COST EFFECTIVENESS ANALYSIS OF A PHARMACEUTICAL CARE SERVICE IN LITHIUM CLINIC FOR PATIENTS WITH BIPOLAR DISORDER

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CHAPTER I
INTRODUCTION

1.1 Background and rational

Bipolar disorder is a long term and severe mental disorder present up to 2% of the population (1). Bipolar disorder is reported to be the sixth leading cause of disability worldwide among patients ages 15 to 44, and recently estimation reveal that the annual medication and treatment costs for bipolar patients more than $17,000 per patient (2). The characteristic of bipolar disorder is the appearance of episodes of mania or hypomania alternating with depressive episodes. Approximately 70% of bipolar patients have more than one recurrence within 4 years of the index episode. Unfortunately, these high rates of relapse, symptomatic illness, and impairment are frequently reported even in bipolar patients who maintain with pharmacotherapy (3).

Many factors associated with relapse or recurrence in bipolar patients include medication adherence, social support and psychotherapy (4). Of these, adherence problem is direct associate with pharmacist responsibility. Adherence problems in bipolar patients result in poor treatment response and can cause earlier relapse. Non-adherence also aggravates occupational and social problems associated with episodes in these patients. Rate of non-adherence in bipolar disorder on long-term prophylactic pharmacotherapy is approximately 20- 60% (5).

Hospitalization is an important risk for patients with bipolar disorder. Seventy five percent of these patients have been hospitalized more than one time during the course of illness. In addition, the risk of hospitalization caused by relapse is especially high for these patients.

To prevent relapse or recurrence in these patient, many pharmacological interventions have been proposed (3). Lithium is the first line pharmacotherapy for treatment of bipolar disorder to prevent exacerbation of acute mood episodes, switching to another pole and suicide. The clinical use of lithium is associated with an extremely narrow therapeutic range. Therapeutic drug monitoring (TDM) is needed in patient who is treated with lithium because lithium has many characteristics including dose-dependent efficacy and individual variation in absorption, distribution and excretion. Lithium level varies according to many factors such as non-compliance, medication-related changes in lithium excretion, dietary changes and medical illness. Monitoring on serum lithium concentration is useful both in safety and efficacy vigilance.

Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. (6).

The role of the pharmacist for psychiatric patients has evolved over the past few years from primarily drug distribution and centralized drug monitoring to more direct role. As a result, become involved in designing and monitoring treatment plan

and make pharmacotherapy recommendations. Pharmaceutical care in psychiatric patient has been implemented in several setting. Previous study on the effects of psychiatric pharmacy services about clinical outcomes of acute care psychiatric inpatients found that providing pharmaceutical service was associated with improvement in clinical response (7). In addition, the other study show that impact of clinical pharmacist on psychiatric patients included improvement in patient compliance, better side effect monitoring, fewer unnecessary drugs, reducing in number of hospitalization, cost saving, improvement in patient satisfaction and functioning. Also, pharmaceutical care has been found to reduce overall hospitalizations by 2.8% (8-10).

Lithium clinic, one of the specialized clinics was performed in several clinical setting (11-19). Of these, only 3 clinical settings have provided pharmaceutical care service (11, 17, 20). Result of the previous lithium clinic suggested that it was useful and should be adopted in other psychiatric settings.

The fourth pharmacist-run lithium clinic is lithium clinic of Somdet Chaopraya Institute of Psychiatry. It is the first and only lithium clinic in Thailand. It has been set up at outpatient department of Somdet Chaopraya Institute of Psychiatry since October 2000. Although this clinic has been established and has been implemented in this institute for more than 10 years, there has been no analysis to date of long term impact of a pharmaceutical care service in this clinic. Such an analysis will

provide decision makers with beneficial information for the evaluation of any proposed treatment activities plan and will be generalized to other psychiatric hospitals.

1.2 Objectives

1. To compare the clinical outcomes of bipolar patients who are treated with lithium as maintenance therapy between patients who receive standard care plus pharmaceutical care service and patients who receive standard care alone.

2. To study the cost-effectiveness of a pharmaceutical care service in lithium clinic adjunct to standard care for bipolar patients who are treated with lithium as maintenance therapy.

1.3 Area of interest

This study was performed as an economic evaluation by using a cost effectiveness analysis to study about the impact of pharmaceutical care service for bipolar patients who maintain with lithium as maintenance therapy.

1.5 Expected outcomes

The expected outcomes of this study are as follow:

1. The result of this study may be applied to other psychiatric hospital in developing a pharmaceutical care service for patients with bipolar disorder.

2. Suggestions are provided for improving the quality of care for patients with

bipolar disorder who maintain with lithium therapy and for reducing the economic burden of bipolar illness for mental healthcare provider.

CHAPTER II

LITERATURE REVIEW

This chapter includes 5 sections as follow

- Bipolar disorder
- Maintenance treatment for bipolar disorder
- Lithium in long term maintenance treatment
- Lithium clinic
- Pharmaceutical care in psychiatric patients

2.1 Bipolar disorder

Bipolar disorder or manic-depressive disorder is a chronic and severe mental illness present in 1% to 2% of the general population which associates with significant morbidity and mortality (1, 21). It is characterized by recurrent mood episodes of mania, hypomania and depression as show in Figure 1.

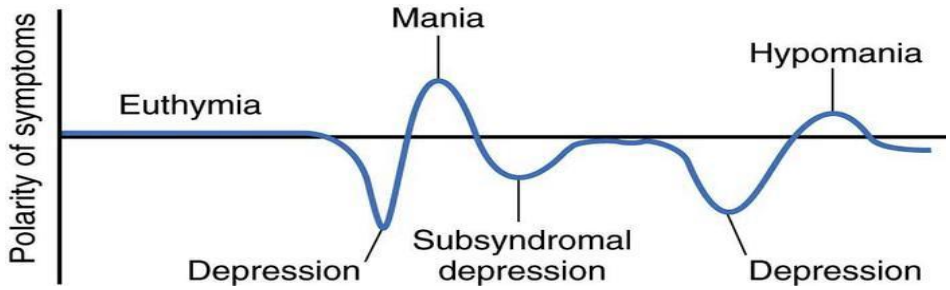


Figure 1 Mood episode in bipolar disorder

Bipolar disorder is top 10 causes of disability among adults worldwide. A diagnostic criterion for bipolar disorder is presented in Figure 2 (22). Early diagnosis and treatment improves outcomes of bipolar patients. Treatment of bipolar disorder relies on the phase of illness which may be mania, hypomania, depression, mixed state or maintenance (23). Pharmacotherapy is effective in eliminating signs and symptoms of each episode. Patients need to be treated for longtime medication to prevent relapse or recurrence. Many factors associated with relapse or recurrence in these patients include medication adherence, psychotherapy and social support (4). In addition, several studies found that some residual depressive or manic symptoms at recovery and proportion of days depressed or anxious in the preceding year were significantly associated with shorter time to depressive recurrence. Furthermore, residual manic symptoms at recovery and proportion of days of elevated mood in the preceding year were significantly associated with shorter time to manic, hypomanic, or mixed episode recurrence (24). Number of previous episode, stressful life events, and psychodemographic/psychosocial factors are also the predictors of relapse or recurrence in bipolar disorder. Psychodemographic/psychosocial factors which associated with relapse or recurrence in patients are poor work functioning, poor occupational functioning, poor social support, positive psychiatric family history, poor social adjustment, female gender, age of onset, family history of substance abuse, high stress, lower social support, family expressed emotion, critical comments,

caregiver emotional over-involvement, high expressed emotion (predicts depressive recurrence only, not manic), childhood behavior problems, lower household income, and maladaptive coping style (4).

Diagnostic criteria for bipolar disorder (based on DSM-IV)

Bipolar I disorder*: Presence, or history of, at least one manic (or mixed) episode

Bipolar II disorder*: Presence, or history of, at least one major depressive episode and at least one hypomanic episode (with no history of a manic or mixed episode)

The symptoms are not attributable to physical illness or physiological effects of a drug or other substance and are not better accounted for by another psychiatric disorder

Manic symptoms	Depressive symptoms
Elevated, expansive, or irritable mood	Depressed mood
Increased activity that is goal directed or psychomotor agitation	Markedly reduced interest in nearly all activities
Reduced need for sleep	Increased or decreased appetite or weight
Excessive involvement in pleasurable activities with likely adverse consequences	Insomnia or hypersomnia
Inflated self esteem or grandiosity	Psychomotor retardation or agitation
Increased or pressured speech	Fatigue or loss of energy
Flight of ideas or racing thoughts	Feelings of excessive worthlessness or guilt
Distractibility	Impaired concentration or indecisiveness
	Recurrent thoughts or actions of death or suicide

Manic episode: At least four manic symptoms including altered mood that persists for at least a week and causes marked functional impairment, hospital admission, or there are psychotic symptoms

Hypomanic episode: As for manic episode but less severe; symptoms persist for at least four days and functioning is noticeably altered but not enough to lead to hospital admission or to greatly impair function. There are no psychotic symptoms

Major depressive episode: Five or more persistent depressive symptoms (which must include depressed mood or diminished interest), which last for at least two weeks and occur on most days, and that cause serious distress or functional impairment

Mixed episode: Persistent mood symptoms for at least a week that meet criteria (apart from duration) for both a manic and major depressive episode, which occur at different times or rapidly alternate

Psychotic symptoms: These may occur during manic episodes in bipolar I disorder (but by definition not during hypomanic episodes) and during depressive episodes in either bipolar I or bipolar II disorder

*The World Health Organization classification ICD-10 does not distinguish between bipolar I and bipolar II disorder and requires another mood episode in addition to a single manic episode

Figure 2 Diagnostic criteria for bipolar disorder

National survey by Ministry of Public Health, Thailand found that prevalence of bipolar disorder in Thai population was about 0.38% and 0.49% in male and female, respectively (25). Because of personal and social functional impairment,

hospital beds occupation, direct treatment expenses, stress on family functions, waste of time and many suicides, recurrence and relapse waste many human and financial supplies (26).

2.2 Maintenance treatment for bipolar disorder

Adherence to maintenance therapy in bipolar patients is positively associated with higher satisfaction with medication, monotherapy, a college degree, and fear of relapse. On the other hand, it is negatively associated with substance use, previous hospitalization, psychotic symptoms, reduced insight into illness, medication side effects, no perceived daily benefit on medication, difficulties with medication routines, and patient attitudes such as belief that medications are unnecessary, negative attitudes toward medications, perceived change in appearance, and perceived interference with life goals (1).

Predictors of remission and recovery during 1–2 years of follow-up in patients with manic episodes include: Caucasian ethnicity, a previous manic episode, good social functioning, outpatient treatment, and being neither satisfied nor dissatisfied with life (1). Factors associated with non-stabilization in patients with rapid cycling treated with lithium or divalproex consist of a history of recent substance use disorder (SUD), early-life verbal abuse, female gender, and late onset of first depressive episode (27). The risk of recurrence among long-term lithium therapy responders is higher in those with atypical features, inter-episodic residual symptomatology, and rapid cycling (28).

Psychosocial intervention which are interpersonal and social rhythm therapy (IPSRT), group psychoeducation and cognitive behavior therapy (CBT) when use adjunct to pharmacotherapy has illustrated benefit in long-term treatment. It reduces recurrence, fluctuation in mood, medication needed, and hospitalizations. Furthermore, it enhance functioning and medication adherence (1).

Various pharmacotherapies have been determined for preventing relapse in patients with bipolar disorders. Lithium is considered as a mainstay for the management in these patients in many guidelines. Valproate, lamotrigine and carbamazepine have also been used for maintenance treatment of this illness. Both conventional antipsychotics and atypical antipsychotics have sometimes been used for prevention of relapse. Antidepressants have been used in the short-term treatment of bipolar depression. However, particularly tricyclic antidepressant may result in switching to mania or hypomania. Therefore, treating with combination of antidepressant and mood stabilizer is often recommended for bipolar depression. Nevertheless, newer antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are also effective for treating bipolar depression and have a lower risk of switching to mania (1). Pharmacotherapy recommended for maintenance treatment of bipolar disorder is displayed in Table 1 (1) and Figure 3 (29) .

Table 1 Recommendations for maintenance pharmacotherapy of bipolar disorder

First line	Monotherapy : lithium, lamotrigine (limit efficacy in preventing mania), divalproex, olanzapine[a], quetiapine, risperidone LAI[b] , aripiprazole[b]
	Adjunctive therapy with lithium or divalproex : quetiapine, risperidone LAI[b], aripiprazole[b] , ziprasidone[b]
Second line	Monotherapy : carbamazepine, paliperidone ER[c]
	Combination therapy : lithium + divalproex, lithium + carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine, olanzapine + fluoxetine
Third line	Monotherapy: asenapine[c]
	Adjunctive therapy : Phenytoin, clozapine, ECT, topiramate, omega-3-fatty acids, oxcarbazepine, gabapentin, asnapine[c]
Not recommended	Monotherapy : Gabapentin, topiramate, or antidepressants
	Adjunctive therapy: flupenthixol

LAI = long acting injection, ER = extended release, EC = electroconvulsive therapy

[a] given a metabolic side effect, use should be carefully monitored

[b] mainly for the prevention of mania

[c] new or change to recommendation

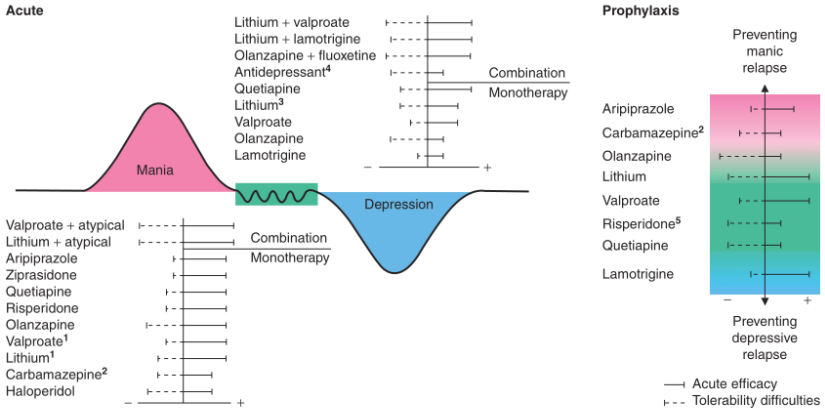


Fig. 1. Overview of efficacy and tolerability ratings for pharmacological treatments commonly used in bipolar disorder. This figure captures the relative merits of agents in terms of efficacy and tolerability. The top and bottom schematics deal with the acute (mania and depression) and maintenance phases of bipolar disorder, respectively. The joint presentation of the relative efficacy and tolerability for each agent provides a useful guide as regards effectiveness in clinical practice. Tolerability ratings have variable impact depending on duration of treatment and urgency of need for treatment. Therefore, they are of greater importance in prophylaxis than in the acute treatment of mania or depression. **1** While the efficacy of agents are comparable to antipsychotics, lithium and valproate can be slower to take clinical effect; **2** slow-release formulation is better tolerated; **3** there can be a 6- to 8-week delay in antidepressant effect; **4** adjunctive; **5** no randomized controlled trial data available, rating based on open-label studies. + indicates good efficacy; – indicates poor tolerability.

Figure 3 Overview of efficacy and tolerability rating for pharmacological treatments commonly used in bipolar disorder

Many researches about clinical effectiveness of maintenance treatment for bipolar disorder have been published. Various outcome measures of these studies were presented. Most common primary outcome is all relapses of bipolar episode which are describe as (i) the number of hospitalizations among each group, (ii) the number of patients who got the additional intervention to treat mania or depression or (iii) as defined by the researchers. Secondary outcomes are presented in several types such as manic relapses, depressive relapses, drop-out before complete the study duration, adverse events causing to terminate and other treatment due to adverse effects, suicidal attempt or suicide, time to recurrence of any mood event, and hospitalizations. Manic relapse was showed in (i) the number of hospitalizations among each group or (ii) the number of patients who obtained the additional intervention to treat mania. Depressive relapse was also showed in (i) the number of hospitalizations among each group, (ii) the number of patients who obtained an additional intervention to treat depression or (iii) as defined by the researchers. Hospitalization was defined as number of hospitalization per patient or mean number of days of hospitalization per patient (30, 31).

2.3 Lithium in long-term maintenance treatment

Lithium is a monovalent cation. It was discovered in 1817 and was first reported beneficial in psychiatric patient since 1949 by John Cade. It remains the first line medication in long-term maintenance treatment for patients with bipolar (32). Lithium is considered the first truly antimanic drug and used primarily in the therapy

of bipolar disorder. It is effective in the acute treatment of manic depressive episode and in the prevention of recurrent manic and depressive episode. Lithium is the only drug that approximates to define as the best mood stabilizer, because it has an effect upon depressive and manic phases of bipolar disorder both in acute and long term treatment (29).

Many evidences have demonstrated clearly the efficacy of lithium in bipolar disorder and have confirmed its maintenance efficacy, particularly in manic relapse of bipolar disorder which demonstrated that lithium decreases the risk of manic relapses by 38% (RR 0·62, 95% CI 0·50–0·84) and depressive relapse by 28% (0·72, 0·40–0·95). Furthermore, there is strong evidence that long term maintenance treatment of lithium decreases the risk of suicide and suicidal behavior in both bipolar disorder and recurrent depression (33). Regarding suicide, lithium is the only drug that has the anti-suicidal property with evidence of decrease the risk of suicide for more than 50% (33). Besides this, some previous evidence indicated that the suicide rate among patients who maintain on long-term systematic lithium treatment has been 1.3 per 1,000 patient-years while those who were not given long-term systematic lithium treatment had a suicide rate of 7.3 per 1,000 patient-years (34).

Although, lithium has many benefits on long term maintenance treatment of bipolar disorder, the clinical use of this medication is restricted by its adverse effects and extremely narrow therapeutic range. Up to 35-93% of patients treated with lithium experience some adverse effects. Most adverse effects are either minor and

can be reduced or eliminated by decreasing the lithium dose or changing in dosage schedule. Lithium adverse effect might manifest both in acute or late appearing side effect. Acute side effect, including tremor and gastrointestinal side effect, will be happen in the early phase of lithium administration and usually associated with the rise in serum lithium concentration during its absorption. Late appearing side effect of lithium will be presented in many kinds such as weight gain, edema, cardiovascular, cognitive, dermatologic, and renal side effect. The risk of congenital malformations in the newborn baby of mothers who have received lithium during pregnancy is still uncertain, but probably lower than previous report. The balance of risks and benefits should be considered before stop taking lithium during pregnancy. (35).

