DOI: 10.37990/medr.1716257 Med Records 2025;7(3):697-702

MEDICAL RECORDS-International Medical Journal

Research Article

The Effect of Individual Valproic Acid and Albumin Variation on the Risk of Episodes in Patients with Bipolar Disorder

Seyma Sehlikoglu[1], Esra Gocer[2], Saniye Basak Oktay[3]

[1]Adıyaman University, Faculty of Medicine, Department of Psychiatry, Adıyaman, Türkiye
[2]Batman İluh State Hospital, Clinic of Psychiatry, Batman, Türkiye
[3]Alanya University, Faculty of Medicine, Department of Biochemistry, Alanya, Türkiye

Abstract

Aim: This study aimed to investigate the association between the coefficient of variation (CV%) of valproic acid (VPA) and albumin levels and mood episode status in patients with bipolar disorder who maintained therapeutic VPA concentrations.
Material and Method: Patients diagnosed with bipolar disorder who had been under follow-up for at least two years between 2018 and 2023 were retrospectively analyzed. Inclusion criteria required at least three annual measurements of simultaneous serum VPA and albumin levels, with VPA consistently within the therapeutic range (45–100 µg/mL). Patients were categorized based on episode occurrence. Mean values, standard deviation (SD), and CV% were calculated for VPA and albumin levels.
Results: A total of 90 patients with bipolar disorder were included, with 45 experiencing episodes and 45 remaining episode-free. The mean of the last six albumin measurements was significantly lower in the episode group (t=−2.688, p=0.009). While the CV% of total VPA levels did not differ significantly between groups, the CV% of albumin-adjusted VPA levels was significantly higher in the episode group (z=−2.005, p=0.045). Episode frequency showed a statistically significant but weak positive correlation with both normalized SD (r=0.281, p=0.007) and normalized CV% (r=0.260, p=0.013).
Conclusion: This study found that individuals with bipolar disorder who experienced episodes had significantly lower serum albumin levels, and that albumin-adjusted VPA fluctuations showed a weak but positive correlation with episode occurrence. Prioritizing the CV% of albumin-adjusted VPA measurements may play a significant role in monitoring episode risk in patients with bipolar disorder.

Keywords: Bipolar disorder, valproic acid, coefficient of variation, albumin, mood episode

INTRODUCTION

Bipolar disorder is a chronic psychiatric illness marked by recurrent episodes of depression and either mania or hypomania (1). While bipolar I disorder includes episodes of both depression and full mania, bipolar II disorder is defined by the occurrence of depressive episodes accompanied by hypomanic episodes—milder periods of mood elevation that typically do not lead to marked functional impairment (2). Epidemiological studies indicate that the lifetime prevalence of bipolar disorder is approximately 2.4%, with a 12-month prevalence of around 1.5% (3).

In patients diagnosed with bipolar disorder, regular treatment and follow-up are necessary to reduce the frequency of episodes and to minimize the negative psychological and social impacts associated with the illness. Since 70% of patients are at risk of relapse within 5 years, continuity of treatment and regular follow-up are of great importance (4,5). Preventing the recurrence of depressive or manic episodes is a major challenge in the long-term management of patients with bipolar disorder. Valproic acid (VPA) is considered a reliable treatment option for individuals with bipolar disorder due to its long-term efficacy in reducing episode recurrence and enhancing overall quality of life (6-9). Due to its narrow therapeutic window, potential for drug–drug interactions and significant variability in pharmacokinetics across individuals, VPA treatment necessitates routine monitoring of serum levels (10). In addition, the absorption and elimination of VPA are affected by its non-linear kinetics

CITATION
Sehlikoglu S, Gocer E, Oktay SB. The Effect of Individual Valproic Acid and Albumin Variation on the Risk of Episodes in Patients with Bipolar Disorder. Med Records. 2025;7(3):697-702. DOI:1037990/medr.1716257

