COST-UTILITY ANALYSIS OF CHOLINESTERASE INHIBITORS IN THE TREATMENT OF MILD TO MODERATE ALZHEIMER'S DISEASE

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**A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF SCIENCE IN PHARMACY
(PHARMACY ADMINISTRATION)
FACULTY OF GRADUATE STUDIES
MAHIDOL UNIVERSITY
2008**

Thesis
Entitled

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COST-UTILITY ANALYSIS OF CHOLINESTERASE INHIBITORS IN THE TREATMENT OF MILD TO MODERATE ALZHEIMER'S DISEASES

was submitted to the Faculty of Graduate Studies, Mahidol University
for the Degree of Master of Science in Pharmacy
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ACKNOWLEDGEMENTS

This study would have not been accomplished without through all generous help of many people. First, I would like to acknowledge with very special thanks and appreciation to my major advisor, Assistant Professor Usa Chaikledkaew, for her valuable guidance, supervision, kindness, and encouragement always. I also would like to sincerely thank and greatly appreciate to Dr. Yot Teerawattananon, my co-advisor, for his invaluable advice, suggestion and he always pointed me to the right direction to explore economic evaluation. My grateful appreciation is expressed to Dr Sirintorn Chansirikarnchana, my co-advisor, who suggested the fruitful ideas and willingly answered all of my questions throughout this study. Without her support, this study would have not been possible. I would like to thank Dr. Nantika Thavichachart and all experts for their suggestions and helpful comments and discussion.

My special appreciation is extended to Mrs. Naiyana Praditsitthikorn and Ms. Yupin Tamteeranon, who devoted their time to advice, assisted and patiently answered my questions. Moreover, I would like to thank all staffs at Health Intervention and Technology Assessment Program (HITAP) who provided the administrative and facilities of this work. I am very grateful for all of caregivers who were interviewed or who participated in discussion groups especially Ms. Yindee Phoolvitayakit for their time and information.

I am also indebted to BMA Medical College & Vajira Hospital for giving me a good opportunity for studying the Master degree. In addition, my special thank is extended to all of professors, staffs and my friends at Pharmacy Administration program, Mahidol University, for their helpfulness and encouragement me along with my project. Finally, I would like to sincerely thank my parents and my beloved family for their endless love, always supports and encourages me throughout the study.

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ABSTRACT

The purposes of this study were (i) to evaluate the cost-utility of cholinesterase inhibitors (i.e. donepezil, rivastigmine and galantamine) relative to no drug treatment in patients with mild to moderate Alzheimer's disease (AD), based on the governmental and societal perspectives, and (ii) to estimate the budget impact when providing the cost-effective treatment for mild to moderate AD.

A pharmacoeconomic model was used to simulate disease progression, predict and compare lifetime costs and health outcomes of drug treatment options versus no drug treatment. The Assessment of Health Economics in Alzheimer's Disease (AHEAD) model was used and input parameters were obtained by a systematic review of the literature on the clinical and cost-effectiveness of cholinesterase inhibitors. The costs associated with AD were obtained from the Thai setting and were determined in 2008 Thai (baht). The results were presented as an incremental cost effectiveness ratio (ICER) of the drug treatment options versus no drug treatment. Both costs and health outcomes were discounted at 3%. Probabilistic sensitivity analysis was used to assess uncertainty in main parameter inputs.

Based on the governmental and societal perspectives, at the 'willingness to pay' (WTP) of 300,000 baht per QALY gained in Thailand, galantamine might be cost-effective interventions for all scenarios compared with other drugs and the no treatment option. The ICER of galantamine was 229,367 and 157,247 baht per QALY gained using the governmental and societal perspectives, respectively. Moreover, when providing galantamine for the patients with the ADAS-cog score ranging from 17 to 30, EPS, or psychotic symptoms associated with AD, it was more cost-effective compared with the base case scenario. Furthermore, the additional budgets required for providing galantamine at the first year were 12,740 million baht for all patients with mild to moderate AD. In addition, the most important part of caring for AD patient is not only the drug treatment but also the relationship between patients and caregivers including a health care system that supports and helps provide the best long term care of AD patients.

KEY WORDS : COST-UTILITY ANALYSIS / ALZHEIMER'S DISEASE/ PRE FULL TIME CARE/ FULL TIME CAR / CHOLINESTERASE INHIBITORS

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การประเมินต้นทุน-อรรถประโยชน์ของการใช้ยากลุ่ม Cholinesterase inhibitors ในการรักษาโรคอัลไซเมอร์ระดับรุนแรงน้อยถึงปานกลาง
(COST-UTILITY ANALYSIS OF CHOLINESTERASE INHIBITORS IN THE TREATMENT OF MILD TO MODERATE ALZHEIMER'S DISEASE)

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บทคัดย่อ

วัตถุประสงค์ของการศึกษาเพื่อประเมินต้นทุนอรรถประโยชน์ของยาในกลุ่ม cholinesterase inhibitors ได้แก่ donepezil rivastigmine และ galantamine เปรียบเทียบกับการไม่ใช้ยา ในการรักษาโรคอัลไซเมอร์ระดับรุนแรงน้อยถึงปานกลาง ในมุมมองของรัฐบาลและมุมมองทางสังคม และประเมินผลกระทบด้านงบประมาณหากมีการใช้ยากลุ่มนี้ในการรักษาผู้ป่วยโรคอัลไซเมอร์ระดับรุนแรงน้อยถึงปานกลาง

การศึกษานี้ใช้แบบจำลองทางเศรษฐศาสตร์ที่สร้างขึ้นเพื่อทำนายการดำเนินของโรค เพื่อคำนวณต้นทุนและผลลัพธ์ทางสุขภาพหรืออรรถประโยชน์ ของการใช้ยาเปรียบเทียบกับการไม่ใช้ยารักษาแบบจำลองและตัวแปรที่ใช้ในแบบจำลองได้จากการทบทวนวรรณกรรมทางด้านประสิทธิผลทางคลินิกและต้นทุนประสิทธิผลอย่างเป็นระบบ ส่วนข้อมูลต้นทุนวิเคราะห์จากสถานพยาบาลในประเทศไทย และวิเคราะห์ความไวด้วยวิธี probabilistic sensitivity analysis เพื่อลดความคลาดเคลื่อนของตัวแปรที่นำมาใช้

พบว่า หากความเต็มใจจ่ายของรัฐบาลและสังคมเท่ากับ 3 เท่าของรายได้ต่อหัวประชาชาติหรือ 300,000บาท ต่อปีสุขภาวะที่ยืนยาวขึ้น(QALY gained) การรักษาด้วยยา galantamine มีความคุ้มค่าที่สุดในกลุ่มนี้และคุ้มค่าเมื่อรักษาในทุกสภาวะ เมื่อเปรียบเทียบกับการไม่ใช้ยา ต้นทุนอรรถประโยชน์ของการรักษาด้วยยา galantamine คิดเป็น 229,367 และ 157,247 บาทต่อปีสุขภาวะที่ยืนยาวขึ้น ในมุมมองของรัฐ และมุมมองของสังคม นอกจากนั้นพบว่า ผู้ป่วยอัลไซเมอร์ที่มีคะแนน ADAS-cog 17 ถึง 30 หรือผู้ที่มีอาการทางจิตประสาท หรือผู้ที่มีอาการทาง extra pyramidal symptom เป็นสภาวะที่ควรให้การรักษาเป็นอันดับแรกเนื่องจากมีความคุ้มค่ามากที่สุด หากพิจารณาภาระด้านงบประมาณหากมีการใช้ยากลุ่มนี้ในการรักษาผู้ป่วยโรคอัลไซเมอร์ระดับรุนแรงน้อยถึงปานกลาง พบว่ามีมูลค่า 12,740 ล้านบาทในปีแรก นอกจากนั้นคุณภาพของการดูแลผู้ป่วยและผู้ดูแล รวมถึงการให้การสนับสนุนและให้การช่วยเหลือจากภาครัฐ ถือว่าเป็นสิ่งที่สำคัญที่ช่วยให้การรักษาผู้ป่วยอัลไซเมอร์ได้ดียิ่งขึ้น

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LIST OF ABBREVIATIONS

AChEI	=	Acetylcholinesterase inhibitor
ADAS-cog	=	Alzheimer's Disease Assessment Scale-cognitive subscale
ADL	=	Activities of Daily Living
AHEAD	=	Assessment of Health Economics in Alzheimer's disease
CDR	=	Clinical Dementia Rating Scale
CBA	=	Cost benefit analysis
CEA	=	Cost effectiveness analysis
CGIC	=	Clinical Global Impression of Change
CIBIC	=	Clinician's Interview-based Impression of Change
CI	=	Confidence interval
CMA	=	Cost minimization analysis
CT	=	Computed tomography
CUA	=	Cost utility analysis
DALYs	=	Disability-Adjusted Life Years
EPS	=	Extrapyramidal symptoms
FTC	=	full-time care
GDP	=	Gross Domestic Product
GDS	=	Global Deterioration Scale
HUI	=	Health Utilities Index
IADL	=	Instrumental Activities of Daily Living
ICD-10	=	International Classification of Disease
ICER	=	Incremental cost effectiveness ratio
mMMSE	=	modified MMSE
MMSE	=	mini-mental state examination
MRI	=	magnetic resonance imaging

LIST OF ABBREVIATIONS (cont.)

NICE	=	National Institute for Health and Clinical Excellence
NINCDS- ADRDA	=	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NMDA	=	*N*-methyl-D-aspartate
NPI	=	Neuropsychiatric Inventory
OR	=	odds ratio
PDS	=	Progressive Deterioration Scale
PGA	=	Patient Global Assessment Scale
PSS	=	Personal Social Services
QALYs	=	Quality-Adjusted Life-Years
QoL	=	Quality of Life
RCT	=	Randomized controlled trial
RR	=	Relative risk
SD	=	standard deviation
SHTAC	=	Southampton Health Technology Assessment Centre
UK	=	United Kingdom
US	=	United States
VAD	=	vascular dementia
WTP	=	Willingness to pay
WHO	=	World Health Organization

CHAPTER I
INTRODUCTION

Thailand is currently experiencing the most rapid rate of ageing population in the developing world and will soon become an aging society that there is about to face a silent epidemic of dementia. Dementia is a collective name for progressive degenerative brain syndrome which describes a loss of memory, intellect, rationality, social skills and normal emotional reactions (1). These symptoms are not normal parts of ageing, but they are sufficient to interfere with normal social functioning, quality of life and ultimately lead to death.

While the risk of dementia increases with age, most individuals with the illness are 65 years and older (2). Today the global prevalence of dementia is estimated to be 24.3 million, with 4.6 million new cases of dementia every year(1). In Thailand there are currently 229,000 people with dementia. In next 20 years, the number will be increased to 450,000, and next 50 years it will reach one million (3).

According to the global burden of disease from the 2003 World Health Report(4), dementia contributed 11.2% of years lived with disability among people aged 60 years and older, which was more than stroke (9.5%), musculoskeletal disorders (8.9%), cardiovascular disease (5,0%), and all forms of cancer (2.4%). The disability weight for dementia was estimated by an international and multidisciplinary expert consensus. Moreover, life extension foundation(2002) (5) estimated that in addition to heart disease, cancer and stroke, Alzheimer's disease (AD) was the fourth leading cause of death in developed nations among the population aged 65 years and over.

The economic burden associated with AD reflects the progressive nature of this disease and the cost of caring for patients increases substantially as they become less able to care for themselves (6). The cost of caring for patients with dementia was estimated to be more than double compared to that of caring for patients who were not demented (7-9). AD is the most common cause of dementia and the second most

common form is vascular dementia, which may be preventable. Health professionals often divide the symptoms of AD into cognitive and behavioral and psychiatric categories. The U.S. Food and Drug Administration (FDA) has approved two types of medications to treat cognitive symptoms of AD (2). The first type was cholinesterase inhibitors which were approved to treat mild to moderate AD, and the second type was memantine which was approved in 2003 for the treatment of moderate to severe AD. The benefit of each drug treatment is to improve or maintain cognitive status and functional abilities, reduce behavioral disturbances, improve the quality of life for people with dementia and caregivers and delay in the nursing home placement or institutionalization (2, 3, 10).

Because of the rise in cost of caring for patients with AD and the availability of expensive of medications to treat AD (i.e., cholinesterase inhibitors), together with the limited budget in health care, the cost-utility analysis of cholinesterase inhibitors in the treatment of mild to moderate AD may help policy maker in determining whether these drugs should be included on the National List of Essential Drugs (NLED).

Objectives

1. To estimate the cost-utility analysis of the cholinesterase inhibitors (i.e., donepezil, galantamine and rivastigmine) compared with no drug treatment in patients with mild to moderate AD in Thailand based on the societal and government perspectives.

2. To estimate the budget impact of the cholinesterase inhibitors when including these drugs on the NLED for prescribing to the mild to moderate AD patients with different age group.

Expected outcomes and Benefits

This study will provide the information about the cost-utility of the cholinesterase inhibitors in the treatment of mild to moderate AD based on the perspectives of government and society and the adoption of qualitative methods within clinical research on drug treatment of AD would acknowledge that AD is not a simple biological process characterized by cognitive and functional decline, but also a socially constructed experience negotiated and interpreted by those with the disease and their caregivers. The expected outcomes and benefits from this study are

1. The cost-utility analysis of cholinesterase inhibitors can be used to provide the information for policy makers or healthcare providers to determine which treatment or whether treatment should be given to mild to moderate AD patients.

2. The results from this study can be used as the information to help make decision whether the treatment of AD should be included on the National List of Essential Drugs.

Definition of terms

Pre-FTC health state

Pre-FTC health state is the state that the patients are assumed to live at home or in a residence where does not provide extensive care(11).

FTC health state

FTC health state is the state that the patients have a requirement for a significant amount (for the greater part of the day) of paid care and supervision each day, regardless of the location of care (i.e., institution or community setting), or who provides the care(11).

The characteristic of patients living in households who required full-time care were defined as fulfilling one or more of the following criteria(12):

1. Patients needed help getting into or out of bed or chair, or getting to or using the toilet, or losing control of the bladder or bowels at least once per day or severely mentally disturbed.
2. Patients were considered severely mentally disturbed if they exhibited behavioral problems such as inappropriate, antisocial, violent, or risky behavior.

Primary caregiver

Primary caregiver is the caregiver who is the main career and provides the most hours of care for patients with AD.

Informal care

Informal care is to provide care by family members, friends, or neighbors of patients without financially compensation (13, 14).

Incremental cost

Incremental cost is the added cost with the alternative.

Incremental effectiveness

Incremental effectiveness is the added effectiveness with the alternative.

Incremental cost-effectiveness ratio (ICER)

Incremental cost-effectiveness ratio (ICER) is the ratio that the alternatives are compared on the basis of the increments in costs and effectiveness**,** calculated by incremental cost divided by incremental effectiveness. The lower value of this ratio is higher priority of the intervention in terms of maximized the benefit achieved from a given expenditure.

$$ICER = \frac{Cost_{\text{drug treatment}} - Cost_{\text{no drug treatment}}}{QALY_{\text{drug treatment}} - QALY_{\text{no drug treatment}}}$$

CHAPTER II
LITERATURE REVIEW

This chapter is divided into three parts as follows:

Part I The description of dementia including classification, risk factor, diagnosis, burden of disease, epidemiology, pharmacological and non-pharmacological interventions for AD, assessment of effectiveness of cholinesterase inhibitors and outcome measurement scales and clinical effectiveness of cholinesterase inhibitors.

Part II Economic evaluation (EE) in health care.

Part III Cost-effectiveness analysis of cholinesterase inhibitors for treatment AD .

Part IV Qualitative research and research into dementia.

