ปัจจัยที่ส่งผลกระทบต่อความร่วมมือในการรักษาด้วยยาต้านซึมเศร้า ในผู้ป่วยโรคซึมเศร้าชาวไทย

นางสาวอภิรดี ศรีสว่าง

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
สาขาวิชาเภสัชกรรมคลินิก ภาควิชาเภสัชกรรม
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2550

FACTORS INFLUENCING ADHERENCE TO ANTIDEPRESSANTS IN THAI DEPRESSED PATIENTS

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A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Science in Pharmacy Program in Clinical Pharmacy

Department of Pharmacy

Faculty of Pharmaceutical Sciences

Chulalongkorn University

Academic Year 2007

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อภิรดี ศรีสว่าง : ปัจจัยที่ส่งผลกระทบต่อความร่วมมือในการรักษาด้วยยาต้านซึมเศร้าในผู้ป่วยโรคซึมเศร้าชาวไทย. (FACTORS INFLUENCING ADHERENCE TO ANTIDEPRESSANTS IN THAI DEPRESSED PATIENTS) อ. ที่ปรึกษา : รศ.ดร. ควงจิตต์ พนมวัน ณ อยุธยา, อ.ที่ปรึกษาร่วม : นพ. นิพัทธ์ กาญจนธนาเลิศ, 102 หน้า.

การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาปัจจัยที่ส่งผลกระทบต่อความร่วมมือในการรักษาด้วยยาต้านซึมเศร้าของผู้ป่วยซึมเศร้าชาวไทย ทำการศึกษาโดยใช้แบบสอบถาม การสัมภาษณ์ และเก็บข้อมูลจากเวชระเบียน กลุ่มตัวอย่างของการศึกษานี้มีอายุระหว่าง 18-60 ปี ได้รับการวินิจฉัยว่าเป็นโรคซึมเศร้าโดยจิตแพทย์ และเป็นผู้ป่วยนอกที่คลินิกจิตเวช ณ โรงพยาบาลจุฬาลงกรณ์ ที่มารับการรักษาในระหว่างเดือนเมษายน 2550 ถึงเดือนธันวาคม 2550 ผู้ป่วยทั้งหมดที่เข้าร่วมการศึกษามีจำนวน 217 ราย ผู้ป่วยส่วนมากมีความร่วมมือในการรักษาด้วยยาค่อนข้างสูงทั้งจากการวัดความร่วมมือด้วย Likert scale (คะแนนเฉลี่ย 22.63 ± 3.25) และ Visual analog scale (ร้อยละเฉลี่ย 87.68 ± 16.81) ผู้ป่วยร้อยละ 80.6 เกิดอาการไม่พึงประสงค์จากยาโดยอาการไม่พึงประสงค์ที่พบมากคือ ปากแห้ง ง่วงนอน อ่อนเพลีย นอนไม่หลับ และน้ำหนักเพิ่ม ตามลำดับ สาเหตุส่วนใหญ่ที่ทำให้ผู้ป่วยไม่ให้ความร่วมมือในการรับประทานยาคือ ลืมรับประทาน ผู้ป่วยรู้สึกดีขึ้นจึงหยุดรับประทานหรือรับประทานน้อยลง เกิดอาการไม่พึงประสงค์จากยาและกลัวติดยา ผู้ป่วยส่วนมากมีทัศนคติต่อการรักษาด้วยยาค่อนข้างดี (คะแนนเฉลี่ย 3.69 ± 0.48) และมีทัศนคติต่อแพทย์ค่อนข้างดีกว่า (คะแนนเฉลี่ย 4.06 ± 0.54) จากการหาความสัมพันธ์ระหว่างตัวแปรต่าง ๆ พบว่าความไม่ร่วมมือในการรักษาด้วยยามีความสัมพันธ์กับผู้ป่วยที่มีรายได้น้อย ระดับของผลกระทบจากอาการไม่พึงประสงค์ ผู้ป่วยที่ลืมรับประทานยา และผู้ป่วยที่มีทัศนคติที่ไม่ดีต่อการรักษาด้วยยาต้านซึมเศร้า จากการวิเคราะห์ในสมการถดถอยพหุแบบขั้นตอน พบว่าระดับของผลกระทบจากอาการไม่พึงประสงค์ การลืมรับประทานยา และทัศนคติของผู้ป่วยต่อการรักษาด้วยยาต้านซึมเศร้าในด้านประสิทธิภาพของยาและการรับประทานยาน้อยลงเมื่ออาการดีขึ้น สามารถทำนายความร่วมมือในการรักษาด้วยยาได้อย่างมีนัยสำคัญทางสถิติ โดยสามารถทำนายความสัมพันธ์ได้ร้อยละ 12.6 (R^2 = 0.126) ดังนั้นการเพิ่มความร่วมมือในการรักษาด้วยยาต้านซึมเศร้าอาจทำได้โดยการช่วยให้ผู้ป่วยมีทัศนคติที่ดีต่อการรักษาด้วยยาต้านซึมเศร้า ช่วยหาวิธีในการช่วยเตือนความจำในการรับประทานยาของผู้ป่วย และลดผลกระทบจากอาการไม่พึงประสงค์จากยาต้านซึมเศร้า

ภาควิชา.....เภสัชกรรม.....ลายมือชื่อนิสิต.....

สาขาวิชา.....เภสัชกรรมคลินิก..... ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา.....2550.....ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

4876619033 : MAJOR CLINICAL PHARMACY

KEY WORD: ADHERENCE / ASSOCIATION / ANTIDEPRESSANTS / DEPRESSION

APIRADEE SRISAWANG : FACTORS INFLUENCING ADHERENCE TO ANTIDEPRESSANTS IN THAI DEPRESSED PATIENTS. THESIS ADVISOR : ASSOC. PROF. DUANGCHIT PANOMVANA NA AYUDHYA, Ph.D., THESIS COADVISOR : NIPATT KARNJANATHANALERS, M.D., 102 pp.

This study aimed at examining factors influencing adherence to antidepressants treatment in Thai depressed patients focusing on socioeconomic characteristics, treatment characteristics and attitudes towards antidepressant treatment and physicians. The study design was a descriptive cross-sectional survey by using questionnaires. The study samples were Thai depressed patients diagnosed of depression by psychiatrists and admitted as outpatients at psychiatric clinic of King Chulalongkorn Memorial Hospital during April to December 2007. The study samples were 217 patients. Most of the patients had high adherence using both Likert scale measurement (mean ± SD; 22.63 ± 3.25) and visual analog scale (mean ± SD; 87.68 ± 16.81). The study showed that 80.6 % of patients experienced side effects from antidepressants. Most common side effects were dry mouth, somnolence, fatigue, insomnia and weight gain, respectively. The main reasons for antidepressant nonadherence were medicine forgotten, feeling better, adverse events, fear of antidepressant dependence, respectively. Most of the patients had favorable beliefs about antidepressants (mean ± SD of score; 3.69 ± 0.48) and had higher favorable beliefs about physicians (mean ± SD of score; 4.06 ± 0.54). Patients with low income, increased impact of side effects, forgetting of drugs and unfavorable attitudes towards antidepressants were related to nonadherence to treatment. Multiple regression of adherence to antidepressants found impact of side effects, medicine forgotten and two aspects of attitudes towards medications; i.e., efficacy of antidepressants and taking less when feeling better, significantly predicted the adherence to antidepressant treatment and accounted for 12.6 % of the coefficient of determination. Thus, adherence to antidepressants treatment was improved by increasing favorable attitudes towards medications, enhancing awareness to take medications and decreasing impact of antidepressant side effects.

Department……Pharmacy…….. Student's signature.....Apiradee.....

Field of study…..Clinical Pharmacy ..... Advisor's signature.....Duangchit Panomvana.....

Academic year …. ….2007…….. ……..Co-advisor's signature.....นิพัทธ์ กาญจนเธียร.....

Acknowledgements

First of all, I would like to express my sincere gratitude to my thesis advisor, Associate Professor Duangchit Panomvana Na Ayudhya of the Department of Pharmacy, Faculty of Pharmaceutical Science, Chulalongkorn University, for the valuable advice, continual guidance, suggestions, encouragement and very kindness throughtout the course of this study.

To my thesis co-advisor, Nipatt Karnjanathanalers, M.D., Department of Psychiatry, King Chulalongkorn Memorial Hospital, I wish to express my deeply thankfulness for his encouragement, suggestions and kindness.

Unforgettably, I would like to thank the members of the thesis committees for giving me invaluable guidance, suggestions and kindness.

My gratefulness is extended to Ms. Wannee Ittiwattanakul and Miss Pinkamon Sukkhasem for their suggestions and kindness.

My thankfulness is also extended to all physicians, nurses and nurse aids at the psychiatric outpatient clinic of King Chulalongkorn Memorial Hospital for their helpfulness and kindness.

Most of all I am deeply grateful to my parents, my roommate, all of lovely classmates of Clinical Pharmacy and all of my friends for their encouragement, understanding and supporting throughout my graduate study.

Finally, I would like to express my thanks and gratitude to all patients who participate in this study and all of those whose name have not been mentioned for helping me in any way for this study.

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LIST OF ABBREVIATIONS

5-HT	:	Serotonin
B	:	Coefficient
Beta	:	Regression Coefficient
CI	:	Confidence Interval
DA	:	Dopamine
df	:	Degrees of Freedom
DRI	:	Dopamine reuptake inhibitor
DSM-IV-TR	:	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision
ECT	:	Electoconvulsive Therapy
MAOI	:	Monoamine oxidase inhibitor
Mean	:	Mean value
MEMS	:	Medication event monitoring system
N	:	Number of Samples
NE	:	Norepinephrine
NRI	:	Norepinephrine reuptake inhibitor
OPD	:	Outpatient Department
OR	:	Odds Ratio
p-value	:	The partial F test
r	:	Correlation Coefficient
R^2	:	Correlation Coefficient Square
SD	:	Standard Deviation
SRI	:	Serotonin reuptake inhibitor
SSRI	:	Selective serotonin reuptake inhibitor
t	:	Square root of the F value
TCA	:	Tricyclic antidepressant

VAS	:	Visual analog scale
x	:	Number of factor
χ^2	:	Chi-Square Statistic

CHAPTER I

INTRODUCTION

Background and rationale

Depressive disorders are significant public health problems, usually associated with symptom severity and role impairment. The prevalence of major depressive disorder for lifetime was 16.2% and for 12-month was 6.6%*(1)*. Depressive disorders are associated with significant suffering, high morbidity and mortality, and psychosocial functional impairment. Depression also constitutes a substantial economic burden for society*(2)*. In addition, they cause substantial disability and cost in the US alone $43.7 billion/year. Depression is the most important risk factor for suicide, with about 21% and 18% for the patients with recurrent depressive disorders and dysthymia attempting suicide, respectively. About two thirds of suicides occure in depressed patients. Depressive disorders are likely to cause more disabilities than many other chronic diseases such as osteoarthritis and diabetes*(3, 4)*. A WHO report ranked depression as the fourth medical condition with the greatest disease burden worldwide, measured in disability-adjusted life years. The same report predicted that depression would be the condition with the second greatest disease burden worldwide by 2020. Several studies indicate that depression significantly influences the course of concomitant medical diseases. Appropriate antidepressant therapy improves the daily functioning and overall health of patients with depressive disorders*(3)*. Despite the availability of new effective antidepressants, recurrence and relapse rates for depression are high (up to 80%), treatment failures are common (40% to 60%), and as many as 20% of patients remain inadequately treated*(5)*.

Depression, a chronic and highly recurrent illness, often requires a life-long antidepressant treatment to prevent relapses and recurrence*(6, 7)*. Adherence is a significant problem for antidepressant therapy because rates of nonadherence are high in depressed patients*(3, 6, 8-10)*. Demyttenaere reviewed that depression was related to nonadherence*(6)*. About 50% of patients who receive an initial prescription for an antidepressant discontinue treatment within the first month*(3)*. Olfson et al. found that 42% discontinued their antidepressants during the first 30 days and 72% had stopped within 90 days. In addition, in a large study of 240,604 patients who were given a new prescription for an antidepressant, 70% discontinued within 6 months*(11)*.

In clinical trial settings found that 30% of patients do not complete treatment, thus considerably diminishing the effectiveness of antidepressants*(12)*. In addition, patients who discontinue antidepressant treatment may have relapse rates over 50%*(13)*, so that adherence greatly influences effectiveness of antidepressant treatment.

Rates of nonadherence to antidepressant treatment are high among all classes of antidepressants. Among 164 patients taking any type of antidepressant, 28% discontinued treatment within the first month and 44% discontinued treatment within 3 months of initiation of therapy*(5)*. Important factors influencing adherence of depressed patients are side effects of antidepressants, fear of drug dependence, delayed onset of antidepressant action, complicated dosing, cost of medication and perceiving medication as ineffective*(5, 6, 14)*. The 2000 British Survey of National Psychiatric Morbidity found that 217 from 634 patients (34.2%) reported incomplete adherence to their psychiatric medication included antidepressants. Reasons for incomplete adherence included medicine forgotten, losing and running out (37.4%); thinking medication unnecessary (24.6%); reluctance to take drugs (18.9%) and side effects (14.2%). This survey showed that taking less medication than prescribed is most likely to be a intentional decision by patients who do not think they need it or do not want to take it. Discussion about medication may help to reduce nonadherence*(10)*.

Ashton et al. found that 60% of patients indicated they had completely discontinued at least 1 antidepressant medication at some point in their lives. The most frequently cited reason for discontinuation was lack of efficacy. In addition, patients currently being treated with an antidepressant, 22% reported nonadherence. The 10 most common reasons for nonadherence indicated by patients included medicine forgotten, weight gain, sexual dysfunction, lost interest in sex, takes less when feels better, wants to take less medication, headaches, cost of medication, worried about safety of medication and too frequent administration, respectively. This study showed that ways enhancing treatment adherence included understanding about patients'expectation and need from antidepressant therapy and selecting antidepressants for patients by providing data regarding which side effects might be most difficult for patients to accept*(9)*.

Moreover, important factors influencing adherence included physician-patient relationship. Several studies had shown that physician-patient communication and understanding about patients both impact treatment adherence*(5, 8, 15, 16)*. In addition, unnecessary complexity of multiple daily dosing regimen could contribute to nonadherence and might account for a substantial proportion of treatment failure*(17)*.

However, there are few studies that determine factors influencing adherence to antidepressants of Thai depressed patients. Therefore, it is important to examine these factors in Thai depressed patients. Because treatment of depression requires long-term therapy, antidepressant adherence greatly impacts effectiveness of treatment. Thus, providing of patients'data about antidepressant treatment can help health professionals to promote effectiveness of depression treatment.

Objectives

To examine

1. Socioeconomic factors influencing adherence to antidepressants of depressed patients
2. Attitudes towards antidepressant medications and physicians influencing adherence to antidepressants of depressed patients
3. Treatment characteristics influencing adherence to antidepressants of depressed patients

Benefits

1. Providing data about patients'attitudes towards antidepressant treatment and physician, side effects, dosing regimen, and sociodemographic and socioeconomic factors that influencing adherence to antidepressants
2. Providing suggestion of promoting effectiveness of antidepressant therapy

CHAPTER II

LITERATURE REVIEW

Depressive disorders

Major depressive disorder is a disorder of mood in which the individual experiences one or more major depressive episodes without a history of manic, mixed, or hypomanic episodes. A major depressive episode is defined by the criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR), published by the American Psychiatric Association. Depression is associated with significant functional disability, morbidity, and mortality.

The etiology of depressive disorders is too complex to be totally explained by a single social, developmental, or biologic theory. Several factors appear to work together to cause or precipitate depressive disorders. The symptoms reported by patients with major depression consistently reflect changes in brain monoamine neurotransmitters, specifically norepinephrine (NE), serotonin (5-HT), and dopamine (DA)*(18-20)*.

A patient diagnosed with major depressive disorder can expect to have one or more episodes of major depression during their life-time. According to the DSM-IV-TR a single major depressive episode is characterized by five or more of the symptoms described in Table 1. At least one of the symptoms is depressed mood or loss of interest or pleasure in nearly all activities. These symptoms must have been present nearly every day for at least 2 weeks and must represent a change from the patient's previous level of functioning*(18)*. An episode may be characterized by sadness, indifference, apathy, or irritability and is usually associated with: changes in sleep patterns, appetite, and weight; motor agitation or retardation; fatigue; impaired

concentration and decision-making; feelings of shame or guilt; and thoughts of death or dying*(21)*.

Table 1 DSM-IV-TR criteria for major depressive episode*(18)*

A.	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition or mood-incongruent delusions or hallucinations. 1. Depressed mood most of the day nearly every day 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day nearly every day 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day 4. Insomnia or hypersomnia nearly every day 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) 6. Fatigue or loss of energy nearly every day 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B.	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C.	The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
D.	The symptoms are not better accounted for by bereavement (i.e., after the loss of a loved one), the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

In some depressed patients, the mood disorder does not appear to be episodic and is not clearly associated with either psychosocial dysfunction or change from the individual's usual experience in life. Dysthymic disorder consists of a pattern of chronic (at least 2 years), ongoing, mild depressive symptoms that are less severe and less disabling than those found in major depression; the two conditions are sometimes difficult to separate, however, and can occur together (double depression). Dysthymic disorder exists in ~5% of primary care patients. The term minor depression is used for individuals who experience at least two depressive symptoms for 2 weeks, but who do not meet the full criteria for major deprssion*(21)*.

