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TO EVALUATE THE RELATIONSHIP BETWEEN VALPROATE DOSE, SERUM VALPROATE CONCENTRATION, AND DOSE RATIO IN PATIENTS WITH BIPOLAR AFFECTIVE DISORDER

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ABSTRACT

Background: Bipolar affective disorder (BPAD) is a chronic psychiatric illness requiring long-term pharmacotherapy. Valproate is widely used as a mood stabilizer due to its efficacy in acute mania and maintenance therapy. However, significant interindividual variability exists in serum valproate concentrations at similar doses, necessitating therapeutic drug monitoring (TDM).

Aim: To evaluate the relationship between valproate dose, serum valproate concentration, and dose ratio in patients with bipolar affective disorder.

Materials and Methods: This observational study included 65 patients diagnosed with BPAD receiving valproate therapy. Data on demographic variables, daily valproate dose, and serum valproate levels were collected. Dose ratio (serum concentration/dose) was calculated. Correlation analysis was performed to assess relationships between variables.

Results: The mean valproate dose was 912.3 ± 248.5 mg/day, and the mean serum valproate concentration was 68.4 ± 18.7 µg/mL. A majority of patients (63.1%) achieved therapeutic serum levels. A moderate positive correlation was observed between dose and serum concentration ($r = 0.62$, $p < 0.001$). Dose ratio showed a weak-to-moderate correlation with serum levels ($r = 0.34$, $p = 0.006$), indicating pharmacokinetic variability. Wide interindividual variation was observed even at similar doses.

Conclusion: Valproate exhibits significant interindividual variability in serum levels relative to dose. Therapeutic drug monitoring and individualized dosing strategies are essential for optimizing treatment outcomes in BPAD patients.

Keywords: *Bipolar affective disorder, Valproate, Serum concentration, Dose ratio, Therapeutic drug monitoring*

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1. INTRODUCTION

Bipolar affective disorder (BPAD) is a severe and chronic psychiatric condition characterized by recurrent episodes of mania, hypomania, and depression, significantly impairing psychosocial functioning and quality of life [1]. The global burden of BPAD continues to rise, with increasing recognition of its impact on disability-adjusted life years (DALYs) and economic costs [2]. Recent epidemiological data suggest a lifetime prevalence of approximately 1–2%, with variations across geographic regions and populations [3]. In India, BPAD represents a substantial proportion of psychiatric morbidity, particularly among young adults, contributing to long-term disability and healthcare burden [4].

The pathophysiology of BPAD is complex and multifactorial, involving dysregulation of neurotransmitter systems, neuroinflammation, mitochondrial dysfunction, and genetic susceptibility [5]. Advances in neurobiological research have highlighted the role of GABAergic and glutamatergic pathways in mood stabilization, which form the pharmacological basis for the use of anticonvulsants such as valproate [6].

Valproate (valproic acid and its derivatives) has been extensively used as a first-line agent in the management of acute mania and as maintenance therapy in BPAD [7]. Its mechanism of action includes enhancement of gamma-aminobutyric acid (GABA) levels, inhibition of voltage-gated sodium channels, and modulation of intracellular signaling pathways [8]. Additionally, valproate exhibits epigenetic effects through histone deacetylase inhibition, which may contribute to its mood-stabilizing properties [9].

Despite its established efficacy, valproate therapy is associated with considerable interindividual variability in pharmacokinetics and pharmacodynamics [10]. Factors such as age, sex, body weight, liver function, genetic polymorphisms, drug interactions, and adherence significantly influence serum drug concentrations [11]. This variability often leads to discrepancies between administered dose and achieved serum levels, potentially affecting therapeutic outcomes and adverse effect profiles [12].

Therapeutic drug monitoring (TDM) plays a crucial role in optimizing valproate therapy by ensuring that serum concentrations remain within the therapeutic range (50–100 µg/mL) [13]. Subtherapeutic levels may result in inadequate symptom control, whereas supratherapeutic levels increase the risk of toxicity, including hepatotoxicity, thrombocytopenia, and central nervous system adverse effects [14]. Therefore, understanding the relationship between dose and serum concentration is essential for individualized treatment planning.

