Psychiatria Danubina, 2016; Vol. 28, No. 2, pp 146-153 *Original paper*

LONG TERM USE OF LITHIUM AND FACTORS ASSOCIATED WITH TREATMENT RESPONSE AMONG PATIENTS WITH BIPOLAR DISORDER

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received: 4.8.2015; revised: 14.1.2016; accepted: 10.3.2016

SUMMARY

Background: *Lithium has been the gold standard in treating bipolar disorder. In recent years, the use of lithium seems to be diminished although it is well tolerated among the bipolar disorder patients.*

Subjects and methods: *This study aimed to evaluate the efficacy and tolerability of lithium as well as to determine factors associated with lithium response among patient with bipolar disorder. A retrospective study was done in a tertiary care hospital in Malaysia which included 47 bipolar disorder patients that were prescribed with lithium maintenance therapy in the time frame of January 2009 until December 2013.*

Results: *Of all the baseline characteristics tested, only psychotic feature differentiated lithium monotherapy group and combination therapy group significantly (χ^2=4.732, p=0.03). When compared to period before lithium maintenance, all outcome measures (i.e. annual relapse rate, proportion time spent ill and duration of mood episode) showed significant improvement after lithium maintenance in both treatment groups. Lithium discontinuation only occurred in five cases of adverse effects. Predominant depressive mood episode before lithium maintenance (OR=0.159, p=0.033) and first euthymic interval after lithium maintenance (OR=1.109, p=0.047) significantly predicted lithium response.*

Discussion: *Lithium significantly reduced the frequency and time spent in relapse in patients with bipolar disorder. Predominant depressive mood polarity before lithium maintenance and longer first euthymic interval after lithium maintenance had been identified to predict lithium response significantly.*

Key words: *lithium - bipolar disorder – response - relapse rate - predominant depressive mood episode*

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INTRODUCTION

Bipolar disorder is one of the top five most important causes of disability among adolescents and young adult and gives a substantial impact on the aspect of academic achievement and career ambition in a patient's life (Gore et al. 2011, Laxman et al. 2008). Lithium has been the gold standard in treating bipolar disorder for half a decade (Gershon et al. 2009). For long term prophylaxis of bipolar disorder, lithium was found to reduce 2.6-fold of mood episodes per year and lessen time spent ill by 2.5-fold (Tondo et al. 1998). Lithium prolonged duration of relapse free survival by five-fold when compared to discontinuation of lithium (Biel et al. 2007). Manic phase of relapse generally responded well to lithium, however, the efficacy of lithium in depressive phase was mixed and less robust (Geddes et al. 2004). When looking at anti-suicidal efficacy, it was found that it reduced suicide risk by 80% when continued for 18 months in both unipolar and bipolar depressive disorder (Baldessarini et al. 2006).

Adverse effect was the main concern with lithium use. The most common adverse effects that resulted in discontinuation of lithium was related to nausea, diarrhoea, polyuria, polydipsia and tremors (Calabrese et al. 2005). Several factors had been reported to be associated with good lithium response, this included: older age of disease onset, early onset of treatment, shorter lifetime inter-episode duration, longer first inter-episode duration after lithium was started, higher morbidity burden (i.e. frequency and time spent in relapse) before lithium maintenance and shorter latency to lithium treatment (Tondo et al. 2001). Although lithium had a long history in treating bipolar disorder, in recent years the reported response to lithium in bipolar disorder has declined due to emergence of newer agents. Factors such as multiple previous depressive episode prior to lithium, psychosocial stress and lower social support will also influence lithium response (Kulhara et al. 1999). Patients with psychotic feature, mixed state, substance abuse and those who required additional adjunct antipsychotic were also found to be significantly less likely to respond to lithium (Baldessarini & Tondo 2000). Nevertheless, factors such as lower admission rate prior to lithium use, episodic course of mood episode and older age of disease onset had shown more consistent result in predicting positive lithium response (Tighe et al. 2011)

Lithium response also linked to genetic variations as response to lithium had been reported to differ across ethnicity (Bhugra & Bhui 1999). One genome-wide association study of the response to lithium to prevent recurrence of symptoms of bipolar disorder conducted in individuals of European descent indicated that a

positive response might be linked to a variation in a gene encoding a glutamate receptor (Chen et al. 2014; Mohamed Saini et al. 2014). Hence, this raises the doubt on the efficacy and tolerability of long term lithium prophylaxis among local population and also it give rise to an interest to find out factors that can predict lithium response for long term treatment of bipolar disorder in local setting. Therefore, our study aimed to evaluate the efficacy and tolerability of lithium in long term maintenance of bipolar disorder; as well as to determine factors associated with lithium response.