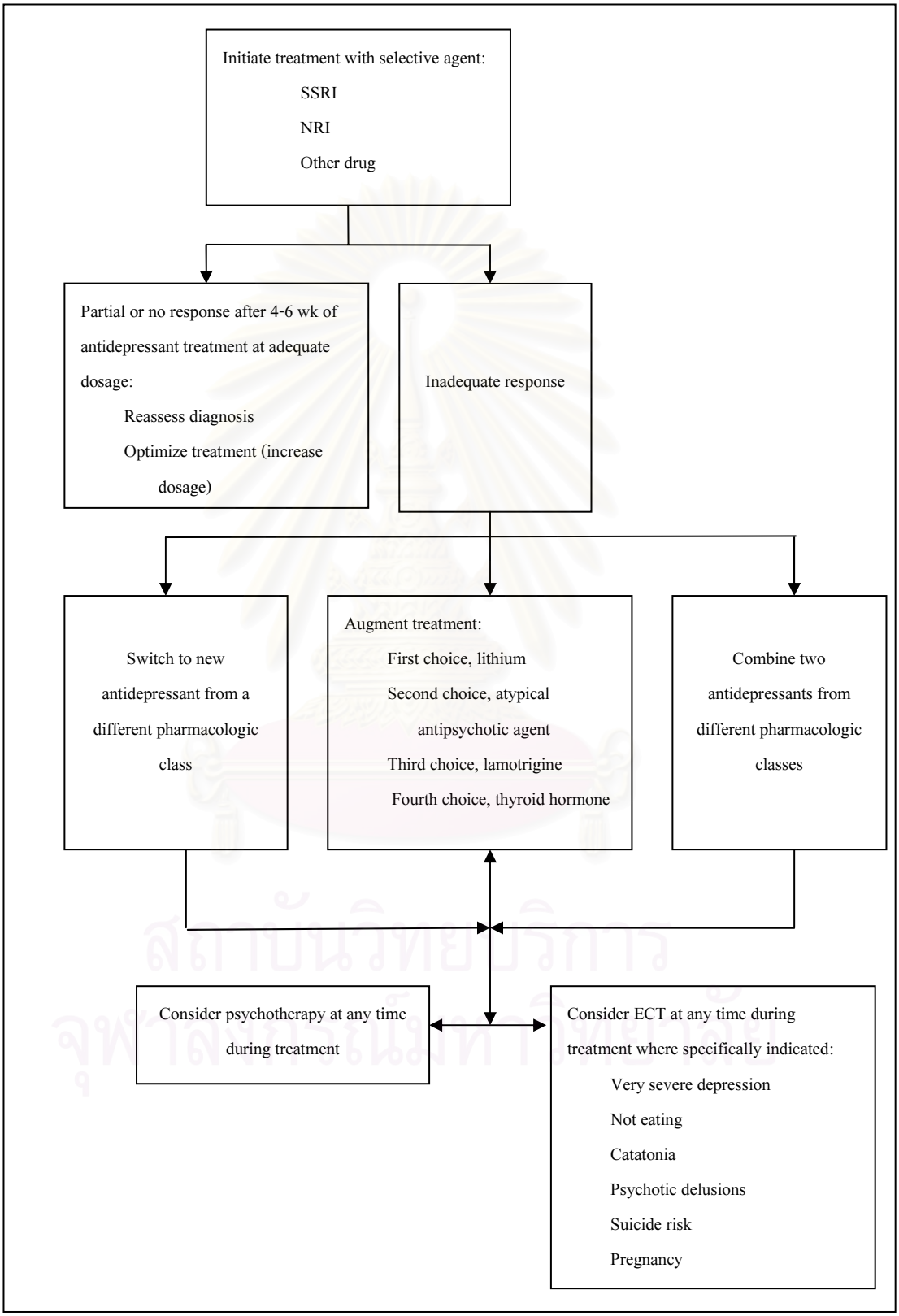
A subtype of major depression, melancholic features, more closely resembles endogenous depression. The current diagnosis requires anhedonia or lack of pleasure from enjoyable stimuli. In addition, three of the following six symptoms must be present: diurnal variation, marked psychomotor retardation or agitation, early-morning awakening, significant anorexia or weight loss, excessive or inappropriate guilt, and distinct quality of the depressed mood. DSM-IV-TR includes a specifier to indicate a subtype of major depression that has been described for many years in the psychiatric literature: atypical depression. This disorder is characterized by significant reactivity of mood to pleasurable stimuli, in addition to at least two of four other symptoms: significant weight gain or increase in appetite, excessive sleeping, sensitivity to interpersonal rejection, and heaviness in the limbs. DSM-IV-TR also includes mixed anxiety-depressive disorder as a disorder for further study. The criteria for this disorder include persistent or recurrent dysphoric mood for at least 1 month, with symptoms including worry, irritability, fatigue, sleep disturbance, and difficulty concentrating. Finally, a very important subtype of major depressive episode, major depressive episode with psychotic features, by definition involves delusional thinking, evidenced by guilt or nihilistic delusions, hallucinations, and even communicative incompetence. This subtype represents some 15% of all major depressions*(22)*.

Antidepressant treatment

Treatment of patients with depressive disorders consists of an acute phase, during which remission is induced; a continuation phase, during which remission is preserved; and a maintenance phase, during which the susceptible patient is protected against the recurrence of depressive episode*(23)*. Specific objectives of each treatment phase for depressive disorder include: acute phase aims to stabilize acute symptoms, return symptoms and restoration of psychosocial functioning; continuation phase aims to maintain stabilization, prevent return of acute symptoms (relapse); maintenance phase aims to ensure against relapse or prevent recurrence*(24)*.

In acute phase, hospitalization is needed if symptoms are severe and there is a risk of suicide (previous suicide attempts or current plan for suicide). Antidepressants are the treatment of choice for moderate-to-severe episodes of depression. Since most antidepressants that are used for major depressive disorder have similar effectiveness, the choice of medication depends on depressive symptoms, the history of responses to medication, medication tolerability, adverse effects, and the likelihood of adherence. Other considerations are concurrent medical conditions, use of nonpsychiatric drugs, and cost of medication*(23, 25)*. SSRIs and other newer antidepressant drugs with a greater safety margin constitute first-line medications for moderate-to-severe depression. The acute treatment phase usually lasts 6 to 10 weeks. Doses should be low initially and gradually increased, depending on the clinical response and side effects.

Figure 1 Algorithm for the acute treatment phase of a major depressive episode in major depressive disorder*(25)*



Continuation phase of treatment, generally lasting 6 to 9 months after the induction of remission, aims to eliminate residual symptoms, restore the prior level of functioning, and prevent recurrence or early relapse. Treatment should continue until residual symptoms have resolved. Episodes lasting more than 6 months and psychotic depression require a longer continuation phase, up to 12 months*(25)*. The same medications and doses used to achieve relief in the acute phase are used during the continuation phase*(23, 25)*.

If there is no recurrence or relapse during continuation therapy, gradual discontinuation may be planned for most patients after at least 6 months of treatment. Early discontinuation is associated with higher risk of relapse as compared with continuation treatment*(25, 26)*. The tapering of medication over several weeks also permits detection of returning symptoms. It also minimizes the continuation syndrome, which consists of physical symptoms of imbalance, gastrointestinal and influenza-like symptoms, and sensory and sleep disturbances, as well as psychological symptoms such as anxiety, agitation, crying spells, and irritability. The discontinuation syndrome is sometimes called the withdrawal syndrome.

Maintenance treatment for 12 to 36 months reduces the risk of recurrence by two thirds. This approach is indicated for patients with episodes that occur yearly, who have impairment because of mild residual symptoms, who have chronic major depression or dysthymia, or who have extremely severe episodes with a high risk of suicide. The duration of maintenance treatment will depend on the natural history of the illness and may be prolonged or indefinite in the case of recurrent illness. The first choice of medication for this phase is the antidepressant that brought about remission. Medication tolerability is greatly important during the maintenance phase, because it affects patients' adherence to treatment. It is important to monitor adherence and breakthrough symptoms so that problems are detected early*(25)*.

Although psychological treatments of proven efficacy are available for the management of depression, the most common form of treatment worldwide is antidepressant medication. For patients with a definitive diagnosis of depression, pharmacotherapy guidelines advocate that treatment should continue for at least 6 months following remission of symptoms. Furthermore, for patients who have suffered two or more episodes of significant depression within 5 years, long-term preventive treatment is suggested*(27)*.

Studies have found that antidepressants are of equivalent efficacy when administered in comparable doses. Approximately 65% to 70% of patients with varying types of depression improve with drug therapy, compared with 30% to 40% who improve with placebo*(18)*. Antidepressants are not effective for all patients. In clinical practice, 40% to 50% of episodes do not completely respond to initial antidepressant drug therapy. Respond to antidepressant medication is also delayed, with weeks to months until remission for those who do respond*(28)*. Among some subgroups of patients with major depressive disorder, efficacy may differ. Antidepressant medications also differ in their potential to cause particular side effects. Antidepressant medications have been grouped as follows: 1) tricyclic antidepressant medications, which also include the tetracyclic antidepressant medication maprotiline; 2) SSRIs, which include fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram; 3) other antidepressant medications, including bupropion, nefazodone, trazodone, venlafaxine, mirtazapine, and reboxetine; and 4) MAOIs, which include phenelzine, tranylcypromine, and isocarboxazid*(23)*.

Table 2 Commonly used antidepressant medications*(23, 25)*

Generic name	Starting dose (mg/day)	Usual dose (mg/day)
Tricyclics and tetracyclics		
Tertiary amine tricyclics		
Amitriptyline	25 – 50	100 – 300
Clomipramine	25	100 – 250
Doxepin	25 – 50	100 – 300
Imipramine	25 – 50	100 – 300
Secondary amine tricyclics		
Desipramine	25 – 50	100 – 300
Nortriptyline	25	50 – 200
Tetracyclics		
Amoxapine	50	100 – 400
Maprotiline	50	100 – 225
SSRIs		
Citalopram	20	20 – 60
Fluoxetine	20	20 – 60
Fluvoxamine	50	50 – 300
Paroxetine	20	20 – 60
Sertraline	50	50 – 200
Dopamine-norepinephrine reuptake inhibitors		
Bupropion	150	300
Serotonin-norepinephrine reuptake inhibitors		
Venlafaxine	37.5	75 – 225
Serotonin modulators		
Nefazodone	50	150 – 300
Trazodone	50	75 – 300
Norepinephrine-serotonin modulator		
Mirtazapine	15	15 – 45
MAOIs		
Phenelzine	15	15 – 90
Moclobemide	150	300 – 600
Selective noradrenaline reuptake inhibitor		
Reboxetine	4 – 8	8 – 12

Tricyclic antidepressants

Tricyclic andtidepressants block the reuptake of norepinephrine and serotonin and are competitive antagonists at the muscarinic acetylcholine, histamine H_1, and α_1– and α_2– adrenergic receptors*(29)*. Heterocyclic antidepressant medications, including tricyclics and tetracyclics, have been found to be statistically significantly superior to placebo in approximately 75% of studies. The efficacy of individual agents and subclasses of tricyclics (e.g., secondary amines or tertiary amines) appears to be comparable. Results of some investigations have suggested that tricyclic antidepressants may possess superior efficacy among subgroups of patients with severe major depressive disorder symptoms.

Table 3 Common side effects of tricyclic and tetracyclic drugs*(22)*

Anticholinergic	**Central nervous system**
Dry mouth	Tremor
Constipation	Sedation
Urinary hesitancy	Stimulation
Esophageal reflux	Myoclonic twitches
Cardiovascular	Seizure (maprotiline)
Orthostatic hypotension	Extrapyramidal symptoms (amoxapine)
Palpitations	**Other**
Conduction slowing	Perspiration
Hypertension	Weight gain
	Sexual dysfunction
	Impotence

Selective serotonin reuptake inhibitors

SSRIs selectively block the reuptake of 5-HT through their inhibiting effects on the Na+/K+ adenosine triphosphase (ATPase) – dependent carrier in presynaptic neurons*(22)*. SSRIs currently available include fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram. A large body of literature supports the premise that SSRIs are superior to placebo in the treatment of major depressive disorder. In over 50 investigations the effectiveness of SSRIs has been compared to that of other antidepressant medications, mainly tricyclic antidepressants; in these trials, SSRIs have generally had comparable efficacy to antidepressant medications from other classes*(23)*. In general, significant differences in efficacy between individual SSRIs have not been observed*(23, 25)*. The active metabolite of fluoxetine has a half-life that is longer than that of other SSRIs, which permits once-daily dosing and thereby reduces the effect of missed doses and mitigates the SSRI discontinuation syndrome.

SSRIs can be helpful in patients who do not have a response to tricyclic antidepressants and appear to be better tolerated with lower rates of discontinuation and fewer cardiovascular effects. Although tricyclic antidepressants may have greater efficacy than SSRIs in severe major depressive disorder or depression with melancholic features, they are less effective than SSRIs for bipolar depression, since they can trigger mania or hypomania. SSRIs appear to be less effective than either tricyclic antidepressants or selective norepinephrine-reuptake inhibitors for depression in which physical symptoms or pain is prominent*(25)*.

Monoamine oxidase inhibitors

MAOIs have also been shown in multiple trials to be effective treatments for major depressive disorder. Although some earlier comparisons employing lower doses of MAOIs found tricyclic antidepressants to be superior, MAOIs are now considered to have comparable efficacy to tricyclic antidepressants for typical cases of major depressive disorder. There are no significant differences in efficacy among the MAOIs*(23)*. MAOIs are not first-line drugs because patients who receive them must adhere to a low-tyramine diet to prevent hypertensive crisis and because MAOIs carry greater drug-interaction risks than do other medications. However, MAOIs are useful for treating patients who do not have a response to tricyclic antidepressants*(25)*.

Other antidepressant medications

Trazodone appears to be antagonism of the postsynaptic 5-HT_{2A} and 5-HT_{2C} receptors*(22)*. In most trials, trazodone has had superior efficacy relative to placebo; however, its efficacy relative to other antidepressant medications remains controversial. Nefazodone has an analogous structure to trazodone but somewhat different pharmacologic properties. In controlled trials, nefazodone has had superior efficacy to placebo; in five trials, nefazodone has been found to have comparable efficacy to tricyclic antidepressants.

Bupropion appears to inhibit the reuptake of both norepinephrine and dopamine, although tis mechanism of action remains unclear. Trial data have shown that bupropion is superior to placebo and generally comparable in efficacy to both tricyclic antidepressants and SSRIs.

Venlafaxine appears to act through inhibition of reuptake of both norepinephrine and serotonin*(23)*. Mirtazapine enhances the release of

norepinephrine by blocking α_2-adrenergic autoreceptors as well as serotonin 5-HT_{2A} and 5-HT_3 receptors and histamine H_1 receptors*(25)*. Reboxetine is a new selective noradrenaline reuptake inhibitor. In four trials, reboxetine has been shown to be more effective than placebo; in 6 trials against active treatment, reboxetine has been found to possess at least comparable effectiveness as tricyclic antidepressants and SSRIs*(23)*.

Table 4 Classification and side effects of antidepressants*(25)*

Functional Classification	**Side Effects**						
	Insomnia and agitation	Sedation	Hypotension	Anticholinergic Effects	Nausea or Gastrointestinal Effects	Sexual dysfunction	Weight Gain
Selective serotonin-reuptake inhibitors (SSRIs)							
Fluoxetine	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Paroxetine	Moderate	None or mild	None or mild	Mild	Moderate	Moderate	Mild
Sertraline	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Fluvoxamine	Moderate	Mild	None or mild	None or mild	Moderate	Moderate	Mild
Citalopram	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Escitalopram	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	Mild
Selective norepinephrine-reuptake Inhibitors (NRIs)							
Reboxetine	Mild	None or mild	None or mild	None or mild	Mild	Mild	None or mild
Nonselective norepinephrine-reuptake Inhibitors							
Desipramine	Mild	None or mild	Moderate	Mild	None or mild	Mild	Mild
Nortriptyline	Mild	Mild	Mild	Mild	None or mild	Mild	Mild
Maprotiline	Mild	None or mild	Mild	Mild	None or mild	Mild	Moderate

Table 4 Classification and side effects of antidepressants (Continued)*(25)*

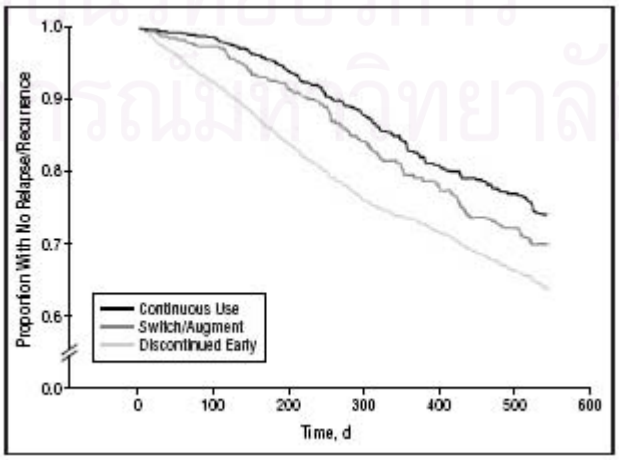
Functional Classification	Side Effects						
	Insomnia and agitation	Sedation	Hypotension	Anticholinergic Effects	Nausea or Gastrointestinal Effects	Sexual dysfunction	Weight Gain
Mixed or dual-action reuptake inhibitors							
Older agents (TCAs)							
Amitriptyline	None or mild	Moderate	Moderate	Severe	None or mild	Mild	Moderate
Clomipramine	Mild	Moderate	Moderate	Moderate	Mild	Mild	Moderate
Newer agents (non-TCAs)							
Venlafaxine (NRI plus SRI)	Moderate	None or mild	None or mild	None or mild	Moderate	Moderate	None or mild
Bupropion (NRI plus DRI)	Moderate	None or mild	None or mild	Mild	Mild	None or mild	None or mild
Duloxetine (NRI plus SRI)	None or mild	Mild	None or mild	Mild	Mild	None or mild	None or mild
MAOI							
Phenelzine	Moderate	Mild	Moderate	Mild	Mild	Moderate	Mild
Moclobemide	Mild	None or mild	None or mild	Mild	Mild	None or mild	None or mild
Mixed-action newer agents							
Mirtazapine	None or mild	Severe	Mild	None or mild	None or mild	None or mild	Severe
Mianserin	None or mild	Moderate	Mild	Mild	None or mild	None or mild	Mild
Nefazodone	None or mild	Moderate	Mild	Mild	Mild	None or mild	Mild
Trazodone	None or mild	Severe	Mild	None or mild	Mild	Moderate	Mild

Adherence to antidepressants

The adherence project has adopted the following definition of adherence to long-term therapy, a merged version of the definitions of Haynes and Rand : the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.

Adherence was a primary determinant of the effectiveness of treatment because poor adherence decreases optimum clinical benefit and increases risk of relapse and recurrence*(26, 27)*. Melfi et al. reported that patients who continued therapy with their initial antidepressant were least likely to experience relapse or recurrence, while those who discontinued their antidepressant early were most likely to experience relapse or recurrence (Figure 2)*(26)*. Good adherence improved the effectiveness of interventions aimed at promoting healthy lifestyles. It also affect secondary prevention and disease treatment interventions. Level of adherence had been positively correlated with treatment outcomes in depressed patients, independently of the anti-depressive drugs used. In addition to their positive impact on the health status of patients with chronic illnesses, higher rates of adherence conferred economic benefits*(27)*.

