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Metabolic Differentiation in Manic Episode of Bipolar Disorder Compared to Substance-Induced Psychosis and Substance Use Disorder Based on Serum Valproate Level

Bipolar Bozukluğun Manik Epizodunda, Maddeye Bağlı Psikoz ve Madde Kullanım Bozukluğu ile Karşılaştırıldığında Serum Valproat Düzeyine Göre Metabolik Farklılaşma

Elvan ÇİFTÇİ[1,2]
0000-0002-7452-2616
Emine CENGİZ ÇAVUŞOĞLU[3]
0000-0002-9598-1803
Merih ALTINTAŞ[4]
0000-0001-7045-3046

[1]Department of Psychiatry, Üsküdar University Faculty of Medicine, İstanbul, Türkiye
[2]Psychiatry Clinic, NP İstanbul Brain Hospital, İstanbul, Türkiye
[3]Psychiatry Clinic, Başakşehir Çam and Sakura City Hospital, İstanbul, Türkiye
[4]Psychiatry Clinic, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Türkiye

Corresponding Author
Sorumlu Yazar
Elvan ÇİFTÇİ
elvanlciftci@gmail.com

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ABSTRACT

Aim: Valproic acid (VPA) is primarily used in the treatment of epilepsy but also has uses in the treatment of manic episodes in bipolar disorder and substance use disorders. Manic episodes and psychosis may also affect hepatic clearance and drug distribution volume. The aim of this study was to assess the effect of mania and psychosis compared to substance use on VPA pharmacokinetics, specifically changes in total and unbound clearance.
Material and Methods: Fifty patients with a manic episode of bipolar disorder, and 51 patients with substance use disorder, 38 of whom were considered as substance-induced psychosis, were included in this retrospective study. All patients received a constant dose of 1000 mg VPA daily for at least five days, and serum VPA concentrations were measured.
Results: The mean serum levels of VPA were 59.2±17.4 µg/ml in the substance use disorder group, 60.9±13.5 µg/ml in the substance-induced psychosis group, and 61.8±13.7 µg/ml in the manic episode of bipolar disorder group. No significant difference was found between the groups (p=0.840). When considering substance use disorder and substance-induced psychosis as one group, the mean VPA level of 60.5±14.4 µg/ml in this group showed no significant difference compared to 61.8±13.7 µg/ml in the manic episode of bipolar disorder (p=0.630).
Conclusion: After reaching steady-state plasma levels, no significant difference in serum VPA levels was observed between the three groups. This suggests that manic episodes do not lead to a significant increase in VPA metabolism compared to substance use disorder or substance-induced psychosis.
Keywords: Serum valproate level; manic episode of bipolar disorder; substance use disorder; substance-induced psychosis.

ÖZ

Amaç: Valproik asit (VPA) öncelikle epilepsi tedavisinde kullanılır, ancak aynı zamanda bipolar bozukluktaki manik atakların ve madde kullanım bozukluklarının tedavisinde de kullanımları vardır. Manik ataklar ve psikoz hepatik klerensi ve ilaç dağıtım hacmini de etkileyebilir. Bu çalışmanın amacı, madde kullanımına kıyasla mani ve psikozun VPA farmakokinetiği, özellikle toplam ve bağlanmamış klerensteki değişiklikler üzerindeki etkisini değerlendirmektir.
Gereç ve Yöntemler: Bu geriye dönük çalışmaya bipolar bozukluk manik atağı olan 50 hasta ve 38'i maddeye bağlı psikoz olarak değerlendirilen madde kullanım bozukluğu olan 51 hasta dahil edildi. Tüm hastalara en az beş gün boyunca sabit dozda günlük 1000 mg VPA verildi ve serum VPA konsantrasyonları ölçüldü.
Bulgular: Ortalama serum VPA düzeyi madde kullanım bozukluğu grubunda 59,2±17,4 µg/ml, maddeye bağlı psikoz grubunda 60,9±13,5 µg/ml ve bipolar bozukluğun manik döneminde ise 61,8±13,7 µg/ml idi. Gruplar arasında anlamlı bir fark bulunamadı (p=0,840). Madde kullanım bozukluğu ve maddeye bağlı psikoz tek grup olarak ele alındığında bu grupta ortalama 60,5±14,4 µg/ml olan VPA düzeyi, bipolar bozukluğun manik dönemindeki 61,8±13,7 µg/ml ile karşılaştırıldığında anlamlı bir fark göstermedi (p=0,630).
Sonuç: Kararlı durum plazma seviyelerine ulaştıktan sonra, üç grup arasında serum VPA seviyelerinde anlamlı bir fark gözlenmedi. Bu, mani epizodunun madde kullanım bozukluğu veya maddeye bağlı psikoz ile karşılaştırıldığında VPA metabolizmasında anlamlı bir artışa yol açmadığını düşündürmektedir.
Anahtar kelimeler: Serum valproat düzeyi; bipolar bozukluğun manik dönemi; madde kullanım bozukluğu; maddeye bağlı psikoz.