Part I The description of dementia

1. Dementia is a collective name for progressive degenerative brain syndromes which describes a loss of memory, intellect, rationality, social skills and normal emotional reactions(1). These symptoms are sufficient to interfere with normal social functioning, quality of life and ultimately lead to death and there are not a normal part of aging. AD is the most common types of dementia and is characterized by an insidious onset and slow deterioration in cognition, functional ability (e.g., activities of daily living , behavior and mood). Changes in one or more of these domains and their effects on the patients and their careers' well-being provide the basis for diagnosis, assessing severity and progression of the syndrome(2) .

2. Classification of dementia

World Health Organization (WHO) classifies types of dementia according to ICD-10(15)

- AD
- Vascular dementia
    - Multi-infarct dementia
    - Subcortical vascular dementia
- Dementia due to other general medical conditions
    - Pick's disease
    - Huntington's disease
    - Parkinson's disease
    - Human immunodeficiency virus (HIV) disease
- Unspecified Dementia

3. Risk factors of Alzheimer's disease

AD is thought to be caused by many interacting factors(2, 16).

- **Age**: The greatest known risk factor for AD is increasing age. Most individuals with the illness are 65 and older. The likelihood of developing AD approximately doubles every five years after age 65. After age 85, the risk reaches nearly 50%.
- **Family history**: Another risk factor is family history. Most research has shown that those who have a parent, brother or sister with AD are two to three times more likely to develop the disease. The risk increases if more than one family members have the illness.
- **Genetics**: The E4 allele of the APOE gene has been confirmed to increase the risk of developing AD.
- **Other potential risk factors** are hypertension, vascular pathology, head injury and herpes simplex infection.

4. The clinical diagnostic criteria for AD (17)

The National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) NINCDS-ADRDA provides clinical guidance for 'possible', 'probable' and 'definite' diagnosis of AD. A diagnosis of possible AD is made when no other disease appears to be primarily responsible for the dementia or when the onset of symptoms is not

typical of AD. A diagnosis of probable AD requires a patient to have dementia and a history and pattern of symptoms consistent with those generally seen in AD. Definite AD is diagnosed when evidence is shown through brain biopsy or at autopsy. The sensitivity and specificity of the 0.13 and 0.80, respectively, compared with pathological diagnosis(18).

4.1 The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)

Diagnosis is also often made according to the DSM criteria. The DSM criteria include loss of intellectual ability, with resulting social and occupational handicap, memory impairment at all levels of encoding, storage and retrieval, one or more of impaired thinking and judgment, and aphasia, apraxia, agnosia, constructional difficulties and personality changes. The DSM-IV is based on clinical judgment. It is reasonably broad and lack of detailed clinical and radiological guidelines.

4.2 The International Classification of Diseases (ICD-10)

The ICD-10 requires the presence of a dementia with characteristic neuropathological and neurochemical features, insidious onset with slow deterioration and an absence of clinical evidence to suggest that the mental state may be due to other systemic or brain disease which can induce a dementia. It defines two subtypes: early onset (dementia in AD beginning before the age of 65 years with relatively rapid deterioration and marked multiple disorders of the higher cortical functions) and late onset (clinically observable onset after the age of 65 years and usually in the late 70s or thereafter, with a slow progression, and usually with memory impairment as the principal feature).

Other diagnosis of AD is on the basis of a review of a full medical history corroborated by a close relative or career. Evaluating mood and mental status, physical examination, blood investigations and neurological examination, studying the brain's structure with magnetic resonance imaging (MRI) or computed tomography (CT) may also include. MRIs and CT can reveal tumors and evidence of small or large strokes, damage from severe head trauma or a buildup of fluid (2).

5. Burden of disease

Burden of disease is a concept relating to loss of health, the original global burden of disease used the disability adjusted life years (DALYs) to quantify the burden of disease. One DALY represents the loss of one year of equivalent full health. DALYs for a disease are the sum of the years of life lost due to premature mortality in the population and the years of healthy life lost due to disability(3). Dementia contributes 11.2% of years lived with disability in people aged 60 years and over, which was more than stroke (9.5%), musculoskeletal disorders (8.9%), cardiovascular disease (5.0%) and all forms of cancer (2.4%). The disability weight for dementia, estimated by international and multidisciplinary expert consensus, was higher than for almost any other health condition, apart from spinal-cord injury and terminal cancer (4).

Mortality: The dementia specific mortality rate is twice the rate of people without dementia, controlling for co-morbidities and socio-demographic factors. Seventy percent of people over 75 with dementia died within five years(3). The average life expectancy for patients with AD, from onset of disease, is around of 7 to 10 years(19). Life extension foundation (2002) estimated that in addition to heart disease, cancer and stroke, AD was the fourth leading cause of death in developed nations(5) .

Morbidity: Morbid effects of dementia can depend on type and include gradual memory loss, decline in ability to perform routine tasks, disorientation to time and place, impaired judgment, abstract thinking and physical coordination, difficulty in learning and concentration, loss of language and communication skills, changes in personality, behavior and mood. The prevalence of neuropsychiatric symptoms that commonly accompany AD is agitation (60% to 70%), apathy (60% to 70%), depression (50%), anxiety (50%), irritability (50%), delusional disorders and psychosis (40% to 50%), disinhibition (30%) or hallucinations (10%). The symptoms and behaviors of dementia, as well as the decreased functionality in activities of daily living (ADL), can be physically and emotionally difficult for families and care givers to manage (1).

Thai National Burden of Disease study in 1999 found that dementia was the fifth leading cause of DALYs lost in female and was the ninth leading cause of DALYs lost in male patients aged 60 years and over **(Table 1)** (20).

Table 1 Disability Adjusted Life Years (DALYs) of disease in people age ≥ 60 years ,Thailand 1999 (20).

Male			Female		
Rank	**Disease**	**DALYs (x100,000)**	**Rank**	**Disease**	**DALYs (x100,000)**
1	Stroke	1.50	1	Stroke	1.95
2	COPD	1.06	2	Diabetes	1.34
3	Liver cancer	0.90	3	Cataracts	0.74
4	IHD	0.75	4	IHD	0.72
5	Diabetes	0.66	5	Dementia	0.66
6	Lung cancer	0.51	6	Liver cancer	0.59
7	Cataracts	0.42	7	COPD	0.55
8	Tuberculosis	0.38	8	Osteoarthritis	0.42
9	Dementia	0.34	9	Tuberculosis	0.34
10	Osteoarthritis	0.31	10	Nephritis	0.31

6. Epidemiology of Alzheimer's disease

In 2005 The Asia-Pacific Working Group on Dementia estimated that 13.7 million people in this region suffered from dementia. The number of people with dementia will reach 64.6 million in next 50 years. The number of people with dementia in Thailand is 229,000 and it will reach 450,000 in next 20 years, and by 2050 it will exceed one million **(Table 2)** (3).

Table 2 Prevalence and Incidence, Alzheimer's Disease International (ADI) Asia Pacific and Non-ADI Asia Pacific(3) .

	2005		2020		2050	
'000 people	**Prevalence**	**Incidence**	**Prevalence**	**Incidence**	**Prevalence**	**Incidence**
Australia	195.4	60.2	301.3	91.1	664.1	199.7
China (inc Macao)	5,541.2	1,721	9,596.3	2,916.7	27,004.4	8,269
Hong Kong SAR	59.7	18.5	109.2	32.6	332	99.6
India	3,248.5	1,026.8	5,541.8	1,714.4	16,290.1	4,974.6
Indonesia	606.1	191.4	1,016.8	314.1	3,042	932
Japan	1,871.2	570.2	3,251.3	983.4	4,873.1	1,417.1
Malaysia	63	20.1	126.8	39	453.9	138.8
New Zeland	38.2	11.8	54.6	16.6	117.6	35.5
Pakistan	330.1	107.3	566.6	179.3	1,916.2	584.3
Philippines	169.8	54.8	316.3	99.2	1,158.9	353.9
Singapore	22	6.8	52.6	15.7	186.9	56.7
South Korea	246.3	75.5	542.2	164.3	1,569.9	475.4
Sri Lanka	86	26.9	148	45.1	409	125
TADA Chinese Taipei	138	43.1	253.4	76.6	659.3	199.4
Thailand	229.1	71.4	450.2	137.2	1,233.2	377
Total region	**13,703.6**	**4,282.1**	**23,727.1**	**7,262.3**	**64,641.5**	**19,687.3**

Based on the report of the Nation wide study, investigating the prevalence of dementia in four major regions covering 23 provinces and 37,157 cases by using mini-mental state examination (MMSE-Thai 2002) in 2003, it was found that the prevalence of older peoples with dementia was 11.4% of the elderly people's age ≥60 years. The prevalence was higher in women (13.9%) than men (8%) and the mean of age was 68.67 and 68.81 in women and men, respectively **(Table 3)** (21).

Table 3 The prevalence of older people with dementia and mean of age in Thai elderly age ≥60 years sorted by a region in 2003.

Region	Prevalence (%)	Mean age (yrs)
North	11.8	68.39
Northeast	15.6	69.15
Central	9.4	68.91
South	10.6	68.73

Table 4 The prevalence of older people with dementia in Thai elderly age ≥60 years sorted by age group in 2000 (21)

Age (years)	Elderly with dementia	Elderly peoples	% Elderly with dementia
60-64 year	674	11,781	5.72
65-69 year	864	10,595	8.15
70-74 year	957	7,884	12.13
75-79 year	719	4,051	17.75
80-84 year	575	1,873	30.70
≥ 85 year	439	973	45.12
Total	**4,228**	**37,157**	**11.38**

The prevalence from this study reported that the older the age, the higher the prevalence. The percentage of elderly with dementia in people aged ≥ 80 year group (41.44%) was much higher than that in people age 60-69 year age group (8.85%). Although dementia can occur at any age, it is rare to have dementia below the age of 60 years **(Table4).**

7. Pharmacological and Non- Pharmacological Intervention for AD

7.1 Non-pharmacological

– Waking exercises

– Maintain basic Activities of Daily Living (ADL)

– Try to preserve instrumental & social functions

7.2 Pharmacological(2)

– Cholinesterase inhibitors: donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl)

– Glutamate blocking drug: NMDA receptor antagonist: memantine (Eblixa)

– Others : tranquilizers, antidepressants, antipsychotics, multivitamins

Health professionals often divide the symptoms of AD into cognitive and behavioral and psychiatric categories.

- Cognitive symptoms affect memory, language, judgment, planning, ability to pay attention and other thought processes.

- Behavioral and psychiatric symptoms affect the way we feel and act.

Medication treatment for cognitive symptoms of AD

The U.S. Food and Drug Administration (FDA) has approved two types of medications to treat cognitive symptoms of AD. These drugs affect the activity of two different chemicals involved in carrying messages between the brain's nerve cells.

1. Cholinesterase inhibitors prevent the breakdown of acetylcholine, a chemical messenger important for learning and memory. These drugs are support communication among nerve cells by keeping acetylcholine levels high. Three drugs of cholinesterase inhibitors are approved to treat mild to moderate AD

Three cholinesterase inhibitors are commonly prescribed:

- Donepezil (Aricept), approved in 1996
- Rivastigmine (Exelon), approved in 2000
- Galantamine (Razadyne), approved in 2001

2. Memantine (Namenda) works by regulating the activity of glutamate, a different messenger chemical involved in learning and memory. Memantine was approved in 2003 for treatment of moderate to severe AD. It is currently the only drug of its type approved to treat AD**(Table 5)**

Table 5 Medication treatment of AD .

Drug name	Drug type and treatment	Manufacturer's recommended dosage
Eblixa® (memantine) Blocks the toxic effects associated with excess glutamate and regulates glutamate activation.	N-methyl D-aspartate (NMDA) antagonist prescribed to treat symptoms of moderate to severe AD.	5 mg, once a day, available in tablet form. Increase to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day) at minimum of one week intervals if well tolerated.
Reminyl® (galantamine) Prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain .	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate AD.	4mg, twice a day (8mg/day, available in tablet or capsule form Increase by 8mg/day after 4 weeks to 8mg, twice a day (16mg/day) if well tolerated. After another 4 weeks, increase to 12mg, twice a day (24mg/day) if well tolerated.
Exelon® (rivastigmine) Prevents the breakdown of acetylcholine and butyrylcholine (a brain chemical similar to acetylcholine) in the brain .	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate AD	1.5mg, twice a day (3mg/day, available in capsule and liquid form Increase by 3mg/day every 2 weeks to 6mg, twice a day (12mg/day) if well tolerated.

Drug name	Drug type and treatment	Manufacturer's recommended dosage
Aricept® (donepezil) Prevents the breakdown of acetylcholine in the brain .	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate, and moderate to severe AD.	5mg, once a day, available in tablet form Increase after 4-6 weeks to 10mg, once a day if well tolerated.

Table 6 Cost of Cholinesterase inhibitors (23) .

Cholinesterase inhibitors	Price (baht/tablet)
Donepezil film-coat tablet 5 mg.	121.98
Donepezil film-coat tablet 10 mg.	166.92
Rivastigmine cap 1.5 mg.	69.55
Rivastigmine cap 3 mg.	69.55
Rivastigmine cap 4.5 mg.	69.55
Rivastigmine cap 6 mg.	69.55
Galantamine tab 4 mg.	42.80
Galantamine tab 8 mg.	64.96

Goals of treatment (2, 3, 10)

1. Improving or maintaining cognitive status and functional abilities.

2. Reducing behavioral disturbances.

3. Improving the quality of life for people with dementia and care givers.

4. Delaying in the nursing home placement or in the institutionalization of a person with dementia .

8. Assessment of effectiveness of Cholinesterase inhibitors and Outcome measurement scales (17) .

Global outcomes: It can be measured by

- Clinician's Interview-based Impression of Change (CIBIC): examines overall improvement in patient health status assessed by clinician (–with caregiver) 1 (very much improved) – 7 (very much worse).

- Clinical Dementia Rating (CDR): examines cognitive impairment in memory, orientation, judgment/problem-solving, community affairs, home/hobbies, and personal care 0 = none, 0.5 = questionable, 1 = mild, 2 = moderate, 3 = severe.

- Global Deterioration Scale GDS): examines progressive stages of cognitive impairment 1 (no cognitive decline) – 7 (very severe cognitive decline).

Functional/QoL outcomes: It can be measured by

- Progressive Deterioration Scale (PDS): examines activities of daily living and instrumental activities of daily living with distance along the line on a scale from 0 to 100, with higher scores reflecting better functionality.

Behavior and mood outcome: It can be measured by

- Neuro-psychiatric Inventory (NPI): evaluates 12 items: delusions, hallucinations, dysphoria, anxiety, agitation, euphoria, apathy, irritability, disinhibition, aberrant motor behavior, night-time behavior and changes in appetite/eating behavior. Total score for each domain is calculated by multiplying frequency rating by severity rating, adding domain scores to get a total score. Higher scores represent more problems. Maximum scores is 12 per domain.

Cognitive Outcome: It can be measured by

- AD Assessment Scale –cognitive subscale (ADAS-cog): examines orientation, memory, language and praxis 0–70, with higher scores indicating greater impairment.

- Mini-mental state examination (MMSE): examines 11 questions on orientation, memory, concentration, language and praxis. Scale ranges from 0 to 30. Higher score indicates less impairment. Although there is no range of scores that can be rigidly and universally applied to indicate dementia severity, mild AD is often associated with an MMSE of 21–26, moderate AD with an MMSE of 10–20 and severe AD with an MMSE of <10.

In Thailand, the Mini-Mental State Examination-Thai version (MMSE-Thai) is used to measure cognition outcome. This method has been translated from MMSE
The cut-of point is set to be diagnosed patients with dementia according to the MMSE-Thai, cut-off point was as follows(22).