Figure 2 Proportion of patients with no relapse/recurrence following 6-month treatment period, according to antidepressant treatment cohort*(26)*

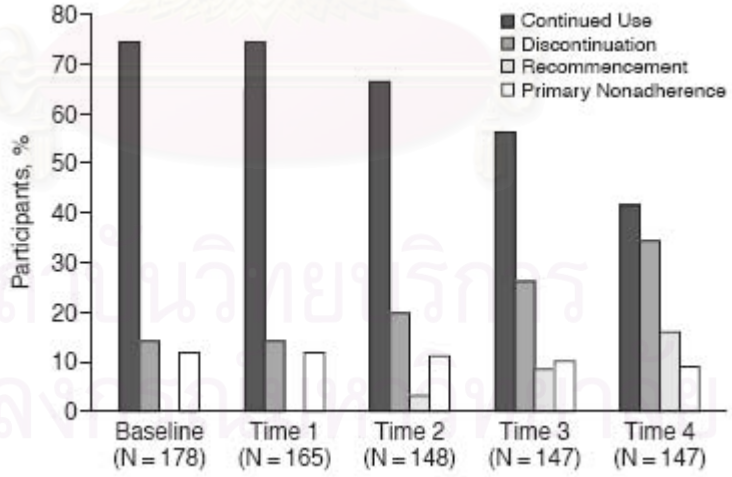


Adherence to antidepressant treatment is often poor. Maddox et al. found that 52% of patients had stopped their medication at 10-12 week period. Eleven percent of patients reported having stopped their tablets within 1 week, 24% after 2 weeks, 28% after 4 weeks, 32% after 6 weeks, 43% after 8 weeks, 50% after 10 weeks, 52% after 11 weeks and 48% were still taking them*(30)*. Ayalon et al. showed that 34.6% of the black patients and 28.5% of the Latino patients were classified as intentionally nonadherent. Eighteen percent of the black patients and 36% of the Latino patients reported unintentional nonadherence*(31)*. Gonzalez et al. reported that patients who were prescribed an antidepressant medication, 68% refilled their prescription at 1 month, and 57% were adherent at 6 months*(8)*.

Olfson et al. found that approximately 4 of 10 patients (42.4%) who initiated antidepressant treatment for depression discontinued the antidepressant medication during the first 30 days of treatment. Among those who continued antidepressant therapy beyond 30 days, roughly one-half (52.1%) discontinued the medication during the subsequent 60-day period. Overall, only about one-quarter of the patients (27.6%) continued antidepressant therapy for more than 90 days*(32)*. Akincigil et al. showed that the acute-phase (first 16 weeks) adherence rate of patients diagnosed with depression was 51%. Among patients adherent during the acute phase, 41.5% remained adherent during the continuation phase (17-33 weeks)*(33)*.

Hunot et al. found that 19% of 147 patients took antidepressants in accordance with clinical guidelines over the 6-month period. Several types of adherence behavior were reported (Figure 3). Based on self-report data, 9% of patients did not start their antidepressants during the follow-up period, and 73 patients (50% of the total sample who completed the study) discontinued antidepressants, of whom one third (16% of the total sample who completed the study) restarted treatment 2 to 3 months later. Sixty-five patients (89% of those who discontinued treatment) ceased treatment without discussion with their physicians*(34)*.

Figure 3 Incidence of primary nonadherence, discontinuation, recommencement, and continued antidepressant use at each timepoint*(34)*



Measurement of adherence

The methods available for measuring adherence can be divided into direct and indirect methods of measurement, as shown in Table 5. Each method has advantages and disadvantages and no method is considered the gold standard.

Direct measurements

Direct methods usually involve the detection of a chemical in body fluid. Direct methods are considered to be the most accurate but can be invasive. Also, they are often difficult to perform and are costly. Direct observation is practical only in single-dose therapy, intermittent administration and hospitalized patients.

Indirect measurements

Indirect methods are more frequently reported in the literature than direct methods. They include process measures such as interviews, diaries, tablet counts, prescription filling dates, collecting patient questionnaires, clinical response measures and using electronic medication monitors.

Interviews and all self-report methods are vulnerable to overestimate of adherence and underestimate of nonadherence. Interviews have been shown to identify 80 % of the true nonadherence as assessed by pill count. However, interviews are not equally sensitive for all subgroups of patients.

The validity of prescription refill dates depends on the completeness of the pharmacy database and counting tablets often overestimates adherence.

The use of electronic devices or MEMS (medication event monitoring system) can measure both frequency and time of opening of the medication bottle. This method provides the most accurate and valuable data on adherence in difficult clinical situations. However, patients may open a container and not take the medication or take the wrong amount of medication.

Although a variety of methods has been used, there are problems with each method for generating valid and reliable data to give an accurate estimates of extent of adherence*(35, 36)*.

Table 5 Methods of measuring adherence*(35)*

Test	Advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of level of medicine or metabolite in blood	Objective	Variations in metabolism; expensive
Measurement of biologic marker in blood	Objective	Requires expensive quantitative assays
Indirect methods		
Patient questionnaire, patient self-reports	Simple; inexpensive; the most useful method in clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by patients
Pill counts	Objective, quantifiable, easy to perform	Data easily altered by patients
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medicine; requires a closed pharmacy system
Assessment of the patients' clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials

Factors influencing adherence to antidepressants

Adherence to antidepressant treatment greatly influences to outcome of depression therapy. There were many studies regarding factors that affecting adherence to antidepressant treatment. From study of 46 patients commenced on an antidepressant by their GP, side effect burden was significantly associated with nonadherence. SSRIs showed a slight but nonsignificant adherence advantage in this small study. When comparing the score of the severity of side effects with the length of time the tablets were taken (in weeks), there was a significant correlation ($r = -0.3884$, $p=0.008$), i.e. the worse the side effects, the less time the tablets were taken. This study was found that fourteen (30%) patients stopped their medication due to the experience of side effects. Sixteen (35%) stopped because they felt better, seven (15%) because they felt the medication was having no effect, seven (15%) stopped when their doctor told them to stop and eight (17%) stopped for other reasons, e.g. not wanting to become dependent on tablets or not believing tablets to be the correct approach to treatment. In addition, it was reported that the different types of medication had a small but nonsignificant effect on adherence*(30)*.

In a study of 88 patients commencing tricyclic antidepressants in the setting of UK general practice, fourteen patients volunteered reasons for premature cessation of their antidepressant including side effects (5 patients), feeling better (3 patients), lack of benefit (2 patients), concerns about potential adverse effects (2 patients), hospitalization (1 patient) and going on holiday (1 patient)*(37)*. From a patient survey, Ashton et al. found that the most common reason for antidepressant discontinuation was lack of efficacy (44%). Side effects accounted for the second most common reason for discontinuation. In addition, common reasons for nonadherence indicated by patients included “have trouble remembering to take it” (43%), “gained a lot of weight” (27%), “couldn’t have an orgasm” (20%), and “lost interest in sex” (20%)*(9)*.

In study using data for all participants taking oral psychotropic medication (n=634) from the 2000 British Survey of National Psychiatric Morbidity, younger participants were less adherent (OR=0.98, 95 % CI: 0.96-0.99). The total number of medications prescribed, and taking additional medication for a physical disorder had no effect on any of the aspects of adherence studied. Of people who were nonadherent to psychotropic medication, 76 (37.4%) said they had forgotten, lost or run out of their medication; 55 (24.6%) had thought it was not needed and 45 (18.9%) had not wanted to take drugs. For 29 (14.2%) the reason given was side-effects; while 18 (7.2%) gave other reason*(10)*.

From a qualitative study of understanding treatment adherence in affective disorder, although most patients considered drugs as essential for their treatment, not all experiences with drugs were positive. Four patients reported that they had stopped drugs against the advice of the psychiatrist when they started feeling better, to test whether the disease had gone away, but that they relapsed and had to take treatment again. Only one patient mentioned the fear of drug addiction, and one the latency period of the drug as cause of nonadherence. Adverse reactions were considered as the major potential cause of nonadherence (eight times), followed by the slow onset of action of antidepressant drugs (six times), the non-cooperation of the family (six times), fear of drug addiction (three times), and the need for a long treatment regimen (three times). Patients reported problems concerning treatment, including adverse reactions and nonadherence, more frequently to nurses than to doctors. According to both nurses and psychiatrists, the most important factors to ensure good adherence were the cooperation of the family (eight times), a good relationship with the patient (six times), forewarning patients about adverse effects (six times), and providing frequent follow-up visits at beginning of treatment (three times)*(15)*.

Demyttenaere suggested that nonadherence was found to be higher in women than in men (68% versus 49%). However, it is not clear whether this difference is due to gender differences in plasma level of psychotropics or to gender differences in reporting non-adherence, in experiencing side effects or in general acceptability of taking drugs for mental illness. In addition, low socioeconomic status, younger age and substance abuse have been correlated with higher non-adherence. Other variables associated with nonadherence include divorced marital status, membership in a minority group, presense of paranoid ideation*(38)*.

Olfson et al. concluded that antidepressant discontinuation during the first 30 days of treatment was significantly more common among Hispanics (53.8%) than non-Hispanics (41.3%); patients with fewer than 12 years of education (50.8%), compared with those with 12 or more years (39.3%); and patients with low family incomes (50.2%), compared with those with medium or high family incomes (38.6%). In conclusion, early discontinuation of antidepressant therapy is widespread in the community treatment of depression, especially among socioeconomically disadvantaged patients*(32)*. From retrospective study of 4,312 depressed patients, younger age, comorbid alcohol or other substance abuse, comorbid cardiovascular/metabolic conditions, use of older generation antidepressants, and residence in lower-income neighborhoods were associated with lower acute phase adherence*(33)*.

Kihlstrom concluded that attitudes towards illness and medication in general will influence the degree to which patients adhere to treatment. Moreover, the cost of the medication and medical care might inhibit patients from prescribed medications. Therefore, it was necessary to consider the socioeconomic status of patients when adherence to medication regimens were examined. In addition, the social support influenced adherence to treatment. Features of antidepressants could affect patients'

willingness to adhere to medication. For example, some medications might produce a greater number of side effects. In addition, family or a partner might exhibit fears or concerns about side effects, behavioral changes, or dependence on medication that influenced patients' willingness to adhere to medications*(39)*.

Van Dijk et al. found that risk factors in antidepressant nonadherence included non-western immigrants, type of medication, and somatic co-morbidity. Women were less likely and non-western immigrants were more likely to be an early dropout. Users of TCAs were overrepresented among the early dropouts. In addition, non-western immigrants were more likely to be nonadherent. Refill nonadherence was highest for SSRIs and lowest for TCAs. A complex medication regimen (i.e. more different types of medication) was moderately negatively associated with refill nonadherence. Patients were more likely to be nonadherent the more other chronic complaints they had*(40)*.

In a meta-analysis of administration of single and multiple antidepressant dosing, none found a significant difference in therapeutic efficacy. Furthermore, the improvement rates in depression scores between the two groups were almost identical (single daily dosing versus multiple daily dosing). This meta-analysis found no advantage for multiple daily dosing. Administration of antidepressants in single daily doses appeared sufficient to achieve an therapeutic response. Moreover, a single daily dosing regimen offer the potential advantages of simplicity, increased adherence, and reduced adverse effects, which would increase the overall success rate in treatment of depression*(17)*.

Keller et al. concluded that a major factor influencing patient adherence was the tolerability and efficacy of the drug. It is well established that the adverse events associated with TCAs result from an interaction at α_1-adrenergic receptors,

acetylcholine (muscarinic), histamine and dopamine receptors. This profile resulted in a broad range of unwanted effects including sedation, hypotension, dry mouth, tachycardia, constipation, urinary hesitancy, weight gain and aggravation of psychosis. Despite an improved tolerability profile due to greater receptor selectivity, SSRIs could bring adverse events that might lead patients to discontinue treatment, including nausea, anxiety/nervousness, insomnia and sexual dysfunction. Moreover, patient and physician education and developing a supportive physician-patient relationship were important factors influencing adherence*(41)*. In study of 4,860 adult first-time users of antidepressants from 174 general practices in Denmark, one in three patients did not purchase antidepressants in the 6 months following first prescription (early discontinuation). Rates of early discontinuation were higher among those prescribed tricyclic compared with new generation antidepressants. Patients' age and sex did not have an influence, but early discontinuation was more frequent among patients of low socioeconomic status*(42)*.

From study of black and Latino elderly patients who had been prescribed antidepressant medications, results indicated that greater concerns about antidepressant medications, lesser beliefs in the importance of antidepressant medications, and lesser satisfaction with the patient-physician relationship were significant predictors of intentional nonadherence*(31)*. In study of 573 depressed patients who prescribed SSRIs, results indicated that the only significant predictor of discontinuation risk was baseline antidepressant skepticism, which was associated with a 62% increase in the risk of discontinuation. Of 180 side effects reported as leading to SSRI discontinuation, the most prevalent were upper gastrointestinal symptoms (nausea and vomiting), followed by anxiety/agitation, insomnia and sexual dysfunction. From this study, Aikens et al. concluded that antidepressant attitudes was an important predictor of SSRI course and outcome*(43)*.

Sirey et al. showed that antidepressant adherence was associated with lower perceived stigma, higher self-rated severity of illness, age over 60 years, and absence of personality pathology. Surprisingly, neither the overall report of side effects nor the report of very bothersome side effects was associated with adherence. This study demonstrated the influence of patients' attitudes toward both their illness and their treatment on adherence. The impact of perceived stigma might be even more powerful in non-mental health settings that provide treatment for depression, such as primary care*(44)*. From study of perceived stigma among 92 outpatients with major depressive disorder, younger adults reported higher level of overall perceived stigma than the older adults ($t=2.00$, $df=89$, $p=0.05$). Although younger patients reported perceiving more stigma than older patients, stigma predicted treatment discontinuation only among the older patients*(45)*. Lin et al. found that predictor of adherence to long-term pharmacotherapy was favorable attitudes toward antidepressant treatment*(46)*.

From study of 192 depressed patients, patients commonly endorsed beliefs that their current or future health depended on antidepressant medication; more than half of them reported that their antidepressant kept them from getting worse. However, concerns about taking antidepressants were also commonly reported. Many indicated that they worried about the long-term effects of antidepressants (49.2%), about becoming too dependent on antidepressants (37.2%) , or that their medication was a mystery to them (40.3%). Commonly reported beliefs about medication in general included concerns about the overuse of medication. Few patients endorsed beliefs that medications were harmful; however, over 20% believed that most medicines are addictive. This study showed that severity of depressive symptoms and specific concerns about antidepressants were the only variables significantly associated with self-reported medication adherence ($R=0.43$, adjusted $R^2=0.13$, $F=3.3$, $df=12, 178$, $p<0.001$)*(47)*.

In a patient belief survey of 81 primary care patients given maintenance antidepressant medications, beliefs about the necessity for and concerns about antidepressant medications were the only variables that accounted for adherence. Specifically, both recent and general adherence were highest among patients whose perceived need for medication exceeded their concerns about taking medication, and lowest for those whose concerns about taking medication exceeded the perceived need. This study showed that patient beliefs about medication affected adherence to antidepressant treatment*(14)*. From a cohort study of 147 patients prescribed antidepressants at primary care practice, specific concern about antidepressant side effects (OR=3.30, 95 % CI: 2.20-4.97) was independent predictor of antidepressant nonuse. However, illness perceptions were not associated with adherence. Concerns about antidepressants and a mismatch between patients' preferred and prescribed treatment acted as significant barriers to sustained adherence*(34)*.

In study of patients' beliefs about the necessity and harmfulness of antidepressants, Aikens et al. found that perceived necessity was associated with older age ($p<0.001$), more severe symptoms ($p=0.03$), longer anticipated duration of symptoms ($p=0.001$), attribution of symptoms to chemical imbalance ($p=0.005$). Perceived harmfulness was highest among patients who had not taken antidepressants before ($p=0.02$), attributed their symptoms to random factors ($p=0.04$), and had a subjectively unclear understanding of depression ($p=0.003$). In conclusion, skepticism about antidepressants was strongest among younger patients who had never taken antidepressants, viewed their symptoms as mild and transient, and felt unclear about the factors affecting their depression*(48)*.

Sher et al. reported that the kinship between the caregiver and the patient was the only significant demographic variable that predicted patients' adherence. Patients whose caregiver were their spouses were more likely than other family members or friends to adhere to antidepressant medication(χ^2=4.08, df=1, p<.05). Caregivers' belief that the patients' illness stemmed from cognitive and attitudinal problems was the only variable that significantly predicted poor adherence to the recommended medication treatment. This study suggested that caregivers' and patients' beliefs might play important roles in the patients' treatment adherence*(49)*.

Among 40 veterans prescribed antidepressants for mental health conditions, 62.5% (n=25) discussed these medications with their provider during the visits. Providers stated information about antidepressants during 55.0% of the encounters. Providers presented information on the following areas during the most encounters: purpose (27.5%), dose (22.5%), supply (15.0%), which antidepressant the patient was or should be taking (15.0%), and timing (12.5%). However, providers asked about adherence during 5.0% of encounters, problems and barriers to use in 5.0% of encounters, and adverse effects during 7.5% of encounters. If antidepressants were discussed during the visit, physicians asked only 72.0% (n=18) of patients questions about their antidepressants. This means that more than one quarter of patients who discussed antidepressants during their visits were asked no questions by their physicians about their antidepressant use*(50)*.

From study of 401 telephone interviews of depressed patients and 137 prescribing physicians, ninety-nine physicians (72%) reported that they usually asked patients to continue using antidepressants for at least 6 months, but 137 patients (34%) reported that their physicians asked them to continue using antidepressants for this duration and 228 (56%) reported receiving no instructions. Patients who discussed

adverse effects with their physicians were less likely to discontinue therapy than patients who did not discuss them (OR=0.49, 95 % CI: 0.25-0.95). Fewer than 3 follow-up visits for depression, adverse effects, and lack of therapeutic response to medication were also associated with patients' discontinuing therapy. The reasons for stopping the use of medication included adverse effects (36%), feeling better (24%), lack of efficacy (20%), other reasons (20%). Communication about adverse effects significantly decreased the odds of discontinuing antidepressant therapy. Patients who were separated, divorced, or widowed were more likely to discontinue antidepressant treatment than patients who were currently married*(51)*.