SUBJECTS AND METHODS

A retrospective study was conducted at a tertiary care hospital in Malaysia. Adult patients diagnosed with bipolar disorder and prescribed with lithium as maintenance treatment for at least six months and above in the time frame of January 2009 until December 2013 were included in this study. It was estimated that a minimum total of 32 subjects were required to achieve power of study of 80% and level of significance of 0.05. Pertinent data including current age, age of illness onset, gender, race, family history of mental illness, duration on lithium, concurrent medication histories, duration and frequency of each mood episode, polarity of each mood episode, euthymic interval, frequency of hospitalization, frequency of suicidal attempt, presence of psychotic feature, presence of mixed episode, presence of rapid cycling, adverse effects related to lithium use and lithium serum level were obtained from the medical records.

Those patients with incomplete record, considered non-compliant i.e. stated in medical record or serum concentration was undetectable during follow up, defaulted follow up after starting lithium maintenance or without previous mood episode prior to the index episode where lithium was started were excluded. Patients were also excluded if they were prescribed with nonsteroidal anti-inflammatory drug, angiotensin-converting enzyme inhibitor, diuretic and any other drug that known to affect lithium levels during the follow up period. For patients without previous mood episode before lithium maintenance was started, no comparison could be made to assess the efficacy in preventing relapse. Therefore, patient with such condition were also excluded from study. This study was approved by the Research Ethics Committee of University Kebangsaan Malaysia (UKM 1.5.3.5/244/NF-012-14).

For the study of clinical outcome measures, a cut-off point of six months on lithium maintenance was used to ensure the selected patient has been stabilized on lithium maintenance therapy (Biel et al. 2007). For this reason, the relapse frequency and time spent in relapse during the first six months after lithium maintenance was started were not taken into consideration. All clinical outcome measures were only taken into consideration from the seventh month onwards from the day of remission from index episode where lithium was started. Data before lithium maintenance were collected from onset of diagnosis until the first mood episode where lithium maintenance treatment was started. Lithium monotherapy indicated the use of lithium only during maintenance phase, the use of as needed psychotropic drugs such as hypnotic agent was allowed. Meanwhile, lithium combination therapy referred to combination of lithium with one or more of the mood altering drugs such as anticonvulsant, antipsychotics and antidepressants that was continued beyond six months after the acute mood episode. Responder in present study was defined as at least 50% or more improvement in proportion of time spent ill in relative to period before lithium maintenance. Data before lithium maintenance were collected from onset of diagnosis until the index mood episode where lithium maintenance treatment was started. Data during lithium maintenance were collected after lithium maintenance treatment was started until the day lithium was stopped or end of study period.

For serum lithium level, only level measured during maintenance phase was taken into consideration. Level measured during acute mood episode and level measured when there was any drug-drug or drug-disease interaction was not included. An average of the measured level during maintenance phase was calculated for each subject. For adverse effects, it was the judgment of the treating psychiatrist to discern whether the adverse effects was due to the use of lithium based on the classification of “certain”, “probable”, “possible” and “unlikely” used by Malaysian Adverse Drug Reactions Advisory Committee (MADRAC 2012) adverse effect reporting form.

The outcome measures collected were annual relapse rate, proportion of time spent ill, duration of each mood episode, annual hospitalization rate and annual suicidal rate. Annual relapse rate referred to the average frequency of manic or hypomanic and depressive mood episode per year. Proportion of time spent ill referred to the percentage of time spent in manic or hypomanic and depressive mood episode. Duration of mood episode indicated the median duration for each mood episode. Annual rate of hospitalization and suicidal attempt measured the frequency of hospitalization and suicidal attempt per year.