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INTRODUCTION

Valproic acid (VPA) is a short-chain branched fatty acid used in the treatment of psychiatric disorders, migraine, neuropathic pain, and seizures (1). It is effective in the treatment of acute manic episodes of bipolar disorder and used in the long-term prevention of relapse (2). Valproate has also been used for the improvement of abstinence and impulse control in substance use disorder (SUD) (3). When combined with psychosocial therapies, it can be a safe and effective treatment for cocaine dependence (4).

The pharmacokinetic profile of VPA is complex: VPA has a low clearance (CL) due to high albumin binding (5) and the serum concentration of physiologically active free VPA changes in a non-linear manner (6). At least three different processes are involved in the almost complete first-order kinetic metabolism of valproate in humans, including glucuronidation, mitochondrial oxidation, and oxidation mediated by cytochrome P450s (7). It increases brain GABA levels (8,9), which can induce a sedative state and reduce anxiety and may be useful in the treatment of moderate mania (10,11). Valproate also inhibits voltage-gated sodium ion channels (12), blocks calcium channels, and modulates serotonergic and dopaminergic neurotransmission (8,9). Valproate may inhibit the activity of an enzyme (active protein kinase) that has been associated with an increase in cell surface area in people with bipolar disorder (13-16). Valproate, a fatty acid, has also been suggested to influence lipid metabolism in the brain (17). Beyond short-term biochemical effects, there appears to be consistent and strong evidence that valproate works through long-term effects at the genomic level (18,19).

There are no approved indications for its use in addiction psychiatry. However, its use in SUDs is increasing (20). Valproate is prescribed by consultant psychiatrists to reduce abstinence scores and to help with impulse control problems in patients hospitalized for substance-induced psychosis (SIP) and SUDs. Studies have shown that manic episodes in bipolar disorder affect drug pharmacokinetics. This can lead to increased CL of drugs such as lithium and carbamazepine. Clinical effects of VPA and serum drug concentrations are closely correlated, with significant inter-individual variability influenced by variables such as age, total body weight, and concomitant medication. Patients who do not respond to treatment are given higher doses/serum levels than patients who have responded to lower doses/serum levels (channeling effect) (21). Studies of lithium (22) and carbamazepine (23) show that serum levels of these drugs are lower, and CL is higher in acute mania. Similarly, the pharmacokinetics of carbamazepine have been shown to be affected in acute mania, with a significantly higher CL/bioavailability ratio than in epileptic patients (24).

Research on the effects of VPA in different conditions is limited. This is the first study to assess the effects of mania and psychosis on the pharmacokinetics of total and unbound (u) VPA, which may predict changes in total CL and unbound clearance (CLu). We hypothesized that serum levels of VPA will be lower in patients with manic episodes of bipolar disorder and SIP than in patients with SUDs, as we expect VPA CL to increase during mania or psychosis. If we find differences in serum valproate levels in different disorders, serum VPA levels can be used as a diagnostic marker and the initial dose of VPA can be adjusted according to the different disorders. Therefore, this study aimed to assess the effect of mania and psychosis compared to substance use on VPA pharmacokinetics specifically changes in total and CLu.

MATERIAL and METHODS

Participants were recruited from Erenköy Mental and Nervous Diseases Training and Research Hospital during a therapeutic drug monitoring male psychosis service. The following inclusion criteria were met by all patients seen at the male psychosis service: 1) receiving 1000 mg of VPA daily for at least five days, 2) being between 18 and 65 years of age, 3) weighing between 50 and 80 kg, 4) being male patients, and 5) smoking. The exclusion criteria were as follows: 1) previous valproate treatment, 2) patients with abnormal renal function tests (serum creatinine >1.2 mg/dl in adult males and 1.1 in adult females), 3) patients with abnormal liver function tests (AST and ALT >2.5 times of normal), 4) use of drugs that interfere with VPA metabolism (eg. phenytoin, phenobarbital, felbamate, ethosuximide, acyclovir and rifampine), 5) severe medical history, and 6) patients with a history of bipolar mood disorder and those with substance use problems.