In study of physician communication style on client medication beliefs and adherence with antidepressants, Bultman et al. found that physician initial communication style positively influenced client knowledge, initial beliefs about the medication, satisfaction with the antidepressant and medication adherence. Approximately sixty percent of clients strongly agreed that their physician encouraged expression of problems, asked about and listened to concerns during the follow-up visit. In addition, physician follow-up communication was positively correlated with predicted client outcomes, satisfaction with treatment and medication adherence. As predicted, client satisfaction with treatment was positively correlated with client adherence. While client knowledge of the medication regimen was necessary for following treatment recommendations, it was client beliefs about the medication that greatly influenced client behavior in following treatment recommendations*(52)*.

From these research, factors affecting adherence to antidepressant therapy might be grouped into four aspects including socioeconomic, antidepressant medication, attitudes towards medication, and attitudes towards physician aspects. Although these studies provided useful information regarding factors influencing adherence to antidepressant treatment, there are few studies that determine factors influencing adherence to antidepressant medications of Thai depressed patients.

Therefore, it is important to examine these factors in Thai depressed patients. Because treatment of depression requires long-term therapy, antidepressant adherence greatly affects effectiveness of treatment. Thus, providing of patients' data about factors affecting adherence to antidepressant therapy, especially patients' attitudes towards medication and physicians, can improve health professionals' ability to educate patients about their treatment regimen and help guide the development of interventions to promote antidepressant medication adherence.

CHAPTER III

MATERIALS AND METHODS

Materials

1. Antidepressant adherence questionnaire

This instrument was used to measure self-reported tendency to adhere to antidepressant regimen. It was adapted from the Antiretroviral General Adherence Scale (AGAS)*(53)* and is composed of five items that focus on ability of taking antidepressant medications as the physician recommended and one item that measures approximation extent of taking antidepressant medications by using visual analog scale (VAS) (see Appendix A). In the five-item questionnaire, all responses were on a 5-point Likert scale from *none of the time* to *all of the time*. Adherence scores can be calculated by summation of the achieved score in each item. The alpha reliability coefficient for the five-item questionnaire was 0.8389 for this sample.

2. Attitudes towards antidepressant medication and physician questionnaires

The attitudes towards antidepressant medication and physician questionnaires were adapted from the Antidepressant Compliance Questionnaire (ADCQ)*(54)* and the attitudes towards antidepressant medication questionnaire by Lin et al.*(46)* Each item of these questionnaires is rated on a 5-point Likert scale from *strongly disagree* to *strongly agree* (see Appendix A).

The attitudes towards antidepressant medication questionnaire is composed of nine items. A medication attitude summary score was calculated by averaging

the 9 items. A score of three indicated a neutral stance towards antidepressant medications, above three reflected favorable attitudes, and below three reflected unfavorable beliefs*(46)*. The alpha reliability coefficient for this questionnaire was 0.8194 for this sample.

The attitudes towards physician questionnaire is composed of seven items. A physician attitude summary score was calculated by averaging the 7 items. A score of three indicated a neutral stance towards physician, above three reflected favorable attitudes, and below three reflected unfavorable attitudes*(46)*. The alpha reliability coefficient for this 7-item scale was 0.8924 for this sample.

3. Patient information sheet of demographic and clinical data

(see Appendix A)

Methods

1. Definitions

1.1 **Adherence to medication** means the extent of a patient's behavior of taking medication, and/or executing lifestyle changes that corresponding with agreed recommendations from a health care provider.

1.2 **Factors influencing adherence** mean factors affecting adherence to medication that resulting in change of adherence**.**

1.2.1 Socioeconomic factors including marital status, incomes, and caregiver

1.2.2 Attitudes towards antidepressant medications

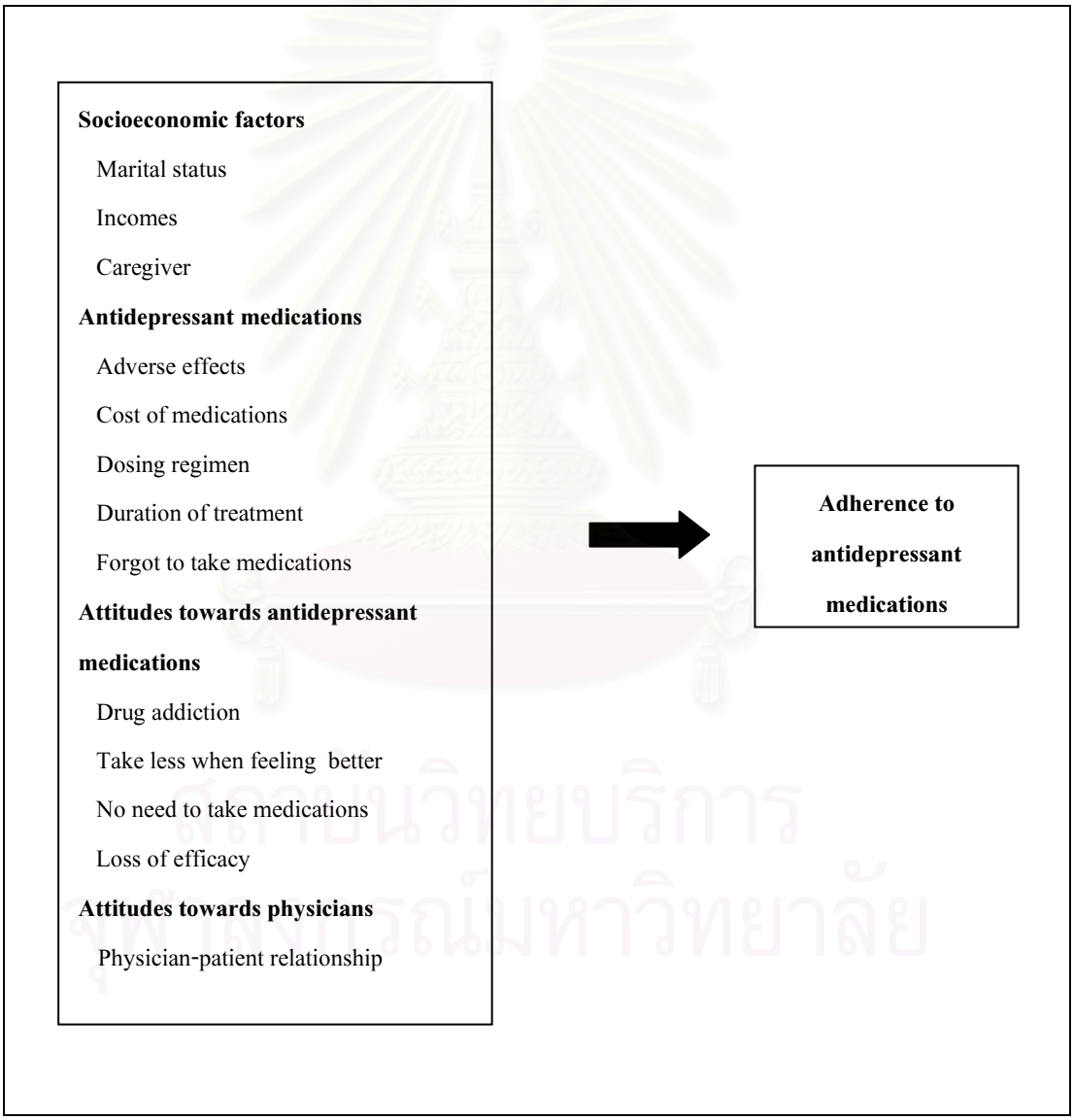
1.2.3 Attitudes towards physicians

1.2.4 Antidepressant medications including adverse effects, dosing regimen, cost, and duration of treatment

1.3 **Depressed patients** mean patients who diagnosed with depression by psychiatrists, aged not less than 18 years, and were outpatients at psychiatric clinic of King Chulalongkorn Memorial Hospital.

1.4 **Adverse effects** mean effects from individual response to medications, in usual dose, that impact on medication users.

Figure 4 A conceptual framework



2. Study hypothesis

The objectives of this study examined the influence of socioeconomic factors, attitudes towards antidepressant medications and physicians and treatment characteristics on the adherence to antidepressant treatment through 13 hypotheses.

Hypothesis 1: Marital status is associated with adherence

Hypothesis 2: Income level is associated with adherence

Hypothesis 3: Patients who have caregivers have higher or lower adherence than those who do not have caregivers

Hypothesis 4: Patients who treated with multiple daily dosing have higher or lower adherence than those who treated with single daily dosing

Hypothesis 5: Patients who have impact from medication cost have higher or lower adherence than those who do not have impact

Hypothesis 6: Patients who forget to take medications have higher or lower adherence than those who do not forget

Hypothesis 7: Impact of adverse effects is associated with adherence

Hypothesis 8: Duration of treatment is associated with adherence

Hypothesis 9: Attitudes towards necessary of antidepressants are associated with adherence

Hypothesis 10: Attitudes towards drug addiction are associated with adherence

Hypothesis 11: Attitudes towards efficacy of antidepressants are associated with adherence

Hypothesis 12: Attitudes towards taking less when feeling better are associated with adherence

Hypothesis 13: Attitudes towards physicians are associated with adherence

3. Study design

This study was a descriptive cross-sectional survey.

4. Patients

Depressed patients who admitted as outpatients at psychiatric clinic of King Chulalongkorn Memorial Hospital were recruited during April 2007 to December 2007. The inclusion and exclusion criteria of these patients were as the following:

Inclusion criteria

1. Depressed patients who diagnosed with depression by psychiatrists
2. Depressed patients who aged not less than 18 years
3. Depressed patients who are willing to join the research and give their consents

Exclusion criteria

1. Depressed patients who have severe symptoms including patients who have suicidal ideas
2. Depressed patients who can not give the information to researcher

5. Sample size estimation

The number of sample was calculated by the following formula*(55)*:

$n = 15 (x)$; x = number of factor

From many studies, factors influencing adherence to antidepressant medications were marital status, incomes, caregiver, adverse effects, fear of drug addiction, thinking of loss of efficacy, take less when feeling better, no need to take medications, forgot to take medications, dosing regimen of antidepressants, cost of

medications, duration of treatment, and patient-physician relationship*(5, 6, 8-10, 15, 17, 47, 49, 50)*. Overall, number of factor were 13 factors (x=13).

n = 15 (13)

= 195 patients

Estimated data error of 10% was expected, totally 217 patients were recruited into the study.

6. Sampling method

This study recruited all depressed patients who came to see the psychiatrists in each visit and met the inclusion criteria of the study. The study clinic was psychiatric out patient clinic.

7. Ethical issue

The protocol of this study was approved at May 3, 2007 by the Research Ethics Committee of Faculty of Medicine, Chulalongkorn University prior to the beginning of the study.

8. Methods

8.1 **Pre-study period**

8.1.1 Literatures on adherence to antidepressant medications and factors influencing adherence to antidepressant medications were reviewed.

8.1.2 Prepared patient information sheet.

8.1.3 Developed, tested and edited the questionnaires which measuring adherence to antidepressant medications and attitudes towards medications and physicians. The sample of twenty-three patients were used to test reliability of the questionnaires.

8.2 **Study period**

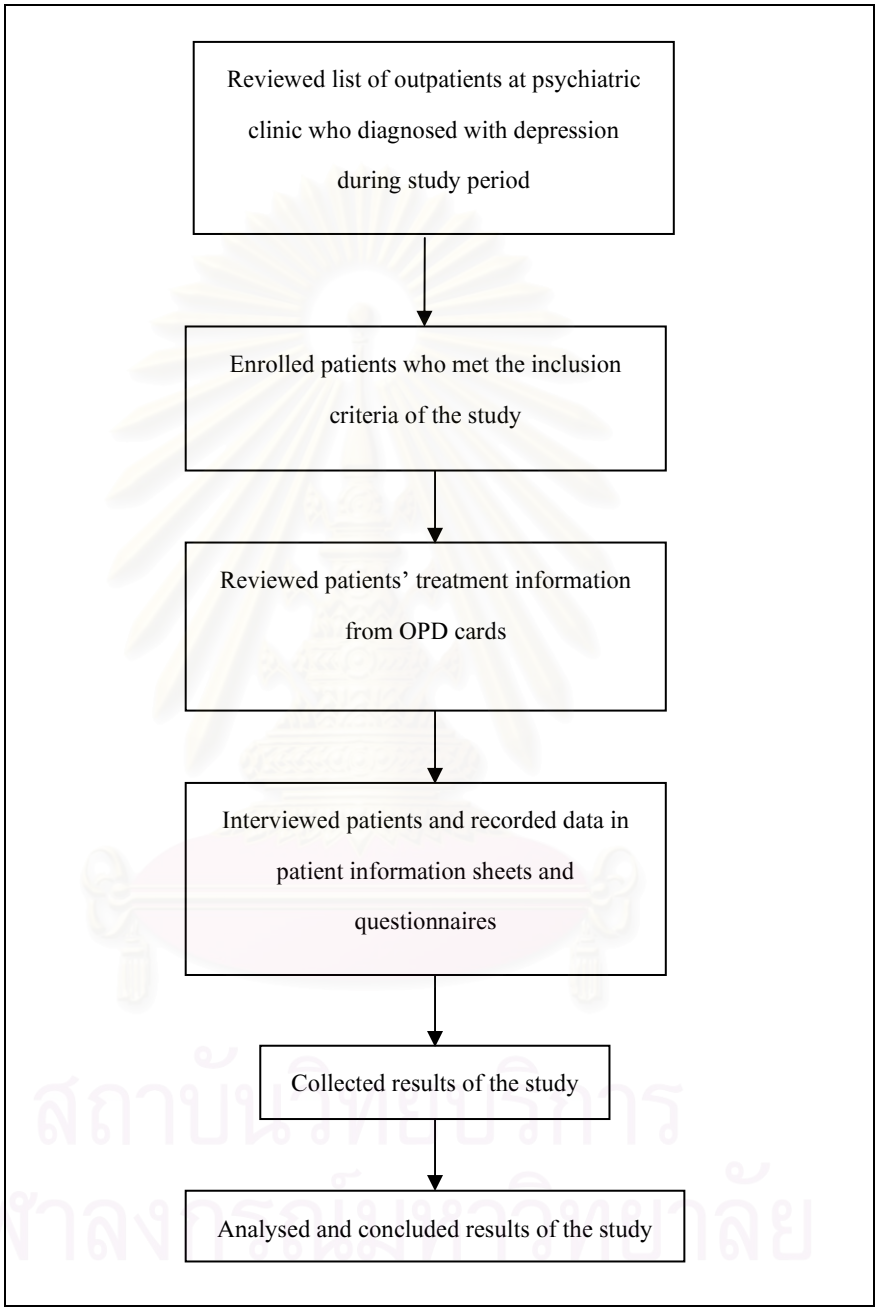
Depressed patients were diagnosed by the psychiatrists of King Chulalongkorn Memorial Hospital. The enrolled patients were fully explained about the study objectives, procedure and had signed their names in the consent forms.

Study procedure was:

1. Reviewed list of patients who diagnosed with depression and had admitted as outpatients at psychiatric clinic of King Chulalongkorn Memorial Hospital during study period.
2. Enrolled patients who met the inclusion criteria of the study.
3. Reviewed patients' treatment information from OPD cards and recorded data in patient information sheets.
4. Interviewed patients and recorded data in patient information sheets and questionnaires
5. Patients whose caregivers had an important role in the treatment, researcher would interviewed patients and caregivers together.

Study procedure was presented in figure 5.

Figure 5 Workflow of the study



9. Data collection

The following data were recorded in patient information sheet and questionnaires.

9.1 Patients' data

- Demographic data included sex, age, marital status, education, occupation, income and caregiver

9.2 Treatment data

- Diagnosis, duration of treatment, comorbidity, and treatment regimen

9.3 Assessment of adherence to antidepressant medications

- By using 5-point Likert scale (none of the time to all of the time) and visual analog scale

9.4 Reasons of nonadherence to antidepressant medications

9.5 Attitudes towards medications and physicians

- By using 5-point Likert scale (strongly disagree to strongly agree)

9.6 Adverse effects from antidepressants

- Measured level of impact of side effects by using 5-point Likert scale (slightly impact to high impact) and calculated a summary score of impact by dividing the summation of level of impact from experienced side effects by the total number of side effects.

10. Data analysis

Descriptive statistical analysis such as means, standard deviation, frequency and percentage was used to analyse sociodemographic, clinical and treatment characteristics, adherence to antidepressant medications and patients' attitudes. Independent t-test was used to analyse difference of percentage of adherence in dichotomous variables. Analysis of variance (F test) was used to analyse difference of percentage of adherence in nominal variable with more than 2 categories. Spearman correlation was used to analyse relationship between percentage of adherence and independent variables that classified as ordinal scale. Pearson correlation was used to analyse relationship between percentage of adherence and independent variables that classified as quantitative data. In addition, multiple regression analysis using stepwise was used to analyse factors influencing adherence to antidepressants.

CHAPTER IV

RESULTS

The study determined factors influencing adherence to antidepressant treatment, i.e., socioeconomic factors, clinical and treatment characteristics and patients' attitudes towards medications and physicians. The research design was a descriptive survey. The patients were recruited from Thai depressed patients who admitted as outpatients at psychiatric clinic of King Chulalongkorn Memorial Hospital during April 2007 to December 2007 and who were met the inclusion criteria of the study.

The results of the study were presented into 2 parts:

Part 1: Descriptive analysis of patients' characteristics including socioeconomic and treatment characteristics, adherence to antidepressants and attitudes towards medication and physician

Part 2: Statistical analysis to examine factors influencing adherence to antidepressant treatment

Part 1: Descriptive analysis of the study samples

Characteristics of the 217 patients recruited are shown in Table 6. In general, patients were middle-aged (mean ± SD, 43.25 ± 11.33 years) and female (78.3 %). Nearly half of the patients were married (105 patients) while one third of them were single (71 patients). More than half of the patients had education level which were lower than bachelor (122 patients) and more than half (136 patients) had income which were less than 10,000 baht/month. More than half of the patients were employed.