Received: 09.06.2025 **Accepted:** 30.06.2025 **Published:** 09.09.2025
Corresponding Author: Seyma Sehlikoglu, Adıyaman University, Faculty of Medicine, Department of Psychiatry, Adıyaman, Türkiye
E-mail: seymashlk@gmail.com

and variable protein binding, factors that can change notably between different age groups (9). Leading clinical guidelines such as those from the British Association for Psychopharmacology (11), the Canadian Network for Mood and Anxiety Treatments (8), the International Society for Bipolar Disorders, and the National Institute for Health and Care Excellence (12) do not recommend a specific optimal serum VPA range; instead, they emphasize the importance of maintaining serum levels within the generally accepted therapeutic range (e.g., 50–100 µg/mL) (9). The 2013 guideline of the World Federation of Societies of Biological Psychiatry recommended a VPA concentration range of 45–100 µg/mL for patients with bipolar disorder (13).

VPA is transported in the blood with approximately 90% bound to serum proteins, particularly albumin. Research indicates that variations in serum albumin concentrations may influence the proportion of unbound VPA in the bloodstream (9,14). The free drug concentration is the active portion responsible for the drug's therapeutic effect. Due to the technical difficulty of analyzing free drug levels in many laboratories, total VPA levels are commonly measured instead. In cases where free drug levels cannot be analyzed to assess drug efficacy, corrected VPA levels—calculated using total VPA levels in conjunction with serum albumin levels—are considered to be more informative. Although these calculation formulas are utilized in research settings, they have not been routinely implemented in everyday clinical practice (15).

The coefficient of variation (CV) is a statistical metric used to assess the relative variability of a data set, independent of both the measurement unit and the magnitude of the mean. The coefficient is calculated by taking the ratio of the standard deviation (SD) to the mean and then multiplying by 100 to express the result as a percentage. Since CV reflects the dispersion of values relative to the mean, it is unitless and particularly advantageous when comparing variability across data sets with different scales or units. Unlike the SD, the CV enables more meaningful comparisons between groups with distinct magnitudes and measurement units, making it especially useful for classified or heterogeneous data series (16).

There are studies that examine the relationship between patients' serum VPA levels and the risk of experiencing episodes (9,17,18). Although serum VPA levels may remain within the therapeutic range, some patients continue to experience manic and/or depressive episodes, suggesting that treatment response cannot be explained solely by serum concentrations (19). To the best of our knowledge, no existing study has conducted a detailed analysis of variability in serum VPA levels. This study aims to examine the relationship between fluctuations in VPA and albumin levels, and the frequency and risk of mood episodes, in patients diagnosed with bipolar disorder who experience episodes despite maintaining therapeutic VPA serum levels (45–100 µg/mL).

MATERIAL AND METHOD

thical approval for the study was granted by the Non-Interventional Clinical Research Ethics Committee of Adıyaman University (Approval No: 2023/3-20, dated 14 November 2023), and all procedures adhered to the ethical standards outlined in the Declaration of Helsinki. Bipolar disorder diagnoses were established based on criteria defined in the DSM-5. According to the DSM-5 (20): "A manic episode is characterized by a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week and present most of the day, nearly every day. During this period, individuals must exhibit at least three of the following symptoms (or four if the mood is irritable): inflated self-esteem or grandiosity, decreased need for sleep, increased talkativeness or pressure to speak, flight of ideas or subjective experience of racing thoughts, distractibility, an increase in goal-directed activity or psychomotor agitation, and excessive involvement in activities with a high potential for painful consequences. A major depressive episode is defined by the presence of five or more symptoms during the same two-week period, with at least one being either depressed mood or a marked loss of interest or pleasure. Other associated symptoms include significant changes in weight or appetite, sleep disturbances (insomnia or hypersomnia), psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, indecisiveness, and recurrent thoughts of death or suicidal ideation."

