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Clinical outcomes of a pharmaceutical care service in lithium clinic adjunct to standard care compared with standard care alone in patients with bipolar disorder: 10 years naturalistic retrospective cohort study

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ABSTRACT

Objective: To compare the long-term clinical outcomes of bipolar patients following lithium maintenance therapy between patients who received standard care plus pharmaceutical care service (lithium clinic group) and patients who received standard care alone (usual care group). **Materials and Methods:** This study was a single-center retrospective cohort study. Clinical outcomes were compared between the lithium clinic (n = 120) and usual care groups (n = 240) between January 2006 and December 2015. **Results and Discussion:** Average study observation time was 6.11 ± 3.14 years. Hospitalization rate due to any recurrence in lithium clinic group was significantly less than usual care group (2.61 cases per 100 patient-years [95% confidence interval (CI), 1.65–4.14]vs. 9.02 cases per 100 patient-years [95% CI, 7.34–11.04], $P < 0.0001$). Furthermore, hospitalization rate from manic recurrence and emergency room visit rate in lithium clinic group (2.60 cases per 100 patient-years [95% CI, 1.64–4.13]and 1.89 cases per 100 patient-years [95% CI, 1.10–3.26], respectively) was significantly lower than usual care group (7.40 cases per 100 patient-years [95% CI, 5.96–9.19]and 7.40 cases per 100 patient-years [95% CI, 5.95–9.20], respectively). Furthermore, lithium clinic group had risk of any recurrence (relative risk [RR]= 0.744, P = 0.02), manic recurrence (RR = 0.613, P = 0.001), and manic admission (RR = 0.439, P = 0.0001) significantly less than usual care group. Median time to manic recurrence was 4.44 (interquartile range [IQR]3.59–5.29) years for lithium clinic group, but 3.54 (IQR 3.08–3.99) years for usual care group. Median 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 groups, respectively. Moreover, the median time to emergency room visit was 5.36 (IQR 4.93–5.80) years in lithium clinic and 4.09 (IQR 3.46–4.72) years in usual care groups. **Conclusion:** Lithium clinic group had better long-term clinical outcomes than usual care group. Therefore, pharmaceutical care in bipolar disorder patients is beneficial and should be implemented for other psychiatric hospitals.

INTRODUCTION

Bipolar disorder is a severe long-term mental disorder which is prevalent in up to 2% of the population.[1] Bipolar disorder is stated to be the sixth leading cause of disability worldwide among patients ages 15–44, and annual treatment and medication costs for bipolar patients were recently estimated to be more than $17,000 each.[2] The bipolar disorder characteristic presents as episodic hypomania or mania which alternates with depressive episodes. About 70% of bipolar patients experience >1 recurrence during 4 years of their index episode. Unfortunately, these high recurrence rates, together

with impairment and symptomatic illness are frequently reported even in bipolar patients on pharmacotherapy.[3]

To prevent recurrence, many pharmacological interventions have been suggested.[3] The first line pharmacotherapy treatment for bipolar disorder is lithium which prevents exacerbation of acute mood episodes, suicide and switching to another pole. Lithium had proven to avert both manic and depressive recurrence in long-term treatment.[4] However, lithium is more effective in averting manic recurrence than depressive recurrence.[5] Risk of early recurrence of bipolar illness, particularly of mania, is evidently increased following discontinuation of lithium use.[6] Therefore, adherence to lithium therapy is vital for preventing recurrence in these patients.

Lithium's clinical use shows an extremely narrow therapeutic range. In addition, lithium has many characteristics such as individual absorption variation, dose-dependent efficacy as well as excretion and distribution. Lithium level can be varied by many factors such as medication-related changes in lithium excretion, medical illness, non-compliance, and dietary changes. Therefore, monitoring of serum lithium concentration is beneficial both in efficacy and safety vigilance.

Pharmaceutical care involves responsible drug therapy provision to achieve specific outcomes to improve patient's quality of life.[7] Pharmaceutical care for psychiatric patients has been applied in several clinical settings.

The lithium clinic of Somdet Chaopraya Institute of Psychiatry, the first lithium clinic in Thailand, is a pharmacist-run lithium clinic. It has been established for more than 10 years. However, there has been no analysis to date of long-term outcomes of the pharmaceutical care service provided. This study will provide decision makers with beneficial information for the evaluation of any proposed intervention plan and may be generalized to other psychiatric hospitals.

MATERIALS AND METHODS

Study Design

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 standard care (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).