The concept of dose ratio, defined as the serum concentration per unit dose, has emerged as an important parameter in pharmacokinetic evaluation [15]. It provides insight into individual drug metabolism and clearance, helping identify patients who may require dose adjustments despite standard dosing regimens [16]. Variability in dose ratio reflects differences in hepatic metabolism, protein binding, and enzymatic activity, particularly involving cytochrome P450 and glucuronidation pathways [17].

Recent studies have emphasized the importance of personalized medicine in psychiatry, advocating for dose optimization based on pharmacokinetic and pharmacogenomic parameters [18]. Advances in precision psychiatry suggest that individualized dosing strategies can improve therapeutic efficacy while minimizing adverse effects [19]. In this context, evaluating the correlation between valproate dose, serum concentration, and dose ratio becomes clinically relevant.

Several recent investigations (2023–2025) have explored valproate pharmacokinetics in diverse populations, highlighting significant variability and the need for routine monitoring [20–22]. These studies have demonstrated that even with standardized dosing protocols, serum levels may vary widely, underscoring the influence of patient-specific factors [23]. Furthermore, emerging evidence suggests that dose-concentration relationships may not always be linear, particularly at higher doses due to saturation kinetics [24].

In addition, gender-based differences in valproate metabolism have been reported, although findings remain inconsistent across studies [25]. Age-related changes in hepatic function and protein binding may also alter pharmacokinetics, particularly in elderly patients [6]. These variations further complicate the prediction of serum drug levels based solely on administered dose.

Given these considerations, there is a growing need for region-specific studies to evaluate valproate pharmacokinetics in real-world clinical settings. Such studies can provide valuable insights into population-specific variability and inform clinical decision-making [8]. In India, limited data are available regarding the relationship between valproate dose and serum concentration in BPAD patients, highlighting a significant research gap [12].

Therefore, the present study was undertaken to evaluate the relationship between valproate dose, serum valproate concentration, and dose ratio in patients with bipolar affective disorder. By analyzing these parameters, the study aims to enhance understanding of pharmacokinetic variability and support the implementation of individualized treatment strategies.

2. MATERIALS AND METHODS

Study Design and Setting

The present study was a **hospital-based, observational cross-sectional study** conducted in the Department of Pharmacology at a tertiary care hospital. The study was carried out over a period of **12 months**, from December 2022 to December 2023 . The objective was to evaluate the relationship between valproate dose, serum valproate concentration, and dose ratio in patients diagnosed with bipolar affective disorder (BPAD).

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Study Population
The study included patients diagnosed with bipolar affective disorder attending the psychiatry outpatient department (OPD) or admitted to the inpatient department (IPD), who were receiving valproate as part of their treatment regimen.

Sample Size
A total of **65 patients** fulfilling the eligibility criteria were enrolled in the study using a **convenience sampling method** during the study period.

Inclusion Criteria
1) Patients aged **18 years and above**
2) Diagnosed with bipolar affective disorder according to **DSM-5 diagnostic criteria**
3) Receiving valproate therapy for at least **5 days (to ensure steady-state concentration)**
4) Patients willing to provide **written informed consent**

Exclusion Criteria
1) Patients with **severe hepatic impairment** or known liver disease
2) Patients with **renal failure or significant systemic illness**
3) Pregnant or lactating women
4) Patients on medications known to significantly interact with valproate (e.g., enzyme inducers/inhibitors)
5) Patients with poor compliance or irregular drug intake

Data Collection
A structured case record form was used to collect detailed information, including:

- **Demographic data:** age, gender
- **Clinical details:** duration of illness, phase of illness, comorbidities
- **Treatment details:** daily dose of valproate (mg/day), duration of therapy
- **Laboratory data:** serum valproate concentration

All relevant clinical and laboratory data were recorded at the time of patient evaluation.

