD and receiving atypical antipsychotic drugs, (risperidone or olanzapine), in which adverse events and relapses are taken in account for the analysis for costs in Thailand or in general. The thesis also highlights costs of BPSD patients and receiving atypical antipsychotic drugs by classifying patients with cognitive severity and dependence status. However, this is based on a view of the dearth of evidence on costs of patients with BPSD and treated with olanzapine or risperidone. The findings in this thesis are also specific to healthcare system in Thailand. Therefore there might be concerned over a generalisability when these results are exercised in different circumstances. Furthermore, cost analyses in this chapter were focused only on the descriptive analysis. A further study associated with the costs of patients with BPSD should take into account other adverse events, such as gait disturbance, urinary tract infection, prolactin increase and cerebrovascular events, and indirect costs due to productivity loss of patients not included in this thesis. Taking these factors into account might lead to different aspects of costs being highlighted and also impact on the decision-making of patients, caregivers and physicians on the treatment of BPSD patients.

Chapter 6: Utility analyses of patients with behavioural and psychological symptoms of dementia in Thailand

Abstract

Introduction: Behavioural and psychological symptoms of dementia (BPSD) are major problems in patients with dementia. Dealing with BPSD has much more difficulties, therefore these symptoms are leading to individual suffering and impact on the caregiver burden as well as healthcare systems. The development of BPSD is also associated with a reduction in quality of life of patients and their caregivers because it is a major source of distress for patient themselves and relevant to family caregivers. Currently, a guideline for the treatment of BPSD remains uncertain; however, atypical antipsychotic drugs are often used in a clinical practice for BPSD patients. Owing to a paucity of data on health-related quality of life weights, (utility weights), of patients with BPSD received atypical antipsychotics, then it is challenging to ascertain an accurate picture at present.

Aim: The objective of this chapter is to assess the utility weights of patients with BPSD and being treated with atypical antipsychotics, (risperidone or olanzapine), in different their disease stages, (mild, moderate and severe stages), and different their dependence status (Pre-FTC and FTC states).

Methods: In two hospitals, Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital in Thailand, a cross-sectional study was conducted based on 82 outpatients with BPSD and being treated with atypical antipsychotics, by face-to-face interviews using the EQ-5D-5L instrument. The data gathering was performed in two phases as follows: Phase I - from February 2017 to March 2017 and Phase II- from October 2017 to November 2017. In cases where the patients were not able to participate in the process their caregivers were approached to respond on their behalf. Responses to the questionnaire were converted into a utility score, (between a zero to one score), using Thai value sets. Utility

analysis of risperidone prescribed and olanzapine prescribed patients was performed based on patient classifications by cognitive function and dependence.

Results: The mean EQ-5D-derived utility weights for the risperidone treated patients were 0.59 in mild, 0.27 in moderate, and 0.26 in severe stages of dementia, whereas for olanzapine treated patients they were 0.62 in mild, 0.53 in moderate, and 0.39 in severe stages of dementia based on a classification of patients by cognitive function. The levels of cognitive impairment were associated with the utility weights of the patients. Patients with more severe cognitive impairment were likely to have a lower utility weight compared with patients with less cognitive impairment. For the classification of patients by their dependence, the utility weights of risperidone prescribed patients were 0.46 in the Pre-FTC state and 0.12 in the FTC state and olanzapine prescribed patients were 0.63 in the Pre-FTC state and 0.23 in the FTC state. The higher utility weights correlated with the lower level of the dependence of patients.

Conclusions: Major BPSD complications are associated with decreased HRQoL in both patients and their caregivers. Utility weights estimated from this chapter are incorporated for health outcomes and can be used in cost-utility analysis of patients with BPSD and being treated with atypical antipsychotics to aid decision-making of stakeholders, including patients, caregivers, physicians and policy-makers, for planning and selecting the relevant treatment and resource allocation decisions for those BPSD sufferers.

6.1 Introduction

Dementia is a chronic disease causing significant problems across the world due to a rapid growth in the number of ageing people (World Health Organisation 2012). The management of dementia is complicated because of non-cognitive symptoms or behavioural and psychological symptoms of dementia, namely psychosis, agitation, aggression and emotional change, which almost 50-90% of people with dementia have experienced during the course of their illness (Cerejeira, Lagarto and Mukaetova-Ladinska 2012, Tible et al. 2017). The presence of BPSD are more frustrating to deal with than the actual cognitive deterioration and also lead to potentially reduced health-related quality of life in patients and caregivers (Hersch and Falzgraf 2007, Tible et al. 2017). By comparison, individuals with BPSD have a lower quality of life than those without BPSD (Hurt et al. 2008).

To measure the health-related quality of life, two main methods are applied: disease-specific instruments and generic instruments. The generic instruments comprise of health profiles and utility measures (Guyatt et al. 1989, Drummond et al. 2005). With regard to disease-specific instruments, Alzheimer Disease Related Quality of Life (ADRQOL), Dementia Quality of Life Instrument (D-QoL), Quality of Life in Late-stage Dementia scale (QUALID), the Quality of Life in Alzheimer's Disease (QOL-AD) and DEMQOL, these are examples of dementia-specific instruments (Ready and Ott 2003, Ettema et al. 2005, Moyle and Murfield 2013, Perales et al. 2013).

The types of instruments to measure health profiles are the Sickness Impact Profile (SIP), the Nottingham Health Profile (NHP), the Short Form health survey-36 (SF-36) and the World Health Organization Quality of Life (WHOQOL-BREF) (Hunt et al. 1980, Bergner et al. 1981, Ware et al. 1992, the WHOQOL Group 1998, Drummond et al. 2005). For utility measures, these consist of direct and indirect methods. The Standard Gamble (SG), the Time Trade-Off (TTO), the Visual Analog Scale (VAS) are patterns of direct instruments (Von

Neumann and Morgenstern 1944, Torrance, Thomas and Sackett 1972, Torrance 1986, Drummond et al. 2005). Indirect methods are multi-attribute utility instruments, such as the Quality of Well-Being (QWB), the Health Utilities Index (HUI), the EQ-5D and the SF-6D. The values from these instruments are converted to produce utility weights, (sometimes known as weights, utilities, utility values, health utilities, quality of life scores or health-related quality of weights), in which the scores range between zero and one, (zero denoted death and one perfect health) (Guyatt et al. 1989, O' Brien 1994, Kaplan and Anderson 1988, The EuroQol Group 1990, Torrance et al. 1995, Feeny et al. 1995, Kaplan and Anderson 1996, Brazier et al. 2002, Herdman et al. 2011, EuroQol Group 2015).

The utility weights are applied by multiplying with the quantity of life, (duration), which produces the quality-adjusted life years (QALYs) which is widely used as a measure of incremental effect in economic evaluations of medical interventions, in particular the cost-utility analysis (CUA). Estimating QALYs then requires utility weights for given health states that are relevant to the conditions of interest (Drummond et al. 2005, McIntosh and Luengo-Fernandez 2006).

For health economic evaluation by cost-utility analysis, the EQ-5D is recommended by several agencies including the National Institute of Health and Clinical Excellence, (NICE), in the UK, The Pharmaceutical Benefits Advisory Committee, (PBAC), in Australia and the Health Intervention and Technology Assessment Program of Thailand (HITAP), in Thailand.

The literature review of model-based economic evaluation in dementia (Chapter 2, section 2.6), based on the CERAD conceptual framework, the cost-effectiveness studies of donepezil in Alzheimer's disease by Neumann et al. (1999) and Fuh and Wang et al. (2008) took the health utilities from Neumann et al. (1999). The study by Neumann et al. (1999), conducted a cross-sectional study of 528 caregivers of patients with Alzheimer's disease in the US between July 1996 and February 1997 using HUI:2 by proxy respondents, reported that the

utility weights were 0.68, 0.54 and 0.37 for mild, moderate and severe stages respectively. The utility weights in the cost-effectiveness analysis of donepezil in Alzheimer's disease by Lopes-Bastida et al. (2009) were 0.5249 in the mild stage, 0.1818 in the moderate stage and -0.2014 for the severe stage, based on the cross-sectional study in outpatients with Alzheimer's disease in the Canary Island, in Spain by proxy respondents using the EQ-5D and a Spain value set for converting to utility weights. The cost-effectiveness analysis of donepezil treatment in Alzheimer's disease conducted by Ikeda, Yamada and Ikegami (2002) reported the utility weights were 0.33, 0.16 and 0.22 for mild, moderate and severe stages based on the survey in the elderly people with dementia in Japan using HUI:3 by proxy respondents. According to Kirbach et al. (2008), a cost-utility analysis of olanzapine in the treatment of agitation and psychosis in patients with Alzheimer's disease obtained utility data from Murman and Colenda (2005). The Murman and Colenda's study investigated the relationship between the utility weights from Neumann et al. (1999) and the assessment of cognition, functioning and behavior and then the utility weights were reported as 0.54, 0.43 and 0.29 for mild, moderate and severe stages in patients with Alzheimer's disease and showing the presence of problematic behavioural disturbances (Murman and Colenda 2005).

From the economic evaluation based on the FTC conceptual framework, five studies of cost-effectiveness evaluations of the use of galantamine in Alzheimer's disease and one of an analysis of the cost-effectiveness of donepezil, galantamine, rivastigmine and usual care in Alzheimer's disease (Green et al. 2005) derived utility weights from Neumann et al. (1999) as previously mention above. The utility weights were 0.6 of the Pre-FTC state, (from Alzheimer's patients with mild and moderate stages), and 0.34 of the FTC state, (from Alzheimer's patients with severe, profound and terminal stages). According to the cost-effectiveness of the use of memantine in Alzheimer's disease by Rive et al. (2010), the utility weights of the Pre-FTC stage was based on the mapping of the EQ-5D and the Twelve-Item Health Status Questionnaire (HSQ-12), the Ferm's D-test and the quality of life scale in

Alzheimer's disease (QoL-AD), using the UK value set for translating to utility weights and then calculated by an equation. The mapping was also exercised for the utility weights of the FTC state based on the FTC sub-group of patients with moderate to severe classification in the LASER-AD study in the UK and the utility weights were reported as 0.336 of the FTC state (Rive et al. 2010).

Currently, there is a dearth of studies evaluating the HRQoL of patients with BPSD and being treated with antipsychotic drugs using a preference-weighted instrument. Only one study by Rosenheck et al. (2007) reported that an assessment of HRQoL in Alzheimer' patients receiving atypical antipsychotics, namely risperidone, olanzapine and quetiapine, compared with a placebo, was conducted alongside a clinical trial in the US and used the Health Utilities Index Mark 3 (HUI-3) as the instrument.

However, this thesis aimed to conduct an economic evaluation using a decision-analytic model, (known as a Markov model). Then the utility weights associated with each health state, corresponding to the health-related quality of life weights for given health states, were needed to be incorporated in calculating health outcomes of this thesis, as measured in terms of quality-adjusted life years (QALYs). In addition, it is important to note that the health-related quality of life measurement of patients treated with olanzapine or risperidone according to the health states of the developed models based on the CERAD conceptual framework and the FTC conceptual framework is not well explored.

As a result, the purpose of this chapter is intentionally to assess the utility weights, as measured by EQ-5D-5L, of patients with BPSD and treated with atypical antipsychotics (risperidone or olanzapine). The results from this chapter will be further adopted in the calculation of QALYs for a cost-utility analysis of atypical antipsychotics, (risperidone versus olanzapine), for patients with BPSD in Thailand.

6.2 Methods

6.2.1 Target population

Patients with BPSD aged 60 and over from two outpatient departments at Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital were included. For more details of the inclusion and exclusion criteria of participants in this thesis see Chapter 3, (section 3.4.4), where they are presented.

6.2.2 Data settings and data collection process

The data settings took place at two hospitals in Thailand as stated above. The process was undertaken in two phases: Phase I (from February to March 2017) and Phase II (between October and November 2017). More details of the data setting were described in chapter 3, (section 3.4.3).

Before initiating the data collection process, ethics approval was secured (see Appendix 3). A cross-sectional study was then undertaken to investigate the utility weights of patients with BPSD and being treated with olanzapine or risperidone. Face-to-face interviews were conducted at only one point in time during some point in 2017 using the recent EQ-5D-5L instrument in a Thai version, with patients and/or their caregivers. Then patients and/or their caregivers who met the criteria, were asked to participate in the study. Generally, patients with BPSD had difficulties concerning judgement due to their condition of cognitive impairment. Therefore, caregivers were asked to complete the quality of life questionnaire instead as proxies. The consent form was then given to those participants who had agreed to participate in the study. The interview was then undertaken in which patients and/or their caregivers were interviewed for approximately 30-45 minutes in total, including the completion of the cost questionnaire. However, the part about the quality of life questionnaire was completed within a few minutes.

6.2.3 Data analysis

Data on utility weights of patients receiving olanzapine or risperidone were analysed by descriptive statistics, categorised according to the classification of patients, including cognitive function and dependence. The analysis produced the results in percentage, mean and standard deviation which were performed using Microsoft® Excel version 2013.

6.3 Results

6.3.1 Patient characteristics and caregiver characteristics

Utility weights were derived from the data collection of patients and/or caregivers. The face-to-face interviews were conducted at the outpatient departments of both the Thammasat University Hospital and the Khon Kaen Rajanagarindra Psychiatric Hospital, Thailand. The recruitment of patients in the study was based on the same inclusion criteria as the cost data, as stated in Chapter 5 (section 5.2.1). The data collections were similarly conducted from two phases as the cost data Chapter 5 (section 5.2.2), but the utility weights were done based on one interview. Utility weights were collected on a sample of 82 patients with Alzheimer's disease and/or caregivers. Only one patient (1.22%) with the mild stage of dementia and being treated with olanzapine and 81 caregivers (98.78%) completed the EQ-5D-5L questionnaire measures of health-related quality of life.

Based on the gathered data using the EQ-5D-5L instrument, value sets from the Thai population were applied to estimate individual utility weights as shown in Table 6.1 (Pattanaphesaj 2014).

Table 6.1: **Value sets of health dimensions based on the Thai population (Pattanaphesaj 2014)**

Health dimension	Coefficient
Mobility (MO)	
1	0
2	0.056
3	0.114
4	0.231
5	0.307
Self-care (SC)	
1	0
2	0.033
3	0.108
4	0.225
5	0.254
Usual activities (UA)	
1	0
2	0.043
3	0.075
4	0.165
5	0.207
Pain/discomfort (PD)	
1	0
2	0.040
3	0.068
4	0.233
5	0.266
Anxiety/depression (AD)	
1	0
2	0.032

Health dimension	Coefficient
3	0.097
4	0.202
5	0.249

6.3.2 Utility weights of patients with behavioural and psychological symptoms receiving risperidone or olanzapine for at least two months, according to cognitive function

Patients in this chapter were classified by cognitive function according to mild, moderate and severe stages. More details are presented in Chapter 5 (section 5.3.1.3)

Table 6.2 shows the distribution of responses of the five dimensions by the level of problems according to patients' cognitive function. The profile of patients receiving risperidone were categorised according to severity in percentage terms being, mild (24.39%), moderate (36.59%), and severe stages (39.02%) of the disease. The profile of patients receiving olanzapine were mild (29.27%), moderate (46.34%), and severe stages (24.39%).

Amongst the risperidone group in the mild stage, about 80.00% of patients were having problems with mobility, 70.00% with self-care, 80.00% with usual activities, 90.00% with pain/discomfort and 80.00% with anxiety/depression.

Patients within the moderate stage and being treated with risperidone, between 6.67% and 26.67% of patients in this group reported having no problem with mobility, self-care, usual activities, pain/discomfort and anxiety/depression respectively. However, more than four in five of patients in this group also reported problems with mobility, self-care, usual activities and pain/discomfort being, ranging between 86.67% and 100%. Only 73.33% of these patients had reported having problems with anxiety/depression.

Considering patients within the severe stage and being treated with risperidone, the range of those reporting no problems was 6.25% to 18.75%. Patients in this group reported their having problems with mobility (87.50%), self-care (93.75%) and usual activities (93.75%),

followed by pain/discomfort (93.75%) and anxiety/depression (81.25%), leading to those patients having a low health-related quality of life.

For those patients treated with olanzapine the health-related quality of life measures were as follows. In the mild stage the percentages of patients who reported having no problem with mobility were (25.00%), self-care (58.33%), usual activities (50.00%), pain/discomfort (25.00%) and anxiety/depression (33.33%). More than half of the patients in this group reported having problems with mobility, usual activities, pain/discomfort and anxiety/depression which ranged between 50.00% and 75.00%.

Olanzapine treated patients within the moderate stage reported having problems with mobility at (84.21%), self-care (52.63%), usual activities (78.95%), pain/discomfort (78.95%) and anxiety/depression (89.47%).

In total 90.00% of olanzapine treated patients in the severe stage had problems with mobility, 80.00% with self-care, 90.00% with usual activities, 80.00% with pain/discomfort and 80.00% with anxiety/depression.

The responses from the five dimension of the EQ-5D-5L questionnaire were then combined with Thai value sets for the EQ-5D-5L to convert the information into utility weights, (health-related quality of life weights), of individuals reflecting the benefits of living in each health state, as measured between zero and one. The mean utility weights of patients receiving risperidone classified by cognition, (as be assigned to health states), were 0.59 mild, 0.27 moderate and 0.26 severe stages. Patients under olanzapine treatment were 0.62 mild, 0.53 moderate and 0.39 severe stages of their utilities. Based on classifying patients by cognitive function, the overall utility weights of patients receiving olanzapine had higher values across all severity levels when compared with the risperidone group.

Table 6.2: **Distribution of levels of perceived problems in each of the dimension of the EQ-5D-5L descriptive system and utility weights of patients with BPSD receiving risperidone or olanzapine for at least two months, according to cognitive function**

The dimension of the EQ-5D-5L	Risperidone (N=41)						Olanzapine (N=41)					
	Mild (n=10)		Moderate (n=15)		Severe (n=16)		Mild (n=12)		Moderate (n=19)		Severe (n=10)	
	n	%	n	%	n	%	n	%	n	%	n	%
Mobility												
Level 1	2	20.00	-	-	2	12.50	3	25.00	3	15.79	1	10.00
Level 2	3	30.00	2	13.33	-	-	1	8.33	2	10.53	2	20.00
Level 3	2	20.00	4	26.67	4	25.00	3	25.00	7	36.84	1	10.00
Level 4	3	30.00	5	33.33	7	43.75	5	41.67	5	26.32	2	20.00
Level 5	-	-	4	26.67	3	18.75	-	-	2	10.53	4	40.00
Self-care												
Level 1	3	30.00	2	13.33	1	6.25	7	58.33	9	47.37	2	20.00
Level 2	4	40.00	-	-	1	6.25	1	8.33	2	10.53	1	10.00
Level 3	2	20.00	3	20.00	4	25.00	1	8.33	4	21.05	2	20.00
Level 4	-	-	4	26.67	4	25.00	1	8.33	1	5.26	1	10.00
Level 5	1	10.00	6	40.00	6	37.50	2	16.67	3	15.79	4	40.00
Usual activities												
Level 1	2	20.00	1	6.67	1	6.25	6	50.00	4	21.05	1	10.00
Level 2	1	10.00	-	-	1	6.25	1	8.33	4	21.05	1	10.00
Level 3	3	30.00	2	13.33	3	18.75	-	-	2	10.53	2	20.00
Level 4	3	30.00	4	26.67	1	6.25	4	33.33	4	21.05	1	10.00
Level 5	1	10.00	8	53.33	10	62.50	1	8.33	5	26.32	5	50.00
Pain/Discomfort												
Level 1	1	10.00	1	6.67	1	6.25	3	25.00	4	21.05	2	20.00
Level 2	3	30.00	2	13.33	2	12.50	5	41.67	8	42.11	2	20.00
Level 3	5	50.00	8	53.33	7	43.75	2	16.67	5	26.32	4	40.00

The dimension of the EQ-5D-5L	Risperidone (N=41)						Olanzapine (N=41)					
	Mild (n=10)		Moderate (n=15)		Severe (n=16)		Mild (n=12)		Moderate (n=19)		Severe (n=10)	
	n	%	n	%	n	%	n	%	n	%	n	%
Level 4	1	10.00	3	20.00	6	37.50	2	16.67	2	10.53	2	20.00
Level 5	-	-	1	6.67	-	-	-	-	-	-	-	-
Anxiety/Depression												
Level 1	2	20.00	4	26.67	3	18.75	4	33.33	2	10.53	2	20.00
Level 2	4	40.00	1	6.67	2	12.50	6	50.00	8	42.11	3	30.00
Level 3	2	20.00	7	46.67	5	31.25	-	-	5	26.32	2	20.00
Level 4	2	20.00	2	13.33	4	25.00	2	16.67	3	15.79	3	30.00
Level 5	-	-	1	6.67	2	12.50	-	-	1	5.26	-	-
Utility weight [mean (SD)]	**0.59 (0.20)**		**0.27 (0.26)**		**0.26 (0.25)**		**0.62 (0.34)**		**0.53 (0.30)**		**0.39 (0.35)**	

* Level 1 (no problems), level 2 (slight problems), level 3 (moderate problems), level 4 (severe problems), and level 5 (extreme problems)

6.3.3 Utility weights of patients with behavioural and psychological symptoms receiving risperidone or olanzapine for at least two months, according to dependence

In this chapter, the definition of patients' physical dependency used is given in Chapter 5 (section 5.3.1.4) in which patients are divided into the Pre-FTC and FTC states.

Table 6.3 shows that the total of risperidone treated patients were 65.85% in the Pre-FTC state and 34.15% in the FTC state. For olanzapine treated patients, there were 73.17% in the Pre-FTC state and 26.83% in the FTC state.

In total 85.19% of the risperidone group in the Pre-FTC state had problems with mobility, 77.78% with self-care, 85.19% with usual activities, 88.89% with pain/discomfort and 81.48% with anxiety/depression.

For the FTC state and being treated with risperidone, all patients had problems with mobility, self-care, usual activities, pain/discomfort and anxiety/depression, reflecting their low health-related quality of life. However, 71.43% of patients in this group had a problem with anxiety/depression.

Patients with the Pre-FTC state and receiving olanzapine reported having problems with mobility (76.67%), self-care (43.33%), usual activities (63.33%), pain/discomfort (70.00%) and anxiety/depression (86.67%).

In the FTC state and treated with olanzapine, all patients reported problems of health-related quality of life with mobility, usual activity and pain/discomfort. Whilst 90.91% of those patients had a problem with self-care and 63.64% had a problem with anxiety/depression, reflecting their low health-related quality of life.

Mean utility weights of patients using risperidone treatment classified by dependence, (as given health states), were 0.46 of the Pre-FTC state and 0.12 of the FTC state whilst for the olanzapine treated patients the values were 0.63 of the Pre-FTC state and 0.23 of the FTC state. Based on classifying patients by dependence, the overall utility weights of patients receiving olanzapine had higher values across all severity levels when compared with the patients receiving risperidone.