Study Population

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

The inclusion criteria were as follows:

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

The exclusion criteria were as follows:

a. 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.
b. Patient who received non-pharmacologic treatment during the study period such as psychotherapy and cognitive behavior therapy.
c. Patient who was diagnosed as mixed episodes or rapid cycling bipolar disorder.

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 the 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 age and gender. For each case of lithium clinic group, an age- and gender-matched usual care group was identified from hospital database. The criteria for matching required that the age of each case of usual care group was within 5 years of their matched case of lithium clinic group. Usual care group subjects were selected by computerized random number generator from the pool of matches if more than 1 qualified patient were available. The present sample size was 120 subjects for lithium clinic group and 240 subjects for usual care group, with significance being set at $P = 0.05$.

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 in the lithium clinic. Usual care group received only standard care treatment without activities of pharmaceutical care service. Details of intervention were shown in Table 1.

Calendar Time and Study Time

This study started accrual on January 1, 2006, and accrued for 7 years until December 31, 2012, with an additional 3 years of follow-up ending on December 31, 2015. The study period was between January 1, 2006 and December 31 2015 [Figure 1].

Index date of each patient could happen anytime during accrual period. Index date was defined as the date of recruiting subject into the study. The study observation period of each patient was time between index date and end of observation

Table 1: Intervention for lithium clinic and usual care group

Intervention	Lithium clinic group	Usual care group
Standard care		
Standard pharmacologic treatment	✓	✓
Pharmaceutical care activities		
Reviewing patient's medication profile to identify, prevent and correct drug therapy problems which might occur in the treatment regimen	✓	
Writing up consultation with the patient and transferring them to the psychiatrist for making medication and treatment plan	✓	
Counseling patient about the importance 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	✓	
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 serum 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	✓	

date. Events which happened during the observation period were counted for analysis.

Study completion

Patients were recruited to this study in bipolar stable phase. From this phase, they could remain in the stable phase, or could recur to manic, or depressive episode. Patients who had recurrence might be hospitalized or not depending on their severity as shown in Figure 2.

The observation for each subject could end anytime in the study period if the patient met the end of study criteria. All events, including manic episode, depressive 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 observation period. If one of them ended the study, the observation period of the rest also stopped. The outcomes were measured based on this duration.

Outcomes

The primary outcome of this study was hospitalization rate from any recurrence because it represents the efficacy of this pharmaceutical intervention for long-term prevention of any new mood episode. The other outcomes including hospitalization rate due to manic recurrence, hospitalization rate due to depressive recurrence, time to event, and relative risk were measured as the secondary outcomes of the study.

Assessment

Recurrence criteria

Recurrence in this study was defined as a new acute mood episode (manic or depressive episode) meeting DSM-IV

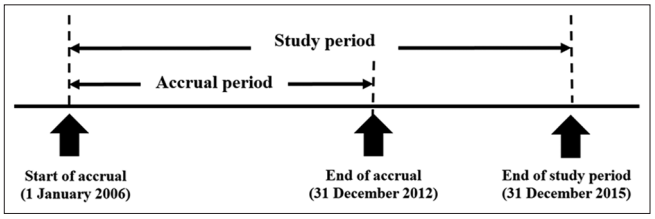

Figure 1: Calendar time and study time

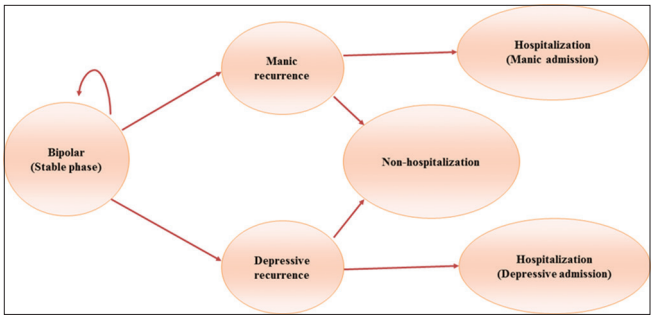

Figure 2: Disease state for bipolar patient

symptom and duration criteria. If data in outpatient medical records were not clearly identified, the psychiatrist would make a decision whether the patients met the recurrence criteria or not.

Hospitalization rate was total number of hospitalizations in a specific period.

Accrual period (or recruitment period) was the period during which subjects were being enrolled (recruited) into a study.

Observation period was the period that each subject entered the study until ending the observation. The observation

for each subject could end at any time in the study period if the patient met the end of study criteria.