Table6 Sociodemographic characteristics of the 217 depressed patients recruited into the study

Characteristic	
Age in years, mean (SD)	43.25 (11.33)
Age range, n (%)	
18 - 30	37 (17.0)
31 - 50	116 (53.5)
51 - 60	64 (29.5)
Sex, n (%)	
Male	47 (21.7)
Female	170 (78.3)
Marital status, n (%)	
Married	105 (48.4)
Single	71 (32.7)
Widow	14 (6.5)
Divorced	27 (12.4)
Education in years, mean (SD)	11.43 (5.42)
Education level, n (%)	
No education	7 (3.2)
Primary school	54 (24.9)
Secondary school	61 (28.1)
Diploma/bachelor	79 (36.4)
Master/doctor	16 (7.4)
Income per month in baht, n (%)	
Less than 5,000	91 (42.1)
5,000-10,000	45 (20.8)
10,001-20,000	36 (16.7)
More than 20,000	44 (20.4)
Employment status, n (%)	
Unemployed	86 (40.2)
Employed	128 (59.8)

Table 7 Treatment characteristics of the 217 depressed patients recruited into the study

Characteristic	
Treatment duration in months, mean (SD)	32.37 (37.76)
Antidepressants, n (%)	
Older generation	8 (3.7)
Newer generation	196 (90.3)
Older and newer generation	13 (6.0)
Dosing regimen, n (%)	
Single daily dosing	150 (69.1)
Multiple daily dosing	67 (30.9)
Number of comorbid condition, n (%)	
0	105 (48.4)
1 to 2	97 (44.7)
3 or more	15 (6.9)
Caregiver, n (%)	
No caregiver	98 (45.4)
Have caregiver	118 (54.6)
Adherence to antidepressants, mean (SD)	
Measured by likert scale (score)	22.63 (3.25)
Measured by VAS (%)	87.68 (16.81)
Patients' attitudes, mean (SD)	
Attitudes towards antidepressant treatment (score)	3.69 (0.48)
Attitudes towards physicians (score)	4.06 (0.54)
Experienced side effect, n (%)	
0	42 (19.4)
1 to 2	96 (44.2)
3 or more	79 (36.4)
Impact of side effects, mean score (SD)	0.69 (0.64)

Clinical and treatment characteristics of the patients are shown in Table 7. In general, patients were treated with newer generation antidepressants (90.3 %) and were prescribed as single daily dosage regimen (69.1 %). Approximately 80 % of these patients had experienced side effects from antidepressants. Mean of score of side effect impact was 0.69 (SD = 0.64) and the maximum and minimum scores of impact were 3.25 and 0.00, respectively. Slightly higher than one half of the patients had comorbid conditions. Ninety-eight patients did not have caregiver.

Adherence to antidepressants was measured by questionnaire (Likert scale and visual analog scale; VAS). The average of adherence score from the study samples measured by Likert scale was 22.63 (SD = 3.25) while the maximum possible score was 25. In addition, the average of adherence percentage measured by visual analog scale was 87.68 (SD = 16.81). The study samples had favorable attitudes towards antidepressant medications and towards physicians (score above three). The average attitude score towards physicians (4.06 scores) was higher than the average attitude score towards antidepressant treatment (3.69 scores).

Most of the patients were diagnosed by psychiatrists with major depressive disorder (50.23 %), dysthymia (16.13 %), depressive disorder (12.90 %) and mixed anxiety-depressive disorder (10.14 %), respectively. The results are shown in Table 8.

Table 8 Diagnosis in depressed patients

Diagnosis	N	%
Major depressive disorder	109	50.23
Dysthymia	35	16.13
Depressive disorder	28	12.90
Mixed anxiety-depressive disorder	22	10.14
Depression with psychosis	19	8.76
Double depression	3	1.38
Bipolar depression	1	0.46

From 112 patients who had comorbid conditions, most of the patients had comorbid conditions as hypertension, hyperlipidemia, diabetes mellitus, migraine and personality disorder, respectively. The results are shown in Table 9.

Table 9 Comorbid conditions of depressed patients

Comorbid conditions	N	%
Hypertension	23	13.29
Hyperlipidemia	20	11.56
Diabetes mellitus	11	6.36
Migraine	10	5.78
Personality disorder	9	5.20
Chronic headache	8	4.62
Cardiac disease	7	4.05
Thyroid disease	6	3.47
Epilepsy	6	3.47
Obsessive-compulsive disorder	6	3.47
Panic disorder	5	2.89
Allergy	5	2.89
Cancer	4	2.31
Other	53	30.64

Most of the depressed patients were treated with newer generation antidepressants, for example, *selective serotonin reuptake inhibitors (SSRIs)*: fluoxetine, escitalopram, sertraline, fluvoxamine and paroxetine; *serotonin-norepinephrine reuptake inhibitor (SNRI)*: venlafaxine; *dopamine-norepinephrine reuptake inhibitor*: bupropion; *serotonin modulator*: trazodone; *norepinephrine-serotonin modulator*: mirtazapine; *selective serotonin reuptake enhancer*: tianeptine; and *mixed-action newer agent*: mianserin. Only twenty-one patients (7.84 %) were treated with older generation antidepressants, tricyclic antidepressants (TCA): amitriptyline, nortriptyline, imipramine. The results are shown in Table 10.

Table 10 The frequency of antidepressant used to treat depressed patients

Antidepressant	N	%
Selective serotonin reuptake inhibitors	165	61.57
Serotonin modulator	28	10.45
Tricyclic antidepressants	21	7.84
Norepinephrine-serotonin modulator	15	5.60
Mixed-action newer agent	14	5.22
Serotonin-norepinephrine reuptake inhibitor	13	4.85
Selective serotonin reuptake enhancer	8	2.99
Dopamine-norepinephrine reuptake inhibitors	4	1.49

In general, patients were treated with single antidepressant (167 patients), only about 23 percents were treated with combination antidepressants. From fifty patients who treated with antidepressant combination, nineteen patients were treated with SSRIs and trazodone and twelve patients were treated with SSRIs and TCAs, as shown in Table 11.

Table 11 Percentage of antidepressant combination used

Antidepressant	**N**	**%**
SSRIs + Trazodone	19	38.00
SSRIs + TCAs	12	24.00
SSRIs + Mianserin	7	14.00
Venlafaxine + Trazodone	3	6.00
SSRIs + Mirtazapine	2	4.00
Other	7	14.00

SSRIs: selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants

Depressed patients were mostly also treated with other medications (182 patients). The most common other medications used were benzodiazepines, antipsychotics and mood stabilizers, respectively. The results are shown in Table 12.

Table 12 Other medication used

Other medications	**N**	**%**
Benzodiazepines	158	68.70
Antipsychotics	41	17.83
Mood stabilizers	19	8.26
Other	12	5.22

The side effects which patients mostly experienced were dry mouth, somnolence, fatigue, insomnia, weight gain, palpitation, postural hypotension and nausea/vomitting, respectively. The results are shown in Table 13.

Table 13 Self-report side effects from antidepressants

Side effect	**n (%)**
Dry mouth	90 (18.79)
Somnolence	88 (18.37)
Fatigue	50 (10.44)
Insomnia	50 (10.44)
Weight gain	50 (10.44)
Palpitation	41 (8.56)
Postural hypotension	37 (7.72)
Nausea/vomitting	30 (6.26)
Headache	22 (4.59)
Decreased weight	5 (1.04)
Sexual dysfunction	2 (0.42)
Other	14 (2.92)

From the 175 patients (80.6 %) who experienced side effects from antidepressants, the severity of side effects were mostly fell in the scales of low impact (154 patients), moderate impact (148 patients) and rather high impact (112 patients), respectively. Most patients experienced moderate impact to rather high impact of somnolence, insomnia and weight gain. In general, patients experienced low impact to moderate impact of dry mouth, fatigue and postural hypotension. The results are shown in Table 14. Most of the patients who had high impacts of side effects were treated with newer generation antidepressants while only one patient were treated with both newer and older generation antidepressants (SSRI and TCA). The average of adherence scores measured by Likert scale and adherence percentage measured by visual analog scale of those who had high impacts of side effects were 22.67 and 94.08, respectively.

Table 14 Different impacts of side effects from antidepressants experienced by patients

	Impact				
Side effect	**Slightly**	**Low**	**Moderate**	**Rather high**	**High**
Dry mouth	6	35	31	18	0
Somnolence	9	23	27	26	3
Fatigue	3	20	15	9	1
Insomnia	1	10	21	16	1
Weight gain	6	6	18	17	3
Palpitation	6	22	7	6	0
Postural hypotension	4	18	10	5	0
Nausea/vomitting	4	9	8	9	0
Headache	0	10	7	5	0
Decreased weight	1	1	3	0	0
Sexual dysfunction	0	0	1	1	0
Total	**40**	**154**	**148**	**112**	**8**

Different reasons for not taking antidepressants according to the physicians' recommendation as reported by the patients were recorded. The most common reasons were medicine forgotten, feeling better, adverse events, fear of antidepressant dependence, medication cost, long treatment period and do not think that antidepressants are needed, respectively. The results are shown in Table 15.

Table 15 Reasons for antidepressant nonadherence

Reason	**n (%)**
Forgetting	86 (33.46)
Feeling better	43 (16.73)
Adverse events	24 (9.34)
Fear of antidepressant dependence	24 (9.34)
Cost of medicines	17 (6.61)
Long treatment period	16 (6.23)
Do not think that antidepressants are needed	12 (4.67)
Lack of efficacy	6 (2.33)
Do not want to take medication	6 (2.33)
Communication problem with physician	4 (1.56)
Complex regimen	2 (0.78)
Other	17 (6.61)

Table 16 Patients' attitudes towards antidepressant medications

Item No.	Cronbach's alpha	Mean (SD)
Attitudes towards antidepressant treatment	0.82	
1 Antidepressants are necessary for depression treatment		4.04 (0.75)
2 When I have taken antidepressants for a long period I become addicted to them		2.99 (0.92)
3 Antidepressants make me better		4.08 (0.60)
4 Antidepressants help me to control my thoughts and feelings		3.89 (0.72)
5 Antidepressants help me to worry less about my problems		3.77 (0.75)
6 My emotional problems are solved by the antidepressants		3.88 (0.71)
7 Antidepressants make me stronger and able to deal with my problems		3.82 (0.80)
8 Antidepressants are not necessary when I feel better		2.73 (0.98)
9 Antidepressant treatment is a good therapy for me		3.98 (0.64)

This study showed that patients had favorable attitudes (score above three; mean = 4.04) towards necessary of antidepressant treatment (item no. 1). In addition, patients had favorable attitudes (score above three; mean = 3.90) towards efficacy of antidepressant treatment (item no. 3, 4, 5, 6, 7 and 9). However, patients had unfavorable attitudes (score below three; mean = 2.99) towards drug dependence (item no. 2). Moreover, patients had unfavorable attitudes (score below three; mean = 2.73) towards taking less when felt better (item no. 8). The results are shown in Table 16.

Table 17 Number of the patients who expressed their opinions about each item of the attitudes towards antidepressant medication questionnaire rated on a 5-point Likert scale

Item	N (%)				
	1 Strongly disagree	**2 Disagree**	**3 Not sure**	**4 Agree**	**5 Strongly agree**
1 Antidepressants are necessary for depression treatment	1 (0.46)	11 (5.07)	18 (8.29)	136 (62.67)	51 (23.50)
2 When I have taken antidepressants for a long period I become addicted to them	11 (5.07)	50 (23.04)	88 (40.55)	61 (28.11)	7 (3.23)
3 Antidepressants make me better	0	5 (2.30)	15 (6.91)	154 (70.97)	43 (19.82)
4 Antidepressants help me to control my thoughts and feelings	0	10 (4.61)	40 (18.43)	131 (60.37)	36 (16.59)
5 Antidepressants help me to worry less about my problems	2 (0.92)	13 (5.99)	41 (18.89)	138 (63.59)	23 (10.60)
6 My emotional problems are solved by the antidepressants	0	11 (5.07)	36 (16.59)	137 (63.13)	33 (15.21)
7 Antidepressants make me stronger and able to deal with my problems	2 (0.92)	11 (5.07)	47 (21.66)	122 (56.22)	35 (16.13)
8 Antidepressants are not necessary when I feel better	7 (3.23)	42 (19.35)	72 (33.18)	77 (35.48)	19 (8.76)
9 Antidepressant treatment is a good therapy for me	1 (0.5)	3 (1.38)	32 (14.75)	145 (66.82)	36 (16.59)

From the questionnaire items about patients' attitudes towards antidepressant medications, ninety-one percent of depressed patients believed antidepressants made them better. However, forty-four percent believed antidepressants were not necessary when they felt better. Thirty-one percent of patients believed that they will become addicted to antidepressants if they take them for a long time. The results are shown in Table 17.

Table 18 Patients' attitudes towards physicians

Item No.	Cronbach's alpha	Mean (SD)
Attitudes towards physicians	0.89	
1 My doctor takes sufficient time to listen to my problems		3.99 (0.81)
2 My doctor understands my feelings and thoughts in depression		4.07 (0.68)
3 I receive sufficient encouragement from my doctor		4.18 (0.63)
4 My doctor takes sufficient time to discuss my problems		3.96 (0.78)
5 My doctor is interested in my problems		4.10 (0.62)
6 My doctor listens to my thoughts		4.12 (0.56)
7 My doctor make me feel confident that antidepressants help me better		4.12 (0.65)

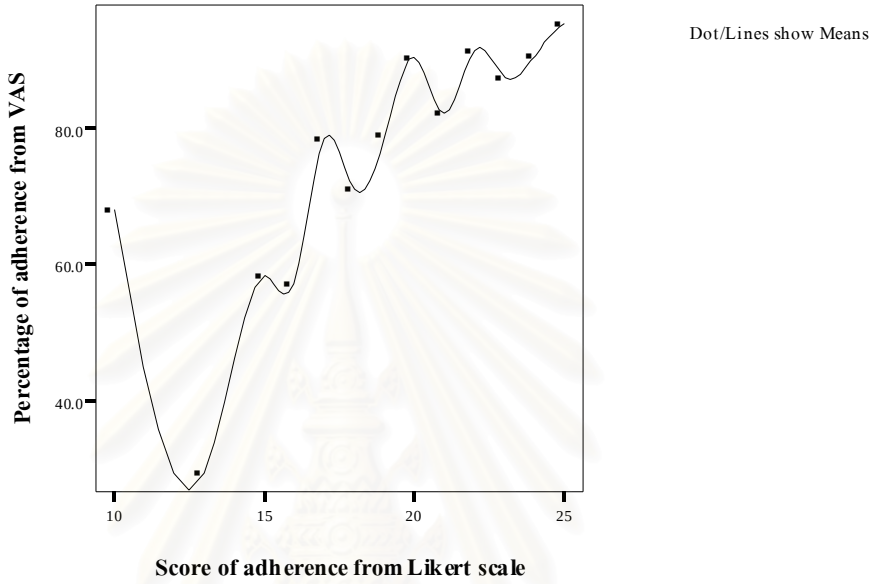
From each item of the attitudes towards physician questionnaire, patients had attitude scores above three. This showed that patients had favorable attitudes towards physician-patient relationship. The results are shown in Table 18.

Table 19 Number of the patients who expressed their opinions about each item of the attitudes towards physician questionnaire rated on a 5-point Likert scale

Item	N (%)				
	1 Strongly disagree	**2 Disagree**	**3 Not sure**	**4 Agree**	**5 Strongly agree**
1 My doctor takes sufficient time to listen to my problems	2 (0.92)	11 (5.07)	27 (12.44)	125 (57.60)	52 (23.96)
2 My doctor understands my feelings and thoughts in depression	1 (0.5)	5 (2.30)	22 (10.14)	139 (64.06)	50 (23.04)
3 I receive sufficient encouragement from my doctor	1 (0.47)	3 (1.40)	12 (5.58)	139 (64.65)	60 (27.91)
4 My doctor takes sufficient time to discuss my problems	0	15 (6.98)	25 (11.63)	129 (60.00)	46 (21.40)
5 My doctor is interested in my problems	0	4 (1.87)	19 (8.88)	143 (66.82)	48 (22.43)
6 My doctor listens to my thoughts	0	3 (1.38)	13 (5.99)	156 (71.89)	45 (20.74)
7 My doctor make me feel confident that antidepressants help me better	0	4 (1.84)	22 (10.14)	134 (61.75)	57 (26.27)

From the questionnaire items about patients' attitudes towards physicians, ninety-three percent of patients believed that their doctors listen to their thoughts. Ninety-two percent of patients believed that they received sufficient encouragement from their doctors. Moreover, eighty-eight percent of patients thought that their doctors were interested in their problems and made them felt confident that antidepressants help them better. The results are shown in Table 19.

Figure 6 Relationship between adherence measured by Likert scale and by visual analog scale (VAS)



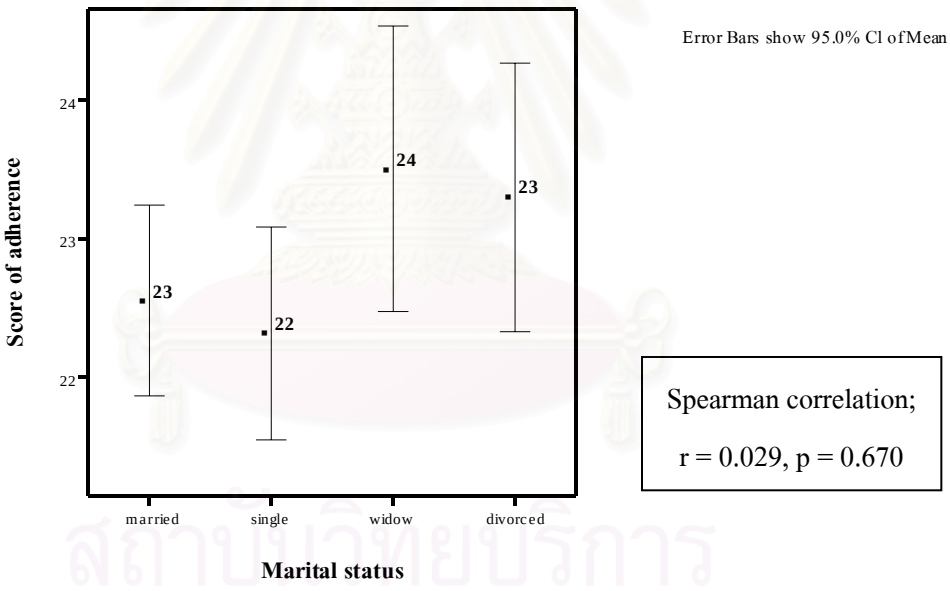
This study used Likert scale and visual analog scale to measure adherence to antidepressant treatment. The finding showed that the measurement using Likert scale was significant associated with the measurement using visual analog scale ($r = 0.687$, $p < 0.01$). This found that the adherence measurement using Likert scale was likely respectable because it showed positive correlation with the measurement using visual analog scale. Moreover, the measurement using Likert scale showed higher magnitude of relationship between adherence and factors influencing adherence than the measurement using visual analog scale. Figure 6 showed that the measurement using visual analog scale was not sensitive at the lower end. This showed that it could not detect the adherence in the lower level. As a result, this study used adherence measurement using Likert scale to analyse the factors influencing adherence.