- Score ≤ 14 from 23 points in the elderly persons who can't read and write (uneducated).

- Score ≤17 from 30 points in the elderly persons who have studied primary school education.

- Score ≤ 22 from 30 points in the elderly persons who have studied higher than primary school education.

9. Clinical effectiveness of cholinesterase inhibitors

These data are from Southampton Health Technology Assessments Centre, finding from a systematic review of the clinical effectiveness literature of donepezil, rivastigmine and galantamine for mild to moderate AD. The results demonstrated that all three drugs produced similar improvements on cognitive and global outcome measures. Mixed results were demonstrated on functional outcome measures and on measures of behavior and mood. A total of twenty-three published randomized placebo-controlled trials were include in the review as follows thirteen for donepezil (5-10mg daily; trial length 12–60weeks)(24-36); four for rivastigmine (variable dose trial length 13–26 weeks)(37-40); and six for galantamine (8–36mg daily over 12–26 weeks)(41-46) see Appendix.

Part II Economic evaluation (EE) in health care

Economic evaluation is defined as a comparative analysis of alternatives in terms of both their costs and outcomes. The cost component is always measured in monetary unit, while the outcome component can be measured in various ways. Based on different outcome measurements, the full economic evaluation is divided into four types of analysis. There are cost-benefit analysis (CBA), cost-minimization analysis (CMA), cost-utility Analysis (CUA), and cost-effectiveness analysis (CEA)(47) .

1. **Cost-Benefit Analysis (CBA)** compares costs and consequences of two or more alternatives that have different outcomes. Costs and outcomes are measured in monetary unit. The benefit from a program and all the costs of providing a program are identified and converted into equivalent dollars in the year in which they occur. The objective of cost-benefit analysis is to find the alternative with the most favorable cost- to-benefit ratio. The limitation of cost-benefit analysis is valuation of outcome in monetary units. Many outcomes such as years of life saved or quality of life, are difficult to value in monetary terms.

2. **Cost-Minimization Analysis (CMA)** compares costs of two or more alternatives that have equivalent outcomes. The outcomes of the alternatives are assumed to be equal, only costs of each alternative have been estimated. Cost-minimization analysis shows only cost savings of one program or treatment over another.

3. **Cost-Utility Analysis (CUA)** is similar to cost-effectiveness analysis, except the outcomes are measured in terms of patient preference of quality of health care outcome. Cost-utility analysis is most useful in evaluating health programs that extend life but with serious side effects such as cancer chemotherapy or arthritis are not recommended.

4. **Cost-Effectiveness Analysis (CEA)** is the tool that is used to address the limitations of cost-benefit analysis by using physical or natural units as outcome measures. Cost-effectiveness analysis compares costs and consequences of alternatives that achieve the objective at the least cost. When treatment alternatives are not therapeutically equivalent, or when it is inappropriate to express benefits (outcome) in monetary units, cost-effectiveness analysis may provide a more appropriate evaluation

technique. Cost-effectiveness analysis is one of the tools that is used to evaluate treatment alternatives. For drug therapy, these alternatives may be different drugs or comparison between drug treatment and non drug treatment. Cost-effectiveness analysis involves assessing the cost and consequences of pharmaceutical products and services, with non-equivalent therapeutic outcome. After the costs and effectiveness of the alternatives are obtained, two approaches have been used to compare them in CEA:

1) Cost-effectiveness ratio approach: the alternatives are compared on the basis of the average cost per unit of effectiveness (sometimes, average effectiveness per unit cost). Generally, the most cost-effective alternative has the lowest average cost per unit of effectiveness.

2) Incremental cost-effectiveness ratio (ICER) approach: the alternatives are compared on the basis of the increments in costs and effectiveness.

Normally, lower ICER is preferable because it implies less incremental cost for a unit of effectiveness. The ICER indicates the additional costs that an alternative has over another as compared to the additional effectiveness.

Incremental cost effectiveness ratio (ICER) is calculated by incremental cost divided by incremental effectiveness

$$\text{ICER} = \frac{\text{Cost}_{\text{drug treatment}} - \text{Cost}_{\text{no drug treatment}}}{\text{QALY}_{\text{drug treatment}} - \text{QALY}_{\text{no drug treatment}}}$$

Part III Cost-effectiveness analysis of cholinesterase inhibitors for the treatment of AD

A Systematic review of the literature on the cost-effectiveness of cholinesterase inhibitors for the treatment of AD from electronic Medline database. Seventeen published randomized controlled trials (RCTs) were included (i.e., 8 RCTs of donepezil, 4 of rivastigmine, 5 of galantamine, and 3 of memantine). The summary of each drug is as follows. see Appendix.

1. The cost-effectiveness of donepezil included 8 published RCTs studies.

- Most economic evaluations of donepezil (five out of the eight published studies) (48-52) have used a state transition model (Markov model) to estimate the cost-effectiveness of donepezil compared with no drug treatment. see Appendix
- Three studies used MMSE scores to define either four or five levels of AD severity (48, 50, 51) and one studies used CDR scores to define three levels of disease severity.
- Three studies used cost-effectiveness analysis (48, 50, 51), whereas three studies used CUA(49, 52, 53) and two studies used cost analysis (54, 55).
- The main outcome measures were years saved by preventing patients from entering the next, more severe stage of AD or delay in disease progression. It was used to calculate the total cost savings associated with treatment according to disease severity and/or QALYs gains.
- Three studies (49-51)found that donepezil was more cost-effective than a non-drug treatment strategy, and two studies(54, 55) concluded that donepezil was cost neutral, and three studies (48, 52, 53) found that donepezil use was associated with additional costs.
- O'Brien et al (51) estimated that cost savings per year in non-severe AD state over 5 years of donepezil treatment would equal to Can $4,410 per patient. A European study by Jonsson et al(50) predicted cost savings per year in non-severe AD state over 5 years of SKr 29,925 per patient for donepezil 5 mg and SKr 6,344 per patient for donepezil 10 mg. The CUA by Lanctot et al (49) predicted cost savings of Can 24,219 per patient over 12.5 years.

2. The cost-effectiveness of rivastigmine included 4 published RCTs studies.

- Three of four studies (56-58) used a hazard model to examine disease progression in their estimation of the cost-effectiveness of rivastigmine. (hazard model was developed by Fenn and Gray(56)). see Appendix.

Three studies (56-58) used MMSE scores to define either three or four stages of disease severity.

- Three studies (56-58) reported the cost-effectiveness of rivastigmine. One studies (59) estimated the cost-utility by using simple calculation.

- Three studies (56-58) measured the main outcome as the days saved by preventing patients from entering the next, more severe stage of AD or delay in disease progression. It was used to calculate the total cost savings associated with treatment according to disease severity. One studies(59) measured the cost per QALY base on drug costs only.

- Three studies(56-58) found that rivastigmine was more cost-effective than a no-drug treatment strategy and one study(59) found that rivastigmine use was associated with additional costs.

- Three studies (56-58) presented economic data for 3 durations of treatment (i.e., 6 months, 1 year, and 2 years) and predicted increasing cost savings with increased duration of treatment. Cost savings became significant when the time horizon was extended to 2 years) .

3. The cost-effectiveness of Galantamine included 5 published RCTs studies.

- All studies(60-64) use the Assessment of Health Economics in AD (AHEAD) model for modeling disease progression in their estimation of the cost-effectiveness of galantamine. The model was developed by Caro and colleagues. see Appendix

- Cognitive function was assessed at baseline using the Mini-Mental State Examination (MMSE) and efficacy was assessed based on changes in the ADAS-cog, the cognitive subscale of the AD Assessment Scale .

- All studies(60-64) reported the cost-effectiveness of galantamine. Cost savings over time were calculated on patient benefits in terms of a reduction in time spent in FTC, and/or a delay in requiring FTC, as the main outcome, with an incremental 10-year cost. Three studies(60, 62, 64) reported the mean gain in QALYs over time and two studies (61, 63) estimated Number needed to treat (NNT) with galantamine to avoid 1 year of full time care.
- Four studies (60-63) found that galantamine was more cost-effective than a no-drug treatment strategy and one study (64) found that the average ten-year incremental costs per month of full-time care avoided was £192 per patient and £8,693 per QALY.

CHAPTER III
METHODOLOGY

The methodology of this study was consisted of 13 parts:

1. Study design
2. Perspective
3. Target population
4. Intervention
5. Model structure
6. Model parameters
   - 6.1 Transitional probability for requiring FTC
   - 6.2 Mortality data
   - 6.3 Effectiveness data
   - 6.4 Health state utilities
   - 6.5 Cost data
7. Model assumptions
8. Time horizon
9. Discounting rate
10. Sensitivity analysis
11. Health outcomes
12. Study procedure
13. Data analysis

1. Study design

A pharmacoeconomic model was used to simulate the disease progression and compare lifetime costs and health outcomes between mild to moderate AD patients receiving treatment (i.e., donepezil, rivastigmine and galantamine) and those without treatment. The Assessment of Health Economics in Alzheimer's Disease (AHEAD)

model was used and input parameters were obtained by a systematic reviews of the literature on the clinical and cost-effectiveness of cholinesterase inhibitors.

2. Perspective

This study was analyzed based on the perspectives of the government and society.

3. Target population

Thai men and women were diagnosed with probable AD according to the National Institute of Neurologic and Communicative Disorders and Stroke and AD and Related Disorders Association (NINCDS-ADRDA) classification and/or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, were describe on literature review chapter. The cognitive function was assessed using Mini-mental state examination (MMSE) and efficacy of the drugs treatment was assessed based on changes in the ADAS-cog. The patients were assessed severity of mild to moderate stage of cognitive decline was included (using MMSE scores between11 to 23 points or ADAS-cog score 17 to 44 points).

4. Intervention

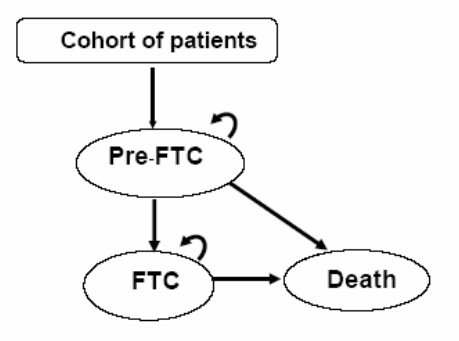
Interventions included providing cholinesterase inhibitors (i.e., donepezil, galantamine or rivastigmine) compared with no drug treatment in mild to moderate AD patients.

5. Model structure

The Markov model in this study was developed based on the Assessment of Health Economics in Alzheimer's Disease (AHEAD) model(11), which applied predictive risk equations derived from longitudinal epidemiological data (65). The AHEAD model simulated the cohort of patients across three possible health states: pre full-time care (FTC), FTC and death. At the pre-FTC health state, patients were assumed to live at home and did not received extensive care. Patients at full time care (FTC) health state were defined as the patients who consistently needed the greater part of the day of paid care and supervision each day (11). The model determined the

proportion of the patients in each health state overtime to a level at which FTC was required according to patients' characteristic at a given time. The model used a one-month cycle period. It was assumed that the AD treatment had no survival advantage.

Figure1 Model structure.



ADAS-cog = AD assessment scale-cognitive subscale;
FTC= Full-Time Care.

6. Model parameters

6.1 Transitional probability for requiring FTC

The predictive risk equations used to calculate the risk (transitional probability) of patients progressing from the pre-FTC heath state to a level requiring full-time care (FTC) in each month included a three-stage process.

Table7 The predictive risk equation to calculate transitional probability of requiring FTC in each month (11).

Stage 1						
Risk index equation	Variable	EPS	PSY	Young at onset	mMMSE	Duration
	Coefficient	–0.9419	–0.4027	–0.4848	0.0724	0.0617
Stage 2						
Equations for risk over time	Coefficient[a]	A	B	C	D	E
	≤73 years	0.0231	–1.8117	0.0373	0.1532	–4.7903
	>73 years	0	–0.6846	0.0118	0.1413	–6.4172

[a] These coefficients have no clinical interpretation. Coefficients A–E for >73 years corrected by the present authors.
Source: Caro and colleagues.[131]
EPS, extrapyramidal symptoms; PSY, presence of psychotic symptoms.

At the first stage, a risk index was calculated using the coefficients of the presence of extra pyramidal symptoms (EPS), the presence of psychotic symptoms (PSY) (e.g. delusions, hallucinations), a young age at disease onset (i.e.<65 years), cognitive function (as measured by ADAS-cog score), and duration of illness **(Table7)**. At the second stage, the baseline risk (λ^t_0) in each month (t) was calculated using the equations were calculated separately for patients who were 73 years and younger and for patients who were over the age of 73 years, the function was

$$\lambda^t_0 = e^{(A*t+B+C\sinh(D*t+E)}$$

At the third stage divided the baseline risk by the exponential of the risk index to get the risk (transitional probability) in each month. (λ^t_{index}), the function was

$$\lambda^t_{index} = (\lambda^t_0)/ e^{index}$$

For example, the characteristics of patient A were age ≤ 73 years, no EPS symptoms, no PSY symptoms, No early onset, duration of illness was 1 year and mMMSE=42 (or ADAS-cog=17 ,the method of convert ADAS-cog into mMMSE were described below)

Risk index = (-0.9419*0) + (-0.4027*0) + (-0.4848*0) + (-0.0724*42) + (-0.0617*1) = 3.10

Baseline risk (λ^t_0) in a month 1 (t=1) = $e^{(0.0231*1+ (-1.8117) +0.0373*\sinh((0.1532*1)+(-4.7903))}$ = 0.024

The risk (transitional probability) in a month1 (λ^t_{index})= 0.024/ $e^{(3.10)}$ =0.0011

The cost-effectiveness of three cholinesterase inhibitors was estimated using similar model method. The clinical effectiveness defined as the difference in cognitive function (ADAS-cog score) after receiving the drugs treatment was used to modify the transitional probability of requiring full-time care (FTC) in each month

6.2 Mortality data

The probability of death was calculated using the mortality rate of the Thai general population classified by age group **(Table 8)** and multiplied by the relative risk (RR) of death in patients with AD classified by the limitation in physical function (i.e., RR of pre-FTC to death=1.45 (SE=0.09)and RR of FTC to death=3.3 (SE=0.44)) (66) .

Table 8 Probability of death in general population (67) .

Age group	Total deaths	Population	Mortality rate per year	Prob. of death
<1 year	6,079	749,196	0.00811	0.00808
1-4 year	3,100	3,261,740	0.00095	0.00095
5-9 year	2,804	4,801,405	0.00058	0.00058
10-14 year	2,620	4,868,102	0.00054	0.00054
20-24 year	9,274	5,263,047	0.00176	0.00176
25-29 year	13,715	5,486,871	0.00250	0.00250
30-34 year	18,234	5,652,337	0.00323	0.00322
35-39 year	19,465	5,603,429	0.00347	0.00347
40-44 year	20,601	5,054,287	0.00408	0.00407
45-49 year	22,035	4,240,392	0.00520	0.00518
50-54 year	24,211	3,329,029	0.00727	0.00725
55-59 year	24,954	2,398,162	0.01041	0.01035
60-64 year	28,578	2,004,326	0.01426	0.01416
65-69 year	36,021	1,713,735	0.02102	0.02080
70-74 year	40,343	1,257,952	0.03207	0.03156
75-79 year	40,050	788,292	0.05081	0.04954
80-84 year	33,588	418,246	0.08031	0.07717
85+ year	40,983	339,885	0.12058	0.11359

Probability= 1-exp(-rate*time).