Table 6.3: **Distribution of levels of perceived problem in each of the dimension of the EQ-5D-5L descriptive system and utility weights of patients with BPSD receiving risperidone or olanzapine for at least two months, according to dependence status**

The dimension of the EQ-5D-5L	Risperidone (N=41)				Olanzapine (N=41)			
	Pre-FTC (n=27)		FTC (n=14)		Pre-FTC (n=30)		FTC (n=11)	
	n	%	n	%	n	%	n	%
Mobility								
Level 1	4	14.81	-	-	7	23.33	-	-
Level 2	5	18.52	-	-	5	16.67	-	-
Level 3	8	29.63	2	14.29	10	33.33	1	9.09
Level 4	10	37.04	5	35.71	8	26.67	4	36.36
Level 5	-	-	7	50.00	-	-	6	54.55
Self-care								
Level 1	6	22.22	-	-	17	56.67	1	9.09
Level 2	5	18.52	-	-	4	13.33	-	-
Level 3	8	29.63	1	7.14	7	23.33	-	-
Level 4	4	14.81	4	28.57	1	3.33	2	18.18
Level 5	4	14.81	9	64.29	1	3.33	8	72.73
Usual activities								
Level 1	4	14.81	-	-	11	36.67	-	-
Level 2	2	7.41	-	-	5	16.67	1	9.09
Level 3	7	25.93	1	7.14	3	10.00	1	9.09
Level 4	7	25.93	1	7.14	7	23.33	2	18.18
Level 5	7	25.93	12	85.71	4	13.33	7	63.64
Pain/Discomfort								
Level 1	3	11.11	-	-	9	30.00	-	-
Level 2	4	14.81	3	21.43	9	30.00	6	54.55
Level 3	16	59.26	4	28.57	8	26.67	3	27.27
Level 4	4	14.81	6	42.86	4	13.33	2	18.18

The dimension of the EQ-5D-5L	Risperidone (N=41)				Olanzapine (N=41)			
	Pre-FTC (n=27)		FTC (n=14)		Pre-FTC (n=30)		FTC (n=11)	
Level 5	-	-	1	7.14	-	-	-	-
Anxiety/Depression								
Level 1	5	18.52	4	28.57	4	13.33	4	36.36
Level 2	7	25.93	-	-	15	50.00	2	18.18
Level 3	7	25.93	7	50.00	4	13.33	3	27.27
Level 4	5	18.52	3	21.43	6	20.00	2	18.18
Level 5	3	11.11	-	-	1	3.33	-	-
Utility weight [mean (SD)]	**0.46 (0.26)**		**0.12 (0.13)**		**0.63 (0.30)**		**0.23 (0.22)**	

*Level 1 (no problems), level 2 (slight problems), level 3 (moderate problems), level 4 (severe problems), and level 5 (extreme problems); Pre-FTC (not requiring for full time care); FTC (requiring for full time care)

6.4 Discussion

In this thesis, the findings are challenging in measuring the health utilities, (or utility weights), of patients with behavioural and psychological symptoms of dementia and being treated with atypical antipsychotics, (risperidone or olanzapine), according to their cognitive function, (mild, moderate and severe stages), and dependency, (the Pre-FTC and FTC states), using the EQ-5D-5L. Based on the two treatments, the findings contribute ten values of utility weights for given different health states of patients as follows: the risperidone treated patients with the mild stage; the risperidone treated patients with the moderate stage; the risperidone treated patients with the severe stage; the risperidone treated patients with the Pre-FTC state; the risperidone treated patients with the FTC state; the olanzapine treated patients with the mild stage; the olanzapine treated patients with the moderate stage; the olanzapine treated patients with the severe stage; the olanzapine treated patients with the Pre-FTC state; and the olanzapine treated patients with the FTC state.

Considering the completed questionnaires, they were in the majority of cases, completed by patients' primary caregivers as proxies during the face-to-face interviews. However, it is unavoidable in patients with BPSD due to them having difficulties in making realistic and accurate judgements related to their conditions.

When considering the classification of patients by cognitive function, patients with BPSD in the mild stage receiving risperidone reported more problems in all dimensions than those receiving treatment with olanzapine. In the moderate stage, patients with BPSD receiving risperidone reported more problems than those receiving the treatment with olanzapine in the dimensions of mobility, self-care, usual activities and pain/discomfort, while in the anxiety/depression dimension it was the opposite. Furthermore, patients with BPSD in the severe stage and receiving risperidone reported more problems in self-care, usual activities, pain/discomfort and anxiety/depression dimensions, whereas the mobility dimension was reversed with the olanzapine patients. This implies that patients with BPSD in the mild, moderate and severe stages receiving olanzapine had a better HRQoL than those patients receiving risperidone, leading to the higher utility weights of the olanzapine group compared with the risperidone group.

When considering the classification of patients by dependence, patients with BPSD in the Pre-FTC state receiving risperidone reported more problems than those receiving the olanzapine treatment in the mobility, self-care, usual activities and pain/discomfort dimensions, while in the anxiety/depression dimension it was different with the olanzapine group reporting more problems. Patients with BPSD in the FTC state receiving risperidone reported more problems than those receiving the olanzapine treatment in all dimensions. This indicates that patients with BPSD in the Pre-FTC and FTC states receiving olanzapine had a better HRQoL than those patients receiving risperidone, leading to the higher utility weights of the olanzapine group compared with the risperidone group.

In addition, the findings in this thesis also indicate that the more advanced stages of cognition impairment and the more dependence status are significantly correlated with much lower scores of the utility weights in patients with BPSD and treated with olanzapine or risperidone. A possible explanation is that both patients in the late stage of dementia and patients with dementia in the FTC state had experienced serious memory disturbances, resulting in poor conditions in self-care, change in mobility, unable to recognise, change in personality, behavioural changes, emotional changes and needed more assistance (WHO 2012).

Furthermore, the findings associated with the utility weights in this thesis are consistent with previous studies conducting an assessment of HRQoL in patients with dementia, in particular Alzheimer's disease, where those previous studies reported that a lower HRQoL was correlated with the higher dependence status of those patients and the greater severity of cognitive impairment (Neumann et al. 1999, Ikeda, Niwata and Igarashi 2001, Murman and Colenda 2005). However, it should be noted that there are differences in the target populations, the cognitive test in evaluating cognitive function, the instrument in measuring HRQoL, the settings of the studies as well as country-specific healthcare systems amongst those published studies and this thesis.

The utility analyses presented in this chapter have several limitations to note. Firstly, owing to the utility data not being conducted in a longitudinal assessment, thus there are uncertainties in monitoring changes in utility scores influenced by the treatment. Regarding utility data derived from a cross-sectional survey using the EQ-5D, this might be associated with a limitation of the thesis to know how changes over time were due to the two drugs. This thesis might be unable to answer 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. Also, current utility weights might be due to other conditions, such as the improvement of co-conditions of patients.

Secondly, some limitations should be noted because the respondents in the interviews might not properly be representative of the population of patients with BPSD, due to the utility weight data in this thesis being based on the data collected from two hospital in Thailand, (Thammasat University Hospital and Khon Kaen Rajanagarindra Psychiatric Hospital).

Thirdly, the findings are focused on outpatients with BPSD and being on risperidone or olanzapine, its generalizability to patients with BPSD in nursing home or institutionalisation is unknown.

Additionally, it is important to note that the EQ-5D-5L instrument is not a dementia-specific instrument, therefore it might not have captured other conditions of interest.

Finally, the questionnaires were mainly completed by caregivers as proxy respondents. Several studies reported that the proxy-rating scale under the assessment of HRQoL in people with dementia were affected by several factors, including caregiver burden, caregivers' anxiety, caregivers' distress, caregivers' depression, patients' functioning, severity of dementia and neuropsychiatric symptoms. These factors were significant impacts on lower HRQoL scores rated by the caregivers (Karlawish et al. 2001, Markowitz et al. 2003, Bryan et al. 2005, Samus et al. 2006, Naglie 2007, Valimaki et al. 2009, Naglie et al. 2011, Black et al. 2012, Sheehan et al. 2012, Orgeta et al. 2013, Gräske, Meyer and Wolf-Ostermann 2014). However, it is imperative to consider proxy respondents instead patients with cognitive impairment and behavioural disturbances for the HRQoL assessment. Thus, it is necessary to interpret the utility weights from this study with caution.

In conclusion, the utility data in this thesis are directly derived from patients with BPSD and/or their caregivers in the actual clinical setting. To the best of my knowledge, this study can be highlighted as the first study to conduct the health utility weights in patients with BPSD and being treated with atypical antipsychotics, (risperidone or olanzapine), using the EQ-5D-5L instrument. The study also highlights utility weights by classifying patients with cognitive severity and physical dependence. Further, the finding could be adopted in the cost-utility analysis of atypical antipsychotics for the treatment of patients with BPSD.

Chapter 7: The application of the cost-effectiveness of olanzapine in comparison to risperidone for the treatment of patients with behavioural and psychological symptoms in dementia in Thailand

Abstract

Introduction: Dementia has been highlighted as a significant burden of several countries which are becoming ageing societies, including Thailand. This syndrome comes together with the behavioural and psychological symptoms of dementia (BPSD) which nearly all patients of those with dementia tend to encounter at any one point during the course of disease. 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. To date, no treatments have been approved for the treatment of BPSD by the US FDA leading to a variety of treatments for those patients. However, antipsychotics, (especially atypical antipsychotics), have been widely used and recommended by many experts as a first-line therapy to treat BPSD in clinical practice, although these drugs are off-label use for patients with BPSD due to a 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. Thus, this economic evaluation may provide the information potentially to enable decision makers in making a better-informed decision in this area.

Aim: The aim of this chapter is to examine 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 (Chapter 2) and a justification for the most appropriate model for a Thai setting (Chapter 4), 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 cost-effective therapeutic strategy for the management of patients with behavioural and psychological symptoms in Thailand.

7.1 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 (World Health Organisation 2012). The decline in cognitive abilities is known as 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 (Liperoti, Pedone and Corsonello 2008).

Behavioural and psychological symptoms of dementia, sometimes known as neuropsychiatric symptoms, non-cognitive symptoms or behavioural disturbances, are major problems in people with dementia which frequently occur at some point during the course of their illness (Benoit et al. 1999, Desai and Grossberg 2001, Cerejeira, Lagarto and Mukaetova-Ladinska 2012). These symptoms, such as agitation, aggression, psychosis, wandering, sleep disturbances and oppositional behaviour, lead to a significant impact on caregiver burden and caregiver stress over and above the functional and cognitive impairment in those patients (Rymer et al. 2002, Benoit et al. 2006, Hersch and Falzgraf 2007, Liperoti, Pedone and Corsonello 2008, Cerejeira, Lagarto and Mukaetova-Ladinska 2012, Kales, Gitlin and Lyketsos 2015).

Currently, there is no cure for BPSD and no FDA-approved medications for the treatment of BPSD (Desai, Schwartz and Grossberg 2012, Zdanys et al. 2016). Moreover, 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 (Andrade and Radhakrishnan 2009, Kales, Gitlin and Lyketsos 2015).

Atypical antipsychotics are one class of pharmacological approaches which are favourable to prescribe in patients with BPSD as a 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 (Alexopoulos et al. 2005, Liperoti, Pedone and Corsonello 2008, Zec and Burkett 2008, and Mather and Theodore 2012). 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 (Kales, Gitlin and Lyketsos 2015).

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.

The purpose of this chapter 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.

7.2 Methods

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.

7.2.1 Model structure

The existing model-based economic evaluations in dementia have been critically reviewed through the comprehensive literature search (see Chapter 2). 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 in selecting the most

appropriate model for applying to the cost-utility analysis of olanzapine compared with risperidone in the treatment of patients with BPSD in Thailand (see Chapter 4).

The model used in this thesis was an adaptation of a Markov model based on the FTC conceptual framework developed by Rive et al. (2010) 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), (Rive et al. 2010). The patients' dependency status was assessed by physical and functional disability. Health states of the model consisted of not requiring FTC (Pre-FTC), FTC and death.

In this thesis, the dependency status of patients was measured by physicians as well as 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 (Prasat Neurological Institute 2014). Subsequently, the FTC and Pre-FTC states were defined by a score of 0-8 and 9 and over, respectively.

Due to this thesis focusing on the treatment of patients with BPSD, behavioural disturbances associated with patients requiring atypical antipsychotics for their treatment were then incorporate into the health states of the model (Figure 7.1).

Based on 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 heath state (Pre-FTC), whereas some of them transitioned to the other possible pathways of FTC and death.
- From FTC state, some patients remained in the same state whilst others progressed to death.
- Death was 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, (a total of 60 Markov cycles). These were chosen because they covered the chronically progressive disease and reflected the nature 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 (Green et al. 2005, Rive et al. 2010, Turongkaravee et al. 2011, Rive et al. 2012). Further, Microsoft® Excel version 2013 was used to construct the decision-analytic model of this thesis.

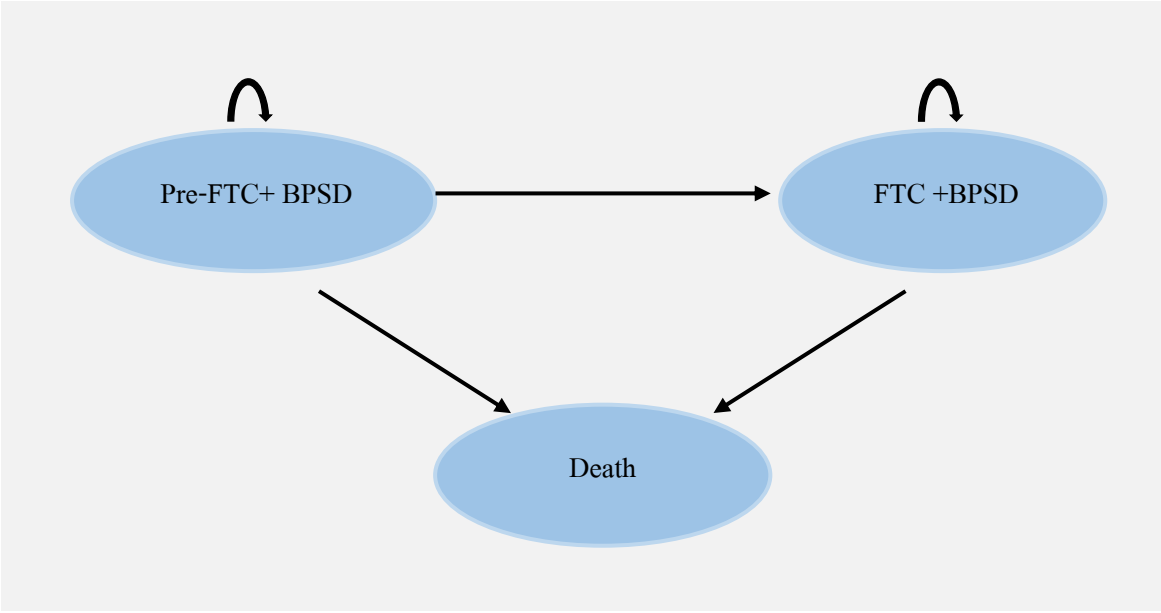


Figure 7.1: **Diagram of the Markov model based on the FTC conceptual framework for the cost-utility analysis of olanzapine compared with risperidone**

7.2.2 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.

7.2.2.1 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 thesis reflected the disease progression which was represented through three health states: Pre-FTC, FTC and, finally, death. Due to a lack of data associated with predicting time until patients deteriorate to a level requiring full-time care (FTC) in Thailand, this thesis applied a new predictive equation by Rive et al. (2010) which was developed based on data from the UK longitudinal epidemiological study of 117 Pre-FTC patients with Alzheimer's disease, LASER-AD cohort (Livingston et al. 2004), 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 Rive et al. (2010), the potential predictors for predicting the need for FTC were based on baseline values of cognition, (as measured by the Alzheimer's Disease Assessment Scale-cognitive subscale, ADAS-cog), function, (as measured by the Alzheimer's Disease Cooperate Study-Activities of Daily Living Scale total, ADCS-ADL), behaviour, (as measured by the neuropsychiatric inventory total, NPI-total) and the rates of change, (i.e. slopes), in deterioration of ADAS-cog and ADCS-ADL scores. To predict the time to FTC, the equations used in this model are outlined below.

- *The equation for predicting the time to FTC*

$$p_j = 1 - \exp(-\exp\left(-11.1343 + 0.0330 \times ADAS - cog_{total-score}^{baseline} - 0.0877 \times ADCS - ADL_{total-score}^{baseline} + 0.0377 \times NPI_{total-score}^{baseline} + 0.8122 \times ADAS - cog_{total-score}^{slope}(j) - 2.4072 \times ADCS - ADL_{total-score}^{slope}(j)\right) \times \exp(3.3195 \times \ln(interval_j)))$$

where p_j was probability for the time interval *j*

$ADAS - cog_{total-score}^{baseline}$ was the Alzheimer's Disease Assessment Scale-Cognitive Subscale at baseline

$ADCS - ADL_{total-score}^{baseline}$ was the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale at baseline

$NPI_{total-score}^{baseline}$ was the Neuropsychiatric Inventory total score at baseline

$ADAS - cog_{total-score}^{slope}(j)$ was the Alzheimer's Disease Assessment Scale-Cognitive Subscale for the time interval *j*

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

- *Based on the assumption of the constant risk of FTC within each time interval, the estimation of the monthly transition probability to the FTC state was computed by*

$$p_{ji}^{FTC} = 1 - \sqrt[length(j)]{(1 - Pj)}$$

where p_{ji}^{FTC} was the monthly probability

p_j was the probability for the time interval *j*

In addition, the calculation of the transition process from the Pre-FTC to FTC states due to drug treatments was based on three steps as outlined below.

- 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 was defined as either patients having no pharmacological therapy or background therapy with ChEIs (Rive et al. 2010).

- 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.
- 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 (Ryu et al. 2005, Rive et al. 2010).

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 thesis (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 of this thesis were distributed to 26.83% mild, 41.46% moderate and 31.71% with 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 thesis patients had a presence of agitation/aggression and psychosis accounting for 60.98% and 53.66%, 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 used in Alzheimer's disease or dementia in several countries (Rive et al. 2010). However, ADAS-cog, ADCS-ADL and NPI scores were not generally used in the routine clinical practice in Thailand. For instance, the cognitive function was generally assessed by Thai Mental State Examination, (TMSE) or MMSE-Thai 2002. The "activities of living" was measured by basic activities of daily living, (bADL), and instrumental activities of daily living, (iADL), (Prasat Neurological Institute 2014). Whilst an assessment of BPSD was mostly based on the ABCs approach and Four Ds approach (Sittironnarit 2011, Prasat Neurological Institute 2014).

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 (Livingston et al. 2004). In addition, other reasons were considered as follows: the population of patients in this thesis were similar in their characteristics to the population used to develop the predictive equation by Rive et al. (2010) as stated above and the predictive equation was also able to apply broadly in other settings due to the equation being developed 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 (Rive et al. 2012).

7.2.2.2 The estimation of transition probabilities of dying

The transition probabilities between states to death in the thesis were calculated by multiplying the available data of the monthly probability on age-specific death, focusing on age 60 and over, of the general Thai population from the epidemiological data in Thailand (The Thai working group on burden of disease and injuries 2002) and the relative risk (RR) of patients dying from Alzheimer's disease associated with each health state, (Pre-FTC and FTC). According to Gambassi et al. (1999), this study showed 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 (Turongkaravee et al. 2011).

There are several studies indicating an increased risk of death in the elderly atypical antipsychotic users (Maher et al. 2011, Ma et al. 2014); however, this was in contrast with the results from the study by Schneider et al. (2006). According to Schneider et al. (2006), the clinical trial-the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's disease, (CATIE-AD), a large double-blind randomised controlled trial of 421 outpatients with Alzheimer's disease with psychosis, aggression or agitation and assigned to olanzapine, risperidone, quetiapine or placebo, reported that there were no significant differences amongst treatment groups compared with placebo regarding an increased risk of death. In addition, the study by Kales et al. (2012) conducted a retrospective study in 33,604 patients with dementia based on the national data of Veterans Affairs between 1999 and 2008, in the USA. This found that olanzapine treated patients had lower mortality rates than risperidone treated patients (RR 0.99, 95% CI 0.89–1.10); however, it was not statistically significant between two drug treatments. Thus, the assumption in this thesis with regard to transition

probabilities of the death of BPSD patients and being treated with olanzapine or risperidone was that any treatment did not reflect 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 (Kirbach et al. 2008). Table 7.1 shows the monthly probabilities of dying for the general Thai population classified by age group, focusing on aged 60 and over.

Table 7.1: **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

7.2.2.3 Clinical effectiveness data of olanzapine or risperidone

The effectiveness data were derived from a critical review of published studies based on a comprehensive literature search from 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 treatment effects of the model made the same assumptions in line with previous published pharmaco-economic studies of ChEIs and memantine models in Alzheimer's disease (Green et al. 2005, Rive et al. 2010, Rive et. 2012). Thus, 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 (Deberdt et al. 2005, Sultzer et al. 2008). 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, 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 Rive et al. (2010) to estimate the time to the FTC state (Rive et al. 2010, Rive et. 2012, Zala et al. 2017).

According to the literature review, the effectiveness data of olanzapine and risperidone were obtained mainly from two published clinical trials (Deberdt et al. 2005, Sultzer et al. 2008). With regard to cognitive function and functional ability, the effects of olanzapine and risperidone were derived from the Phase 1 outcomes, were measured as primary outcomes of the CATIE-AD study, a double-blind randomised controlled trial of 421 outpatients with Alzheimer's disease, who had psychosis, aggression or agitation and were assigned either olanzapine, risperidone, quetiapine or a placebo (Sultzer et al. 2008). 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 (Sultzer et al. 2008). The NPI-total scores were derived from the study by Deberdt et al. (2005), double-blind randomised controlled trial of 496 patients with psychotic symptoms associated with dementia and assigned to olanzapine, risperidone or placebo. According to Deberdt et al. (2005), the study reported that the changes of 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 Leeuwen et al. (2018) suggested patients with Alzheimer's disease with more severe neuropsychiatric symptoms, especially agitation, aggression, or psychosis, responded well to long-term antipsychotic treatment. As a result, the assumption of this model was that the effects of drugs were assumed to be constant over a five-year time horizon.

Table 7.2 details the baseline characteristics of patients and the clinical effectiveness data of olanzapine and risperidone. As Table 7.3 shows, 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 7.2: **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)

Variable	Baseline	Olanzapine effect (Change in scores)	Risperidone effect (Change in scores)	Reference
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 7.3: **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)

Then, the 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 of both treatments, (olanzapine and risperidone), are shown in Table 7.4.

Table 7.4: **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

7.2.2.4 Cost data of olanzapine and risperidone-treated patients with behavioural and psychological symptoms of dementia at each health state of the model from a societal perspective

Costs of patients with BPSD and treated with olanzapine and risperidone were obtained from primary collected data from two hospitals: Thammasat Hospital University and Khon Kaen Rajanagarindra Psychiatric Hospital in Thailand using the cost questionnaire completed by face-to-face interviews with the outpatients and/or their caregivers. More details of the process of data collection and calculating costs can be seen in Chapter 5.

In this thesis, 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 also taken into account in the cost analysis in this thesis. Cost data were classified into the Pre-FTC and FTC states. All costs were expressed in the Thai currency at 2017 values (1£ =45). Cost parameters of olanzapine and risperidone treated patients with BPSD in the model are shown in the Table 7.5.

Table 7.5: **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			
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			

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

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

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

The cross-sectional survey based on the face-to-face interviews using the EQ-5D-5L was conducted in the outpatients departments with BPSD patients who were being 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). More details are given previously in Chapter 6. Utility weight parameters of olanzapine- and risperidone-treated patients with BPSD in the model are shown in Table 7.6.

Table 7.6: **Utility weight parameters for the cost-utility analysis for olanzapine compared with 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

7.2.2.6 Discount rates of the study

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

7.2.2.7 Data analysis

7.2.2.7.1 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.

$$\text{ICER} = \frac{\text{Cost of Olanzapine - Cost of Risperidone}}{\text{QALY of Olanzapine - QALY of Risperidone}}$$

where: ICER was an incremental cost-effectiveness ratio

QALY was the quality-adjusted life year

7.2.2.7.2 Sensitivity analyses of the model

The model underwent deterministic 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 on the basis of 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 thesis was performed using Microsoft® Excel version 2013.

In this thesis, 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 thesis, the willingness to pay was defined as a range between THB 0 - 500,000. Moreover, the willingness to pay was the valuation of the health benefit in monetary terms. This was the maximum price at which a consumer will definitely pay for their health benefit (Bertram et al. 2016) (see more details in Chapter 3, section 3.5.2).

