Rate of Serum Valproate Concentration Monitoring in Patients with Bipolar Disorder Type I at Srinagarind Hospital Outpatient Clinic

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Objective: *Determine in the out-patient setting the rate and the purpose of serum valproate concentration monitoring during treatment with valproate, either single valproate or valproate in combination with other psychotropics in patients with bipolar disorder type I (BD-I), to determine the rate of recording valproate associated adverse effects, the rate of the follow-up and the length (days) that the patients were in the condition of full remission/recovery and symptomatic.*
Material and Method: *The present study was a retrospective descriptive study done between January 1, 2007 and December 31, 2008. The data were from the medical records of DSM-IV-TR BD-I out-patients at Srinagarind Hospital, Khon Kaen who were treated either by single valproate or valproate in combination with other drugs for at least six weeks long. The studied variable included the annual rate and the reason that psychiatrist requested serum valproate concentration (SVC) monitoring per patient, the annual rate that psychiatrist recorded the valproate associated adverse effects, the annual rate that the patient returned to have a follow-up visit, and the length (days) that the patient was in full remission/recovery and symptomatic.*
Results: *During the study period, of the 199 patients with BD-I, only 57 patients (28.6%) that were treated with valproate had complete records. The SVC monitoring occurred 17 times from 13 patients (22.8%). The mean SVC was 76.4 microgram/ml (SD = 31.8). The mean value ±SD and range of SVC during the remission/recovery period were 75.1±17.5 µg/ml and 43.5-96.8 µg/ml, which was not significantly different from the symptomatic period, which was 77.1±39.9 µg/ml and 0.7 to 124.9 µg/ml. However, the oral dosage of valproate during the remission/recovery period (944.7±275.4 mg/day, median 1,000 mg/day) was significantly higher than during the symptomatic period (699.0±592.5 mg/day, 1,000 mg/day) (t = 2.7, df = 104 and p = 0.009). Of all the SVC monitoring, 58.8% occurred during the symptomatic period and most of the monitoring was due to the emergence of adverse effects. The causes for requesting the SVC determination were the emergence of adverse effects (29.4%), no reason specified (29.4%), and to monitor the clinical response (11.8%). The rate of valproate associated adverse effects recording was 1.1 times/person/year, which was 18.6% of the average rate of follow-up visits (6.6 times/person/year). The most frequent adverse effect was sedation. The treatment of BD-I by valproate or in combination with other psychotropics resulted in the remission/recovery period lasting 470.2 days (SD 256.8, median 517.0) while the symptomatic period lasted 176.1 days (SD 157.5, median 139.5).*
Conclusion: *During treatment of BD-I, the rate of serum valproate concentration monitoring was very few. However, when determination was requested, the SVC was within the therapeutic range. In addition, rate of recording of valproate associated adverse effects was very low and the most frequent adverse effect was mild. The reason for monitoring the clinical response was rarely found. Valproate seems to be easily administered. The dosage can be adjusted using only clinical response and adverse effects. Therefore, valproate was effective and safe in treatment of BD-I.*

Keywords: *Monitoring, Rate, Serum valproate concentration, Valproate, Bipolar disorder type I, BD-I*

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The one year and lifetime prevalence of bipolar disorder type I (BD-I) are 0.6 and 1.0 %[1]. BD-I runs chronic, 40% have residual symptoms, and 45% have recurrences[2,3]. After the first episode of illness, the next recurrence occurs within 7.9 months[4]. Patients with BD-I usually have at least one other psychiatric disorder: 16-70% had any anxiety disorder and 21 to 34% had substance abuse[5]. The estimated rate of hospital admission was 39.1% and premature mortality of patients was 18%[6]. BD-I lowers almost all aspects of quality of life of patients compared to general