Two psychiatrists diagnosed the patients with manic episodes of bipolar disorder, SUD, and SIP based on the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-V) criteria during the hospitalization period. The DSM-V defines a SIP as a psychiatric disorder with delusions and/or hallucinations during or within one month after the intoxication or withdrawal of a substance, and that the substance can produce the symptoms. Patients with SIP whose psychotic symptoms persisted after one month were included in our study. We included patients receiving valproate for the first time in their lives. Sodium valproate was prescribed to each study participant on the recommendation of their psychiatrist and according to standard practice.

We retrospectively searched the data of the Erenköy Mental and Nervous Diseases Training and Research Hospital for four years until we selected a total of 101 patients according to the study criteria; 51 patients with substance use problems, of whom 38 with SIP and 13 with SUD, and 50 patients with manic episode of bipolar disorder. A psychiatrist verified the diagnoses by means of a review of each patient's records. This helped to ensure that the diagnoses were correct. As described above, the study also had strict exclusion criteria. Almost all patients received injections of haloperidol and biperiden as needed during the first few days of treatment. The study was approved by the ethics committee of Erenköy Mental and Nervous Diseases Training and Research Hospital (dated Nov 3, 2014, approval number: 18/8).

Blood Sampling and Drug Assays

The patients' laboratory tests were performed on the first morning of treatment. For the measurement of serum VPA concentration, serum samples were taken before administration of the morning dose and 12 hours after administration of the evening dose on days 5 to 7 of valproate treatment at 1000 mg/day. Sodium valproate concentration was determined after samples were thawed to room temperature. The sodium valproate concentration

was determined after thawing the samples to room temperature. The photometric methods were carried out using the Abbott Architect ci4100. VPA serum levels below or above 50 μg/ml (lowest effective dose) were also categorized.

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess whether a variable is normally distributed. Normally distributed variables were reported as mean±standard deviation and non-normally distributed variables were reported as median (interquartile range) [minimum-maximum]. To compare two groups of normally distributed quantitative variables an independent samples t-test was used. For a parametric comparison of the three groups for quantitative variable ANOVA with Tukey's post hoc test was used while Kruskal-Wallis was used for the non-parametric comparison of the three groups. The chi-squared test was used to determine whether there is a significant association between two or more categorical variables. Fisher's exact test was used when more than 20% of the cells had an expected number of less than 5. Spearman correlation was used for the association between nonparametric measures of rank correlation. IBM SPSS v.21.0 was used to calculate all statistics. The significance level was set at $p<0.05$.

RESULTS

Fifty hospitalized patients with manic episodes of bipolar disorder and a total of 51 hospitalized patients with SUD and SIP were recruited for the study. Among the 51 patients with substance use, 38 patients had psychotic features and were diagnosed with SIP, while the other 13 were diagnosed with SUD.

In the comparison of patients with SUD, patients with SIP, and patients with manic episodes of bipolar disorder with each other in three different groups, the median age was significantly different between the three groups (p=0.003), while there was no significant difference between the three groups in terms of disease duration (p=0.370). When the education status was categorized as having studied for less than or more than 8 years, there was no significant difference between the three groups when comparing the groups (p=0.370). Also, there was no significant difference in terms of employment status when considered as working or not working (p=0.503) and in terms of marital status (p=0.156) between the three groups (Table 1).

Regarding the three groups in terms of pharmacological treatment received in addition to VPA treatment, almost all patients were receiving antipsychotics. In the SUD group, 2 patients were receiving risperidone, 4 patients were receiving olanzapine, 2 patients were receiving other antipsychotics, 3 patients were receiving combined antipsychotic treatment, and 2 patients were not receiving any medication other than VPA. In the SIP group, 6 patients received risperidone, 12 patients received olanzapine, 17 patients received combined antipsychotics and 3 patients received antidepressants. In the manic episodes of bipolar disorder group, 11 patients received risperidone, 7 patients received olanzapine, 6 patients received other antipsychotics, 23 patients received combined antipsychotics, 1 patient received antidepressants, and 2 patients were treated with VPA alone (Table 2). There is no difference between one type of medication and a combined type of medication between the three groups (p=0.175).