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 (Teerawattananon 2018). 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 Thavorncharoensap et al. (2013). Thus, these values, adjusted to 2017 currencies by the Consumer Price Index, were also applied in this thesis to consider at what price society would be willing to pay to gain an additional QALY.

7.3 Results

7.3.1 Base-case results

As Table 7.7 shows, over the 5-year time period 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 7.7: **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

7.3.2 Sensitivity analyses

7.3.2.1 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 assessed by varying each parameter, including costs, utility weights and discount rates.

In this thesis, the 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 7.8 shows parameters for one-way sensitivity analysis.

The results of the one-way sensitivity analyses in this thesis are presented by 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 7.2, 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 ± 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 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 less significant impact on the ICER, accounting for 3% changed from the base-case analysis.

Table 7.8: **Parameter for the base-case and for sensitivity analyses of olanzapine or risperidone for the treatment of patients with BPSD**

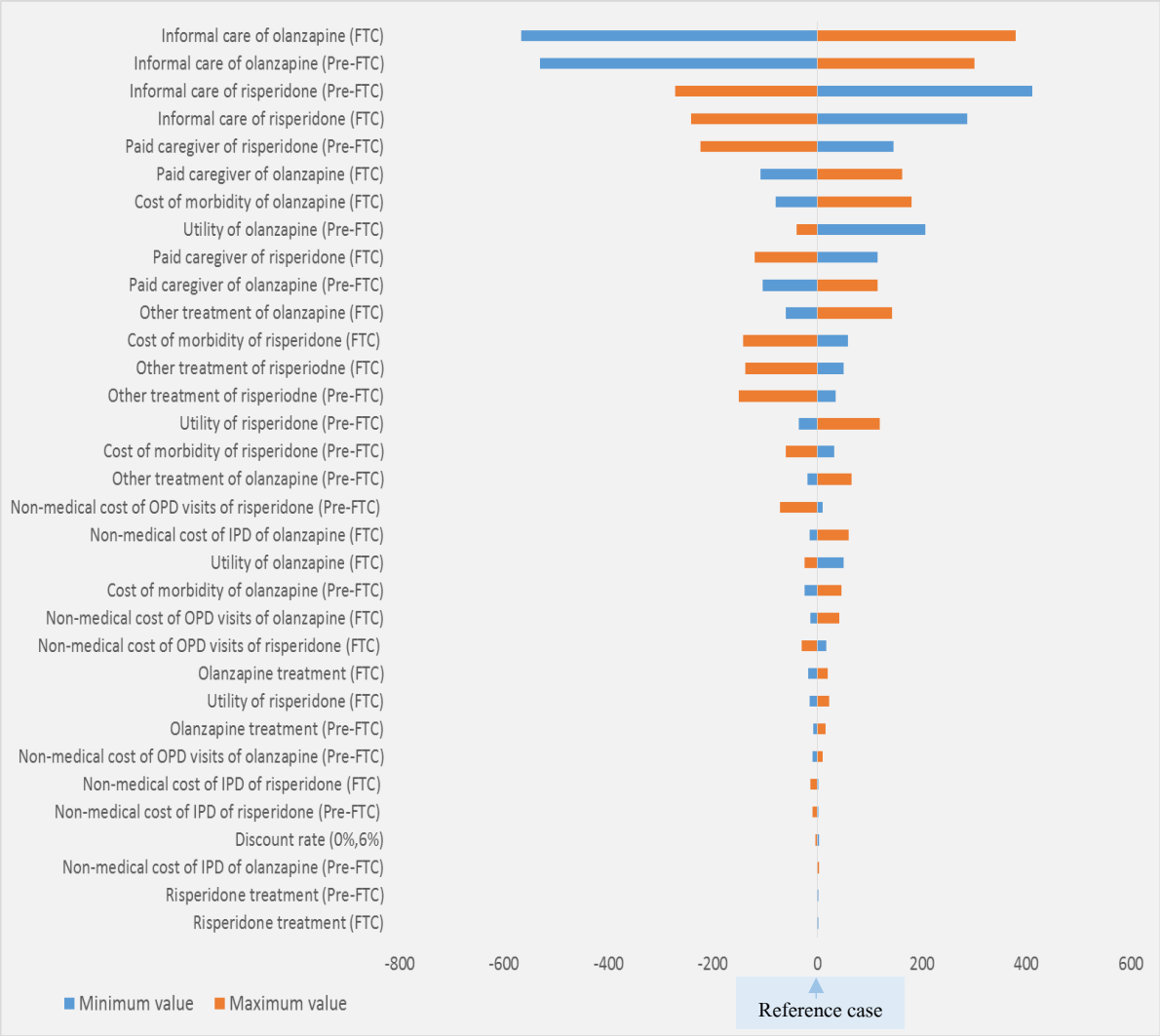
Model Parameter	Base-case	Sensitivity Analysis
Medication use (THB)		
Risperidone in the Pre-FTC state	70.51	26.48 to 158.85
Risperidone in the FTC state	76.24	52.95 to 105.90
Olanzapine in the Pre-FTC state	939.29	462.53 to 1,850.10

Model Parameter	Base-case	Sensitivity Analysis
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)		
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

Model Parameter	Base-case	Sensitivity Analysis
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 7.2: 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

7.3.2.2 Probability sensitivity analysis (PSA)

According to Figure 7.3 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 7.3: **Cost-effectiveness plane for olanzapine compared with risperidone based on 1,000 PSA iterations of a willingness to pay for an additional QALY at THB 500,000**

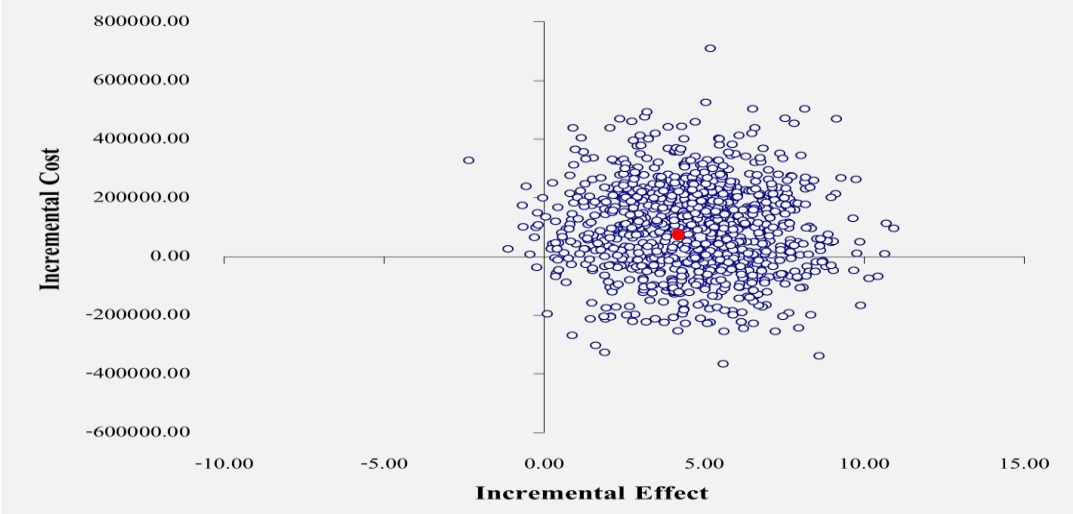


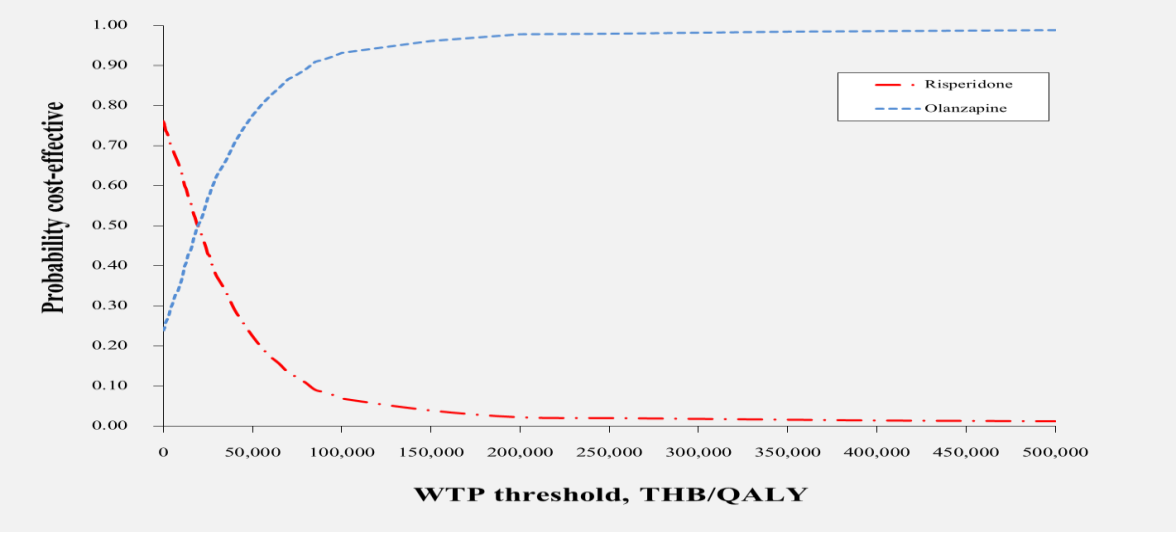
Figure 7.4 shows the cost-effectiveness acceptability curve for the willingness to pay threshold for an additional QALY at THB 500,000. From the societal perspective, at a willingness to pay threshold of THB 0 per QALY, risperidone had a greater probability of a cost-effective treatment than olanzapine 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 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 to be more effective, less costly and cost effective at THB 160,000 per QALY, defined by the Sub-committee of the NLEM of Thailand (Teerawattananon 2018). The results showed that olanzapine was a cost effective treatment for patients with BPSD compared with risperidone from a societal perspective, accounting for 96.60%.

Figure 7.4: **Cost-effectiveness acceptability curve of willingness to pay for an additional QALY at THB 500,000 based on a societal perspective**



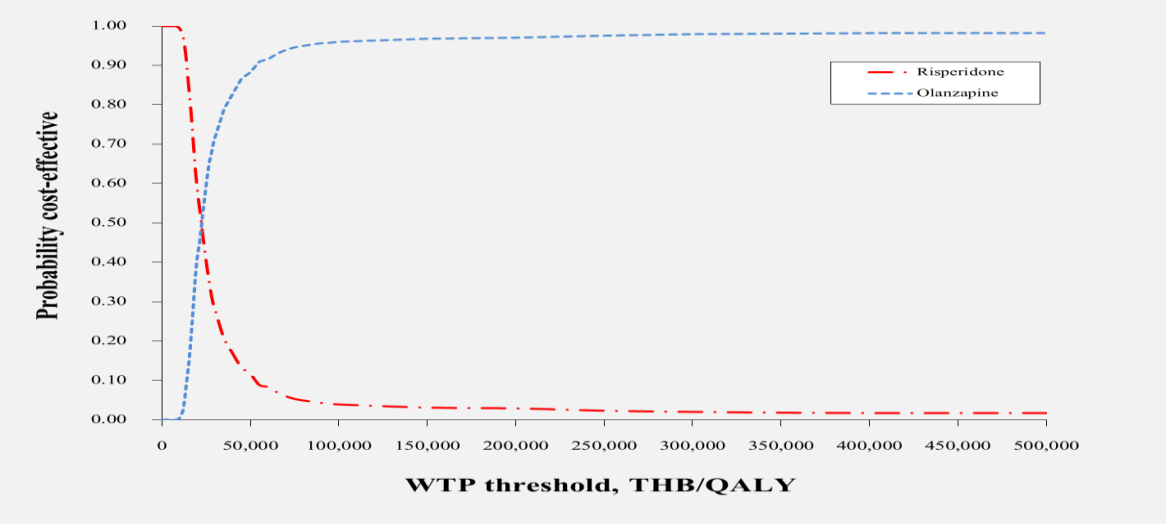
** WTP, willingness to pay for an additional QALY in Thai currency, (THB), 1£ = 45 Baht

Figure 7.5 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 a 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 year 2017 values), according to the proposal by Thavorncharoensap et al. (2013), 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 (Teerawattananon 2018). The results showed that olanzapine was a cost effective treatment for patients with BPSD compared with risperidone from a healthcare perspective, accounting for in 96.80%.

Figure 7.5: **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

7.4 Discussion

The analyses presented in this chapter 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 previously been performed before in Thailand and Asia in general.

From a societal perspective over a five-year time period, 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 (Kirbach et al. 2008). The study by Kirbach et al. (2008) reported that olanzapine was the cost-effective treatment, (ICER= US 13,230 per QALY), however, the comparator used for analysis was no treatment. Thus, the findings from the Kirbach's study might not be directly compared with this thesis due to the difference in a scope of an economic evaluation. In another study, Rosenheck et al. (2007) 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 a 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 in a different way from this thesis. This might be partly caused by 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 thesis 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 in both studies.

Additionally, the model in this thesis is constructed by adapting from the FTC model framework; however, it is different from the original model (Rive et al. 2010) due to this thesis focuses 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 thesis 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 (Gambassi et al. 1999, The Thai working group on the burden of disease and injuries 2002). This might lead to more accuracy and be more reflective of a 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. As a consequence, 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 WHO et al (2012) 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 thesis 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 Turongkaravee (2008), informal care costs of both states, (Pre-FTC and FTC), had lower costs when compared with this thesis. This might be associated with a difference in time spent in patients' care of both studies as this thesis focused on patients with BPSD. In addition, several studies also suggested patients with BPSD correlated with increasing caregiver burden (Mohamed et al 2010, Sasoni et al. 2013, Pinidbunjerdkool, Saengwanitch and Sithinamsuwan 2014, Reed et al. 2014, Lanctot et al. 2017). Therefore, this thesis is able to imply 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 in the societal costs of patients with dementia. Therefore, policy-makers should exercise or interpret the results with caution if this information is adopted in to 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. By comparing the results between the viewpoints of a societal perspective, (focusing on direct medical and non-medical costs), and a healthcare perspectives, (considering only direct medical costs), the ICER per QALY of olanzapine versus risperidone from the healthcare perspective has a

higher value when compared with the societal perspective, by 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 a 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. As a consequence it implies 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.

As with any model, economic evaluation has its limitations. Firstly, the predictive equation used in this thesis is based on the LASER-AD study deriving from the UK population (Livingston et al. 2004). 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 (see more information in Chapter 5).

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 (Deberdt et al. 2005, Schneider et al. 2006 and Ma et al. 2014).

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 thesis 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. Also, current utility weights might be due to other conditions, such as the improvement of co-conditions of patients.

In conclusion, this model-based economic evaluation 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 thesis 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 policy makers in

providing improved treatments and suitably allocated resources for sufferers from behavioural disturbances in Thailand.

Chapter 8: Conclusions and recommendations for future research

The overall aim of this thesis is to examine a cost-utility analysis of olanzapine and risperidone for the treatment of patients with behavioural and psychological symptoms of dementia, (BPSD), in Thailand. In order to achieve this aim, three objectives were devised which included developing the decision-analytic model for an evaluation, examining costs and health-related quality of life, (or utility weights), of patients with BPSD and treated with olanzapine or risperidone in a Thai setting and calculating the incremental cost-effectiveness ratio, (ICER), of olanzapine versus risperidone for behaviourally disturbed patients with dementia in Thailand.

The purpose of this chapter is to describe how the aim of thesis was achieved by providing an overview of all chapters in the thesis. The summary of findings is provided and a contribution to knowledge is also highlighted. The strengths and limitations as well as the post research evaluation are then identified. Policy implements are also addressed. In addition, further research opportunities will be recommended.

8.1 Overview of the thesis

The rationale for this thesis set out in Chapter 1 documented a dearth of studies associated with the health economic evaluation of atypical antipsychotics for patients with BPSD, specifically in Thailand and Asia in general. Also, an increase in the number of people living with dementia which provokes a negative effect on families, communities and healthcare systems, across several countries, along with Thailand (World Health Organisation 2012, Prince et al. 2015). Non-cognitive symptoms or BPSD were common co-conditions in people with dementia which affects up to 90% of these people over the course of their illness. These symptoms were a significant trouble in dementia people more than their cognitive impairment, leading to a complicated management, caregiving burden, a financial burden of

families and healthcare and a poor quality of life of both patients and caregivers (Cerejeira, Lagarto and Mukaetova-Ladinska 2012). For the BPSD management in Thailand, research evidence reported there were a variety of atypical antipsychotics administrated for patients with BPSD in the routine clinical settings; however, risperidone and olanzapine were the most common drugs prescribed for these patients (Chanthawong et al. 2012, Rapeepatchai and Promma 2015). Currently, a difference between olanzapine and risperidone is not well defined in terms of health economic evaluation for the treatment of patients with BPSD in Thailand.

Chapter 2 details the literature review regarding definitions of dementia and BPSD, the BPSD management, health economic evaluations and the model-based health economic evaluations in dementia. The conclusion from this chapter was that there were some criticisms that were debatable about effectiveness and concern over adverse events associated with atypical antipsychotic use in people with dementia (Schneider, et al 2006, Angelini et al 2007, Maher et al. 2011, Tempi et al. 2016); notwithstanding, it is clear that the modest efficacy of these drugs associated with reducing behavioural disturbances has a potential effect to improve of quality of life for patients and caregivers and decrease caregivers' distress (Masopust, et al. 2018). The literature review also documented the very few studies relevant to economic evaluation on the treatment of patients with BPSD, especially atypical antipsychotics. To date, only two studies examined atypical antipsychotics for agitation/aggression and psychosis in Alzheimer's disease. One study was a comparison of olanzapine to no treatment using modelling in the US (Kirbach et al. 2008), whilst another study conducted involved atypical antipsychotics, (risperidone, olanzapine, quetiapine), and placebo, (as a watchful waiting strategy), alongside a clinical trial based on the CATIE-AD study, in the US (Rosenheck et al. 2007). Based on this review, it allowed the thesis to pinpoint the gaps in the literature and defined the direction of the research study from this point.

Chapter 3 identified and developed the research design, methodology and methods of economic evaluation as conducted for the evaluation of the atypical antipsychotics for the treatment of BPSD patients in Thailand.

Chapter 4 reports the model development based on the literature review, on model-based economic evaluation in dementia. The findings from this chapter yielded different models that were formulated from different model conceptual frameworks and then tested these models incorporating the key parameters. Then a comparison amongst those models was conducted to justify and select the most appropriate model to be adopted for an evaluation of olanzapine and risperidone in Thailand. This chapter answered objective number 1 of this thesis (see Chapter 1, section 1.3.2).

Additionally, Chapter 5 answered objective number 2 (see Chapter 1, section 1.3.2) by analysing the costs of patients with BPSD and being treated with olanzapine and risperidone. The costs relating to these patients were categorised by cognitive function, (mild, moderate and severe), and dependence status, (Pre-FTC and FTC).

Chapter 6 analysed the health-related quality of life, (or utility weight), of olanzapine- and risperidone-treated patients with BPSD and this answered research objective number 2 (see Chapter 1, section 1.3.2). The utility weights of these patients were also classified by cognitive function and dependence.

Chapter 7 covers the assessment of the cost-utility analysis of olanzapine and risperidone for the treatment of patients with BPSD in Thailand. This chapter shows the main findings answering the research question, the main aim and objective number 3, (see Chapter 1, sections 1.3.1 and 1.3.2), of this thesis. Furthermore, based on the literature review, there is currently no model-based economic evaluation that undertook a comparison between olanzapine and risperidone for the treatment of patients with BPSD, specifically in Thailand

and Asia in general. Hence, the findings from this chapter have produced a new scientific assessment that is relevant to this field.

8.2 Summary of findings of the thesis

8.2.1 Defining the scope of the study

This thesis was conducted to investigate the economic evaluation of atypical antipsychotic drug use for the treatment of outpatients with BPSD aged 60 years and above in Thailand. This was based on a literature review of the use of atypical antipsychotic drugs for the treatment of BPSD in patients with dementia. Olanzapine had been presented that it was an efficacy for the treatment of dementia patients with behavioural disturbances (see Chapter 2, section 2.4). This drug is frequently prescribed to patients experiencing BPSD in Thailand; however, it is more expensive than an existing atypical antipsychotic drug. Olanzapine has been classified in the non-National List of Essential Medicines (non-NLEM) of Thailand. This drug was then paid for BPSD patients as out-of-pocket expenses rather than the primary healthcare system, leading to a restriction of these patients to access or receive the most appropriate medication and having a financial impact on the households who chose to fund the use of the drug for the patients. Consequently, olanzapine was chosen as the treatment of interest in this thesis.

8.2.2 Selection comparator

Risperidone is an atypical antipsychotic drug approved in the NLEM and is currently in common use for the treatment of BPSD in Thailand. Thus, this drug was chosen as a comparator for an economic evaluation on the treatment of dementia patients with BPSD, in this thesis.

8.2.3 Defining the type of economic evaluation and the model framework

A cost-utility analysis was conducted in this thesis. A decision-analytic model, known as a Markov model, was used to estimate the costs and outcomes regarding olanzapine compared with risperidone, using a one-month Markov cycle over a five-year evaluation period and reflecting the clinically progressive disease of behaviourally disturbed patients with dementia. The health states used in the model were the Pre-FTC state, the FTC state as well as death. The transition probability was calculated from the predictive equation to estimate the probability of BPSD patients in the Pre-FTC state requiring the FTC state. The study used three main dimensions related to the disease progression of patients with dementia, including cognition as measured by ADAS-cog scale, functional status as measured by ADCS-ADL scale and behavioural ability as measured by NPI score, which were incorporated in the equation. The probabilities of dying were based on the epidemiological data of the general Thai population as classified by age multiplied by the relative risk of mortality in patients with Alzheimer's disease.

8.2.4 Measurement of costs and health utility weights

Since the main aim of this thesis was to evaluate the cost-effectiveness in routine setting, the study was conducted using a cross-sectional survey by face-to-face interviews, designed to gather data of costs and utility weights through the cost and the EQ-5D-5L questionnaires, in outpatients and/or their caregivers from Thammasat University hospital and Khon Kaen Rajanagarind Psychiatric hospital, in Thailand.

For cost analysis, only direct medical and direct non-medical costs were included. The direct medical costs were medication costs, additional costs, hospitalised costs, additional payments from the patients' healthcare insurance coverage, costs associated with comorbidity, adverse events-related costs and relapse-related costs. Direct non-medical costs included the patients' out-of-pocket expenses, informal care costs, paid caregiver costs for paying the caregivers for providing care to patients and costs of transportation, accommodation, and extra food for

patients. All costs were from a societal perspective and presented as Thai baht (THB) in 2017 values (£1 = THB 45). The finding showed that the costs of risperidone-treated patients were THB 44,717.09 in the Pre-FTC state and THB 53,167.03 in the FTC state. For olanzapine-treated patients, costs were THB 44,347.28 and THB 58,294.20 in the Pre-FTC and FTC states, respectively.

In addition, the utility weights were collected based on a five-dimensional questionnaire with five-levels of severity in each dimension. The Thai preference weights, (tariffs or value sets), were used to calculate the utility weights used in this thesis. According to the findings from the analysis, the utility weights of risperidone-treated patients were 0.46 of the Pre-FTC state and 0.12 of the FTC state. Whilst the utility weights of olanzapine-treated patients were 0.63 and 0.23 of the Pre-FTC and FTC states, respectively.

8.2.5 Handling time in an evaluation of a cost-utility analysis

A discount rate of 3% per annum was applied to both costs and QALYs. This rate was recommended by Thailand's Health Technology Assessment guidance as well as the World Health Organization.