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population[7]. Patients with BD-I usually have poor insight to their illness and do not adhere to their treatment schedule[2,3]. Thirty to sixty percent of patients remain with functional impairment even when achieving complete remission of the bipolar symptoms[8]. The purpose of BD-I treatment is to shorten and stabilize the acute phase, and then to keep the stabilization throughout the continuation and maintenance phase simultaneously with improving the quality of life[3]. Currently several medications have been approved for treatment of bipolar disorder. Recommended medications for treatment in acute bipolar manic phase include lithium, divalproex, olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, and ziprasidone. In acute bipolar depression, the medication includes lithium, lamotrigine, quetiapine, quetiapine XR, lithium, divalproex or olanzapine plus SSRI, lithium plus divalproex, and lithium or divalproex plus bupropion. In bipolar maintenance, the therapy includes lithium, lamotrigine, divalproex, olanzapine, quetiapine, lithium or divalproex plus quetiapine, risperidone LAI, adjunctive risperidone LAI, aripiprazole, and adjunctive ziprasidone[9]. Valproate is widely used to treat every phase of BD-I and even to treat rapid cycling course[10-12]. Its postulated biochemical mechanism for therapeutic effects includes enhancement of gamma-aminobutyric acid (GABA) activity and modulation of voltage-sensitive sodium channels[3]. Therapeutic effect of valproate occurs when serum of valproate concentration is between 50 to 100 microgram/mL[3]. Although valproate treatment is generally well tolerated and safe, the two most serious adverse effects of valproate treatment affect the pancreas and the liver. The other adverse effects include polycystic ovary disease, metabolic syndrome, nausea, vomiting, dyspepsia, diarrhea, sedation, ataxia, dysarthria, and tremor[13]. Therefore, for effectiveness, valproate administration needs serum concentration and adverse effect monitoring[14,15].

Objective

The primary objective was to determine in the clinical setting the annual rate of serum valproate concentration (SVC) monitoring during treatment of patients with BD-I with valproate, either single valproate or valproate in combination with other psychotropics. The secondary objectives were to find out the annual rate of the following parameters, 1) the various reasons specified by the in-charge psychiatrist for SVC monitoring, 2) the rate of recording of the valproate treatment associated adverse effects, 3) the rate of patients' following-up visit, and 4) the length (days) during which the patient with BD-I was in remission/recovery or symptomatic.

Material and Method

The present study was retrospective. The Khon Kaen University Ethical Review Board approved the study proposal (HE521084). The inclusion criteria were 1) outpatient records at psychiatric unit of Srinagarind Hospital between January 1, 2007 and December 31, 2008, 2) patients were in any stage of DSM-IV-TR BD-I (namely: any active mood episode, partial or full remission, or recovery), 3) valproate was used to treat BD-I, which could be used either as single drug or in combination with other psychotropic drugs, and 4) valproate must be used for at least six weeks.

In Srinagarind hospital the serum valproate concentration was determined by fluoro-immunoassay with fluorescence polarization (Abbott TDX) machine and was reported from the research unit, Faculty of Pharmacy, Khon Kaen University.

The number of remission/recovery days means the number of days specified by the in-charge psychiatrist that the patient was in any or combination of the following circumstances, doing well, functioning well, no symptom, and DSM-IV-TR criteria met for full remission or recovery stage. It was a traditional practice for psychiatrists at Srinagarind Hospital to use these brief terms to describe the patient's mental status during the follow-up visit. Thus, the remission/recovery days were equivalent to any or combination of the following treatment phase, continuation, maintenance, or continuation-maintenance. In this report, the wording "symptomatic period" means the patient with BD-I was recorded to be in any or combination of the following circumstances: active mood period of BD-I depressed, manic, mixed; partial remission, not well, worse, or chronic. To define if the period of interest was either the remission/recovery or symptomatic period and how long each period lasted, two independent psychiatrists who did not know the patients must have the same opinion. In case of disagreement, the final decision was sought from the third psychiatrist.

Data were excluded from the study if treatment of BD-I with valproate was less than six weeks and the data was inadequate for counting either the number of remission/recovery or symptomatic days. Those could be lost to follow-up for longer than three months or few detail of the illness situation in the follow-up record except for the refilling of the medication covering a period of more than three months.