Part 2: Statistical analysis to examine factors influencing adherence to antidepressant treatment

Socioeconomic characteristics

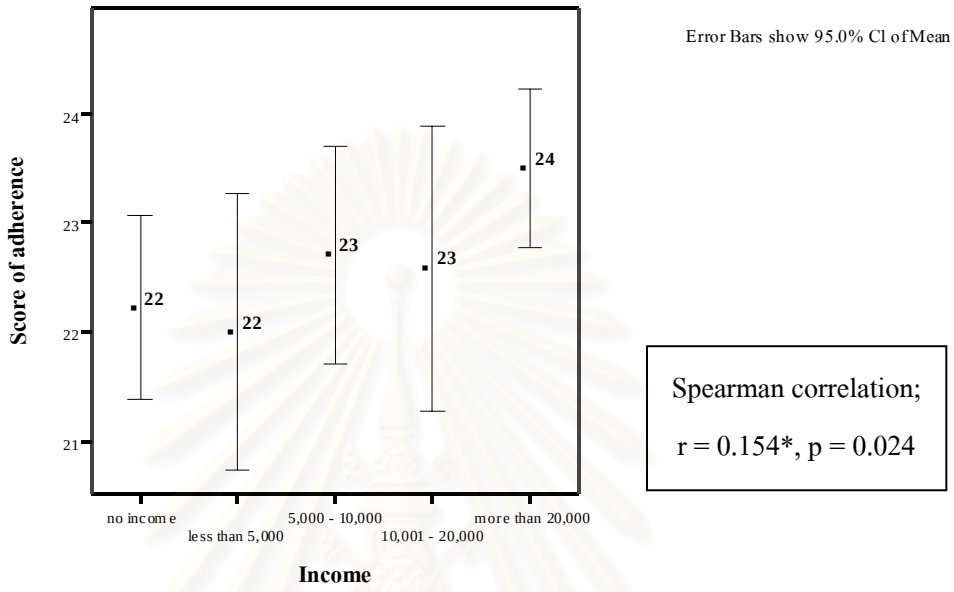
Socioeconomic characteristics included marital status, income and caregiver.

Figure 7 Relationship between score of adherence and marital status



Our finding showed that there was no relationship between adherence and marital status (r = 0.029, p = 0.670).

Figure 8 Relationship between score of adherence and income



* Correlation is significant at the 0.05 level (2-tailed).

This study found that there was a significant positive relationship between adherence and income (r = 0.154, p = 0.024). Patients who had high income had the scores of adherence more than those who had low income.

Table 20 Compare mean of score of adherence across caregiver

Variables		N	Mean	SD	t	Sig. (2-tailed)
Caregiver	Not having caregiver	97	22.55	3.370	-0.390	0.697
	Having caregiver	118	22.72	3.151		

Our finding showed that there was not difference between patients who having caregiver and not having caregiver in score of adherence (p = 0.697).

Clinical and treatment characteristics

Clinical and treatment characteristics included side effects (level of impact), medication cost, dosing regimen, medication forgotten and treatment duration.

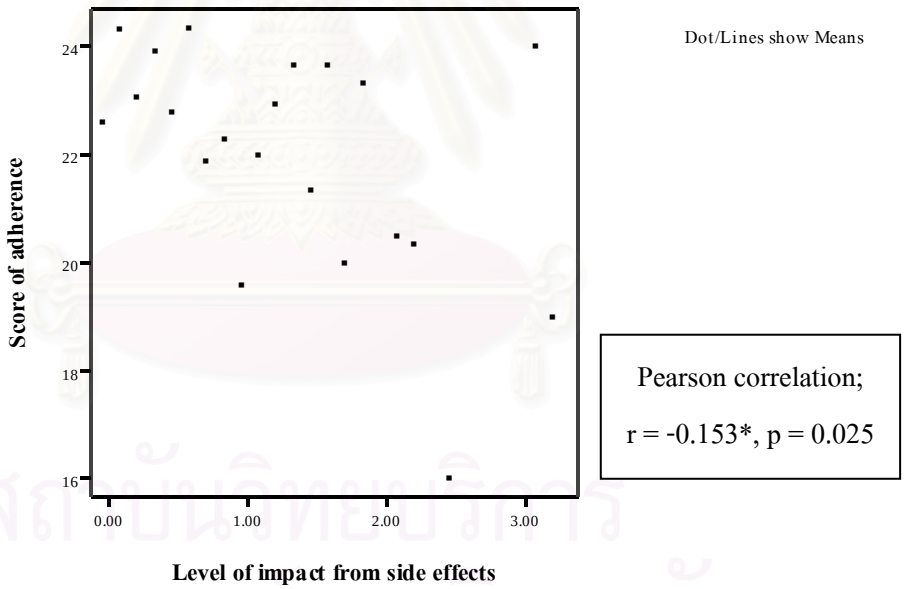
Table 21 Compare mean of score of adherence across dosing regimen, cost of medication and medicine forgotten

Variables		N	Mean	SD	t	Sig. (2-tailed)
Dosing regimen	Single daily dosing	149	22.71	3.165	0.582	0.561
	Multiple daily dosing	67	22.43	3.439		
Cost of medication	Not impact	199	22.74	3.197	1.849	0.066
	Impact	17	21.24	3.597		
Medicine forgotten	No	131	23.07	3.263	2.524	0.012*
	Yes	85	21.94	3.118		

* Difference is significant at the 0.05 level (2-tailed).

Our finding showed that there was not difference between patients who treated with single and multiple daily dosing in score of adherence (p = 0.561). There was difference between patients who impacted and not impacted from medication cost in score of adherence but not significant at alpha = 0.05 (p = 0.066). Patients who forgot and not forgot to take medicines significantly differenced in score of adherence (p = 0.012). The results are shown in Table 21.

Figure 9 Relationship between score of adherence and level of impact of side effects



* Correlation is significant at the 0.05 level (2-tailed).

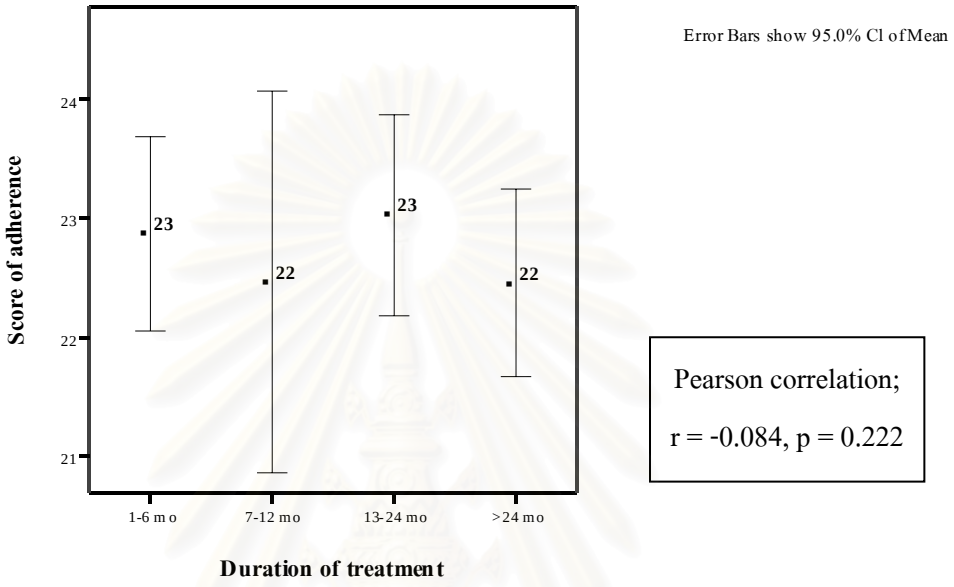
Our finding showed that there was a significant negative relationship between adherence and level of impact from side effects (r = -0.153, p = 0.025). If the patients have high level of impact from side effects, they will have low score of adherence to treatment.

Table 22 Pearson correlation between score of adherence and impact of each type of side effects

Impact of each type of side effects (N)	Score of adherence	
	Pearson correlation	Sig. (2-tailed)
Weight gain (50)	-0.110	0.109
Palpitation (41)	-0.096	0.162
Dry mouth (90)	-0.089	0.196
Postural hypotension (37)	-0.065	0.346
Somnolence (88)	-0.039	0.571
Insomnia (50)	-0.035	0.606
Fatigue (50)	-0.082	0.230
Nausea/vomitting (30)	-0.102	0.138

Our finding showed that there was no relationship between score of adherence and level of impact from each type of side effects ($p > 0.05$). The side effects including headache, decreased weight and sexual dysfunction were not analysed because the numbers of patients who experienced with these side effects lower than 30 patients.

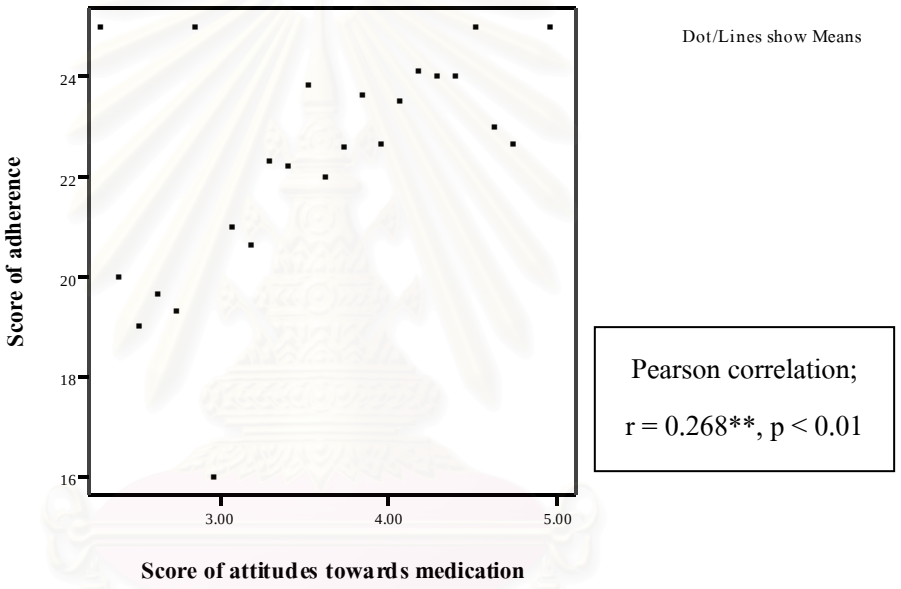
Figure 10 Relationship between score of adherence and duration of treatment



Our finding showed that there was no relationship between adherence and treatment duration (r = -0.084, p = 0.222).

Attitudes towards antidepressant medication and physician

Figure 11 Relationship between score of adherence and score of attitudes towards medication



** Correlation is significant at the 0.01 level (2-tailed).

Our finding showed that there was a significant positive relationship between score of adherence and score of attitudes towards medication ($r = 0.268$, $p < 0.01$). If the patients have high score of attitudes towards medication, they will have high score of adherence.

Table 23 Pearson correlation between score of adherence and the four aspects of attitudes towards medication

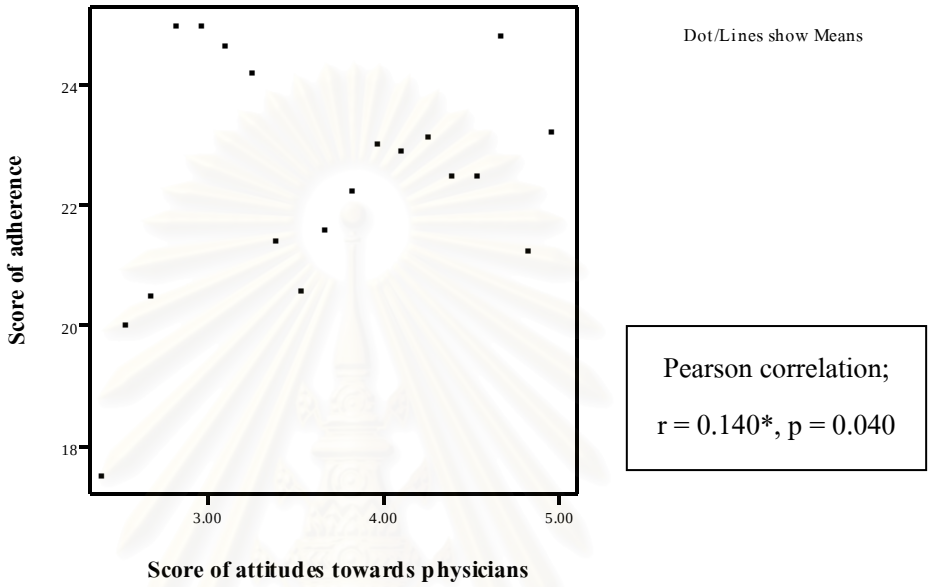
Aspects of attitudes towards medication	Score of adherence	
	Pearson correlation	**Sig. (2-tailed)**
Drug addiction	0.079	0.248
Take less when feeling better	0.174*	0.011
No need to take medications	0.166*	0.015
Loss of efficacy	0.221**	0.001

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Our finding showed that the adherence was significantly associated with attitudes towards taking less when feeling better, necessary and efficacy of antidepressant treatment. From this finding, if the patients have high scores of these three aspects of attitudes towards medication, they will have high adherence. However, there was no relationship between adherence and attitudes towards drug addiction. From this study, if the patients do not believe taking less when feeling better, they will have high adherence. In addition, if the patients believe the antidepressant treatment are needful and believe in efficacy of antidepressant, they will have high adherence.

Figure 12 Relationship between score of adherence and score of attitudes towards physicians



* Correlation is significant at the 0.05 level (2-tailed).

Our finding showed that there was a significant positive relationship between score of adherence and score of attitudes towards physicians (r = 0.140, p = 0.040). If the patients have high score of attitudes towards physicians, they will have high score of adherence.

Multiple Regression Analysis between independent variables and adherence to antidepressant treatment

In this study, independent variables included socioeconomic characteristics (marital status, income and caregiver), treatment characteristics (impact of side effect, dosing regimen, treatment duration, medication cost and drug forgotten), four aspects of attitudes towards antidepressant treatment and attitudes towards physicians. The dependent variable for this study was adherence to antidepressant treatment. The next step of data analysis was performed by taking independent variables into multiple regression analysis by using stepwise.

Table 24 Pearson correlation between dependent variable (adherence) and independent variables

Independent variables	Adherence	
	Pearson correlation	**Sig. (1-tailed)**
Single status	-0.059	0.196
Married status	-0.032	0.322
Divorced status	0.078	0.128
Income less than 5,000 baht/month	-0.076	0.136
Income 5,000-10,000 baht/month	0.025	0.360
Income 10,001-20,000 baht/month	-0.007	0.462
Income more than 20,000 baht/month	0.136*	0.023
Having of caregiver	0.031	0.328
Medicine forgotten	-0.162**	0.009
Impact of medication cost	-0.126*	0.032
Multiple daily dosing	-0.041	0.274
Duration of treatment	-0.084	0.111
Impact of side effects	-0.146*	0.017
Drug addiction	0.082	0.117
Taking less when feeling better	0.172**	0.006
Necessary of antidepressant treatment	0.170**	0.006
Efficacy of antidepressant treatment	0.232**	0.000
Attitudes towards physicians	0.118*	0.042

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Table 25 Multiple regression of adherence to antidepressant treatment using stepwise[a]

Variables	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	18.223	1.592		11.446	0.000
High income[b]	0.844	0.535	0.105	1.578	0.116
Medicine forgotten	-1.173	0.433	-0.177	-2.708	0.007
Impact of side effects	-0.674	0.331	-0.132	-2.036	0.043
Efficacy of antidepressants[c]	0.994	0.396	0.170	2.514	0.013
Take less when feeling better[c]	0.473	0.218	0.143	2.166	0.031

a : Model summary; $R^2 = 0.126$

b : Income more than 20,000 baht/month

c : Aspects of attitudes towards medication

From multiple regression analysis, if the patients have incomes which were more than 20,000 baht/month (high income), the score of adherence will increase by 0.844 score. If the patients forget to take medicines, the score of adherence will decrease by 1.173 score. Moreover, if the level of impact of side effects increases 1 unit, the score of adherence will decrease by 0.674 score. From the aspects of attitudes towards medication, if the score of attitudes towards efficacy of antidepressants increases 1 score, the score of adherence will increase by 0.994 score. Finally, if the score of attitudes towards taking less when feeling better increases 1 score, the score of adherence will increase by 0.473 score.

The result showed that four independent variables: medicine forgotten, impact of side effects and two aspects of attitudes towards medications (efficacy of antidepressants and taking less when feeling better); significantly predicted the adherence to antidepressant treatment and accounted for 12.6 % of coefficient of determination ($R^2 = 0.126$). This analysis found that medicine forgotten had the most effect on the adherence to antidepressant treatment with standardized coefficient (beta) of -0.177 ($p = 0.007$). The two aspects of attitudes towards medication; i.e., efficacy of antidepressant and taking less when feeling better, had effect on the adherence to antidepressant treatment with beta of 0.170 ($p = 0.013$) and 0.143 ($p = 0.031$), respectively. In addition, impact of side effects with beta of -0.132 had negative effect on adherence to antidepressant medications ($p = 0.043$).