Therapeutic serum lithium concentration is within the range of 0.5–1.5 mEq/L. However, many patients will experience some toxic effect with level above 1.5 mEq/L. Serum lithium concentrations which more than 2.0 mEq/L are normally associated with serious toxicity. Furthermore, elderly patients may experience toxic effect at lower level and have a narrower therapeutic range. Factors that can lead to lithium intoxication such as diarrhea, change in diet, change in activity/habits, change in water supply, change in electrolyte balance, prolonged unconsciousness, surgery with narcosis, low intake of table salt, and travel to a hot climate (36). Clinical signs and symptoms of lithium intoxication are described in Table 2.

Table 2 Signs and symptoms of lithium intoxication

Toxic effect	Serum lithium concentration (mEq/L)	Signs and symptom
Mild	1.0 - 1.5	Impaired concentration, lethargy, irritability, muscle weakness, tremor, slurred speech, and nausea
Moderate	1.6 - 2.5	Disorientation, confusion, drowsiness, restlessness, unsteady gait, coarse tremor, dysarthria, muscle fasciculation, and vomiting.
Severe	> 2.5	Impaired consciousness with progression to coma, delirium, ataxia, generalized fasciculations, extra pyramidal symptoms, convulsions, and impaired renal

Lithium has many characteristic that make it particularly well suited to therapeutic drug monitoring including dose dependent efficacy and individual variation in absorption, distribution and excretion. Little elevations in its serum concentration may be associated with toxic reactions. Lithium level varies according to a wide range of factors such as non-adherence, drug interaction-related changes in lithium excretion, dietary change and current medical illness. Monitoring on serum lithium concentration is useful both in safety and efficacy vigilance. Regular lithium monitoring has been shown to decrease the risk of lithium toxicity when no clinical symptoms or side effects are present to indicate dangerously high serum lithium level. It also can help increase detection of subtherapeutic drug level and may help protect medical provider from liability claims. Finally, it can be used to help identify nonresponse from non-adherence.

2.4 Lithium clinic

The sophistications of managing bipolar patients and long term lithium treatment require the provision of specialist resources (36). Lithium clinic, one of the specialized clinics was performed in several clinical setting to deal with these complexities. Lithium clinic was first introduced by psychiatrists in the 1960s (12). The major role of the lithium clinic is to provide an expert assessment and treatment setting in which treatment is supervised, lithium levels are regularly monitored and other laboratory tests such as thyroid and renal function are provided. One of the precious components of the service is risk reduction, by regularly monitor and support. The previous study showed that lithium clinic has been saving 179 bed-occupancy weeks per year per 100,000 populations, which at £12 per bed per day saves the UK over £9 million per annum. This study excluded costs of ambulances, second opinions of medical professional, social workers' time, Appeal Tribunals, loss of income and productivity and social security payments for patient and family (34).

Although, lithium clinic has been performed in several clinical setting (11-19), only 3 clinical settings have provided pharmaceutical care service. The pharmacy department of the Buffalo General Hospital Community Mental Health Center (BGH-CMHC), the first one, has operated lithium clinic since 1975. Pharmaceutical care has been provided to the manic-depressive who were on lithium therapy. The pharmacist activities included: drawing serum lithium sample, consulting with the patient on lithium side effects, assessing patient physically, controlling lithium dosage

and supplying, reviewing patient's medication profile, writing up consultations with the patients, and forwarding them to the psychiatrist and counselor, issuing patient identification card, maintaining a lithium toxicity hotline (17) . The second, pharmaceutical involved lithium clinic was set up in a distinct general hospital. Pharmacist provided pharmaceutical care service in order to save medical staff time and utilizes pharmacist skill to provide an efficient lithium monitoring program (11). The third pharmacist-run lithium clinic is a clinic in North West London which has been set up since 2002. The objective of this lithium clinic was to ensure that patients were being monitored appropriately and were being provided with the best possible care during treatment (20). Result of the previous lithium clinics suggested that it was useful and should be adopted in other psychiatric settings.

The fourth pharmaceutical involved lithium clinic is the lithium clinic of Somdet Chaopraya Institute of Psychiatry. It is the first and only lithium clinic in Thailand. It has been set up at outpatient department of Somdet Chaopraya Institute of Psychiatry since October 2000. There is the pharmacist run lithium clinic which cooperation with the 2 psychiatrists. The pharmacist activities in lithium clinic include educating patient, monitoring and adjusting serum lithium concentration according to individual pharmacokinetic, scheduling and monitoring laboratory data, issuing lithium card, identifying, preventing and correcting drug therapy problems. Evaluating the clinical benefit of the pharmaceutical care process provided to bipolar patients who

receive lithium as maintenance therapy in this clinic was performed. This study was designed a randomized single blind control study. The eligible cases (n=60) were randomized into an experimental (n=30) and control group (n=30) and were followed up for 4 visits with a one month interval. The experimental group were provided with pharmaceutical care in which the pharmacist activities included counseling patients on how to avoid lithium intoxication, providing medication reminder card and lithium card, monitoring serum lithium concentration and adjusting dosage of lithium according to the pharmacokinetic of each patient, determining patient's adherence and assessing drug therapy problems (DTPs). The control group did not receive pharmacist intervention except when their DTPs were serious. At the end of study, parameters including DTPs, serum lithium concentration, patient's knowledge, patient's adherence and the clinical outcome were compare between both groups. The result of this study revealed that a pharmaceutical care provided to bipolar patients who received lithium as maintenance therapy was associated with a decrease in DTPs, an increase in the number of patients whose serum lithium concentration was within therapeutic range and enhanced patient knowledge on lithium usage. Although there was no statistically significant difference in clinical outcomes between both groups, patients in control group rehospitalized more than those in experimental group. The reason that the result cannot be detected the difference of clinical outcome between both groups may come from the small sample size and short study duration (37). The other study of this clinic

performed to study the differences of therapeutic outcomes between patients attending in lithium clinic and patient receiving treatment as usual at Somdet Chaopraya Institute of Psychiatry. There is one year retrospective cohort study which included patients in various psychiatric illness to the study. It was shown that patients in study group were hospitalized less than those one in control group (1.25 % vs 11.25%, respectively) and study group also associated with a significant reduction in risk of hospitalization (RR = 0.099, 95%CI = 0.0123-0.8083, p = 0.018). Furthermore, study subjects visited to emergency department less than control subjects (2.50 % vs 11.25%, respectively) and it also revealed that study group associated with a significant reduction in risk of visiting to emergency department (RR = 0.19, 95%CI = 0.0423-0.9681, p = 0.029). Number needed to treat (NNT) to prevent hospitalization and prevent visiting to emergency department was 10 and 11.43, respectively. Moreover, the adverse drug reaction (ADR) and laboratory tests had been recorded in study group more than in control group significantly. The most frequent ADR which found in this study were memory impairment (25%) and dry mouth (25%) followed by hypothyroidism (21.25%). However, renal tubular impairment was also occurred in 5% of patients. This study concluded that patients attending in lithium clinic had the preferable clinical benefit more than those who receiving treatment as usual (38).

2.5 Pharmaceutical care in psychiatric patients

Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. Pharmaceutical care process includes a pharmacist cooperating with a patient or other healthcare professionals in designing, implementing, and monitoring a therapeutic plan. The result of pharmaceutical care process is specific therapeutic outcomes for each patient. It involves three major functions which consist of identifying, resolving and preventing both actual and potential drug-related problems (6).

The role of the pharmacist for psychiatric patients has evolved over the past few years from primarily drug distribution and centralized drug monitoring to more direct role. As a result, become involved in designing and monitoring treatment plan and make pharmacotherapy recommendations. Pharmaceutical care in psychiatric patient has been implemented in several setting. Previous study on the effects of psychiatric pharmacy services about clinical outcomes of acute care psychiatric inpatients found that providing pharmaceutical service was associated with improvement in clinical response (7). In addition, the other study show that impact of clinical pharmacist on psychiatric patients included improvement in patient compliance, better side effect monitoring, reducing in number of hospitalization, fewer unnecessary drugs, cost saving, improvement in patient satisfaction and

functioning . Also, pharmaceutical care has been found to reduce overall hospitalizations by 2.8% (8-10).

2.6 Pharmacoeconomic studies of a pharmaceutical care service in psychiatric patients

Appendix I shows the articles related with the impact of pharmacist intervention in psychiatric patients published between 1977 and 2016. It is found that there is a little number of studies published in this area. Only 39 studies have been published, of these, 11 studies measured on economic outcomes (10, 39-48) which consist of eight cost analysis studies, one cost and outcome description study and two economic evaluation studies as show in Table 3.

Table 3 Analytic methods used in economic evaluations of pharmaceutical care involve in psychiatric patients

Method	No (%) of studies (n=39)	References
Outcome analysis	22 (56.4)	(7, 37, 49-68)
Economic evaluation	2 (5.1)	(47, 48)
Outcome description	6 (15.4)	(63, 69-73)
Cost and outcome description	1 (2.6)	(46)
Cost analysis	8 (20.5)	(10, 39-45)
Cost description	0	-

For these eight cost analysis studies, six studies were presented the outcome as cost saving after implemented pharmacist intervention (10, 39, 41, 43-45) and other two studies were presented outcome in other aspects (40, 42).

One study is suspected that it is an economic evaluation study (47). It investigated the economic benefits of clinical pharmacy services at an outpatient mental health clinic. Pharmacy costs before and after initiation of the clinical pharmacy service is summarized. The findings of this study showed that the clinic's pharmacy costs were dramatically reduced and the perceived quality of drug therapy was improved after the initiation of the clinical pharmacy service. However, data of this study is not enough for evaluation due to the unavailable of its full text.

Recent study performed in Thai patients to examine the short term outcomes of pharmaceutical care in schizophrenic patients. This study found that the number of DRPs decreased significantly more in the intervention group than in the control group ($p < 0.001$). The mean knowledge score increased greater in the intervention group ($p < 0.001$). The mean QOL score showed a trend towards improvement in the intervention group (both $p < 0.001$). Cost-effectiveness ratios (CER) of pharmaceutical care and usual care for achieving good medication adherence was 16.54 and 16.06 USD/successful patient, respectively and CER for improved QOL was 17.30 and 14.98 USD/successful patient, respectively (48).

Until now, research about impact of pharmacist intervention for psychiatric patients is still scarce. Data about the impact of this intervention on clinical and economic outcomes in long term treatment still have been not enough. Furthermore, no research has been done in well-designed full economic evaluation particularly for patients with bipolar disorder.

CHAPTER III

METHODOLOGY

This chapter describes the methodology of this study with brief reviews of the conceptual framework and Markov model for cost effectiveness analysis. There are 4 sections in this chapter including effectiveness, cost, transition probability and utility. Also, uncertainly analysis was also described.

3.1 Study flow chart

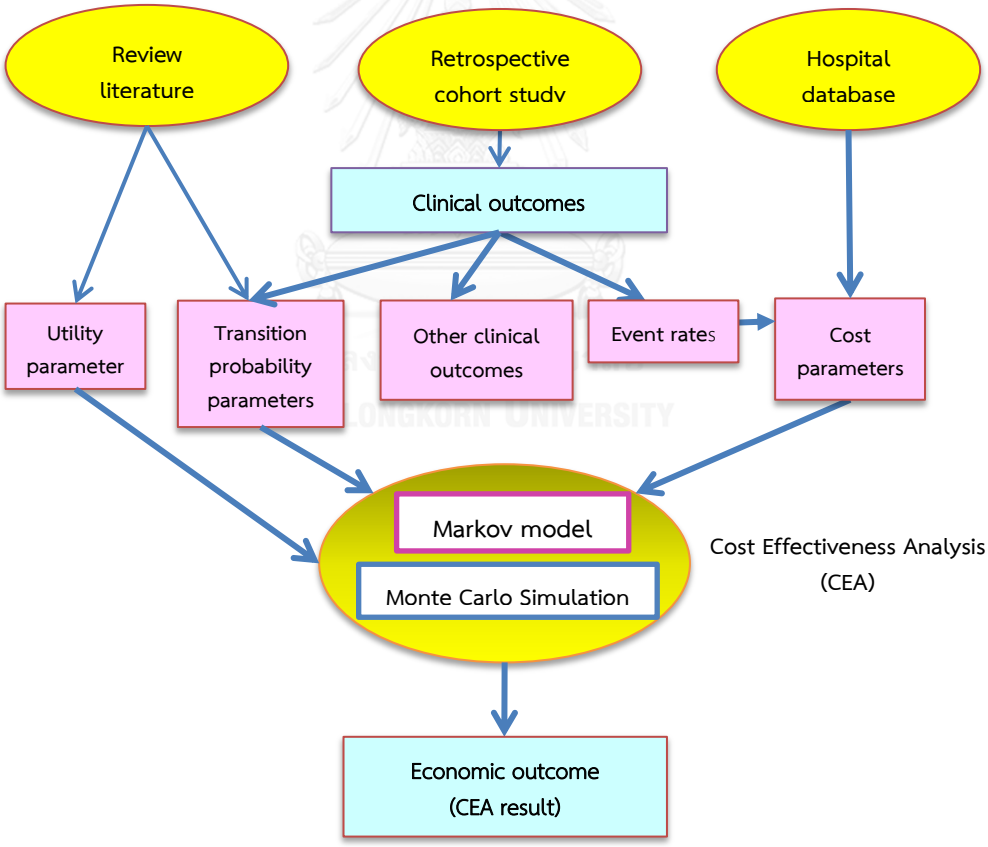


Figure 4 Study flow chart

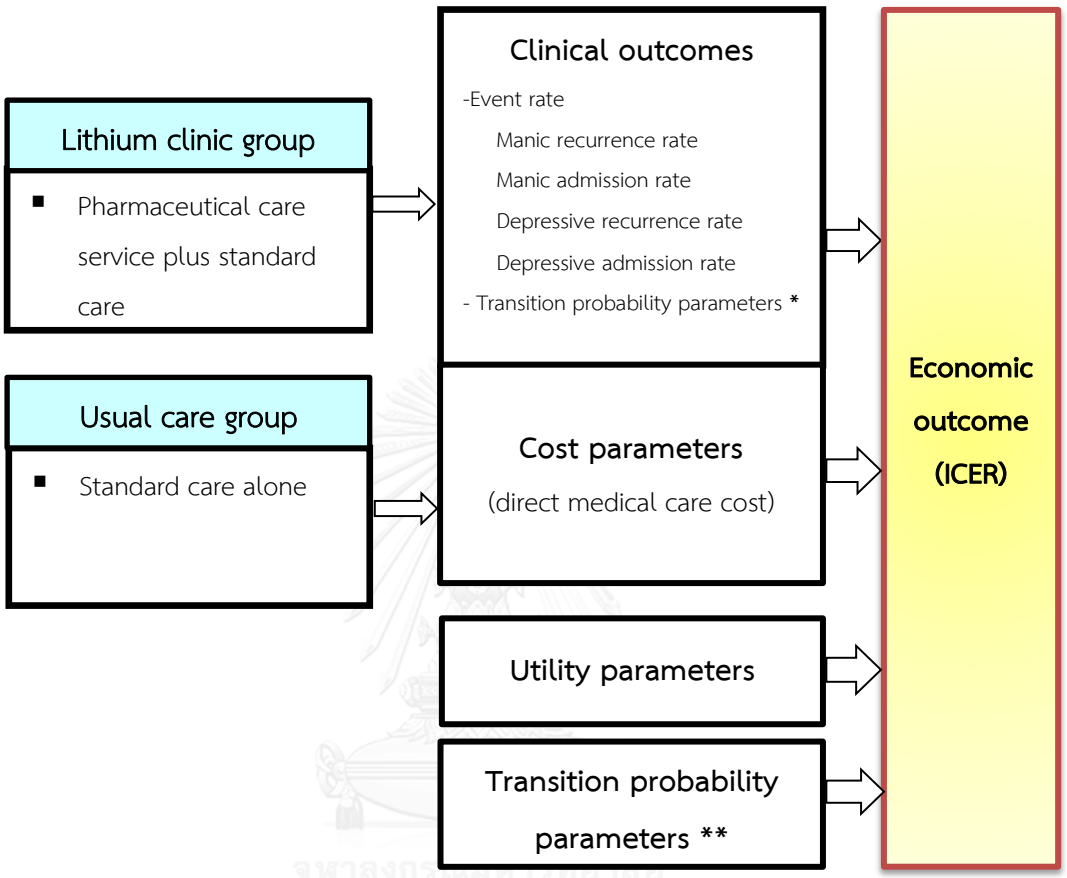
The data of this study came from various sources including review literature, retrospective cohort study, and hospital database as shown in Figure 4. Utility parameters obtained from review literatures. Some transition probability parameters were from review literatures and some were from retrospective cohort study. Cost parameters were estimated from event rate and hospital database. The event rate and other clinical outcomes were received from retrospective cohort study.

The outcomes of this study were divided to clinical outcomes and economic outcome. The clinical outcomes obtained from retrospective cohort study. These outcomes were further separated into transition probability parameters, even rates, and other clinical outcomes including time to event and relative risk. The economic outcomes derived from Markov Model with Monte Carlo simulation which required parameters including utility parameters, transition probability parameters and cost parameters as shown in Figure 4.

3.2 Conceptual framework of cost effectiveness analysis (CEA) study

Participants who meet inclusion and exclusion criteria will be recruited into the study (detail will show in part 3.7.1). There were two groups of participants which were lithium clinic group and standard care group. Lithium clinic group included all eligible cases who attended a pharmaceutical care service plus standard care at outpatient lithium clinic for at least one year. Standard care group included the eligible cases who receive standard care without attended a pharmaceutical care service in the lithium clinic. Subjects for standard care group were selected from

name lists of bipolar patients who followed the outpatient appointment by this hospital in the same period of time when recruited cases of lithium clinic group.