End of study criteria for each patient was the ending conditions including completed study period, lost to follow-up, stopped taking lithium, or referred to another hospital.

The analysis on recurrence subgroup for this study indicated the efficacy or treatment effect of a pharmaceutical care service for preventing hospitalization in a group of patients who recur new mood episodes.

Sample size estimation

Primary outcome measure of this study was hospitalization rate. To compare hospitalization rate between lithium clinic and usual care group, the sample size should be estimated by using Chi-square test on proportions. We calculated sample sizes of this study using sample size estimation program from http://biomath.info/power. The previous study on the effectiveness of lithium clinic showed that patients who attended in lithium clinic had been hospitalized less than that one in control group. The proportion of hospitalization in lithium clinic group was 1.25% and the proportion of hospitalization in usual care group was 11.25%.[8] Regarding this program for sample size estimation, for alpha was 0.05, power was 0.80, and ratio of usual care group/lithium clinic group was 2:1, the number of patients for lithium clinic group was at least 88 cases, and number of patients for usual care group was at least 176 cases. For this study, sample sizes of lithium clinic and usual care groups were 120 and 240 cases, respectively, which were greater than the suggested sample size.

Statistical Analysis

The demographic characteristics at baseline included age at index date, age at first diagnosis, gender, follow-up time and preexisting comorbid condition which 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. Incidence rates (hospitalization rate, emergency room visit rate, and lithium intoxication admission rate) were compared by Pearson's Chi-square test. Overall, survival function and time to event were performed by survival analysis using log-rank test and Cox-proportional hazards. Relative risk of recurrence and hospitalization was compared between lithium clinic and usual care group. Relative risk was estimated both from bipolar stable phase group and recurrence subgroup (manic recurrence and depressive recurrence subgroups). The statistical significance for these tests was set at $P < 0.05$.

RESULTS

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 two groups of patients, 120 patients in lithium clinic group and 240 patients for usual care group.

Study observation time of each patient in this research varied from 0.25 to 10 years according to when they entered and ended the study. The average study observation time was equal for both groups. There were no significant differences between demographic characteristics between lithium clinic groups and usual care group as shown in Table 2.

Hospitalization rate due to any recurrence in lithium clinic group was significantly less than usual care group. Moreover, hospitalization rate from manic recurrence in lithium clinic group was significantly lower than usual care group. In addition, emergency room visiting rate in lithium clinic group was significantly less than usual care as shown in Table 3.

Regarding patients with bipolar disorder in a stable phase, lithium clinic group was associated with a lower risk of any recurrence, risk of manic recurrence, and risk of hospitalization due to manic recurrence (manic admission). However, there

Table 2: Demographic and baseline characteristics of participants

Characteristics	Lithium clinic group (*n*=120)	Usual care group (*n*=240)	*P* value
Age at index, mean±SD, year	46.25±10.70	45.06±10.57	0.316[a]
Age at first diagnosis, mean±SD, year	30.67±10.24	29.92±10.38	0.518[a]
Male sex, No. (%)	74 (61.7)	148 (61.7)	1.000[b]
Study observation time, mean±SD, year	6.11±3.14	6.11±3.14	1.000[a]
Pre-existing comorbid conditions, No. (%)			
Diabetes mellitus	17 (14.2)	42 (17.5)	0.421[b]
Hypertension	28 (23.3)	51 (21.3)	0.653[b]
Renal disease	2 (1.7)	2 (0.8)	0.477[b]
Gout	4 (3.3)	4 (1.7)	0.312[b]
Asthma	2 (1.7)	5 (2.1)	0.787[b]
Hypothyroidism	2 (1.7)	2 (0.8)	0.477[b]

SD: Standard deviation. [a]Statistical test: *P* value from independent samples *t*-test. [b]Statistical test: *P* value from Pearson's Chi-square test

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 recurrence subgroups, patients in lithium clinic group had a risk of hospitalization significantly less than usual care group both for manic recurrence subgroup and depressive recurrence subgroup as presented in Table 4.

Time to Event

Survival analysis of patients remaining in stable phase for each condition was shown in Table 5. Median time to manic recurrence, median time to manic admission, and median time to emergency room visit for lithium clinic group were significantly longer than for usual care group.