Therefore, adherence to antidepressant treatment was improved by enhancing awareness to take medicines, increasing favorable attitudes towards antidepressant medications, especially the aspects of efficacy of antidepressants and taking less when feeling better, and decreasing impact from antidepressant side effects. Pharmacists could support patients by advising them about need, benefit and effect of antidepressants in order to help them clearly understood usage of antidepressant treatment and had positive attitudes towards antidepressant medications. In addition, pharmacists could enhance patients' awareness to take medicines by using support equipments such as pill boxes and calendars. Pharmacists could advise patients about side effects from antidepressants. Also, pharmacists could follow up patients and watch out for side effects in order to alleviate side effect impact on patients. These ways were expected to increase adherence to antidepressant treatment of depressed patients.

CHAPTER V

DISCUSSION

It is well known that adherence greatly influence clinical outcome of depression treatment. Therefore, study of factors affecting adherence to antidepressant medications is necessary. This study used indirect measurement: patient questionnaire, to estimate adherence to antidepressant medications in depressed patients and multiple regression to analyse variables that predicting adherence to medications. The study found that the variables that could predict the adherence to antidepressants included medicine forgotten, patients' attitudes towards antidepressant medications (the aspects of efficacy of antidepressant and taking less when feeling better) and impact of side effects.

Sociodemographic and economic characteristics

Several studies reported that sociodemographics did not associate with adherence to antidepressant treatment. Aikens et al. who surveyed 81 primary care patients given maintenance antidepressant medications, found that adherence were broadly dispersed and unrelated to demographics*(14)*. Osterberg and Blaschke reviewed that sex and socioeconomic status had not been consistently associated with levels of adherence*(35)*. Vermeire et al. reviewed that demographic variables including age, sex and marital status were poor indicators of adherence. Although some associations had been found, the direction of these associations was inconsistent between studies*(36)*. In addition, Lingam and Scott reviewed that sociodemographic variables had failed to consistently predict nonadherence*(56)*.

However, there were several studies found that sociodemographics and socioeconomics related to adherence to medications. A meta-analysis by Dimatteo showed that marital status and living with another person (for adults) increase adherence modestly. For adults, living with someone had a positive effect on adherence*(57)*. In addition, Bull et al. found that patients who were separated, divorced or widowed were more likely to discontinue antidepressant treatment than patients who were currently married*(51)*. However, Gonzalez et al. found that being unmarried increased the likelihood of adherence ($p < 0.05$)*(8)*. Olfson et al. showed that antidepressant discontinuation was significantly more common among patients with low family incomes (50.2 %), compared with those with medium or high family incomes (38.6 %)*(32)*. In addition, Hansen et al. concluded that early discontinuation of antidepressant was more frequent among patients of low socioeconomic status*(42)*. Sher et al. found that the kinship between the caregiver and the patient significantly predicted patients' adherence*(49)*.

This study found that marital status and caregiver did not associate with adherence to antidepressant treatment. This finding is consistent with several previous studies which stated that sociodemographic variables were poor indicators of adherence. This study showed that income associated with adherence to antidepressant medications ($r = 0.154$, $p = 0.024$). This finding is consistent with previous studies which stated that nonadherence to antidepressants was more frequent among patients of low incomes.

Clinical and treatment characteristics

This study examined dosing regimen of antidepressants, impact of side effects, treatment duration, cost impact and medicine forgetting.

Van Dijk et al. reported that a complex medication regimen was moderately negatively associated with refill nonadherence*(40)*. In addition, Demyttenaere reviewed that some studies demonstrated that a once-daily regimen resulted in a better adherence than a three-time or more daily regimen*(38)*. Moreover, Osterberg and Blaschke reviewed that adherence was inversely proportional to frequency of dose and patients taking medication on a schedule of four times daily achieved average adherence rate of about 50 %*(35)*. Yyldyz and Sachs reviewed that there was no difference in therapeutic efficacy between single and multiple daily dosing. The unnecessary complexity of multiple daily dosing regimen could contribute to nonadherence to treatment*(17)*. However, Schectman et al. found that once daily dosing was associated with greater adherence in bivariate analyses but it was not independently predictive*(58)*. Vermeire et al. reviewed that high frequency of dosing was related to low adherence but this variable was inconsistently correlated with adherence and thus could not be used to predict adherence adequately*(36)*. This study showed that dosing regimen (single/multiple daily dosing) was not associated with adherence to antidepressant treatment.

Maddox et al. found that the score of severity of side effects negatively associated with the length of time the tablets were taken ($r = -0.3884$, $p = 0.008$) i.e. the worse the side effects, the less time the tablets were taken*(30)*. Masand reviewed that side effect was factor contributing to treatment discontinuation*(5)*. Moreover, Kihlstrom reviewed that some medications which produced a greater number of side effects could affect patients' adherence*(39)*. Surprisingly, Vermeire et al. reviewed that side effects were only mentioned by 5-10 % as a reason for nonadherence*(36)*.

This study found that level of impact of side effects was significantly associated with adherence to antidepressant medications ($r = -0.153$, $p = 0.025$). Patients who experienced with increased impact of side effects had negative effect on adherence to treatment. This finding is consistent with previous studies which stated that severity of side effects negatively associated with adherence. Nevertheless, the study found that high level of impact of side effects did not associate with adherence. This might be due to a small number of patients (8 patients) who experienced with high level of impact of side effects.

Kihlstrom reviewed that adherence to antidepressant treatment was more troublesome due to long-term of treatment*(39)*. Vermeire et al. reviewed that factor related to low adherence included duration of treatment but this variable was inconsistently correlated with adherence and thus could not be used to predict adherence adequately*(36)*. Aikens et al. reported that adherence was unrelated to treatment duration*(14)*. Also, Centorrino et al. found that visit adherence was not associated with the number of years a patient had been receiving treatment*(59)*. This study found that treatment duration was not associated with adherence to antidepressant treatment.

Masand reviewed that factor contributing to treatment discontinuation included cost of medication*(5)*. Kihlstrom reviewed that cost of medication might inhibit patients from prescribed medication*(39)*. In addition, Kennedy and Erb reported that prescription nonadherence due to cost was a serious problem for many adults with chronic disease or disability*(60)*. However, Vermeire et al. reviewed that factor related to low adherence included cost but this variable was inconsistently correlated with adherence and thus could not be used to predict adherence adequately*(36)*. This study found that patients who cost impacted and cost did not impact them were

different in adherence to antidepressant medications, but not significant at the 0.05 level (p = 0.066).

Cooper et al. suggested that patients who were nonadherence to medication, 37.4 % said they had forgotten; 24.6 % had thought it was not needed and 18.9 % had not wanted to take drugs*(10)*. This study found that the most reason for nonadherence in the study samples was medicine forgetting (33.46 %). This study compare mean of adherence across patients who forgot and did not forget to take antidepressants and found that patients who forgot to take medicines had lower adherence percentage than those who did not forget to take drugs (p = 0.012).

Attitudes towards antidepressant treatment

There were several studies that examined regarding patients' attitudes towards antidepressant medications. Vermeire et al. reviewed that the most salient influences on adherence were patients' beliefs about medications and about medicine in general*(36)*. Lingam and Scott reviewed that the role of the patients' attitudes had been increasingly emphasized. Patients' perceptions of stigma about depression at the start of treatment predicted their subsequent medication adherence*(56)*. In addition, Sirey et al. demonstrated the influence of patients' attitudes towards their treatment on adherence*(44)*. Lin et al. concluded that predictor of adherence to long-term depression therapy was favorable attitudes towards antidepressant treatment*(46)*. Aikens et al. concluded that only predictor of discontinuation risk was baseline antidepressant skepticism, which was associated with a 62 % increase in the risk of discontinuation of SSRIs. Thus, antidepressant attitudes were an important predictor of antidepressant outcome*(43)*. Brown et al. found that beliefs about medications were significantly associated with self-reported adherence. Specific concerns about antidepressants are significantly associated with self-reported medication-taking

behavior*(47)*. Moreover, Hunot et al. found that concerns about antidepressants acted as significant barrier to sustained adherence. Specific concern about antidepressant side effects (OR = 3.30, 95 % CI: 2.20-4.97) was independent predictor of antidepressant nonuse*(34)*. Also, Ayalon et al. concluded that greater concerns about antidepressant medication (OR = 0.78, 95 % CI: 0.64-0.94) was significant predictor of adherence to antidepressants*(31)*. This study found that attitudes towards antidepressant treatment were significant associated with adherence to treatment ($r = 0.268$, $p < 0.01$). Patients' attitudes towards antidepressant treatment had positive effect on adherence to medications. This finding is consistent with several previous works which stated that patients' attitudes were related to adherence to antidepressant therapy.

Attitudes towards physicians

There was mounting evidence that establishing a good physician-patient relationship had an important role in increasing adherence. A clinician's initial communication style influenced patients' beliefs about and understanding of antidepressants and that subjects with more positive beliefs were more engaged in and satisfied with their treatment*(56)*. Hunot et al. showed significant association for continued/noncontinued antidepressant use and satisfaction with physician consultation ($t = -2.42$, $p = 0.02$). Patients with noncontinued antidepressant uses had lower satisfaction with physician consultation*(34)*. Bull et al. found that patients who discussed adverse effects with their physicians were less likely to discontinue antidepressant therapy than patients who did not discuss them (OR = 0.49, 95 % CI: 0.25-0.95). Communication about adverse effects significantly decreased the odds of discontinuing antidepressant therapy*(51)*. In addition, Demyttenaere reviewed that patients presented a higher adherence when their physicians expressed positive verbal communications. Adherence was indeed greater when patients felt their expectations

had been fulfilled, when the physicians elicited and respected patients' concerns and provided responsive information, and when sincere concern and sympathy were shown*(38)*. Moreover, Masand reviewed that poor physician-patient communication was factor contributing to treatment discontinuation*(5)*. Bultman and Svarstad found that physician initial communication style positively influenced patient knowledge and initial beliefs about medication. Patients with more positive beliefs about the treatment were more likely to see the physician in follow-up and were more satisfied with treatment*(52)*. Also, Gonzalez et al. showed that having a provider with a participatory decision making style ($p = 0.03$) increased the likelihood of adherence to treatment*(8)*. However, Vermeire et al. reviewed that the physician-patient relationship seemed to be an important variable in adherence, including the process of prescribing, but it was extremely difficult to assess the nature of this interaction and to measure its components*(36)*. This study found that patients' attitudes towards physicians were significant associated with adherence to antidepressant medications ($r = 0.140$, $p = 0.040$). This finding is consistent with several previous studies which stated that physician-patient relationship was related to adherence to treatment.

CHAPTER VI

CONCLUSION

The aim of this study was to examine factors influencing adherence to antidepressant treatment in Thai depressed patients. The study samples were depressed outpatients from psychiatric clinic at King Chulalongkorn Memorial Hospital during April 2007 to December 2007. This study used questionnaires as instruments to measure adherence to antidepressant therapy and attitudes towards antidepressant medications and physicians. The reliability coefficient of antidepressant adherence questionnaire was 0.8389, attitudes towards medication questionnaire was 0.8194 and attitudes towards physicians questionnaire was 0.8924.

The study samples were 217 depressed outpatients. This study found that most of the patients had high adherence from both Likert scale measurement (mean ± SD; 22.63 ± 3.25) and visual analog scale (mean ± SD; 87.68 ± 16.81). There was a significant association between measurement of both scale ($r = 0.687$, $p < 0.01$). The study showed that 80.6 % of patients experienced side effects from antidepressants. The most common side effects were dry mouth (18.79 %), somnolence (18.37 %), fatigue (10.44 %), insomnia (10.44 %), weight gain (10.44 %), palpitation (8.56 %), postural hypotension (7.72 %), nausea/vomitting (6.62 %) and headache (4.59 %), respectively. The most common reasons for antidepressant nonadherence were medicine forgotten (33.46 %), feeling better (16.73 %), adverse events (9.34 %), fear of antidepressant dependence (9.34 %), cost of medications (6.61 %), long period treatment (6.23 %) and not thinking antidepressant needed (4.67 %), respectively.

This study found that most of the patients had favorable beliefs about antidepressant medications (mean ± SD of score; 3.69 ± 0.48) and had higher favorable beliefs about physicians (mean ± SD of score; 4.06 ± 0.54). Most of the patients believed that antidepressants made them better (90.8 %). However, there was a number of patients believed that antidepressants were not necessary when they felt better (44.2 %) and believed that they became addicted to antidepressants when they had taken them for a long period (31.3 %). From attitudes towards physicians, most of the patients believed that their physicians listen to their thoughts (92.6 %).

This study found that adherence to antidepressant treatment significantly associated with patients' income, impact of side effects, medicine forgetting and patients' attitudes towards antidepressant therapy and towards physicians. Patients with low income, increased level of impact of side effects, forgetting of drugs and unfavorable attitudes towards antidepressant medications and towards physicians were related to nonadherence to treatment. Multiple regression analysis of adherence to antidepressant treatment found that impact of side effects, medicine forgotten and two aspects of attitudes towards medications; i.e., efficacy of antidepressant treatment and taking less when feeling better, significantly predicted the adherence to antidepressant treatment and accounted for 12.6 % of coefficient of determination.

Thus, adherence to antidepressant treatment was improved by increasing favorable attitudes towards antidepressant medications, enhancing awareness to take medicines and decreasing impact from antidepressant side effects.

Study limitation

1. This study using patients' data from OPD cards for some retrospective information, thus some information might be incomplete.
2. The study samples did not truly represent populations because the reseacher studied in only one hospital (in only tertiary care hospital) and depressed patients were treated by only psychiatrists.
3. The total numbers of depressed patients who met the inclusion criteria were 344 patients. Only 217 patients (63.08 %) were enrolled into the study because the rest 122 patients (35.47 %) did not come to visit the physicians during the studied time while 5 patients (1.45 %) refused to join the study and/or lost of interview (because of the incomplete time and process setting during the initial period of the study). The patients who did not come to visit their doctors might have tendency of nonadherence and were not enrolled into the study. If these patients were enrolled, the study results may be different.
4. This study did not measure patient outcomes either efficacy or side effects

Suggestions

1. Healthcare providers should pay attention to patients' attitudes towards antidepressants because patients' beliefs about treatment mostly influenced adherence to antidepressant therapy and there were a number of patients believed that antidepressants were not necessary when they felt better, antidepressants were addicted and antidepressants were not necessary for depression treatment.
2. Pharmacists should pay attention to advise patients about side effects from antidepressants in order to help the patients have better understanding and ability of self-management of side effects.
3. Further studies should include the relationships between clinical outcomes (efficacy and side effects) to adherence. Clinical outcomes should be collected from long term monitoring, the data should come from records evaluated by physicians.

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Appendices

Appendix A

Questionnaire

No. ____

แบบสอบถามปัจจัยที่ส่งผลต่อความร่วมมือในการรักษาด้วยยาต้านเศร้า

ส่วนที่ 1 ข้อมูลส่วนตัว (กรุณาเติมรายละเอียดในช่องว่าง และเขียนเครื่องหมาย ✓ ในช่องที่ตรงกับคุณ)

เพศ (1) ชาย (2) หญิง

อายุ _____ ปี

สถานภาพสมรส (1) โสด (2) สมรส (3) หย่า/แยกกันอยู่ (4) หม้าย

การศึกษาสูงสุด (1) ประถมศึกษา (2) มัธยมศึกษา (3) อนุปริญญา / ปริญญาตรี
(4) ปริญญาโทขึ้นไป (5) ไม่ได้ศึกษา

จำนวนปีที่ศึกษา _____ปี

อาชีพ (1) รับจ้าง (2) แม่บ้าน (3) เกษตรกร
(4) ข้าราชการ/พนักงานรัฐวิสาหกิจ (5) ค้าขาย/ธุรกิจส่วนตัว
(6) พนักงานบริษัท (7) นักศึกษา (8) ไม่ได้ประกอบอาชีพ
(9) อื่นๆ _____

รายได้ (1) น้อยกว่า 5,000 บาท (2) 5,000-10,000 บาท
(3) 10,001-20,000 บาท (4) มากกว่า 20,000 บาท
(5) ไม่มีรายได้

ผู้ดูแล (1) คู่สมรส (2) บุตร (3) บิดา-มารดา
(4) ญาติพี่น้อง (5) อื่น ๆ (กรุณาระบุ)_____
(6) ไม่มีผู้ดูแล

ส่วนที่ 2 ข้อมูลการรักษา (ผู้วิจัยเป็นผู้กรอกข้อมูล)

การวินิจฉัย (1) Major depressive disorder (2) Bipolar depression
(3) Atypical depression (4) Dysthymia
(5) Depression with psychosis (6) อื่น ๆ _____

ระยะเวลาการเจ็บป่วย _____(ว/ด/ป) :_____วัน

โรคประจำตัว (1) Hypertension (2) Diabetes (3) Hyperlipidemia
(4) Cardiac disease (5) อื่น ๆ _____

ข้อมูลการใช้ยา:

วันที่	รายการยา	จำนวน

วันที่	รายการยา	จำนวน

<u>ส่วนที่ 3 ความร่วมมือในการรักษาด้วยยา</u>

กรุณาเขียนเครื่องหมาย / ในช่องที่ตรงกับความเห็นของคุณมากที่สุด

1. **ฉันรู้สึกว่ามัน<u>ยาก</u>ที่ต้องรับประทานยาต้านเศร้าตามคำแนะนำของแพทย์**
   (1) ไม่เคยเลย (2) นานๆครั้ง (3) บางครั้ง (4) บ่อยครั้ง (5) ตลอดเวลา

2. **ฉันรับประทานยาต้านเศร้าตามคำแนะนำของแพทย์<u>อย่างเคร่งครัด</u>**
   (1) ไม่เคยเลย (2) นานๆครั้ง (3) บางครั้ง (4) บ่อยครั้ง (5) ตลอดเวลา

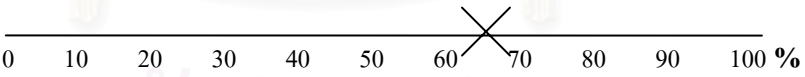
3. **ฉัน<u>ไม่</u>สามารถรับประทานยาต้านเศร้าตามคำแนะนำของแพทย์ได้**
   (1) ไม่เคยเลย (2) นานๆครั้ง (3) บางครั้ง (4) บ่อยครั้ง (5) ตลอดเวลา

4. **ฉันสามารถรับประทานยาต้านเศร้าตามคำแนะนำของแพทย์ได้<u>เป็นอย่างดี</u>**
   (1) ไม่เคยเลย (2) นานๆครั้ง (3) บางครั้ง (4) บ่อยครั้ง (5) ตลอดเวลา