* Transition probability parameters which obtained from retrospective cohort study : P(1,2), P(2,3), P(1,3), P(1,4), P(4,5), P(1,5)

** Transition probability parameters which got from other sources besides retrospective cohort study

- estimation from previous study : P(2,2), P(4,4)
- estimation from WHO life table : P(1,6), P(2,6), P(3,6), P(4,6), P(5,6)
- calculation : P(1,1), **P(2,1), P(3,2), P(4,1), P(5,4)**

Figure 5 Conceptual framework of CEA study

All participants were identified by reviewing outpatient medical records. Clinical outcomes and costs were measured. Some parameters of clinical outcomes (transition probability, event rate) and costs were used in the MARKOV model for

analyzing the cost-effectiveness of this intervention. Conceptual framework of this study is shown in Figure 5.

3.3 Perspective of the study

This study is a cost effectiveness analysis study. The perspective of this study focused on the provider perspective. Thus, costs in this study included only direct medical care costs which consist of medication cost, pharmaceutical care service cost, laboratory monitoring cost, admission cost, emergency room visit cost and outpatient visit cost. All costs will be derived from hospital database.

3.4 Comparator

This study compared outcomes of a pharmaceutical care service in lithium clinic group versus usual care group in patients with bipolar disorder.

3.5 Economic outcome

The health outcome measures were QALY and LYG. QALY was used to measure overall health-related quality of life, which was the preferred approach in economic evaluation of health intervention. LYG was a modified mortality measure when remaining life expectancy was taken into account. Life years were calculated as the remaining life expectancy at the point of each averted death. The results of CE analysis were presented as (1) incremental cost effectiveness ratio (ICER) per QALY, which estimated the additional cost per additional QALY gained attending a pharmaceutical care service of lithium clinic group compared with treatment as usual care group of patients with bipolar disorder; (2) ICER per life-year gained, which

estimated the additional cost per additional life-year gained from attending a pharmaceutical care service of lithium clinic

3.6 Model structure and assumption

Markov model is useful when a decision problem involves risk that is continuous over time, when the timing of events is important, and when events can occur more than once. So Markov model was used to evaluate the incremental costs and effects of a pharmaceutical care service in patients with bipolar disorder. The model of this study was developed using Microsoft Excel version 2010.

The developed model is based on a Markov state transition model with one-year cycle length. The assumption for this model is that each patient has to be in one health state at any time. Patients could only be either depressive or manic episode for each yearly cycle of the model. Also, the probability of being in this episode is constant over time (31). From Figure 4, the considered health states are represented by the circles and the possible transitions that a patient may follow are indicated as the arrows. Patients enter the model in the stable phase. From this state, they can then remain in the stable phase, or be in a manic or depressive episode for the first cycle of the model. The model for severity level is represented by separate states for episodes both requiring and not requiring hospitalization treatment. In the cycle following a manic or depressive episode, the patient can either turn back to stable phase or experience another episode. Patients can also turn to death state from any state within the model.

The rate that the patients move through the model is defined by transition probabilities, which describe the probabilities of moving from one state to another in each model cycle. The transition between each state and event is defined by adjusted factors and probabilities from retrospective cohort study and hospital database. The model will stop running when the patients are 117 years old or die.

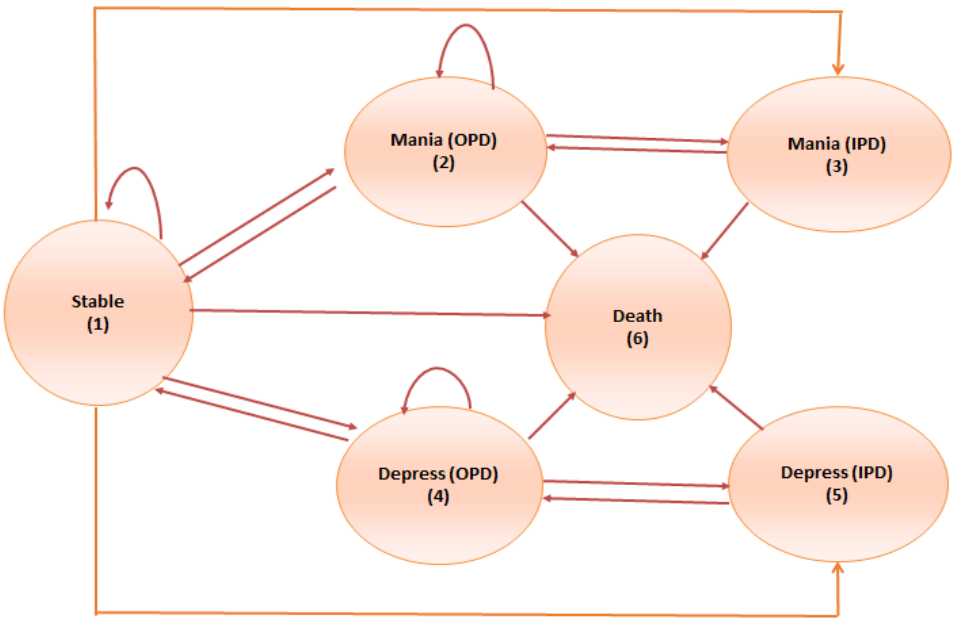


Figure 6 MARKOV MODEL

The key clinical input parameter for the model is recurrence rate for mania and depression associated with different interventions which patients received. Data on recurrence rate will be obtained from hospital database undertaken as part of this study. Recurrence rate will be obtained from two groups of patients which were lithium clinic group and usual care group.

Both outcomes and costs are discount at the rate of 3%. The time horizon of the model and the effects in life expectancy were life-long calculation.

3.7 Data required

The following 4 components which were effectiveness data (event rate), transition probability, utility, and costs are required for conducting this cost effectiveness analysis as show in Figure 4.

3.7.1 Effectiveness data

The effectiveness of a pharmaceutical care service in lithium clinic got from 10-years retrospective cohort study of a pharmacist intervention in lithium clinic of Somdet Chaopraya Institute of Psychiatry. Effectiveness data of this study presented as event rate, transition probability and other clinical outcomes which were relative risk (RR) and time to event. However, relative risk and time to event were not included in the MARKOV model for analyzing cost effectiveness results.

3.7.1.1 Study design of retrospective cohort study

This study was designed as a single-center retrospective cohort study. Clinical outcomes were compared between patients attending pharmaceutical care service in lithium clinic adjunct to a standard pharmacologic treatment (lithium clinic group) and patients who received standard care alone (usual care group). Data included recurrence of mood episodes in the studied population. All data were extracted from retrospective chart review and hospital database. The Ethics Committee of Somdet

Chaopraya Institute of Psychiatry reviewed and approved by the Helsinki Declaration the study protocol (April 2014).

3.7.1.2 Study population

The study population was all consecutive patients with bipolar I disorder who came for follow up at outpatient department of Somdet Chaopraya Institute of Psychiatry between January 2006 and December 2015.

The inclusion criteria were as follows:

- all participants who were diagnosed as bipolar I disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV).
- patient who was in stable mood state (euthymic) and treated with lithium as maintenance therapy.
- age 18 years or more.
- the patient must have been treated with lithium at this hospital for at least 1 year prior to enrollment.

The exclusion criteria were as follows:

- patient who was missing information on the year of birth, age at first diagnosis, duration of illness and/or duration of lithium treatment before recruitment.
- patient who received non-pharmacologic treatment during the study period such as psychotherapy, cognitive behavior therapy (CBT), etcetera.

- patient who was diagnosed as mixed episodes or rapid cycling bipolar disorder.

3.7.1.3 Participant recruitment

Participants who met inclusion criteria were recruited into the study. There were two groups of participants which were lithium clinic group and usual care group. Lithium clinic group included all eligible cases who attended a pharmaceutical care service plus standard care at outpatient lithium clinic for at least one year. Usual care group included the eligible cases who received standard care alone without pharmaceutical care service. Subjects for usual care group were selected from name lists of bipolar patients who followed the outpatient appointment by this hospital in the same period of time as recruited cases of lithium clinic group.

Two subjects of usual care group were matched for each case of lithium clinic group by gender and age at index. Each patient in lithium clinic group was matched with usual care group for age at index that was equal or different no more than 5 years (± 5 years). Usual care group subjects were selected by random from the pool of matches if more than 1 qualified patient were available.

3.7.1.4 Description of intervention

Participants in lithium clinic group received a pharmaceutical care service in addition to standard care treatment which was carried out by a pharmacist of lithium

clinic. The pharmaceutical care activities in lithium clinic comparing with activity in usual care group show in Table 4.

Table 4 Activities of pharmaceutical care service in lithium clinic group compare with usual care group

Activities	Lithium clinic group	Usual care group
Reviewing patient's medication profile to identify, prevent and correct drug therapy problems	✓	✓
Writing up consultation with the patient and transferring them to the psychiatrist for making medication and treatment plan	✓	
Counseling patient about the important of continuing on medication and treatment, how to detect the early sign of manic, hypomanic and depressive episode and what should to do if a new episode occurs	✓	
Intensive monitoring on drug-drug and drug-food interaction between lithium and other medications or food	✓	
Educating patient how to detect the early signs of lithium toxicity and other side effects and how to resolve lithium intoxication if it happens	✓	
Monitoring serum lithium concentration regularly every 3-4 months	✓	
Scheduling for laboratory monitoring program including renal function test, thyroid function test and urine analysis every year and interpreting laboratory data	✓	
Adjusting lithium dosage according to the pharmacokinetic of each patient	✓	
Determining patient's medication adherence and treatment adherence	✓	✓
Providing lithium card to the patient and counseling how to use it	✓	
Dispensing medication to the patients	✓	✓

3.7.1.5 Conceptual framework of retrospective cohort study

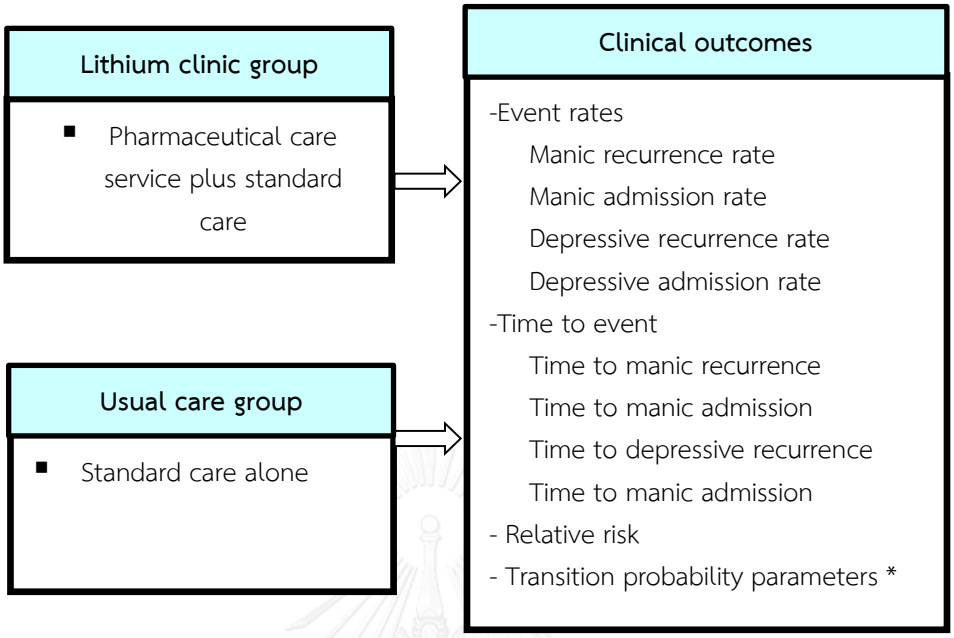


Figure 7 Conceptual framework of retrospective cohort study

3.7.1.6 Calendar time and Study time

This study started accrual on 1 January 2006, and accrued for 7 years until 31 December 2012, with an additional 3 years of follow-up ending on 31 December 2015. The study period was between 1 January 2006 and 31 December 2015. Index date could happen any time during accrual period. The follow-up period of each patient was time between index date and end of follow-up date.

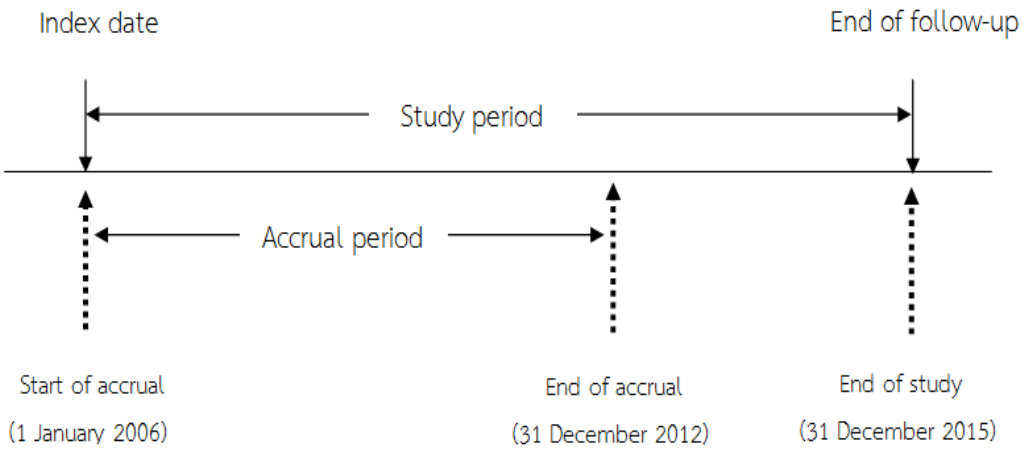


Figure 8 Calendar time and study time

3.5.1.7 Study completion

The subjects could end the study at any time in the study period if they were lost to follow-up, stopped taking lithium or referred to other hospital. All events, including depressive episode, manic episode and hospitalization, which occurred during the study period, were collected. Each patient in lithium clinic group and usual care group who were matched together had outcomes compared in the same follow up period. If one of them ended the study, the follow up period of the rest also stopped. The outcomes were measured based on this duration.

3.5.1.8 Outcomes

The main outcome of this study was recurrence, which was categorized as manic recurrence or depressive recurrence. Number of subjects who had recurrence, rate of recurrence and time to event were measured as the outcomes of study. All data were obtained from retrospective chart review. All participants were identified

by reviewing outpatient medical records for the individual's age, age at first diagnosis, duration of illness, time to recurrence to any new episode, time to hospitalization, any record of medication, laboratory monitoring pattern and follow up time.

3.5.1.9 Assessment

Recurrence in this study was defined as a new acute mood episode (manic or depressive episode) meeting DSM-IV symptom and duration criteria (74) which has starting signs and symptoms after 2 months of remission (26). If data in outpatient medical records were not clearly identified, the psychiatrist would make a decision whether the patients met recurrence criteria or not.

3.5.1.10 Statistical analysis

The demographic characteristics at baseline included age at index date, age at first diagnosis, gender, follow up time, and preexisting comorbid condition(s) were summarized by count and percentages. Baseline characteristics of the participants were analyzed by chi-square test for categorical data and independent sample t-test for continuous data. Event rate was compared by independent sample t-test. Overall survival function and time to event were performed by survival analysis using Kaplan-Meier curve. The statistical significance for these tests was set at $P < 0.05$.

3.5.1.11 Sample size estimation

Primary outcome measure of this study is recurrence rate. To compare mean of recurrence rate between intervention and control group, the sample size should be estimated from Cohen J. method (75). According to power table for sample size

estimation (see figure 9), for alpha = 0.05, power= 0.80, effect size (ES) = 0.20, u = 1, the number of patients for each group is at least 99 cases.

n to detect f by F test at a = .05
for u = 1, 2, 3, 4

u = 1
f

Power	.05	.10	.15	.20	.25	.30	.35	.40	.50	.60	.70	.80
.10	84	22	10	6	5	4	3	3	2	--	--	--
.50	769	193	86	49	32	22	17	13	9	7	5	4
.70	1235	310	138	78	50	35	26	20	13	10	7	6
.80	1571	393	175	99	64	45	33	26	17	12	9	7
.90	2102	526	234	132	85	59	44	34	22	16	12	9
.95	2600	651	290	163	105	73	54	42	27	19	14	11
.99	3675	920	409	231	148	103	76	58	38	27	20	15

Figure 9 Power table for sample size estimation

3.5.1.12 Definition

- Clinical outcome of a pharmaceutical care service in lithium clinic for bipolar patients treated with lithium as maintenance therapy represents by the recurrence of any new mood episode.
- Recurrence is defined as the emergence of a new acute mood episode according to DSM-IV criteria (74) which has starting signs and symptoms after 2 months of remission (26).
- Recurrence rate is total number of recurrence in a specify time period.
- Remission is defined as no longer meeting diagnostic criteria for bipolar disorder (26).

- Time to event or survival time means duration between index date and the date of emerging event which classify as time to recurrence to any new episode and time to hospitalization.

- Accrual period or recruitment period or accrual means the period during which subjects are being enrolled (recruited) into a study.

- Index date is defined as the date of recruiting subject into the study.

- Follow-up period is the period after each subject entered the study until the end of the study. The follow-up defines the phase of a study during which subjects are under observation.

- Euthymia or euthymic state is simply defined as a relatively stable mood state, neither manic/hypomanic nor depressed.

- Stable phase in this study means euthymia or euthymic state

3.5.2 Cost data

As the perspective in this evaluation is provider perspective, only the direct health care costs of bipolar treatment, paid by the provider, were used. Costs in this study included only direct medical care costs which consist of medication cost, pharmaceutical care service cost, laboratory monitoring cost, admission cost, emergency room visit cost and outpatient visit cost. All costs will be derived from

hospital database.The discount rate of 3% was applied to all costs according to HITAP guidance (76). All costs were adjusted to 2015 values using Consumer Price Index (CPI) of medical care group from the Bureau of Trade and Economic Indices, Ministry of Commerce, as show in Appendix II.

3.5.3 Utility data

The utility weights for patients with bipolar stable phase, mania (OPD), mania (IPD), depression (OPD) and depression (IPD) were obtained from published articles. The utility score is between 0 and 1, where 0 represents death and 1 represents perfect health. Utility data for bipolar patients in each state is presented as Table 5.

Table 5 Utility data of bipolar disorder in each health state

	Utility	Reference
QoL for bipolar stable phase who were on lithium	0.71-0.80	Published source (2, 77)
QoL for inpatient mania	0.23-0.26	Published source (2, 78)
QoL for outpatient acute mania	0.53-0.64	Published source (2)
QoL for inpatient (severe) depression	0.28	Published source (2)
QoL for outpatient (moderate) depression	0.63	Published source (2)

3.5.4 Transition probability

The transition probability is the chance that each clinical event will occur. In a specified period, the patient can move between health states. The rate of moving from one health state to another is regulated by the transition probability. It ranges from 0 to 1.