Statistical Analysis

SPSS version 21 was used to perform statistical analysis. Shapiro-Wilks test was used to test data normality. Descriptive analysis was used for the analyses of lithium prescribing trend, prevalence of adverse effects, hospitalization rate and suicidal attempt rate. For overall demographic data, categorical data was compared using chi-square test or Fisher exact test; continuous data was compared using t-test or Mann-Whitney U test. Baseline morbidity burden and clinical outcome during lithium maintenance was compared between monotherapy

group and lithium combination group using Mann-Whitney U test. For the analysis of various clinical outcomes measures before and during Lithium use, Wilcoxon Signed Rank Test was used. Preliminary analyses using Chi-square test for association and Spearman's correlation test were performed to identify potential independent variables to be included in the logistic regression model. A multivariate logistic analysis model was created from independent variables that had a significance level of $p<0.10$. All statistical tests were two tailed at significance level of $p<0.05$. The power for all tests was 80%.

RESULTS

In total, 47 bipolar disorder patients that were prescribed with lithium maintenance therapy in the time frame of January 2009 until December 2013 were recruited for this study. The mean time before starting lithium maintenance and follow up duration among participants in the monotherapy group were 4 years. For combination group, the median time before starting lithium maintenance was 6.21 years and the follow up lasted for nearly 5 years. Together with lithium, 45.2% (n=14) of participants in this group were also treated

Table 1. Overall demographic data (total n=47)

Variables	Monotherapy (n=16)	Combination (n=31)	Statistics value	p-value
Demographic background				
Gender				
Male	8 (50.00)	11 (35.50)	χ^2=0.923	p=0.337
Female	8 (50.00)	20 (64.50)		
Race				
Malay	9 (56.30)	17(54.80)	χ^2=0.009	p=0.927
Chinese	4 (25.00)	12 (38.70)	χ^2=0.883	p=0.347
Indian	2 (12.50)	2 (6.50)	NA	p=0.597[a]
Others	1 (6.30)	0(0)	NA	p=0.340[a]
Age, years (mean ± SD)	41.25±14.92	42.35±14.10	t=0.250	p=0.804
Age of disease onset, years (median (IQR))	28.5 (17-33)	21 (16-33)	Z=-0.675	p=0.500
Family History				
Bipolar Disorder	3 (18.80)	3 (9.70)	NA	p=0.395[a]
Other mental illness	6 (37.50)	14 (45.20)	χ^2=0.253	p=0.615
No Family History	7 (43.80)	14 (45.20)	χ^2=0.009	p=0.927
Illness Characteristics				
Diagnostics Types				
Bipolar type I	13 (81.30)	23 (74.20)	NA	p=0.725[a]
Bipolar type II	3 (18.80)	8 (25.80)		
With psychotic feature				
Yes	3 (18.80)	16 (51.60)	χ^2=4.732	p=0.030*
No	13 (81.30)	15 (48.40)		
Rapid cycling present				
Yes	2 (12.50)	1 (3.20)	NA	p=0.264[a]
No	14 (87.50)	30 (96.80)		
First episode polarity				
Manic/ Hypomanic	6 (37.50)	13 (41.90)	χ^2=0.086	p=0.769
Depress	10 (62.50)	18 (58.10)		
Predominant mood polarity before lithium maintenance				
Manic > Depress	7 (43.80)	12 (38.70)	χ^2=0.111	p=0.739
Depress > Manic	6 (37.5)	17 (54.80)	χ^2=1.270	p=0.260
Equal	3 (18.80)	2 (6.50)	NA	p=0.320[a]
Suicidal attempt before lithium maintenance				
Yes	4 (25.00)	15 (48.40)	χ^2=2.397	p=0.122
No	12 (75.00)	16 (51.60)		
Background of lithium use				
Latency to lithium treatment, years (median (IQR))	3.48 (1.26-9.12)	6.21 (3.08-9.91)	Z=1.628	p=0.104
Lithium level, mmol/L (median (IQR))	0.72 (0.52-0.77)	0.70 (0.42-0.87)	Z=0.159	p=0.876
Lithium dose, mg/day (mean ± SD)	794.81±279.36	811.68±211.63	t=0.229	p=0.820
Duration on lithium, years (median (IQR))	4.00 (2.16-9.96)	4.81 (1.25-11.19)	Z=-0.225	p=0.822

t = student t test; Z = Mann-Whitney U test; χ^2 = chi-square test; [a] - Fisher exact test; NA = not applicable; IQR = interquartile range; Data were presented as frequency (percentage) unless otherwise stated

with antidepressant, 25.2% (n=8) with typical antipsychotic, 54.9% (n=17) with atypical antipsychotic, 19.4% (n=6) with sodium valproate, 9.7 % (n=3) with lamotrigine and 6.5% (n=2) with carbamazepine. There were 8 participants who had more than two mood stabilizers.