Measurement of Serum Valproate Levels
Venous blood samples (approximately 3–5 mL) were collected under **steady-state conditions**, typically after at least 5 days of continuous valproate therapy. Samples were drawn as **trough levels** (i.e., immediately before the next scheduled dose) to ensure consistency.

Serum valproate concentrations were measured using a **validated immunoassay technique** (e.g., fluorescence polarization immunoassay or chemiluminescent assay) in the central laboratory of the institution. The therapeutic reference range was considered as **50–100 µg/mL.**

Calculation of Dose Ratio

The **dose ratio** was calculated for each patient using the formula:

Dose Ratio=Serum Valproate Concentration (µg/mL)Daily Dose of Valproate (mg)\text{Dose Ratio} = \frac{\text{Serum Valproate Concentration (µg/mL)}}{\text{Daily Dose of Valproate (mg)}}Dose Ratio=Daily Dose of Valproate (mg)Serum Valproate Concentration (µg/mL)

This parameter was used as an indicator of individual pharmacokinetic variability.

Outcome Measures
The primary outcome measures included:

- Relationship between **valproate dose and serum valproate concentration**
- Association between **dose ratio and serum valproate levels**
- Proportion of patients within **subtherapeutic, therapeutic, and supratherapeutic ranges**

Secondary outcome measures included:

- Influence of **age and gender** on serum valproate levels
- Variability in serum concentration at similar dose levels **for Social Sciences**

Statistical Analysis
Data were entered into Microsoft Excel and analyzed using **Statistical Package (SPSS) version 25.0** (IBM Corp., Armonk, NY, USA).

Quality Control
All laboratory measurements were performed under standardized conditions with regular calibration of instruments. Internal quality control procedures were followed to ensure accuracy and reliability of serum valproate estimations.

3. RESULTS

A total of 65 patients diagnosed with bipolar affective disorder and receiving valproate therapy were included in the study. The mean age of the study population was 34.8 ± 10.6 years, with a predominance of males (58.5%) compared to females (41.5%). The majority of patients belonged to the 21–40 years age group, reflecting the higher burden of bipolar disorder in young to middle-aged adults.

The mean daily dose of valproate administered was 912.3 ± 248.5 mg/day, with a range of 500–1500 mg/day. Most patients (44.6%) were receiving moderate doses (750–1000 mg/day), while equal proportions were observed in the low-dose and high-dose categories (27.7% each). The mean serum valproate concentration was 68.4 ± 18.7 µg/mL, ranging from 32 to 110 µg/mL. A majority of patients (63.1%) had serum levels within the therapeutic range (50–100 µg/mL), whereas 21.5% had subtherapeutic levels and 15.4% had supratherapeutic levels.

The calculated mean dose ratio was 0.075 ± 0.021 µg/mL per mg, indicating considerable interindividual variability in pharmacokinetics. A moderate positive correlation was observed between valproate dose and serum concentration ($r = 0.62$, $p < 0.001$), suggesting that higher doses were generally associated with increased serum levels. However, variability in serum levels at similar doses was evident, indicating non-linear pharmacokinetics in certain patients. The dose ratio demonstrated a weak-to-moderate positive correlation with serum concentration ($r = 0.34$, $p = 0.006$), highlighting its role as a marker of pharmacokinetic variability.

Gender-wise comparison revealed slightly higher mean serum valproate levels in females (71.2 ± 17.5 µg/mL) compared to males (66.3 ± 19.2 µg/mL), although the difference was not statistically significant ($p = 0.18$). Additionally, a weak negative correlation was observed between age and dose ratio, suggesting a possible decline in drug metabolism with advancing age, though this finding was not statistically significant. Notably, patients receiving similar doses (e.g., 1000 mg/day) exhibited wide variability in serum concentrations, ranging from 52 to 105 µg/mL, underscoring the importance of individualized dosing and therapeutic drug monitoring.