3.6 Uncertainly analysis

3.6.1 Deterministic sensitivity analysis

Univariate sensitivity analyses were conducted to identify the variables which have significant impacts on the results. Ranges will be selected based on the high and low values from studies previously identified. The key individual variables which influence the result of CE were shown in Tornado diagram. The variables tested are as follows:

(a) Pharmacist salary

The pharmacist salary was varied between -50% and +50% of the average salary of pharmacist who work in lithium clinic of Somdet Chaopraya Institute of Psychiatry in year 2015.

(b) Costs of mania (IPD)

The costs of mania (IPD) were increased and decreased by 50% of the average manic admission cost between years 2014 to 2015 of Somdet Chaopraya Institute of Psychiatry to see the change of ICERs.

(c) Costs of depression (IPD)

The costs of mania (IPD) were increased and decreased by 50% of the average depressive admission cost between years 2014 to 2015 of Somdet Chaopraya Institute of Psychiatry to see the change of ICERs.

(d) Discount rate

The discount rates of 0% and 6% of costs and outcomes were used.

3.6.2 Probabilistic sensitivity analysis

To examine the uncertainty of inputs in the model, the probabilistic sensitivity analysis using a second-order Monte-Carlo simulation was performed. Monte Carlo simulation was used by involving random sampling of each variable under the specified probability distribution of each input parameter which was assigned based on their feature to indicate the feasible value range in which each input variable could achieve. Beta distribution was chosen for the probability and utility variables, Gamma distribution was used for all cost parameters. The simulation of 1000 times could provide a range of possible values given the specified probability distribution of parameters used in the analysis. The results were presented as costs, effectiveness (QALY, LYG) and ICER per QALY.

CHAPTER IV
RESULTS

4.1 Clinical outcomes from retrospective cohort study

These parameters were obtained from retrospective cohort study at Somdet Chaopraya Institute of Psychiatry. Number of patients changed to each health state was recorded. Event rate and time to event were compared between lithium clinic and usual care group. Relative risk of change from one health state to another health state was calculated.

4.1.1 Baseline characteristics and clinical status

At baseline, this study consisted of 360 patients with bipolar I disorder who were in stable phase and got maintenance treatment with lithium carbonate. There were 2 groups of patients, 120 patients in lithium clinic group and 240 patients for usual care group.

As shown in Table 6, there were no significant differences between demographic characteristics between lithium clinic groups and usual care group. Study follow up time of each patient in this research varied from 0.25 to 10 years according to when they entered and ended the study. The follow-up period of each patient was time between index date and end of follow-up date. The subjects could enter or end the study at any time during the study period. The average study follow-up time was 6.11 $\pm$ 3.14 years for both groups.

Table 6 Demographic and baseline characteristics

	Lithium clinic group (n=120)	Usual care group (n=240)	p-value
Age at index, mean (SD), years	46.25 (10.70)	45.06 (10.57)	0.316
Age at first diagnosis, mean (SD), years	30.67 (10.24)	29.92 (10.38)	0.518
Male sex, No. (%)	74 (61.7)	148 (61.7)	1.000
Follow up time, mean (SD), years	6.11 (3.14)	6.11 (3.14)	1.000
Preexisting comorbid condition, No.(%)			
Diabetes mellitus	17 (14.2)	42 (17.5)	0.421
Hypertension	28 (23.3)	51 (21.3)	0.653
Renal disease	2 (1.7)	2 (0.8)	0.477
Gout	4 (3.3)	4 (1.7)	0.312
Asthma	2 (1.7)	5 (2.1)	0.787
Hypothyroidism	2 (1.7)	2 (0.8)	0.477
Medications received at index date, No.(%)			
Lithium alone	13 (10.8)	20 (8.3)	0.438
Antipsychotics			
Conventional antipsychotics	81 (67.5)	168 (70)	0.628
Atypical antipsychotics	4 (3.33)	16 (6.67)	0.193
Benzodiazepines	47 (39.17)	104 (43.33)	0.450
Anticholinergics	66 (55.00)	130 (54.17)	0.881
Antidepressants	15 (12.5)	35 (14.58)	0.590

Abbreviation: SD, standard deviation

4.1.2 Event rate

Hospitalization rate from all psychiatric causes in lithium clinic group was significantly less than usual care group. There was 0.0545 $\pm$ 0.170 and 0.1815 $\pm$ 0.428 time per year for lithium clinic and usual care groups, respectively. Also, hospitalization rate from manic recurrence in lithium clinic group was significantly lower than control group, which were 0.0449 $\pm$ 0.147 and 0.1582 $\pm$ 0.392 time per year for lithium clinic and usual care groups, respectively. In addition, emergency room visiting rate in lithium clinic group was significantly less than usual care group

which were 0.0286 ± 0.133 and 0.1507 ± 0.474 time per year for lithium clinic group and usual care group, respectively as shown in Table 7.

Table 7 Event rate

Event rate per year	Lithium clinic group (n = 120)	Usual care group (n = 240)	P - value
Hospitalization rate			
all psychiatric causes, mean (SD)	0.0545 (0.170)	0.1815 (0.428)	<0.001*
manic recurrence, mean (SD)	0.0449 (0.147)	0.1582 (0.392)	<0.001*
depressive recurrence, mean (SD)	0.0096 (0.087)	0.0233 (0.185)	0.443
ER visit rate, mean (SD)	0.0286 (0.133)	0.1507 (0.474)	<0.001*
Lithium intoxication admission rate, mean (SD)	0.0009 (0.010)	0.0049 (0.030)	0.068

Abbreviation: ER, emergency room

4.1.3 Relative risk

Patients in lithium clinic group had a significantly less risk of any recurrence than the usual care group (RR = 0.59, 95% CI 0.377-0.923). Also, the risk of manic recurrence and the risk of hospitalization due to manic recurrence (manic admission) was significantly less than the usual care group. The risk of manic recurrence and manic admission were 0.459 (95% CI 0.287-0.736) and 0.340 (95% CI 0.193-0.600), respectively. However, there were no significant differences in the risk of depressive recurrence and risk of hospitalization due to depressive recurrence (depressive admission) between the two groups.

Considering the manic recurrence subgroup, patients in the lithium clinic group had risk of hospitalization significantly less than usual care group (RR = 0.398, 95% CI 0.180 - 0.881). Moreover, for patients with depressive recurrence subgroup,

participants in the lithium clinic group had lower risk of hospitalization than those in the usual care group (RR 0.150, 95% CI 0.033-0.680) as shown in Table 8.

Table 8 Relative risk

Clinical variables	Lithium clinic group (n = 120)	Usual care group (n = 240)	Relative risk (95%CI)
Bipolar stable phase			
Any recurrence, No. (%)	45 (37.5)	121 (50.4)	0.590 (0.377-0.923)*
Manic recurrence, No. (%)	34 (28.3)	111 (46.3)	0.459 (0.287-0.736)*
Depressive recurrence, No. (%)	15 (12.5)	24 (10.0)	1.286 (0.648-2.553)
Hospitalization from manic recurrence, No (%)	18 (15.0)	82 (34.2)	0.340 (0.193-0.600)*
Hospitalization from depressive recurrence, No (%)	3 (2.5)	15 (6.3)	0.385 (0.109-1.355)
Subgroup analysis	**(n=34)**	**(n=111)**	
Hospitalization in manic recurrence subgroup, No. (%)	18 (52.9)	82 (73.9)	0.398 (0.180-0.881)*
	(n=15)	**(n=24)**	
Hospitalization in depressive recurrence subgroup, No. (%)	3 (20.0)	15 (62.5)	0.150 (0.033-0.680)*

Abbreviation: CI, confidence interval

4.1.4 Time to event

Survival analysis of patients remaining in stable phase for each condition was shown in Table 9. There were significant differences in median time to manic recurrence, median time to manic admission and median time to emergency room visit between lithium clinic and usual care group. Time to manic recurrence was 4.44 (IQR 3.59-5.29) years for lithium clinic group while it was 3.54 (IQR 3.08-3.99) years for usual care group. Moreover, time to manic admission was 5.36 (IQR 4.81-5.92) and 3.98 (IQR 3.21-4.76) years for lithium clinic and usual care group, respectively. In addition, time to emergency room visit was 5.36 (IQR 4.93-5.80) years in lithium clinic group and it was 4.09 (IQR 3.46 – 4.72) years in usual care group.

Table 9 Time to events

	Lithium clinic group (n = 120)		Usual care group (n = 240)	
	Median	IQR	Median	IQR
Time to manic recurrence, year	4.44	3.59 - 5.29	3.54	3.08 - 3.99
Time to depressive recurrence, year	5.36	4.87 - 5.86	5.33	4.95 - 5.70
Time to manic admission, year	5.36	4.81 - 5.92	3.98	3.21 - 4.76
Time to depressive admission, year	5.73	4.73 - 6.72	5.45	5.10 - 5.80
Time to ER visit, year	5.36	4.93 - 5.80	4.09	3.46 - 4.72

Abbreviations: IQR, interquartile range; ER, emergency room

As shown in figures 10, 11 and 12, the survival curve for lithium clinic group and usual care group were significantly different for overall survival distribution by using log rank test in manic recurrence (Chi-square = 6.135, df = 1, P = 0.013), manic admission (Chi-square = 6.264, df = 1, P = 0.012) and manic admission in a specific subgroup (manic recurrence subgroup) (Chi-square = 6.19, df = 1, P = 0.013). However, there were no significant differences for depressive recurrence and depressive admission between both groups.

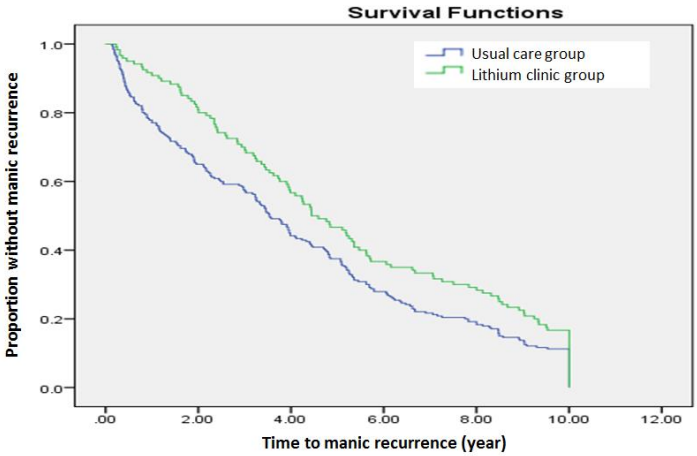


Figure 10 Survival curve for manic recurrence in bipolar stable phase

Log Rank: Chi-square = 6.135, df = 1, P = 0.013

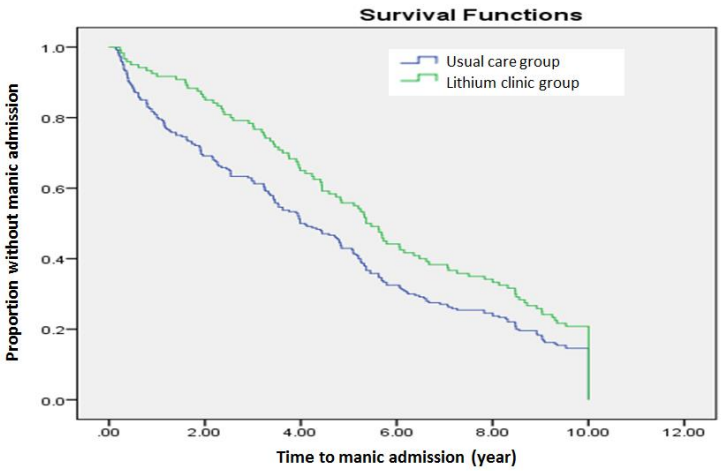


Figure 11 Hospitalization from manic recurrence in bipolar stable phase

Log Rank: Chi-square = 6.264, df = 1, P = 0.012

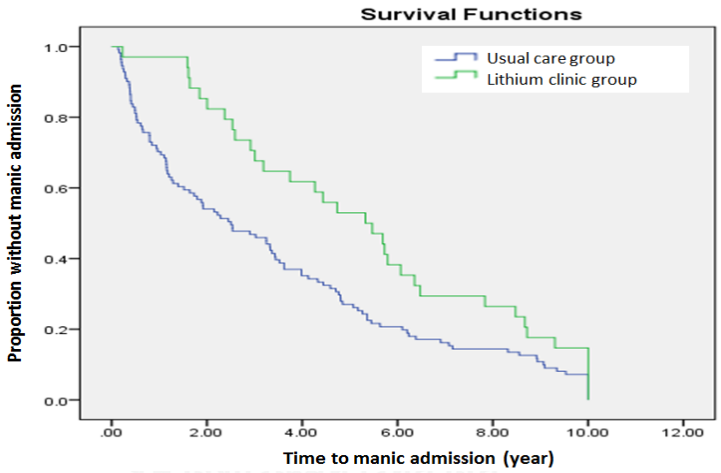


Figure 12 Hospitalization in manic recurrence subgroup

Log Rank: Chi-square = 6.19, df = 1, P = 0.013

4.1.4 Transition probability parameters

Some transition probabilities obtained from retrospective cohort study including P(1,2), P(2,3), P(1,3), P(1,4), P(4,5) and P(1,5). Detail of these transition probabilities will show in part 4.2.1.1.

4.2 Parameters

4.2.1 Transition probability parameters

Transition probability parameters which used in this study came from various methods included obtaining from retrospective cohort study, estimating from WHO life table, estimating from previous study, and calculation.

4.2.1.1 Obtaining from retrospective cohort study

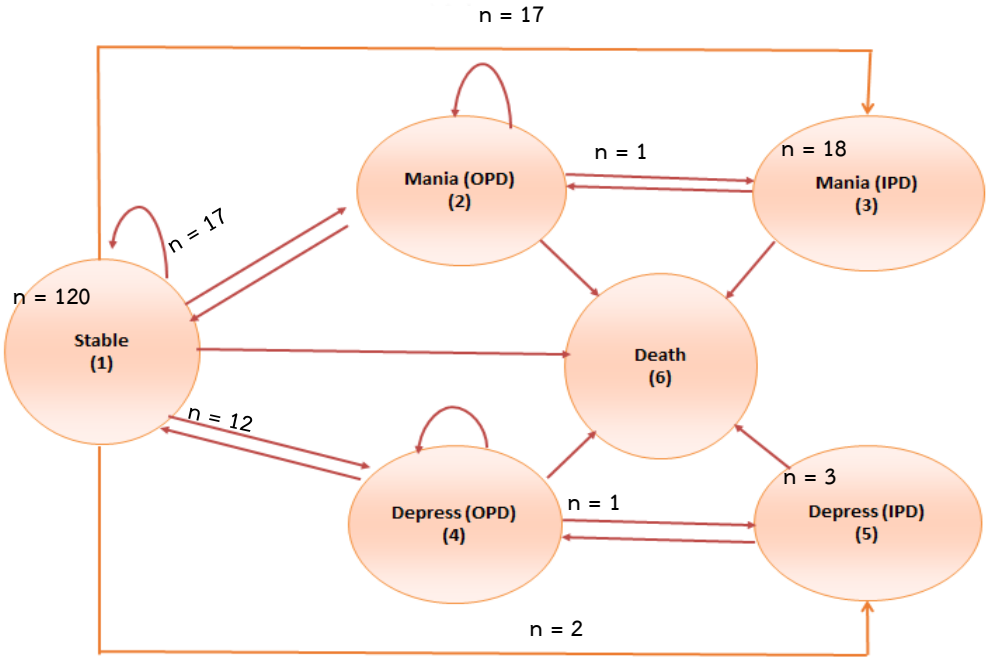


Figure 13 Number of patients changed to each health state for lithium clinic group

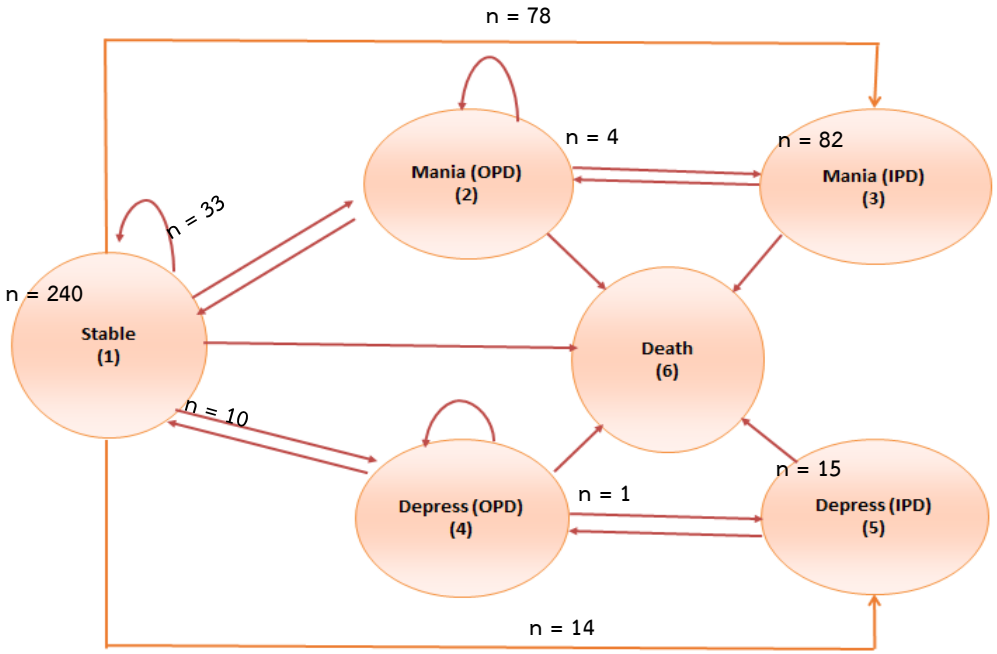


Figure 14 Number of patients changed to each health state for usual care group

(1) Probability of bipolar patient changing from stable phase to mania (OPD) state or P(1,2)

Data from retrospective cohort study performed for this current cost effectiveness study as show in Figure 13 and 14. Seventeen of one hundred and twenty participants in lithium clinic group changed from bipolar stable phase to mania (OPD). On the other hand, 33 of 240 participants in standard care group changed from bipolar stable phase to mania (OPD).