The clinical notes and laboratory results of bipolar disorder patients who presented to the psychiatry clinic of Adıyaman Training and Research Hospital between 2018 and 2023 were retrospectively reviewed in the hospital information system. Patients were included in the study based on the following criteria: absence of organic diseases such as hepatic or renal disorders that could affect serum VPA and albumin levels; a diagnosis of bipolar disorder with regular follow-up over a two-year period; availability of at least three annual measurements of serum VPA and simultaneous albumin levels; and serum VPA levels consistently within the therapeutic range (45–100 µg/mL). Patients were excluded if they had organic conditions (e.g., liver or kidney diseases) that could influence serum VPA concentrations, had fewer than three annual VPA measurements, lacked simultaneous albumin data, or failed to attend regular follow-up visits. Patients were divided into two groups based on their most recent clinical evaluation: those who had serum VPA levels within the therapeutic range and experienced at least one episode within the two-year period, and those with therapeutic serum VPA levels who remained episode-free during the same period.

At the mental health and psychiatry clinic of Adıyaman Training and Research Hospital, VPA levels of bipolar patients in remission are routinely monitored at intervals of 3 to 6 months. To evaluate VPA and albumin levels,

5 cc of venous blood samples were collected from patients 12 hours after the nighttime VPA dose using the antecubital vein. The samples were analyzed using the spectrophotometric method on the Abbott Architect c16000 analyzer (Abbott Diagnostics Inc., Lake Forest, IL, USA), and the results were uploaded to the patient records system within a maximum of 3 days. According to this device, the reference range for VPA is 45–100 µg/mL. The patients' serum VPA levels, normalized according to their albumin values, were calculated using an online calculation tool designed based on the study by Hermida et al. (15).

The study data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows, with a significance level set at $p<0.05$. For each patient included in the study, the mean, SD, and percent CV% of serum VPA, albumin levels, and albumin-normalized VPA values over a two-year period were calculated. The CV% was computed using the formula: (SD/mean) × 100. The normality of data distribution was evaluated using the Kolmogorov–Smirnov test. Descriptive statistics for quantitative variables were presented as medians along with interquartile ranges (IQRs). For comparisons, the Mann–Whitney U test was applied to non-normally distributed variables, while normally distributed data were analyzed using the Student's t-test. Categorical variables of the groups were compared through the Chi-square test. Associations between variables were explored using Spearman's rank correlation. To determine the diagnostic performance of normalized CV% and SD in predicting episode risk, Receiver Operating Characteristic (ROC) curve analysis was utilized, assessing both sensitivity and specificity.

RESULTS

Between 2018 and 2023, a total of 1563 patients presented to the hospital, and after applying the exclusion criteria, 90 patients were included in the study—45 in the patient group and 45 in the control group. Of the patients included in the study, 32.2% (n=29) were female, with a median age of 39 years (33–46). No statistically significant differences were found between the two groups (those who experienced episodes and those who did not) in terms of age and gender ($p=0.944$ and $p=0.259$, respectively). The demographic data of the patients are presented separately for each group in Table 1.

The mean and SD values of the last VPA and albumin results—measured at the most recent visit and over the past two years (six values) —as well as the CV% values calculated using these two parameters, are presented in Table 1. No significant differences were found between bipolar patients with and without episodes in terms of duration of illness, last VPA level, or albumin level.

When the data obtained from the last six VPA values of the patients were compared, no significant differences were found between the groups in terms of mean and CV% values; however, the SD values were found to be significantly higher in the group that experienced episodes ($p=0.048$).

When the data obtained from the last six albumin levels of the patients were compared, the mean value was found to be significantly lower in the episode group [3.80 (3.55–4.11) vs 3.94 (3.78–4.21), $p=0.009$], while no statistically significant differences were observed in SD and CV% values.

Table 1. Demographic data and laboratory results of the patients with bipolar disorder

