Clinical Outcome of Valproate Maintenance Treatment in Bipolar I Disorder at Srinagarind Hospital

Suchat Paholpak MD*,
Sirikul Jaikasemwong MD**, Ajchara Roumcharoenkiat MD*,
Patharee Paholpak MD*, Poonsri Rangseekajee MD*

** Department of Psychiatry, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*
*** Khon Kaen Rajanagarindra Psychiatric Hospital, Khon Kaen, Thailand*

Objective: *To determine-in a clinical setting-the rate and time to recurrence of any mood episode during valproate maintenance treatment for bipolar I disorder.*

Material and Method: *A retrospective cohort based on medical records of both in- and out-patient with bipolar I disorder (DSM-IV-TR) seen at Srinagarind Hospital between January 1, 2009 and December 31, 2010 was done. A recurrence was observed if the patient had fulfilled the remission criteria and valproate was the maintenance drug. Survival analysis and Cox regression analysis were used to analyze the data.*

Results: *Eighty-five patients with 124 remitted mood episodes met the inclusion criteria. Of the 85 patients, the average age was 41.4±17.1 years (range, 18-89); 49.4% were males; 48.2% married; 42.4% completed secondary school, 30.6% completed a bachelor degree; 35.3% were unemployed, and 34.1% were government employees. Twenty remitted mood episodes (16.1%) were in maintenance treatment with valproate only. The remaining 104 (83.9%) were in maintenance treatment with valproate in combination with other agents. There were 50 recurrences from 36 patients during the two years of study, the recurrence per a patient ranged from 1 to 3 times. The rate of recurrence was 21%/year or 2.2/100 person-months (95% CI = 1.65-2.93). The average time to recurrence to any mood episode was 33 months (95% CI = 15.06-50.94). With multivariable Cox regression, a statistically significant greater risk for a recurrence was associated with: (a) the previous episode being hospitalized (adjusted hazard ratio = 5.88, 95% CI = 2.76-12.36, p<0.001); (b) blood valproate concentration during maintenance treatment <50 µg/mL (adjusted hazard ratio = 3.07, 95% CI = 1.11-8.53, p = 0.03); and (c) time duration (month) of valproate maintenance treatment (adjusted hazard ratio = 0.98, 95% CI = 0.96-0.99, p = 0.001). With the adjusted hazard ratio 0.98, it could be interpreted in the other way that each additional month of taking valproate was associated with a statistically significant protective factor that decreased the risk of recurrence by 2% from the previous month.*

Conclusion: *In the authors' clinical setting, valproate both singly and in combination with other psychotropic agents used for maintenance treatment of bipolar I disorder yielded a recurrence rate of 21% per year or 2.2 per 100 person-months and time to any mood episode recurrence of 33 months. The present result has importance for both clinical treatment decision-making and patient economic status.*

Keywords: *Maintenance treatment, Bipolar I disorder, Valproate, Recurrent rate, Time to recurrence*

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Bipolar I disorder is prevalent worldwide (2.4%)[1]. Patients with bipolar I disorder have an annual rate of suicide of 1%[2], a hospitalization rate of 21%[3], and a high rate of comorbidity, including alcohol use disorder (54%)[4], panic disorder (20.1%), and obsessive compulsive disorder (13.6%)[5]. Bipolar I disorder has both chronic[6] and impairing courses (40%)[7]. Only 7% of patients have neither a relapse nor a recurrence. Frequent recurrence and/or chronicity interfere with mental, physical, interpersonal, and occupational capacities[8].

After successful treatment in the acute and continuation phases, the maintenance phase treatment dominates the clinical course. Lithium was the first agent used as a mood stabilizer in the history of bipolar I disorder prophylaxis. Due to its narrow therapeutic range and numerous side-effects, 40% of patients do not respond to it. Consequently, anticonvulsants (i.e., valproate, carbamazepine, and lamotrigine) and atypical antipsychotics are substituted or used as adjuncts[9]. Valproate has a wider spectrum of activity than lithium - i.e., a good efficacy profile in subtypes of mania for which the effects of lithium are

Correspondence to:
Paholpak S, Department of Psychiatry, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Phone: 043-348-384
E-mail: suchat_p@kku.ac.th

mediocre e.g., sufferers of dysphoric mania, rapid cycling mania, mania secondary to organic brain disease. Valproate also has prophylactic activity in bipolar disorder. Additionally valproate usage is easily managed and is well-tolerated in the long-term[10]. Valproate is thus extensively used internationally to treat bipolar disorder[11,12]. Due to the popularity of valproate, the authors proposed investigating the recurrence rate of bipolar I disorder and time of recurrence to any mood episode during valproate maintenance treatment of bipolar I disorder in a normal clinical setting.