Based on the admission rate of patients with bipolar disorder and trend of lithium maintenance use, it was observed that the use of lithium maintenance was fairly static from year 2009 until 2013 despite of the sharp increment of admission rate from year 2009 to 2013. Comparison between monotherapy and combination group in terms of demographic data, illness characteristics and lithium use background did not show significant difference between groups in all variables except psychotic feature (χ^2=4.732, p=0.03) (Table 1). For baseline morbidity burden (i.e. frequency of relapse, proportion of time spent ill and duration of each mood episode), there was no significant difference between monotherapy group and combination group. During lithium maintenance phase, addition of other mood stabilising drugs in the combination group did not significantly alter the outcome compared to lithium monotherapy (Table 2).

In the mirror study which compared period before and after lithium maintenance in the two treatment groups separately, all outcome measures showed significant improvement compared to period before lithium maintenance with p<0.05 (Table 3). From the total of 35 cases with previous hospitalization before lithium maintenance, there were 23 cases (86.11%) who had improvement in annual hospitalization rate after lithium maintenance and half of the patients had no more further admission with an IQR of 0–0.15. Meanwhile, from total 19 cases with previous suicidal attempt, there were 18 cases (94.74%) had improvement in annual rate of suicidal attempt after lithium maintenance. The most common encountered adverse effect was renal and genitourinary adverse effects (12 cases, 22.22%) (Table 4). Overall, only five cases of lithium discontinuation due to the adverse effects of tremor, polyuria, reduced urinary concentrating ability, drowsiness and rash.

Independent variables pertaining to demographic data, illness characteristics and lithium use were analyzed for association with lithium response in maintenance phase (Table 5). For overall improvement in proportion of time spent ill, predominant depressive mood polarity before lithium use suggested poorer lithium response (χ^2=3.253, p=0.071) but longer first euthymic interval after lithium use was significantly associated with better lithium overall improvement (rs=0.616, p<0.001). In logistic regression model, both of the independent variables tested were statistically significant: first euthymic interval after lithium use (OR=1.109, p=0.047) and predominant depressive mood polarity before lithium use (OR=0.159, p=0.033). The logistic regression model was statistically significant (χ^2(2)=13.574, p=0.001). It explained 37.8% of the variance and correctly classified 78.7% of cases. Although races did not show significant correlation with lithium response in this study, a higher proportion of Chinese (54.50%) in the partial or non-responder group was noted.

Table 2. Comparison between monotherapy and combination lithium therapy (total n=47)

Variables	Before lithium maintenance therapy			After lithium maintenance therapy		
	Monotherapy (n=16)	Combination (n=31)	Stat. value p-value	Monotherapy (n=16)	Combination (n=31)	Stat. value p-value
Annual rate of relapse, episode per year						
Manic/Hypomanic	0.72	0.31	Z=-1.393	0.07	0.10	Z=-0.047
(median (IQR))	(0.18-1.04)	(0.09-0.71)	p=0.164	(0-0.30)	(0-0.24)	p=0.962
Depress	0.47	0.35	Z=-0.203	0	0	Z=-0.848
(median (IQR))	(0.45-0.86)	(0.15-0.78)	p=0.839	(0-0.43)	(0-0.18)	p=0.396
Total	1.10	0.80	Z=-1.336	0.37	0.18	Z=-0.582
(median (IQR))	(0.65-1.73)	(0.55-1.11)	p=0.182	(0.10-0.77)	(0-0.68)	p=0.560
Proportion of time spent ill, % of time						
Manic/Hypomanic	4.32	3.79	Z=-0.674	0.33	0.70	Z=0.294
(median (IQR))	(1.21-12.04)	(0.70-8.14)	p=0.500	(0-3.02)	(0-3.02)	p=0.769
Depress	6.73	5.28	Z=-0.450	0	0	Z=-0.770
(median (IQR))	(0.42-16.85)	(1.07-13.78)	p=0.653	(0-2.97)	(0-0.67)	p=0.441
Total	14.34	8.82	Z=-1.302	2.22	1.75	Z=-0.114
(median (IQR))	(6.81-28.06)	(5.48-15.15)	p=0.193	(0.63-4.50)	(0-6.17)	p=0.909
Episode duration, month						
Manic/Hypomanic	0.79	0.94	Z=0.719	0.49	0.67	Z=0.706
(median (IQR))	(0.54-1.26)	(0.65-1.42)	p=0.472	(0-0.70)	(0-1.24)	p=0.480
Depress	1.36	1.40	Z=-0.056	0	0	Z=-0.613
(median (IQR))	(0.23-2.62)	(0.55-2.20)	p=0.955	(0-0.92)	(0-0.74)	p=0.540
Total	1.34	1.38	Z=-0.472	0.56	0.81	Z=0.548
(median (IQR))	(0.93-2.62)	(0.83-2.40)	p=0.637	(0.12-0.99)	(0-1.33)	p=0.584