As shown in Figures 3-5, the survival curve for lithium clinic group and usual care group was significantly different for overall survival distribution in manic recurrence, manic admission and manic admission in a specific subgroup (manic recurrence subgroup). Patients in lithium clinic group had lower risk of manic recurrence (Hazard ratio [HR]= 0.504, 95% confidence interval [CI]0.343–0.740, $P < 0.001$), manic admission (HR = 0.368, 95% CI 0.220–0.613, $P < 0.001$), and hospitalization in manic recurrence subgroup (HR = 0.489, 95% CI 0.293–0.816, $P = 0.006$).

Table 3: Crude overall incidence rates between lithium clinic and usual care group (per 100 patient-years)

Incidence rate	Lithium clinic group (*n*=120)		Usual care group (*n*=240)		*P* value[a]
	Rate	95% CI	Rate	95% CI	
Hospitalization rate					
Any recurrence	2.61	1.65–4.14	9.02	7.34–11.04	<0.0001
Manic recurrence	2.60	1.64–4.13	7.40	5.96–9.19	<0.001
Depressive recurrence	0.41	0.13–1.27	1.07	0.64–1.77	0.057
ER visit rate	1.89	1.10–3.26	7.40	5.95–9.20	<0.0001
Lithium intoxication admission rate	0.14	0.02–0.97	0.49	0.23–1.02	0.113

ER: Emergency room, CI: Confidence interval. [a]Statistical test: *P* value from Pearson's Chi-square test

Table 4: Relative risk of recurrence and hospitalization associated with attending and non-attending a pharmaceutical care service in lithium clinic

Clinical variables	Lithium clinic group (*n*=120)	Usual care group (*n*=240)	RR	ARR	*P* value[a]
Bipolar stable phase					
Any recurrence, No. (%)	45 (37.5)	121 (50.4)	0.744	0.129	0.020*
Manic recurrence, No. (%)	34 (28.3)	111 (46.3)	0.613	0.180	0.001*
Depressive recurrence, No. (%)	15 (12.5)	24 (10.0)	1.250	(0.025)	0.472
Hospitalization due to manic recurrence, No. (%)	18 (15.0)	82 (34.2)	0.439	0.192	0.0001*
Hospitalization due to depressive recurrence, No. (%)	3 (2.5)	15 (6.3)	0.400	0.038	0.124
Recurrence subgroup	(*n*=34)	(*n*=111)			
Hospitalization in manic recurrence subgroup, No. (%)	18 (52.9)	82 (73.9)	0.717	0.210	0.021*
	(*n*=15)	(*n*=24)			
Hospitalization in depressive recurrence subgroup, No. (%)	3 (20.0)	15 (62.5)	0.320	0.425	0.010*

RR: Relative risk, ARR: Absolute risk reduction. [a]Statistical test: *P* value from Pearson's Chi-square test

Table 5: Time to events between lithium clinic and usual care group

Time to events	Lithium clinic group (*n*=120)		Usual care group (*n*=240)		*P* value[a]
	Median	IQR	Median	IQR	
Time to manic recurrence, year	4.44	3.59–5.29	3.54	3.08–3.99	0.013*
Time to depressive recurrence, year	5.36	4.87–5.86	5.33	4.95–5.70	0.957
Time to manic admission, year	5.36	4.81–5.92	3.98	3.21–4.76	0.012*
Time to depressive admission, year	5.73	4.73–6.72	5.45	5.10–5.80	0.561
Time to ER visit, year	5.36	4.93–5.80	4.09	3.46–4.72	0.012*

IQR: Interquartile range, ER: Emergency room. [a]Statistical test: *P* value from Cox-proportional hazards