Material and Method

The present study was a retrospective cohort drawing data from both in- and out-patient medical records between January 1, 2009 and December 31, 2010, at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. The study protocol was approved by the Khon Kaen University Ethics Committee (registration number: HE 510510).

The inclusion criteria are the available of medical records and the treating psychiatrist(s) indicated the patient had the following characteristics (a) diagnosed as DSM-IV-TR bipolar I disorder, (b) passed through the acute phase treatment of any subtype of mood episode (whether manic, mixed, hypomanic or depressive), (c) had a mood symptom free period for at least two months i.e., indicated clinically in the medical record by the treating psychiatrist(s) as having any of the following, in remission (DSM-IV-TR), doing well, functioning well, or in the continuation-maintenance phase, and (d) patients were under treatment with valproate throughout the period of both (b) and (c) at any dosage as per the clinical discretion of the treating psychiatrist(s).

The exclusion criteria included any of the following, (a) inadequate detail of the medical records, (b) patient was lost to follow-up for >3 months, (c) the patient died before reaching remission. Observation for the present study began with the first appearance of any of the following written conditions in the medical record (a) mood symptom free (from any DSM-IV-TR mood episode subtype) lasting more than two months, (b) in remission, (c) well doing, (d) functioning well, or (e) in a continuation-maintenance phase. The primary outcome was the rate of recurrence of bipolar I disorder illness. The secondary outcomes included time to the next recurrence and the factors associated with the recurrence of the mood episode.

Statistical analysis

The sample size was computed from the formula:

$$n = \frac{(Z_{\alpha/2})^2 \, p(1 - p)}{d^2}$$

where n = sample size, Z = 1.96, $p = 0.35$ (relapse rate in the valproate-treated population) and $d = 0.05\%$. This formula yielded 349 cases (n). The independent variables were sex, age, marital status, educational level, occupation, duration of bipolar I disorder, number of lifetime hospitalizations, in- or out-patient status during the last mood episode, duration of valproate treatment, valproate dosage, serum concentration of valproate, side-effects, duration of mood symptom free period, and number of suicide attempts.

The data were analyzed by using SPSS version 19 to compute the statistics of the demographic data. The demographic data were presented as number, mean ± SD or (when appropriate) median, range and percentage. A comparative analysis was done by using STATA version 10 to compute the survival analysis and the Cox regression.

Results

During the present study period, there were 288 DSM-IV-TR bipolar disorder patients. Seventy-one of 288 patients had either bipolar II disorder, bipolar III disorder, bipolar disorder not otherwise specified (NOS), or bipolar disorder induced by a general medical condition. Twenty-one patients were lost to follow-up, six did not fulfill the remission criteria, and five did not have complete medical records. Drugs other than valproate were used to treat in maintenance phase in 100 of the patients. After applying the inclusion and exclusion criteria, the authors included 85 bipolar I disorder patients records of which had a total of 124 remitted mood episodes.

Demographics

The 85 patients demographic characteristics were age (year): mean ± SD 41.4±17.1, median 40, and range 18 to 89, sex: male n = 42 (49.4%), marital status: married n = 41 (48.2%), educational level: completed secondary school n = 36 (42.4%), bachelor degree n = 26 (30.6%), and occupational status: unemployed n = 30 (35.3%) and government employees n = 29 (34.1%).

Course of illness

At recruitment to the study or at baseline, of the 85 patients, the mean ± SD, median and range of

time duration for having bipolar I disorder illness were 72.86±66.01, 58.00 and 3-396 months. The number of previous mood episode was 3.73±3.20 (median = 3, range = 1-14) episodes. The median number of lifetime hospitalizations for treatment of mood episodes per a patient was 0, mean ± SD = 0.48±1.37 and range = 0-8 times.