	Episode group (n=45) (Median)	Non-episode group (n=45) (Median)	P value
Age*	37 (33.5-45.5)	40 (32.5-46)	0.944 (z=-0.008)
Gender, (n%)			
Female	12 (26.7%)	17 (37.8%)	0.259 (χ^2=1.272)
Male	33 (73.3%)	28 (62.2%)	
Duration of illness*	15(10-22.5)	12 (7.5-17.5)	0.082 (t=1.762)
Frequency of manic episodes in the last two years*	2 (2-3)	0	
Frequency of depressive episodes in the last two years*	1 (1-1)	0	
Total episode frequency in the last two years*	3 (2.5-4)	0	
Last VPA level*	79.2 (65.5-89.6)	77.5 (62.5-86.65)	0.487 (t=0.730)
Mean of the last 6 VPA levels*	70.18 (67.78-85.12)	76.11 (68.49-84.12)	0.331 (z=-0.972)
SD of the last 6 VPA levels*	13.25 (9.78-17.17)	9.96 (7.29-15.22)	**0.048 (z=-1.973)**
CV% of the last 6 VPA levels*	18.26 (13.78-21.34)	14.20 (10.32-19.81)	0.084 (t=1.748)
Last ALB level*	3.90 (3.6-4.25)	4.00 (3.75-4.25)	0.171 (t=-1.381)
Mean of the last 6 ALB levels*	3.80 (3.55-4.11)	3.94 (3.78-4.21)	**0.009 (t=-2.688)**
SD of the last 6 ALB levels*	0.31 (0.21-0.4)	0.29 (0.19-0.39)	0.534 (z=-0.621)
CV% of the last 6 ALB levels*	7.87 (5.26-10.44)	7.44 (4.86-9.97)	0.345 (z=-0.944)

*The data is presented as median (Interquartile range); CV%: coefficient of variation, SD: standard deviation, VPA: valproic acid, ALB: albumin

The data of VPA values normalized based on the patients' current albumin levels are presented in Table 2. While no significant difference was found between the groups in the adjusted mean values of the last 6 normalized VPA results, the normalized SD and normalized CV% values were significantly higher in the group that experienced episodes [normalized SD: 23.28 (16.09–37.53) vs 20.09 (12.46–28.01), p=0.030; normalized CV%: 23.57 (18.02–36.15) vs 20.26 (15.17–28.68), p=0.045]. The lower mean albumin levels in the episode group led to relatively higher calculated normalized VPA values in this group, although the difference was not statistically significant.

Table 2. Valproic acid levels of the patients normalized based on serum albumin

	Episode group (n=45) (Median)	Non-episode group (n=45) (Median)	P value
Mean of the last 6 normalized VPA levels*	99.26 (84.64-115.08)	93.55 (76.78-105.23)	0.058 (z=-1.896)
SD of the last 6 normalized VPA levels*	23.28 (16.09-37.53)	20.09 (12.46-28.01)	**0.030 (z=-2.175)**
CV% of the last 6 normalized VPA levels*	23.57(18.02-36.15)	20.26 (15.17-28.68)	**0.045 (z=-2.005)**

*The data is presented as median (Interquartile range); CV%:coefficient of variation, SD: standard deviation, VPA: valproic acid

A statistically significant but weak correlation was observed between episode frequency and both normalized SD and normalized CV% (p=0.007, r=0.281; p=0.013, r=0.260, respectively). In the ROC analysis performed to assess the predictive value of normalized SD and CV% for mood episodes, the area under the curve (AUC) was 0.633 (95% CI: 0.518–0.748; p=0.030) for SD and 0.623 (95% CI: 0.507–0.739; p=0.045) for CV%. Based on the Youden index, the optimal cutoff value for CV% in predicting episode occurrence was ≥17.55, yielding a sensitivity of 82% and specificity of 40%. Similarly, the optimal cutoff for SD was ≥14.95, with the same sensitivity (82%) and specificity (40%) (Figure 1).