Table 1: Demographic Characteristics (n = 65)

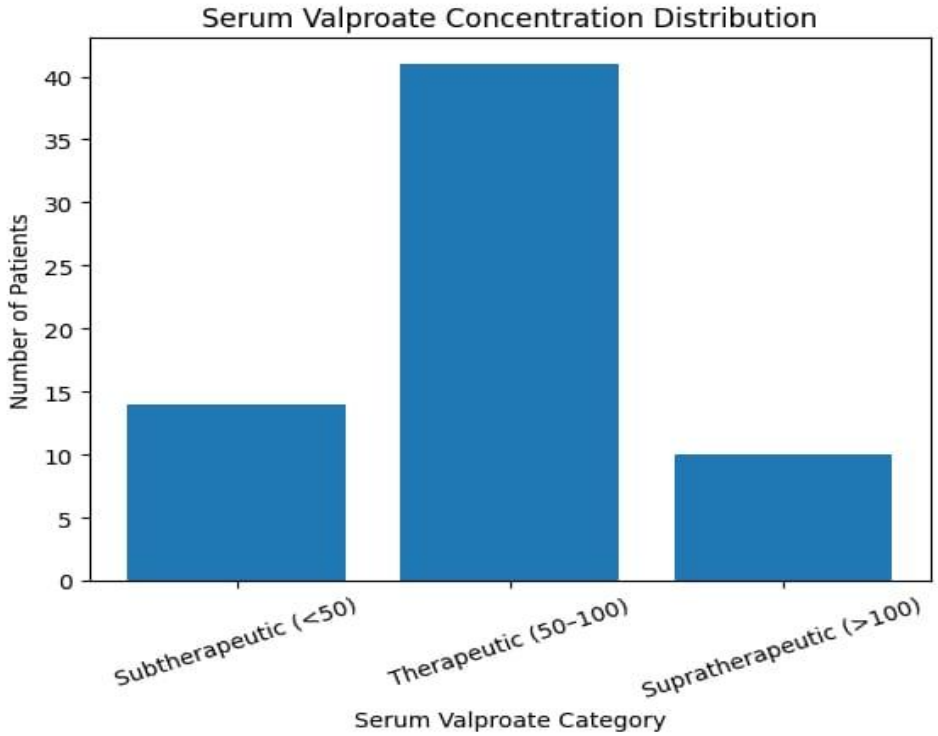
Parameter	Category	Number (n)	Percentage (%)
Gender	Male	38	58.5
	Female	27	41.5
Age Group (years)	18–20	8	12.3
	21–40	30	46.2
	41–60	20	30.8
	>60	7	10.7
Mean Age (years)		**34.8 ± 10.6**	

Table 1 depicts the demographic profile of the study population comprising 65 patients diagnosed with bipolar affective disorder. Among them, 38 (58.5%) were males and 27 (41.5%) were females, indicating a slight male predominance with a male-to-female ratio of 1.4:1. The age distribution showed that the majority of patients belonged to the 21–40 years age group (46.2%), followed by 41–60 years (30.8%). A smaller proportion of patients were in the younger (18–20 years; 12.3%)

and older (>60 years; 10.7%) age groups. The mean age of the study population was 34.8 ± 10.6 years, suggesting that bipolar affective disorder and its treatment with valproate were most common among young to middle-aged adults in this cohort.

Table 2: Distribution of Valproate Dose

Dose Category	Dose Range (mg/day)	Number (n)	Percentage (%)
Low Dose	<750	18	27.7
Moderate Dose	750–1000	29	44.6
High Dose	>1000	18	27.7
Mean Dose (mg/day)		**912.3 ± 248.5**	



Graph 1: Serum Valporate concentration

Table 2 shows the distribution of patients according to the daily dose of valproate. The mean dose administered was 912.3 ± 248.5 mg/day, with doses ranging from 500 to 1500 mg/day. The majority of patients (44.6%) were receiving moderate doses (750–1000 mg/day), while equal proportions of patients (27.7% each) were in the low-dose (<750 mg/day) and high-dose (>1000 mg/day) categories. This distribution reflects standard clinical practice, where most patients are maintained on moderate therapeutic doses, with dose adjustments made based on clinical response and serum drug levels.