Comorbid medical disorder/disease

Thirty-three (38.8%) patients had at least a comorbid medical disorder/disease. The respective median and the range of the number of comorbid medical disorders per a patient was 0 and 0-6. The comorbidity in 24 of 33 (77.7%) patients was from non-psychiatric medical disorders/diseases, six (18.2%) from psychiatric disorder(s), and three (9.1%) from both psychiatric and non-psychiatric medical disorders. The common comorbid non-psychiatric medical disorders/diseases were diseases of the circulatory system (23.8%) (e.g., hypertension, ischemic heart disease, and cerebral infarction); endocrine, nutritional and metabolic diseases (12.7%) (e.g., diabetes mellitus, hyperlipidemia, and hypothyroidism); and diseases of the nervous system (9.5%) (e.g., Parkinson's and migraine). The common comorbid psychiatric disorders were alcohol dependence syndrome (44.4%), dementia either dementia in Alzheimer's, or vascular dementia (22.2%).

Index remitted episode

Of the 124 remitted mood episodes, 70 (56.5%) were remitted manic, 37 (29.8%) depressive, 11 (8.9%) hypomanic, and six (4.8%) mixed. Before remission, 107 (86.3%) episodes were treated as out-patient and the remainder as in-patient. Remission had already lasted nine months (median) at baseline (range 2-78). During the study period, 74 remitted episodes (59.7%) remained in remission while each of the remaining 50 (40.3%) episodes had at least a recurrence. These 50 remitted mood episodes were in 36 patients. Therefore, the average recurrence rate was 21% per year. Regarding the recurrence, single recurrence in each patient was found in 25 of the 36 patients, two recurrences in each of eight and three recurrences in each of the remaining three patients. Thirteen patients were hospitalized for treatment of their recurrent mood episodes: nine patients once and four twice. The median number of hospitalization per a patient was 0 and the range was 0 to 2, or in average 0.37 times/recurrent mood episode. Among the remitted 50 mood episode that had a recurrence, before the next recurrence, 25 (50.0%) were the remitted manic, 17 (34.0%) depressive, six (4.8%) hypomanic, and two (1.6%) mixed. Regarding the recurrent episode, two patients made suicide attempts, one once, and the other twice. The median number of attempted suicide was 0 time per a patient (mean ± SD = 0.04±0.24, range = 0-2).

Of the 124 remitted mood episodes in the 85 valproate maintenance treatment patients, there were 2,252 episode-months under observation of which 50 recurrences in 36 patients occurred. Hence the recurrence rate was 2.22 per 100 patient-month (95% CI = 1.65-2.93) and the median months of symptom-free before the next recurrence was 33 months (95% CI = 15.06-50.94) (Fig. 1). The recurrence rate for the remitted hypomanic, depressive, manic and mixed episode were 1.90/100, 2.11/100, 2.21/100, and 3.51/100 person-month, respectively. The median time to the next recurrence for the remitted depressive, manic, hypomanic and mixed episode were 31, 26, 24, and seven months respectively (Fig. 2). Of the 70 remitted manic episodes under observation the next recurrence by subtype was (a) mania

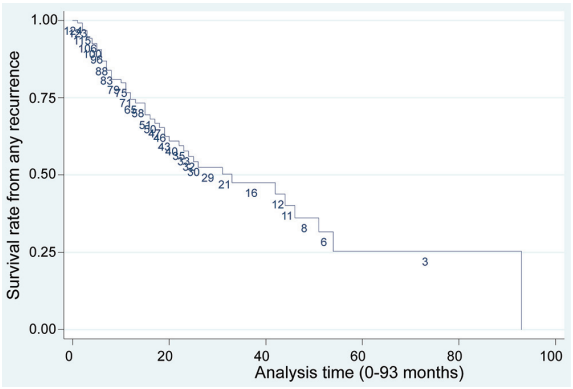

Fig. 1 Kaplan-Meier survival estimate time: time to any recurrence of the total sample.