a. Lithium clinic group

The probability of change from stable phase to mania (OPD) in 6.11 years-follow up = 17/120 = 0.14167

The rate per year = -[ln(1-0.14167)]/6.11 = 0.02500

The probability per year = $1-e^{-(0.02500x1)}$ = 0.02469

b. Usual care group

The probability of change from stable phase to mania (OPD) in 6.11 years-follow up = 33/240 = 0.13750

The rate per year = -[ln(1-0.13750)]/6.11 = 0.02421

The probability per year = $1-e^{-(0.02421x1)}$ = 0.02392

(2) Probability of bipolar patient changing from mania (OPD) to mania (IPD) state or P(2,3)

Regarding our retrospective cohort study, 1 of 17 participants in lithium clinic group changed from mania (OPD) to mania (IPD). In addition, 4 of 33 participants in usual care group changed from mania (OPD) to mania (IPD).

a. Lithium clinic group

The probability of change from mania (OPD) to mania (IPD) in 6.11 years-follow up = 1/17 = 0.0588

The rate per year = -[ln(1-0.05882)]/6.11 = 0.00992

The probability per year = $1-e^{-(0.00992x1)}$ = 0.00987

b. Usual care group

The probability of change from mania (OPD) to mania (IPD) in 6.11 years-follow up = 4/33 = 0.12121

The rate per year = -[ln(1-0.12121)]/6.11 = 0.02115

The probability per year = $1-e^{-(0.02115x1)}$ = 0.02093

(3) Probability of bipolar patient changing from stable phase to depression (OPD) state or P(1,4)

Data from our retrospective cohort study, 12 of 120 participants in lithium clinic group changed from bipolar stable phase to depression (OPD) state. In addition, 10 of 240 participants in usual care group changed from bipolar stable phase to depressive episode (OPD) state.

a. Lithium clinic group

The probability of change from bipolar stable phase to depression (OPD) in 6.11 years-follow up = 12/120 = 0.1000

The rate per year = -[ln(1-0.1000)]/6.11 = 0.0219

The probability per year = $1-e^{-(0.0219x1)}$ = 0.00137

b. Usual care group

The probability of change from bipolar stable phase to depression (OPD) in 6.11 years-follow up = 10/240 = 0.04167

The rate per year = -[ln(1-0.04167)]/6.11 = 0.00697

The probability per year = $1-e^{-(0.00697x1)}$ = 0.00694

(4) Probability of bipolar patient changing from depression (OPD) to depression (IPD) state or P(4,5)

Regarding our retrospective cohort study, 1 of 12 participants in lithium clinic group changed from depression (OPD) to depression (IPD). In addition, 1 of 10 participants in usual care group changed from depression (OPD) to depression (IPD).

a. Lithium clinic group

The probability of change from depression (OPD) to depression (IPD) in 6.11 years-follow up = 1/12 = 0.08333

The rate per year = -[ln(1-0.08333)]/6.11 = 0.01424

The probability per year = $1-e^{-(0.01424x1)}$ = 0.01414

b. Usual care group

The probability of change from depression (OPD) to depression (IPD) in 6.11 years-follow up = 1/10 = 0.1000

The rate per year = -[ln(1-0.1000)]/6.11 = 0.01724

The probability per year = $1-e^{-(0.01724x1)}$ = 0.01710

(5) Probability of bipolar patient changing from stable phase to mania (IPD) state or P(1,3)

Regarding our retrospective cohort study, 17 of 120 participants in lithium clinic group changed from bipolar stable phase to mania (IPD) while it was 78 of 240 participants for usual care group.

a. Lithium clinic group

The probability of change from bipolar stable phase to mania (IPD) in 6.11 years-follow up = 17/120 = 0.14167

The rate per year = -[ln(1-0.14167)]/6.11 = 0.02500

The probability per year = $1-e^{-(0.02500x1)}$ = 0.02469

b. Usual care group

The probability of change from depressive episode (OPD) to depressive episode (IPD) in 6.11 years-follow up = 78/240 = 0.32500

The rate per year = -[ln(1-0.32500)]/6.11 = 0.06433

The probability per year = $1-e^{-(0.06433x1)}$ = 0.06230

(6) Probability of bipolar patient changing from stable phase to depression (IPD) state or P(1,5)

Regarding our retrospective cohort study, 2 of 120 participants in lithium clinic group changed from bipolar stable phase to depression (IPD) while it was 14 of 240 participants for usual care group.

a. Lithium clinic group

The probability of change from bipolar stable phase to depression (IPD) in 6.11 years-follow up = 2/120 = 0.01667

The rate per year = -[ln(1-0.01667)]/6.11 = 0.00275

The probability per year = $1-e^{-(0.00275x1)}$ = 0.00275

b. Usual care group

The probability of change from bipolar stable phase to depression (IPD) state in 6.11 years-follow up = 14/240 = 0.05833

The rate per year = -[ln(1-0.05833)]/6.11 = 0.00984

The probability per year = $1-e^{-(0.00984x1)}$ = 0.00979

4.2.1.2 Estimating from WHO life table

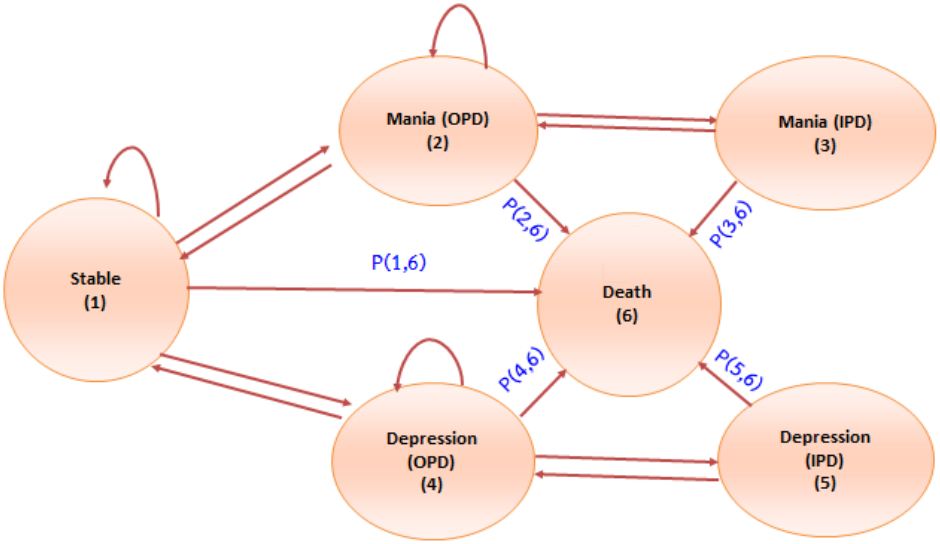


Figure 15 Transition probabilities which estimated from WHO life table

Some transition probabilities (Figure 15) including P(1,6), P(2,6), P(3,6), P(4,6) and P(5,6) were estimated from WHO life table as shown in Appendix III. These probabilities were transition probability from each health to death. From data of a systematic review and meta-analysis of premature death in bipolar disorder revealed that all-cause mortality in bipolar disorder was 2.05 times more than mortality in general population (79) as present in Figure 16.

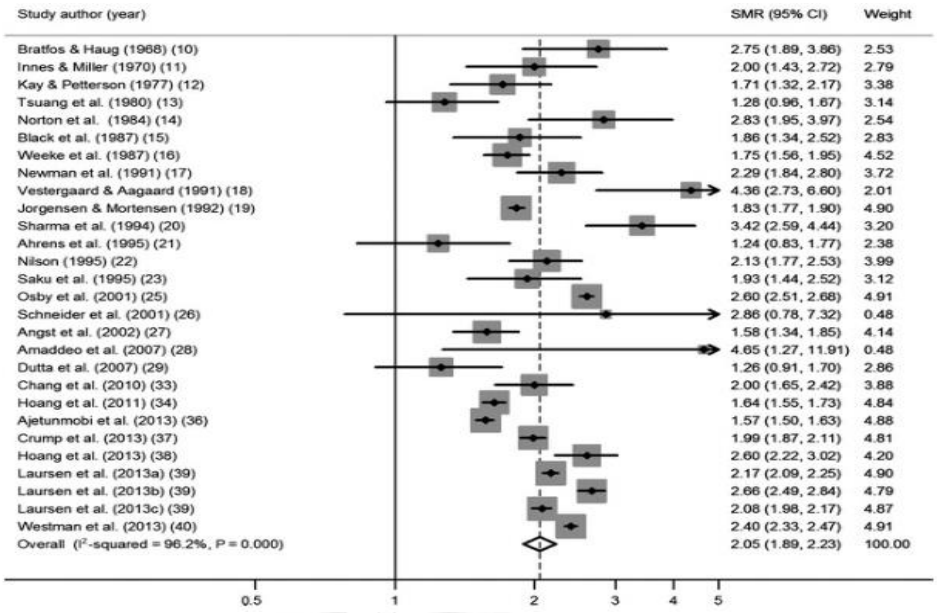


Figure 16 Standardized mortality ratio (SMR) of all-cause mortality in patients with bipolar disorder

Mortality rate in patients with bipolar disorder was estimated by multiplying standardized mortality ratio (SMR) of all-cause mortality, which was 2.05, with mortality rate of Thai general population. Probability of dying was calculated from mortality rate. Rates are instantaneous but probabilities are expressed over a time period. To convert an instantaneous rate to probability over a particular time period, the rate is assumed to be constant over that time period. Transition probability and could be calculated by using the below equation.

$$p = 1 - \exp\{-rt\}$$

where p is the probability

r is the rate

t is the time period of interest

Transition probability (or probability of dying) which was estimated from WHO life table is presented in Table 10. Transition probability of dying was assumed to be equal for all health state and also assumed to be equal both for lithium clinic and control group.

Table 10 Probability of dying in bipolar disorder classify by age

Mortality rate			Probability of dying
Age Group	General population	Bipolar disorder	Total
<1 year	0.0110605	0.0226740	0.0224189
1-4 years	0.0004405	0.0009030	0.0009026
5-9 years	0.0003825	0.0007841	0.0007838
10-14 years	0.0003790	0.0007770	0.0007766
15-19 years	0.0008230	0.0016872	0.0016857
20-24 years	0.0010525	0.0021576	0.0021553
25-29 years	0.0013770	0.0028229	0.0028189
30-34 years	0.0017475	0.0035824	0.0035760
35-39 years	0.0026665	0.0054663	0.0054514
40-44 years	0.0033880	0.0069454	0.0069213
45-49 years	0.0040520	0.0083066	0.0082722
50-54 years	0.0055310	0.0113386	0.0112745
55-59 years	0.0082470	0.0169064	0.0167642
60-64 years	0.0128865	0.0264173	0.0260714
65-69 years	0.0207670	0.0425724	0.0416789

Mortality rate			Probability of dying
Age Group	General population	Bipolar disorder	Total
70-74 years	0.0361905	0.0741905	0.0715052
75-79 years	0.0580065	0.1189133	0.1121152
80-84 years	0.0821650	0.1684383	0.1550166
85-89 years	0.1204880	0.2470004	0.2188596
90-94 years	0.1827395	0.3746160	0.3124467
95-99 years	0.2862795	0.5868730	0.4439366
100+ years	0.4628940	0.9489327	0.6128460

4.2.1.3 Estimating from previous study

(1) Probability of patients in mania (OPD) and depression (OPD) remained in the same state or P(2,2) and P(4,4)

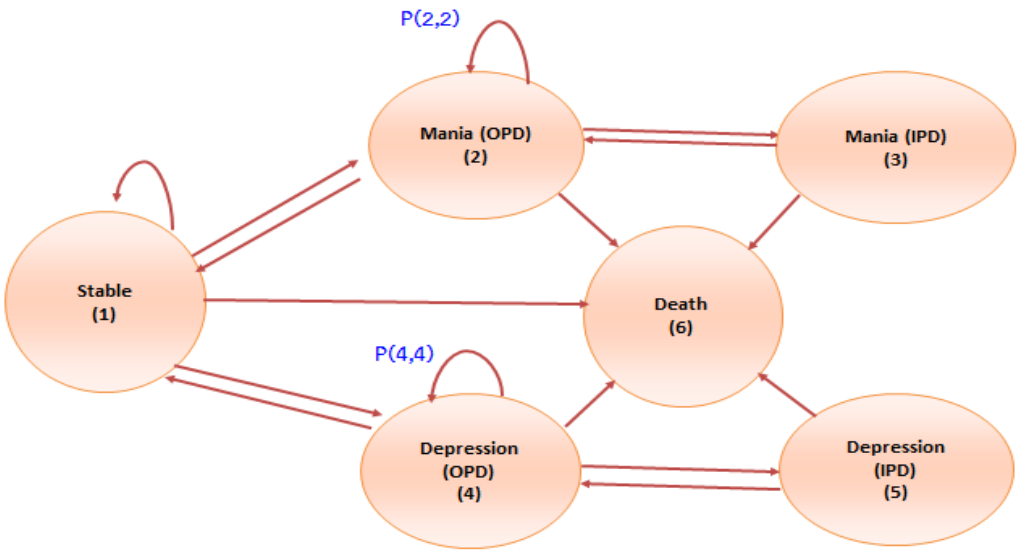


Figure 17 Probability of patients in mania (OPD) state and depression (OPD) state remaining in the same state

Probability of patients in mania (OPD) state and depression (OPD) state remained in the same state are presented in Figure 17. They were estimated from previous cohort study of 123 first-admission inpatients with bipolar disorder with psychotic features which was followed for 4 years. This study found that only 3 of patients did not change to remission state (80). Therefore, we assumed the probability of remain in mania (OPD) or depression (OPD) state from the data of this study.

The probability in 4 years-follow up = 3/123 = 0.0244

The rate per year = -[ln(1-0.0244)]/4 = 0.00617

The probability per year = $1-e^{-(0.00617x1)}$ = 0.00615

4.2.1.4 Calculation

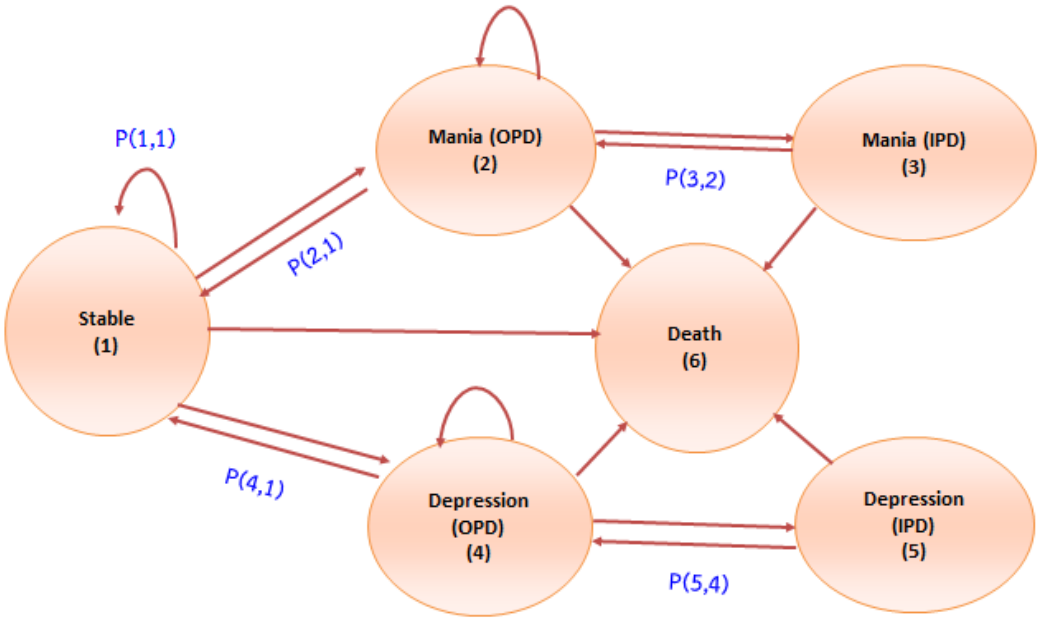


Figure 18 Transition probabilities which come from calculation method

Some transition probabilities including P(1,1), P(2,1), P(3,2), P(4,1) and P(5,4) were estimated from calculation method as shown in Figure 18.

(1) Probability of bipolar patient changing from mania (IPD) to mania (OPD) state or P(3,2)

There are 2 probabilities going out from mania (IPD) state and the sum of them should equal to 1. Thus the probability of P(3,2) be calculated as shown in the below equation.

$$P(3,2) = 1 - P(3,6)$$

(2) Probability of patients changing from depression (IPD) to depression (OPD) state or P(5,4)

There are 2 probabilities going out from depression (IPD) state and the sum of them should equal to 1. Therefore, the probability of P(5,4) can be calculated as shown in the below equation.

$$P(5,4) = 1 - P(5,6)$$

(3) Probability of bipolar patient changing from mania (OPD) to stable phase or P(2,1)

There are 4 probabilities going out from mania (OPD) state and the sum of them should equal to 1. Therefore, the probability of P(2,1) can be estimated as shown in the below equation.

$$P(2,1) = 1- P(2,2) – P(2,3) – P(2,6)$$

(4) Probability of bipolar patient changing from depression (OPD) to stable phase or P(4,1)

There are 4 probabilities going out from depression (OPD) state and the sum of them should equal to 1. Therefore, the probability of P(4,1) can be calculated as shown in the below equation.

$$P(4,1) = 1- P(4,4) – P(4,5) – P(4,6)$$

(5) Probability of bipolar patients who remain in stable state or P(1,1)

There are 6 probabilities going out from depression (OPD) state and the sum of them should equal to 1. Therefore, the probability of P(1,1) can be calculated as shown in the below equation.

$$P(1,1) = 1- P(1,2) – P(1,3) – P(1,4) – P(1,5) - P(1,6)$$

Summary of transition probabilities for lithium clinic and control group are displayed in Table 11 and Table 12 respectively.

