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# The Use and Side Effect Profile of Valproate and Lamotrigine in Child and Adolescent Psychiatry

## Valproat ve Lamotrijinin Çocuk ve Ergen Psikiyatrisinde Kullanımı ve Yan Etki Profili

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### ABSTRACT

**Aim:** Depressive and bipolar disorder are increasingly recognized psychiatric disorders in children and adolescents. Pharmacotherapy plays a significant role in managing symptoms in these patients. The research aims to investigate the effects and treatment side effect profiles of drugs such as lamotrigine and valproate commonly used in youth.

**Materials and Methods:** A total of 80 patients who had received treatment at a tertiary care psychiatric hospital were included in the study. These patients were diagnosed with major depressive disorders bipolar disorder, conduct disorder, early-onset schizophrenia, and autism spectrum disorder. Demographic characteristics, diagnoses, and treatment durations of the patients were recorded. Treatment response was evaluated using symptom severity scales. Side effects after the start of medication were recorded.

**Results:** Lamotrigine and valproate treatment have been found to be effective in treating mood disorders and irritability symptoms in children and adolescents. Mild side effects such as sedation (n=29) and easy fatigue (n=33) were more frequent in patients receiving lamotrigine and valproate treatment. Rash (n=2) and polycystic ovary syndrome (n=1) were seen much less frequently. Tremor and polycystic ovary syndrome were more frequent in patients receiving valproate treatment, while itching and rash were reported in those receiving lamotrigine.

**Conclusion:** The findings of the investigation suggest that lamotrigine and valproate are easily tolerated in the treatment of mood disorders and irritability symptoms during child and adolescence. The use of valproate and lamotrigine treatments should be considered for children and adolescents where appropriate. Side effects that could significantly impact treatment adherence are rarely observed.

**Keywords:** Lamotrigine, valproate, children and adolescents, irritability

### ÖZ

**Amaç:** Depresif ve bipolar bozukluklar, çocuklar ve ergenlerde giderek daha fazla tanınan psikiyatrik bozukluklardır. Bu hastaların semptomlarını yönetmede farmakoterapi önemli bir rol oynamaktadır. Bu araştırmanın amacı, çocuk ve ergenlerde lamotrijin ve valproat gibi ilaçların kullanımını, etkilerini ve tedavi yan etki profillerini incelemektir.

**Gereç ve Yöntem:** Çalışmaya, üçüncü basamak psikiyatri hastanesinde tedavi almış toplam 80 hasta dahil edilmiştir. Bu hastalara majör depresif bozukluk, bipolar bozukluk, davranış bozukluğu, erken başlangıçlı şizofreni ve otizm spektrum bozukluğu tanıları konmuştur. Hastaların demografik özellikleri, tanıları ve tedavi süreleri kaydedilmiştir. Tedavi yanıtı, semptom şiddet ölçekleri kullanılarak değerlendirilmiştir. İlaç kullanımının başlamasından sonraki yan etkiler kaydedilmiştir.

**Bulgular:** Lamotrijin ve valproat tedavisi, çocuk ve ergenlerde duygudurum bozuklukları ve irritabilite semptomlarının tedavisinde etkili bulunmuştur. Sedasyon (n=29) ve kolay yorulma (n=33) gibi semptomlar daha sık görülmüştür. Döküntü (n=2) ve polikistik over sendromu (n=1) gibi daha nadir görülen yan etkiler tespit edilmiştir. Tremor ve polikistik over sendromu valproat kullanan hastalarda daha sık görülürken, kaşıntı ve döküntü lamotrijin kullananlarda tespit edilmiştir.

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**Sonuç:** Bu araştırmanın bulguları, lamotrijin ve valproat tedavilerinin çocukluk ve ergenlik döneminde duygudurum bozuklukları ve irritabilite semptomlarının tedavisinde iyi tolere edilebildiğini göstermektedir. Valproat ve lamotrijin tedavileri, çocuk ve ergenlerde tedavi seçeneği olarak değerlendirilmelidir. Tedavi uyumunu olumsuz etkileyebilecek ciddi yan etkiler nadiren gözlemlenmektedir.