6.3 Effectiveness data

Effectiveness was defined as a change in cognitive function in AD using the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) for each of drug treatment compared with no drug treatment based on the systematic review of randomized controlled trials (RCTs) studies (68).**(Table 9)**

Table 9 Effectivess data

Drug treatment	Mean reduction	SE	Distribution
Donepezil 10 mg/day	3.00	0.34	gamma
Rivastigmine 3–12 mg/day	3.17	0.42	gamma
Galantamine 24 mg/day	3.19	0.28	gamma

The difference in ADAS-cog score after receiving the drug treatment was used to modify the transitional probability of requiring full-time care (FTC) in each month and ADAS-cog score is related to the mMMSE score. Therefore, ADAS-cog was converted into mMMSE using a two stage process. At the first stage, the ADAS-cog values were transformed to the MMSE scores (i.e., a 1 unit decrease in MMSE is equal to a 2.33 unit increase in ADAS-cog) (2)..

MMSE=(30-(ADAS_cog*(30/70)))

At the second stage, the MMSE scores were transformed to the mMMSE scores using a linear regression equation (69) as follows:

mMMSE =(1.73*MMSE)=2.81)

Finally the equation has been provided:

mMMSE = ((1.73*(30-(ADAS_cog*(30/70))))+2.81)

6.4 Health state utilities

Health state utilities among different health states were derived from published data (70) based on Health Utility Index (HUI). Health state utilities for pre-FTC care and FTC were valued 0.60 and 0.34, respectively. These utilities were used to calculate quality adjusted life years (QALYs).

6.5 Cost data

The cost analysis was performed based on societal and governmental perspectives. The costs associated with AD included both direct and indirect costs. All costs were reported in year 2008 values (baht). Monthly cost was estimated and multiplied by the proportion of patients in each state over time**. (Table 10)**

6.5.1 Direct medical costs

Direct medical costs comprised of disease and drug treatment costs associated with AD.

6.5.1.1 Disease treatment costs

Disease treatment costs associated with AD were consisted of the cost of inpatient department (IPD), the cost of outpatient department (OPD) and the cost of home health care (HHC).

1) The costs of inpatient department (IPD) were calculated by the number of service utilisation multiplying by its unit cost for pre-FTC and FTC health state.

Cost of IPD = Number of in-patient stays per month * unit cost of IPD services (baht/in-patient day).

The number of in-patient stays per month for pre-FTC health state was obtained from Kavanagh and colleagues (74) who estimated the quantities of service providing for elderly people by degree of cognitive disability in households and FTC health state were obtained from expert opinion. The unit costs of IPD services were obtained from the cost study at Prasat Neurological Institute (73) and calculated using the average cost method.

2) The costs of outpatient department (OPD) were calculated by the number of service utilisation multiplying by its unit cost for pre-FTC and FTC health state.

Cost of OPD = Number of OPD visits per month * unit cost of OPD services (baht/visit).

The number of OPD visits per month for Pre-FTC and FTC health state was studied at Ramathibodi hospital. Data were collected from one hundred primary caregivers taking care of the patients with dementia who received the medical care from the out-patient clinics at the internal medicine and/or psychiatric and/or family medicine departments by using questionnaires. The unit costs of OPD services were calculated using the average cost method and obtained from the cost study at Prasat Neurological Institute(73).

3) The costs of home health care (HHC) were calculated by the number of service utilisation multiplying by its unit cost for pre-FTC and FTC health state.

Cost of HHC = Number of HHC visits per month * unit cost of HHC services(baht/visit) .

The number of HHC visits per month for Pre-FTC and FTC health state and unit cost were obtained from Melee and colleagues in 2001. The unit costs of HHC for the elderly people with dementia in Ramathibodi hospital were calculated including labour costs and traveling cost.

Total direct medical cost for pre-FTC and FTC were 3,280 and 6,071 baht/month, respectively.

6.5.1.21 Drug treatment costs

Drug treatment costs were the cost of cholinesterase inhibitors derived from the reference price database of the Drugs and Medical Supplies Information Center (DMSIC), Ministry of Public Health (71).

6.5.2 Direct non-medical costs

Direct non-medical costs included the cost of traveling, the cost of paid caregiver and the cost of informal care (unpaid caregiver). Data were collected from one hundred primary caregivers taking care of the patients with dementia who received the medical care from the out-patient clinics at the internal medicine and/or psychiatric and/or family medicine departments by using questionnaires. The cost of paid caregiver and informal caregiver were estimated by the severity of cognitive function (see Appendix A).

In this study, it was assumed that the direct non-medical costs for mild to moderate cognitive function were the same as the costs of the patients in pre-FTC health state and the direct non-medical costs for severe cognitive function were the same as the cost of the patients in FTC health state. The cost of paid caregivers and informal caregivers were calculated as follows:

The cost of paid caregiver was estimated by the paid amount for employed caregivers per month (see Appendix A).

The cost of informal care was calculated using the opportunity cost method (72) to evalute the time spent in providing care by family caregivers. The time

spent on providing informal care was the additional time of providing care associated with the activities of daily living (ADL) (i.e eating, bathing and dressing, toileting and mobility), and/or instrumental activities of daily living (IADL) (i.e assistance with financial/legal work, shopping and take to hospital) and/or household activities of daily living (HDL) (i.e preparing meals, preparing medication, housekeeping and laundry). The cost of informal care was calculated as follows.

Cost of informal care = Hours spent on informal care * the real income for employed caregivers or minimum wage rate for unemployed caregivers.

Table 10 The monthy cost of paid and unpaid caregivers in patients with dementia by severity of cognitive function.

	Severity of cognitive function			
	Mild to moderate		Severe	
	Mean	SE	Mean	SE
Paid caregivers (n=13)	4,029	543	15,404	4,822
Unpaid caregivers (n=87)	4,814	949	25,872	11,507

Total direct non-medical costs for pre-FTC and FTC were 9,241 and 41,642 baht/month, respectively.

Table 11 The costs associated with AD (baht)

Resource cost parameters	Mean cost	SE	Reference
Direct medical costs			
Drug cost (Dose mg./ day)			
Donepezil 10 mg.per month	5,338	0.10	(71)
Rivastigmine 12 mg.per month	4,448	0.10	(71)
Galantamine 24 mg.per month	4,155	0.10	(71)
Cost of out-patient(OPD) service (Unit cost baht per visit)	173	173	(73)
Number of OPD visits per month for Pre-FTC	0.59	0.06	(72)
Number of OPD visits per month for FTC	0.54	0.07	(72)
Cost of in-patient(IPD) service (Unit cost baht per inpatient day)	1,115	1,115	(73)
Number of in-patient stays per month for Pre-FTC	2.63	2.63	(74)
Number of in-patient stays per month for FTC	5.00	5.00	Expert opinion
Cost of Home Help Care ,visits by professionals to people in households (Unit cost baht per visit)	971	971	
freHHC_Pre-FTC	0.25	0.25	
freHHC_FTC	0.42	0.42	
Total Direct medical cost for Pre-FTC without Alz.drug	**3,280**		
Total Direct medical cost for FTC without Alz.drug	**6,072**		
Direct non-medical costs			
Cost of traveling per visit	679	158	(72)
Cost of paid caregiver by Pre-FTC households (baht/month)	4,029	543	(72)
Cost of paid caregiver by FTC households (baht/month)	15,404	4,822	(72)
Cost of Informal care(un-paid caregiver) for Pre-FTC household	4,814	949	(72)
Cost of Informal care(un-paid caregiver) for FTC household	25,872	11,507	(72)
Total Direct non-medical cost for Pre-FTC	**9,241**		
Total Direct non-medical cost for FTC	**41,643**		

7. Model assumptions

The model assumptions were as follows.

1. Eligible patients started the treatment immediately and the benefit of treatment was assumed to be an immediate effect delaying disease progression from pre-FTC to FTC health state.

2. Patients continued to receive drug treatment while they were in the pre-FTC health state and stopped drug treatment when they progressed to FTC.

3. The difference in cognitive function (ADAS-cog score) after receiving the treatment was used to modify disease progression over time.

8. Time horizon

This study was performed using a pharmacoeconomic model to predict cost and health outcomes for lifetime period.

9. Discounting rate

The costs and health outcomes were discounted at 3% per annum based on the WHO guide to cost-effectiveness analysis (75) .

10. Sensitivity analysis

Sensitivity analysis was undertaken to address the uncertainty in the cost-effectiveness analysis. Multivariate probabilistic sensitivity analysis was performed to assess the uncertainty in main parameters such as efficacy of drug treatment and cost using Monte Carlo simulation.

11. Health outcomes

The number of life-years saved by delaying disease progression to FTC and quality-adjusted life years (QALYs) were used as a measure of overall health-related quality of life.

QALYs = Life year saved * health state utilities

12. Study procedure

Steps of study procedure are presented as follows.

1. Review the model structure from the literature on the cost-effectiveness of AD treatment and the available methods for modeling disease progression in AD.

2. Determine the efficacy of drug treatment from a systematic review of randomized controlled trials (RCTs) of the clinical effectiveness literature.

3. Determine the costs associated with AD including both direct and indirect costs

4. Develop the model using cost and effectiveness data

5. Calculate incremental cost effectiveness ratio (ICER)

The recommended outcome of CEA and CUA is the incremental cost-effectiveness ratio (ICER) (76). ICER was calculated by incremental cost divided by incremental effectiveness as the following formula.

$$ICER = \frac{Cost_{\text{drug treatment}} - Cost_{\text{no drug treatment}}}{QALY_{\text{drug treatment}} - QALY_{\text{no drug treatment}}}$$

13. Data analysis

The Microsoft Excel spreadsheet version 2003 was used to analyze the data. The analysis was consisted of two parts.

1. Cost -utility analysis

The cost-utility analysis of donepezil, rivastigmine and galantamine was presented as the incremental cost-effectiveness ratio (ICER). Costs were measured in baht and effectiveness was measured in QALYs gained. The comparison of incremental cost, incremental effectiveness, and the ICER between each drug treatment strategy and no drug treatment was presented.

2. Sensitivity analysis

Probabilistic sensitivity analysis (PSA) was used to analyze the uncertainty of the results due to data and methodological method. PSA was varied on main parameters such as the efficacy of drug treatment and the cost of AD treatment. The result was repeated 1,000 times using Monte Carlo simulation approach and Microsoft Excel software program were applied. Cost-effectiveness acceptability curves were

presented to show the relationship between varied willingness to pay per QALY gained and the probability of cost-effectiveness of intervention.

3. Budget impact analysis

The most cost-effective drug was selected and compared its budget impact with no drug treatment in order to determine the additional budgets required for providing drug treatment next 10 years.

CHAPTER IV
RESULTS

Base upon the AHEAD model, the results are divided into three parts:

1. Cost-utility analysis
2. Sensitivity analysis
3. Budget impact analysis

Part one: Cost-utility analysis

The results were presented in 9 scenarios of AD patients according to patients' characteristics.

1. **Base case scenario** was defined as the 60 year-old patients who had AD disease for 1 year, an ADAS-cog score of 17, no presence of psychotic and EPS symptoms.
2. **Age=70 years scenario** was defined as the 70 year-old patients who were initially diagnosed with AD and had other characteristics the same as base case scenario.
3. **Age=80 years scenario** was defined as the 80 year-old patients who were initially diagnosed with AD and had other characteristics the same as base case scenario.
4. **Duration of 2 years scenario** was defined as the patients who had AD disease for 2 years and other characteristics the same as base case scenario.
5. **Duration of 4 years scenario** was defined as the patients who had AD disease for 4 years and other characteristics the same as base case scenario.
6. **ADAS-cog of 30 score scenario** was defined as the patients who had an ADAS-cog score of 30 and other characteristics the same as base case scenario.
7. **ADAS-cog of 44 score scenario** was defined as the patients who had an ADAS-cog score of 44 and other characteristics the same as base case scenario.

8. Psychotic symptom scenario was defined as the patients who had the presence of delusion or hallucination signs and other characteristics the same as base case scenario.

9. EPS symptom scenario was defined as the patients who had the presence of extra pyramidal signs and other characteristics the same as base case scenario.

These scenarios were based on the equations that allowed full prediction of the course of AD over any period of time according to a patient's characteristics which were potentially influential factors to predict the need of FTC.

The cost-utility analysis was used to estimate costs and health outcomes among patients with mild to moderate AD with drug treatment compared with those without treatment group based on societal and government perspectives.

Cost analysis

Table 11 shows the lifetime costs of donepezil, rivastigmine, galantamine and no drug treatment according to difference scenarios based on governmental and societal perspectives. Based on the government's perspective meaning that only direct medical cost was considered, the estimated cost was 649,734 baht in the 60 year-old patients who had AD disease for one year, an ADAS-cog score of 17, no presence of psychotic and EPS symptoms (base case scenario). The lifetime costs of providing care increased when AD patients had EPS or psychotic symptoms, longer duration of illness, but decreased when AD patients had higher ADAS-cog score and patients' age was higher than 60 years old. The cost of providing care decreased when the ADAS-cog score increased, AD patients with ADAS-cog score = 30 had lifetime costs of 749, 545 baht, whereas those with ADAS-cog score = 44 was 721,933 baht, because the patients with ADAS-cog score = 30 had less severity, so that they tended to stay at pre-FTC state longer and consumed higher costs of treatment than those with ADAS-cog score = 44 who were more severe and tended to require FTC state, where no treatment was not given. The lifetime costs of AD patients with EPS or psychotic symptoms were 679,120 or 693,760 baht, respectively. In addition, AD patients with 4-year duration of illness (684,106 baht) had higher lifetime cost compared to those with 2-year duration of illness (680,583 baht). However, the 70-year old patients with

AD (433,319 baht) spent more lifetime costs than those aged 80 years old (228,259 baht). The inpatient cost for FTC was 78% of total lifetime costs **.**

Moreover, the lifetime costs based on societal perspective including both direct medical and non-medical costs were higher than those based on governmental perspective in all scenarios**.** The estimated total cost was 4,756,137 baht in base case scenario. The informal care cost for FTC accounted for 49% of total lifetime costs because due to the productivity loss from missing work of caregivers who were in paid employment.

In addition, the estimated total lifetime costs of AD patients receiving cholinesterase inhibitors (i.e., donepezil, rivastigmine and galantamine) were higher than those without treatment based on both perspectives Based on the perspectives of the government and society, the lifetime costs of AD patients taking donepezil (852,682 and 4,911,875 baht) were the highest compared with those taking rivastigmine (818,529 vs 4,875,409 baht) and galantamine (807,362 vs 4,863,569 baht), respectively **(Table12).** .

Table 12 Lifetime cost of donepezil, rivastigmine, and galantamine and no drug treatment according to
different scenarios based on governmental and societal perspective (Baht) .