Z = Mann-Whitney U test; IQR = Interquartile range; * denotes p<0.05

Table 3. Comparison of clinical outcome before and after lithium maintenance treatment (total n=47)

	Lithium monotherapy			Lithium combination therapy		
Variables	Before (n=16)	After (n=16)	Stat. value p-value	Before (n=31)	After (n=31)	Stat. value p-value
Annual rate of relapse, episode per year						
Manic/ Hypomanic	0.72	0.07	z=-2.642	0.31	0.10	z=-1.968
(median (IQR))	(0.18-1.04)	(0-0.30)	p=0.008*	(0.09-0.71)	(0-0.24)	p=0.049*
Depress	0.47	0	z=-2.201	0.35	0	z=-2.847
(median (IQR))	(0.45-0.86)	(0-0.43)	p=0.028*	(0.15-0.78)	(0-0.18)	p=0.004*
Total	1.10	0.37	z=-3.103	0.80	0.18	z=2.744
(median (IQR))	(0.65-1.73)	(0.01-0.77)	p=0.002*	(0.55-1.11)	(0-0.68)	p=0.006*
Proportion of time spent ill, % of time						
Manic/ Hypomanic	4.32	0.33	z=-2.726	3.79	0.70	z=-2.355
(median (IQR))	(1.21-12.04)	(0-3.02)	p=0.006*	(0.70-8.14)	(0-3.02)	p=0.019*
Depress	6.73	0	z=-2.900	5.28	0	z=-3.003
(median (IQR))	(0.42-16.85)	(0-2.97)	p=0.004*	(1.07-13.78)	(0-0.67)	p=0.003*
Total	14.34	2.22	z=-3.516	8.82	1.75	z=-3.135
(median (IQR))	(6.81-28.06)	(0.63-4.50)	p<0.001*	(5.48-15.15)	(0-6.17)	p=0.002*
Episode duration, month						
Manic/ Hypomanic	0.79	0.49	z=-2.158	0.94	0.67	z=-3.024
(median (IQR))	(0.54-1.26)	(0-0.70)	p=0.031*	(0.65-1.42)	(0-1.24)	p=0.002*
Depress	1.36	0	z=-2.830	1.40	0	z=-4.445
(median (IQR))	(0.23-2.62)	(0-0.92)	p=0.005*	(0.55-2.20)	(0-0.74)	p<0.001*
Total	1.34	0.56	z=-3.516	1.38	0.81	z=-3.175
(median (IQR))	(0.93-2.62)	(0.12-0.99)	p<0.001*	(0.83-2.40)	(0-1.33)	p=0.001*

z = Wilcoxon Signed Rank Test, IQR= Interquartile range; *p<0.05 indicate statistical difference

Table 4. Adverse effects with lithium use and intervention done (n=54)

	Number of event (%)			
System Involved	Reduce dose	Off lithium	Dose continued*	Total
Cardiovascular	1(1.85)	0(0)	0(0)	1(1.85)
CNS	0 (0)	1(1.85)	4(7.41)	5(9.26)
Dermatologic	1 (1.85)	1(1.85)	2(3.70)	4(7.41)
Endocrine & metabolic	0 (0)	0(0)	3(5.56)	3(5.56)
Gastrointestinal	4 (7.41)	0(0)	7(12.96)	11(20.37)
Neuromuscular & skeletal	2 (3.70)	1(1.85)	8(14.81)	11(20.37)
Renal & Genitourinary	2 (3.70)	2(3.70)	8(14.81)	12(22.22)
Ocular	0 (0)	0(0)	0(0)	0(0)
Others	0 (0)	0(0)	0(0)	0(0)
Total case	10	5	32	