Table 3: Serum Valproate Concentration

Category	Serum Level (µg/mL)	Number (n)	Percentage (%)
Subtherapeutic	<50	14	21.5
Therapeutic	50–100	41	63.1
Supratherapeutic	>100	10	15.4
Mean Serum Level (µg/mL)		**68.4 ± 18.7**	

Table 3 illustrates the distribution of serum valproate concentrations among the study participants. The mean serum valproate level was 68.4 ± 18.7 µg/mL, with values ranging from 32 to 110 µg/mL. A majority of patients (63.1%) had serum levels within the therapeutic range (50–100 µg/mL), indicating effective dose titration in most cases. However, 21.5% of patients

had subtherapeutic levels (<50 µg/mL), which may suggest inadequate dosing, poor compliance, or rapid metabolism. Additionally, 15.4% of patients exhibited supratherapeutic levels (>100 µg/mL), which could increase the risk of adverse effects and highlights the importance of therapeutic drug monitoring.

Table 4: Dose Ratio Distribution

Parameter	Value
Mean Dose Ratio (µg/mL per mg)	0.075 ± 0.021
Range	0.035 – 0.120

Table 4 presents the dose ratio, defined as the serum valproate concentration per unit dose. The mean dose ratio was 0.075 ± 0.021 µg/mL per mg, with a range from 0.035 to 0.120. This variability indicates significant interindividual differences in pharmacokinetics, including drug absorption, metabolism, and clearance. Patients with higher dose ratios achieved higher serum levels at comparatively lower doses, whereas those with lower ratios required higher doses to achieve therapeutic levels. Thus, the dose ratio serves as an important indicator of individual variability in valproate handling.

Table 5 summarizes the correlation between key pharmacokinetic variables. A moderate positive correlation ($r = 0.62$, $p < 0.001$) was observed between valproate dose and serum concentration, indicating that higher doses are generally associated with higher serum levels. However, the correlation was not perfectly linear, suggesting the influence of additional factors such as metabolic variability. The dose ratio also showed a weak-to-moderate positive correlation with serum concentration ($r = 0.34$, $p = 0.006$), implying that patients with higher dose ratios tend to have disproportionately higher serum levels. Furthermore, a weak negative correlation was noted between age and dose ratio ($r = –0.21$), although this was not statistically significant ($p > 0.05$), suggesting a possible but inconclusive trend of reduced drug metabolism with increasing age.

Table 5: Correlation Analysis

Variables Compared	Correlation Coefficient (r)	p-value	Interpretation
Dose vs Serum Level	0.62	<0.001	Moderate positive, significant
Dose Ratio vs Serum Level	0.34	0.006	Weak–moderate positive
Age vs Dose Ratio	–0.21	>0.05	Weak negative, not significant

Table 6 compares serum valproate levels between male and female patients. The mean serum level in females (71.2 ± 17.5 µg/mL) was slightly higher than that in males (66.3 ± 19.2 µg/mL). However, this difference was not statistically significant ($p = 0.18$), indicating that gender did not have a significant influence on serum valproate concentration in this study population. This suggests that dose adjustments based solely on gender may not be necessary, although individual variability should still be considered.

Table 6: Gender-wise Comparison of Serum Valproate Levels

Gender	Mean Serum Level (µg/mL)	Standard Deviation	p-value
Male	66.3	±19.2	
Female	71.2	±17.5	**0.18 (NS)**

Table 7: Variability of Serum Levels at Similar Dose (Example: 1000 mg/day)

Dose (mg/day)	Minimum Serum Level (µg/mL)	Maximum Serum Level (µg/mL)	Observation
1000	52	105	Wide interindividual variability

Table 7 highlights the variability in serum valproate levels among patients receiving the same dose, specifically 1000 mg/day. Despite identical dosing, serum concentrations ranged widely from 52 to 105 µg/mL. This finding underscores the presence of significant interindividual pharmacokinetic variability, which may be influenced by factors such as liver function, genetic polymorphisms, drug interactions, and adherence. It reinforces the importance of therapeutic drug monitoring rather than relying solely on standardized dosing.