Table 11 Transition probabilities for lithium clinic group

Parameters	Distribution	Probabilistic	Mean	SE	alpha	beta
Stable to Mania (0PD)	Beta	0.01723	0.02469	0.02469	0.95062	37.54813
Mania (0PD) to Mania (IPD)	Beta	0.00651	0.00987	0.00987	0.98025	98.30471
Stable to Depression (OPD)	Beta	0.02771	0.01710	0.01710	0.96581	55.52699
Depression (OPD) to Depression (IPD)	Beta	0.04023	0.01414	0.01414	0.971720	67.75017
Stable to Mania (IPD)	Beta	0.01916	0.02469	0.02469	0.950616	37.54813
Stable to Depression (IPD)	Beta	0.00192	0.00275	0.00275	0.994506	361.04217
Remain in mania (OPD) *	Beta	0.01605	0.00615	0.00615	0.987692	159.50459
Remain in depression (OPD) *	Beta	0.00489	0.00615	0.00615	0.987692	159.50459

* Estimate from previous study (80)

Table 12 Transition probabilities for usual care group

Parameters	Distribution	Probabilistic	Mean	SE	alpha	beta
Stable to Mania (0PD)	Beta	0.00018	0.02392	0.02392	0.95216	38.85593
Mania (0PD) to Mania (IPD)	Beta	0.02718	0.02093	0.02093	0.95815	44.83034
Stable to Depression (OPD)	Beta	0.00128	0.00694	0.00694	0.98612	141.07779
Depression (OPD) to Depression (IPD)	Beta	0.04084	0.01710	0.01710	0.96581	55.52699
Stable to Mania (IPD)	Beta	0.10261	0.06230	0.06230	0.87540	13.17535
Stable to Depression (IPD)	Beta	0.00151	0.00979	0.00979	0.98042	99.17765
Remain in mania (OPD)	Beta	0.00513	0.00615	0.00615	0.987692	159.50459
Remain in depression (OPD)	Beta	0.01007	0.00615	0.00615	0.987692	159.50459

* Estimate from previous study (80)

4.2.2 Utility parameters

Utility parameters of bipolar disorder in each health state used for this analysis are shown in Table 13.

Table 13 Utility parameters using for the analysis

Parameters	Distribution	Probabilistic	Mean	SE	alpha	beta
Utility for BPD Stable phase	Beta	0.79	**0.80**	0.22	1.84	0.46
Utility for BPD mania (OPD)	Beta	1.00	**0.64**	0.45	0.09	0.05
Utility for BPD mania (IPD)	Beta	0.17	**0.25**	0.25	0.51	1.57
Utility for BPD depression (OPD)	Beta	0.00	**0.63**	0.45	0.10	0.06
Utility for BPD depression (IPD)	Beta	0.77	**0.28**	0.28	0.44	1.13

4.2.3 Cost parameters

As the perspective in this study was provider perspective, only the direct health care costs of bipolar treatment were used. Direct health care costs included OPD visit cost (bipolar stable phase), OPD visit cost (manic recurrence), OPD visit cost (depressive recurrence), emergency room visit cost, laboratory cost (OPD), manic admission cost, depressive admission cost and pharmaceutical care cost. All costs were already adjusted to 2015 value by using consumer price index (CPI) as show in Appendix II.

4.2.3.1 OPD visit cost (bipolar stable phase)

From data of Somdet Chaopraya Institute of Psychiatry, the average OPD visit cost of bipolar patients who were in stable phase was estimated from 168 medical records of the participants who came to follow up between January 2006 and December 2015. The average OPD visit cost was 586.93 THB (SE 125.85)

4.2.3.2 OPD visit cost (manic recurrence)

Data of Somdet Chaopraya Institute of Psychiatry, OPD visit cost from manic recurrence was calculate from the available data of all participants who experienced manic recurrence but could be treated as OPD case. Of these, 52 medical records were reviewed. The average cost provided by the hospital was 727.10 THB (SE 330.53).

4.2.3.3 OPD visit cost (depressive recurrence)

Data of Somdet Chaopraya Institute of Psychiatry, OPD visit cost from depressive recurrence was calculate from the available data of all participants who experienced depressive recurrence but still be treated as OPD case. Of these, 20 medical records were reviewed. The average cost provided by the hospital was 627.63 THB (SE 171.36).

4.2.3.4 Emergency room visit cost

From data of Somdet Chaopraya Institute of Psychiatry, the average cost of emergency room visit of bipolar patients was estimated from 28 medical records of the bipolar patients who came to ER between January 2015 and September 2015. The average OPD visit cost was 305.58 THB (SE 52.48)

Table 14 Outpatient cost (cost/visit)

	Cost (Baht)	
	mean	**SE**
OPD visit cost		
Stable	586.93	125.85
Mania	727.1	330.53
Depression	627.63	171.36
ER visit cost	290.28	46.85

4.2.3.5 Laboratory monitoring cost (OPD)

Laboratory monitoring which recommended in patients receive lithium is serum lithium concentration, serum creatinine, thyroid stimulating hormone and urine analysis. The unit cost of each laboratory monitoring is presented in Table15.

Table 15 Unit Cost of laboratory monitoring

Test	Cost per test (THB)
Serum lithium concentration	100
Serum creatinine	50
Thyroid stimulating hormone	200
Urine analysis	50

Source: Somdet Chaopraya Institute of Psychiatry

(a) Lithium clinic group

Participants in lithium clinic group were monitored for serum lithium concentration every 3 months, while serum creatinine, thyroid stimulating hormone and urine analysis were monitored every year. Laboratory cost per year for this group was calculated as presented in Table 16.

Table 16 Laboratory monitoring cost per year for lithium clinic group

Test	Monitoring rate per year	Cost (THB)
Serum lithium concentration	4	400
Serum creatinine	1	50
Thyroid stimulating hormone	1	200
Urine analysis	1	50
	Total	700

(b) Usual care group

Laboratory monitoring cost per year for usual care group was estimated according to rate of monitoring for each test per year as shown in Table 17.

Table 17 Laboratory monitoring cost per year for usual care group

Test	Monitoring rate per year	Cost (THB)
Serum lithium concentration	0.29972	29.97
Serum creatinine	0.22509	11.25
Thyroid stimulating hormone	0.02434	4.868
Urine analysis	0.10040	5.02
	Total	51.108

4.2.3.6 Manic admission cost

From data of Somdet Chaopraya Institute of Psychiatry, 191 medical records of patients admitted from manic recurrence between January 2014 and December 2015 were reviewed to estimate manic admission cost. The average cost provided by the hospital was 36,154.67 THB (SE 2,340.65). This cost was already adjusted to 2015 value by using consumer price index (CPI).

4.2.3.7 Depressive admission cost

From data of Somdet Chaopraya Institute of Psychiatry, 54 medical records of patients admitted from depressive recurrence between January 2014 and December 2015 were reviewed to estimate depressive admission cost. The average cost provided by the hospital was 33,423.08THB (SE 3,078.03). This cost was already adjusted to 2015 value by using consumer price index (CPI).

4.2.3.8 Lithium intoxication admission cost

This cost obtained from our retrospective cohort study. Nine patients in this cohort experience lithium intoxication admission. Six of them admitted at other hospital. Only 3 patients admitted at Somdet Chaopraya Institute of Psychiatry for

treating this cause, therefore, lithium intoxication admission cost of this study calculated from these patients. The average intoxication admission rate was 28,523.06 THB (SE 21,020.06).

4.2.3.9 Pharmaceutical care cost

All patients in this study were assumed to come to follow up every 1 month period. Only patients in lithium clinic group receive a pharmaceutical care service. Time spent for a pharmaceutical care service for each patient was approximately 20 minute/time. Pharmaceutical care cost was calculated by the below formula.

$$\text{Pharmaceutical care cost (THB/year)} = \frac{\text{12 times/year x 20 minutes/time x pharmacist salary THB/month}}{\text{20 days/month x 7 hours/day x 60 minutes/hour}}$$

Table 18 Summary of cost parameters using for this analysis

Parameters	Distribution	Probabilistic	Mean	SE	alpha	beta
ER cost/visit	Gamma	326.03	305.58	52.48	33.90	9.01
Intoxication admission cost (per visit)	Gamma	22,445.04	28,523.06	21,020.06	1.84	15,490.73
Pharmacist salary (per month)	Gamma	36,207.11	32,346.00	4,580.28	49.87	648.58
Manic admission cost (per visit)	Gamma	36,537.58	36,154.68	2,340.65	238.59	151.53
Depressive admission cost (per visit)	Gamma	28,374.01	33,423.08	3,078.03	117.91	283.46
Manic OPD cost (per visit)	Gamma	861.33	727.10	330.53	4.84	150.25
Depress OPD cost (per visit)	Gamma	648.61	627.63	171.36	13.41	46.79
Stable OPD cost (per visit)	Gamma	377.33	586.93	125.85	21.75	26.98

4.3 Economic outcome

4.3.1 Cost-effectiveness result

The life time costs and effectiveness were obtained from the results of Markov model with Monte Carlo simulations for lithium clinic and usual care group. The incremental cost, incremental cost-effectiveness ratios (ICERs) and quality-adjusted life years (QALYs) of long-term maintenance treatments for lithium clinic and usual care group were estimated as present in Table 19. The quality-adjusted life years (QALYs) of lithium clinic group was increased by 0.61 and 0.62 from deterministic and probabilistic analysis respectively. ICER from deterministic analysis was 64,574.75 THB per QALY while it was 62,349.04 THB per QALY from probabilistic analysis. Life year of patients in lithium clinic group was not different from usual care group. It was about 25.52 years.

Table 19 Cost Effectiveness result

Prevention of bipolar recurrence	**Lithium Clinic versus Usual care group**	
	Deterministic	**Probabilistic**
Incremental cost	39,097.18	38,518.84
Incremental QALYs	0.61	0.62
ICER per QALY gained	64,574.75	62,349.04

4.3.2 Uncertainty Analyses

4.3.2.1 Deterministic analysis

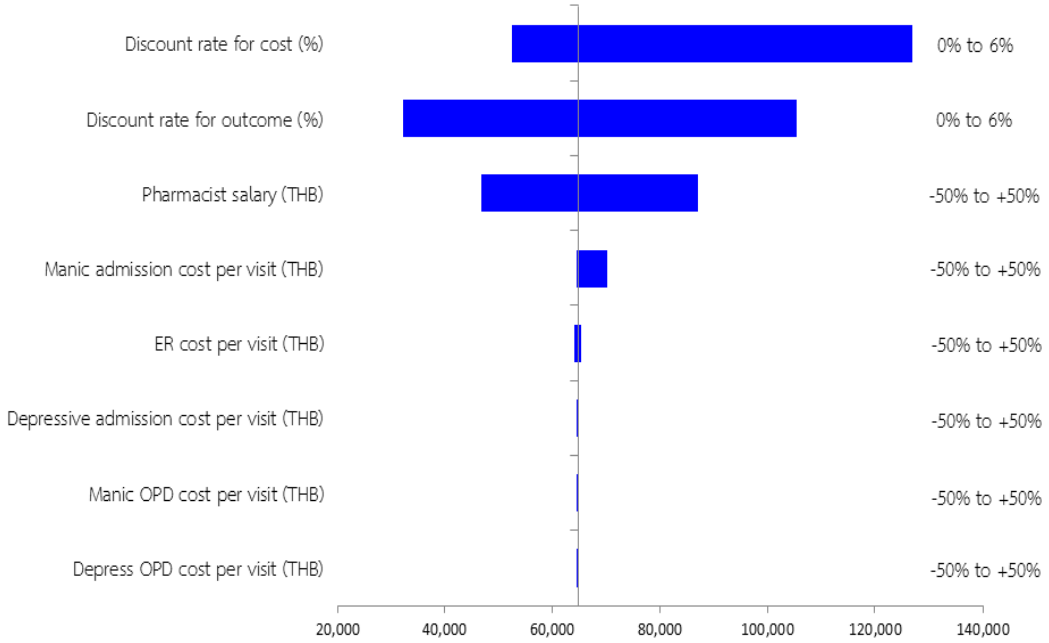


Figure 19 Tornado diagram comparing the relative importance of model parameters on the cost effectiveness result

The effect of discount rate for cost showed the greatest impact to the result as shown in the Tornado Diagram (Figure 19), followed by discount rate for outcome, pharmacist salary, manic admission cost, ER visit cost, depressive admission cost, manic OPD cost and depressive OPD cost.

4.3.2.2 Probabilistic Sensitivity Analysis

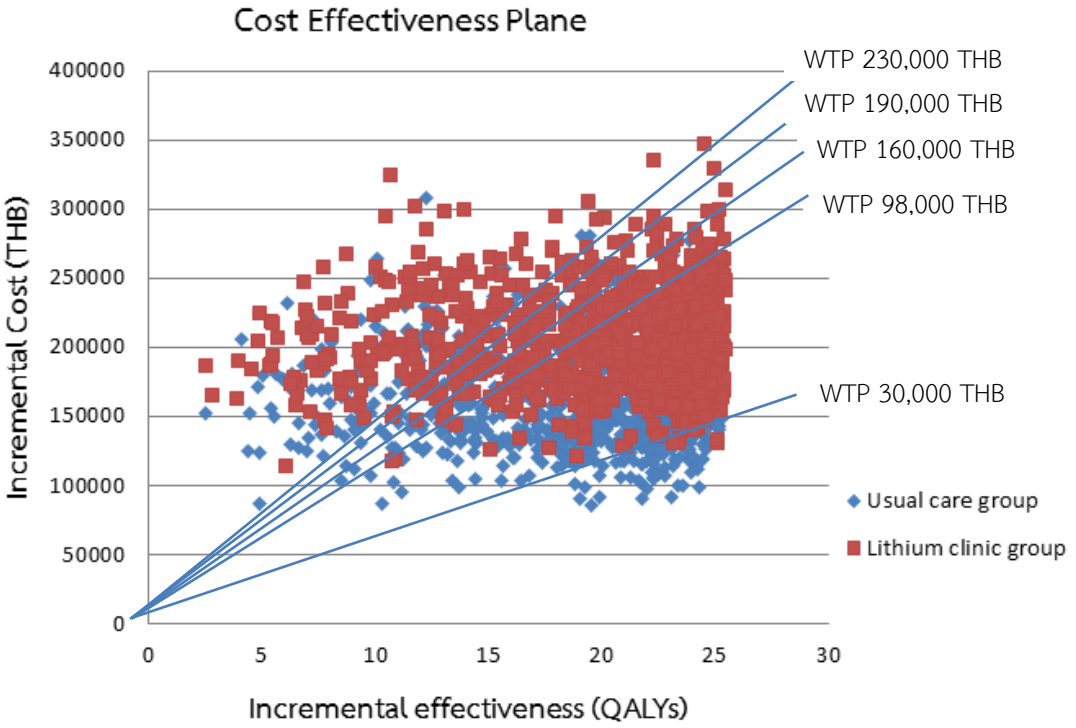


Figure 20 Cost Effectiveness Plane

Cost effectiveness plane (CE plane), X axis represents the incremental level of effectiveness of the outcome (QALYs) and the Y axis represents the additional total cost of implementing this outcome. When considering both parameters together, the CE plane allows determining the relative cost and relative effectiveness. Figure 20 shows scatter plot of Monte Carlo simulation 1,000 iterations of incremental cost and incremental effectiveness (QALYs) of both groups. The majority of iterations demonstrate that a pharmaceutical care service adjunct to standard care (lithium clinic group) is more effective and more costly than standard care alone (usual care group). At willingness to pay (WTP) 98,000 THB, approximately 50% of iterations is

above the line of WTP. Moreover, at WTP 160,000 THB (willingness to pay threshold of Thailand in year 2013 for determining whether strategy is cost effectiveness or not), the probability of cost effectiveness from this intervention is 57.1% as show in Figure 20 and Table 20.

Table 20 Probability of cost effectiveness from lithium clinic group vary by the willingness to pay (WTP) threshold

Willingness to pay (THB)	Probability
30,000	0.204
98,000	0.500
160,000	0.571
190,000	0.589
230,000	0.607
300,000	0.630
400,000	0.649
500,000	0.665
1,000,000	0.674
2,000,000	0.682
3,000,000	0.687
4,000,000	0.689
5,000,000	0.691

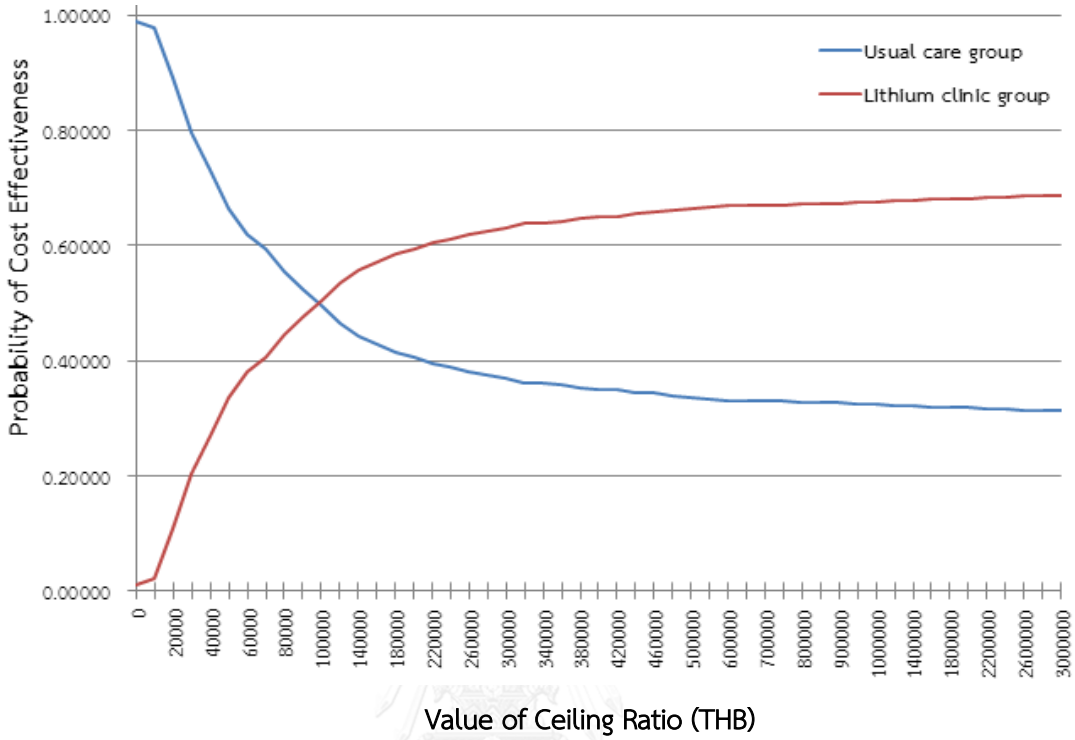


Figure 21 Cost Effectiveness Acceptability Curve (CEAC) of a pharmaceutical care service adjunct to standard care (lithium clinic group) versus standard care alone (usual care group)

The cost effectiveness acceptability curve in Figure 21 shows the probability that each group is cost effective over a range of potential maximum willingness to pay values that the payer can afford to pay for an additional QALY.