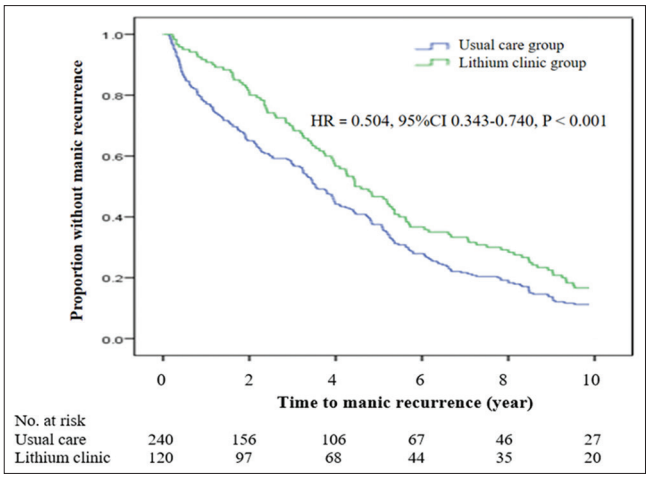

Figure 3: Survival curve for manic recurrence in bipolar stable phase

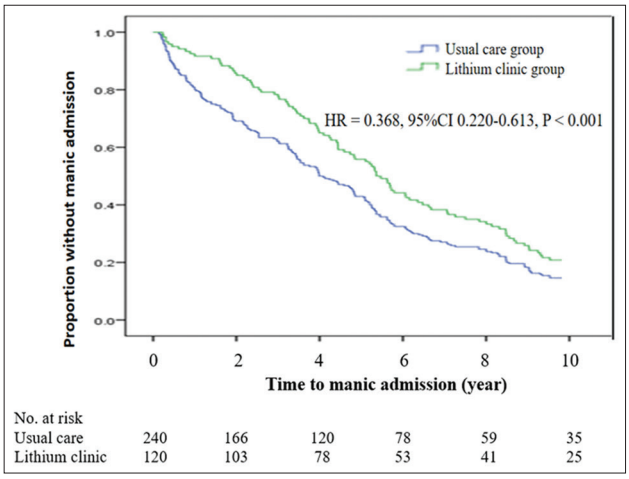

Figure 4: Hospitalization due to manic recurrence in bipolar stable phase

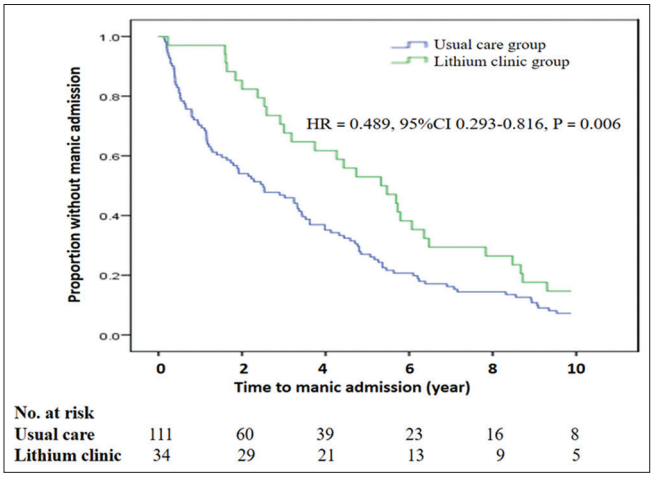

Figure 5: Hospitalization in manic recurrence subgroup

However, there were no significant differences for depressive recurrence and depressive admission between both groups.

DISCUSSION

The role of the pharmacist for psychiatric patients has evolved over the past few years from primarily drug distribution and centralized drug monitoring to a more direct role. As a result, a pharmacist has become involved in designing and monitoring treatment plans and make pharmacotherapy recommendations. Pharmaceutical care for psychiatric patients has been applied in several settings. Previous studies about the psychiatric pharmacy services effects on clinical outcomes for acute care psychiatric inpatients discovered that pharmaceutical service provision correlated with clinical response improvement.[9] In addition, other studies showed that clinical pharmacist impact on psychiatric patients included patient compliance improvement, improved adverse effect monitoring, cost savings, fewer unnecessary drugs, reduction in number of hospitalizations, improvement in patient satisfaction and functioning. Moreover, pharmaceutical care has shown 2.8% reduction in overall hospitalizations.[9-11]

Specialized lithium clinics operate in several clinical settings.[12-19] Of these, just three settings have given pharmaceutical care service.[13,15,17] Results from these three lithium clinics have suggested their usefulness and have been recommended for other psychiatric settings. The fourth pharmaceutical lithium clinic is the lithium clinic of Somdet Chaopraya Institute of Psychiatry.

Lithium clinic of Somdet Chaopraya Institute of Psychiatry is the first and only lithium clinic in Thailand. It has been established as a pharmacist-run lithium clinic with cooperation of 2 psychiatrists at the outpatient department since October 2000. The first study of this clinic was conducted to determine the effectiveness of the pharmaceutical care process provided to bipolar patients. It was a randomized single-blind controlled study. The eligible cases (n = 60) were randomized into experimental (n = 30) and control groups (n = 30) which were followed up at 1 month intervals for four visits. The results found that pharmaceutical care given to bipolar patients using lithium as maintenance therapy correlated with decreased drug therapy problems increased patients whose serum lithium concentrations were within therapeutic range and improved patient understanding about lithium usage. However, both groups showed no statistically significant difference in clinical outcomes. The reason that no significant difference was detected might be a small sample size and short study duration.[20] Therefore, our current study examined long-term clinical outcomes of a pharmaceutical care service in this clinic. Clinical outcomes of this study were recurrences which were classified as manic recurrence, depressive recurrence, and hospitalization. Since reduced hospitalization was the ultimate outcome indicating the success of treatment process, this study measured hospitalization instead of drug-related problems which were intermediate outcomes as in the previous studies which were conducted.