Table 1. Demographic characteristics of the groups

	BMP (n=50)	SUD (n=13)	SIP (n=38)	p
Age (years)	32 (16.5) [19-59]	25 (5) [20-36]	25 (7.25) [15-43]	**0.003**
Duration of illness (years)	2 (12.5) [0.5-24]	4 (6) [1-25]	2.5 (5) [0.5-10]	0.370
Education, n (%)				
≤8 years	21 (42.0)	8 (61.5)	20 (52.6)	0.370
>8 years	29 (58.0)	5 (38.5)	18 (47.4)	
Working status, n (%)				
Working (or student)	32 (64.0)	6 (46.2)	23 (60.5)	0.503
Nonworking (or retired)	18 (36.0)	7 (53.8)	15 (39.5)	
Marital status, n (%)				
Single (or divorced)	34 (68.0)	11 (84.6)	32 (84.2)	0.156
Married	16 (32.0)	2 (15.4)	6 (15.8)	

BMP: bipolar manic phase, SUD: substance use disorder, SIP: substance-induced psychosis

Table 2. Medication of three different groups besides VPA

	BMP (n=50)	SUD (n=13)	SIP (n=38)	p
Medication, n (%)				
One type	26 (52.0)	10 (76.9)	18 (47.4)	0.175
Combined type	24 (48.0)	3 (23.1)	20 (52.6)	
One type of medication, n (%)				
Risperidone	11 (22.0)	2 (15.4)	6 (15.8)	
Olanzapine	7 (14.0)	4 (30.8)	12 (31.6)	
Other Antipsychotics'	6 (12.0)	2 (15.4)	0 (0.0)	
No other medication	2 (4.0)	2 (15.4)	0 (0.0)	
Combined type of medication, n (%)				
Combined Antipsychotics	23 (46.0)	3 (23.1)	17 (44.7)	
Antidepressants+Antipsychotics	1 (2.0)	0 (0.0)	3 (7.9)	

VPA: valproic acid, BMP: bipolar manic phase, SUD: substance use disorder, SIP: substance-induced psychosis

The substances used in the last three months by those with SUD and those with SIP were cannabinoids, synthetic cannabinoids, volatile substances, psychostimulants, and a combination of these (Table 3). The difference between the two groups in terms of single or mixed substance use was not significant (p=0.734).

The mean serum levels of VPA were 59.2±17.4 μg/ml in the SUD group, 60.9±13.5 μg/ml in the SIP group, and 61.8±13.7 μg/ml in the manic episode of bipolar disorder group (Table 4). No significant difference was found between the groups for serum valproate levels (p=0.840). When VPA levels were categorized as less than or greater than 50 μg/ml, no significant difference was found between the three groups (p=0.310).

No significant correlation was found between age and VPA concentration (r_s=-0.092, p=0.361). Also, there was no significant correlation between disease duration and VPA concentration (r_s=-0.031, p=0.757).

When considering SUDs and SIPs together as one group of substance use (Table 5), the median age was found statistically significantly different between the SUD+SIP and manic episode of bipolar disorder groups (p=0.001), while there was no significant difference in median disease duration between these two groups (p=0.780). The mean VPA level was found 60.5±14.4 μg/ml in the SUD+SIP group showing no significant difference compared to 61.8±13.7 μg/ml in the manic episode of bipolar disorder group (p=0.630). Also, no significant difference was found between two groups when VPA levels were categorized as less than or greater than 50 μg/ml (p=0.667).

Table 3. Substances used in the last three months in SUD and SIP groups

	SUD (n=13)	SIP (n=38)	p
Substance, n (%)			
One type	4 (30.8)	10 (26.3)	0.734
Mixed type	9 (69.2)	28 (73.7)	

SUD: substance use disorder, SIP: substance-induced psychosis

DISCUSSION

In this study, the difference in VPA pharmacokinetics and pharmacodynamics between groups may provide some clues to the mechanism of manic episodes of bipolar disorder, SUD, and SIP. Although we observed that serum VPA levels may vary in the clinical setting, we did not find a significant difference in serum VPA levels between the manic episode of bipolar disorder patients compared with SUD and SIP patients, and we did not find a relationship between drug pharmacokinetics.