At the WTP values less than approximately 98,000 THB, usual care group seem to be more cost effective than lithium clinic group. However, if the WTP was more than 98,000 THB, lithium clinic group is more cost effective.

CHAPTER V
CONCLUSION AND RECOMMENDATIONS

This chapter composes of discussion, conclusion, limitation of the study, recommendation for further study and recommendation for policy maker.

5.1 Discussion

Pharmaceutical care for psychiatric patients has been applied in several clinical settings. Previous studies about the psychiatric pharmacy services effects on acute care psychiatric inpatients clinical outcomes discovered that pharmaceutical service provision correlated with clinical response improvement (7). The medical literature that examined the impact of pharmacist in mental health from 1972 to 2003 has been evaluated both quantity and quality through a systematic review. The 16 studies evaluated the impact of pharmacists in mental health demonstrated improvements in outcomes, prescribing practices, patient satisfaction and resource use. Nine of 16 studies featured pharmacists' role as treatment recommendations and patient education. Five of the studies investigated the role of pharmacists as providing prescriptive authority. Finally, two of the studies reported the impact of pharmacists on educating the psychiatric staff. Further comparison is limited due to restriction in study design and a small number of participants (81). Other studies examined the impact of pharmacist intervention for medication information on knowledge, adherence, clinical, economic and humanistic outcomes. From these

studies, the intervention group increased knowledge by 14-28% comparing to the control group. Also, the intervention group had higher adherence than the control group by 11-30%. There were no significantly different in number of side-effects, symptoms or quality of life, and admission or relapse rates. The economic impact for the intervention had not been reported for these 17 studies (82).

Previous 2 studies of the effectiveness of a pharmaceutical care service in lithium clinic had been performed in year 2002 and 2011, however, they were outcome description analysis study and examined for short-term clinical outcomes (37, 38). The first study was designed as a randomized single blind control study. The eligible cases (n=60) were randomized into an experimental (n=30) and control group (n=30) and were followed up for 4 visits with a one month interval. The experimental group were provided with pharmaceutical care in which the pharmacist activities included counseling patients on how to avoid lithium intoxication, providing medication reminder card and lithium card, monitoring serum lithium concentration and adjusting dosage of lithium according to the pharmacokinetic of each patient, determining patient's adherence and assessing drug therapy problems (DTPs). The control group did not receive pharmacist intervention except when their DTPs were serious. At the end of study, parameters including DTPs, serum lithium concentration, patient's knowledge, patient's adherence and the clinical outcome were compare between both groups. The result of this study revealed that a pharmaceutical care

provided to bipolar patients who received lithium as maintenance therapy was associated with a decrease in DTPs, an increase in the number of patients whose serum lithium concentration was within therapeutic range and enhanced patient knowledge on lithium usage. Although there was no statistically significant difference in clinical outcomes between both groups, patients in control group hospitalized more than those in experimental group. The reason that the result cannot be detected the difference of clinical outcome between both groups may come from the small sample size and short study duration (37). The second study for this lithium clinic performed to study the differences of therapeutic outcomes between patients attending in lithium clinic and patient receiving treatment as usual at Somdet Chaopraya Institute of Psychiatry. There is one-year retrospective cohort study which included patients in various psychiatric illness to the study. It was shown that patients in study group were hospitalized less than those one in control group (1.25 % vs 11.25%, respectively) and study group also associated with a significant reduction in risk of hospitalization (RR = 0.099, 95%CI = 0.0123-0.8083, p = 0.018). Furthermore, study subjects visited to emergency department less than control subjects (2.50 % vs 11.25%, respectively) and it also revealed that study group associated with a significant reduction in risk of visiting to emergency department (RR = 0.19, 95%CI = 0.0423-0.9681, p = 0.029). Number needed to treat (NNT) to prevent hospitalization and prevent visiting to emergency department was 10 and 11.43, respectively. Moreover, the adverse drug reaction (ADR) and laboratory tests had

been recorded in study group more than in control group significantly. The most frequent ADR which found in this study were memory impairment (25%) and dry mouth (25%) followed by hypothyroidism (21.25%). However, renal tubular impairment was also occurred in 5% of patients. This study concluded that patients attending in lithium clinic had the preferable clinical benefit more than those who receiving treatment as usual (38).

Recent study about impact of a pharmaceutical care service performed in Thai patients to examine the short term outcomes of pharmaceutical care in schizophrenic patients. This study found that the number of DRPs decreased significantly more in the intervention group than in the control group ($p < 0.001$). The mean knowledge score increased greater in the intervention group ($p < 0.001$). The mean QOL score showed a trend towards improvement in the intervention group (both $p < 0.001$). Effectiveness of this study was an achieving for good medication adherence. Cost effectiveness of this study used decision tree model as a tool for analyzing cost effectiveness result which was cost-effectiveness ratios (CER). This study revealed that cost-effectiveness ratios (CER) of pharmaceutical care and usual care for achieving good medication adherence was 16.54 and 16.06 USD/successful patient, respectively and CER for improved QOL was 17.30 and 14.98 USD/successful patient, respectively (48).

Until now, research about impact of pharmacist intervention for psychiatric patients is still scarce. Data about the impact of this intervention on clinical and

economic outcomes in long term treatment still have been not enough. Furthermore, no research has been done in well-designed full economic evaluation particularly for patients with bipolar disorder.

For our study, this is the first full economic evaluation study of a pharmaceutical care service in bipolar disorder. It demonstrates the achievement of pharmacists in mental health care setting. It also indicates cost-effectiveness of pharmacist intervention by considering both clinical and economic outcomes in reinforcing the role of psychiatric pharmacist. This study used MARKOV model with Monte Carlo Simulation as the tool for analyzing cost effectiveness result. Results of a systematic and critical review of model-based economic evaluations of pharmacotherapeutics in bipolar disorder patients revealed that, nine in fourteen studies used Markov, three used discrete-event simulation (DES) and two used decision-tree models (83). Therefore, this result implied that MARKOV model have been the most popular model use for evaluating bipolar patients.

MARKOV model using in this study apply from NICE guideline (2) and other previous studies (77, 84-86). Transition probabilities were obtained from 10-year retrospective cohort study performed especially for this study. Cost parameters were estimated from rate of event happen in each group and the hospital database. Manic admission cost and depressive admission cost in this study were lower than unit cost per admission of Thai previous study. In this study, manic admission cost and depressive admission cost were 36,154.68 and 33,423.08 THB per visit respectively.

Previous study showed unit cost per visit of admission of bipolar affective disorder was 61,737.61 THB per visit in fiscal year 2005 (87) or 66,823.46 THB in year 2015 (adjusted with CPI to year 2015). Because cost in this study was only direct medical care cost without management, depreciation or facility cost, therefore, it was the reason that why cost in this study was lower than the previous study.

Majority of transition probability in this study derived from single center of Thai Psychiatric Hospital, therefore it can represent in context of Thai bipolar patients.

Probability of death in this study was estimated from mortality rate of general Thai population multiply by SMR of all-cause mortality in bipolar disorder. This transition probability from all health state to death was set equally. In addition, it was assumed to be equal both for lithium clinic and usual care group. Therefore, the outcome of life year calculated from this model was not different between both groups. However, a systematic review of economic evaluations in bipolar disorder revealed that all study using MARKOV model in the analysis used constant transition probabilities implying that patients with bipolar disorder would have a constant annual likelihood of dying irrespective of their length of stay in a given health state (85).

5.2 Conclusion

Lithium clinic group had life expectancy not differ from usual care group. The quality-adjusted life years (QALYs) increased by 0.62 and incremental cost effectiveness ratio (ICER) increased by 62,349.04 THB per QALY from adjunct pharmaceutical care service to standard care. Lithium clinic group was more cost effective than usual care group if the willingness-to-pay (WTP) threshold was more than 98,000 THB. Furthermore, the pharmaceutical care service adjunct to standard care seems to be more cost-effective than the standard care alone in consideration of the current WTP threshold of Thailand at 160,000 THB/QALY.

In addition, current study also examined long-term clinical outcomes of a pharmaceutical care service in this clinic. Results of this study found that this intervention was superior to usual care by reducing any recurrence, manic recurrence and hospitalization from manic recurrence. Moreover, this intervention seemed to lengthen the time to manic recurrence, time to manic admission and time to ER visit for 0.9, 1.38 and 1.27 years, respectively.

5.3 Limitations of the study

5.3.1 Although majority of transition probabilities were obtained from Thai bipolar patients of the single center setting, the completeness of data which got from retrospective chart review should be concerned. These transition probabilities might be lower than it should be because some detail of clinical manifestation did

not record completely, therefore, the researcher could not identify whether patients changed to the other health state or not.

5.3.2 Transition probability of death for all health state in this study was assumed to be equal. Also, it was assumed to be equal both for lithium clinic and usual care group. It would be better if transition probability of dying was identified specifically for each health state.

5.3.3 Since lithium clinic of Somdet Chaopraya Institute of Psychiatry is the first and only lithium clinic in Thailand, some parameters such as transition probability and costs were obtained from single center which was Somdet Chaopraya Institute of Psychiatry. Thus, some input parameters might be derived from a few numbers of patients and might not completely represent the real value of these parameters for Thai bipolar disorder patients.

5.3.4 Utility parameters from published data of other countries which were used in the Markov model and assumptions on these parameters might not completely reflect the outcome of bipolar patients in Thailand.

5.4 Recommendation

5.4.1 Recommendation for further study

(1) The utility parameters used in this analysis were gotten from populations of other countries. Further studies to collect these data in Thai bipolar patients would be useful and would be the good representative of Thai context.

(2) The perspective of this study focused on provider perspective. Thus, costs in this study included only direct medical care costs. If possible, societal perspective should be performed for measuring all impacts on health and resource use from the intervention (88). Use of societal perspective, all parties must realize and concern the interests of others.

5.4.2 Recommendation for policy maker

Regarding result of this analysis, patients in lithium clinic group had more favorable economic and clinical outcomes than patients in usual care group. Therefore, a pharmaceutical care service adjunct to standard care in patients with bipolar disorder who was on lithium as maintenance therapy is beneficial and should be adopted in other Thai psychiatric hospitals or general hospital which provide psychiatric service.

Finally, there should be a process or procedure to allow the related parties or person to learn CEA information that affected their views and decisions. The process might be applied to related decision maker such as government, health care organization and other stakeholders.

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APPENDIX

APPENDIX I

Pharmacist involvement in psychiatric patients

	Sample size	Study design	Intervention	Results
Ellenor et al, 1977 (39)	208	Retrospective chart review, historical control (before-after design)	Clinical pharmacist intervention	-total number of drugs decreased by 37% ($p<0.001$) -significant decreases in antipsychotic, antianxiety, and antidepressant use - annual savings of more than $10,000 in drug use - nonsignificant increase in maladaptive behavior -no relapses reported.
Rosen et al, 1978 (40)	196	Retrospective chart review; control group treated by other mental health professionals	Provided case management services, such as drug monitoring and education; pharmacist permitted to adjust or prescribe drugs under protocol	-role skills and community adjustment score slightly increase for pharmacist-managed patients -increase patient satisfaction - cost of psychiatrist services 2.5 times greater than pharmacist services
Bond et al, 1979 (41)	25	Retrospective chart review; historical control (before-after design), cost and function assessment	Provided drug monitoring services for approved patients; drug adjustments required psychiatrist approval.	-decrease in hospital readmissions (42 admissions 1 year before intervention vs 3 admissions 1 year after) -decrease of 1332 days of hospitalization ($p<0.001$) -estimated $230,000 savings in annual hospitalization cost -decrease in drug side effects reported (38 before intervention vs 4 after, $p<0.005$) -average decline of 39% in fluphenazine dosage requirements, 42% decline in anticholinergic use

	Sample size	Study design	Intervention	Results
Gray et al, 1979 (49)	19	Retrospective; historic control (before-after design)	Provided drug monitoring and weekly drug groups; pharmacist permitted to adjust or prescribe drugs under protocol	-Nonsignificant improvement in clinical outcomes -significant decrease in adverse effects (61 before intervention vs 20 after, p <0.005) -significant decrease in number of prescribed drugs (decrease of 1.32 drugs/patient/month, p <0.05) -improvement in patient's drug knowledge (53% before, 77% after)
Inoue F, 1982 (50)	608	Retrospective chart review; historic control (before-after design)	Performed drug management review (drug monitoring, treatment recommendations); pharmacist permitted to order laboratory tests under protocol	-73% of recommendations implemented immediately -45% decrease in number of psychotropic drugs prescribed -50% of patients with improved cognitive function after treatment changes -8% with symptom worsening
Stimmel GL et al, 1982 (51)	Not applicable; 158 prescriptions by intervention; 120 prescriptions by control.	Not a blinded study; retrospective cohort; quality of prescribing practices graded by panel of four expert clinical judges; three pharmacists compared with two psychiatrists prescribing	Allowed to prescribe under protocol with supervision of physician (certified as prescribers)	-Most prescriptions well within appropriate range -pharmacist prescribing comparable to physician prescribing for anticholinergics but significantly better for antipsychotics and antidepressants

	Sample size	Study design	Intervention	Results
Berchou, 1982 (52)	715 (intervention site), 1049 (control site).	Retrospective chart review; historic control (before-after design) and comparison with other facility of similar size and patient population nearby	Provided treatment recommendations to multidisciplinary team and provided education sessions for team.	-Long-term drugs decreased by 19% at intervention site (from 76% to 57%, p <0.001) -significant difference in type of antipsychotic prescribed -antipsychotics more commonly prescribed at control site (16.8% at intervention site vs 34.2% at control site), and more frequent use of long-term psychotropics (71% at control site vs 57% at intervention site)
Alexander et al, 1983 (53)	58 patients (before), 49 patients (after)	Retrospective chart review; historical control (before-after design)	Provided education program for psychiatric staff (physicians and medical students) 1 hour/week for 2 years	-Number of psychotropic orders and type of psychotropics similar before and after intervention -significant decrease in multiple daily doses of psychotropics
Saklad et al, 1984 (54)	31 patients (before), 30 patients (after)	Retrospective chart review; historical control (before-after design).	Performed clinical pharmacy services, such as drug monitoring, consultation, and patient education.	-Significant decrease in number of antipsychotic and anticholinergic drugs by day 14 (28% and 40% reduction, respectively, p<0.05) - nonsignificant increase in antipsychotic dosage (453 chlorpromazine equivalents before intervention vs 657 after) -significant increase in hospital discharge rates, significant decrease in readmissions

	Sample size	Study design	Intervention	Results
Lobeck et al, 1989 (47)	Unknown (total of 4734 visits before intervention and 2662 visits afterward)	Retrospective chart review and satisfaction questionnaires; historical control (before-after design)	Performed clinical pharmacy services, such as chart review, treatment recommendations before clinic visit, and drug education	-66% of recommendations implemented -very favorable provider response to survey (average satisfaction score of 4.41 on a 1-5 scale) -$22,241 savings during 3-month intervention
Hartlaub et al, 1993 (55)	Group 1 consisted of two clinics with 9049 patients, group 2 of eight clinics with 6279 patients; the control group consisted of one clinic with 8012 patients.	Prospective cohort study with nonrandom clinic allocation	Provided education program to prescribing physicians; one treatment group received presentation, written materials, brief individual review, and feedback; the other treatment group received presentation and written materials	No apparent impact on benzodiazepine-prescribing behavior with either treatment group
Schmidt et al, 1998 (56)	Total of 562 residents at intervention sites, 1243 at control sites	Randomized controlled trial; 15 homes randomized to intervention group, 18 to control group (no multidisciplinary review of regimen)	Coordinated monthly team meetings (involving physicians, nurses, and nurse aides) to review psychotropic drug therapy at the facility; spent 1 day/month at site.	-No change in percentage of patients receiving psychotropics in either group (2% increase in overall drug use with each group) -significant decrease in antipsychotic use in intervention group (19% decrease vs 7% in control group) -significant increase in acceptable prescribing of antidepressants (584% vs 315%) & anxiolytics (50% vs 5%)

	Sample size	Study design	Intervention	Results
Canales et al, 2001 (7)	Forty-five (intervention group), 48 (control group).	Prospective cohort; historic controls (before-after design); control group received traditional pharmacy services (centralized drug distribution and physician-initiated consults).	Performed intensive pharmacist services, such as obtaining drug histories, baseline assessments, drug monitoring, treatment recommendations, and drug education	Superior clinical outcomes for intervention group with thought disorders (93% with > 20% decline on the Brief Psychiatric Rating Scale vs 23% for controls [p<0.05], 13% with Clinical Global Impression score ≥ 4 for intervention patients vs 63% for controls [p<0.05]); superior clinical outcomes for mood disorders (65% of intervention group with ≥ 50% decline on Hamilton Depression Scale vs 9% of controls, p=0.003); greater improvements in adverse-effect scales with intervention group; no difference between patient groups in length of hospital stay (average 29 days for each group); daily drug costs of $252/patient in intervention group, $151 in control group (p=NS); cost-effectiveness analysis reported cost of successful outcome as $2.48/patient (e.g., > 20% decrease on Brief Psychiatric Rating Scale)

	Sample size	Study design	Intervention	Results
Finley et al, 2002 (57)	Depression N = 220 91(intervention group), 129 (control group).	Nonrandomized, prospective, controlled cohort study; 13 physicians assigned to intervention group (referred patients to protocol), 17 other physicians to provide usual care (6 months)	Pharmacists provided drug management, patient education, assessed medication therapy, and provided therapeutic recommendations. Pharmacists had limited prescribing privileges under protocol.	-Significant increase in antidepressant adherence (drug possession ratio of 0.81 in intervention group vs 0.66 in control group, p<0.005) -significant increase in 6-month treatment completion rates (intent-to-treat analysis 76% vs 49% for intervention and control groups, respectively, p=0.008) -significant improvements in patient satisfaction (several measures) -significant decline in primary care visits (39.4% in intervention group vs 12.2% in controls, p=0.029) -no significant difference in total resource utilization
Bultman, et al (2002) (69)	Patients newly prescribed antidepressant medication N=100	Prospective field study (2 months)	Pharmacists monitored patients taking antidepressant medications. Pharmacists answered patient questions, helped solve medication related problems, and listened to patient concerns	-83% of patients reported missing doses or taking additional doses. -32% of patients found pharmacists to be helpful in solving problems related to their antidepressant medications (42% neither agreed nor disagreed).