Scenario	No treatment		Donepezil 10 mg/day		Rivastigmine 6-12 mg/day		Galantamine 16 mg/day	
	Perspective		Perspective		Perspective		Perspective	
	Govern-ment	Societal	Govern-ment	Societal	Govern-ment	Societal	Govern-ment	Societal
Base case	649,734	4,756,137	852,682	4,911,875	818,529	4,875,409	807,362	4,863,569
ADAS-cog score = 30	749,545	4,862,776	906,073	4,973,320	879,785	4,944,932	870,976	4,935,450
ADAS-cog score = 44	721,933	5,170,739	831,965	5,243,381	813,667	5,222,677	807,363	5,216,202
Presence EPS	679,119	5,067,830	819,609	5,162,892	796,060	5,136,854	788,133	5,128,527
Presence PSY	693,760	4,911,197	870,376	5,038,572	840,773	5,006,078	830,755	4,995,829
Duration 2 yrs.	680,583	4,788,445	887,229	4,947,699	852,484	4,910,464	840,957	4,898,770
Duration 4 yrs.	684,106	4,672,450	898,191	4,842,138	862,315	4,803,768	850,317	4,791,745
Age =70 years	433,319	2,827,677	656,908	3,018,118	619,638	2,979,161	607,171	2,966,480
Age =80 years	228,259	1,434,381	420,615	1,596,549	388,814	1,562,929	378,266	1,552,328

Health outcomes

Health outcomes were defined as the number of life years saved by delaying disease progression to FTC health state and the quality of adjusted life years (QALYs). All treatments reduced the time requiring FTC. It was assumed that all treatments had no survival advantage. The mean reduction in the time spent in the FTC health state (increased time in pre-FTC) at base case scenario was 2.07 months with galantamine (GALAN), 2.06 months with rivastigmine (RIVA), and 1.95 months with donepezil (DNZ) **(Table 13).**

In addition, QALYs gained of the AD patients receiving galantamine compared to no drug treatment were 0.69, 0.68 with rivastigmine, and 0.64 with donepezil at base case scenario **(Table 14).**

Table 13 Life months gained by delaying disease progression to FTC health state for donepezil, rivastigmine, and galantamine compared with no drug treatment by different scenarios .

Scenario	Life months			
	no drug treatment	DNZ	RIVA	GALAN
Base case	**36.66**	38.61	38.71	38.73
ADAS-cog score = 30	27.93	29.93	30.04	30.06
ADAS-cog score = 44	19.47	21.12	21.21	21.23
Presence EPS	24.99	26.91	27.02	27.03
Presence PSY	31.62	33.65	33.76	33.78
Duration =2 years	37.41	39.33	39.44	39.45
Duration= 4 years	38.89	40.76	40.86	40.88
Age =70 years	40.60	42.18	42.27	42.28
Age =80 years	34.20	36.19	36.30	36.31

Table 14 Health outcomes for donepezil, rivastigmine, and galantamine compared with no drug treatment by different scenarios .

Scenario	Life months gained				QALYs gained			
	no treatment	DNZ	RIVA	GALAN	no treatment	DNZ	RIVA	GALAN
Base case	**126.30**	**126.70**	**126.72**	**126.72**	**52.47**	**53.11**	**53.15**	**53.15**
ADAS-cog score 30	124.51	124.93	124.95	124.95	49.59	50.26	50.29	50.30
ADAS-cog score 44	122.66	123.04	123.06	123.06	46.77	47.32	47.36	47.36
Presence EPS	123.89	124.30	124.32	124.32	48.62	49.26	49.29	49.30
Presence PSY	125.28	125.69	125.72	125.72	50.81	51.48	51.52	51.53
Duration =2 yrs.	126.46	126.85	126.87	126.87	52.72	53.35	53.39	53.39
Duration = 4 yrs.	126.76	127.13	127.15	127.16	53.21	53.82	53.86	53.86
Age =70 years	88.81	89.25	89.28	89.28	40.75	41.31	41.34	41.35
Age =80 years	55.31	56.12	56.17	56.17	27.70	28.49	28.54	28.54

Incremental cost-effectiveness ratio (ICER)

Table 15 and 16 present the incremental cost effectiveness ratio (ICER), cost per life years saved (LYs saved) and cost per QALYs gained for drug treatment compared with no drug treatment based on the perspectives of government and society at base case scenario.

Based on the governmental perspective, galantamine was the most cost-effective compared with other two drugs (i.e., donepezil and rivastigmine), because it was the cheapest and most effective. The ICER of galantamine was 375,293.55 baht per LY saved or 229,367 baht per QALY gained at base case scenario **(Table15).** The results were similar in others scenario **(Table 17).**

In addition, based on societal perspective, galantamine was also the most cost-effective compared to other two drugs. The ICER of galantamine was 255,911 baht per LY saved or 157,247 baht per QALY gained at base case scenario **(Table16)** and others scenario **(Table 18)**..The ICER results based on the societal perspective were lower than those of the government perspective.

Table 15 Cost-effectiveness results at base case scenario for donepezil, rivastigmine, and galantamine compared with no drug treatment base on governmental perspective .

Drug treatment	Incremental cost	Life-years saved	QALYs gained	ICER (baht/LY)	ICER (baht/QALY)
Donepezil	202,949	0.39	0.64	517,357.20	315,806
Rivastigmine	168,796	0.41	0.67	405,413.83	247,424
Galantamine	157,629	0.42	0.68	375,293.55	229,367

Table 16 Cost-effectiveness results at base case scenario for donepezil, rivastigmine, and galantamine compared with no drug treatment base on societal perspective .

Drug treatment	Incremental cost	Life-years saved	QALYs gained	ICER (baht/LYs)	ICER (baht/QALYs)
Donepezil	155,737	0.39	0.64	394,767	242,766
Rivastigmine	119,271	0.41	0.67	287,768	176,740
Galantamine	107,432	0.42	0.68	255,911	157,247

Table 17 Incremental cost effectiveness ratio (ICER) for donepezil, rivastigmine, and galantamine compared with no drug treatment base on government perspective, by different scenario .

Scenario	Baht per life year saved			Baht per QALY gained		
	DNZ	RIVA	GA LAN	DNZ	RIVA	GA LAN
Base case	**517,357**	**405,414**	**375,294**	**315,806**	**247,424**	**229,367**
ADAS-cog score = 30	372,999	295,258	273,043	232,868	184,701	170,625
ADAS-cog score = 44	294,707	231,486	215,431	200,736	157,316	146,244
Presence EPS	342,541	269,292	249,468	218,509	172,424	159,389
Presence PSY	426,700	330,185	310,966	264,744	204,920	193,058
Duration =2 yrs.	529,847	418,798	388,512	322,301	255,443	236,478
Duration =4 yrs.	569,025	445,967	413,054	352,019	275,314	255,603
Age =70 years	500,143	394,544	365,662	398,715	314,243	291,934
Age =80 years	236,923	188,400	174,306	239,604	190,477	176,380

Table 18 Incremental cost effectiveness ratio (ICER) for donepezil, rivastigmine, and galantamine compared with no drug treatment base on societal perspective, by different scenario .

Scenario	Baht per life year saved			Baht per QALY gained		
	DNZ	RIVA	GA LAN	DNZ	RIVA	GA LAN
Base case	**394,767**	**287,768**	**255,911**	**242,766**	**176,740**	**157,247**
ADAS-cog score = 30	263,820	187,460	163,738	167,269	118,859	103,825
ADAS-cog score = 44	194,535	130,932	114,221	131,675	88,404	77,269
Presence EPS	230,051	159,346	138,419	144,342	99,829	86,792
Presence PSY	306,209	216,086	191,766	190,535	184,774	119,128
Duration =2 yrs.	408,894	298,040	267,071	253,510	184,774	165,236
Duration =4 yrs.	447,719	328,474	297,605	272,130	199,927	180,570
Age =70 years	425,192	321,167	292,358	338,629	254,977	232,554
Age =80 years	200,858	150,097	137,348	204,141	152,537	139,853

Figure 2 presents the cost-effectiveness plane of galantamine, the most cost-effective treatment of AD at base case scenario compared with other different scenarios using a societal perspective. The ICER results showed the scenario that the patients had ADAS-cog score = 30 (103,825 baht per QALY gained), psychotic symptom (119,128 baht per QALY gained), or EPS symptom (86,792 baht per QALYs gained) had less cost and more QALYs gained than base case scenario (157,247 baht per QALY gained). Therefore the AD patients who had ADAS-cog score ranging from 17 (base case) to 30 or had psychotic or EPS symptom associated with AD should be the first criteria for receiving the treatment of AD **(Table 19).** The scenario that the AD patients had ADAS-cog score = 44, disease duration more than 2 years, or age over 60 years had higher cost per QALY gained than base case scenario.

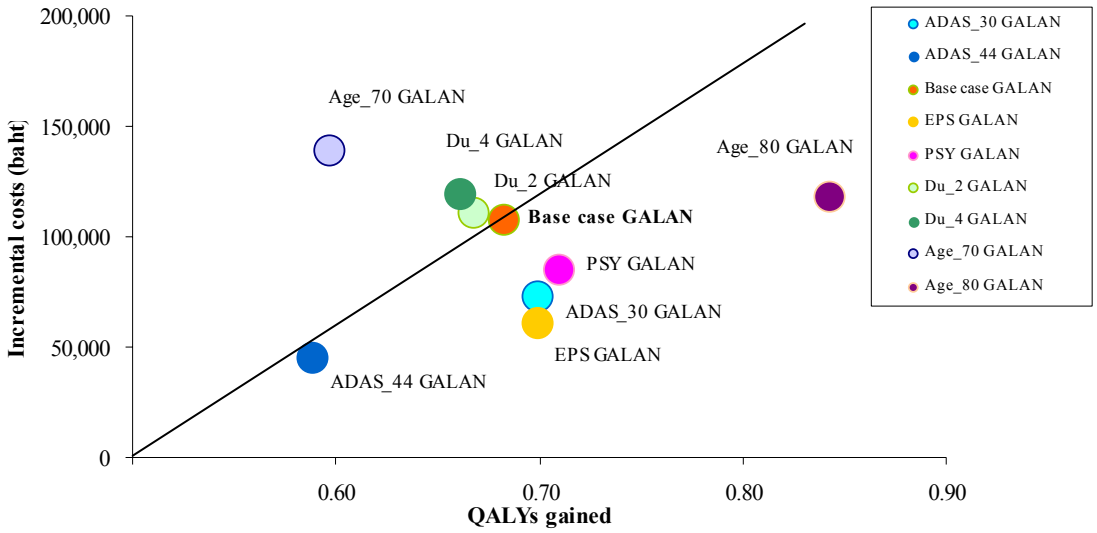


Figure 2 Cost-effectiveness plane (Baht/QALYs gained) of providing galantamine according to different scenarios based on societal perspective.

Table 19 ICER of providing galantamine according to different scenario based on societal perspective (Baht/QALYs gained) .

Scenario	Incremental		ICER (baht/QALYs)
	Cost (baht)	Effectiveness (QALYs)	
Base case	**107,432**	**0.68**	**157,247**
ADAS-cog score = 30	72,674	0.70	103,825
ADAS-cog score = 44	45,463	0.59	77,269
Presence EPS	60,697	0.70	86,792
Presence PSY	84,631	0.71	119,128
Duration 2 years	110,325	0.67	165,236
Duration 4 years	119,295	0.66	180,570
Age =70 years	138,803	0.60	232,554
Age =80 years	117,947	0.84	139,853

Part two: Sensitivity analysis

Sensitivity analysis was performed by Microsoft Excel 2000 to examine the robustness of the model. One-way sensitivity analysis and probabilistic sensitivity analysis using Monte Carlo simulation were performed to identify how the incremental cost-utility of one treatment relative to another would change by varying different parameters in the model. The main parameters such as efficacy of drug treatment (cholinesterase inhibitors), drugs cost and cost of AD were examined over the 95% confident interval (CI). In addition, sensitivity analysis was also performed on health outcomes and cost at the discounting rates of 0% and 6%.

2.1 One-way sensitivity analysis

Based on societal perspective, one-way sensitivity analysis results of providing galantamine at the base case scenario showed that the cost of informal care for FTC was more sensitive than the efficacy of drugs treatment, drug cost, cost of paid caregiver for FTC, discounting rate , cost of informal care for Pre-FTC. On the other hand, the cost of paid caregiver for Pre-FTC was the least sensitive compared to other variables **(Figure 3)**.

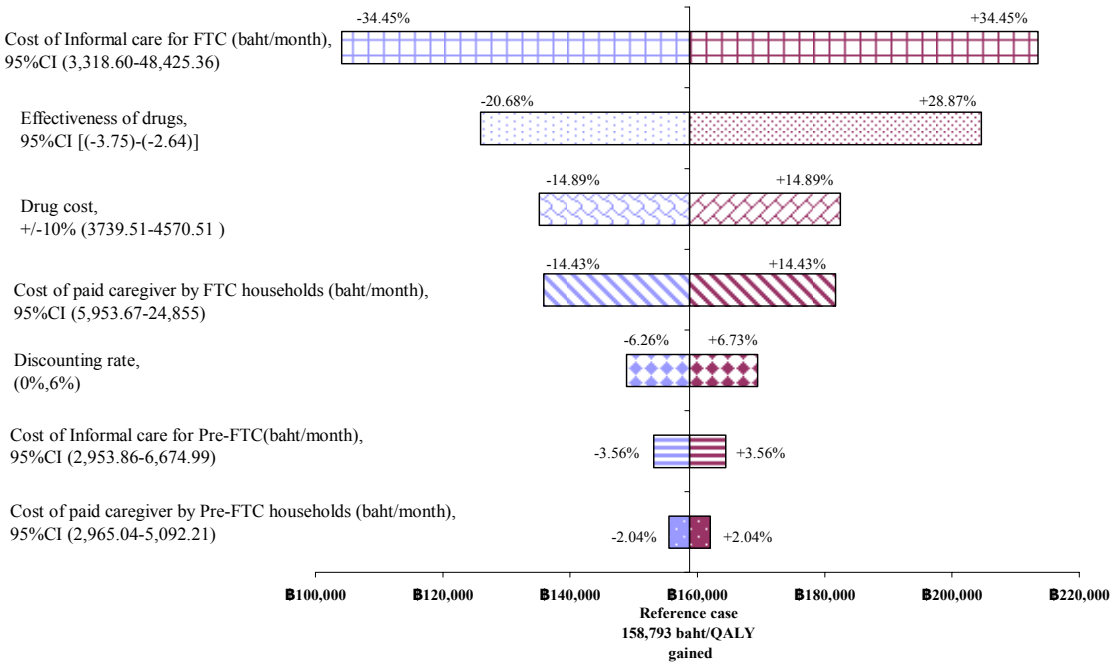


Figure 3 One way sensitivity analysis of providing galantamine in base case scenario , by societal perspective.

2.2 Probabilistic sensitivity analysis

Based on societal perspective, probabilistic sensitivity analysis (PSA) was used to evaluate the impact of the uncertainty in main parameter inputs (e.g., efficacy of drugs treatment, utilities, and cost) of which distributions were defined **(Table9 and 10)**. The cost and QALYs of each intervention were calculated 1,000 times using Monte Caro simulation to determine the percentage of times in which intervention would be the most cost-effective strategy.

Cost-effectiveness acceptability curves were presented using PSA based on societal perspective in order to inform the probability of multiple treatment options being cost–effective at different levels of willingness to pay (WTP) per QALY gained.

WHO recommended that for developing countries, the ICER per QALY gained of medical interventions below one time of Gross Domestic Product (GDP) per capita was very cost-effective, between 1 and 3 times of GDP per capita was cost-effective, and more than 3 times might be not cost-effective (77).

Figure 4 shows that at the WTP was equal to one time of GDP per capita or 100,000 Baht per QALY, no drug treatment option was the best choice. Furthermore, at the WTP of 300,000 baht per QALY gained, providing galantamine and rivastigmine might be cost-effective with the probability of cost-effective was 54% and 30% respectively..