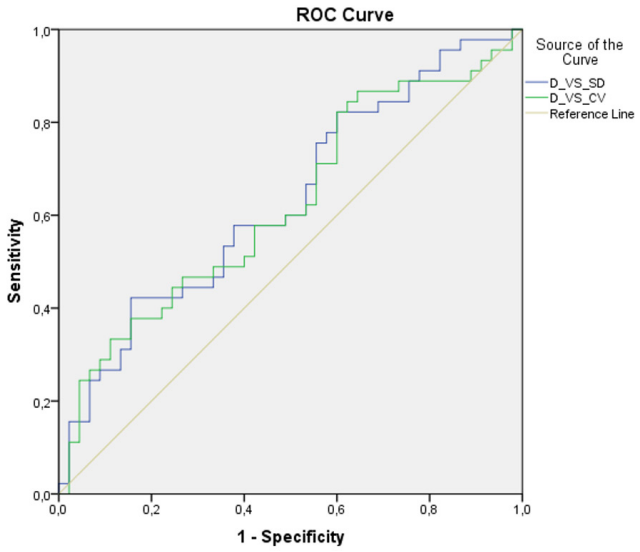

Figure 1. ROC analysis of normalized standard deviation and coefficient of variation in predicting mood episode risk

DISCUSSION

In this study, no statistically significant difference in gender distribution was found between the groups: patients who experienced manic or depressive episodes and those who did not, despite having therapeutic VPA levels. This finding is partially inconsistent with some reports in the literature. For instance, studies by Slyepchenko et al. (21) and Menculini et al. (22) have reported that rapid cycling episodes are more frequently observed in female patients. However, in our sample, gender did not significantly influence the likelihood of experiencing episodes. This discrepancy may be attributed to methodological differences such as the relatively small sample size, the potential influence of unmeasured biological or environmental factors affecting treatment response, or the fact that our study focused on episode frequency rather than the presence of rapid cycling. In addition, no statistically significant age difference was found between individuals diagnosed with bipolar disorder who experienced episodes and those who did not. However, it is noteworthy that both groups had a relatively higher mean age (approximately 37–40 years) compared to the general bipolar disorder population. This finding may reflect a greater motivation for regular clinical follow-up among older individuals, potentially due to age-related changes in VPA metabolism that increase the proportion of free drug and, consequently, the risk of toxicity, as reported in previous studies (23,24). Another possible explanation is that clinicians may adopt closer monitoring strategies for older patients in anticipation of age-related pharmacokinetic alterations. In this context, advanced age may not only indicate increased vulnerability to adverse effects but also signal the need for more careful clinical supervision.

In this study, no significant difference has been found in the duration of illness between bipolar disorder patients with therapeutic VPA levels who experienced episodes and those who did not. This finding suggests that the duration of illness alone is not a determining factor for episode frequency. Bukh et al. (25) have reported that the frequency of episodes increases with the progression of illness duration in bipolar disorder. In contrast, Gitlin and Frye (26) have found that, over long-term follow-up, consistent adherence to pharmacological treatment and the presence of individual protective factors are more decisive in determining episode frequency. In our study, since both patient groups had VPA levels within the therapeutic range, the presence of biological treatment adherence may have masked any potential differences in episode risk associated with illness

duration. Nevertheless, it is suggested that the impact of illness duration on episode occurrence may be more strongly linked not solely to the length of the illness, but to accompanying factors such as early onset, psychotic features, comorbid substance use, and affective temperament (27).

In the analysis of the last six albumin levels of the patients, the SD and CV% values did not show a significant difference between individuals diagnosed with bipolar disorder who experienced episodes and those who did not. However, the mean albumin levels were found to be significantly lower in the episode group, which resulted in relatively higher calculated normalized VPA values in this group. As is well known, VPA is a drug that binds extensively to albumin, and in cases of hypoalbuminemia, the free (active) fraction increases (28). This increase may lead to free VPA levels exceeding therapeutic limits, even when total VPA levels remain within the therapeutic range, potentially enhancing both the drug's effects and the risk of side effects. In the study conducted by Chen et al. (9), it has been reported that individuals diagnosed with bipolar disorder who have serum VPA levels above 75 µg/mL exhibited more variable and statistically non-significant outcomes regarding mood episode recurrence compared to those with levels between 50–74 µg/mL. The researchers explained this by suggesting that a certain threshold level may be exceeded at the protein-binding sites of VPA in the serum. Accordingly, an increase in VPA levels does not always confer a protective effect against mood episodes; in fact, once the binding sites become saturated, the resulting rise in the free VPA fraction may lead to unpredictable effects on therapeutic efficacy. Therefore, in bipolar disorder patients receiving VPA treatment, it is clinically important to monitor not only total serum levels but also albumin levels, and, if possible, to evaluate free VPA levels to guide appropriate dose adjustments.