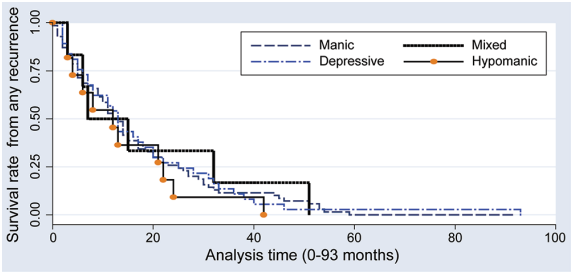

Fig. 2 Kaplan-Meier survival estimates: time to any recurrence from each subtype of the remitted episode.

two episodes, time to recurrence = 12 months (95% CI = 7.56-16.45 months), (b) hypomania four episodes, time to recurrence = 10 months and 95% CI = (-3.72)-23.72 months, (c) depression 4 episodes, time to recurrence = 4 months (95% CI = 7.76-15.76 months), (d) mixed 0 episode, and (e) no recurrence for 41 remitted episodes, time under observation = 21.43±19.35 months (range = 2-92). Of the six remitted mixed episodes, the next recurrence by subtype was (a) mania two episodes, time to recurrence = six months (95% CI could not be computed), (b) depression two episodes, time to recurrence = three months (95% CI could not be computed), (c) no recurrence (one non-recurrence lasted 15 and the other 32 months), and (d) there was no recurrent episode to be hypomania or mixed. Of the 37 remitted depressive episodes, the next recurrence by subtype was (a) mania one episode, time to recurrence and its 95% CI could not be computed, (b) mixed two episodes, time to recurrence = 16 months (95% CI could not be computed), (c) depression 10 episodes, time to recurrence = 8 months (95% CI = 1.80-14.20 months), (d) hypomania one episode, time to recurrence and its 95% CI could not be computed, and (e) no recurrence for 23 remitted episodes, time under observation = 17±13.57 months (range = 2 to 46). Of the 11 remitted hypomanic episodes, the next recurrence by subtype was mania one episode, hypomanic one episode and depression one episode, their time to recurrence and 95% CI could not be computed, and no recurrence occurred in the remaining eight episodes (time under observation was 10.50±7.80 months, range = 3-22).

Valproate administration

Of the 124 remitted mood episodes, the respective mean±SD, range and median for (a) months duration (b) daily dosage, and (c) serum concentrations of valproate during maintenance treatment was (a) 42.62±29.08, 3-121, 34 months, (b) 989.52±360.74, 200-2,000, 1,000 mg/day, and (c) 76.87±25.94, 10.94-149.56, 75.94 µg/mL. The frequency of measuring the plasma concentration of valproate ranged from zero to three times during the study period and was determined by the treating psychiatrists according to the clinical necessity. The plasma concentrations were usually assessed in the morning before the first daily dose. The respective average of duration of remission maintained by valproate for a remitted mixed, manic, depressive and hypomanic episode was 23.50, 21.43, 17.00, and 10.50 months.

Twenty remitted mood episodes (16.1%) were treated in maintenance phase with valproate only, the remaining 104 (83.9%) with valproate in combination with other agents, (a) 21 with other mood stabilizer like lithium (n = 9), topiramate (n = 9), lamotrigine (n = 3); (b) 62 with an antipsychotic of which 46 were with an atypical antipsychotic [viz., quetiapine (n = 17), risperidone (n = 12), olanzapine (n = 9), clozapine (n = 4), ziprasidone (n = 3), and aripiprazole (n = 1)], and 23 with a typical antipsychotic [viz., haloperidol (n = 16), perphenazine (n = 5), and chlorpromazine (n = 2)]; (c) 16 with antidepressant of which 14 were with any SSRI and two with trazodone; (d) 57 with benzodiazepine like lorazepam (n = 36), clonazepam (n = 15), midazolam (n = 3), diazepam (n = 2), and clorazepate (n = 1), and (e) 4 with β blockers.

Adverse effects from valproate treatment were recorded in only 24 remitted episodes (19.4%). These were (a) body weight increase n = 14 (11.3%), (b) nervous system problem (sedation and tremor) n = 8 (6.5%), and (c) other adverse effects n = 2 (1.6%). Valproate maintenance treatments were terminated in 18 (14.52%) episodes. No record of death was noted in the present study.