They can affect it in two different ways. First, increased release of several neurotransmitters, including norepinephrine and other catecholamines, may increase hepatic blood flow during the acute episode of mania. The dose rate divided by the trough total VPA concentration was used to calculate the CL. The CLu, or intrinsic CL, was calculated as the ratio of the dose to the unbound concentration of VPA. VPA is a hepatically metabolized drug. It has a low extraction ratio. CLu is the intrinsic or metabolic CL. VPA levels are similar in all three groups, indicating that changes in liver perfusion caused by drug and other medication use do not affect sodium valproate serum levels. Other variables affecting hepatic metabolism are medication and age. Higher rates of antipsychotic medications and substance usage might have influenced the entire results by affecting hepatic metabolism. All three groups' antipsychotic medications were like each other which is compatible with our results that it did not change the serum level of VPA. Even though the median age of the groups was like each other, all in young adulthood, it was statistically different among groups of SUD and SIP, and manic episodes of bipolar disorder. We could not find a relationship between the serum concentration of VPA and age, and duration of illness. According to reports, there is a nonlinear relationship between VPA dosage and serum concentration, which means that serum concentration did not rise proportionately as the dose increased. The patient's blood drug concentration may not rise as expected when the drug dose is increased; this could be because the drug CL rate has also increased (25).

Table 4. Comparison of VPA concentration in three different groups

	BMP (n=50)	SUD (n=13)	SIP (n=38)	p
VPA concentration (μg/ml)	61.8±13.7	59.2±17.4	60.9±13.5	0.840
VPA concentration, n (%)				
<50 μg/ml	10 (20.0)	5 (38.5)	7 (18.4)	0.310
≥50 μg/ml	40 (80.0)	8 (61.5)	31 (81.6)	

VPA: valproic acid, BMP: bipolar manic phase, SUD: substance use disorder, SIP: substance-induced psychosis

Table 5. Age, duration of illness, and VPA Concentration in two different groups

	BMP (n=50)	SUD+SIP (n=51)	p
Age (years)	32 (16.5) [19-59]	25 (6) [15-43]	**0.001**
Duration of illness (years)	2 (12.5) [0.5-24]	4 (6) [0.5-25]	0.780
VPA concentration (μg/ml)	61.8±13.7	60.5±14.4	0.630
VPA concentration, n (%)			
<50 μg/ml	10 (20.0)	12 (23.5)	0.667
≥50 μg/ml	40 (80.0)	39 (76.5)	

VPA: valproic acid, BMP: bipolar manic phase, SUD: substance use disorder, SIP: substance-induced psychosis, descriptive statistics were reported with mean±standard deviation for normally distributed variables, and median (interquartile range, Q_3-Q_1) [minimum-maximum] for nonnormally distributed

In bipolar acute manic episodes, abnormalities in membrane transport systems and secondary messenger systems reduce erythrocyte Na+/K+/ATPase activity (23), increasing the volume of drug distribution and decreasing serum valproate levels. VPA is often used as a first-line treatment in patients with rapid cycles. As VPA has a limited therapeutic window, therapeutic drug monitoring is an essential component of drug therapy. It appears to be effective in treating mania at serum levels between 50 and 125 μg/ml, but the risk of toxicity increases above 125 μg/ml (26). It appears that the pharmacokinetics of some drugs may change depending on the bipolar disorder state (27).

Studies support the use of VPA in the treatment of cocaine dependence and alcohol dependence. It has been shown to be successful in preventing relapse. It has also been effective in controlling impulsivity and irritability, making it useful in the treatment of people with borderline personality disorder who are more likely to develop alcohol or drug use disorders. Patients with cocaine dependence may have lower levels of GABA. Several mechanisms in VPA favor the synthesis of GABA, increasing its release and the postsynaptic GABAergic response (20). All these findings support the use of valproate in SUDs or SIP.

Drug-disease interaction is a revolutionary strategy that has just come into vogue. Acute manic-bipolar illness affects the pharmacokinetics and pharmacodynamics of some drugs (28). Estimation of volume of distribution for one-compartment models and peripheral volume of distribution for two-compartment models. Although absorption of VPA is almost complete. Body weight, VPA dose, and age were significant covariates reported to influence the volume of distribution. The volume of distribution of VPA increased with increasing body weight and VPA dose. Saturable protein binding could explain the increased volume of distribution at higher doses (29). Consistent with our results, another study found that neither trough sodium valproate concentration nor internal CL changed between individuals in the acute manic episode and those in the maintenance period. On the other hand, patients with manic episodes require higher doses of VPA to achieve serum concentrations compared with patients with epilepsy (23).