Statistical analysis

Numerical values were analyzed by using percentage, mean value, standard deviation (mean ± SD) and median if appropriate. All statistics were computed by using SPSS version 17.

Results

During the study period, there were 199 patients with DSM-IV-TR BD-I. However, only 57 patients (28.6%) were treated with valproate, either as single drug or in combination with other psychotropics, and their medical records were complete for the analysis.

Demographic characteristics

Of 57 patients, 32 (56.1%) were male and the mean age was 42.8 years old (range 16 to 79). Equal number of patients were in the age range of 21 to 40 and 41 to 60 years old (23 patients or 40.4% for each age range). Thirty patients (52.6%) were married and 21 (36.8%) were single. Twenty-nine patients (50.9%) had a bachelor degree, 14 (24.6%) had a high school level, and seven (12.3%) had a primary school level. Regarding the patient's occupation, 24 (42.0%) were civil servants, 10 (17.5%) were student, seven (12.3%) were housewives, and six (10.5%) were merchants.

Comorbid medical illness

Seventeen patients (12.5%) had co-morbid physical illnesses and included seven (12.3%) with hypertension, seven (12.3%) with dyslipidemia, five (8.8%) with diabetes mellitus, and 10 (17.5%) with other minor physical illness. Only one patient (1.8%) had a comorbid psychiatric illness, that is, mixed Alzheimer's and vascular dementia.

Bipolar disorder type I illness course

At the beginning of the present study, the mood episode of interest was a single episode in seven patients (12.3%) and a recurrent episode in 50 patients (87.7%). The mean ± SD, median, and minimum-maximum number of the total previous lifetime mood episode of any subtypes per patient were 2.6±2.5, 2.0, and 0.0 to 14.0 episodes, total previous manic 1.7±2.1, 1.0 and 0 to 10 episodes, total previous hypomanic 0.09±0.3, 0.0 and 0.0 to 1.0 episodes, total previous mixed 0.09±0.3, 0.0 and 0 to 2 episodes and total previous depressive 0.8±0.9, 0.0 and 0 to 4 episodes. During the two years of study, 23 patients (40.4%) did not have any recurrence (that is, they were in the well control maintenance treatment stage), each of the rest 34 (59.6%) had a recurrence in an average of 0.8±0.7 episodes (median = 1 episode), ranged from one recurrence in 24 patients (42.1%) to 2 recurrences in 10 patients (17.5%). The current recurrent episode was manic, depressive, mixed, and hypomanic episode for 28 patients (49.1%), 6 (10.5%), 3 (5.3%) and 3 (5.3%) respectively.

Valproate administration

At baseline the mean ± SD, median and minimum-maximum of the number of days that the patients were taking valproate were 600.3±202.1, 720.0, and 113.0 to 720.0 days. Thirty patients (52.6%) were taking valproate for 720 days. Valproate was used as the single medication in 10 patients (17.5%), in combination with one other psychotropic agents in 20 patients (35.1%), with two other psychotropic agents in 13 (22.8%), with three other psychotropic agents in nine (15.8%) and with four other psychotropic agents in five (8.9%). Most of other psychotropic agents used were benzodiazepines (29 or 50.9%) and atypical antipsychotics (20 or 35.1%).

Valproate dosage

The mean ± SD, median and min-max of daily oral valproate dosage during the symptomatic period were 699.0±592.5, 1,000 and 0.0 to 1,750.0 mg; during the remission/recovery period were 944.7±275.4, 1,000.0 and 200.0 to 1,500.0 mg. Daily valproate dosage during remission/recovery period was statistically significant higher than during symptomatic period ($t = 2.7$, $df = 104$ and $p = 0.009$).

Valproate monitoring

Seventeen times of SVC determination were found from 13 patients (22.8% of 57), causing the average of SVC monitoring 0.15 time/patient/year. The concentration determination was done for once in nine of 13 (69.2%) patients and twice for four (30.8%). Ten out of 17 (58.8%) SVC determinations were requested during the symptomatic period and the other seven (41.2%) during remission/recovery period. Reason for requesting SVC determination was five requests (29.4%) were for monitoring the adverse effect, five (29.4%) with no reason specified, four (23.5%) for compliance problem, and the other two (11.8%) for treatment unresponsive problem. When SVC determinations were requested during the remission/recovery period, psychiatrists in-charge usually did not specify the reason for SVC monitoring but during the symptomatic period the most frequent reason for SVC monitoring was for side effect monitoring.