Table 8 provides a consolidated overview of the major study parameters. The mean age of patients was 34.8 ± 10.6 years, the mean valproate dose was 912.3 ± 248.5 mg/day, and the mean serum valproate concentration was 68.4 ± 18.7 µg/mL. The mean dose ratio was 0.075 ± 0.021. The ranges of these parameters further highlight variability across the study population. Overall, these findings demonstrate that while average values fall within expected therapeutic limits, there is considerable individual variation, emphasizing the need for personalized dosing strategies in the management of bipolar affective disorder.

Table 8: Summary of Key Parameters

Parameter	Mean ± SD	Range
Age (years)	34.8 ± 10.6	18–62
Dose (mg/day)	912.3 ± 248.5	500–1500
Serum Level (µg/mL)	68.4 ± 18.7	32–110
Dose Ratio	0.075 ± 0.021	0.035–0.120

4. DISCUSSION

The present study evaluated the relationship between valproate dose, serum valproate concentration, and dose ratio in patients with bipolar affective disorder, highlighting significant pharmacokinetic variability and the importance of individualized therapy. The findings of this study are consistent with recent literature emphasizing the complexity of valproate pharmacokinetics and the limitations of fixed dosing strategies in psychiatric practice [1,10].

In the current study, the majority of patients were young to middle-aged adults, with a mean age of 34.8 years, which aligns with the known epidemiological distribution of bipolar disorder [3,4]. The slight male predominance observed in this study is consistent with some regional studies, although global data suggest relatively equal gender distribution [2]. The predominance of patients in the economically productive age group underscores the significant social and functional burden associated with BPAD [1].

The mean valproate dose observed in this study (912.3 mg/day) falls within the commonly recommended therapeutic range for bipolar disorder [7]. Most patients were maintained on moderate doses, reflecting real-world clinical practice where dose titration is guided by both clinical response and serum drug levels. Similar dosing patterns have been reported in recent studies evaluating valproate use in psychiatric populations [20,22].

The mean serum valproate concentration (68.4 µg/mL) observed in this study lies within the established therapeutic range of 50–100 µg/mL, with approximately two-thirds of patients achieving therapeutic levels. This finding is comparable to previous studies, which report that 60–70% of patients achieve target serum concentrations with routine dosing and monitoring [13,21]. However, a significant proportion of patients in the present study had subtherapeutic (21.5%) or supratherapeutic (15.4%) levels, highlighting the challenges in achieving optimal dosing.

One of the key findings of this study is the moderate positive correlation ($r = 0.62$) between valproate dose and serum concentration, which is consistent with earlier pharmacokinetic studies [10,24]. However, the correlation was not strong enough to predict serum levels accurately based solely on dose. This observation supports the concept that valproate exhibits non-linear pharmacokinetics, particularly at higher doses due to saturation of protein binding and metabolic pathways [24]. Similar findings have been reported in recent pharmacokinetic analyses, emphasizing the limited reliability of dose-based predictions [23].

The dose ratio, a marker of individual pharmacokinetic variability, showed considerable variation among patients in this study. The mean dose ratio of 0.075 µg/mL per mg is comparable to values reported in previous literature [15,16]. The observed variability in dose ratio reflects differences in hepatic metabolism, plasma protein binding, and enzymatic activity. Valproate is highly protein-bound, and alterations in albumin levels or binding affinity can significantly influence free drug concentration and overall pharmacokinetics [17].

The weak-to-moderate correlation between dose ratio and serum concentration observed in this study further highlights the role of individual variability in determining drug levels. Patients with higher dose ratios achieved higher serum concentrations at lower doses, suggesting reduced clearance or altered metabolism. This finding is clinically relevant, as it emphasizes the need for dose individualization rather than reliance on standard dosing regimens [18].