Factor(s) associated with a recurrence of mood episode

The authors tested the risk factors for a recurrence of mood episodes using the univariable Cox's regression method. The selected factors were sex (male), age (<20 years), presence of comorbidity, positive for history of previous hospitalization, number of previous hospitalizations, duration of valproate treatment (months), valproate concentration <50 µg/ml, and history of suicide attempts. At this initial statistical step, the factors associated with a significantly increased risk for a mood episode recurrence (crude hazard ratio >1 with p-value ≤0.05) were (a) positive for previous hospitalization, crude hazard ratio = 4.17, 95% CI = 2.29-7.60, p<0.001, (b) number of previous hospitalizations, crude hazard ratio = 1.26, 95% CI = 1.13-1.42, p<0.001, and (c) duration of valproate maintenance treatment, crude hazard ratio = 0.99, 95% CI = 0.98-1.00, p = 0.03 (Table 1).

Further analysis with the multivariable Cox's regression method revealed that the significant risk factors for a mood episode recurrence were (a) a history of previous hospitalization (adjusted hazard ratio = 5.88, 95% CI = 2.76-12.36, p<0.001), (b) a blood valproate concentration <50 µg/ml (adjusted hazard ratio = 3.07, 95% CI = 1.11-8.53, p = 0.03), and (c) the time duration (month) of valproate

Table 1. Factors and their respective crude hazard ratio for a recurrence to any mood episode using univariable Cox's regression

Factor	Incidence rate/ 100 persons-month	Crude hazard ratio (95% CI)	*p*-value
Sex			0.97
Male	2.14	1	
Female	2.31	0.98 (0.50-1.92)	
Age			0.81
<20 years	3.13	1	
20 years or older	2.21	1.27 (0.17-9.37)	
Presence of comorbidity			0.75
Non	2.02	1	
Presence	2.52	0.90 (0.46-1.74)	
Previous hospitalization			<0.001
No	1.65	1	
Yes	6.77	4.17 (2.29-7.60)	
No. of previous hospitalizations			<0.001
Median number = 0			
Range = 0-8	1.65	1.26 (1.13-1.42)	
Duration of valproate maintenance treatment (months)			0.03
Mean ± SD (42.62±29.08)	4.17	0.99 (0.98-1.00)	
Blood valproate concentration			0.18
<50 µg/ml	2.76	1	
≥50 µg/ml	2.19	1.92 (0.73-5.02)	
Presence of suicide attempts in the remitted episode			0.34
No	1.79	1	
Yes	0.00	2.67 (0.35-20.42)	

Cox regression-Breslow method for ties

Table 2. Risk factors for a mood episode recurrence after multivariable Cox regression

Factor	Crude hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)	*p*-value of the adjusted hazard ratio
Previous hospitalization			<0.001
No	1	1	
Yes	4.17 (2.29-7.60)	5.88 (2.76-12.36)	
Blood valproate concentration			0.03
<50 µg/ml	1	1	
≥50 µg/ml	1.92 (0.73-5.02)	3.07 (1.11-8.53)	
Duration of valproate maintenance treatment (months)			0.001
Mean ± SD (42.62±29.08)	0.99 (0.98-1.00)	0.98 (0.96-0.99)	

Cox regression-Breslow method for ties

* Each adjusted hazard ratio was adjusted by the other factors

maintenance treatment (adjusted hazard ratio = 0.98, 95% CI = 0.96-0.99 and $p = 0.001$) (Table 2).

Discussion

The present study is the first retrospective study in a clinical setting on the effectiveness of valproate maintenance treatment of patients with bipolar I disorder i.e., a two-year study on valproate singly or in combination with other psychotropic, mostly atypical antipsychotics. The study revealed a recurrence rate of bipolar I disorder of 21% per year or 2.2 per 100 patient-month and a median time to

recurrence of 33 months. Based on the literature, the respective mean survival time during maintenance treatment of bipolar disorder with valproate, quetiapine, lithium and lamotrigine was 26.3 (2.0 s.e.) months, 24.9 (2.7 s.e.), 33.1 (2.5 s.e.), and 30.1 (3.1 s.e.) months[13]. The current study suggests that valproate maintenance treatment can yield clinical outcomes comparable with lithium in the literature.