In this study, analysis of the last six VPA levels in patients revealed no significant difference in the CV% of total VPA levels between individuals diagnosed with bipolar disorder who experienced episodes and those who did not. However, the CV% of the corrected VPA levels, calculated using serum albumin concentrations, was found to be significantly higher in the episode group. This finding suggests that fluctuations in corrected VPA levels may increase the risk of experiencing episodes. Variability in the levels of a drug like VPA, which has a narrow therapeutic range, may contribute to both pharmacokinetic instability and clinical variability (9,29).

In the ROC analysis conducted to determine the predictive value of SD and CV% for episodes, we observed that the CV% had a sensitivity of 82% and a specificity of 40% in predicting episode risk. These findings suggest that normalized SD and CV% may serve as sensitive but not highly specific indicators for predicting the risk of episodes. In other words, while these parameters may be valuable in minimizing missed episodes, it should be noted that when used alone as clinical decision-support tools, they may be associated with a high rate of false positives.

This study has several methodological limitations. First, due to its retrospective design, it was not possible to standardize or control for environmental, psychosocial (stress, sleep disturbances), or biological variables that may have played a role in the emergence of bipolar episodes. Second, the use of antipsychotics, lithium, or other mood stabilizers in addition to VPA treatment poses a potential risk of affecting the pharmacokinetic properties and bioavailability of VPA. Such drug interactions may increase interindividual variability in VPA levels. Another limitation of this study is that the VPA doses and dosing intervals were not provided; instead, the mean, SD, and CV% values of the last six VPA levels were reported. Thirdly, due to an insufficient sample size, episode type could not be included in the subgroup analysis. Fourthly, discrepancies between the timing of blood sample collection and the administration of VPA doses—particularly in the outpatient group—may have complicated the interpretation of measured serum VPA levels. Finally, the weak correlation coefficients between episode frequency, and normalized SD and normalized CV may require to reinterpret of hypotheses in longitudinal studies. Therefore, future prospective and controlled studies are recommended to more closely monitor variables such as dose-time consistency and the effects of concomitant treatments.

CONCLUSION

In conclusion, this study revealed that individuals with bipolar disorder who experienced episodes had significantly lower serum albumin levels compared to those who did not, and that fluctuations over time in VPA levels corrected for serum albumin showed a weak but positive correlation with episode occurrence. These findings suggest that in clinical settings where free VPA levels cannot be directly measured, focusing not only on total VPA levels but also on albumin-corrected VPA values may provide more guidance in patient management. Especially in outpatient follow-up, monitoring the CV% of corrected VPA levels may serve as a supportive parameter for assessing clinical stability and predicting the risk of episodes. In light of these results, future studies with larger sample sizes, prospective designs, and multivariate analyses are warranted.

Financial disclosures: *The authors declared that this study has received no financial support.*

Conflict of interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *Ethical approval for the study was granted by the Non-Interventional Clinical Research Ethics Committee of Adıyaman University (Approval No: 2023/3-20, dated 14 November 2023), and all procedures adhered to the ethical standards outlined in the Declaration of Helsinki.*

Acknowledgement: *The authors wish to acknowledge Ayşe Vlok for her support in the linguistic revision and refinement of the manuscript.*