**Anahtar Kelimeler:** Lamotrijin, valproat, çocuk ve ergen, irritabilite

## INTRODUCTION

Bipolar disorder and major depressive disorder (MDD), which also include mood disorders, are quite common in adolescents and are associated with serious mortality and morbidity[1]. Mood-stabilizing anticonvulsant medications like lamotrigine and valproate have shown efficacy in treating mood disorders and irritability. However, there is insufficient data regarding their utilization and adverse reactions in this demographic[2]. The guidelines of the American Psychiatric Association have begun recommending lamotrigine as one of the first-line treatment options for depression episodes and maintenance therapy in bipolar disorder[3]. In a meta-analysis including 8 double-blind, randomized controlled trials, lamotrigine augmentation has been suggested as a potential option for patients with treatment-resistant unipolar depression[4].

There is moderate evidence supporting the efficacy of lamotrigine as both an augmenting agent and monotherapy for pediatric mood disorders[5]. Efficacy, tolerability, and safety are essential considerations in optimizing pharmacotherapy for mood disorders, which often require long-term medication use. The most reported side effects of lamotrigine are headache, insomnia, and rash. Other side effects include nausea, dizziness, infection, dry mouth, ataxia, and tremor[6]. Rashes occurring with lamotrigine use are typically morbilliform, maculopapular, and often pruritic, with an incidence of 1-36%[7-12]. In adults receiving lamotrigine treatment, the rate of rash-related hospitalization is 0.3%, while in pediatric patients, it is 1.0%. The frequency of Stevens-Johnson syndrome is 0.1% in adults and 0.5% in child patients[13]. A preferred side effect of lamotrigine compared to other drugs used in bipolar disorder is weight loss[14].

In a placebo-controlled 18-month study of maintenance therapy with lamotrigine and lithium in patients who had recently experienced mania or hypomania with bipolar disorder, both lamotrigine and lithium were found to prolong the duration until intervention for any mood episode, and lamotrigine was superior to placebo in extending the time to depressive episodes[15]. The safety and tolerability of lamotrigine have been demonstrated in eight placebo-controlled clinical trials involving patients with bipolar disorder. These studies, conducted over 3 to 76 weeks, utilized lamotrigine in doses ranging from 50 to 500 mg, with four trials focusing on maintenance therapy and four on acute treatment of mood episodes. The data from these clinical trials have provided a significant source of safety facts regarding lamotrigine[16].

In a meta-analysis comprising five randomized controlled trials evaluating lamotrigine treatment in adults with bipolar depression, lamotrigine was found to be superior to placebo in individuals treated with lamotrigine, who had a Hamilton Depression Rating Scale score >24[17]. In the study evaluating lamotrigine as augmentation in patients with treatment-resistant MDD receiving fluoxetine treatment, the effect of lamotrigine on Clinical Global Impression scores was found to be significant both in MDD and bipolar disorder[18]. In a meta-analysis of agents for manic episodes, lamotrigine was not found to be superior to placebo[19]. Lamotrigine did not have any significant impact on body weight[20].

Adolescents with bipolar disorder and depressive episodes have shown a good response to treatment with lamotrigine in terms of both overall clinical impression and depression scores, and lamotrigine has been well tolerated. No rash considered to be related to the medication or requiring discontinuation of the drug has been observed[21].

Several pilot studies have shown promising results for lamotrigine, particularly in depressive symptoms, in treatment-resistant mood disorders in both youth and adults[8,22]. A pilot study on treatment-resistant mood disorders demonstrated that lamotrigine was effective and well-tolerated[8]. In a prospective study with adolescent bipolar depression patients, most patients responded to lamotrigine, with no observed weight gain or rash[21]. In a study investigating the efficacy and safety of lamotrigine in treating depressive episodes in adolescents, an average dose of 65.4±37.5 mg/day was used in 37 adolescent patients. Lamotrigine was well tolerated in this study, with the most common side effect being skin rash (n=5, 13.5%), which spontaneously resolved after the discontinuation of the medication[12].

Valproate is primarily used in the psychiatric treatment of bipolar disorder. It has also been used in schizophrenia and borderline personality disorder[23]. In patients with Cluster B personality disorders, valproate has been observed to provide benefits both in terms of aggression scores and treatment purposes[24]. Two small randomized controlled trials, one with 25 patients and the other with 18 patients with bipolar depression, compared valproate with placebo in bipolar depression, and both reported a positive outcome[25,26].