Serum valproate concentration

As the total data, the mean ± SD, median and minimum-maximum of the SVC were 76.4±31.8, 82.6 and 0.7 to 125.0 µg/ml. The concentration was below 75 µg/ml in 6 examinations (35.3%), between 75 to 100 µg/ml in 8 (47.0%) and above 100 µg/ml in three examinations (17.7%). During the remission/recovery period, the SVC was 75.1±17.5 µg/ml, ranging from 43.5 µg/ml to 96.8 µg/ml. During the symptomatic period, the valproate level was 77.1 µg/ml ±39.9 µg/ml, ranging from 0.7 µg/ml to 124.95 µg/ml. The SVC between during the remission/recovery and symptomatic period were not different with statistical significance (t = 0.24, df = 15 and p = 0.82).

Recording of valproate associated adverse events

Thirty-seven (64.9%) and 20 patients (35.1%) were found to have and not have a record from in-charge psychiatrist on valproate associated adverse events, respectively. The total number of records on adverse effect was 123 times or 18.6% of the number of follow-up visits and causing a record of 1.1±1.2 times/patient/year (median = 0.5 min-max = 0-2.5 times/patient/year) in spite of the average of 6 to 12 follow-up visits/patient/year. The common adverse effects recorded in descendent order were as the follows, central nervous system adverse effects [30 patient (81.1% of 37 patients) or 51 records (41.5% of the total 123 records)] followed by weight gain [23 (62.2%) or 46 (37.4%)], tremor [12 (32.4%) or 46 (37.4%)], tinnitus [1 (2.7%) or 1 (0.8%)] and hepatotoxicity (rising serum glutamic-oxaloacetic transaminase) [1 (2.7%) or 1 (0.8%)]. Most of the central nervous system (CNS) adverse effects was sedation (43 records or 34.9% of all records or 84.3% of the CNS adverse effects). The remaining CNS adverse effects were memory and cognitive impairment, ataxia, and dizziness.

The cause of some adverse effects

Sedative effect was found in the treatment by the single valproate in 12 records (27.9%), in treatment by valproate in combination with atypical antipsychotics in 14 records (32.6%), with both benzodiazepines and conventional antipsychotics in 11 records (25.6%). Weight gain was caused by valproate alone in 12 records (26.1%), by valproate in combination with atypical antipsychotics in nine records (19.6%), and with typical antipsychotics in seven records (15.2%). Tremor was caused by valproate alone in four records (20.0%), by valproate in combination with atypical antipsychotics in one record (5.0%), with typical antipsychotics in two records (10.0%), and with both benzodiazepines and atypical antipsychotics in 13 records (65.0%).

Discontinuation of valproate administration

Discontinuation was found in three patients (5.4%), one due to loss follow-up, one changing medication, and the other one due to pregnancy. No lethality was found.

Number of follow-up visits

Forty-nine patients (86.0%) and the remaining eight patients (14.0%) kept on and left the follow-up visit respectively. The number of follow-up visit was 6.6±3.7 times/patient/year, ranging from 2 to 22 times/patient/year. Among those who kept on the follow-up visits, missing appointment was found 0.1±0.2 time/patient/year, min-max 0 to 1 time/patient/year, median = 0.

The remission/recovery and symptomatic period

During the two years of the study, thirty-nine patients (68.4%) could reach either well, remission, or recovery period of BD-I. The remission/recovery period lasted 470.2±256.8 days, median = 517.0, min-max = 0.0 to 720.0 days. Of note, fifteen patients (26.3%) had a remission/recovery period as long as 720.0 days. The remaining 18 patients were symptomatic, which lasted 176.1±157.5 days (median = 139.5, min-max = 8.0 to 424.0 days).