REFERENCES

1. Phillips ML, Kupfer DJ. Bipolar disorder diagnosis: challenges and future directions. Lancet. 2013;381:1663-71.
2. Müller-Oerlinghausen B, Berghöfer A, Bauer M. Bipolar disorder. Lancet. 2002;359:241-7.
3. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011;68:241-51.
4. Price AL, Marzani-Nissen GR. Bipolar disorders: a review. American family physician. 2012;85:483-93.
5. Karaytuğ MO, Tamam L, Demirkol ME, Namli Z. Treatment compliance and related factors in patients with bipolar disorder. Arşiv Kaynak Tarama Dergisi. 2022;31:21-7.
6. Baldessarini RJ, Tondo L, Vázquez GH. Pharmacological treatment of adult bipolar disorder. Mol Psychiatry. 2019;24:198-217.
7. Macritchie K, Geddes JR, Scott J, et al. Valproate for acute mood episodes in bipolar disorder. Cochrane Database Syst Rev. 2003;CD004052.
8. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20:97-170.
9. Chen YCB, Liang CS, Wang LJ, et al. Comparative effectiveness of valproic acid in different serum concentrations for maintenance treatment of bipolar disorder: a retrospective cohort study using target trial emulation framework. EClinicalMedicine. 2022;54:101678.
10. Lin WW, Jiao Z, Wang CL, et al. Population pharmacokinetics of valproic acid in adult Chinese epileptic patients and its application in an individualized dosage regimen. Ther Drug Monit. 2015;37:76-83.
11. Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guide- lines for treating bipolar disorder: revised third edition recommen- dations from the British Association for Psychopharmacology. JPsychopharmacol. 2016;30:495-553.
12. Bipolar disorder: assessment and management (CG185). London: NICE; 2018.
13. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry. 2013;14:154-219.
14. Gugler R, von Unruh GE. Clinical pharmacokinetics of valproic acid. Clin Pharmacokinet. 1980;5:67-83.
15. Hermida J, Tutor JC. A theoretical method for normalizing total serum valproic acid concentration in hypoalbuminemic patients. J Pharmacol Sci. 2005;97:489-93.
16. Abdi H. Coefficient of variation. In: Salkind N, Ed., Encyclopedia of Research Design. Thousand Oaks, CA: Sage. 2010.
17. Keck PE, Bowden CL, Meinhold JM, et al. Relationship between serum valproate and lithium levels and efficacy and tolerability in bipolar maintenance therapy. Int J Psychiatry Clin Pract. 2005;9:271-7.
18. Paholpak S, Jaikasemwong S, Roumcharoenkiat A, et al. Clinical outcome of valproate maintenance treatment in bipolar I disorder at Srinagarind Hospital. J Med Assoc Thai. 2014;97:431-8.
19. Carli M, Risaliti E, Francomano M, et al. A 5-year study of lithium and valproic acid drug monitoring in patients with bipolar disorders in an Italian clinical center. Pharmaceuticals. 2022;15:105.
20. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Virginia: American Psychiatric Association, 2013. https://doi.org/10.1176/appi.books.9780890425596
21. Slyepchenko A, Frey BN, Lafer B, et al. Increased illness burden in women with comorbid bipolar and premenstrual dysphoric disorder: data from 1 099 women from STEP-BD study. Acta Psychiatr Scand. 2017;136:473-82.
22. Menculini G, Steardo Jr L, Sciarma T, et al. Sex differences in bipolar disorders: impact on psychopathological features and treatment response. Front Psychiatry. 2022;13:926594.
23. Wu J, Li J, Jing W, et al. Valproic acid-induced encephalopathy: a review of clinical features, risk factors, diagnosis, and treatment. Epilepsy Behav. 2021;120:107967.
24. Ma P, Shang S, Huang Y, et al. Joint use of population pharmacokinetics and machine learning for prediction of valproic acid plasma concentration in elderly epileptic patients. Eur J Pharm Sci. 2024;201:106876.
25. Bukh JD, Andersen PK, Kessing LV. Rates and predictors of remission, recurrence and conversion to bipolar disorder after the first lifetime episode of depression–a prospective 5-year follow-up study. Psychol Med. 2016;46:1151-61.
26. Gitlin M, Frye MA. Maintenance therapies in bipolar disorders. Bipolar disorders. 2012;14:51-65.
27. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev. 2011;35:804-17.
28. Patsalos PN, Spencer EP, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs in epilepsy: a 2018 update. Ther Drug Monit. 2018;40:526-48.
29. Tseng YJ, Huang SY, Kuo CH, et al. Safety range of free valproic acid serum concentration in adult patients. PLoS One. 2020;15:e0238201.