Hospitalization rates, due to any recurrence and due to manic recurrence, and emergency room visit rate of lithium clinic group were lower than usual care group. Providing a pharmaceutical care service for this study including the pharmaceutical activities in Table 1 might increase patient awareness in medication adherence, increase appropriate regimen design, increase lithium concentration within the

therapeutic range and decrease adverse drug reactions. All these reasons contributed to a better outcome for the lithium clinic group.

The outcomes of this study were aligned with the previous study which revealed that pharmaceutical care significantly reduced hospitalizations and emergency service consultations in outpatients with bipolar I disorder.[21] Moreover, a study of short-term outcomes of pharmaceutical care in Thai patients with schizophrenia showed that pharmaceutical care could increase adherence score significantly.[22]

For this study, it implied that patients in the lithium clinic group had medication adherence higher than usual care group and they had serum lithium concentration within therapeutic range more than the usual care group. The results of this study showed that the lithium clinic group was associated with a lower risk of any recurrence, risk of manic recurrence, and risk of hospitalization due to manic recurrence (manic admission). 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. It could be explained that although lithium was evidently preventing both manic and depressive recurrence in long-term treatment,[4] it was more effective in preventing manic recurrence than depressive recurrence.[5]

Lithium clinic group was associated with an absolute risk reduction (ARR) of any recurrence, manic recurrence, hospitalization due to manic recurrence (manic admission), hospitalization in manic recurrence subgroup, and hospitalization in depressive recurrence subgroup by 12.9%, 18%, 19.2%, 21%, and 42.5%, respectively. There was marked a reduction in the risk of hospitalization in recurrence subgroups. These results showed that even though patients had a recurrence, some patients in lithium clinic still did not require hospitalization treatment. It showed that a pharmaceutical care service had an impact on preventing hospitalization both for manic and depressive recurrence subgroups. Numbers needed to treat for preventing any recurrence, manic recurrence, hospitalization due to manic recurrence, hospitalization in manic recurrence subgroup and hospitalization in depressive recurrence subgroup of lithium clinic group compared to the usual care group were 7.75, 5.56, 5.21, 4.76, and 2.35, respectively. In addition, this intervention seemed to lengthen the time to manic recurrence, time to manic admission and time to emergency room visit by 0.9, 1.38, and 1.27 years, respectively.

Although lithium intoxication admission rate was not significantly different, lithium clinic group tended to have lower rate than usual care group (0.14 cases per 100 patient-years [95% CI, 0.02–0.97]vs. 0.49 cases per 100 patient-years [95% CI 0.23–1.02]for the lithium clinic and the usual care group, respectively). The insignificant difference might be explained that Somdet Chaopraya Institute of Psychiatry is the tertiary care psychiatric hospital. When the patient occurred lithium intoxication, most of them preferred to go to the general hospital. Therefore, data about lithium intoxication might be under-recorded in the medical record if they did not report this event to the psychiatrist when they went to the hospital after the event. Thus, the incidence of lithium intoxication in psychiatric hospital might be underreported.

Limitations and Suggestions

All data of this retrospective cohort study were obtained from medical records and hospital database. Some data were absent due to incomplete recording in medical records. Moreover, some existing data were subjective statements which did not have enough detail for analysis. This subjective statement might cause underestimated or overestimated results. In addition, some patients did not provide important information to their psychiatrist such as treatment of lithium intoxication from other hospitals.

This study focused on long-term clinical outcomes. Further study on the long-term economic outcome of a pharmaceutical care service in this clinic should be conducted to evaluate the cost-effectiveness of this intervention.

CONCLUSION

Patients in lithium clinic group had more favorable clinical outcomes than patients in usual care group in the following parameters; hospitalization rate due to any recurrence, hospitalization rate due to manic recurrence, emergency room visit rate, risk of any recurrence, risk of manic recurrence, risk of manic admission, time to any recurrence, time to manic recurrence, and time to manic admission. Therefore, pharmaceutical care in patients with bipolar disorder is beneficial and should be implemented in other psychiatric hospitals.

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