Of note, patients in the present study had an overall relatively problem-free illness course, even with a long-term illness, i.e. mean duration of 72.86 months; they had only 3.73 mood episodes in their lifetime, regardless of subtype. By comparison, up to nine manic episodes in a lifetime have been reported[1]. In the long-term i.e., 42.62 months on average, well-followed-up maintenance treatment either with valproate alone or valproate in combination with other medications[14] - within the therapeutic dosage of valproate (mean = 76.87 mg/dL) - patients with bipolar I disorder in the present study had less recurrences. Regarding the episode of recurrence, the remitted mixed episode subtype had the highest rate of recurrence, i.e., 3.51 per 100 person-month. As a total result, most of the recurrent mood episodes were of manic type, i.e., 50% compared to 35% in the study by Macritchie et al[15].

When a recurrence did occur (a) the recurrent episode from the remitted manic episodes were mostly manic, (b) the remitted mixed episodes either manic or hypomanic, (c) the remitted hypomanic episodes either manic, hypomanic or depressive, and (d) the remitted depressive episodes mostly hypomanic.

The present study also revealed that the significant risk factors for a mood episode recurrence were (a) the inpatient status of the previous episode, (b) blood valproate concentration <50 µg/ml, and (c) the time duration of valproate maintenance treatment. Additionally, as the time duration of valproate maintenance treatment had an adjusted hazard ratio of 0.98 with its 95% CI as 0.96 to 0.99 and *p*-value as 0.001, it can be interpreted that each additional month when valproate was taken would decrease the chance of recurrence by 2% from the previous month.

Strengths and limitations

(1) Data in the present study reflect the actual phenomenon in the authors' practice and may or may not be generalized. (2) Diagnosis and intensity assessment of any mood episode in the present study was done only in a clinical setting. No rigid diagnostic and intensity instrument were used. (3) Treatment of these bipolar I patients was performed by several staff so the detail and style of record-keeping varied. (4) The sample size was small obviating some statistical calculations. Notwithstanding, some of the factors behind the good treatment results might include a good therapeutic relationship and a good psycho-education ensuring the patients to have valproate administration as a long-term treatment and within the therapeutic dosage. An additional positive aspect of the present study was its being a retrospective on a normal psychiatric service setting.

What is already known in this topic?

The most appropriate maintenance treatment of bipolar I disorder is a combination of mood stabilizer and atypical antipsychotic[16].

What this study add?

In an actual clinical setting of a total population of long-term well followed-up bipolar I disorder patients, valproate which is a mood stabilizer for maintenance treatment, both single valproate and in combination with other psychotropic particularly atypical antipsychotic, can lead to as less as 21% recurrence per year and quite a long time period of mood symptom free i.e. 33 months before the next recurrence.

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Disclosure statement

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Potential conflicts of interest

None.

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ผลการรักษาผู้ป่วยโรค bipolar I ระยะป้องกันด้วยยาวาลโพรเอตของโรงพยาบาลศรีนครินทร์

สุชาติ พหลภาคย์, สิริกุล ใจเกษมวงศ์, อัจฉรา รวมเจริญเกียรติ, ภัทรี พหลภาคย์, พูนศรี รังษีขจี

วัตถุประสงค์: เพื่อศึกษาในสภาวะทางคลินิกเรื่องอัตราการกลับเป็นซ้ำและระยะเวลาที่นำไปสู่การกลับเป็นซ้ำในโรค bipolar I ระยะป้องกันการกลับเป็นอีก (maintenance therapy) ด้วยยา valproate (วาลโพรเอต)

วัสดุและวิธีการ: เป็นการศึกษาแบบ retrospective cohort จากเวชระเบียนผู้ป่วยในและผู้ป่วยนอก ที่ได้รับการวินิจฉัยว่าเป็นโรค bipolar I ตามเกณฑ์การวินิจฉัยโรค DSM-IV-TR ที่โรงพยาบาลศรีนครินทร์ ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2552 ถึง 31 ธันวาคม พ.ศ. 2553 เริ่มต้นติดตามการกลับเป็นซ้ำตั้งแต่ผู้ป่วยเข้าเกณฑ์ของ remission และกำลังได้รับการรักษาแบบ maintenance ด้วยยาวาลโพรเอต (valproate) วิเคราะห์ข้อมูลทางสถิติด้วย survival analysis และ Cox regression analysis