8.2.6 Handling uncertainty of an economic evaluation

One-way and probabilistic sensitivity analyses were performed for the parameter uncertainties. One-way analyses were conducted by varying the values of key parameters, including costs, utility weights and discount rates. Costs of drug treatments associated with each health state were varied between plausible extreme values of data. The utility weights of drug treatments associated with each health state were defined by a variance of ± 30%. The discount rate was varied between 0% and 6% based on the recommendation of the guideline of health technology assessment in Thailand (HITAP 2014).

For the probabilistic sensitivity analysis, Monte Carlo simulations were also undertaken with 1,000 iterations of the model parameters according to a pre-defined distribution for additional testing of the robustness of the results.

8.2.7 The cost-utility analysis of atypical antipsychotics for the treatment of patients with behavioural and psychological symptoms in Thailand

To analysis the cost-effectiveness in this thesis, the main outcome measure was the cost per QALY gained or ICER. The results indicated olanzapine is predicted for better outcomes and lower costs compared to risperidone. Therefore, olanzapine may be the cost-effective therapeutic option for the treatment of patients with dementia and suffering with behavioural and psychological symptoms in Thailand (ICER < THB 160,000).

By comparing the findings with the studies in this field, the result of this thesis is consistent with a previous study which conducted an economic evaluation on atypical antipsychotics in Alzheimer's patients with agitation and psychosis by Kirbach et al. (2008). Kirbach and collegues undertook a cost-utility analysis of olanzapine versus no treatment in those patients, over a 13-year period or until patients died from the disease progression, based on the US health system perspective. Based on that study, the findings suggested that olanzapine was a dominant strategy for the treatment for agitation and psychosis of patients with Alzheimer's disease. However, it should be noted that there are differences in comparators between Kirbach's study and this thesis. Kirbach and colleagues conducted an analysis against no treatment, whereas this thesis compared olanzapine to risperidone. Moreover, parameters used in the model, the settings of the studies as well as country-specific healthcare systems between Kirbach's study and this thesis are significant differences.

Conversely, the study by Rosenheck et al. (2007), a cost-benefit analysis of atypical antipsychotics in a randomised trial from the follow-up of patients for nine months from an economic perspective, reported that total costs of treating groups with risperidone,

quetiapine, or olanzapine were higher than a placebo group. By the comparison of QALYs, there were no significant differences amongst the groups treated with atypical antipsychotics and a placebo. However, there are differences in the methods of the thesis, the instrument in measuring HRQoL, the settings of the studies as well as country-specific healthcare systems between Rosenheck's study and this thesis.

8.3 Contribution to Knowledge of the Thesis

The findings of this thesis that emerged from the model development, face-to-face interviews examining costs and utility weights of patients with BPSD and treated with olanzapine and risperidone and the cost-utility analysis of atypical antipsychotics, (olanzapine and risperidone), have made several contributions to knowledge at different points which will now be outlined.

Chapter 4 details the different models that were developed based on adaptations with one using the CERAD conceptual framework (Neumann et al. 1999) and two others of the FTC conceptual framework using a predictive equation to estimate the time until patients required FTC, in which one equation was developed by Caro et al. (2001) based on longitudinal epidemiological data (Stern et al. 1997) and the other was developed by Rive et al. (2010) based on longitudinal epidemiological study of LASER-AD study (Livingston et al. 2004). These models were then tested by incorporating key variables, including transition probabilities, clinical effectiveness data, costs and utility weights of olanzapine or risperidone. Further, costs and utility weights of patients with BPSD treated with olanzapine and risperidone were derived from a primary data collected in a Thai setting. A comparison in line with characteristics, strengths and weaknesses amongst those different models was also conducted. The most appropriate model was then chosen for applying further analysis of those BPSD patients in Thailand (Chapter 7). To the researcher's knowledge, the findings of

this chapter have not been presented, certainly in the outlined literature review, in this area because health states of each model uniquely focused on the severity of cognitive function, (mild, moderate and severe), or the dependence status, (Pre-FTC and FTC), and patients with BPSD requiring atypical antipsychotic drugs for their treatments. This thesis also documented the significant characteristics as well as strengths and weaknesses of each model when the models were applied to patients with BPSD and being treated with atypical antipsychotics, as focused only on olanzapine and risperidone.

Additionally, Chapter 5 provides a further contribution to knowledge of associated costs, including direct medical costs and direct non-medical costs, of patients with BPSD and being treated with either olanzapine or risperidone from a societal perspective. The costs were based on primary data collected from the actual routine clinical setting in Thailand. Interestingly, both relapse rates and frequent adverse events, (extrapyramidal symptoms, constipation and falls), due to atypical antipsychotic use in BPSD patients were also included for cost analyses which increases the values of the data as being as realistic as possible. Subsequently, the findings in this chapter represents an original contribution to knowledge towards establishing costs for olanzapine and risperidone treated patients with BPSD by classifying these patients according to cognitive function, (mild, moderate and severe stages), and dependency, (Pre-FTC and FTC states). To the researcher's knowledge, this has never previously been done before, specifically in Thailand or Asia in general.

Chapter 6 also contributes to knowledge in other areas that surround the utility analyses of olanzapine and risperidone treated patients with BPSD. The utility weight data was also derived from primary collected data of those patients using the EQ-5D-5L questionnaire from the routine clinical setting in Thailand. These utility weights were then used in calculating the health outcomes, as presented in terms of QALYs. The findings also provided new information of utility weights of olanzapine and risperidone treated patients with BPSD according to a classification of patients by cognitive function and dependency as stated

above. To the researcher's knowledge, these have not previously been presented before in Thailand or Asia in general.

Chapter 7 has contributed to knowledge in the area of health economic evaluation of atypical antipsychotics, (olanzapine and risperidone), for the treatment of patients with BPSD. To the researcher's knowledge, this previously has never been done before in Thailand, or Asia in general. The selected model based on the model development, (see Chapter 4), was constructed to assess the cost-effectiveness of olanzapine compared with risperidone from a societal perspective over a five-year time horizon. The incremental cost-effectiveness ratio (ICER) was calculated to indicate the dominant strategy of the BPSD treatment. The robustness of the results was performed based on sensitivity analyses. Therefore, the findings of this chapter have contributed useful information to stakeholders, namely physicians, patients, caregivers and policy-makers, for their decision making to manage and select the recommended effective treatment for sufferers with BPSD, specifically in Thailand.

8.4 Policy Implications

By conducting the cost-utility analysis, the improved understanding of evaluating atypical antipsychotics, (olanzapine versus risperidone), in the treatment of BPSD has implications for policy-makers, professionals, caregivers and people with BPSD in light of the findings of this thesis as outlined below.

- *For people affected by behavioural and psychological symptoms of dementia and their caregivers*

The impact of people with BPSD on the financial burden and quality of life is enormous for patient themselves and their caregivers. As the major part of costs for people with BPSD is direct non-medical costs, particularly informal care due to time spent in patients' care. Stress is a significant problem for most caregivers who are living with and caring for BPSD

patients. Thus, people affected by BPSD need the recommended cost-effective treatment to reduce or eliminate behavioural symptoms as the condition persisted. The findings from this thesis have provided information for people affected by BPSD to select the best choice for their treatment. Then, an improvement in patients' conditions associated with BPSD leads to a greater wellbeing, a better quality of life of patient themselves and their caregivers as well as a reduction in household financial burden associated with physician visits, hospital admissions, relapses, adverse events, transportation, food, accommodation, other treatments, paid caregivers and informal care costs. This also helps to improve the quality of life and reduce the distress of both patients with BPSD and their caregivers.

- *For providers in health care sectors*

To overcome the difference of access to medications for managing of BPSD, the health economic evaluation of treatments is used in healthcare decision making. This not only considers medication costs but also integrates all relevant costs and QALYs gained of patients with BPSD. Subsequently, the findings from this thesis have provided physicians and/or healthcare providers additional new information to help in deciding the prescription of the best choice of treatment and offers support in developing the most appropriate care and strategies for coping with patients with BPSD in the routine clinical setting of Thailand.

- *For policy-makers*

To maximise the benefits from spending of healthcare budget, the thesis findings may provide information to facilitate policy-makers in deciding whether health systems should be funded. It may seem reasonable that if the treatment is more cost-effective than another that is already funded, it should also be funded, leading to a reimbursement of patients or service providers if they use a cost-effective drug.

In conclusion, for the implications to a clinical practice and policy in Thailand, this thesis was conducted based on the routine clinical practices in a real setting. Therefore, the results

are appropriate to be considered for the implementation in the treatment of BPSD sufferers in Thailand. Aside from that, this is also useful information contributing to the stakeholder knowledge in providing better management and patients' care, allocating the constrained resources efficiently and preparing suitable healthcare systems for patients with BPSD in Thailand.

8.5 Strengths and Limitations of the Research

8.5.1 Strengths of the research

To the researcher's best knowledge, this is the first cost-utility analysis study to compare atypical antipsychotic drugs, (olanzapine versus risperidone), for the treatment of patients with dementia and suffering with behavioural and psychological symptoms in Thailand or Asia.

This study is unique in that it includes adverse events and relapses to estimate the total cost analysis of atypical antipsychotics use for those patients, leading to greater accuracy of the economic evaluation of these drugs, for the treatment of BPSD patients in a routine clinical practice. In addition, all data input associated with costs and utility weights in the model are derived from a primary, real setting, collection source of patients with BPSD, from two hospitals in Thailand. Interestingly, the findings of the cost analysis from this thesis also introduce new information associated with cost data for patients with BPSD being on olanzapine or risperidone, by the classification of patients in terms of cognitive function and physical dependence. Similarly, utility weights associated with patients with BPSD and treated with olanzapine or risperidone provide unique information based on the classification by cognitive function and physical dependency, of olanzapine-treated and risperidone-treated patients with behavioural disturbances.

8.5.2 Limitations of the research

In this thesis, there are some limitations identified as listed below.

8.5.2.1 Model limitation

It is clearly an important limitation associated with the movement from the Pre-FTC state to the FTC state of patients driven by the transition probability which uses a predictive equation based on data from the LASER-AD study in the UK due to a lack of any similar information available in Thailand.

8.5.2.2 Data limitations

Regarding data limitations, a cross-sectional study is a concern over the restriction to produce information associated with monitoring changes in costs and utility values of patients, influenced by the treatment during the disease progression over time.

Another concern is that utility values deriving from a primary data collection are mostly rated by caregivers as a proxy report. However, it is essential to consider proxy-ratings instead of patient-ratings in this study due to most patients having cognitive impairment, resulting to the difficulty to respond the HRQoL measure. Thus, the interpretation of the results should be considered with the caution.

Additionally, the application of the EQ-5D-5L instrument was used to measure the health utility values for dementia patients with behavioural disturbances in this thesis. This tool is not a disease-specific instrument; however, the EQ-5D-5L was adopted due to a lack of information of dementia-specific instruments in the Thai language. Apart from that, the main outcome is also measured in terms of the QALY gained which can be calculated as index values from the EQ-5D-5L.

Costs associated with relapses and adverse events are included in the cost analysis in this study. Since atypical antipsychotics are off-label use for the treatment of symptoms related to dementia, there are a lack of studies of atypical antipsychotics associated with drug-induced

adverse events in the different dependence levels and drug-associated relapses, for the treatment of patients with dementia. As a result, the relapse data are adopted from studies of schizophrenia. Thus, the cost analysis might be an over or underestimate from the actual costs of patients with BPSD having risperidone or olanzapine on their prescriptions. In addition, the adverse events associated with costs are assumed to have similar figures in each health state. The adverse events in this thesis include only constipation, falls and extrapyramidal symptoms (EPSs), resulting to the over- or under- estimations of cost analysis due to other hidden adverse events from atypical antipsychotic use for BPSD patients.

8.5.2.3 Generalisability of the research

Generalizability is another limitation due to this thesis being specific to the healthcare system in Thailand. Cost and utility data are conducted by primary collected data in a Thai setting. Hence, the generalising or adoption of results to different circumstances should be interpreted or exercised with caution.

8.6 Post Research Evaluation

In this thesis, sensitivity analyses were conducted in order to assess uncertainty surrounding model parameters by varying parameters in 33 different scenarios across costs, utility weights and discount rates and all model parameters using Monte Carlo simulation of 1,000 repeated random computations. Based on the techniques and procedures used to assess the cost-utility analysis, the author is assured of the validity and robustness of the results of this thesis. If the thesis were to be replicated using similar procedures, it is anticipated that the researcher would acquire the same results.

However, the thesis highlights probabilities of dying, costs and utility weights associated with patients with BPSD were based on data specifically in the Thai setting. Therefore, by replicating this thesis in other settings even using similar procedures, it is possibly that the

researcher might obtain different results. This might associated with differences in medical costs, characteristics of care provision from caregivers and healthcare services provided in different countries.

8.7 Recommendations for further study

This thesis initially contributes the cost-utility analysis of olanzapine versus risperidone for the treatment of patients with dementia with behavioural disturbances in Thailand. The analysis is based on a decision-analytic model, a Markov model, which suggests that olanzapine is the cost-effective option relative to risperidone. However, future research should examine some additional points to fill the gaps in this thesis as follows:

- The cost and utility data may be conducted in a longitudinal assessment in order to evaluate the changes in costs and utility values of patients which are influenced by the treatment during the disease progression over time.
- More patients should be considered leading to greater accuracy of a data analysis.
- Although this thesis includes adverse events in the analysis of cost data of behaviourally disturbed patients treated with atypical antipsychotics, other adverse events, such as weight gain, urinary tract infection, oedema, sedation, and cerebrovascular events, should be considered for further study in order to increase the accuracy of information to help improve the implementation of routine clinical practice of these patients.
- Other atypical antipsychotics, such as aripiprazole and quetiapine, and rates of switching of atypical antipsychotic drugs for the treatment should be considered in a future study, to introduce different aspects of an economic evaluation of atypical antipsychotic use in BPSD patients. This also leads to more precise information for adapting routine clinical practices.

- The predictive equation to calculate the time to FTC state in this thesis was developed from the LASER-AD study of the UK data. Therefore, a further study of the equation to predict length of time to the FTC state in patients with dementia should be developed specifically based on data from the Thai population.
- The relative risk of dying from dementia or Alzheimer's disease in this thesis was obtained from a previous study which conducted in the US. Thus, further studies should investigate especially in Thai patients with dementia and which would be more suitable for use with the Thai population.
- Indirect costs should be included in order to have different points of view of costing analysis being addressed in the thesis, leading to more accuracy in the treatment of patients with BPSD within a realistic situation.
- If patient-level data are available, Discrete Event Simulation (DES) should be considered to simulate unique demographic and clinical characteristics of individuals, as this approach captures data in a realistic environment and manner, resulting in more precise projections and computationally efficiency of an economic evaluation.

8.8 Publications

The researcher has previously published work in this area in an international peer reviewed journal (Thongchundee et al. 2015) (see Appendix 7). Moreover, the researcher has also presented a poster of elements of this work at a Sheffield Hallam University conference. Finally, the researcher anticipates a further four articles for publication which will be linked to the scope of this thesis in near future.

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Appendices

Appendix 1: Examples of search terms and keywords for literature reviews

An explanation of search terms and keywords used in this thesis is presented as follows: / = Mesh Heading Exp, (Exp = exploded MeSH Heading); asterisk (*) = any group of characters, including no character; ti = title word; ab = abstract word; $ = one character or none; “ ” = phrase search; unless otherwise stated, term searched all fields.

1. **Efficacy of atypical antipsychotics for dementia**

Database: MEDLINE and PsycINFO search strategies

1. dementia*:ti,ab.
2. alzheimer*:ti,ab.
3. Behavio$ral and psychological symptom*
4. BPSD:ti,ab.
5. neuropsychiatric* symptom*:ti,ab.
6. or/1-5
7. atypical antipsychotic*:ti,ab.
8. risperidone:ti,ab.
9. olanzapine:ti,ab.
10. aripiprazole:ti,ab.
11. quetiapine:ti,ab.
12. or/6-11
13. 6 and 12

Database: the Cochrane Library

1. dementia
2. Alzheimer’s
3. 1 and 2

2. Health economic evaluations of atypical antipsychotics for dementia

Database: MEDLINE search strategy

1. dementia*:ti,ab.
2. alzheimer*:ti,ab.
3. cost analysis*:ti,ab.
4. cost effective*:ti,ab.
5. cost utilit*:ti,ab.
6. cost benefit*:ti,ab.
7. atypical antipsychotic*:ti,ab.
8. risperidone:ti,ab.
9. olanzapine:ti,ab.
10. quetiapine:ti,ab.
11. aripiprazole:ti,ab.
12. 1 or 2
13. 3 or 4 or 5 or 6
14. 7 or 8 or 9 or 10 or 11
15. 12 and 13 and 14

Database: the Centre for Reviews and Dissemination (CRD) and the National Health System Economic Evaluation Database (NHS EED)

1. cost effectiveness
2. cost benefit
3. cost analysis
4. #1 or #2 or #3
5. dementia
6. dementia.ti
7. dementia/

8. Alzheimer Disease/
9. #6 or #7 or #8
10. atypical antipsychotics
11. risperidone
12. olanzapine
13. quetiapine
14. aripiprazole
15. #10 or #11 or #12 or #13 or #14
16. #4 and #9 and #15

The extended literature search of Health economic evaluations of atypical antipsychotics for dementia

Database: MEDLINE search strategy

1. cost*:ti,ab.
2. finance*:ti,ab.
3. "economic evaluation"
4. pharmacoeconomic*:ti,ab.
5. dementia*:ti,ab.
6. alzheimer's*:ti,ab.
7. risperidone:ti,ab.
8. risperdal:ti,ab.
9. olanzapine:ti,ab.
10. zyprexa:ti,ab.
11. aripiprazole:ti,ab.
12. abilify:ti,ab.
13. quetiapine:ti,ab.
14. seroquel:ti,ab.

15. 1 or 2 or 3 or 4
16. 5 or 6
17. or/7-14
18. 15 and 16 and 17

Database: the Centre for Reviews and Dissemination (CRD) and the National Health System Economic Evaluation Database (NHS EED)

1. dementia
2. alzheimer
3. costs
4. costing
5. finance
6. "economic evaluation"
7. pharmacoeconomic
8. risperidone or risperdal
9. olanzapine or zyprexa
10. aripiprazole or abilify
11. quetiapine or seroquel
12. #1 or #2
13. #3 or #4 or #5 or #6 or #7
14. #8 or #9 or #10 or #11
15. #12 and #13 and #14

3. Modelling-based economic evaluation in dementia

Database: MEDLINE

1. dementia*:ti,ab.

2. alzheimer*:ti,ab.
3. economic model*:ti,ab.
4. markov*:ti,ab.
5. model economic:ti,ab.
6. assessment of health economics in Alzheimer's disease:ti,ab.
7. assessment of health economics in dementia:ti,ab.
8. AHEAD:ti,ab.
9. CERAD:ti,ab.
10. equation*:ti,ab.
11. 1 or 2
12. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
13. 11 and 12

Database: the Centre for Reviews and Dissemination of University of York (CRD)

1. dementia
2. dementia:ti,ab.
3. dementia/
4. alzheimer disease/
5. vascular dementia/
6. frontotemporal dementia/
7. lewy body disease/
8. cost-benefit analysis/
9. cost savings/
10. costs and cost analysis/
11. health care costs/
12. #1 or #2 or #3 or #4 or #5 or #6 or #7
13. #8 or #10 or #11 or #11

14. #12 and #13
15. decision support techniques/
16. models, economic/
17. #15 or #16
18. #14 and #17

4. Costing associated with dementia

Database: MEDLINE

1. dementia*:ti,ab.
2. alzheimer*:ti,ab.
3. BPSD:ti,ab.
4. neuropsychiatric symptom*:ti,ab.
5. bevavio$ral disturban*:ti,ab.
6. non cognitive symptom*:ti,ab.
7. cost*:ti,ab.
8. 1 or 2
9. 3 or 4 or 5 or 6
10. 7 and 8 and 9

5. Health-related Quality of Life in dementia

Database: MEDLINE

1. dementia*:ti,ab.
2. alzheimer*:ti,ab.
3. quality of life:ti,ab.
4. health related quality of life:ti,ab.
5. health utility* index:ti,ab.
6. utility* index:ti,ab.

7. eq-5d:ti,ab.
8. demqol:ti,ab.
9. qol ad:ti,ab.
10. adrql:ti,ab.
11. Alzheimer* related quality of life:ti,ab.
12. SF*:ti,ab.
13. GHQ:ti,ab.
14. activity and affect indicators of quality of life:ti,ab.
15. cornell brown scale for quality of life:ti,ab.
16. dementia care mapping:ti,ab.
17. dementia quality of life:ti,ab.
18. qualidem:ti,ab.
19. quality of life-alzheimer*:ti,ab.
20. qualid:ti,ab.
21. quality of life in late stage of dementia:ti,ab.
22. 1 or 2
23. or/3-21
24. 22 and 23

Appendix 2: The letter of collaborating organisation

Sheffield Hallam University | Centre for Health and Social Care Research

September 18th, 2014

Thammasat University Hospital
Thammasat Hospital, No. 95/8,
Khlongnueng sub-district, Khlongluang district,
Pathumthani province, Thailand 12120

Dear Sir,

I am writing regarding Miss Thongchundee who is a PhD student in the Centre for Health and Social Care Research at Sheffield Hallam University and a Royal Thai Government scholarship student. Her research is entitled "Cost-Effectiveness of Atypical Antipsychotics for the treatment of Behavioural and Psychological Symptoms of Dementia in Thailand". This study aims to examine the value for money for treating patients with behavioural and psychological symptoms of dementia in Thailand. This research is in the process of proposal development and ethics approval. We need a letter from collaborating organisation in Thailand to confirm that the study will be supported by you and you will permit Miss Thongchundee to collect information about the treatment from patients.

Moreover, as the data will be collected outside of the UK, she would also like to interview a few patients and their carer regarding their progress on treatment and their wellbeing. I would like to request you to act as her local supervisor from your hospital. Could you please forward us your acceptance for our records.

The Sheffield Hallam University will be willing to collaborate with this study and would welcome you to be our PhD candidate's local supervisor.

Sincerely yours,

Anil Gumber
Principal Research Fellow (Health Economics)

Centre for Health and Social Care Research
Faculty of Health and Wellbeing Montgomery House 32 Collegiate Crescent Sheffield, S10 2BP UK
Telephone +44 (0) 114 225 5854 Fax +44 (0) 114 225 4377
Email: chscr@shu.ac.uk www.shu.ac.uk/chscr

No. 139/2015

95, 7th floor of Kunakorn Building
Department of Internal Medical Outpatient,
Thammasat University Hospital,
Phaholyotin Road, Klongnueng, Klongluang,
Pathum thani, 12120 Thailand

September 21st, 2015

Title: Local supervisor of Miss Oranuch Thongchundee

Dear: Dr. Anil Gumber

Assoc. Prof. Dr. Sombat Muengtaweepongsa, neurologist and head of internal medical outpatient department at Thammasat University Hospital in Thailand, agree to act as the local supervisor and support Miss Oranuch Thongchundee for the Ph.D. research work at Sheffield Hallam University.

Sincerely yours,

Assoc. Prof. Dr. Sombat Muengtaweepongsa, M.D.
Head of Internal Medical Outpatient Department,
Thammasat University Hospital, Klongnueng,
Klongluang, Pathum thani, 12120 Thailand
E-mail address: sombatm@hotmail.com

Appendix 3: The letter of ethics approval of data collection

• The Faculty Research Ethics Committee of Centre for Health and Social Care Research of Sheffield Hallam University in the UK

Sheffield Hallam University

RESEARCH ETHICS REVIEWER'S FEEDBACK FORM (SHUREC3)

Principal investigator: THONGCHUNDEE, Oum
Reference number: 2015-6/HWB-HSC-37

Other investigators: KHATAB K

Title of project:

Cost-Effectiveness of Atypical Antipsychotics for the treatment of Dementia in Thailand

In my judgement the application should be (tick one box):

☒ Approved

☐ Approved with attention to the items listed below (1). Please email the details of how the issues have been addressed to the FREC and provide confirmation from the supervisor that the issues have been addressed for student projects.