	Sample size	Study design	Intervention	Results
Suanchang O. et al, 2002 (37)	30 (intervention group), 30 (control group)	Randomized single blind control study (4 months)	Pharmacist provided a pharmaceutical care service to bipolar patients who receive lithium as maintenance therapy	-Number of drug therapy problem (DTPs) decrease in intervention group (p=0.0001) -number of patients who reached therapeutic serum lithium concentration in intervention group more than those in control group (p=0.039) -number of patients who had knowledge about missed dose management and dehydrate management in intervention group was more than in control group (p=0.001 and p < 0.0001, respectively) -no statistically significant difference in clinical outcomes and patient's adherence
Finley et al, 2003 (42)	Depression N = 125 75 (intervention group), 50 (control group).	Randomized controlled trial; control patients treated by primary care provider (6 months)	Pharmacist followed up with patients frequently for assessment of therapeutic effect, adverse effects, and adherence. Pharmacist could titrate antidepressant dose as indicated by HMO guidelines and had limited prescribing privileges under protocol for ancillary medications.	-Significant increase in 6-month drug adherence rates (67% vs 48% for intervention and control groups, respectively, Health Employer Data and Information Set pecifications, p=0.038) -significant increase in patient satisfaction (several measures) -significant decrease in primary care visits (p=0.015) -no statistically significant change in total resource utilization (medication costs) or clinical outcomes reported

	Sample size	Study design	Intervention	Results
Virani A et al, 2003 (10)	N = 17	Prospective : evaluate patient outcome between pre and post pharmacist intervention Retrospective : cost analysis on the 12-month period before and the 12-month period immediately after pharmacist intervention	Clinical pharmacist intervention: identify DRPs, therapeutic recommendation	- Eighty-six percent (38/44) of the interventions were assessed as having a positive effect on patient care. - Drug cost per patient-day was 14% lower in the year after implementation of the pharmacy position, and the difference was statistically significant in the last 8 months of that year (p = 0.0019). Total drug costs decreased by 21%, a cost saving of $5485.80.
Capoccia et al, 2004 (58)	Depression N = 74 (Intervention group: 41; control group: 33)	Randomized controlled trial (12 months)	Patients in intervention, or “enhanced care” (EC) group were contacted by a pharmacist at predefined intervals; pharmacist collaborated with PCP to provide patient education, dose adjustment for antidepressants, monitoring of patient adherence to therapy, and management of adverse effects	-No significant difference between intervention and control groups for medication adherence at 12 months (p=0.91). -Mean SCL-20 and SF-12 scores improved significantly for both groups indicating improvement in depression symptoms, but no significant difference between groups. -No difference between groups in number of visits to any type of healthcare provider. -No significant differences between groups for patient satisfaction with psychiatric or overall treatment.

	Sample size	Study design	Intervention	Results
Adler et al, 2004(59)	MDD, dysthymia N = 533 (Intervention group: 268; control group: 265)	Randomized controlled trial, control patients received usual care from PCP (6 month intervention period with 18 month follow-up)	Pharmacists monitored medication therapy, provided therapeutic recommendations to PCPs, provided patient education and advice	-Patients in the intervention group had higher rates of antidepressant medication use at 6 months than patients in the control group (57.5% vs. 46.2%, p=0.03). -Depression outcomes at 6 months, based on mBDI scores, did not vary significantly between intervention and control but favored intervention group (p=0.16).
Bell S et al, 2005 (60)	Twenty-two controlled (randomised and non-randomised) studies of pharmacists' interventioni in community and residential aged care settings	systematic review	pharmacist delivered community-based services	-Pharmacists can contribute to optimizing the use of medications for mental illness in the community setting
Crockett et al, 2006 (62)	Depression N = 119 (Intervention group: 51; control group: 68)	Non-randomized controlled study (2 months)	Pharmacists received additional training via videoconference and provided extra advice and support to patients when dispensing medications	-No statistically significant difference in adherence between groups. Improvement in K10 score for both groups indicated improvement in depressive symptoms but no significant difference between groups. -No significant difference between groups in improvement of Drug Attitude Index.

	Sample size	Study design	Intervention	Results
Rickles et al, 2005 (61)	Depression N = 60, 28 (Interventio n group); 32 (control group)	Randomized controlled trial (3 month intervention period with 5 month follow-up)	Pharmacists called patients in intervention group once monthly for 3 months to provide pharmacist-guided education and monitoring (PGEM)	-The intervention group was significantly more likely to provide feedback to the pharmacist regarding their medication therapy (FPFP score of 23 for intervention group vs. 11 for control group, p<0.001). -The rate of missed doses for the intervention group was significantly lower than for the control group, but this finding was not significant in an ITT analysis, which included patients who did not complete the study. -The intervention had a significant impact on antidepressant knowledge, beliefs about antidepressants, and awareness of treatment progress. -No significant difference in improvement of depression symptoms between the intervention and control groups based on BDI-II scores; however, both groups showed significant improvement in symptoms (p≤0.001).
Caballero et al, 2008 (44)	Various psychiatric illnesses- most common reasons for referral to clinic included depression, dementia/	Naturalistic review (15 months)	Pharmacist consulted with PCP regarding therapy for psychiatric disorders, provided patient education and drug therapy management until therapy was optimized	-Physician or medical director accepted over 90% of pharmacist's clinical recommendations. -After 5.6 weeks of active treatment, patients who were treated for depression or anxiety had a mean decrease in depression and anxiety symptoms as measured by HAM-D or HAM-A scores (Decreases of 52% and 56%, respectively).

	Sample size	Study design	Intervention	Results
	cognitive impairment, anxiety and insomnia N=96			-After 7.7 weeks, patients who were treated for cognitive impairment/dementia had a mean decrease of MMSE scores by 1.4 points, indicating decline in cognitive function. -All patients who were treated for insomnia reported improvements in sleep. -Estimated cost savings generated by the clinic over the 15-month period: $22,380.
Hare et al, 2008 (70)	Depression N = 18	Uncontrolled study (1 day)	Pharmacists used the HANDS screening tool for depression, assessed and discussed results with patients, and referred patients to PCP or emergency department as needed	-Recommendations were made to 6 of the patients (33%) regarding follow-up with PCP for further evaluation and/or continuing current treatment for depression. -One patient transported to emergency department for active suicidal thoughts. -Fourteen patients were found unlikely to have major depression, 3 patients had symptoms consistent with major depression, and 1 patient had symptoms strongly consistent with major depression. -After the screenings, 88% of participants felt “satisfied” or “very satisfied.”

	Sample size	Study design	Intervention	Results
Knight et al, 2008 (71)	Depression N = 45	Retrospective chart review (4 months)	Patients were screened for depression using the Zung self-rating Depression Scale (SDS)	-Of the 12 patients with current diagnoses of depression, 25% were adequately treated, 50% were undertreated, and 25% were not treated at all. -Of the 33 patients without a current diagnosis of depression, 48% screened positive.
Caley et al, 2010 (72)	Patients with various psychiatric illnesses- most commonly depression or anxiety N=27	Retrospective chart review (16 months)	Clinical pharmacists consulted with nurse practitioners, answered drug information questions, provided educational services to staff, and participated in direct consultations with patients.	-88% of pharmacist recommendations were accepted and implemented.
Gable et al, 2010 (73)	Various psychiatric illnesses N=34	Retrospective chart review (6 months)	Clinical pharmacist joined an Assertive Community Treatment (ACT) team. Interventions included: patient education, monitoring of lab results and adverse effects, and making therapeutic recommendations to ACT team for both mental and physical health issues	-100% of recommendations made by pharmacist regarding medication therapy were accepted and implemented.

	Sample size	Study design	Intervention	Results
Marino et al, 2010 (45)	Various psychiatric disorders N = 2,220 intervention	Retrospective chart review (18 months)	Pharmacists clarified orders, formulary conversion, dose recommendations/ adjustments, therapeutic recommendations and lab monitoring	-Estimated cost savings of $125,500 for the 18-month time frame. -Overall acceptance rate of interventions of 98.8%. -Acceptance rates for faculty clinical pharmacists, hospital staff pharmacists, and student pharmacists were 97.7%, 99.8% and 87.5%, respectively.
Finley, et al (2011) (43)	Depression N=130	Prospective non-randomized cohort (18 months)	Pharmacists met face-to-face with patients for evaluation and management of medication therapy and patient education	-Patients had clinically significant improvement in PHQ-9 score indicating improvement in depressive symptoms ($p< 0.0001$). -Estimated total savings for employer of $41,881 per year for the 48 enrollees who were evaluated.
Suehs et al, 2011 (63)	Various psychiatric disorders N=105	Retrospective chart review (9 months)	Pharmacists made recommendations, including initiation of new medication therapy, discontinuing current medications, or obtaining labs	-About 67% of pharmacist recommendations were accepted. -Statistically significant correlation between improved CGI-S scores and higher rates of implementation of pharmacist recommendations ($p=0.036$) indicating improvement of symptoms. -Correlation between pharmacist recommendation implementation and improved CGI-I scores not statistically significant.

	Sample size	Study design	Intervention	Results
Wang I et al, 2011 (64)	Various psychiatric illnesses N=36	Uncontrolled study (7 months)	Pharmacist met with patients for patient education, monitoring of therapeutic effect and adverse effects, and administration of rating scales. Treatment plan was collaborative effort between pharmacist and PCP	-Two patients reached remission from depression -Almost 77% of patients showed clinical improvement. -The mean change in PHQ-9 score from baseline to 7 months was -5.7 ±5.7 (p=0.02).
Valenstein M et al, 2011(65)	Schizophrenia, schizoaffective disorder, bipolar disorder N =118 58 (Intervention group); 60 (control group)	Randomized controlled trial (12 months)	Patients in Meds-Help intervention group received unit of use packaging for all medications, an educational session, and refill reminders 2 weeks before refills were due. Clinicians were notified if refills were not picked up on time. Educational medication session was conducted by pharmacist	-intervention group (Meds-Help patients) had significantly higher medication possession ratios (MPRs) at 6 and 12 months from baseline indicating that the intervention group had improved adherence to medication therapy -There were no significant differences between groups in improvement of symptoms, based on PANSS scores. -No significant differences between groups in quality of wellbeing, based on QWB scores. -No significant difference between groups in patient satisfaction based on CSQ-8 scores

	Sample size	Study design	Intervention	Results
Suehs BT, et al, 2011 (89)	105 patients receiving a pharmacy consult while admitted to the Austin State Hospital	Retrospective study	Completion of consultation pursuant to provider referral	A total of 105 pharmacy consultations and associated physician progress notes were reviewed. Overall, 73% of the primary consultation recommendations were implemented. The most common reasons for referral to the psychopharmacology service were nonresponse to treatment and aggression. Patients with high implementation of consultation recommendations displayed more favorable endpoint CGI-S scores and displayed a greater CGI-I response rate compared with patients with low implementation of consult recommendations. Implementing clinical pharmacists' consult recommendations was associated with significantly greater improvement in oVerall severity of illness and global improvement. This study supports the positive role that pharmacists have in optimizing patient care and clinical outcomes.

	Sample size	Study design	Intervention	Results
Tallian KB et al, 2012 (46)	68	Descriptive	provided direct patient care using a collaborative practice protocol 3 days per week	- 82.3% of patients were clinically stable and remained on the pharmacist caseload. -billed for pharmacist medication management based on face-to-face contact time (medication minutes) and documentation time with each patient - On average, patients had 7.7 patient visits, for 491 total visits (with an average of 26 minutes per visit) that were billed at a rate of $4.82 per minute for medication minutes, translating to $84,542.80.
Aljumah K, et al, 2015 (66)	MDD Intervention gr (n=119) Control gr (n=120)	a randomised controlled study with a 6-month follow-up	Participants were randomly allocated to two groups: 1) intervention group (IG) (usual pharmacy services plus pharmacist interventions based on shared decision making); or 2) control group (CG) (usual pharmacy services). A research assistant blinded to the group allocations collected all data	After 6 months, patients in the IG had significantly more favorable medication adherence, treatment satisfaction, general overuse beliefs, and specific concern beliefs. However, the groups did not differ in severity of depression or health-related quality of life after 6months.

	Sample size	Study design	Intervention	Results
Klang SH, et al, 2015 (67)	MDD: Community pharmacists (CP) gr (n=143), treatment as usual (TAU) gr (n=12,746)	Prospective Studies	To compare the effectiveness of pharmacist intervention with standard care for patients with MDD	At 1 month, the adherence rate was 71% in the CP arm and at 6 months, the rates were 55% versus published norms of 42% (P=0.004). At 1 month, the adherence rate was 57% (N=7256) in the TAU arm and at 6 months, the rate was 15.2% (N=1934) (compared with CP rates: P<0.0001). There were no differences between sites in adherence rates. This is the first trial of pharmacist adherence support in Israel, and shows benefits for patients in the community with MDD.
Wolf C, et al, 2015 (68)	psychiatric patients that were admitted to a psy-chiatric university hospital. (n=269)	prospective, non-randomized, open, controlled study	comprehensive medication reviews by clinical pharmacists at admission, during the hospital stay, and at discharge	The intervention led to a reduced MAI score by 1.4 points per patient (95% confidence interval [CI]: 0.8–2.0) at discharge and 1.3 points (95% CI: 0.7–1.9) at follow-up compared with controls. The number of unsolved DRP in the intervention group was 1.8 (95% CI: 1.5–2.1) less than in control

	Sample size	Study design	Intervention	Results
Kanjanasilp J, et al, 2016 (48)	schizophrenia from 3 psychiatric hospitals. -intervention group=93 -control group=95	Open label, randomised experimental design using two comparison groups	Intervention group received pharmaceutical care while control group did not.	-The number of DRPs decreased significantly more in the intervention group than in the control group ($p<0.001$). -The mean knowledge score increased greater in the intervention group ($p<0.001$). -The mean QOL score showed a trend towards improvement in the intervention group (both $p<0.001$). -Cost-effectiveness ratios (CER) of pharmaceutical care and usual care for achieving good medication adherence was 16.54 and 16.06 USD/successful patient, respectively and CER for improved QOL was 17.30 and 14.98 USD/successful patient, respectively.

APPENDIX II

Consumer Price Index (CPI)

(Base year = 2011)

BE	AD	CPI (All commodities)	CPI (Medical care)
2543	2000	74.51	88.69
2544	2001	75.71	90.77
2545	2002	76.24	91.90
2546	2003	77.62	93.11
2547	2004	79.76	95.29
2548	2005	83.39	96.87
2549	2006	87.26	97.92
2550	2007	89.21	98.39
2551	2008	94.08	98.92
2552	2009	93.28	99.31
2553	2010	96.33	99.41
2554	2011	100.00	100.00
2555	2012	103.02	100.96
2556	2013	105.27	101.94
2557	2014	107.26	103.36
2558	2015	106.30	104.85

Source: Ministry of commerce

APPENDIX III

Mortality in Thai general population

Reference year: 2013

Age Group (year)	Mortality of dying			Probability of dying
	Female	Male	Total	Total
<1	0.0094800	0.0126410	0.0110605	0.0109996
1-4	0.0004020	0.0004790	0.0004405	0.0004404
5-9	0.0002840	0.0004810	0.0003825	0.0003824
10-14	0.0002840	0.0004740	0.0003790	0.0003789
15-19	0.0004310	0.0012150	0.0008230	0.0008227
20-24	0.0005830	0.0015220	0.0010525	0.0010519
25-29	0.0009200	0.0018340	0.0013770	0.0013761
30-34	0.0012400	0.0022550	0.0017475	0.0017460
35-39	0.0018100	0.0035230	0.0026665	0.0026629
40-44	0.0020760	0.0047000	0.0033880	0.0033823
45-49	0.0025300	0.0055740	0.0040520	0.0040438
50-54	0.0036370	0.007425	0.0055310	0.0055157
55-59	0.0055420	0.0109520	0.0082470	0.0082131
60-64	0.0088860	0.0168870	0.0128865	0.0128038
65-69	0.0147130	0.0268210	0.0207670	0.0205529
70-74	0.0267710	0.0456100	0.0361905	0.0355435
75-79	0.0433550	0.0726580	0.0580065	0.0563562
80-84	0.0634090	0.1009210	0.0821650	0.0788800
85-89	0.0983440	0.142632	0.1204880	0.1135123

Age Group (year)	Mortality of dying			Probability of dying
	Female	Male	Total	Total
90-94	0.1550050	0.2104740	0.1827395	0.1670149
95-99	0.2482750	0.3242840	0.2862795	0.2489473
100+	0.4041130	0.5216750	0.4628940	0.3705406

Source : World Health Organization

(http://apps.who.int/gho/data/?theme=main&vid=61640)

APPENDIX IV

Command for Cost Effectiveness Analysis with Monte Carlo Simulation

```
Index = 0
Do While Index < 1000
    Sheets("Parameter").Select
    Range("D2").Select
    Application.CutCopyMode = False
    ActiveCell.FormulaR1C1 = "1"
    Range("D3").Select
    Sheets("simulation").Select
    Range("C4:I4").Select
    Selection.Copy
    Range("C6").Select
    ActiveCell.Offset(Index, 0).Range("A1").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False
    Sheets("Parameter").Select
    Range("D2").Select
    Application.CutCopyMode = False
    ActiveCell.FormulaR1C1 = "0"
    Range("D3").Select
Index = Index + 1
Loop
End Sub
```

APPENDIX V

Command for Cost Effectiveness Acceptability Curve with Monte Carlo Simulation

```
Index = 0
Do While Index < 61
    Range("R6").Select
    ActiveCell.Offset(Index, 0).Range("A1").Select
    Selection.Copy
    Range("M1").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False
    ActiveSheet.Paste
    Application.CutCopyMode = False
    Range("O4:P4").Select
    Selection.Copy
    Range("S6").Select
    ActiveCell.Offset(Index, 0).Range("A1").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False
    Index = Index + 1
Loop
End Sub
```