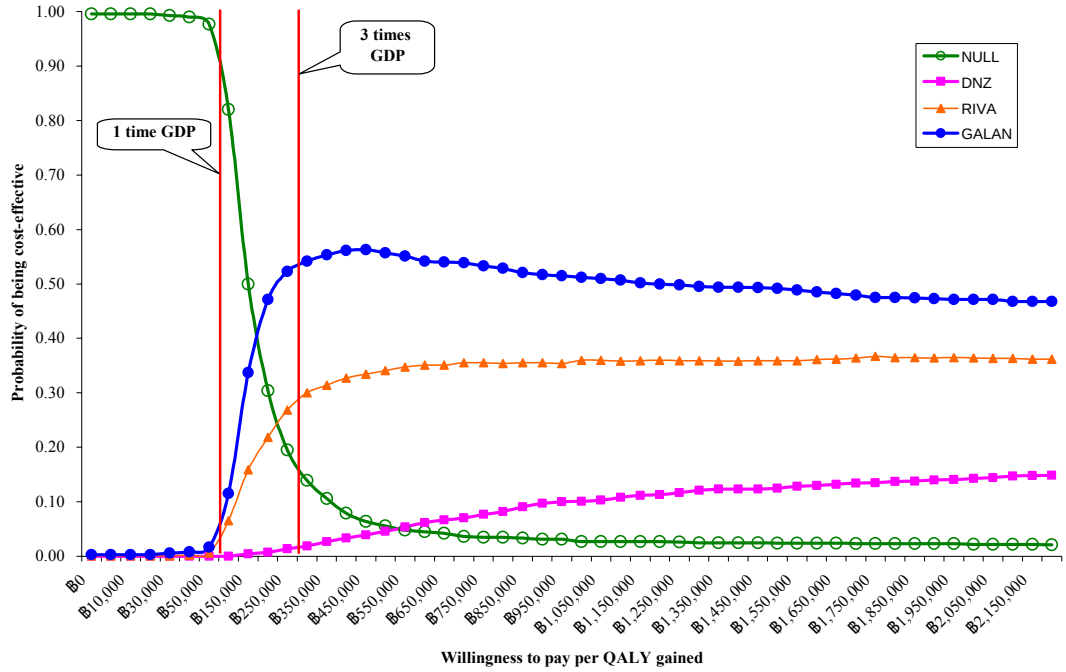


Figure 4 Cost effectiveness acceptability curve for donepezil, rivastigmine, galantamine and no drug treatment.

In addition, the cost effectiveness acceptability curve obtained from probabilistic sensitivity analysis of providing galantamine at base cased scenario were compared with those with different scenarios using a societal perspective **(Figure5)**. The result showed that at WTP of 100,000 Baht per QALY gained, the probability of being cost-effective of providing galantamine to the patients with ADAS-cog score = 44 (66%), EPS symptom (54%), ADAS-cog score = 30 (49%), PSY symptom (34%), or age=80 (19%) was higher than that of the patients with base case scenario (14%). Moreover, at WTP of 300,000 baht per QALY gained, providing galantamine to all scenarios would be cost-effective. The probability of being cost-effective was between 93-96% when providing galantamine to the AD patients with ADAS-cog score = 44, EPS symptom, ADAS-cog score = 30, PSY symptom, age=80 and the probability of being cost-effective was between 82-85% when providing galantamine to the AD patients with base case or duration of disease=2 or 4 years. The probability of being cost-effective was 72% when providing galantamine to the patients aged 70 years.

In summary, at the WTP between 100,000 and 300,000 baht per QALY gained, galantamine might be a cost-effective intervention for all scenarios. The probability of being cost-effective at WTP of 100,000 Baht per QALY gained (1-66%) was lower than at WTP of 300,000 Baht per QALY gained (72-96%).

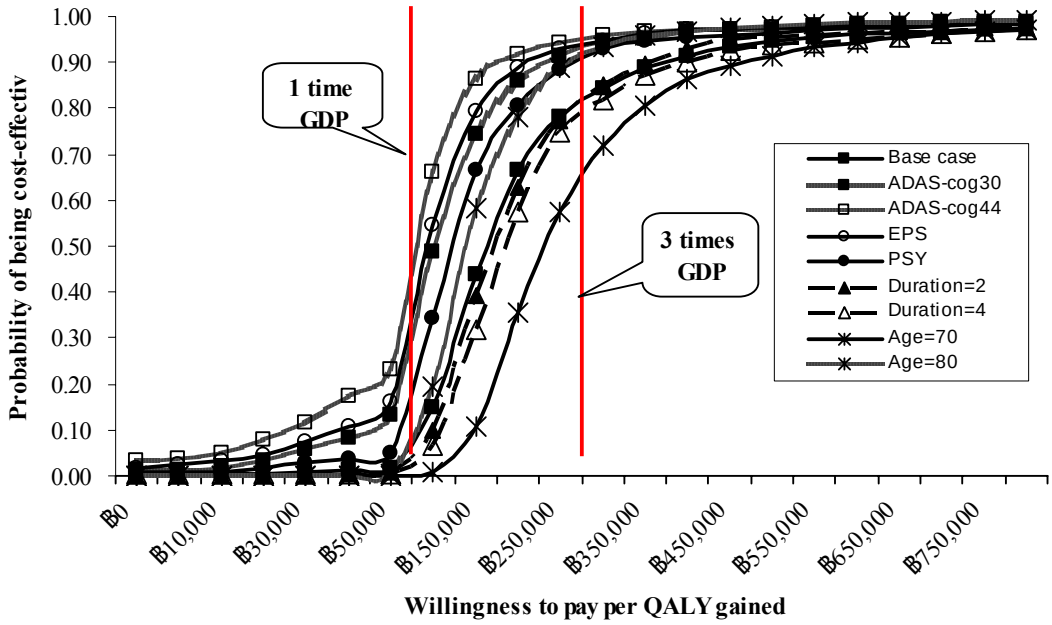


Figure 5 Cost effectiveness acceptability curve of providing galantamine according to difference scenario based on societal perspective.

Part three: Budget impact analysis

Based on the report of the Nation wide study investigating the prevalence of dementia in four major regions covering 23 provinces and 37,157 cases by using mini-mental state examination (MMSE-Thai 2002) conducted by Ministry of Public Health, Department of Medical Service Institute of Geriatric Medicine in 2003, it was found that the prevalence of older peoples with dementia was 5.72% of elderly people's age group 60-64 years, 8.15% of age group 65-69 years, 12.13% of age group 70-74 years, 17.75% of age group 75-79 years, 30.70% of age group 80-84years, and 45.12% of elderly people's age more than 85 years (21). In this study, the prevalence of dementia obtained from the Ministry of Public Health study was used as the prevalence of AD. The Alzheimer's association estimated that AD accounted for 55% of dementia (78) and 60% of patients with AD had mild to moderate AD (79). The number of elderly people's age ≥60 years in 2004 was 6,522,436 people, so that the number of AD patients was estimated to be around 408,957 cases, with 245,374

people having mild to moderate AD. Moreover, it was found that the estimated prevalence of mild to moderate AD in age group 60-64 years was 75,403 people and the prevalence rate increased in the older age group **(Table20)** **.** In addition, the estimated budget impact of providing galantamine in mild to moderate AD was 23,185 million baht, whereas that of without treatment was 10,447 million baht for all age groups at the first year **(Table 21).** Therefore, the additional budget required for providing galantamine at the first year was 12,738 million baht for all age groups (i.e., 3,941 million baht for age group 60-64 years, 3,391 million baht for age group 65-69 years, 2,476 million baht for age group 70-74 years, 1,509 million baht for age group 75-79 years, 1,421 million baht for age more than 80 years) **(Table22).**

The budget impact at the first five years was expected to be high because of the mean time of providing drug treatment was less than 5 years. The majority of AD patients would progress to severe AD or FTC health state within 5 years which the treatment was stopped (80).

Table 20 The estimated prevalence of mild to moderate AD by age group .

Age group (years)	Population of elderly people age ≥60 years	Estimated prevalence of AD	Estimated prevalence of mild to moderate AD
60-64	2,004,326	125,671	75,403
65-69	1,713,735	107,451	64,471
70-74	1,257,952	78,874	47,324
75-79	788,292	49,426	29,656
≥ 80	339,885	47,535	28,521
total ≥ 60	**6,522,436**	**408,957**	**245,374**

Table 21 Budget impact of providing AD without drug treatment over 10 years by age group (million baht)

Year	Age group (years)					
	60-64 yr	**65-69 yr**	**70-74 yr**	**75-79**	**80+**	**Total**
1	3,264	2,758	2,012	1,243	1,170	10,447
2	3,176	2,574	1,853	1,137	1,018	9,758
3	3,419	2,653	1,877	1,135	959	10,043
4	3,608	2,703	1,854	1,046	819	10,030
5	3,770	2,780	1,829	900	643	9,922
6	3,869	3,019	1,900	755	491	10,034
7	3,545	2,720	1,619	628	370	8,882
8	3,229	2,395	1,347	539	289	7,799
9	2,889	2,047	1,068	395	201	6,600
10	2,544	1,702	812	265	135	5,458

Table 22 Additional budgets required for providing galantamine over 10 years, by age group (million baht)

Year	Age group (years)					
	60-64 yr	**65-69 yr**	**70-74 yr**	**75-79**	**80+**	**Total**
1	3,941	3,391	2,476	1,509	1,421	12,738
2	3,048	2,741	1,979	1,087	980	9,835
3	2,313	2,253	1,606	785	679	7,636
4	1,571	1,716	1,199	545	451	5,482
5	800	1,083	741	373	294	3,291
6	65	141	101	255	192	754
7	22	23	21	163	117	346
8	20	20	18	50	37	145
9	18	17	14	17	13	79
10	16	14	11	11	9	61

In addition, the Alzheimer's Disease International (ADI) Asia Pacific (3)'s study estimated the incidence of AD in Thailand to be around 71,400 cases per year . Therefore, the additional budget required for providing galantamine for new cases at the first year was 3,627 million baht for all age groups **(Table 23).**

Table 23 Additional budgets required for providing galantamine for recent and new cases over 10 years (million baht) .

Year ที่	Budget impact for recent cases	Budget impact for new cases	Total
1	12,740	0	12,740
2	9,837	3,627	13,464
3	7,637	6,421	14,058
4	5,485	8,585	14,070
5	3,292	10,091	13,383
6	754	10,882	11,636
7	348	10,713	11,061
8	145	10,434	10,579
9	80	10,155	10,235
10	63	9,879	9,942

CHAPTER V
DISCUSSION

This chapter comprised of cost utility analysis, additionally this study also provided some experiences and perspective of caregivers and health professional in community in order to a understand the overall contextual of AD in Thailand.

Cost utility analysis

Based on the governmental and societal perspectives, compared with no treatment, the ICERs of galantamine,were approximately 229,367 and 157,247 baht per QALY and less than those of rivastigmine (247,424 and 176,740 baht per QALY gained) and donepezil (315,806 and 242,766 baht per QALY), respectively. The ICERs based on the societal perspective were lower than those based on the governmental perspective, since AD treatments would provide more potential cost saving for household sector especially caregiver time costs and expenses than the government sector.

Base on societal perspective when providing galantamine for all scenarios showed that the AD patients who had ADAS-cog score ranging from 17 (base case) to 30 or had psychotic or EPS symptom associated with AD should be the first criteria for receiving the treatment of AD because these scenarios had less cost and more QALYs gained than base case scenario. Although the scenario that the AD patients had ADAS-cog score = 44 was also lower cost per QALY gained than base case scenario, it yielded lower QALYs gained than base case scenario. Moreover, the patients aged 80 years old had more QALYs gained than base case scenario, but more costly (less cost-effective).

In developing countries, WHO recommended that the ICER per QALY gained of medical interventions below one time of Gross Domestic Product (GDP) per capita was very cost-effective, between 1 and 3 times of GDP per capita was cost-effective, and more than 3 times might be not cost-effective (77). Based on the government

perspective , if a ceiling threshold was equal to 3 times of GDP per capita or 300,000 baht per QALY in Thailand (81), galantamine might be cost-effective interventions for all scenarios. and rivastigmine and donepezil might be cost-effective interventions for some scenarios. In additions, based on the societal perspective, galantamine and rivastigmine might be cost-effective interventions for all scenarios, whereas donepezil might be cost-effective interventions for some scenarios. However, if the ceiling threshold was equal to 100,000 baht per QALY, no drug treatment was likely to be cost-effective for both perspectives. In summary, based on the governmental and societal perspectives, the results suggested that providing galantamine was more cost-effective than rivastigmine and donepezil.

However, the results in this study were different from previous published literature from Southampton Health Technology Assessments Centre (SHTAC) (82) submitted to NICE due to differences in perspective and cost components. The SHTAC estimated the cost-effectiveness of the cholinesterase inhibitors based on the NHS and personal social service (PSS) perspectives, while the perspective of society was used in this study. The largest cost associated with AD was the costs accrued from providing FTC. The major cost of providing FTC in the SHTAC study was the institutional cost of which 70% paid by the NHS and PSS budget and 30% paid by private fund, whereas it was calculated from the caregiver time costs and expenses paid by household in a full amount. Therefore, the FTC cost in SHTAC study was higher than that in this study. According to the benefit of drug treatment was to delay disease progression to FTC health state, so that this could reduce the costs associated with FTC and lead to a decrease in the institutional costs and household costs. The results in this study confirmed that the actual cost saving took place in household sector more than the NHS and PSS sectors.

In addition, there were the cost-effectiveness studies of donepezil and rivastigmine conducted using differences in the health states of model, transitional probabilities, and the main outcome measures(24-36). These studies used MMSE alone to define disease severity stage with transitional probabilities and predict disease progression over time (reference). However, there was a limitation when using MMSE, since MMSE was the method of assessing the severity of cognitive function only. Given the concern on the use of cognition alone to predict disease progression, it

might not represent the actual disease progression of AD. This study used AHEAD model(11) to consider disease progression across a broader description of AD than cognitive function, using patient characteristics and other variables (i.e. the presence of psychotic symptoms and extra pyramidal symptoms, a young age at disease onset (65 years of age), and duration of illness. Regarding the cost-effectiveness studies of galantamine, almost all studies were sponsored by the manufacturers except the study of SHTAC. The results of these studies revealed that galantamine was cost-effective by reducing the time spent in FTC approximately 2.5-3 months over a 10 year time horizon and yielding cost saving for patients and caregivers. However, the SHTAC study suggested that galantamine had a cost per QALYs gained of £63,103 (or 3,700,000 baht) per QALY. The incremental QALY gained was small, but the incremental cost for the NHS and PSS was large over 5 years. Although galantamine could delay disease progression to FTC by 1.54-1.73 months, the associated cost savings did not offset the cost of drug treatment.

Limitations of study

This study estimated the cost utility of cholinesterase inhibitors (i.e. donepezil, rivastigmine and galantamine) compared with no drug treatment based on available data. There were some limitations that affected to the results of cost-utility analysis. First, the model in this analysis did not include the consideration of dropouts from drugs treatment. Therefore, it might not represent the real situation and it was a conservative assumption that favored the treatment intervention. Second, this model still had limitations, since the predictive risk equations were used to calculate the transitional probability of patients progressing from the pre-FTC heath state to FTC heath state using only two different regression equations for patients with AD aged≤73 years and for those aged >73 years. Third, in the absence of data and information in Thailand, some parameters used in the model were obtained from other countries such as transitional probabilities (65), health state utilities (70) and relative risk(RR) of mortality in patients with AD (66). ,Forth, this studies used the 17 to 44 points of ADAS-cog for representing mild to moderate AD and it was converted from 11 to 23 points of MMSE. It was noted that ADAS-cog and MMSE were the methods of

assessing the severity of cognitive function, and they were not used to assess the severity of AD. ,Fifth, the cost data including caregiver time cost (informal care cost) and expense (out-of pocket for employed caregivers) were estimated from one university hospital in Bangkok(72). It might not represent other settings. Last, the prevalence of AD patients for estimating the budget impact of providing drug treatment were obtained from other countries studies (78, 79) and were validated by expert opinions in Thailand.

In addition to quantitative analysis described above, this study also investigating the experiences and perspectives of family caregivers and medical doctors using in-depth interview method in order to understand the overall contextual of AD in Thailand. The key informants gave useful insights and suggestions on current situation of AD in Thailand as well as factors affecting to maintain the conditions of AD patients.