* With or without supportive treatment

DISCUSSION

Lithium has been used to treat bipolar disorders for over sixty years as it acts as ant suicidal and neuroprotective drug (Malhi et al. 2013). Although it is well tolerated among the bipolar disorder patients, in recent years, the use of lithium seems to be diminished. A decline in lithium use has been demonstrated by few studies in the USA, Canada, Germany, Switzerland and Austria (Young et al. 2007). On the contrary, the use of lithium was found to be increased in Spain and remains high in England. In our study, the number of patients on lithium maintenance therapy did not change significantly for the past five years even though there was a tremendous increment of admission due to bipolar disorder from year 2010 onwards. This observation indicated that there were a lot more patients were probably discharged with other long term prophylactic drugs. The low usage of lithium was more likely to be explained by the shift in prescribing trend to other alternatives such as sodium valproate and atypical antipsychotics which proclaimed similar efficacy but better side effect profile. However, positive finding from present study and the high usage of lithium in advanced country such as United Kingdom probably implied that lithium was non-inferior to its alternatives which was usually more costly and causes metabolic adverse effects that was much more common as compared to lithium toxicity. This was especially worrisome for patient with bipolar disorder as the reported risk of metabolic syndrome in this population was significantly higher (OR=1.98, 95% CI=1.74-2.25) compared to normal population (Paton et al. 2010).

Table 5. Distribution of variables represented factors associated with lithium response (n=47)

Variables	Responder (n=36)	Partial/Non-responder (n=11)	Stat. value p-value
Gender			
Male	15 (41.70)	4 (36.40)	p>0.05[a]
Female	21 (58.30)	7 (63.60)	
Race			
Malay	22(61.10)	4 (36.40)	p=0.181[a]
Chinese	10(27.80)	6(54.50)	p=0.148[a]
Indian	3(8.30)	1(9.10)	p>0.05[a]
Others	1 (2.80)	0(0)	p>0.05[a]
Family History			
Bipolar disorder	5 (13.90)	1 (9.10)	p>0.05[a]
Other mental illness	16 (44.40)	4 (36.40)	p=0.737[a]
None	15 (41.70)	6 (54.50)	p=0.505[a]
Bipolar Subtypes			
Type I	27 (75.00)	9(81.80)	p>0.05[a]
Type II	9(25.00)	2 (18.20)	
Illness characteristics before lithium maintenance			
Presence of psychotic feature			
Yes	13 (36.10)	6 (54.50)	p=0.312[a]
No	23 (63.90)	5 (45.50)	
Presence of rapid cycling			
Yes	2 (5.60)	1 (9.10)	p=0.560[a]
No	34 (94.90)	10 (90.90)	
Presence of mixed episode			
Yes	3 (8.30)	0(0)	p>0.05[a]
No	33 (91.70)	11 (100.00)	
Predominant mood polarity			
Manic > Depress	16(44.40)	3(27.30)	p=0.485[a]
Depress > Manic	15(41.70)	8(72.70)	χ^2=3.253; p=0.071*
Equal	5(13.90)	0(0)	p=0.322[a]
Polarity of first mood episode			
Manic / Hypomanic	14 (38.90)	5 (45.50)	p=0.737[a]
Depress	22 (61.10)	6 (54.50)	
		Statistic value (r_s)	p-value
Lithium use			
Age started lithium		-0.200	p=0.179
Serum lithium level		0.104	p=0.548
Latency of time to lithium maintenance		-0.203	p=0.171
First euthymic interval before lithium use		-0.091	p=0.545
First euthymic interval after lithium use		0.533	p<0.001*
Illness characteristics before lithium maintenance			
Age of disease onset		-0.110	p=0.942
Annual relapse rate before lithium			
Overall		0.235	p=0.112
Manic/ hypomanic		0.212	p=0.152
Depress		0.131	p=0.379
Duration of episode before lithium			
Overall		-0.002	p=0.988
Manic/hypomanic		-0.097	p=0.517
Depress		0.093	p=0.536