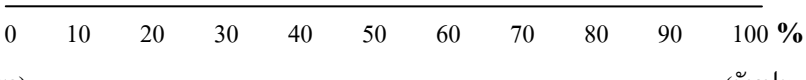
5. **คุณสามารถรับประทานยาต้านเศร้าตามคำแนะนำของแพทย์<u>อย่างครบถ้วน</u>ได้บ่อยเท่าใด**
   (1) ไม่เคยเลย (2) นานๆครั้ง (3) บางครั้ง (4) บ่อยครั้ง (5) ตลอดเวลา

6. **ในช่วงเวลา 6 เดือนที่ผ่านมา คุณรับประทานยาต้านเศร้าคิดเป็น<u>กี่เปอร์เซ็นต์</u>ของยาต้านเศร้าที่คุณต้องรับประทานตามคำแนะนำของแพทย์** (กรุณากากบาท X *ทับเส้น*ข้างล่างนี้)

   ตัวอย่าง



   กรุณากากบาททับเส้นข้างล่างนี้



(ไม่ได้รับประทานยา) (รับประทานยาครบ)

<u>ส่วนที่ 4 เหตุผลของความไม่ร่วมมือในการรักษาด้วยยา</u>

1. **เหตุผลใดบ้างที่ทำให้คุณ<u>ไม่ได้</u>รับประทานยาต้านเศร้าตามที่แพทย์แนะนำหรือรับประทานยาต้านเศร้า<u>น้อยกว่า</u>ที่แพทย์แนะนำ** (คุณสามารถเลือกได้มากกว่า 1 ข้อ)
   (1) เกิดอาการข้างเคียงจากยาต้านเศร้า เช่น น้ำหนักเพิ่ม ง่วงซึม อ่อนเพลีย
   (2) อาการดีขึ้นจึงหยุดรับประทานยาหรือรับประทานยาน้อยลง
   (3) ความรู้สึกกลัวการติดยาต้านเศร้า
   (4) รู้สึกว่ายาไม่มีประสิทธิภาพ
   (5) คิดว่าไม่จำเป็นต้องรับประทานยาต้านเศร้า
   (6) ลืมรับประทานยาต้านเศร้า
   (7) ต้องรับประทานยาหลายครั้งต่อวัน
   (8) ใช้เวลาในการรักษานาน
   (9) ยามีราคาแพง
   (10) ความไม่เข้าใจกันระหว่างคุณและแพทย์
   (11) ปัญหาในการสื่อสารกับแพทย์
   (12) เหตุผลอื่น _____

2. **กรุณาเขียนหมายเลขเหตุผลจากข้อ 1 ที่เป็น<u>*เหตุผลสำคัญที่สุด*</u> ที่ทำให้คุณ<u>ไม่ได้</u>รับประทานยาต้านเศร้าตามที่แพทย์แนะนำหรือรับประทานยาต้านเศร้า<u>น้อยกว่า</u>ที่แพทย์แนะนำ**
   เหตุผลข้อ _____

3. **คุณเคยเกิดอาการข้างเคียงจากยาต่อไปนี้หรือไม่** ***ในกรณีที่เคยเกิดอาการข้างเคียง คุณคิดว่าอาการข้างเคียงดังกล่าวส่งผลกระทบต่อตัวคุณในระดับใด*** (กรุณาเขียน ✓ ในช่องที่ตรงกับความเห็นของคุณมากที่สุด)

อาการข้างเคียง	เคยเกิดอาการข้างเคียงนี้หรือไม่		1 ผลกระทบน้อยที่สุด	2 ผลกระทบน้อย	3 ผลกระทบปานกลาง	4 ผลกระทบมาก	5 ผลกระทบมากที่สุด
	เคย	ไม่เคย					
1. น้ำหนักเพิ่มอย่างผิดปกติ							
2. ใจสั่น							
3. ปากแห้ง คอแห้ง							
4. หน้ามืดคล้ายจะเป็นลมเวลาเปลี่ยนท่าทาง							
5. ง่วงนอน							
6. นอนไม่หลับ							
7. อ่อนเพลียหรือไม่มีแรง							
8. ปวดศีรษะ							
9. มีปัญหาทางเพศสัมพันธ์							
10. คลื่นไส้หรืออาเจียน							
11. อื่น ๆ _____							

ส่วนที่ 5 ทัศนคติต่อการรักษาด้วยยาต้านเศร้า

กรุณาเขียนเครื่องหมาย / ในช่องที่ตรงกับความเห็นของคุณมากที่สุด

ข้อความ	1 ไม่เห็นด้วย อย่างยิ่ง	2 ไม่ เห็นด้วย	3 ไม่แน่ใจ	4 เห็นด้วย	5 เห็นด้วย อย่างยิ่ง
1. ฉันคิดว่าจำเป็นต้องรับประทานยาต้านเศร้าเพื่อรักษาภาวะซึมเศร้า					
2. ฉันคิดว่าเมื่อรับประทานยาต้านเศร้าเป็นเวลานาน จะทำให้ติดยาต้านเศร้า					
3. การรับประทานยาต้านเศร้าทำให้อาการซึมเศร้าของฉันดีขึ้น					
4. เมื่อฉันรับประทานยาต้านเศร้าทำให้ฉันควบคุมความคิดและความรู้สึกได้ดี					
5. ยาต้านเศร้าช่วยให้ฉันกังวลเกี่ยวกับปัญหาส่วนตัวน้อยลง					
6. ยาต้านเศร้าช่วยแก้ไขปัญหาทางด้านอารมณ์ของฉัน					
7. ยาต้านเศร้าทำให้ฉันเข้มแข็งมากขึ้น และสามารถเผชิญกับปัญหาได้ดีขึ้น					
8. ฉันคิดว่าถ้าอาการดีขึ้นแล้วไม่จำเป็นต้องรับประทานยาต้านเศร้า					
9. ฉันคิดว่าการรับประทานยาต้านเศร้าเป็นการรักษาที่ดีสำหรับตัวฉัน					

ส่วนที่ 6 ทัศนคติต่อแพทย์

กรุณาเขียนเครื่องหมาย / ในช่องที่ตรงกับความเห็นของคุณมากที่สุด

ข้อความ	1 ไม่เห็นด้วย อย่างยิ่ง	2 ไม่ เห็นด้วย	3 ไม่แน่ใจ	4 เห็นด้วย	5 เห็นด้วย อย่างยิ่ง
1. แพทย์มีเวลาเพียงพอที่จะรับฟังปัญหาของฉัน					
2. แพทย์เข้าใจความรู้สึกและภาวะซึมเศร้าของฉัน					
3. ฉันได้รับกำลังใจในการรักษาจากแพทย์					
4. แพทย์มีเวลาที่จะให้คำปรึกษาเกี่ยวกับภาวะจิตใจของฉัน					
5. ฉันคิดว่าแพทย์ให้ความสนใจในปัญหาของฉัน					
6. แพทย์รับฟังความคิดเห็นของฉัน					
7. แพทย์ทำให้ฉันรู้สึกมั่นใจว่ายาต้านเศร้าจะช่วยรักษาภาวะซึมเศร้าได้					

Appendix B

Research subject information sheet and consent form

เอกสารชี้แจงข้อมูลแก่ผู้เข้าร่วมโครงการวิจัย (Research Subject Information Sheet)

ชื่อโครงการวิจัย	ปัจจัยที่ส่งผลกระทบต่อความร่วมมือในการรักษาด้วยยาต้านซึมเศร้าในผู้ป่วยโรคซึมเศร้าชาวไทย
ชื่อผู้วิจัย	นางสาวอภิรดี ศรีสว่าง
หน่วยงานที่ทำการศึกษา	คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
โทรศัพท์	086-6996823 (สามารถติดต่อได้ทั้งในและนอกเวลาราชการ)

ท่านได้รับเชิญให้เข้าร่วมการศึกษาวิจัยเรื่องปัจจัยที่ส่งผลกระทบต่อความร่วมมือในการรักษาด้วยยาของผู้ป่วยไทยที่เป็นโรคซึมเศร้า ก่อนที่ท่านจะตัดสินใจเข้าร่วมการศึกษาวิจัยนี้ ท่านจำเป็นต้องเข้าใจรายละเอียดและความสำคัญของการศึกษาวิจัยนี้ กรุณาอ่านข้อมูลต่อไปนี้และสอบถามได้ทันทีถ้าไม่แน่ใจหรือมีข้อสงสัย

ที่มาของโครงการวิจัย

โรคซึมเศร้าพบได้ทั่วไปในประชากร จากการศึกษาพบว่าความร่วมมือในการรักษาเป็นปัญหาสำคัญในการรักษา โดยพบว่าผู้ป่วยจำนวนหนึ่งไม่มารับการรักษาอย่างต่อเนื่อง นอกจากนี้ยังพบว่าการหยุดยาโดยที่อาการยังไม่หมดไปจะมีโอกาสกลับเป็นโรคซ้ำสูง แสดงให้เห็นว่าความร่วมมือในการรักษาของผู้ป่วยมีความสำคัญต่อประสิทธิผลในการรักษาอย่างมาก ดังนั้นการศึกษานี้จึงต้องการทำการสำรวจปัจจัยที่ส่งผลกระทบต่อความร่วมมือในการรักษาด้วยยาต้านเศร้าของผู้ป่วยไทย โดยการสัมภาษณ์ผู้ป่วยด้วยแบบสอบถาม การนำข้อมูลส่วนของผู้ป่วยมารวบรวมและวิเคราะห์ทำให้สามารถสร้างข้อเสนอแนะเพื่อให้การรักษาผู้ป่วยโรคซึมเศร้าด้วยยาเกิดประสิทธิผลสูงสุด

ประโยชน์ที่คาดว่าจะได้จากการทำวิจัย

1. ได้ข้อมูลปัจจัยที่ส่งผลกระทบต่อความร่วมมือในการรักษาด้วยยาของผู้ป่วยโรคซึมเศร้า
2. ได้ข้อเสนอแนะที่จะส่งผลให้การรักษาผู้ป่วยโรคซึมเศร้าด้วยยามีประสิทธิผลดียิ่งขึ้น

วัตถุประสงค์ของการวิจัย

ทราบปัจจัยที่ส่งผลกระทบต่อความร่วมมือในการรักษาด้วยยาของผู้ป่วยโรคซึมเศร้า

วิธีการวิจัย

เป็นการวิจัยเชิงพรรณนา โดยทำการสำรวจปัจจัยที่ส่งผลต่อความร่วมมือในการรักษาด้วยยาต้านเศร้าของผู้ป่วยโดยการสัมภาษณ์และเก็บข้อมูลจากเวชระเบียนผู้ป่วย

สิทธิในการถอนตัวออกจากการศึกษา

ท่านสามารถไม่ตอบคำถามทุกข้อจากการสัมภาษณ์ถ้าท่านรู้สึกไม่สบายใจ และท่านสามารถถอนตัวจากการวิจัยได้ตลอดเวลา โดยการถอนตัวจะไม่มีผลต่อการรักษาใด ๆ ที่ท่านได้รับอยู่

การรักษาความลับของบันทึกทางการแพทย์ และข้อมูลการศึกษา

ผู้วิจัยจะเก็บรักษาความลับของผู้ป่วยทั้งเรื่องส่วนตัวและข้อมูลที่ได้จากการวิจัย โดยจะระมัดระวังไม่ให้เกิดการรั่วไหลของข้อมูลและเมื่อสิ้นสุดการวิจัยข้อมูลทั้งหมดที่ได้รับจะถูกทำลายทันที

การเปิดเผยข้อมูลการศึกษาวิจัย

ผลการวิจัยจะนำเสนอในภาพรวมเท่านั้น โดยจะไม่มีการเปิดเผยชื่อ นามสกุล ที่อยู่ และเบอร์โทรศัพท์ของผู้เข้าร่วมการวิจัยเป็นรายบุคคล ซึ่งจะไม่สามารถบ่งชี้ถึงตัวผู้ป่วยได้

การสอบถามข้อสงสัย

หากมีข้อสงสัยสามารถสอบถามได้จาก นางสาวอภิรดี ศรีสว่าง นิสิตปริญญาโท สาขาวิชาเภสัชกรรมคลินิก คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย โทร. 086-6996823

หนังสือแสดงเจตนายินยอมเข้าร่วมการวิจัย (Consent form)

รับรองโดยคณะอนุกรรมการพิจารณาโครงการวิจัย พบ.

ชื่อโครงการวิจัย ปัจจัยที่ส่งผลกระทบต่อความร่วมมือในการรักษาด้วยยาต้านเสร้าของผู้ป่วยไทย

วันที่ลงนาม……

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย รวมทั้งประโยชน์ที่คาดว่าจะเกิดขึ้นจากการวิจัย และมีความเข้าใจดีแล้ว

ผู้วิจัยรับรองว่าจะตอบคำถามที่ข้าพเจ้าสงสัยด้วยความเต็มใจและไม่ปิดบังซ่อนเร้น จนข้าพเจ้าพอใจ

ข้าพเจ้าเข้าร่วมในโครงการวิจัยนี้ด้วยความสมัครใจ โดยปราศจากการบังคับหรือชักจูง

ข้าพเจ้ามีสิทธิที่จะบอกเลิกการเข้าร่วมในโครงการวิจัยเมื่อใดก็ได้ และการบอกเลิกนี้จะไม่มีผลต่อการรักษาพยาบาลที่ข้าพเจ้าจะพึงได้รับในปัจจุบันและในอนาคต

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเกี่ยวกับตัวข้าพเจ้าเป็นความลับ และจะเปิดเผยเฉพาะในรูปของสรุปผลการวิจัยโดยไม่มีการระบุชื่อนามสกุลของข้าพเจ้า การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่าง ๆ ที่เกี่ยวข้อง จะกระทำด้วยเหตุผลทางวิชาการเท่านั้น

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้ว มีความเข้าใจดีทุกประการ และลงนามในใบยินยอมด้วยความเต็มใจ

ลงชื่อ…… ……..ผู้เข้าร่วมโครงการวิจัย

(……ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ…… ….....ผู้ดำเนินโครงการวิจัย

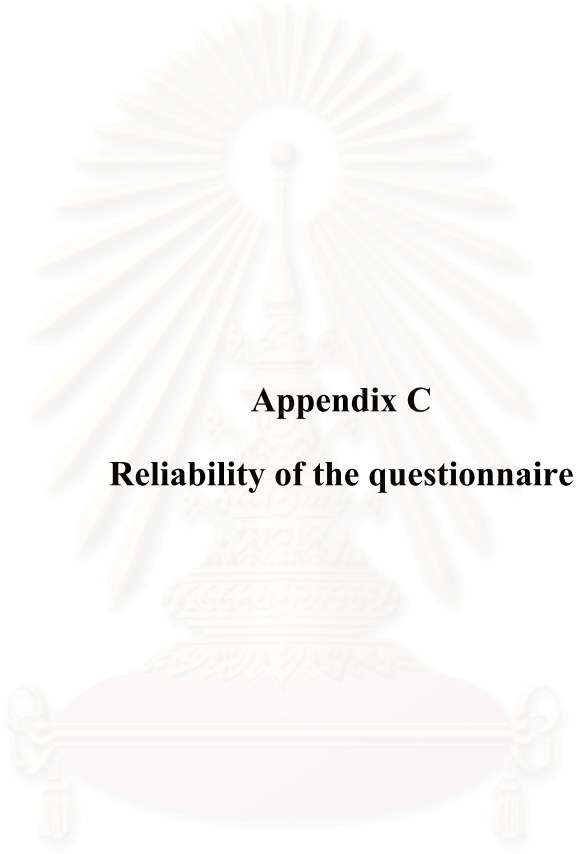
(……ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ…… ….....พยาน

(……ชื่อ-นามสกุล ตัวบรรจง)

ลงชื่อ…… ….....พยาน

(……ชื่อ-นามสกุล ตัวบรรจง)



Appendix C

Reliability of the questionnaire

Antidepressant adherence questionnaire

Item-total Statistics

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Squared Multiple Correlation	Alpha if Item Deleted
Item 1	18.0185	8.0462	.3548	.1444	.8758
Item 2	18.1065	6.7281	.8045	.6989	.7552
Item 3	18.1019	6.7896	.6172	.3969	.8060
Item 4	18.1204	6.6552	.7401	.6246	.7694
Item 5	18.1528	6.9207	.7075	.6099	.7801

Reliability Coefficients: 5 items, Alpha = .8335, Standardized item alpha = .8389

Attitudes towards antidepressant medication questionnaire

Item-total Statistics

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Squared Multiple Correlation	Alpha ifItem Deleted
Item 1	29.1336	15.1256	.4455	.2603	.7798
Item 2	30.1843	16.2992	.1539	.1049	.8258
Item 3	29.0876	15.0247	.6310	.4782	.7614
Item 4	29.2811	14.2956	.6334	.5633	.7556
Item 5	29.4009	14.0931	.6421	.6146	.7535
Item 6	29.2857	14.1217	.6818	.6148	.7497
Item 7	29.3548	13.8596	.6414	.5612	.7523
Item 8	30.4424	15.4700	.2418	.1028	.8170
Item 9	29.1935	15.1105	.5551	.3542	.7679

Reliability Coefficients: 9 items, Alpha = .7948, Standardized item alpha = .8194

Attitudes towards physician questionnaire

Item-total Statistics

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Squared Multiple Correlation	Alpha if Item Deleted
Item 1	24.6066	9.3350	.7016	.6904	.8722
Item 2	24.5166	10.0700	.6842	.5018	.8722
Item 3	24.4076	10.0140	.7654	.6357	.8630
Item 4	24.6209	9.2365	.7828	.7348	.8594
Item 5	24.4834	10.3081	.7468	.6405	.8663
Item 6	24.4597	10.7258	.6998	.5729	.8728
Item 7	24.4597	11.1258	.4561	.2535	.8979

Reliability Coefficients: 7 items, Alpha = .8887, Standardized item alpha = .8924

VITAE

Miss Apiradee Srisawang was born on the 6th of May in 1980 at Ubonratchathani. She graduated with Bachelor degree in Pharmacy in 2003 from Faculty of Pharmacy, Chulalongkorn University. Her current position is a pharmacist at Prasrimahabhodi Hospital, Ubonratchathani.