Discussion

With the knowledge that valproate is used widely and internationally to treat patients with BD-I, the authors tried to elaborate the clinical patterns of using this drug. The authors' present study revealed that only 22.8% of the patients with BD-I who were treated with valproate received SVC monitoring. The rate of SVC monitoring was 15/100 patient/year compared to 57.5% in Marcus et al's study[16]. The very low rate of SVC determination might be accounted for by the preference of the in-charge psychiatrists to use clinical symptoms and signs for monitoring the valproate administration, less recognition of its importance, quite a long time (at least 2 weeks) to get the SVC report, or SVC monitoring was refused by the patient. Fortunately, whenever the SVC was determined, the concentration was within the therapeutic range and most of the patients in the present study were in stable condition (remission/recovery) to be able to cautiously omit the study of blood concentration of valproate.

This assumption was in accordance with the authors' finding that valproate daily dosage during the remission/recovery period was significant higher than during the symptomatic period. Again, this may confirm that clinicians can use clinical conditions, that is, clinical symptoms and valproate associated adverse effects to monitor valproate dosing. The reasons specified for requesting SVC determination in the present study were consistent with the practical principles in using valproate, that is, for monitoring the adverse effects, and compliance problem. Only 11.9% of the SVC determination was for clinical symptoms monitoring. Furthermore, the authors found that 29.4% of the requests did not have any reason specified. This might mean just check it regularly e.g. for every six months in the remission/recovery patients. The fact to support this hypothesis was that whenever valproate level determination was requested among the well doing patients, the lowest concentration of valproate was found to be within 75 to 100 μg/ml, which is the most effective therapeutic and the most tolerable range during maintenance treatment[15]. Although 42.9% of the SVC determination was found to be below 75 μg/ml, the lowest level was still in the suggested range by Sachs, that is, during the maintenance treatment for bipolar I disorder the SVC should be in the range of 56.6±12 μg/ml[17]. This may mean that valproate has good efficacy and pharmacoeconomic profiles as well as a relatively favorable safety profile[18]. With valproate being widely administrated, dosing strategy, serum concentration prediction, adverse effects, and therapeutic efficacy monitoring parameters can be monitored by using clinical signs and symptoms. The present study revealed that only 5.4% of the patients discontinued the valproate treatment. The figure was compatible to the fact that in controlled study valproate was associated with fewer participants dropping out of treatment for any cause when compared to placebo or lithium[19].

Most of the patients with BD-I in the present study were in the well or remission/recovery period which was compatible with the stage of maintenance treatment. Most of them had high education level, had less number of co-morbid psychiatric disorder compared to up to 75% in other study, had good adherence in long term treatment, all of which might underlie their good clinical course, that is, the maximum number of recurrence during the two years of study was only two times and they could have well period as long as 470 days in average. All these explanations may account for, during valproate administration in the well and stable period, the less number of SVC determination and the less number of adverse effects recording. Additionally, the adverse effects found in the present study were only transient and mild symptoms needed only minor adjustment. However, in order to optimize treatment and reduce adverse effects as much as possible, clinician should perform regular and accurate monitoring of serum valproate concentration in BD patients, who are often treated with multiple drugs.

Limitation

Retrospectively study of the present study incurred some limitations; several kinds of data might be incomplete: medical and or psychiatric co-morbidity, psychosocial intervention, factors influencing the infrequent serum valproate concentration determination. The data used for statistical analysis was the number of days when the patients were recorded to be in the well doing, functioning well, remitted, and recovery period; and the number of days when the patients were recorded to be symptomatic, not well, worse, or partial remission. The better way is to use psychometric measures or to have a protocol for following-up. In addition, even some psychiatric symptoms particularly mood symptoms might still appear in the patients, it does not mean that every symptom must be solved. Therefore, recording roughly that the patient was doing well or functioning well might reflect the actuality that the patient can manage daily activities in spite of the presence of some symptoms.