Current situation of AD in Thailand

1. Health professionals described that Alzheimer's disease (AD) had been under recognized in Thai society particularly closed family members of the patients with AD. Usually family member were not aware of the signs of cognitive failure or the early symptoms of AD, they perceived them as the symptoms due to normal aging or senility. In addition, family members did not understand that the behavior of AD patients were unpredictable and the disease was uncertain. As described by one health professional:

> *"Alzheimer's disease (AD) can make caregivers lose their love for AD patients due to the fact that she (daughter's caregiver) simply does not understand her mother's (Alzheimer's patient) symptoms. One moment she (Alzheimer's patient) behaves perfectly normally and the next she behaves in a totally unacceptable way. Her daughter is thoroughly confused and because of her lack of experience in dealing with such patients, she is simply unable to cope with these problems."*

The family members described the AD disease was unpredictable and did not vary by the severity or stage of the disease. Relatives described this experience in terms of the effect on their daily lives, particularly the unpredictability of the disease .

2. Most physicians failed to recognize the patients with early AD and it was a common occurrence. The early diagnosis of AD was suggested by health professionals in order to identify the patients who needed to access to medical treatment. It would help delay the disease progression

3. The costs associated AD was mainly the costs accrued from providing FTC, such as caregiver time cost (informal care cost).which caregivers and households had to bear in a full amount without financial compensation and production loss due to unemployment of family caregivers. However, this showed the moral responsibility for family caregivers to their patients who might be their parents. This is exemplified by a daughter's caregiver:

> *"My whole life are caught up with my mother because of her disease. She needs me 24 hours a day. I can't do my favorite work. I would like to do it but I feel I cannot do so because my first responsibility is to take care of my mother. I have no choice as we do not have anyone else to provide the care she needs, and I am single and have lower income than my relatives. I think no one can provide a better care for my mother than me. This is the only possible decision I can mak, although I feel very sad that it is necessary"*

4. The primary motivation to care was derived from a strong obligation based on the Buddhist traditional belief of "reviprocity" or personal family values. They felt obliged to provide care simply because they belong to the same family. As a daughter's caregiver said.

> "*I have the responsibility to take care of my parents because I am their daughter. If she is provided care by employed caregivers, the care will be different. They are not so closed as me since they are not my family, so they cannot take care of my mother like me. The relationship between daughter and parents is the most important. I ought to take care of them."*

5. The stresses and strains on caregivers were the complaints related to increasing levels of dependence and demands of caring for the AD patients

"I feel so tired with taking care of my mother ,especially when she always walk around the house and don't sleep over 3 days. I can't take care of her alone because she needs to be taken care all day and night."

Factors affecting to maintain the condition of the AD patients

1. The AD treatment (i.e., cholinesterase inhibitors) not only provide the benefit on cognitive outcomes which helped delay disease progression to FTC, but also decrease the care burden for caregivers and encourage them to feel better. As described by one caregiver as follows.

"Sometime she will call my name as well , something she has not done for a long time- and she had forgotten that I am her daughter……(crying)…".

2. In the point of view of physicians, the benefit of drug treatment helped enabling the patients to cope with their daily personal functions. As explained by one physician.

"The current drug treatment will delay the deterioration of the patients' condition over a 5 year period to the extent that they can cope with their daily personal functions, i.e. visiting the bathroom or taking a shower. In other words, the AD treatment generally helps stabilizing the "impairment of the patients' functions" and improving their quality of life and considerably lessen the demands for personal care on the part of the patients' caregivers"

3. The most important part of caring for AD patients was the relationship between patients and careers including health care system which should give the support to maintain the best long term condition of the AD patients.

4. The early diagnosis of AD may help patients seek the treatment in order to delay disease progression to FTC state and decrease burden of career.

In summary, based on the experiences and perspective of caregivers and medical doctors, it was suggested that AD was a heavy burden on caregivers both financially and personally. The early diagnosis and provision AD patients to access to the medical treatment and healthcare system would assist the delay of disease progression. Also

the health care system should support AD patients and their caregivers in order to maintain the best long term condition of the patient.

CHAPTER VI
CONCLUSIONS

The findings from randomized controlled trial and meta-analysis studies showed that donepezil, rivastigmine, and galantamine had significantly benefits on cognitive outcome using the ADAS-cog score when compared with placebo in the treatment of mild to moderate AD(68). In this study, the cognitive outcomes were used to predict the benefit in terms of a reduction in time spent at FTC health state (i.e., a delayed progression time to FTC) and quality-adjusted life years (QALYs). The results were presented as the incremental cost-effectiveness ratios.

Based on the governmental and societal perspectives, at the willingness to pay (WTP) of 300,000 baht per QALY gained in Thailand, galantamine might be cost-effective interventions for all scenarios compared with other drugs and no treatment option. The ICER of galantamine was 229,367 and 157,247 baht per QALY gained using the governmental and societal perspectives, respectively. Moreover, when providing galantamine for the patients with the ADAS-cog score ranging from 17 to 30, EPS, or psychotic symptoms associated with AD, it was less cost per QALY gained compared with the base case scenario. Furthermore, the additional budgets required for providing galantamine at the first year were 13,950 million baht for all recent patients with mild to moderate AD and 3,627 million baht for new cases in all age groups.

In addition, the results of one way sensitivity analysis of providing galantamine at base case scenario based on societal perspective showed that the cost of informal care for FTC was the most sensitive to in the ICER values. Probabilistic sensitivity analysis were presented as the cost-effectiveness acceptability curves demonstrating the probability that multiple treatment options would be cost–effective at different levels of WTP for one QALY gained. The cost effectiveness acceptability curves obtained from probabilistic sensitivity analysis of providing galantamine at base case

scenario were compared with those with different scenarios using a societal perspective. The results showed that at WTP of 100,000 Baht per QALY gained, the probability of being cost-effective of providing galantamine to the patients with ADAS-cog score = 44 (66%), EPS symptom (54%), ADAS-cog score = 30 (49%),PSY symptom (34%), or age=80 (19%) was higher than that of the patients with base case scenario (14%). Moreover, at WTP of 300,000 baht per QALY gained, providing galantamine to all scenarios would be cost-effective. The probability of being cost-effective was between 93-96% when providing galantamine to the AD patients with ADAS-cog score = 44, EPS symptom, ADAS-cog score = 30, PSY symptom, age=80 and the probability of being cost-effective was between 82-85% when providing galantamine to the AD patients with base case or duration of disease=2 or 4 years. The probability of being cost-effective was 72% when providing galantamine to the patients aged 70 years.

Moreover, the estimated budget impact of providing galantamine in mild to moderate AD was 23,187 million baht, whereas that of without treatment was 11,441 million baht for all age groups at the first year. Therefore, the additional budget required for providing galantamine at the first year was 13,950 million baht for all age groups (i.e., 1,978 million baht for age group 60-64 years, 2,425 million baht for age group 65-69 years, 2,635million baht for age group 70-74 years, 2,349million baht for age group 75-79 years, 2,111 million baht for age group 80-84years, and 2,452million baht for age more than 85 years)

In conclusions, the results suggested that cholinesterase inhibitors might be more cost-effective than no drug treatment and galantamine should be the first choice. Furthermore, the most important part of caring for AD patient is not only the drug treatment but also the relationship between patients and caregivers including health care system that support and help provide the best long term care of AD patients.

Recommendations to the further research

1. The number of patients who dropped out from AD treatment should be considered in the disease modeling process for further research.

2. Data on important parameters such as quality of life (utility) and mortality rate should be obtained from Thai data

3. Cost data, caregiver time cost (informal care cost) and expenses should be obtained from a standard costing reference, if available.

4. The prevalence of AD patients may be investigated for representing the AD situation and estimated the budget impact of providing drug treatment.

Recommendations for policy makers

1. As the results of this study, cholinesterase inhibitors especially galantamine may be recommended as the cost-effective options in the treatment of mild to moderate AD patients only. Moreover the first criteria for receiving the treatment of AD should be the AD patients who had ADAS-cog score ranging from 17 (base case) to 30 or had psychotic or EPS symptom associated with AD. Therefore, the policy makers should develop the guidelines on the management of patients with AD such as the criteria for assessing mild to moderate AD and following conditions of AD patients and physicians.

2. The early diagnosis of AD may help patients seek the treatment in order to delay disease progression to FTC state which is the cost burden to society.

3. The most important part of caring for AD patients is not only providing drug treatment but also the support from health care system in order to improve the best long term condition of the patients.

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APPENDIX

APPENDIX A:

The mean annual cost of care per patient with dementia by type of cost and severity of cognitive function.

Severity	Informal costs (Opportunity cost)	Formal costs	Total cost (Informal costs + Formal costs)
Mild	7,476	0	6,347
Moderate	13,513	7,000	16,898
Moderate-Severe	19,893	1,620	15,147
Severe	42,133	7,224	47,407
Total	**83,014**	**15,844**	**85,800**

Cost of care were comprise of the cost of paid caregiver (formal care cost) and the cost of unpaid caregiver (informal care cost). These costs were studied at Ramathibodi hospital, data were collected by questionnaires from one hundred primary caregivers for patients with dementia who received the medical care from out-patient clinics at the internal medicine and/or psychiatric and/or family medicine department. The cost of paid caregiver and unpaid caregiver were estimate by severity of cognitive function see **Appendix A**

The cost of paid caregiver was estimated by the paid amount for employed caregivers per month

The cost of unpaid caregiver (informal care cost) was calculated using the opportunity cost method (72) to value the time spent in providing care by family caregiver . The times spent on providing informal care were the additional time of providing care associated the AD in activities of daily living (ADL)[i.e eating , bathing and dressiong, toileting and mobility] and/or instrumental activities of daily living (IADL) [i.e assistance with financial/legal work, shopping and take to hospital] and/or household activities of daily living (HDL) [i.e preparing meals, preparing medication, housekeeping and laundry].

Costs of informal care = Hours spend on informal care * the real income for employ caregivers or minimum wage rate for unemploy caregivers.

APPENDIX B:

Summary of Economic Evaluation studies for Cholinesterase inhibitors.

I Summary of Economic Evaluation studies for donepezil (DNZ).

Characteristic	Stein et al[a]	Stewart et al[c]	Lanctot et al[d]	Jonsson et al[e]	O'Brien et al[b]	Neumann et al[g]	Small et al[f]	Wilkinson et al[h]
Publication year	1997	1998	1998	1999	1999	1999		
Country setting	UK	UK	Canada	Sweden	Canada	USA	USA	USA
Base year prices	1997 (UK£)	1997 (UK£)	NA (Can$)	1998 (SEK)	1997 (Can$)	1997 (US$)	1997 (US$)	NA
Intervention	-DNZ 5 mg/d , -DNZ 10 mg/d, -no DNZ	-DNZ 5 mg/d -DNZ 10 mg/d, -no DNZ	-DNZ -no DNZ unspecified dose	-DNZ 5 or DNZ 10 mg/d -no DNZ	-DNZ 5 mg/d -no DNZ	-DNZ 5 or DNZ 10 mg/d -no DNZ	-DNZ, -no DNZ unspecified dose	-Before and -after DNZ treatment
Type of analysis	CUA by simple calculation	CEA model	CUA model	CEA model	CEA model	CUA model	Cost analysis	Cost analysis
Target population	Mild to moderate AD	Mild to moderate AD	Mild AD	Mild to moderate AD	Mild to moderate AD	Mild to moderate AD	AD (severity not specified)	AD (severity not specified)
Perspective	Not stated (appears to be health sectors	Not stated (appears to be societal)	Not stated	Not stated (appears to be health and social care sectors)	Societal	Societal	Not stated	Not stated

I Summary of Economic Evaluation studies for donepezil (DNZ) (cont.).

Characteristic	Stein et al[1]	Stewart et al[2]	Lanctot et al[3]	Jonsson et al[4]	O'Brien et al[5]	Neumann et al[6]	Small et al[7]	Elliot et al[8]
Discounting	6%	6%	NA	3%	5%	3%	NA	NA
Time horizon	10 years	5 years	12.5 years	5 years	5 years	1.5 years	0.5 years	1 years
Cost estimation	Direct medical cost	Direct medical and nonmedical costs for patient	NA	Direct medical and nonmedical costs for patient	Direct medical and nonmedical costs for patient, indirect costs for caregiver	Direct medical and nonmedical costs for patient, indirect costs for caregiver	Direct medical and nonmedical costs for patient	Direct medical and nonmedical costs for patient
Relevant costs*	√ Healthcare resources (drug costs only) X Patient/family resources X Social care sector resources √ Patient benefits (estimated IHQL) X Career benefits	√ Healthcare resources √ Patient/family resources √ Social care sector resources √Patient benefits X Career benefits	√ Healthcare resources √ Patient/family resources √ Social care sector resources √Patient benefits X Career benefits	√ Healthcare resources X Patient/family resources √ Social care sector resources √Patient benefits X Career benefits	√ Healthcare resources √ Patient/family resources √ Social care sector resources √Patient benefits X Career benefits	√ Healthcare resources √ Patient/family resources √ Social care sector resources √Patient benefits √Career benefits		
Outcome estimated	QALY estimated base on the IHQL	Number. of years in non-severe AD	QALYs	Number. of years in non-severe AD	Number. of years in non-severe AD	QALY based on caregiver proxy from cross-	cost savings	cost savings

I Summary of Economic Evaluation studies for donepezil (DNZ) (cont.).

Characteristic	Stein et al[1]	Stewart et al[2]	Lamdot et al[3]	Jonsson et al[4]	O'Brien et al[5]	Neumann et al[6]	Small et al[7]	Hillit et al[8]
	(Index of Health Related Quality of Life)	state (by MMSE≥ 10) over 5 years , cost savings		state (by MMSE≥ 10) over 5 years , cost savings	state (by MMSE≥ 10) over 5 years , cost savings	sectional study (HUIs		
Analytical approach to estimating outcome		Markov model of 6 mo/cycle of transition probabilities for AD progression	Markov model of progression of AD through 4 stages until death	Markov model of 6 mo/cycle of transition probabilities for AD progression	Markov model of 6 mo/cycle of transition probabilities for AD progression	Markov model of 6 wk/cycle of transition probabilities for AD progression	Difference in direct medical and non-medical costs of caring per patient in DNZ and no-DNZ groups	Difference in direct medical and non-medical costs/ patient before and after DNZ treatment
RESULTS								
Cost/patient for study period								
DNZ	NA	£45,694 (10 mg) £45,119 (5 mg)	Can $97,698	SKr 757,015 (10 mg) SKr 744,880 (5 mg)	can $80,305	$72,487	$3443	After DNZ, $15.34/d
No DNZ	NA	£44,277	Can $105,206	SKr 760,441	can $81,187	$72,227	$3476 ,	Before DNZ $10.45/d
DNZ vs. No DNZ		↑$1,417 (10 mg)	**Cost savings** ↓Can 7,506	**Cost savings** ↓SKr 3,426	**Cost savings** ↓Can $882	↑$260	**Cost savings** ↓$33	↑$4.89/day

I Summary of Economic Evaluation studies for donepezil (DNZ) (cont.).