☐ Referred back to the applicant for a full resubmission to address all the conditions listed below (1)

☐ Not approved for the reasons listed below (2)

1. The following issues need to be addressed:

Advisory only: I could not find the Data Management Plan - make sure you have it done and in your site file.

Dr Peter ALLMARK 25072016

2. The application is not approved for the following reasons:

I confirm that I do not have a conflict of interest with the project application.

Signature_____ **Date:** _____

• The Human Research Ethics Committee of Thammasat University (Faculty of Medicine) in Thailand

หนังสือรับรองการพิจารณาด้านจริยธรรมการวิจัยในคน

คณะอนุกรรมการจริยธรรมการวิจัยในคน มหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 (คณะแพทยศาสตร์)

95 หมู่ 8 ถ.พหลโยธิน ต.คลองหนึ่ง อ.คลองหลวง จ. ปทุมธานี 12120

โทร. 02-9269704 , โทรสาร 02-5644444 ต่อ 7535

.....

หนังสือรับรองเลขที่	**144/2559**
โครงการวิจัยเรื่อง	การเปรียบเทียบต้นทุนอรรถประโยชน์ของยาจิตเวช Olanzapine และ Risperidone ในการรักษาผู้ป่วยปัญหา พฤติกรรม อารมณ์และความผิดปกติทางจิตในผู้ป่วยโรคสมองเสื่อมในประเทศไทย (Cost-effectiveness of Atypical Antipsychotics for the treatment of Dementia in Thailand)
รหัสโครงการวิจัย	MTU-EC-IM-6-061/59
ผู้วิจัย	นางสาว อรนุช ทองจันดี รองศาสตราจารย์ นายแพทย์สมบัติ มุ่งทวีพงษา
หน่วยงานที่รับผิดชอบ	โครงการจัดตั้งภาควิชาสาขาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์ โทร. 043-221-770

เอกสารที่รับรอง

1. โครงการวิจัย ฉบับที่ 3.0 วันที่ 1 สิงหาคม 2559
2. เอกสารชี้แจงข้อมูลแก่ผู้เข้าร่วมโครงการวิจัยสำหรับอาสาสมัคร ฉบับที่ 3.0 วันที่ 1 สิงหาคม 2559
3. เอกสารชี้แจงข้อมูลแก่ผู้เข้าร่วมโครงการวิจัยสำหรับผู้ดูแล ฉบับที่ 3.0 วันที่ 1 สิงหาคม 2559
4. หนังสือแสดงเจตนายินยอมเข้าร่วมการวิจัย ฉบับที่ 3.0 วันที่ 1 สิงหาคม 2559
5. แบบสอบถาม ฉบับที่ 3.0 วันที่ 1 สิงหาคม 2559

คณะอนุกรรมการจริยธรรมการวิจัยในคน มหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 (คณะแพทยศาสตร์) พิจารณาจริยธรรมการวิจัยโดยยึดหลักของ Declaration of Helsinki, The Belmont Report, CIOMS Guidelines และ the International Practice (ICH-GCP)

คณะอนุกรรมการจริยธรรมการวิจัยในคน มหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 (คณะแพทยศาสตร์) ได้พิจารณาอนุมัติด้านจริยธรรมการทำวิจัยในคนให้ดำเนินการวิจัยข้างต้นได้ ตามมติที่ประชุมครั้งที่ 8/2559 วันที่ 26 เมษายน 2559

ระยะเวลาที่อนุมัติ 1 ปี

กำหนดส่งรายงานความก้าวหน้า 1 ปี : วันที่ 17 สิงหาคม 2560

ลงชื่อ.....

(รองศาสตราจารย์ นายแพทย์ไวพจน์ จันทร์วิเมลือง)

ประธานคณะอนุกรรมการฯ

ลงชื่อ.....

(รองศาสตราจารย์ ดร.ศิริกุล มะโนจันทร์)

อนุกรรมการและผู้ช่วยเลขานุการ

อนุมัติ ณ วันที่ 18 สิงหาคม 2559

หมดอายุ วันที่ 17 สิงหาคม 2560

Certificate of Approval

Human Research Ethics Committee of Thammasat University No.1 (Faculty of Medicine)

95 Moo 8, Paholyotin Road, Auphur Klongluang, Pathumthani. Thailand 12120,

Tel 662-9269704 and Fax 662-5644444 ext 7535

Number of COA	**144/2559**
Title of Project	Cost-effectiveness of Atypical Antipsychotics for the treatment of Dementia in Thailand.
Project No	MTU-EC-IM-6-061/59
Principal Investigator	Oranuch Thongchundee
	Associate Professor Sombat Muengtaweepongsa (M.D.)
Study Center	Thammasat University Hospital
Responsible Department	Internal Medicine, Faculty of medicine,
	Thammasat University, Prathumthani, Thailand 12120
	Tel. 043-221-770

Document Reviewed

1. Protocol Version 3.0 : dated 1 August 2016
2. Information Sheet For Volunteers Version 3.0 : dated 1 August 2016
3. Information Sheet For Administrators Version 3.0 : dated 1 August 2016
4. Consent Form Version 3.0 : dated 1 August 2016
5. Questionnaire Version 3.0 : dated 1 August 2016

The Human Ethics Committee of Thammasat University No.1 (Faculty of Medicine) is in full compliance with international such as Declaration of Helsinki, The Belmont Report, CIOMS Guidelines and the International Practice (ICH-GCP)

This document is a record of review and approval / acceptance of a clinical study protocol. The Human Research Ethics Committee of Thammasat University No.1 (Faculty of Medicine) has approved the above study and the following documents for use in the study at the Ethics Committee meeting on April 26, 2016. (8/2559)

Approval period 1 year.

Progress report deadline : August 17, 2017

Signed: .....

(Associate Professor Sirikul Manochantr)

Assistant Secretary and Committee of the Human Research Ethics Committee of Thammasat University No.1

(Faculty of Medicine)

Signed:.....

(Associate Professor Waipoj Chanvimalueng (M.D.))

Chairman of the Human Research Ethics Committee of Thammasat University No.I (Faculty of Medicine)

Date of Approval: **August 18, 2016**

Date of Expire : **August 17, 2017**

The Human Ethics Committee of Thammasat University No. I (Faculty of Medicine)

(8/2016 April 26, 2016)

Name and Function on Committee (e.g. Chairman, Secretary and etc.)	Profession/ Qualification (s)	Affiliation (place of work)	Gender (M/F)	Tick (✓) If member present When Protocol Reviewed
Consultant Preecha Wanichsetakul	Associate of the Rector for Research Development Assoc.Prof. (M.D.)	Department of Obstetrics-Gynecology, Faculty of Medicine, Thammasat University	M	---
Chairperson Waipoj Chanvimalueng	Assoc.Prof. (M.D.)	Department of Otolaryngology, Faculty of Medicine, Thammasat University	M	---
Vice-Chairperson Sakol Manusook	Asst.Prof. (M.D.)	Department of Obstetrics-Gynecology, Faculty of Medicine, Thammasat University	M	✓
Kongkiat Kulkantrakorn,	Associate Dean for Research Development Professor. (M.D.)	Department of Internal Medicine, Faculty of Medicine, Thammasat University	M	✓
Committee Jaakchai Jungthirapanich	Assoc.Prof. (M.D.)	Department of Internal Medicine, Faculty of Medicine, Thammasat University	M	✓
Committee Pachara Visutakul	Assoc.Prof. (M.D.) (Ph.D)	Department of Reproductive Endocrinology, Faculty of Medicine, Thammasat University	F	✓
Committee Paskorn Sritipsukho	Assoc.Prof. (M.D.)	Department of Pediatrics, Faculty of Medicine, Thammasat University	M	---
Committee Jinda Wangboonskul	Assoc.Prof. ,(Ph.D)	Pharmacopoeia chemistry, Faculty of Pharmacy, Thammasat University	F	---
Committee Ing-Orn Arunakul	Asst.Prof. (M.D.)	Department of Internal Medicine, Faculty of Medicine, Thammasat University	F	✓

The Human Ethics Committee of Thammasat University No. I (Faculty of Medicine)

(8/2016 April 26, 2016)

Name and Function on Committee (e.g. Chairman, Secretary and etc.)	Profession/ Qualification (s)	Affiliation (place of work)	Gender (M/F)	Tick (✓) If member presen When Protocol Reviewed
Committee Kallaya Arree	Asst.Prof. (Ph.D.)	Department of Microbiology, Faculty of Medicine, Thammasat University	F	—
Committee Kanvee Viwatpanich	Assoc.Prof. (Ph.D.)	Chulabhorn international college of Medicine , Thammasat University	M	✓
Committee Muthita Phanasa	(M.D.)	Department of Psychiatry, Faculty of Medicine, Thammasat University	F	✓
Commitee Jintamai Suwanprateeb	Ph.D (Biomaterials)	National Metal and Materials Technology Center	M	✓
Committee Rungtip Hovanotayan	MA. (Library Science)	Retired employee	F	✓
Committee Kumpol Pivpanngam	Business administration	Employee Thammasat University Volunteer Center	M	✓
Committee and Secretary Thipaporn Tharavanij	Assoc.Prof. (M.D.)	Department of Internal Medicine, Faculty of Medicine, Thammasat University	F	✓
Committee and Assistant Sirikul Manochantr	Assoc.Prof. (Ph.D.)	Department of Cell Biology Medicine, Faculty of medicine, Thammasat University	F	✓
Committee and Assistant Thana Khawcharoenporn	Asst.Prof. (M.D.)	Department of Internal Medicine, Faculty of Medicine, Thammasat University	M	✓
Committee and Assistant Secretary Sumalee Kondo	Asst.Prof. (Ph.D.)	Department of Molecular genetics, Faculty of Medicine, Thammasat University	F	✓

The Human Ethics Committee of Thammasat University : I (Faculty of Medicine) is in full compliance with international such as Declaration of Helsinki, The Belmont Report, CIOMS Guidelines and the International Practice (ICH-GCP).

The above EC members who are independent of the investigator and the sponsor of the trial have voted provided opinion on the titled : **Cost-effectiveness of Atypical Antipsychotics for the treatment of Dementia in Thailand.**

Investigator	Oranuch Thongchundee
	Associate Professor Sombat Muengtaweepongsa (M.D.)
Protocol Number	MTU-EC-IM-6-061/59
Date of Approve	August 18, 2016

.....

(Associate Prof. Waipoj Chanvimalueng, M.D.)

Chairman of the Human Research Ethics Committee of Thammasat University No.1 (Faculty of Medicine)

บันทึกข้อความ

ส่วนราชการ สำนักงานคณะอนุกรรมการจริยธรรมการวิจัยในคน มธ. ชุดที่ ๑ โทร. ๐๒๙๒๖ ๙๗๐๔ (วรัญญา)

ที่ ๑๑๔๕ /๒๕๖๐ วันที่ ๒๐ กรกฎาคม ๒๕๖๐

เรื่อง ขอแจ้งผลการพิจารณาขอต่ออายุโครงการวิจัย รหัสโครงการ MTU-EC-IM-6-061/59

เรียน นส.อรนุช ทองจันดี(รศ.นพ.สมบัติ มุ่งทวีพงษา อาจารย์ที่ปรึกษา)

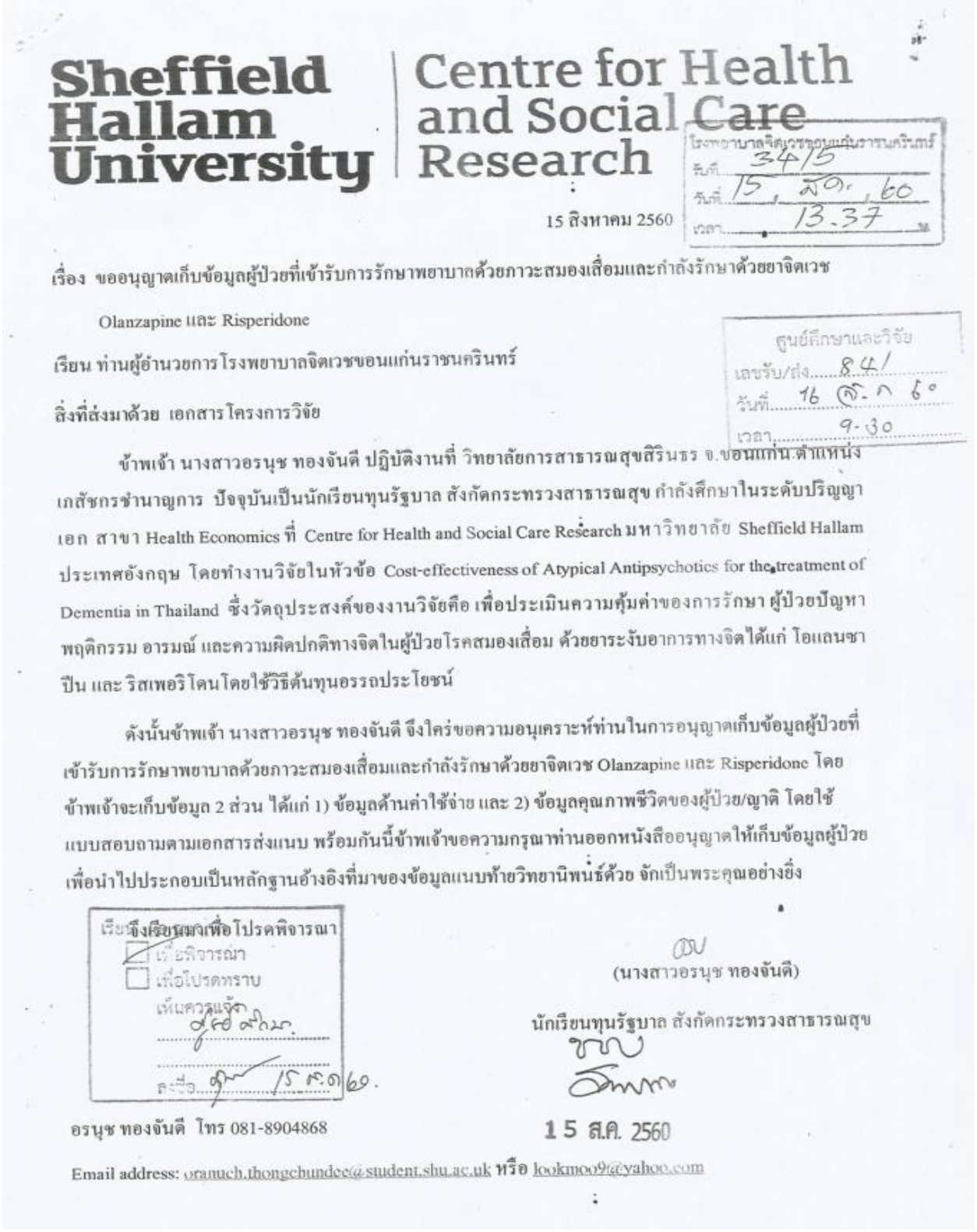
ตามที่ ท่านได้เสนอเอกสารขอต่ออายุโครงการวิจัย เรื่อง "การเปรียบเทียบต้นทุนอรรถประโยชน์ของยาจิตเวช Olanzapine และ Risperidone ในการรักษาผู้ป่วยปัญหา พฤติกรรม อารมณ์และความผิดปกติทางจิตในผู้ป่วยโรคสมองเสื่อมในประเทศไทย : Cost-effectiveness of Atypical Antipsychotics for the treatment of Dementia in Thailand" รหัสโครงการวิจัย MTU-EC-IM-6-061/59 เพื่อเสนอคณะอนุกรรมการจริยธรรมการวิจัยในคน มธ. ชุดที่ ๑ พิจารณาด้านจริยธรรม นั้น

บัดนี้ คณะอนุกรรมการฯ ได้พิจารณาเอกสารดังกล่าวแล้ว และมีมติ "อนุมัติ"โดยต่ออายุโครงการวิจัยให้ ๑ ปี ตั้งแต่วันที่ ๑๘ สิงหาคม ๒๕๖๐ ถึงวันที่ ๑๗ สิงหาคม ๒๕๖๑

จึงเรียนมาเพื่อโปรดทราบ

(รองศาสตราจารย์ นายแพทย์ธนา ขอเจริญพร)
อนุกรรมการและผู้ช่วยเลขานุการ

- **The Human Research Ethics Committee of Khon Kaen Rajanagarindra Psychiatric Hospital in Thailand**



Sheffield Hallam University | Centre for Health and Social Care Research

โรงพยาบาลจิตเวชขอนแก่นราชนครินทร์ รับที่ 3415 วันที่ 15 ส.ค. 60 เวลา 13.37

15 สิงหาคม 2560

เรื่อง ขออนุญาตเก็บข้อมูลผู้ป่วยที่เข้ารับการรักษาพยาบาลด้วยภาวะสมองเสื่อมและกำลังรักษาด้วยยาจิตเวช Olanzapine และ Risperidone

ศูนย์ศึกษาและวิจัย เลขรับ/ส่ง 841 วันที่ 16 ส.ค. 60 เวลา 9.30

เรียน ท่านผู้อำนวยการโรงพยาบาลจิตเวชขอนแก่นราชนครินทร์

สิ่งที่ส่งมาด้วย เอกสารโครงการวิจัย

ข้าพเจ้า นางสาวอรนุช ทองจันดี ปฏิบัติงานที่ วิทยาลัยการสาธารณสุขสิรินธร จ.ขอนแก่น ตำแหน่ง เภสัชกรชำนาญการ ปัจจุบันเป็นนักเรียนทุนรัฐบาล สังกัดกระทรวงสาธารณสุข กำลังศึกษาในระดับปริญญาเอก สาขา Health Economics ที่ Centre for Health and Social Care Research มหาวิทยาลัย Sheffield Hallam ประเทศอังกฤษ โดยทำงานวิจัยในหัวข้อ Cost-effectiveness of Atypical Antipsychotics for the treatment of Dementia in Thailand ซึ่งวัตถุประสงค์ของงานวิจัยคือ เพื่อประเมินความคุ้มค่าของการรักษา ผู้ป่วยปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตในผู้ป่วยโรคสมองเสื่อม ด้วยยาระงับอาการทางจิตได้แก่ โอแลนซาปีน และ ริสเพอริโดน โดยใช้วิธีต้นทุนอรรถประโยชน์

ดังนั้นข้าพเจ้า นางสาวอรนุช ทองจันดี จึงใคร่ขอความอนุเคราะห์ท่านในการอนุญาตเก็บข้อมูลผู้ป่วยที่เข้ารับการรักษาพยาบาลด้วยภาวะสมองเสื่อมและกำลังรักษาด้วยยาจิตเวช Olanzapine และ Risperidone โดยข้าพเจ้าจะเก็บข้อมูล 2 ส่วน ได้แก่ 1) ข้อมูลด้านค่าใช้จ่าย และ 2) ข้อมูลคุณภาพชีวิตของผู้ป่วย/ญาติ โดยใช้แบบสอบถามตามเอกสารส่งแนบ พร้อมกันนี้ข้าพเจ้าขอความกรุณาท่านออกหนังสืออนุญาตให้เก็บข้อมูลผู้ป่วยเพื่อนำไปประกอบเป็นหลักฐานอ้างอิงที่มาของข้อมูลแนบท้ายวิทยานิพนธ์ด้วย จักเป็นพระคุณอย่างยิ่ง

เรียน ผอ. เพื่อโปรดพิจารณา
☑ เพื่อพิจารณา
☐ เพื่อโปรดทราบ
เห็นควรแจ้ง ตอบ ตามนี้
ลงชื่อ ... 15 ส.ค. 60.

(นางสาวอรนุช ทองจันดี)

นักเรียนทุนรัฐบาล สังกัดกระทรวงสาธารณสุข

15 ส.ค. 2560

อรนุช ทองจันดี โทร 081-8904868

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Appendix 4: Information sheet, consent form and costing and quality of life questionnaires

• Information sheet

เอกสารชี้แจงข้อมูลแก่ผู้เข้าร่วมการวิจัยสำหรับผู้ดูแล

โครงการวิจัยเรื่อง:

การเปรียบเทียบต้นทุนอรรถประโยชน์ของยาจิตเวช โอแลนซาปีน และริสเพอริโดน ในการรักษาผู้ป่วยปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตในผู้ป่วยโรคสมองเสื่อมในประเทศไทย

ผู้รับผิดชอบโครงการ:

หัวหน้าโครงการวิจัย : นางสาวอรนุช ทองจันดี
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เรียน ผู้เข้าร่วมโครงการวิจัยทุกท่าน

ท่านได้รับเชิญให้เข้าร่วมในโครงการวิจัยนี้เนื่องจาก ท่านเป็นผู้ดูแลสุขภาพของอาสาสมัครที่ได้รับการวินิจฉัยด้วยโรคสมองเสื่อมที่มีอายุตั้งแต่ 60 ปีขึ้นไปและกำลังได้รับยาระงับอาการทางจิต ได้แก่ ยาโอแลนซาปีน หรือ ยาริสเพอริโดน ในการรักษาอาการปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตในผู้ป่วยด้วยโรคสมองเสื่อมเป็นระยะเวลาอย่างน้อย 2 เดือน

ก่อนที่ท่านจะตกลงใจเข้าร่วมโครงการวิจัยนี้ โปรดอ่านข้อความในเอกสารทั้งหมด เพื่อให้ทราบว่าเหตุใดท่านจึงได้รับเชิญให้เข้าร่วมในโครงการวิจัย โครงการวิจัยนี้ทำเพื่ออะไร หากท่านเข้าร่วมโครงการวิจัยท่านจะต้องทำอะไรบ้าง รวมทั้งข้อดีและข้อเสียที่อาจจะเกิดขึ้นในระหว่างการวิจัย

ในเอกสารนี้ อาจมีข้อความที่ท่านอ่านแล้วยังไม่เข้าใจ ท่านสามารถสอบถามผู้วิจัยที่จัดทำโครงการวิจัยนี้เพื่อขอคำอธิบายจนกว่าท่านจะเข้าใจ และท่านยังสามารถขอคำแนะนำในการเข้าร่วมโครงการวิจัยนี้จากครอบครัว เพื่อน หรือแพทย์ประจำตัวของท่านได้ ท่านมีเวลาอย่างเพียงพอในการตัดสินใจโดยอิสระ การเข้าร่วมในโครงการวิจัยครั้งนี้จะต้องเป็น **ความสมัครใจ**ของท่าน ไม่มีการบังคับหรือชักจูง

โปรดอย่าลงลายมือชื่อของท่านในเอกสารนี้จนกว่าท่านจะแน่ใจว่า ท่านมีความประสงค์จะเข้าร่วมในโครงการวิจัยนี้ และหากท่านตัดสินใจแล้วว่าจะเข้าร่วมในโครงการวิจัยนี้ ขอให้ท่านลงนามในเอกสารแสดงความยินยอมเข้าร่วมการวิจัยของโครงการวิจัยนี้

<u>เหตุที่ต้องทำวิจัยและเหตุผลที่ต้องการศึกษาในคน</u>

ในปัจจุบันความเจริญก้าวหน้าจากการพัฒนาทางด้านการแพทย์ และการดูแลสุขภาพส่งผลให้ประชากรทั่วโลกมีชีวิตที่ยืนยาวขึ้น ทำให้จำนวนประชากรในกลุ่มผู้สูงอายุมีจำนวนเพิ่มขึ้น ภาวะสมองเสื่อมเป็นความเจ็บป่วยที่มีความสำคัญอย่างยิ่งในกลุ่มผู้สูงวัย ซึ่งภาวะดังกล่าวกำลังกลายเป็นปัญหาที่สำคัญกับทุกประเทศทั่วโลกรวมทั้งประเทศไทย เนื่องจากภาวะสมองเสื่อมส่งผลกระทบต่อทั้งทางด้านเศรษฐกิจและสังคมของประเทศเหล่านี้เป็นอย่างมาก