Conclusion

During treatment of BD-I, the rate of serum valproate concentration monitoring was very few. But whenever determination was requested, the SVC was within the therapeutic range. In addition, the rate of recording the valproate associated adverse effects was very few, and the most frequent adverse effects found was mild. The reason as for monitoring the clinical response was found in very few occasions. Valproate seems to be easily administered, the dosage can be adjusted using only clinical response and adverse effects. Therefore, valproate was effective and safe in treatment of BD-I.

What is already known on this topic?

Therapeutic drug monitoring is a powerful tool of chemical-clinical data correlation[20] and allows to tailor-made treatment to the specific needs of individual patients[21].

What this study adds?

An actual clinical use of valproate to treat BD-I in a university hospital reflects that regular serum valproate concentration and adverse effects monitoring are still lacking. Therefore, during treatment with valproate, psychiatrists should be encouraged to have regular and accurate monitoring of SVC.

Potential conflicts of interest

None.

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อัตราการตรวจความเข้มข้นของยา valproate ใน serum ของผู้ป่วยนอกโรคอารมณ์สองขั้วชนิดที่ 1 ที่ โรงพยาบาลศรีนครินทร์

ภัทรี พหลภาคย์, สุชาติ พหลภาคย์, เด่นพงศ์ พัฒนเศรษฐานนท์, พูนศรี รังษีขจี, นิรมล พัจนสุนทร

วัตถุประสงค์: เพื่อศึกษาอัตราการตรวจวัดและเหตุผลของการตรวจวัดความเข้มข้นของยา valproate ใน serum ของผู้ป่วยนอกโรคอารมณ์สองขั้วชนิดที่ 1 (bipolar disorder type I คำย่อคือ BD-I) ที่ได้รับการรักษาด้วยยา valproate ชนิดเดียวหรือยา valproate ร่วมกับยาจิตเวชชนิดอื่น ศึกษาอัตราการบันทึกฤทธิ์ที่ไม่พึงประสงค์จากยา valproate อัตราการกลับมาติดตามการรักษา ระยะเวลาที่ผู้ป่วยสบายดีและระยะเวลาที่ผู้ป่วยมีอาการไม่สบาย จากตัวโรค

วัสดุและวิธีการ: เป็นการศึกษาเชิงพรรณนาแบบย้อนหลัง เก็บข้อมูลจากเวชระเบียนผู้ป่วยนอกที่ได้รับการวินิจฉัยว่าเป็นโรคตามเกณฑ์ DSM-IV-TR ที่มารับการรักษาที่แผนกผู้ป่วยนอกจิตเวช โรงพยาบาลศรีนครินทร์ ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2550 ถึง 31 ธันวาคม พ.ศ. 2551 ผู้ป่วยจะต้องได้รับ การรักษาด้วยยา valproate ชนิดเดียวหรือยา valproate ร่วมกับยาทางจิตเวชชนิดอื่นนานอย่างน้อยที่สุด 6 สัปดาห์ ตัวแปรที่ศึกษาคือจำนวนครั้งและเหตุผลที่จิตแพทย์สั่งให้มีการตรวจวัดความเข้มข้นของยา valproate ใน serum ต่อผู้ป่วยหนึ่งคนต่อปี จำนวนครั้งที่จิตแพทย์บันทึกฤทธิ์ ที่ไม่พึงประสงค์จากยา valproate ต่อผู้ป่วยหนึ่งคนต่อปี อัตราที่ผู้ป่วยกลับมาติดตามการรักษาตามนัดต่อคนต่อปี จำนวนวันที่หายจากโรคและจำนวนวัน ที่มีอาการ วิเคราะห์ข้อมูลทางสถิติด้วยโปรแกรม SPSS version 17 เป็นการแสดงสถิติเชิงพรรณนาด้วยค่าเฉลี่ย ส่วนเบี่ยงเบนมาตรฐาน ค่ามัธยฐาน และค่าร้อยละ