Characteristic	Stein et al[1]	Stewart et al[2]	Lanctot et al[3]	Jonsson et al[4]	O'Brien et al[5]	Neumann et al[6]	Small et al[7]	Ellis et al[8]
		†$ 842 (5 mg)		(10mg) ↓SKr 15,561 (5 mg)				
Outcome/patient								
Outcome measure	QALYs	Estimated no. of years saved with Non-severe AD	QALYs	Estimated no. of years saved with non-severe AD	Estimated no. of years saved with non-severe AD	QALYs	NA	NA
DNZ	No described	1.82 (10 mg) 1.69 (5 mg)	2.27	3.34 (10 mg) 3.32 (5 mg)	2.41	0.95	NA	NA
No DNZ	No described	1.57	1.96	2.80	2.21	0.92	NA	NA
DNZ vs. no DNZ	0.05-0.08	0.25 (10 mg) 0.12 (5 mg)	0.31	0.54 (10 mg) 0.52 (5 mg)	0.20	0.03	NA	NA
Cost/outcome ratio, DNZ vs. no DNZ (ICER)	**Cost/QALYs** †£120,198-£194,720 (10mg) †£85,815-139,020 £ (5 mg)	**Incremental cost/year in non-severe AD** †$5,698 (10 mg) †$7,048 (5 mg)	**Cost/QALYs** Can 24,219 (DNZ dominant over NT)	**Cost savings/ year in non-severe AD** SKr 6,344 (10mg) SKr 29,925 (5 mg) (DNZ dominant over NT)	**Cost saving/ year in non-severe AD** Can $4,410 (DNZ dominant over NT)	**Cost/QALYs** †$8,667	(DNZ dominant over NT)	NA

? means unclear or unknown

√ means judged item suitable to generalize to England and Wales with or without some re-adjustment

X means factor judged not suitable as either not possible to see how an adjustment could be made easily in short/medium term or relevant data unavailable

NA = not applicable.

Dominance means that drug treatment is both cheaper (cost) and better (outcome)

NT = no pharmacological treatment

ICER = incremental cost-effectiveness ratio

Summary

The cost-effectiveness of donepezil included 8 published RCTs studies.

- Most economic evaluations of donepezil (five of the eight published studies [2-6]) have used a state transition model (Markov model) to estimation of the cost effectiveness of donepezil.
- Three studies used MMSE scores to define either four or five levels of AD severity[2,4,5] and one studies used CDR scores to define three levels of disease severity[6]
- Three studies presents Cost-effective analysis (CEA) [2,4,5] , Three studies presents CUA[1,3,6] and two studies presents cost analysis[7,8]
- The main outcome measures are years saved by preventing patients from entering the next, more severe stage of AD or delay in disease progression was used to calculate the total cost savings associated with treatment according to disease severity and/or QALYs gains
- Three studies[3,4,5] found donepezil more cost-effective than a no-drug treatment strategy, 2 studies[7,8] concluded that donepezil was cost neutral, and 3 stud- ies[1,2,6] found donepezil use to be associated with additional costs. O'Brien et al[5] estimated that cost savings per year in non-severe AD state over

5 years of donepezil treatment would equal Can $4,410 per patient. A European study by Jonsson et al[4] predicted cost savings per year in non-severe AD state over 5 years of SKr 29,925 per patient for donepezil 5 mg and SKr 6,344 per patient for donepezil 10 mg. The CUA by Lanctot et al[3] predicted (Cost/QALYs) savings of Can 24,219per patient over 12.5 years.

II Summary of Economic Evaluation studies for Rivastigmine (RIVA)

Characteristic	Stein9	Fenn and Gray10	Hauber et all1	Hauber et all2
Publication year	1998	1999	2000	2000
Country setting	UK	UK	USA	Canada
Base year prices	1997 (UK£)	1997 (UK£)	1997 (US$)	1997 (Can$)
Intervention	-Rivastigmine 6–12 mg -Placebo	-Rivastigmine low dose (1–4 mg), high dose (6–12 mg) -Placebo	-Rivastigmine 6–12 mg -Placebo	-Rivastigmine low dose (1–4 mg), high dose (6–12 mg) -Placebo
Type of analysis	CUA by simple calculation	CEA model	CEA model	CEA model
Target population	Mild to moderate AD	Mild to moderate AD	Mild to moderate AD	Mild, Mild to moderate and Moderate AD
Perspective	NA	Health and social care systems	NA	societal
Discounting	6% for cost, Benefit not discounted	NA	3% for cost	3% for cost
Time horizon	5 years	2 years	2 years	2 years
Cost estimation	Direct medical(drug costs only) and nonmedical costs for patient cost of RIVA included	Direct medical and nonmedical costs for patient, cost of RIVA not included	Direct medical and nonmedical costs for patient, indirect costs for caregivers, cost of RIVA not included	Direct medical and nonmedical costs for patient, indirect costs for caregivers, cost of RIVA included
Relevant costs	√ Healthcare resources (drug costs only)	√ Healthcare resources X Patient/family resources	√ Healthcare resources ? Patient/family resources	√ Healthcare resources √ Patient/family resources

II Summary of Economic Evaluation studies for Rivastigmine (RIVA) (cont.)

Characteristic	Stein9	Fenn and Gray10	Hauber et all1	Hauber et all2
	X Patient/family resources X Social care sector resources √ Patient benefits (estimated IHQL) X Career benefits	√ Social care sector resources √ Patient benefits X Career benefits	? Social care sector resources √ Patient benefits X Career benefits	√ Social care sector resources √ Patient benefits √ Career benefits (threshold analysis)
Outcome estimated	NNT analysis and QALYs estimated base on the IHQL (Index of Health Related Quality of Life)	Number. Of days at MMSE>10	Number of days saved by each baseline cohort delay in progression to more severe stages (by MMSE) , cost savings over time	Number of days saved by each baseline cohort delay in progression to more severe stages (by MMSE) , cost savings over time
Analytical approach to estimating outcome	-NNT were calculated from pooled analyses of three clinical trial -Cost utility estimates based on drug cost only No modelling was undertaken	Hazard model of cognitive decline	Hazard model of cognitive decline	Hazard model of cognitive decline
RESULTS : **Cost/patient for study period**				
RIVA		£ 4619 (mild) £ 6763 (moderate)	Can $ 14,503 (mild) Can $ 29,556 (milddmoderate) Can $ 50,993 (moderate)	$ 1,371 (mild) $ 24,004 (moderate)
No RIVA		£ 5846 (mild) £ 7540 (moderate)	Can $ 19,206 (mild) Can $ 32,574 (milddmoderate) Can $ 52,264 (moderate)	$ 3,468 (mild) $ 26,294 (moderate)

II Summary of Economic Evaluation studies for Rivastigmine (RIVA) (cont.)

Characteristic	Stein9	Fenn and Gray10	Hauber et all1	Hauber et all2
RIVA vs. no RIVA		Cost savings in non-severe AD ↓£ 1227 (mild) ↓£ 777 (moderate)	Cost savings ↓Can $ 4,703(mild) ↓Can $ 3,018 (mild&moderate) ↓Can $ 1,331 (moderate)	Cost savings ↓$ 4,839 (mild) ↓$ 2,290 (moderate)
Outcome/patient:				
Outcome measure	QALYs	Estimated no. of days saved by preventing patients from entering the next, more severe stage AD	Estimated no. of days saved by preventing patients from entering the next, more severe stage AD	Estimated no. of days saved by preventing patients from entering the next, more severe stage AD
RIVA vs. no RIVA	NNTs ranged from 9-25 QALY 0.05-0.08	NA	NA	NA
Cost-outcome ratio, RIVA vs. no RIVA (ICER)	RIVA :Cost/QALYs £ 45,825-£73,320 no RIVA :Cost/QALYs £ 14,543-£ 88,915 N/A	(RIVA dominant over NT)	Cost savings/ day in non-severe AD Can $ 188 (mild) Can $ 106 (mild&moderate) Can $ 44 (moderate) (RIVA dominant over NT)	Cost savings/ day in non-severe AD $ 125 (mild) $ 61 (moderate) (RIVA dominant over NT)

? means unclear or unknown

√ means judged item suitable to generalize to England and Wales with or without some re-adjustment

X means factor judged not suitable as either not possible to see how an adjustment could be made easily in short/medium term or relevant data unavailable

NA = not applicable.

Dominance means that drug treatment is both cheaper (cost) and better (outcome)

NT = no pharmacological treatment

ICER = incremental cost-effectiveness ratio

Summary

The cost-effectiveness of Rivastigmine included 4 published RCTs studies.

- Three of the four studies[10-12] use a hazard model to examine disease progression in their estimation of the cost-effectiveness of rivastigmine.(hazard model was developed by Fenn and Gray[10])

- Three studies[10-12] used MMSE scores to define either three or four stages of disease severity.

- Three studies [10-12] report on the cost-effectiveness of rivastigmine. One studies[9] estimates cost-utility by simple calculations

- Three studies [10-12] the main outcome is measured as a days saved by preventing patients from entering the next, more severe stage of AD or delay in disease progression was used to calculate the total cost savings associated with treatment according to disease severity . One studies[9] is measured as cost per QALY base on drug costs only.
- Three studies[10-12] found rivastigmine more cost-effective than a no-drug treatment strategy and 1 studies[9] found rivastigmine use to be associated with additional costs.
- Three studies[10-12] presented economic data for 3 durations of treatment-6 months, 1 year, and 2 years-and predicted increasing cost savings with increased duration of treatment (Cost savings became significant when the time horizon was extended to 2 years)

III. Summary of Economic Evaluation studies for Galantamine (GALAN)

Characteristic	Getsios et al.[13]	Garfield et al.[14]	Caro et al.[15]	Migliaccio-Walle et al.[16]	Ward et al.[17]
Publication year	2001	2002	2002n	2003	2003
Country setting	Canada	Sweden	The Netherlands	USA	UK
Base year prices	1999 (Can$)	1998 (€/SEK)	1998 (NLG)	2000 (US$)	2001 (UK£)
Intervention	-Galantamine 24 mg daily -Placebo	-Galantamine 12 mg three times daily (36mg) -Placebo	-Galantamine (dose not stated in text) -Placebo	-Galantamine 16 and 24 mg daily -Placebo	-Galantamine 16 and 24 mg daily -Placebo
Type of analysis	CEA model (CUA)	CEA model	CEA model (CUA)	CEA model	CEA model (CUA)
Target population	Mild to moderate AD	Mild to moderate AD	Mild to moderate AD	Mild to moderate AD	Mild to moderate AD
Perspective	Not stated (appears to be third-party payer)	Not stated (appears to be third-party payer)	Health care system	third-party payer	UK NHS and PSS
Discounting				Costs and benefits were discounted at 3%.	6% for cost, 1.5% for outcome
Time horizon	10 years	10 years	10 years	10 years	10 years
Cost estimation	Direct medical(drug costs only) and	Direct medical and nonmedical costs for	Direct medical and nonmedical	Direct costs, including medical and social service	Direct costs, including medical and social

III. Summary of Economic Evaluation studies for Galantamine (GALAN) (cont.)

Characteristic	Getsios, et al.[13]	Garfield et al.[14]	Caro et al.[15]	Migliaccio-Walle et al.[16]	Ward et al.[17]
	nonmedical costs for patient cost of RIVA included	patient, cost of RIVA not included	costs for patient, indirect costs for caregivers, cost of RIVA not included	costs	service costs
Relevant costs	√ Healthcare resources (drug costs only) X Patient/family resources X Social care sector resources √ Patient benefits (estimated IHQL) X Career benefits	√ Healthcare resources X Patient/family resources √ Social care sector resources √ Patient benefits X Career benefits	√ Healthcare resources ? Patient/family resources ? Social care sector resources √ Patient benefits X Career benefits	√ Healthcare resources X Patient/family resources √ Social care sector resources √ Patient benefits X Career benefits (threshold analysis)	√ Healthcare resources X Patient/family resources √ Social care sector resources √ Patient benefits X Career benefits
Outcome estimated	-reduced time in need of full-time care(assessed based on changes in the ADAS-cog); cost savings over time and -QALY gains	-reduced time in need of full-time care (assessed based on changes in the ADAS-cog); cost savings over time and -NNT	-reduced time in need of full-time care(assessed based on changes in the ADAS-cog); cost savings over time and -QALY gains	-reduced time in need of full-time care (assessed based on changes in the ADAS-cog); cost savings over time and -NNT	- reduced time in need of full-time care (assessed based on changes in the ADAS-cog); cost savings over time and -QALY gains

III. Summary of Economic Evaluation studies for Galantamine (GALAN) (cont.)

Characteristic	Getsios et al.[13]	Garfield et al.[14]	Caro et al.[15]	Migliacio-Walle et al.[16]	Ward et al.[17]
Analytical approach to estimating outcome	AHEAD (Assessment of Health Economics in Alzheimer's Disease) model	AHEAD model	AHEAD model	AHEAD model	AHEAD model
RESULTS:					
Cost/patient for study period					
GALAN				NA	£ 28,615 (16 mg.) £ 28,806 (24 mg.)
No GALAN				NA	£ 28,134
GALAN vs. no GALAN				**Cost savings** $2,408 to $3,601 per patient	†£ 481 (16 mg) †£ 672 (24 mg)
Outcome/patient:					
Outcome measure	-Estimated no. of month were delayed to full time care -QALYs	-Estimated no. of month were delayed to full time care -NNT	Estimated no. of month were delayed to full time care -QALYs	-Estimated no. of month were delayed to full time care -NNT	-Estimated no. of month were delayed to full time care -QALYs

III. Summary of Economic Evaluation studies for Galantamine (GALAN) (cont.)

Characteristic	Gabios et al.[13]	Garfield et al.[14]	Caro et al.[15]	Migliaccio-Walle et al.[16]	Ward et al.[17]
GALAN vs. no GALAN				-time spent in pre-FTC would increase by 7% to 8%, and delays in FTC 12% to 14% ,reduce the mean time in FTC to 19.9 months (16 mg) 19.4 months (24 mg) and number needed to treat: (NNT) 4.6 patients needed to start treatment with 16 mg to avoid 1 year of FTC. ,3.9 patients in 24 mg.	2.50 months (16 mg.) 3.02 months (24 mg.) and 0.022 QALY
Cost-outcome ratio, GALAN vs. no GALAN; (ICER)	**(GALAN dominant over NT)**	**(GALAN dominant over NT)**	**(GALAN dominant over NT)**	**(GALAN dominant over NT)**	**-Incremental costs** per month of full-time care avoided average £192 per patient -Cost/QALY £8,693

* ***?*** means unclear or unknown

√ means judged item suitable to generalize to England and Wales with or without some re-adjustment

X means factor judged not suitable as either not possible to see how an adjustment could be made easily in short/medium term or relevant data unavailable

Full-time care (FTC) is defined as the consistent requirement for a significant amount (for the greater part of the day) of caregiving and supervision each day.

NA = not applicable.

Dominance means that drug treatment is both cheaper (cost) and better (outcome)

NT = no pharmacological treatment

ICER = incremental cost-effectiveness ratio

Summary

The cost-effectiveness of Galantamine included 5 published RCTs studies.

- All studies[13-17] use the Assessment of Health Economics in Alzheimer's Disease (AHEAD) model for modeling disease progression in their estimation of the cost-effectiveness of galantamine (model was developed by Caro and colleagues)
- Cognitive function was assessed at baseline using the Mini-Mental State Examination (MMSE) and efficacy was assessed based on changes in the ADAS-cog, the cognitive subscale of the Alzheimer's Disease Assessment Scale
- All studies[**13-17**] report on the cost-effectiveness of galantamine. Cost savings over time were calculated on patient benefits in terms of a reduction in time spent in FTC, and/or a delay in requiring FTC, as the main outcome, with an incremental 10-year cost. Three studies[13,15,17] report the mean gain in QALYs over time and two studies[14,16] estimates Number needed to treat: (NNT) with galantamine to avoid 1 year of full time care.

- Four studies[13-16] found galantamine more cost-effective than a no-drug treatment strategy and one studies[17] found the ten-year incremental costs per month of full-time care avoided average £192 per patient and £8,693 per QALY.

BIOGRAPHY

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