ภาวะสมองเสื่อมเป็นกลุ่มอาการที่ผู้ป่วยเกิดการสูญเสียความจำ การเสื่อมของความจำ ความผิดปกติของเชาว์ปัญญา และการเปลี่ยนแปลงทางด้านพฤติกรรม จากข้อมูลพบว่าโรคสมองเสื่อมอัลไซเมอร์เป็นชนิดของภาวะสมองเสื่อมที่พบในผู้ป่วยได้บ่อยที่สุด ภาวะสมองเสื่อมจัดเป็นความเจ็บป่วยเรื้อรัง อาการและความรุนแรงของโรคจะเพิ่มมากขึ้นตามระยะเวลาการดำเนินไปของโรค ซึ่งพบว่าผู้ป่วยเหล่านี้มักจะประสบกับปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตร่วมด้วย เช่น อาการซึมเศร้า ปัญหาเรื่องการนอน อาการก้าวร้าว อาการพลุ่งพล่านกระวนกระวาย อาการหลงผิด และประสาทหลอน เป็นต้น อาการดังกล่าวเป็นปัญหาที่มีความสำคัญอย่างยิ่งต่อการดูแลรักษาผู้ป่วย และยังส่งผลกระทบต่อทั้งตัวผู้ป่วยและผู้ดูแลอย่างหลีกเลี่ยงไม่ได้

การจัดการปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตในผู้ป่วยโรคสมองเสื่อมสามารถทำได้ 2 วิธี คือ วิธีการไม่ใช้ยาและการรักษาด้วยยา ซึ่งวิธีการไม่ใช้ยาจะถูกใช้เป็นวิธีแรกในการจัดการปัญหา แต่เมื่อการรักษาด้วยวิธีดังกล่าวไม่ได้ผล การรักษาด้วยยาจะเป็นวิธีที่เหมาะสมในการดูแลผู้ป่วย ในปัจจุบันพบว่ามียาหลายประเภทถูกนำมาใช้ในการรักษาภาวะดังกล่าว แต่จากข้อมูลพบว่ายารักษาอาการโรคจิตเวชเป็นยาที่มีการนำมาใช้อย่างกว้างขวาง ซึ่งยาประเภทนี้ยังสามารถแบ่งได้เป็นยารุ่นเก่าและยารุ่นใหม่ แต่เนื่องจากยาจิตเวชรุ่นใหม่พบว่ามีประสิทธิผลที่เหนือกว่าและมีผลข้างเคียงน้อยกว่า จึงได้รับความนิยมและถูกนำมาใช้มากกว่ายารุ่นเก่า ถึงแม้ว่ายารุ่นใหม่จะมีราคาแพงกว่าก็ตาม

ด้วยเหตุนี้การศึกษาต้นทุนอรรถประโยชน์ของยาจิตเวชในการรักษาผู้ป่วยที่ประสบปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตในผู้ป่วยโรคสมองเสื่อมจึงมีความสำคัญเป็นอย่างยิ่ง เนื่องจากภาวะดังกล่าวไม่เพียงส่งผลกระทบต่อความเจ็บป่วยและคุณภาพชีวิตของผู้ป่วยและผู้ดูแล แต่ยังส่งผลกระทบต่อค่าใช้จ่ายในการดูแลสุขภาพของผู้ป่วยอีกด้วย

<u>วัตถุประสงค์ของโครงการ</u>

เพื่อประเมินความคุ้มค่าของการรักษา ผู้ป่วยปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตในผู้ป่วยโรคสมองเสื่อม ด้วยยาระงับอาการทางจิตได้แก่ โอแลนซาปีน และ ริสเพอริโดนโดยใช้วิธีต้นทุนอรรถประโยชน์

<u>ขั้นตอนและกระบวนการทำวิจัย</u>

1. คัดเลือก<u>ผู้ดูแล</u>สุขภาพของผู้ป่วยที่ได้รับการวินิจฉัยด้วยโรคสมองเสื่อม ที่มีอายุตั้งแต่ 60 ปีขึ้นไป และได้รับยาระงับอาการทางจิตได้แก่ โอแลนซาปีน และ ริสเพอริโดน ในการรักษาอาการปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตเป็นระยะเวลาอย่างน้อย 2 เดือน ในผู้รับบริการที่มารับบริการที่โรงพยาบาลธรรมศาสตร์หัวเฉียวเฉลิมพระเกียรติ (ศูนย์รังสิต) อำเภอคลองหลวง จังหวัดปทุมธานี เพื่อเข้าร่วมวิจัย

การวิจัยในครั้งนี้ **<u>ผู้ดูแล</u>** หมายถึง *ญาติหรือผู้ดูแลสุขภาพของผู้ป่วยตามเกณฑ์ดังกล่าวข้างต้น โดยจะต้องเป็นผู้ที่อาศัยอยู่ร่วมกับผู้ป่วย หรือในช่วงเวลาที่ผ่านมาอย่างน้อย 2 เดือน ได้ใช้เวลาอยู่กับผู้ป่วยอย่างน้อย 8 ชั่วโมงต่อวัน เป็นระยะเวลาอย่างน้อย 3 วันใน 1 สัปดาห์*

2. เมื่อท่านยินยอมเข้าร่วมโครงการวิจัย ท่านจะต้องตอบแบบสอบถามจำนวน 2 ชุด ได้แก่ ชุดที่ 1 (แบบสอบถามเกี่ยวกับข้อมูลต้นทุน) และชุดที่ 2 (แบบประเมินคุณภาพชีวิต) โดยใช้เวลาทั้งหมดในการตอบแบบสอบถามประมาณ 30-45 นาที

<u>ประโยชน์ที่อาจได้รับ</u>

"*ท่านจะไม่ได้รับประโยชน์โดยตรงจากการเข้าร่วมในการวิจัยครั้งนี้*" แต่ผลการศึกษาจะนำไปใช้ในการพิจารณาความคุ้มค่าของยาระงับอาการทางจิต ได้แก่ ยาโอแลนซาปีน เปรียบเทียบกับยาริสเพอริโดน ในการรักษาผู้ป่วยปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตในผู้ป่วยโรคสมองเสื่อม และผลการศึกษานี้ยังสามารถนำไปใช้ประกอบการพิจารณาตัดสินใจในการเลือกใช้ยาดังกล่าวโดยแพทย์ผู้ป่วย หรือ ผู้ดูแล ในการวางแผนและเลือกแนวทางการรักษาที่มีความคุ้มค่าและเหมาะสมที่สุดแก่ผู้ป่วย นอกจากนี้ผลการวิจัยจะถูกนำไปใช้เพื่อเป็นข้อมูลพื้นฐานในการสนับสนุน วางแผน และพัฒนาการดูแลผู้ป่วยที่มีภาวะเจ็บป่วยดังกล่าว ซึ่งจะก่อให้เกิดประโยชน์โดยตรงทั้งแก่ตัวผู้ป่วย ผู้ดูแล และแพทย์ ในการดูแลผู้ป่วยโรคสมองเสื่อม และยังเป็นการช่วยเพิ่มคุณภาพชีวิตของผู้ป่วยและผู้ดูแลอีกด้วย

ข้อปฏิบัติของผู้เข้าร่วมวิจัยขณะที่ร่วมในโครงการวิจัย

เพื่อให้งานวิจัยนี้ประสบความสำเร็จด้วยดี ผู้ทำวิจัยใคร่ขอความความร่วมมือจากท่านในการตอบแบบสอบถามให้ตรงตามความเป็นจริง

ความเสี่ยงหรือความไม่สะดวกสบายของผู้เข้าร่วมวิจัยที่อาจได้รับ

การเข้าร่วมการวิจัยในครั้งนี้มีความเสี่ยงเพียงเล็กน้อย โดยความเสี่ยงที่อาจจะเกิดขึ้น ได้แก่ การเสียเวลา ไม่สะดวก ไม่สบาย สูญเสียรายได้ และอาจจะมีความอึดอัดต่อจิตใจ ดังนั้นหากท่านพบอาการดังกล่าวข้างต้น ท่านสามารถแจ้งผู้ทำการวิจัยได้ทันที ซึ่งท่านสามารถขอหยุดพักชั่วคราวหรือขอหยุดการตอบแบบสอบถามหรือทำแบบทดสอบได้

ค่าใช้จ่ายของผู้เข้าร่วมวิจัยในการเข้าร่วมการวิจัย

การวิจัยในครั้งนี้*ท่านจะไม่เสียค่าใช้จ่ายใดๆทั้งสิ้น* นอกจากนี้ท่านจะได้รับค่าตอบแทน คือ ค่าชดเชยค่าเสียเวลาในการตอบแบบสอบถาม เป็นจำนวนเงิน 100 บาท

การเข้าร่วมและการสิ้นสุดการเข้าร่วมโครงการวิจัย

การเข้าร่วมในโครงการวิจัยครั้งนี้เป็นไปโดยความสมัครใจ ในการเข้าร่วมการศึกษา ท่านจะต้องลงนามในใบยินยอมเข้าร่วมการวิจัย อย่างไรก็ตามท่านสามารถบอกยกเลิกได้ทุกเมื่อ และหากท่านไม่สมัครใจจะเข้าร่วมการวิจัย ผู้ป่วยในความดูแลของท่านจะยังคงได้รับการดูแลรักษาตามปกติ ซึ่งจะไม่มีผลต่อการดูแลรักษาโรคของผู้ป่วยแต่อย่างใด

การปกป้องรักษาข้อมูลความลับของผู้เข้าร่วมวิจัย

ในการศึกษาครั้งนี้ผู้วิจัยสามารถเข้าถึงข้อมูลของท่านได้แต่เพียงผู้เดียว ผู้วิจัยรับรองว่าข้อมูลของท่านจะถูกเก็บเป็นความลับ จะไม่มีการเปิดเผยชื่อ – นามสกุล รวมถึงข้อมูลที่สามารถระบุตัวบุคคลของท่าน การนำเสนอผลการวิจัยจะนำเสนอเป็นภาพรวม การเปิดเผยข้อมูลเกี่ยวกับท่านต่อหน่วยงานต่างๆที่เกี่ยวข้องกับการกระทำ จะทำได้เฉพาะในกรณีจำเป็นด้วยเหตุผลทางการเท่านั้น และจะต้องได้รับคำยินยอมจากท่านเป็นลายลักษณ์อักษร

สิทธิในการถอนตัวออกจากโครงการของผู้เข้าร่วมวิจัย

ท่านสามารถถอนตัวจากการเข้าร่วมการวิจัยในครั้งนี้ได้ทุกเมื่อโดยไม่ต้องแสดงเหตุผล การถอนตัวออกจากโครงการจะไม่กระทบต่อสิทธิในการรักษาพยาบาลใดๆของท่านและผู้ป่วยทั้งสิ้น

โครงการวิจัยนี้ได้รับความเห็นชอบจากคณะอนุกรรมการจริยธรรมการวิจัยในคน มหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 (คณะแพทยศาสตร์) หากท่านไม่ได้รับการรักษาพยาบาลหรือการชดเชยอันควรต่อการบาดเจ็บหรือเจ็บป่วยที่เกิดขึ้นโดยตรงต่อการวิจัย หรือท่านไม่ได้รับการปฏิบัติตามที่ปรากฏในเอกสารข้อมูลคำอธิบายสำหรับผู้เข้าร่วมในการวิจัย ท่านสามารถร้องเรียนได้ที่ คณะอนุกรรมการจริยธรรมการวิจัยในคน มหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 อาคารราชสุดา ชั้น 4 โทรศัพท์ 02-9269704 โทรสาร 02-5644444 ต่อ 7535 ไปรษณีย์อิเล็กโทรนิกส์ (e-mail) ec.medtu@gmail.com

ขอขอบคุณผู้เข้าร่วมวิจัยทุกท่านที่ให้ความร่วมมือ

ทีมผู้วิจัย

- **Consent form**

หนังสือแสดงเจตนายินยอมเข้าร่วมการวิจัย

โครงการวิจัยเรื่อง:

การเปรียบเทียบต้นทุนอรรถประโยชน์ของยาจิตเวช โอแลนซาปีน และริสเพอริโดน ในการรักษาผู้ป่วยปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตในผู้ป่วยโรคสมองเสื่อมในประเทศไทย

ผู้รับผิดชอบโครงการ:

หัวหน้าโครงการวิจัย : นางสาวอรนุช ทองจันดี
บ้านเลขที่ 296 หมู่ 2 ต.โคกพระ
อ.กันทรวิชัย จ.มหาสารคาม 44150
โทรศัพท์ 081-8904868 E-mail: lookmoo9@yahoo.com

ผู้ร่วมวิจัย:

(ต่างประเทศ) 1) ดร.เอนิล กัมเบอร์ E-mail: a.gumber@shu.ac.uk
2) ดร.คลาลีด คลาแทบ E-mail: k.khatab@shu.ac.uk
มหาวิทยาลัยเชฟฟิลด์ฮอลแลม เมืองเชฟฟิลด์ ประเทศอังกฤษ S10 2BP
โทรศัพท์: +44 114 225 5854 แฟกซ์: +44 114 225 4377

(ในประเทศ) 1) รศ.นพ.สมบัติ มุ่งทวีพงษา
คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์
ถ.พหลโยธิน อ.คลองหลวง จ.ปทุมธานี 12120
โทรศัพท์: 086-9994208 E-mail: sombatm@hotmail.com

วันที่ให้คำยินยอม วันที่..... เดือน..... พ.ศ. .....

การวิจัยนี้ใช้แบบสอบถามเป็นเครื่องมือในการวิจัย ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีวิจัย อันตราย อาการ รวมถึงผลข้างเคียงที่อาจจะเกิดขึ้นจากการวิจัย รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด และมีความเข้าใจดีแล้ว ซึ่งผู้วิจัยได้เปิดโอกาสให้ข้าพเจ้าซักถามข้อสงสัยอย่างละเอียด และผู้วิจัยได้ตอบคำถามต่างๆด้วยความเต็มใจ ไม่ปิดบัง ซ่อนเร้น จนเป็นที่พอใจของข้าพเจ้า และยินดีเข้าร่วมโครงการวิจัยนี้โดยสมัครใจ

ข้าพเจ้ามีสิทธิ์บอกยกเลิกการเข้าร่วมการวิจัยในครั้งนี้ได้ทุกเมื่อโดยไม่ต้องแสดงเหตุผล และข้าพเจ้าจะไม่เสียสิทธิในการรักษาพยาบาลที่จะเกิดขึ้นตามมาในโอกาสต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับและจะเปิดเผยเฉพาะในรูปที่เป็นสรุปผลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่างๆที่เกี่ยวข้องกับการกระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางการเท่านั้นและจะต้องได้รับคำยินยอมจากข้าพเจ้าเป็นลายลักษณ์อักษร

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้ว มีความเข้าใจดีทุกประการ และได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ในกรณีที่ข้าพเจ้าไม่สามารถอ่านหนังสือได้ ผู้วิจัยได้อ่านข้อความในใบยินยอมนี้ให้ข้าพเจ้าฟังจนเข้าใจดีแล้ว ข้าพเจ้าจึงลงนามในใบยินยอมด้วยความเต็มใจ

ข้าพเจ้าสามารถติดต่อกับ **นางสาวอรนุช ทองจันดี ที่หมายเลขโทรศัพท์ 081-8904868 ไปรษณีย์อิเล็กโทรนิกส์** (e-mail) **lookmoo9@yahoo.com ตลอด 24 ชั่วโมง** หรือสามารถติดต่อคณะอนุกรรมการจริยธรรมการวิจัยในคนมหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 (คณะแพทยศาสตร์) อาคารราชสุดา ชั้น 4 โทรศัพท์ 02-9269704 โทรสาร 02-5644444 ต่อ 7535 ไปรษณีย์อิเล็กโทรนิกส์ (e-mail) ec.medtu@gmail.com

ลงนาม.....ผู้ยินยอม

(.....)

วันที่.....

ลงนาม.....ผู้ดูแล

(.....)

วันที่.....

ลงนาม.....พยาน

(.....)

วันที่.....

ลงนาม.....พยาน

(.....)

วันที่.....

- **The Costing Questionnaire**

แบบสอบถามการเก็บข้อมูลต้นทุนและค่าอรรถประโยชน์
การเปรียบเทียบต้นทุนอรรถประโยชน์ของยาจิตเวช Olanzapine และ Risperidone ในการรักษาผู้ป่วยปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตในผู้ป่วยโรคสมองเสื่อมในประเทศไทย

ส่วนประกอบของแบบสอบถาม

แบบสอบถามชุดที่ 1 - แบบเก็บข้อมูลต้นทุน

ส่วนที่ 1 ข้อมูลทั่วไปของผู้ป่วย

ส่วนที่ 2 การประเมินต้นทุน

ส่วนที่ 3 ข้อมูลทั่วไปของผู้ดูแลสุขภาพ

แบบสอบถามชุดที่ 2 - แบบประเมินคุณภาพชีวิตของผู้ป่วย

แบบสอบถามนี้มีวัตถุประสงค์เพื่อ

ประเมินความคุ้มค่าของยาระงับอาการทางจิตได้แก่ ยาโอแลนซาปีน (olanzapine) และ ยาริสเพอริโดน (risperidone) ในการรักษาผู้ป่วยปัญหาพฤติกรรม อารมณ์ และความผิดปกติทางจิตในผู้ป่วยโรคสมองเสื่อม

ข้อมูลนี้ไม่มีการระบุชื่อและจะถูกเก็บไว้เป็นความลับ โดยมีวัตถุประสงค์สำหรับใช้ในการวิจัยเท่านั้น

แบบสอบถามชุดที่ 1

หมายเลขแบบสอบถาม ❑❑❑

ชื่อ-นามสกุล ผู้สัมภาษณ์ .....

วัน เดือน ปี ที่สัมภาษณ์ ❑❑ ❑❑ ❑❑

ส่วนที่ 1: ข้อมูลทั่วไปของผู้ป่วย

1. เพศ

❑ 1. ชาย ❑ 2. หญิง

2. อายุ.....ปี

3. สถานภาพ

❑ 1. โสด ❑ 2. แต่งงาน ❑ 3. หม้าย ❑ 4. หย่าร้าง/แยกกันอยู่

4. ศาสนา

❑ 1. พุทธ ❑ 2. อิสลาม ❑ 3. คริสต์ ❑ 4. ฮินดู ❑ 5. อื่นๆ (ระบุ).....

5. ระดับการศึกษา

❑ 1. ไม่ได้เรียนหนังสือหรือต่ำกว่าระดับประถมศึกษา ❑ 2. ประถมศึกษา

❑ 3. มัธยาศึกษาตอนต้น ❑ 4. มัธยมศึกษาตอนปลาย/ปวช.

❑ 5. อนุปริญญา/ ปวส. หรือเทียบเท่า ❑ 6. ปริญญาตรีหรือเทียบเท่า

❑ 7. สูงกว่าปริญญาตรี ❑ 8. อื่นๆ (ระบุ).....

6. สถานะการประกอบ**อาชีพในปัจจุบัน**

❑ 1. ไม่ได้ประกอบอาชีพ *(กรุณาข้ามไปทำแบบสอบถาม**ข้อ 8**)*

❑ 2. ประกอบอาชีพ รายได้เฉลี่ยต่อเดือน.....บาท

7. อาชีพหลักในปัจจุบัน

❑ 1. แม่บ้าน/พ่อบ้าน ❑ 2. ผู้ใช้แรงงาน/รับจ้างทั่วไป

❑ 3. เกษตรกรรม/ประมง ❑ 4. ค้าขาย/เจ้าของกิจการ

❑ 5. ข้าราชการ ❑ 6. พนักงานรัฐวิสาหกิจ

❑ 7. พนักงานบริษัทเอกชน ❑ 8. เกษียณ

❑ 9. อื่นๆ (ระบุ).....

8. การประกอบ**อาชีพในอดีต**

❑ 1. ไม่ได้ประกอบอาชีพ *(กรุณาข้ามไปทำแบบสอบถาม**ข้อ 10**)*

❑ 2. ประกอบอาชีพ รายได้เฉลี่ยต่อเดือน.....บาท

9. อาชีพในอดีต

❑ 1. แม่บ้าน/พ่อบ้าน ❑ 2. ผู้ใช้แรงงาน/รับจ้างทั่วไป

❑ 3. เกษตรกรรม/ประมง ❑ 4. ค้าขาย/เจ้าของกิจการ

❑ 5. ข้าราชการ ❑ 6. พนักงานรัฐวิสาหกิจ

❑ 7. พนักงานบริษัทเอกชน ❑ 8. เกษียณ

❑ 9. อื่นๆ (ระบุ).....

10. แหล่งรายได้หลักในปัจจุบัน (สามารถตอบได้มากกว่า 1 ข้อ)

❑ 1. จากการทำงาน (ระบุ).....บาท/เดือน

❑ 2. จากเงินบำเหน็จ/บำนาญ (ระบุ).....บาท/เดือน

❑ 3. จากเงินฝาก/ดอกเบี้ยธนาคาร (ระบุ).....บาท/เดือน

❑ 4. จากเงินทุนสำรองเลี้ยงชีพ (ระบุ).....บาท/เดือน

❑ 5. เงินสนับสนุนจากรัฐบาล (ระบุ).....บาท/เดือน

❑ 6. จากคู่สมรส (ระบุ).....บาท/เดือน

❑ 7. จากบุตร/หลาน (ระบุ).....บาท/เดือน

❑ 8. จากญาติ (ระบุ).....บาท/เดือน

❑ 9. อื่นๆ..... (ระบุ).....บาท/เดือน

11. ที่อยู่ปัจจุบันของท่านอยู่บริเวณใด

❑ 1. ในเขตกรุงเทพมหานคร ❑ 2. ในเขตปริมณฑล

❑ 3. ต่างจังหวัด (ระบุ).....

12. ประเภทของที่อยู่อาศัยในปัจจุบันของท่าน

❑ 1. บ้านเดี่ยว ❑ 2. ทาวน์เฮ้าส์/ บ้านแฝด

❑ 3. คอนโดมิเนียม/แฟลต/อพาร์ทเม้นต์ ❑ 4. ห้องแถว/ร้านขายของ

❑ 5. อื่นๆ (ระบุ).....

13. การครอบครองที่อยู่อาศัยในปัจจุบันของท่าน

❑ 1. เจ้าของบ้าน ❑ 2. เช่า ❑ 3. เช่าซื้อ

❑ 4. อยู่ในฐานะผู้อาศัย ❑ 5. อื่นๆ (ระบุ).....

14. สถานะของการอยู่อาศัย

❑ 1. อาศัยอยู่คนเดียว ❑ 2. อาศัยอยู่กับสามี/ภรรยา

❑ 3. อาศัยอยู่กับบุตร ❑ 4. อาศัยอยู่กับหลาน

❑ 5. อาศัยอยู่กับญาติ ❑ 6. อาศัยอยู่สถานสงเคราะห์

❑ 7. อื่นๆ (ระบุ).....

15. ระยะเวลาที่ท่านถูกวินิจฉัยด้วยภาวะสมองเสื่อม (ระบุ).....ปี

16. ค่า TMSE .....คะแนน

17. ระดับความรุนแรงของโรค

❑ 1. ระดับต้น ❑ 2. ระดับปานกลาง ❑ 3. ระดับรุนแรง

18. โรคประจำตัวอื่นๆ (เลือกได้มากกว่า 1 ข้อ)

❑ 1. ไม่มีโรคประจำตัว ❑ 2. โรคเก๊าต์ ❑ 3. โรคข้อเสื่อม

❑ 4. โรคหอบหืด ❑ 5. โรคถุงลมโป่งพอง ❑ 6. โรคไต

❑ 7. โรคความดันโลหิตสูง ❑ 8. โรคเบาหวาน ❑ 9. โรคไขมันในเลือดสูง

❑ 10. โรคสมองขาดเลือด ❑ 11. โรคมะเร็ง ❑ 12. อื่นๆ(ระบุ).....