ผลการศึกษา: มีผู้ป่วยที่เข้าเกณฑ์การศึกษา 85 ราย โดยมี mood episode remission 124 ครั้ง อายุของผู้ป่วยคือ 41.4±17.1 ปี พิสัย 18-89 ปี ร้อยละ 49.4 เป็นชาย ร้อยละ 48.2 แต่งงานแล้ว ร้อยละ 42.4 จบการศึกษาระดับมัธยมปลาย ร้อยละ 30.6 จบปริญญาตรี ร้อยละ 35.3 ไม่มีอาชีพ และร้อยละ 34.1 เป็นข้าราชการ remitted mood episode จำนวน 20 episode (ร้อยละ 16.1) ได้รับการรักษาในระยะป้องกันการกลับเป็นซ้ำด้วยยาวาลโพรเอตอย่างเดียว remitted episode ที่เหลืออีก 104 episode (ร้อยละ 83.9) ได้รับการรักษาด้วยยาวาลโพรเอตร่วมกับยาอื่น ๆ ในระยะ 2 ปี ของการศึกษาพบการกลับเป็นโรคซ้ำ 50 ครั้ง จากผู้ป่วย 36 ราย จำนวนครั้งของการกลับเป็นซ้ำคือคนละ 1-3 ครั้ง อัตราการกลับเป็นซ้ำคือร้อยละ 21 ต่อปี หรือ 2.2 ครั้ง ต่อ 100 คน-เดือน (95% CI = 1.65-2.93) ระยะเวลาเฉลี่ยที่นำไปสู่การกลับเป็นโรคซ้ำไม่ว่าการกลับเป็นซ้ำจะเป็น mood episode ชนิดใดคือ 33 เดือน (95% CI = 15.06-50.94) จากการคำนวณด้วยวิธี multivariable Cox regression ได้ผลว่าปัจจัยที่ทำให้เสี่ยงอย่างมีนัยสำคัญทางสถิติต่อการกลับเป็นซ้ำคือ episode ครั้งสุดท้ายก่อนหน้านี้ได้รับการรักษาแบบผู้ป่วยใน (adjusted hazard ratio = 5.88, 95% CI = 2.76-12.36, p<0.001) ความเข้มข้นของยาวาลโพรเอตในเลือด ในช่วงการรักษาระยะป้องกันการกลับเป็นซ้ำต่ำกว่า 50 μg/mL (adjusted hazard ratio = 3.07, 95% CI = 1.11-8.53, p = 0.03) และระยะเวลา (เดือน) ของการรักษาในระยะป้องกันด้วยยาวาลโพรเอต (adjusted hazard ratio = 0.98, 95% CI = 0.96-0.99, p = 0.001) ด้วยค่า adjusted hazard ratio 0.98 ทำให้สามารถตีความในอีกมุมมองหนึ่งได้ว่า ระยะเวลาที่รับประทานยาวาลโพรเอตเพิ่มขึ้นอีก 1 เดือน จะช่วยลดความเสี่ยงในการกลับเป็นโรคซ้ำร้อยละ 2 จากเดือนก่อนหน้านี้

ข้อจำกัด: การศึกษานี้มีข้อจำกัด กล่าวคือผลการรักษาผู้ป่วย bipolar I ในการศึกษานี้เกิดจากจิตแพทย์หลายคน การศึกษานี้เป็นการศึกษาย้อนหลัง การบันทึกในเวชระเบียนอาจจะไม่สมบูรณ์นัก ขนาดตัวอย่างอาจจะน้อยเกินไป และผลการรักษาที่ได้อาจเกิดจากการผลของการรักษาด้วยวิธีทางชีวภาพร่วมกับ psychoeducation

สรุป: ในทางคลินิกการรักษาโรค bipolar ในระยะป้องกันทั้งด้วยยาวาลโพรเอตอย่างเดียวและร่วมกับยาทางจิตเวชอย่างอื่นสามารถทำให้อัตราการกลับเป็นซ้ำมีเพียงร้อยละ 21 ต่อปี หรือ 2.2 ต่อ 100 คน-เดือน ช่วงระยะเวลาที่ปลอดการกลับเป็นซ้ำคือ 33 เดือน ผลการศึกษานี้มีความสำคัญต่อการตัดสินใจทางคลินิกและทางการเงินของผู้ป่วย