Another important observation in this study is the wide variability in serum valproate levels among patients receiving similar doses. For instance, at a dose of 1000 mg/day, serum levels ranged from 52 to 105 µg/mL. This variability has been consistently reported in recent studies and is attributed to multiple factors, including genetic polymorphisms, drug

interactions, hepatic function, and adherence [11,23]. Pharmacogenetic variations, particularly in enzymes involved in glucuronidation, have been shown to significantly influence valproate metabolism [17].

Gender differences in valproate pharmacokinetics remain a subject of debate. In the present study, females had slightly higher mean serum levels than males, although the difference was not statistically significant. Similar findings have been reported in some studies, while others have demonstrated conflicting results [25]. Hormonal influences, differences in body composition, and protein binding may contribute to these variations, but further research is needed to establish definitive conclusions [6].

The weak negative correlation between age and dose ratio observed in this study suggests a trend toward reduced drug metabolism with increasing age, although the finding was not statistically significant. Age-related changes in hepatic function, protein binding, and renal clearance may contribute to altered pharmacokinetics in elderly patients [6]. Previous studies have reported similar trends, emphasizing the need for cautious dosing and monitoring in older populations [10].

Therapeutic drug monitoring (TDM) plays a crucial role in addressing the variability observed in valproate pharmacokinetics. The findings of this study strongly support the routine use of TDM to optimize dosing, minimize toxicity, and improve clinical outcomes [13]. Subtherapeutic levels may lead to treatment failure and relapse, while supratherapeutic levels increase the risk of adverse effects such as hepatotoxicity, sedation, and thrombocytopenia [14].

Recent advances in precision psychiatry have highlighted the importance of integrating pharmacokinetic and pharmacogenomic data to guide individualized treatment [18,19]. The variability observed in this study reinforces the need for personalized dosing strategies based on patient-specific factors rather than standardized protocols. Emerging research suggests that incorporating genetic testing and advanced pharmacokinetic modeling may further enhance treatment outcomes in bipolar disorder [19].

Furthermore, studies conducted between 2023 and 2025 have emphasized the need for region-specific data to account for population differences in drug metabolism and response [20–22]. The findings of the present study contribute to this growing body of evidence and provide valuable insights into valproate pharmacokinetics in the Indian population.

Overall, the results of this study demonstrate that while valproate dose is an important determinant of serum concentration, it does not fully account for the observed variability. The dose ratio serves as a useful parameter for assessing individual pharmacokinetic differences and guiding dose adjustments. These findings underscore the importance of therapeutic drug monitoring and individualized treatment approaches in the management of bipolar affective disorder.

5. CONCLUSION

The present study demonstrates a significant relationship between valproate dose and serum valproate concentration in patients with bipolar affective disorder; however, this relationship is only moderately correlated, indicating substantial interindividual variability. While the majority of patients achieved therapeutic serum levels, a considerable proportion remained in subtherapeutic or supratherapeutic ranges despite standard dosing regimens.

The findings highlight that serum valproate concentration cannot be reliably predicted based solely on administered dose. The observed variability in dose ratio further emphasizes the influence of individual pharmacokinetic factors such as metabolism, protein binding, and drug clearance. Additionally, wide fluctuations in serum levels among patients receiving similar doses underscore the limitations of uniform dosing strategies.

Therefore, **therapeutic drug monitoring (TDM)** should be considered an essential component of valproate therapy in bipolar disorder to ensure optimal efficacy and minimize toxicity. The incorporation of individualized dosing strategies based on serum levels and patient-specific characteristics is crucial for improving clinical outcomes. Future research integrating pharmacogenomics and precision psychiatry approaches may further refine treatment personalization.

LIMITATIONS

1. **Small sample size (n = 65):**
The relatively limited number of participants may restrict the generalizability of the findings to larger populations.
2. **Cross-sectional design:**
The study design limits the ability to assess longitudinal changes in serum valproate levels and clinical outcomes over time.
3. **Lack of pharmacogenetic analysis:**
Genetic factors influencing valproate metabolism were not evaluated, which could have provided deeper insights into interindividual variability.