19. ปัจจุบันท่านมีอาการใดบ้างดังต่อไปนี้ หลังจากที่ท่านได้รับยาจิตเวชเพื่อใช้ในการรักษา (เลือกได้มากกว่า 1 ข้อ)

❑ 1. ไม่มีอาการผิดปกติ ❑ 2. อาการมือสั่น ตัวเกร็ง คอแข็ง ❑ 3. หกล้ม

❑ 4. บวมตามมือ เท้า ❑ 5. น้ำหนักเพิ่ม ❑ 6. ติดเชื้อทางเดินปัสสาวะ

❑ 7. อาการง่วงซึม ❑ 8. อื่นๆ(ระบุ).....

ส่วนที่ 2: การประเมินต้นทุน

ต้นทุนผู้ป่วยนอก

20. สิทธิในการรักษาพยาบาล

❑ 1. ประกันสุขภาพถ้วนหน้า

❑ 2. ข้าราชการ/รัฐวิสาหกิจ/เทศบาล/ อบต.

❑ 3. ประกันสังคม

❑ 4. ประกันชีวิต/ประกันสุขภาพเอกชน (วงเงินสูงสุด.....บาท/เดือน)

❑ 5. ประกันสุขภาพโดยนายจ้าง

❑ 6. ชำระค่าใช้จ่ายเอง

❑ 7. อื่นๆ (ระบุ).....

21. ในช่วง 3 เดือนที่ผ่านมา ท่านมารับบริการที่โรงพยาบาล.....ครั้ง

22. เมื่อท่านเดินทางมารับบริการที่โรงพยาบาล ท่านมีค่าใช้จ่ายหรือไม่

❑ 1. ไม่มีค่าใช้จ่าย

❑ 2. มีค่าใช้จ่าย (โปรดระบุรายละเอียด)

รายการ	การมารับบริการครั้งที่ 1	การมารับบริการครั้งที่ 2	การมารับบริการครั้งที่ 3
ค่าเดินทาง (ไป-กลับ)			
ค่าอาหารที่ต้องจ่ายเพิ่มขึ้น			
ค่าที่พัก			
อื่นๆ.....			

23. ท่านมีค่าใช้จ่ายที่ต้องจ่าย**เพิ่มเติม**จากสิทธิการรักษาของท่านหรือไม่

❑ 1. ไม่มี

❑ 2. มี โดยเฉลี่ย .....บาท/ครั้ง

24. ท่านต้องมีญาติ/ผู้ดูแลพามารับการรักษาพยาบาลที่โรงพยาบาลหรือไม่

❑ 1. ไม่มี ❑ 2. มี (โปรดระบุรายละเอียด)

รายการ	การมารับบริการครั้งที่ 1	การมารับบริการครั้งที่ 2	การมารับบริการครั้งที่ 3
รายได้/ค่าจ้างที่ญาติ/ผู้ดูแลสูญเสีย			
ค่าเดินทาง (ไป-กลับ)			
ค่าอาหารที่ต้องจ่ายเพิ่มขึ้น			
ค่าที่พัก			
อื่นๆ.....			

25. ในช่วงเวลา 3 เดือนที่ผ่านมา นอกจากการรับการรักษาที่โรงพยาบาล ท่านได้ไปใช้บริการด้านสุขภาพที่สถานบริการสุขภาพอื่นๆหรือไม่

❑ 1. ไม่ได้ไป

❑ 2. ไป (โปรดระบุรายละเอียด)

ค่าใช้จ่าย (บาท)	โรงพยาบาลอื่นๆ						คลินิก						รพ.สต.						อื่นๆ					
	สมองเสื่อม			โรคอื่นๆ			สมองเสื่อม			โรคอื่นๆ			สมองเสื่อม			โรคอื่นๆ			สมองเสื่อม			โรคอื่นๆ		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
ค่าบริการทางการแพทย์																								
ค่ายา																								
ค่าตรวจวินิจฉัย (X-Ray, อัลตร้าซาวน์)																								

ค่าตรวจชันสูตร (เช่น ตรวจเลือด, ตรวจปัสสาวะ)																							
ค่าเดินทาง																							
ค่าอาหาร																							
ค่าอุปกรณ์ทางการแพทย์																							
อื่นๆ.....																							

26. ในช่วง 3 เดือนที่ผ่านมา ท่านได้ซื้อยา/ผลิตภัณฑ์เสริมอาหาร/อุปกรณ์ทางการแพทย์ เพื่อใช้ในการบรรเทา/รักษาอาการโรคสมองเสื่อมหรือไม่

❑ 1. ไม่ได้ซื้อ

❑ 2. ซื้อ (โปรดระบุรายละเอียด)

รายการ	ยา/ผลิตภัณฑ์เสริมอาหาร/อุปกรณ์ทางการแพทย์	ระยะเวลาในการใช้	ราคา (บาท)
1			
2			
3			
4			
5			

27. การช่วยเหลือตนเองในกิจวัตรประจำวันของท่าน ข้อใดตรงกับท่านมากที่สุด

กิจกรรม	ระดับ	หมายเหตุ
รับประทานอาหาร		
ล้างหน้า หวีผม โกนหนวด แปรงฟัน		
การเคลื่อนย้ายตัว/ลุกจากเตียง		
การใช้ห้องน้ำ		
การเคลื่อนที่ภายในบ้าน/ห้อง		
สวมใส่/ถอดเสื้อผ้า		
การขึ้น-ลงบันได		
การอาบน้ำ		
การกั้นอุจจาระ		
การกั้นปัสสาวะ		

28. ท่านมีผู้ดูแลในการทำกิจวัตรประจำวันของท่านหรือช่วยงานบ้านท่านหรือไม่

❑ 1. ไม่มี (*กรุณาข้ามไปทำแบบสอบถาม**ข้อ 30***)

❑ 2. มี

29. ท่านเสียค่าใช้จ่ายสำหรับจ้างผู้ดูแล โดยเฉลี่ย .....บาท/เดือน

ต้นทุนผู้ป่วยใน

30. ในช่วง 12 เดือนที่ผ่านมา ท่านได้นอนพักรักษาตัวที่โรงพยาบาลหรือไม่

❑ 1. ไม่ได้นอน *(กรุณาข้ามไปทำแบบสอบถาม**ข้อ 34**)*

❑ 2. นอน

31. ระยะเวลาในการนอนพักรักษาตัวที่โรงพยาบาลของท่าน โดยเฉลี่ย.....วัน/ครั้ง

32. ในระหว่างที่ท่านนอนพักรักษาตัวที่โรงพยาบาล ท่านมีญาติ/ผู้ดูแล ดูแลหรือไม่

❑ 1. ไม่มี

❑ 2. มี (โปรดระบุรายละเอียด)

รายการ	ผู้ดูแลคนที่ 1	ผู้ดูแลคนที่ 2	ผู้ดูแลคนที่ 3
เพศ			
ความสัมพันธ์กับท่าน			
ระยะเวลาญาติ/ผู้ดูแล ได้ดูแลท่าน (ชั่วโมง)			
ค่าเดินทาง (ไป-กลับ)			
ค่าอาหารที่ต้องจ่ายเพิ่มขึ้น			
ค่าที่พัก			
อื่นๆ			

33. การนอนพักรักษาตัวที่โรงพยาบาลของท่าน ท่านต้องเสียค่าใช้จ่ายในการรักษาพยาบาล**เพิ่มเติม**จากสิทธิในการรักษาพยาบาลของท่านหรือไม่

❑ 1. ไม่ใช่

❑ 2. ใช่ โดยเฉลี่ย .....บาท/ครั้ง

ผู้ดูแล

34. เพศ

❑ 1. ชาย ❑ 2. หญิง

35. อายุ.....ปี

36. สถานภาพ

❑ 1. โสด ❑ 2. แต่งงาน ❑ 3. หม้าย ❑ 4. หย่าร้าง/แยกกันอยู่

37. ศาสนา

❑ 1. พุทธ ❑ 2. อิสลาม ❑ 3. คริสต์ ❑ 4. ฮินดู ❑ 5. อื่นๆ (ระบุ).....

38. ระดับการศึกษา

❑ 1. ไม่ได้เรียนหนังสือหรือต่ำกว่าระดับประถมศึกษา ❑ 2. ประถมศึกษา

❑ 3. มัธยาศึกษาตอนต้น ❑ 4. มัธยมศึกษาตอนปลาย/ปวช.

❑ 5. อนุปริญญา/ ปวส. หรือเทียบเท่า ❑ 6. ปริญญาตรีหรือเทียบเท่า

❑ 7. สูงกว่าปริญญาตรี ❑ 8. อื่นๆ (ระบุ).....

39. สถานะการประกอบ**อาชีพในปัจจุบัน**

❑ 1. ไม่ได้ประกอบอาชีพ *(กรุณาข้ามไปทำแบบสอบถาม**ข้อ 41**)*

❑ 2. ประกอบอาชีพ (ระบุ) รายได้ต่อเดือน.....บาท

40. อาชีพหลักในปัจจุบัน

❑ 1. แม่บ้าน/พ่อบ้าน ❑ 2. ผู้ใช้แรงงาน/รับจ้างทั่วไป

❑ 3. เกษตรกรรม/ประมง ❑ 4. ค้าขาย/เจ้าของกิจการ

❑ 5. ข้าราชการ ❑ 6. พนักงานรัฐวิสาหกิจ

❑ 7. พนักงานบริษัทเอกชน ❑ 8. เกษียณ

❑ 9. อื่นๆ (ระบุ).....

41. การประกอบ**อาชีพในอดีต**

❑ 1. ไม่ได้ประกอบอาชีพ *(กรุณาข้ามไปทำแบบสอบถาม**ข้อ 43**)*

❑ 2. ประกอบอาชีพ รายได้เฉลี่ยต่อเดือน.....บาท

42. อาชีพในอดีต

❑ 1. แม่บ้าน/พ่อบ้าน ❑ 2. ผู้ใช้แรงงาน/รับจ้างทั่วไป

❑ 3. เกษตรกรรม/ประมง ❑ 4. ค้าขาย/เจ้าของกิจการ

❑ 5. ข้าราชการ ❑ 6. พนักงานรัฐวิสาหกิจ

❑ 7. พนักงานบริษัทเอกชน ❑ 8. เกษียณ

❑ 9. อื่นๆ (ระบุ).....

43. หากท่านว่างงาน ท่านหยุดทำงานเนื่องจากต้องดูแลผู้ป่วยใช่หรือไม่

❑ 1. ไม่ใช่ *(กรุณาข้ามไปทำแบบสอบถาม**ข้อ 45**)*

❑ 2. ใช่

44. ระยะเวลาที่ท่านหยุดการทำงานเพื่อมาดูแลผู้ป่วยจนถึงปัจจุบัน (ระบุ)..... เดือน

45. ความสัมพันธ์ของท่านกับผู้ป่วย

❑ 1. คู่สามี/ภรรยา ❑ 2. บุตรชาย ❑ 3. บุตรสาว

❑ 4. ญาติ/ลูกพี่ลูกน้อง ❑ 5. หลานชาย/หลานสาว ❑ 6. เพื่อน/เพื่อนบ้าน

❑ 7. พยาบาล/คนรับใช้ ❑ 8. อื่นๆ (ระบุ).....

46. ระยะเวลาที่ท่านดูแลผู้ป่วย (ระบุ).....ปี

47. ท่านใช้เวลาในการดูแลผู้ป่วย โดยเฉลี่ยต่อวัน (ระบุ).....ชั่วโมง

48. ท่านอาศัยอยู่กับผู้ป่วย

❑ 1. ไม่ใช่

❑ 2. ใช่

49. หากท่านต้องเดินทางมาดูแลผู้ป่วย ท่านมีค่าใช้จ่ายในการเดินทาง โดยเฉลี่ย.....บาท/วัน

50. ภาวะความเจ็บป่วยของผู้ป่วย ส่งผลกระทบต่อท่าน**ด้านกายภาพ**มากน้อยเพียงใด

❑ 1. น้อยมาก

❑ 2. น้อย

❑ 3. ปานกลาง

❑ 4. มาก

❑ 5. มากที่สุด

51. ภาวะความเจ็บป่วยของผู้ป่วย ส่งผลกระทบต่อท่าน**ด้านจิตใจ**มากน้อยเพียงใด

❑ 1. น้อยมาก

❑ 2. น้อย

❑ 3. ปานกลาง

❑ 4. มาก

❑ 5. มากที่สุด

52. ท่านมีปัญหาสุขภาพจากการดูแลผู้ป่วย

❑ 1. ไม่ใช่

❑ 2. ใช่

53. ปัญหาสุขภาพที่เกิดจากการดูแลผู้ป่วยของท่านได้แก่ข้อใด (ตอบได้มากกว่า 1 ข้อ)

❑ 1. ภาวะซึมเศร้า	❑ 2. ภาวะเครียด
❑ 3. คุณภาพของการนอนหลับพักผ่อน	❑ 4. ปัญหาระบบกระดูก-กล้ามเนื้อ
❑ 5. ภาวะทุกข์ใจ	❑ 6. อื่นๆ (ระบุ).....

• **The quality of life questionnaire: The European Quality of life Measure-5 Domains-5 Levels in Thai version (EQ-5D-5L)**

แบบสอบถามเรื่องสุขภาพ

ฉบับภาษาไทยสำหรับใช้ในประเทศไทย

(Thai version for Thailand)

ในแต่ละหัวข้อ กรุณาทำเครื่องหมาย ✓ ลงในช่องสี่เหลี่ยม **เพียงช่องเดียว** ที่ตรงกับสุขภาพของท่าน**ในวันนี้** มากที่สุด.

การเคลื่อนไหว

ข้าพเจ้าไม่มีปัญหาในการเดิน ❑

ข้าพเจ้ามีปัญหาในการเดินเล็กน้อย ❑

ข้าพเจ้ามีปัญหาในการเดินปานกลาง ❑

ข้าพเจ้ามีปัญหาในการเดินอย่างมาก ❑

ข้าพเจ้าเดินไม่ได้ ❑

การดูแลตนเอง

ข้าพเจ้าไม่มีปัญหาในการอาบน้ำ หรือใส่เสื้อผ้าด้วยตนเอง ❑

ข้าพเจ้ามีปัญหาในการอาบน้ำ หรือใส่เสื้อผ้าด้วยตนเองเล็กน้อย ❑

ข้าพเจ้ามีปัญหาในการอาบน้ำ หรือใส่เสื้อผ้าด้วยตนเองปานกลาง ❑

ข้าพเจ้ามีปัญหาในการอาบน้ำ หรือใส่เสื้อผ้าด้วยตนเองอย่างมาก ❑

ข้าพเจ้าอาบน้ำ หรือใส่เสื้อผ้าด้วยตนเองไม่ได้ ❑

กิจกรรมที่ทำเป็นประจำ (*เช่น ทำงาน, เรียนหนังสือ, ทำงานบ้าน, กิจกรรมในครอบครัว หรือกิจกรรมยามว่าง*)

ข้าพเจ้าไม่มีปัญหาในการทำกิจกรรมที่ทำเป็นประจำ ❑

ข้าพเจ้ามีปัญหาในการทำกิจกรรมที่ทำเป็นประจำเล็กน้อย ❑

ข้าพเจ้ามีปัญหาในการทำกิจกรรมที่ทำเป็นประจำปานกลาง ❑

ข้าพเจ้ามีปัญหาในการทำกิจกรรมที่ทำเป็นประจำอย่างมาก ❑

ข้าพเจ้าทำกิจกรรมที่ทำเป็นประจำไม่ได้ ❑

อาการเจ็บปวด / อาการไม่สบายตัว

ข้าพเจ้าไม่มีอาการเจ็บปวดหรืออาการไม่สบายตัว ❑

ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สบายตัวเล็กน้อย ❑

ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สบายตัวปานกลาง ❑

ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สบายตัวอย่างมาก ❑

ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สบายตัวอย่างมากที่สุด ❑

ความวิตกกังวล / ความซึมเศร้า

ข้าพเจ้าไม่รู้สึกวิตกกังวลหรือซึมเศร้า ❑

ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้าเล็กน้อย ❑

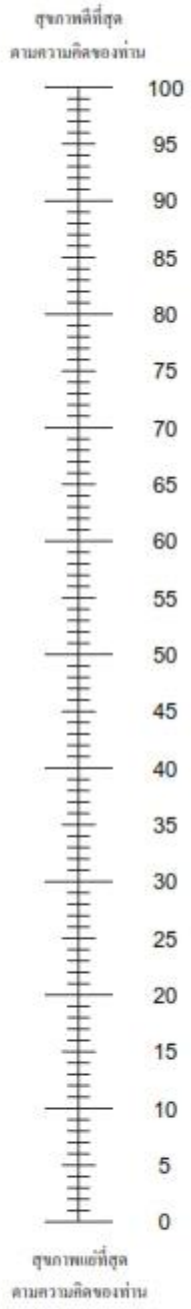
ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้าปานกลาง ❑

ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้าอย่างมาก ❑

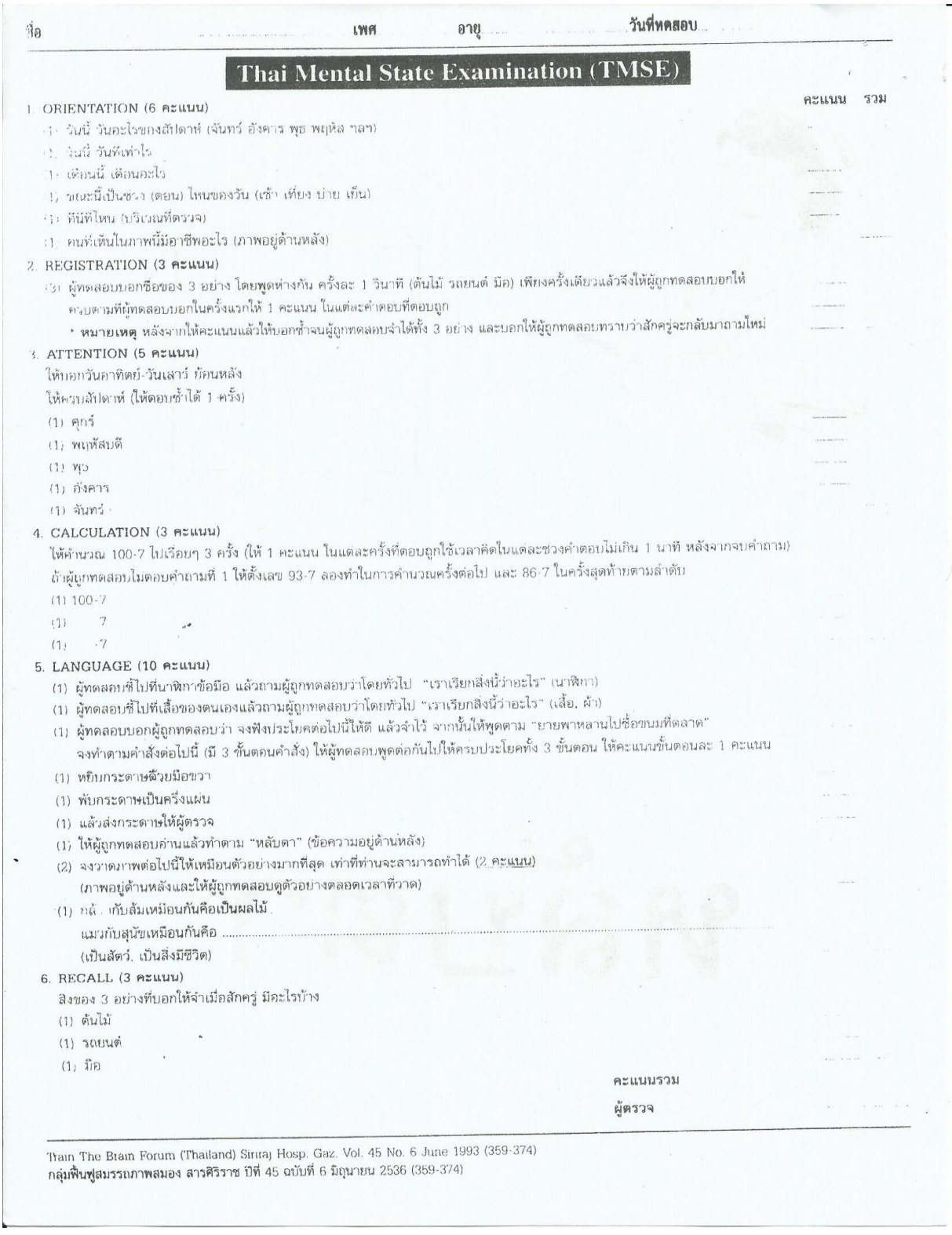
ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้าอย่างมากที่สุด ❑

- เราอยากทราบว่าสุขภาพของท่านเป็นอย่างไร**ในวันนี้**.
- สเกลวัดสุขภาพนี้มีตัวเลขตั้งแต่ 0 ถึง 100.
- 100 หมายถึง สุขภาพ<u>ดีที่สุด</u> ตามความคิดของท่าน.
  0 หมายถึง สุขภาพ<u>แย่ที่สุด</u> ตามความคิดของท่าน.
- ทำเครื่องหมาย **X** บนสเกลเพื่อระบุว่าสุขภาพของท่านเป็นอย่างไร**ในวันนี้**.
- ตอนนี้ กรุณาใส่ตัวเลขที่คุณได้ทำเครื่องหมายไว้บนสเกลในช่องสี่เหลี่ยมด้านล่างนี้.

สุขภาพของท่านในวันนี้ = ☐



Appendix 5: Thai Mental State Examination (TMSE)

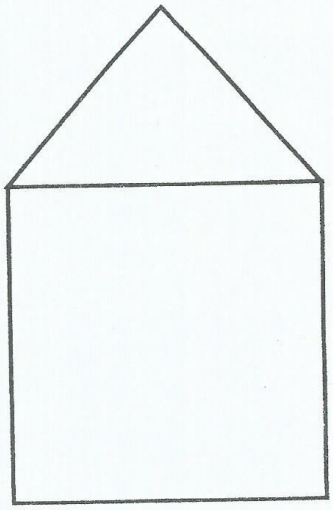


ชื่อ ..... เพศ ..... อายุ ..... วันที่ทดสอบ .....