ผลการศึกษา: ในระยะเวลาของการศึกษามีผู้ป่วยโรค BD-I จำนวน 199 คน เป็นผู้ป่วยที่ได้รับการรักษาด้วยยา valproate และมีเวชระเบียนที่สมบูรณ์จนสามารถใช้ในการวิเคราะห์ได้จำนวน 57 คน (ร้อยละ 28.6) มีการตรวจวัดความเข้มข้นของยา valproate ใน serum 17 ครั้ง จากผู้ป่วย 13 คน (ร้อยละ 22.8) ความเข้มข้นโดยเฉลี่ยที่ตรวจพบคือ 76.4 μg/ml (SD = 31.8) ค่าเฉลี่ย ±SD และพิสัยของความเข้มข้นของยา valproate ใน serum ในระหว่างที่ผู้ป่วยหายจากโรคคือ 75.1±17.5 μg/ml และ 43.5-96.8 μg/ml ในระหว่างที่ผู้ป่วยมีอาการคือ 77.1±39.9 μg/ml และ 0.7-124.9 μg/ml ซึ่งไม่แตกต่างอย่างมีนัยสำคัญทางสถิติ แต่ขนาดยา valproate ที่รับประทานในระหว่างที่หายจากโรค คือวันละ 944.7±275.4 มิลลิกรัม (มก.) ค่า median วันละ 1,000 มก. ซึ่งมากกว่าในระยะที่มีอาการคือ วันละ 699.0±592.5 มก. ค่า median วันละ 1,000 มก. โดยมากกว่า อย่างมีนัยสำคัญทางสถิติ (t = 2.7, df = 104 and p = 0.009) ร้อยละ 58.8 ของการตรวจวัด กระทำในระยะที่ผู้ป่วยมีอาการไม่สบายทางอารมณ์ ตรวจวัดเพราะมีฤทธิ์ที่ไม่พึงประสงค์เกิดขึ้น ในภาพรวมเหตุผลที่ส่งตรวจวัดได้แก่ เพราะเกิดฤทธิ์ที่ไม่พึงประสงค์ (ร้อยละ 29.4) ไม่ระบุเหตุผลใดๆ เลย (ร้อยละ 29.4) และเพื่อติดตามการตอบสนองทางคลินิก (ร้อยละ 11.8) อัตราการบันทึกฤทธิ์ที่ไม่พึงประสงค์จากยา valproate มีจำนวน 1.1 ครั้งต่อคนต่อปีหรือคิดเป็นร้อยละ 18.6 ของจำนวนครั้งที่มาติดตามการรักษา จำนวนครั้งที่มาติดตามการรักษาโดยเฉลี่ยคือ 6.6 ครั้งต่อคนต่อปี ฤทธิ์ที่ไม่พึงประสงค์จากยา valproate ที่พบบ่อยคืออาการง่วง การรักษาโรค BD-I ด้วยยา valproate ตามลำพังหรือร่วมกับยาจิตเวชชนิดอื่น ทำให้จำนวนวัน ที่ผู้ป่วยหายจากโรคทางอารมณ์โดยเฉลี่ย 470.2 วัน (SD 256.8, median 517.0) แต่ระยะที่ป่วยมีอาการคือ 176.1 วัน (SD 157.5, median 139.5)

สรุป: การรักษาผู้ป่วยนอกที่เป็นโรค BD-I อัตราการตรวจวัดความเข้มข้นของยา valproate ใน serum มีน้อย อัตราการบันทึกฤทธิ์ที่ไม่พึงประสงค์ จากยา valproate ก็มีน้อย ตามที่บันทึกพบว่าส่วนใหญ่ของฤทธิ์ที่ไม่พึงประสงค์มีอาการไม่รุนแรง การใช้ความเข้มข้นของยา valproate เพื่อติดตาม ผลการรักษาพบน้อย จะเห็นได้ว่ายา valproate จึงเป็นยาที่ใช้ได้ง่าย สามารถปรับขนาดยาได้ตามการตอบสนองทางคลินิกและตามฤทธิ์ที่ไม่พึงประสงค์ ยา valproate มีประสิทธิภาพและปลอดภัยในการรักษาโรค BD-I