Whether the patients' medication can be considered an important confounding factor. There was no significant difference between the groups in the medications used for the three disorders. Valproate monotherapy is as effective as antipsychotics and lithium in acute mania, but the combination of valproate and an antipsychotic is more effective than either drug alone. Valproate monotherapy has comparable efficacy to olanzapine in the maintenance treatment of bipolar disorder, although placebo-controlled evidence is limited. If an acute episode responds to the combination, maintenance treatment with valproate and quetiapine or olanzapine is more effective than valproate alone. Valproate may reduce plasma SGA concentrations (30). The addition of aripiprazole to lithium or valproate had no clinically meaningful effect on the pharmacokinetics of either drug (31). Smoking is very common in psychiatric inpatients. The prevalence of tobacco use is higher (36.1% versus 21.4%) in people with mental illness than in healthy controls (32). Although smoking does not affect the pharmacokinetics of VPA, we only included smoking patients in order to reduce one of the confounding factors affecting drug levels with other drug interactions. Smoking may induce CYP1A2 enzymes, thereby reducing the expected plasma levels of certain second-generation antipsychotics. Valproate is a minor substrate of CYP2A6, 2B6, 2C9, 2C19, and 2E1 and is almost completely metabolized with first-order kinetics (33). Smoking may have a direct effect on drugs metabolized by CYP1A2, such as olanzapine. It is unclear exactly how valproate and cannabinoids interact with one another. Valproate and cannabinoid treatment together had no discernible impact on each other's plasma levels or metabolites (34). There is no literature regarding the interaction between VPA and the other substances used.

In the study by Machino et al. (35), bipolar I and II patients were successfully treated with stable doses of valproate as prophylactic therapy for at least 12 months. Valproate levels may approximate appropriate valproate levels, and there may be a relationship between the amount of valproate required for stabilization and the subtype of bipolar disorder. In maintenance treatment, the bipolar I disorder group showed a greater trend towards a trough serum valproate level than the bipolar II disorder group.

Valproate was more effective than placebo in preventing the new episodes of mania or depression in bipolar disorder but did not differ significantly from lithium, second-generation antipsychotics, or other anticonvulsants. Overall, the benefits in bipolar depression were not significantly greater than those in mania (36). For the first time, a case series questions the depressogenic potential of valproate in people who have recovered from a severe manic episode. If a patient experiences depressive symptoms after recovery from a manic episode, a reduction in valproate dose should be considered as a therapeutic approach. The cases also show that lower valproate doses and serum levels are effective in the maintenance phase of bipolar disorder compared with the acute manic episode. It is emphasized that different valproate doses and serum levels may be therapeutic in different stages of bipolar disorder (37).

Although we did not find a significant difference, a recent study by Hsueh et al. (38) demonstrated the role of the dopaminergic system in bipolar disorder and the effect of VPA on this system at both clinical and preclinical levels. In euthymic bipolar disorder patients treated with VPA, there was a negative correlation between VPA concentration and striatal dopamine transporter (DAT) availability, whereas bipolar disorder patients had an increased level of striatal DAT availability compared to controls. These findings suggest that the DAT system, specifically DAT availability, is important in the pathophysiology of bipolar disorder. It is involved in VPA-mediated physiological changes. Therefore, a common mechanism in the pathophysiology of bipolar disorder and the therapeutic mechanism of VPA may be mediated by DAT availability. DAT homeostasis may represent a novel therapeutic strategy for bipolar disorder patients.

Ho et al. (39) conducted a genome-wide association study to understand the effects of antiepileptic drugs on mood stabilization in bipolar disorder patients and suggested a possible influence on drug absorption, suggesting that antiepileptic drugs may alter drug pharmacokinetics.

The limitation of this study is that it was conducted only with male patients that sex differences could not be evaluated. VPA level was examined only in the manic period of bipolar disorder. Even though all the patients are in young adulthood, and all are smokers, the age difference was significantly different between groups, and the amount of cigarette smoking is not evaluated in the study. Patients were treated with higher rates of antipsychotic medications by suggested guidelines and algorithms; however, antipsychotic medications may have affected the entire pattern of results. Additional latent but unmeasured variables may have contributed to the current pattern of results like body weight. Finally, if the study had been carried out over a longer period, and with a larger sample of patients, a difference might have been noticed.

CONCLUSION

The main findings of this study are that the concentration of sodium valproate in patients with manic episodes of bipolar disorder, SUD, and SIP did not differ significantly between groups. Mania or psychosis does not lead to a significant increase in VPA metabolism compared to substance use. As we cannot exclude the effects of substance use on liver metabolism, future studies may include patients with impulse control disorder or epilepsy in the comparison group.

Ethics Committee Approval: The study was approved by the Ethics Committee of Erenköy Mental and Nervous Diseases Training and Research Hospital (03.11.2014, 18/8).

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