Thai Mental State Examination (TMSE)

	คะแนน	รวม
1. ORIENTATION (6 คะแนน)		
(1) วันนี้ วันอะไรของสัปดาห์ (จันทร์ อังคาร พุธ พฤหัส ฯลฯ)		
(1) วันนี้ วันที่เท่าไร		
(1) เดือนนี้ เดือนอะไร		
(1) ขณะนี้เป็นช่วง (ตอน) ไหนของวัน (เช้า เที่ยง บ่าย เย็น)		
(1) ที่นี่ที่ไหน (บริเวณที่ตรวจ)		
(1) คนที่เห็นในภาพนี้มีอาชีพอะไร (ภาพอยู่ด้านหลัง)		
2. REGISTRATION (3 คะแนน)		
(3) ผู้ทดสอบบอกชื่อของ 3 อย่าง โดยพูดห่างกัน ครั้งละ 1 วินาที (ต้นไม้ รถยนต์ มือ) เพียงครั้งเดียวแล้วจึงให้ผู้ถูกทดสอบบอกให้ ครบตามที่ผู้ทดสอบบอกในครั้งแรกให้ 1 คะแนน ในแต่ละคำตอบที่ตอบถูก		
* **หมายเหตุ** หลังจากให้คะแนนแล้วให้บอกซ้ำจนผู้ถูกทดสอบจำได้ทั้ง 3 อย่าง และบอกให้ผู้ถูกทดสอบทราบว่าสักครู่จะกลับมาถามใหม่		
3. ATTENTION (5 คะแนน)		
ให้บอกวันอาทิตย์-วันเสาร์ ย้อนหลัง		
ให้ครบสัปดาห์ (ให้ตอบซ้ำได้ 1 ครั้ง)		
(1) ศุกร์		
(1) พฤหัสบดี		
(1) พุธ		
(1) อังคาร		
(1) จันทร์		
4. CALCULATION (3 คะแนน)		
ให้คำนวณ 100-7 ไปเรื่อยๆ 3 ครั้ง (ให้ 1 คะแนน ในแต่ละครั้งที่ตอบถูกใช้เวลาคิดในแต่ละช่วงคำตอบไม่เกิน 1 นาที หลังจากจบคำถาม)		
ถ้าผู้ถูกทดสอบไม่ตอบคำถามที่ 1 ให้ตั้งเลข 93-7 ลองทำในการคำนวณครั้งต่อไป และ 86-7 ในครั้งสุดท้ายตามลำดับ		
(1) 100-7		
(1) 7		
(1) -7		
5. LANGUAGE (10 คะแนน)		
(1) ผู้ทดสอบชี้ไปที่นาฬิกาข้อมือ แล้วถามผู้ถูกทดสอบว่าโดยทั่วไป "เราเรียกสิ่งนี้ว่าอะไร" (นาฬิกา)		
(1) ผู้ทดสอบชี้ไปที่เสื้อของตนเองแล้วถามผู้ถูกทดสอบว่าโดยทั่วไป "เราเรียกสิ่งนี้ว่าอะไร" (เสื้อ, ผ้า)		
(1) ผู้ทดสอบบอกผู้ถูกทดสอบว่า จงฟังประโยคต่อไปนี้ให้ดี แล้วจำไว้ จากนั้นให้พูดตาม "ยายพาหลานไปซื้อขนมที่ตลาด" จงทำตามคำสั่งต่อไปนี้ (มี 3 ขั้นตอนคำสั่ง) ให้ผู้ทดสอบพูดต่อกันไปให้ครบประโยคทั้ง 3 ขั้นตอน ให้คะแนนขั้นตอนละ 1 คะแนน		
(1) หยิบกระดาษด้วยมือขวา		
(1) พับกระดาษเป็นครึ่งแผ่น		
(1) แล้วส่งกระดาษให้ผู้ตรวจ		
(1) ให้ผู้ถูกทดสอบอ่านแล้วทำตาม "หลับตา" (ข้อความอยู่ด้านหลัง)		
(2) จงวาดภาพต่อไปนี้ให้เหมือนตัวอย่างมากที่สุด เท่าที่ท่านจะสามารถทำได้ (2 คะแนน) (ภาพอยู่ด้านหลังและให้ผู้ถูกทดสอบดูตัวอย่างตลอดเวลาที่วาด)		
(1) กล้วย เกี่ยวกับส้มเหมือนกันคือเป็นผลไม้		
แมวกับสุนัขเหมือนกันคือ		
(เป็นสัตว์, เป็นสิ่งมีชีวิต)		
6. RECALL (3 คะแนน)		
สิ่งของ 3 อย่างที่บอกให้จำเมื่อสักครู่ มีอะไรบ้าง		
(1) ต้นไม้		
(1) รถยนต์		
(1) มือ		
คะแนนรวม		
ผู้ตรวจ		

Thai The Brain Forum (Thailand) Siriraj Hosp. Gaz. Vol. 45 No. 6 June 1993 (359-374)
กลุ่มฟื้นฟูสมรรถภาพสมอง สารศิริราช ปีที่ 45 ฉบับที่ 6 มิถุนายน 2536 (359-374)



หลับตา

Appendix 6: An additional assessment associated with the improvement of olanzapine or risperidone for patients with behavioural and psychological symptoms of dementia after measuring using EQ-5D-5L at month 5 or 6

Patient	Treatment with risperidone	Treatment with olanzapine
1	Off risperidone	Loss to follow up
2	2	3
3	Loss to follow up	4
4	3	2
5	Off risperidone	Death
6	Off risperidone	3
7	2	4
8	5	Off olanzapine
9	Off risperidone	4
10	4	Off olanzapine
11	Off risperidone	4
12	Death	Loss to follow up
13	4	4
14	3	4
15	Off risperidone	3
16	4	4
17	3	Off olanzapine
18	Off risperidone	4
19	2	5
20	Off risperidone	4
21	4	4
22	Loss to follow up	4
23	3	Off olanzapine
24	2	4

Patient	Treatment with risperidone	Treatment with olanzapine
25	Off risperidone	4
26	3	4
27	3	Off olanzapine
28	3	4
29	4	Off olanzapine
30	4	4
31	Off risperidone	4
32	5	2
33	3	Off olanzapine
34	4	4
35	Off risperidone	3
36	3	Off olanzapine
37	1	3
38	3	Off olanzapine
39	Loss to follow up	4
40	4	3
41	2	3

* Levels of the improvement: 1 = not at all improved, 2 = slightly improved, 3 = moderately improved, 4 = much improved and 5 = extremely improved

After measuring using EQ-5D-5L after at least five months to six months, an additional assessment was conducted associated with the improvement of patients with BPSD and being treated with either olanzapine and risperidone, based on asking those patients or their caregivers, by face-to-face interviews or telephone interviews, are presented as follows:

A total of 41 patients with BPSD were using risperidone for their treatment. From these patients, 11 patients had stopped taking the risperidone drug. In addition, there were three patients of this group who were lost to follow-up in that time of assessment and a patient

unfortunately for their family died. The remaining 26 risperidone-treated patients rated the improvement on average at level 3, (moderately improved).

For the group being treated with olanzapine there were also a total of 41 patients. Nine patients stopped the olanzapine treatment. Furthermore, two patients were lost to follow up for their appointments and unfortunately again one patient died in this group. A total of 29 patients appraised the improvement based on the olanzapine treatment associated with level 4, (much improved).

Appendix 7: Publication

SMGroup

Neurological Disorders and Stroke

Review Article

Efficacy and Cost of Atypical Antipsychotics in Treatment and Management of Dementia

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Introduction

The current population is living longer than ever before as a result of improved health care services; therefore, the size of the ageing population is increasing [1]. Dementia is emerging as one of the main conditions affecting the elderly population. According to the WHO report, in 2010, there were approximately 35.6 million people suffering from dementia worldwide. This figure continues to rise, doubling approximately every 20 years and it is estimated that this will soon rise to 65.7 million by 2030, and further to 115.4 million by 2050. Current incidence shows an individual is diagnosed with dementia every four seconds. This has substantial socioeconomic and financial implications on people globally and the societal costs associated with disease were estimated at US$ 605 billion in 2010 [2].

Alzheimer's Disease (AD) is the most common of dementia, closely followed by nonspecific degenerative dementia, whereas vascular dementia, dementia from Parkinson's disease and mixed dementia are observed less frequently [3]. Dementia has various impacts on the individual including a progressive loss of memory and deterioration in cognitive and behavioural functions [4]. Behavioural and psychological symptoms of dementia (BPSD) are commonly seen as the illness progresses. The disorder can be organized into four main groups: mood disorders, sleep disorders, psychotic symptoms and agitation [5]. Approximately 50-90% of people with dementia experience at least one symptom of behavioural disturbances at any one point [4,8-9]. Hence, this disorder has shown a significant impact on the quality of life of these individuals, their families and caregivers [10].

Both non-pharmacological and pharmacological interventions are used for the management of BPSD. In general, the non-pharmacological approach is recommended as the first-line intervention. The pharmacological approach should be initiated when the non-pharmacological approaches are unsuccessful; however, integrated interventions are advised for better management of dementia [11]. The management of patients with BPSD is quite complex and the most common pharmacological agents used include: antipsychotics, antidepressants, mood stabilizers, benzodiazepines and cognitive enhancers [1,11-12]. However, antipsychotic drugs are prescribed more frequently for BPSD as compared to other drug classes [1].

In 2005, U.S. Food and Drug Administration (US-FDA) launched an awareness campaign in regard to the adverse effects of Atypical Antipsychotics[1] (AAs) for the elderly BPSD population due to a 1.7% increase in the incidence of all-cause mortality risk [13]. Three years later, the FDA extended the warning to also include typical antipsychotics[2] [14]. Consequently, the trend of prescribing antipsychotics dropped from 2.3% in 2003 to 1.8% in 2011; however, the rate of prescribing AAs is reversing with an escalation from 0.37% to 0.64% [15]. Although there is controversial evidence in their effectiveness and safety, AAs are routinely prescribed for BPSD treatment [16].

Currently, there are no definitive treatments approved by the US-FDA for people with BPSD [5]. In addition, the treatment guidelines for BPSD remain controversial. Physicians have widely prescribed both typical and atypical antipsychotics drugs as the first-line interventions. Despite the high costs, AAs are more likely to be used for the treatment of BPSD, relative to typical drugs due to the increased efficacy and reduced side effect which includes preventing Extra Pyramidal Symptoms (EPS) in the geriatric population [1,4].

In clinical practice, the physicians have a variety of drug prescriptions and care plans in place for patients with BPSD. As a result, it is extremely important to determine the cost-effectiveness of AAs for use in BPSD as it not only affects the quality of life of patients and caregivers but also places additional burden on the health care system. Identifying which drug or combination of drugs is "most cost-effective" will indicate the most appropriate intervention and provide useful information on treatment plans for patients, caregivers, relatives and physicians. Also, the optimal treatment

OPEN ACCESS

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Figure 1: Projected Number of People with Dementia Worldwide, 2010-2050 [22].

pathway should prevent any severe impact on the quality of life of both patients and caregivers. The aim of this study is to explore and review the cost and effectiveness of using atypical antipsychotics in BPSD. Therefore it is pertinent that future research integrates pharmacological, epidemiological and health economic evaluation techniques in order to find most cost-effective treatment of BPSD for dementia patients.

Progression of Dementia

Dementia is a progressive brain disease associated with impairments in normal brain functioning. This includes cognitive, personality, and intellectual dysfunctions. It affects memory, thinking, language, learning ability, calculation, comprehension, judgment, and orientation. Thus, deterioration of the brain in this way can have a significant impact on people living with the condition, as well as on the society as a whole [2,17-19]. Alzheimer's Disease (AD) is the most common type of dementia, accounting for 50-70% of cases. Vascular Dementia (VaD), Dementia With Lewy Bodies (DLB), and Front Temporal Dementia (FTD) are also paramount categories of the disorder accounting for 20%, 10% and 2% of cases, respectively [9,17-18]. According to the World Health Organization, dementia can be classified into three stages: (i) the early stage (first or second year of the condition); (ii) the middle stage (second to fourth or fifth year with condition); and finally (iii) the late stage (fifth year and beyond) [2].

Behavioural and Psychological Symptoms of Dementia (BPSD)

Behavioural and psychological symptoms are commonly observed in the disease. These include neuropsychiatric and non-cognitive symptoms as well as behavioural disturbances [9,20]. Diagnosis of BPSD has no specific approach; therefore, clinical magnitude is more subjective than objective in patients with dementia. The clinical symptoms of BPSD present themselves as: agitation, apathy, anxiety, depression, delusion, hallucination, disinhibition, aberrant motor behavior, elation, irritability, and sleep and appetite changes [9,20-21]. BPSD tends to be more prevalent in the late stages of dementia. This results in distress among caregivers and patients, long term hospitalization, drug abuse, and other healthcare costs [21]. This alongside the decline in patients' and caregivers' quality of life makes BPSD a complex condition to manage.

Prevalence and Economic Impact of Dementia

Dementia is a worldwide problem resulting from the rapid increase in size of the over 60 population which is estimated to reach 2 billion by 2050 [2]. It is predicted that nearly 7% (135 million) of this population will be diagnosed with dementia by 2050 (Figure 1) [22]. This will have significant social and economic impacts worldwide. There are three different types of costs associated with dementia care, namely informal care, direct social costs, and direct medical costs (Figure 2) and their proportion tends to vary according to the size and wealth of the country. In high income countries, the cost of informal care (provided by unpaid family members and friends) and direct social care both exceeded more than 40% of the total costs whereas, the direct medical cost was far less. Conversely, in lower-middle and low income countries there were significant greater costs related to informal care but not of direct social care. This shows that the burden of dementia management and care components impact on different socio-economic costs across the world including informal care wages and health and social care delivery costs.

Management of Behavioural and Psychological Symptoms of Dementia

People with dementia may experience BPSD at any point during its progression. This is associated with poorer health and quality of life outcomes for both patients and caregivers. As previously highlighted, the guidelines for the management of BPSD include both non-pharmacological and pharmacological approaches.

Non-Pharmacological Approach

The non-pharmacological approach is recommended as a first-line management for BPSD [9,11-12,23-25]. Treatment for behavioural disorders is administered after symptoms are reported. The most common approaches are environmental design, music therapy, light therapy, and educating caregivers on behavioural disturbances [9,23]. These also include the stimulation/activities and simple tasks for apathy [26-27]. Furthermore, Fujii et al. suggested that behavioural and psychological symptoms of caregivers (BPSC) which generally occurs as a result of BPSD in patients can impact on the relationship and emotions of the patient [28].

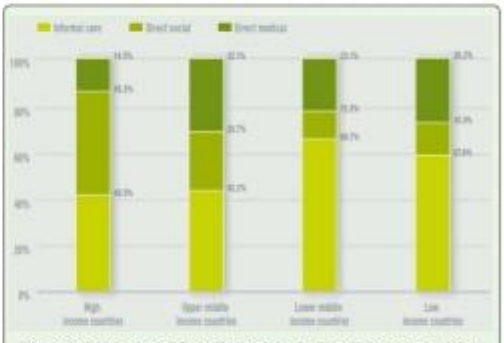

Figure 2: Distribution of Total Societal Costs (%) of Dementia by World Bank Income level [2].

Pharmacological Approach

Implementation of pharmacological methods is necessary when non-pharmacological interventions are unsuccessful or when there is no response to the BPSD treatment [9,23]. There are several classes of drugs that have been utilized for the management of BPSD. The categories are listed below:

Anticonvulsants

There are studies associated with the use of Carbamazepine, sodium valproate, and gabapentin for the treatment of behavioural symptoms related to patients with dementia. However, evidence shows that treatment with valproate was ineffective in managing BPSD [23,29]. Carbamazepine revealed short- term effectiveness for agitated behaviour [23,30]. Although gabapentin alone and combined with psychotropic drugs showed efficacy for the BPSD treatment, however further research is required [23,31-32]. On the basis of current data, anticonvulsant drugs are not recommended for the treatment of BPSD associated with dementia [23,33].

Cholinesterase Inhibitors (ChEIs)

At present, there is evidence accounting for the benefits of ChEIs. Rodda et al. [34] showed that despite limitation of effectiveness data, ChEIs can be used for BPSD in Alzheimer's disease [35]. The US-FDA has approved donepezil, galantamine, and rivastigmine for treatment of symptoms of Alzheimer's disease; however, the recommendations of ChEIs are inconsistent in guidelines [11]. If behavioural symptoms still persist during ChEIs use, alternative drug classes may be considered as therapeutic options [24].

Antidepressants

Symptoms of depression are common in patients with dementia. Selective Serotonin Reuptake Inhibitors (SSRI) was observed for efficacy on depression [36]. Citalopram and sertraline had commensurate efficacy on agitated behaviour relative to risperidone or haloperidol. However, the guidelines around administration of antidepressants for behavioural disturbances are controversial, except when there is a co morbidity of depression [11,23,37].

Memantine or NMDA (N-Methyl-D-Aspartate)

The NMDA receptor antagonist (memantine) is currently the US-FDA approved drug for treatment of moderate to severe stages of Alzheimer's disease [37]. Nevertheless, the recommendation for BPSD is disputed in guidelines. The SIGN guideline highlighted that there is insufficient evidence for using memantine for the management of patients with BPSD [23]. In contrast, the NICE guidelines recommended memantine for non-cognitive symptoms in moderate and severe stages and discourage use of ChEIs and antipsychotics [35].

Antipsychotics

Antipsychotics are divided into two classes: typical and atypical. There are consistent guidelines for introducing antipsychotics for treatment of patients with BPSD, in particular for symptoms such as agitation, aggression, and psychosis [11,35]. Due to the adverse side effects, the NSW guidelines do not recommend conventional antipsychotics as a first-line drug [9]. Atypical antipsychotic drugs are commonly prescribed for BPSD rather than typical antipsychotics. Drouillard, Mitanni and Chan noted that atypical antipsychotics were useful for managing BPSD related to agitation and aggression [38]. However, patients should be investigated prior to administration of these medications. Aripiprazole, olanzapine, and risperidone showed statistically significant effects for psychosis, agitation, and global behavioural symptoms in dementia [39]. And thus, Tampi et al. recommended that risperidone, aripiprazole and olanzapine should be considered as the first-line treatment [12].

The management of BPSD should integrate both non-pharmacological treatments and pharmacological treatments. Non-pharmacological approaches should be introduced as initial strategies. When non-pharmacological interventions show no effect, starting medication is considered appropriate. Atypical antipsychotics are considered to be beneficial as first-line drugs for the treatment of psychotic disorders in elderly people with dementia as they improve symptoms without causing adverse effects. However, the use of these drugs is controversial due to issues around drug safety and because the goal of pharmacological therapy is to reduce problematic disorders than merely eliminate symptoms. The concept of antipsychotic drugs is to "start slow, go slow". Thus, caregivers should be encouraged to take part in the decision-making process in patient care. Also, physicians should scrutinize the risks *vs.* benefits of pharmacological treatments to patients and their prescription should be considered on a case by case basis.

Efficacy and Cost-effectiveness of Atypical Antipsychotic Drugs for Dementia

The database search for the efficacy of atypical antipsychotic (risperidone, olanzapine, quetiapine and aripiprazole) drugs for dementia retrieved 2190 articles from MEDLINE, PsycINFO, and the Cochrane Library. Of these, 1075 articles were retrieved from MEDLINE, 754 articles retrieved from PsycINFO and 361 articles from the Cochrane Library. The titles were screened for inclusion and exclusion criteria. 2063 articles were excluded from the study due to their title. The remaining 127 articles were identified for further scrutiny. A further 81 articles were excluded after screening their abstracts. From the remaining 46 articles a further 26 were excluded due to duplication. 20 articles remained to undergo the next step (screening for full paper). Six articles were excluded due to not meeting the inclusion criteria. Another paper was excluded due to lack of access to the full-text.

Inclusion criteria were:

1) Participants: people with dementia, people with behavioural and psychological symptoms of dementia;
2) Interventions: atypical antipsychotic, risperidone, olanzapine, quetiapine and aripiprazole for treatment of dementia, Alzheimer's disease, behavioural and psychological symptoms of dementia and neuropsychiatric symptoms;
3) Study designs: randomized controlled trial, placebo controlled, double-blind, parallel-group trials comparing drugs with placebo; and
4) Outcomes: Behavioural Pathology in Alzheimer's disease Rating Scale (BEHAVE-AD), Clinical Global Impression

(CGI) scale, Neuropsychiatric Inventory (NPI), Cohen-Mansfield Agitation Inventory (CMAI), Brief Psychiatric Rating Scale (BPRS), Severe Impairment Battery (SIB), time for initial treatment to the discontinuation, and Mini-Mental State Examination (MMSE).

A further search for the cost-effectiveness of atypical antipsychotics from electronic databases was conducted in MEDLINE, the Centre for Reviews and Dissemination (CRD) (containing the National Health System Economic Database (NHS EED), the Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment database) were searched. A total of 37 articles were retrieved. The titles were screened for inclusion and exclusion criteria. After screening the titles, 27 articles were excluded. A further seven articles were excluded after screening the abstracts, whilst another one was excluded as it was not in an English format which left two articles to be included in the study.

Inclusion criteria were:

1) Population: people with dementia, people with Alzheimer's disease;

2) Interventions: risperidone, risperdal, olanzapine, zyprexa, aripiprazole, abilify, quetiapine, and seroquel;

3) Study designs: comparison in terms of cost, and cost and health outcome, costs; and

4) Outcomes: QALYs, monetary costs, health benefits, health outcomes.

A systematic literature search identified only 13 clinical trial studies (with comparators) to demonstrate clinical effectiveness of atypical antipsychotics treatment of dementia with respect to risperidone, olanzapine, aripiprazole or quetiapine [40-52]. The results showed that the adverse events may offset efficacy associated with atypical antipsychotics for the treatment of BPSD. The serious side effects in senile dementia accounted for cerebrovascular events, extra pyramidal symptom, falls, somnolence, sedation, disinhibition, depression, incontinence, Parkinsonism, weight gain, orthostatic hypotension, dyskinesia and cognitive function impairment [46,53].

A cost-effectiveness of atypical antipsychotics retrieved only two quality studies [54-55]. Kirbach et al. focused on olanzapine for agitation and psychosis in Alzheimer's disease, based on the Markov state-transition model to estimate the cost-effective treatment. The results showed that olanzapine was cost-effective compared with an untreated group, for agitation and psychosis in AD in a community dwelling in the United States, using the US health system perspective [54]. However, the limitation of this study was that the cost variables entered into the model were derived from other studies and health utilities were deduced from schizophrenia studies. Rosenheck et al. used the cost-benefit analysis in a randomized controlled trial of second-generation antipsychotics and placebo for treating psychosis, agitation, or aggression in AD with a 9 months follow-up period. The findings demonstrated that risperidone, olanzapine and quetiapine showed no differences in effectiveness compared to the placebo, in a community dwelling in the United States [55].

Discussion

Despite the US-FDA warning in 2005 in relation to using atypical antipsychotics for dementia due to increased incidence in cerebrovascular mortality of approximately 1.5 -1.7 times greater, the trend of prescribing atypical antipsychotic for patients with dementia has not receded. Atypical antipsychotics are significantly prescribed for the treatment of BPSD [56-57]. Recently, evidence showed that second-generation antipsychotic drugs had modest efficacy for the treatment of behavioural and psychological symptoms, namely agitation, aggression, psychosis, depression, anxiety. However, due to the limited and conflicting evidence for efficacy of atypical antipsychotic drugs their use for management of BPSD in patients with dementia is debatable.

Although atypical antipsychotics can be debated on the ground on effectiveness and adverse events, these drugs have been widely used for the treatment behavioural disturbance related to geriatric dementia [58]. This is because the severity of behavioural disturbance worsens as the disease progresses. This has potential impacts on morbidity, caregiver's general health, the burden of care, patients' and caregivers' distress, risk of harm to patients and caregivers, and costs of treatment. Consequently, it is important to weigh the risks and benefits when making judgments regarding the treatment and cost of behavioural problems in people with dementia. The pharmacological approaches are important and these are recommended when non-pharmacological methods fail. Despite the modest efficacy in the reduction of behavioural symptoms, the potential improvement of the condition has a considerable impact on the quality of life of patients and caregivers.

There is a significant lack of pharmacoeconomic research on using atypical antipsychotics for the treatment of dementia. Further comprehensive research should be carried out into this field. We have found a good number of studies exploring the effectiveness and cost-effectiveness of atypical antipsychotics for schizophrenia using a decision-analytical model. However, there were only a couple of studies which have focused on the use of AAs for dementia and that too with several limitations. Therefore, it is pertinent to undertake further systematic and comprehensive research on the safety and efficacy of atypical antipsychotics for the management of BPSD. This is essential in improving clinical practice and suggesting better pathways for dementia treatment as well as in mitigating the adverse impacts on the quality of life of patients and their caregivers.

[1]Atypical antipsychotics are also called second-generation antipsychotics, or narcoleptic drugs such as clozapine, amisulpride, aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, and risperidone.

[2]Typical antipsychotics are also known as conventional, classical or first-generation antipsychotics such as chlorpromazine, haloperidol, flupentixol, prochlorperazine, sulpiride and trifluoperazine.

(https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency)

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