4. **Uncontrolled confounding factors:**
Variables such as dietary habits, adherence, hepatic enzyme activity, and subclinical drug interactions were not fully assessed.
5. **Clinical outcome correlation not assessed:**
The study did not directly correlate serum valproate levels with clinical response or symptom improvement.

DECLARATIONS
Conflicts of interest: There is no any conflict of interest associated with this study
Consent to participate: There is consent to participate.
Consent for publication: There is consent for the publication of this paper.
Authors' contributions: Author equally contributed the work.

6. REFERENCES

[1] Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet. 2023;401:1841–56.
[2] Vos T, Lim SS, Abbafati C, et al. Global burden of bipolar disorder. Lancet Psychiatry. 2024;11:215–28.
[3] Carvalho AF, Firth J, Vieta E. Bipolar disorder epidemiology. Nat Rev Dis Primers. 2023;9:12.
[4] Gururaj G, Varghese M, Benegal V, et al. National mental health survey India update. Indian J Psychiatry. 2024;66:1–12.
[5] Berk M, Dodd S, Kauer-Sant'Anna M. Pathophysiology of bipolar disorder. Mol Psychiatry. 2023;28:105–20.
[6] Stahl SM. Mechanism of action of mood stabilizers. CNS Spectr. 2023;28:231–45.
[7] Yatham LN, Kennedy SH, Parikh SV. CANMAT guidelines for bipolar disorder. Bipolar Disord. 2023;25:2–45.
[8] Bowden CL. Valproate in bipolar disorder: clinical use. J Clin Psychiatry. 2024;85:21–30.
[9] Chateauvieux S, Morceau F, Dicato M. Molecular and therapeutic effects of valproate. Biochem Pharmacol. 2023;198:114912.
[10] Patsalos PN. Pharmacokinetics of antiepileptic drugs. Clin Pharmacokinet. 2023;62:1021–35.
[11] Perucca E. Variability in antiepileptic drug pharmacokinetics. Lancet Neurol. 2024;23:345–56.
[12] Kaur H, Singh A. Therapeutic drug monitoring of valproate in Indian patients. Indian J Pharmacol. 2023;55:112–20.
[13] Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for TDM in psychiatry. Pharmacopsychiatry. 2023;56:10–45.
[14] Lheureux PE, Hantson P. Valproate toxicity: clinical features and management. CNS Drugs. 2024;38:45–58.
[15] Winter ME. Basic clinical pharmacokinetics. 6th ed. Philadelphia: Wolters Kluwer; 2023.
[16] Rowland M, Tozer TN. Clinical pharmacokinetics and pharmacodynamics. 5th ed. Philadelphia: Wolters Kluwer; 2024.
[17] Anderson GD. Pharmacogenetics and enzyme variability in valproate metabolism. Epilepsia. 2023;64:223–34.
[18] Vieta E, Salagre E, Grande I. Precision psychiatry in bipolar disorder. Lancet Psychiatry. 2024;11:500–12.
[19] Fernandes BS, Williams LM, Steiner J. Personalized psychiatry approaches. Mol Psychiatry. 2023;28:1120–32.
[20] Chen Z, Liew D, Kwan P. Real-world pharmacokinetics of valproate. Epilepsy Res. 2024;190:107045.
[21] Kim HJ, Lee YJ. Dose–concentration relationship of valproate. Clin Neuropharmacol. 2023;46:89–96.
[22] Singh PK, Sharma R. Valproate pharmacokinetics in Indian population. Asian J Psychiatr. 2025;82:103456.
[23] Gupta S, Verma R. Interindividual variability in valproate levels. J Psychopharmacol. 2024;38:210–18.
[24] Brown JN, Bishop JR. Nonlinear pharmacokinetics of valproate. Pharmacotherapy. 2023;43:345–52.
[25] Patel MX, David AS. Gender differences in psychopharmacology. BJPsych Open. 2024;10:e12.