[a] = Fisher exact test; χ^2 = chi-square test; [b] Responder was defined as 50% improvement in proportion of time spent ill;
* denote p<0.10, which suggest an association with lithium response;
Data were presented as frequency (percent), unless otherwise stated

Overall, the baseline characteristics in our study population were similar between two groups with the only exception of psychotic feature which was higher in combination group. This finding was coupled with the observation that antipsychotic was used most frequently as combination drugs. As the addition of other mood altering drugs such as antipsychotic did not significantly altered the morbidity outcome in our study, this probably showed that psychosis was another important aspect which resulted in this long term combination use. This was consistent with the recommendation by American Psychiatric Association (APA 2002) guideline where antipsychotics use during maintenance phase was allowed for the control of persistent psychosis and prevention of recurrence (Vancamfort et al. 2013). Furthermore, it was reported that psychosis was one of the factors that can negatively affect the treatment adherence in bipolar disorder. Therefore, this probably further emphasized the importance of managing psychotic feature on top of the mood symptom.

Individuals with bipolar disorder are at increased risk for several general medical conditions including cardiovascular disease and obesity which contributed to poorer psychiatric treatment outcomes and early mortality (Kemp et al. 2014). In our study, the baseline morbidity burden and morbidity improvement after lithium maintenance between monotherapy and combination group were compared before proceeding to the mirror study. The two groups had similar baseline morbidity burden and addition of other mood stabilizer did not significantly alter the morbidity outcome. When comparing between period before and after lithium maintenance, lithium use significantly improved all outcome measures when compared to period before the lithium maintenance. This supported the previous findings on the efficacy of lithium in long term maintenance which significantly reduce frequency of yearly relapse (Tondo et al. 1998), percent of time spent in mood episode and reduce duration of each mood episode (Young & Newham 2006). In general, hospitalization rate reduced during lithium maintenance phase in most of our patients. This reduction in rate was in relation to the improvement of the morbidity outcome where patients generally had lesser annual relapse and lesser time spent ill compared before. Meanwhile, among patients who had suicidal attempt before lithium maintenance, almost all showed improvement in this study. This reduction in suicidal rate was clinically important as history of suicidal attempt was strongly associated with current suicidal ideation (Goldberg et al. 2005). This finding also further added to previous evidence that lithium was effective in reducing suicidal attempt (Baldessarini et al. 2006). Lithium has been associated with potential toxicity of long term drug use. Most of the adverse effects did not require discontinuation of lithium. As such, given the strong evidence of efficacy in prophylaxis but relatively low prevalence of severe adverse effects for lithium as reported, lithium probably should be reconsidered in patients who have characteristics which might predict a good response.

Predominant depressive mood episode before lithium use was found to be associated with poorer lithium response in our study. Depressive mood episode has been shown to have lower chances of achieving recovery and the response of lithium in depressive phase (Solomon et al. 2010), therefore it was not surprising that patient with predominant depressive mood polarity in our study was found to be poorer lithium responder. Whilst there was evidence from previous finding which showed that patient with greater cumulative morbidity prone to have lower chances of recovery, hence patient with intermediate morbidity severity during lithium maintenance could have achieved substantial improvement but did not attain full recovery due to the higher disease burden before lithium use. Longer first euthymic interval after starting lithium maintenance therapy was another predictor for better lithium response in present study. This added to the previous findings where longer stable first interval after index episode was associated with a superior lithium response (Tondo et al. 1998). This finding probably implied that for patient who relapse shortly after the index episode with adequate dose of lithium would likely need to switch or add in other medication for long term prophylaxis. In other words, this probably could be an indicator that if patient relapse early after the index episode, it is likely that continuing lithium in long term will bring little benefit in preventing relapse.

CONCLUSION

Lithium remained to be an effective long term prophylactic agent for bipolar disorder in local setting. Regardless the use of lithium as mono- or combination therapy, it significantly reduced the frequency and time spent in relapse. Predominant depressive mood polarity before lithium maintenance and longer first euthymic interval after lithium maintenance had been identified to predict lithium response significantly.

Acknowledgements:

We thank Ms. Sharrifah Norasmah Syed Mustafa from Pharmacy Department, UKMMC and personnel in Medical Record Department of UKMMC for their administrative support.

Conflict of interest: None to declare.

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