Valproate has gastrointestinal side effects (nausea, vomiting, dyspepsia, diarrhea, constipation)[27]. However, the most common and dose-dependent side effect is postural tremor[28]. Valproate can also cause reversible hair loss and changes in hair structure[29]. Headache, nystagmus, dizziness, and blurred vision can occur. Weight gain is a side effect of long-term use[30]. Weight gain induced by valproic acid has been associated with hyperinsulinism and polycystic ovary syndrome[31,32]. Some patients taking valproate have reported thrombocytopenia, platelet dysfunction, and coagulation abnormalities[33]. It can cause two important idiosyncratic reactions: acute pancreatitis and liver failure[34,35].

Although the side effect profiles of lamotrigine and valproate have been studied, there are limited data on their use in the pediatric population. Specifically, concerns about adverse effects in adolescents, especially in cases of treatment-resistant depression and bipolar disorder, warrant careful consideration. This article aims to evaluate the indications and side effect profiles of these medications in adolescents, demonstrating that with appropriate dosing, they do not pose undue risks. The goal is to facilitate their use in pediatric populations when indicated. Adolescence is a critical period marked by an increased prevalence of psychiatric disorders, highlighting the importance of effective treatment options. This study, therefore, focuses on the use of lamotrigine and valproate in adolescents, providing valuable insights into their clinical application.

**Table 1. The primary diagnoses of the patients**

| Diagnoses | n=80 |
|---|---|
| Major depressive disorder | 30 |
| Bipolar disorder | 23 |
| Conduct disorder | 14 |
| Early-onset schizophrenia | 11 |
| Autism spectrum disorder | 2 |

## MATERIAL AND METHODS

A total of 80 patients admitted to the child and adolescent psychiatry service at the tertiary care psychiatric hospital were included in the study. Patients were diagnosed based on the School-Age Children's Mood Disorders and Schizophrenia Interview Schedule-Current and Lifetime Version[36,37], including MDD (n=30), bipolar disorder (n=23), conduct disorder (n=14), early onset schizophrenia (n=11), and autism spectrum disorder (n=2) according to DSM-5 criteria (Table 1). Nine patients had comorbid ADHD, seven patients had mild intellectual disability, and five patients had substance use disorder. Our patients were not treated with monotherapy; they were concurrently undergoing antipsychotic treatment. Each antipsychotic dose was converted to chlorpromazine equivalents in mg/day[38] and is presented in Table 2. Additionally, among the patients using lamotrigine, 14 were treated with escitalopram, and five were treated with sertraline. The severity of the illness was assessed using the Clinical Global Impression Scale upon hospital admission and discharge. The UKU Side Effect Rating Scale was

**Table 2. The patients' sociodemographic data**

| Variables | Valproate (n=49) | Lamotrigine (n=31) | p-value |
|---|---|---|---|
| Sex, female, n (%) | 15 (30.6) | 24 (77.4) | **<0.001** |
| Ages, y, M ± SD | 16.2±1.5 | 16.0±1.5 | 0.526 |
| Education year, y, M ± SD | 8.7±2.6 | 10.1±1.2 | **0.006** |
| Weight, admission, kg, M ± SD | 71.3±18.9 | 70.4±14.9 | 0.828 |
| Weight, discharge, kg M ± SD | 73.7±18.7 | 72.7±14.1 | 0.803 |
| Weight difference, kg, M ± SD | 2.4±4.2 | 2.3±3.4 | 0.910 |
| Length of hospital stay, day, M ± SD | 171.4±123.1 | 108.4±101.3 | 0.016 |
| CGI-S, admission, M ± SD | 4.9±0.9 | 3.9±0.9 | **<0.001** |
| CGI-S, discharge, M ± SD | 2.6±0.7 | 2.1±0.3 | **<0.001** |
| Lamotrigine, M ± SD | - | 99.1±62.1 | |
| Valproate, M ± SD | 1166.6±429.9 | - | |
| Duration of mood stabilizer use, days, M ± SD | 171.4±123.1 | 108.4±101.3 | **0.020** |
| Average chlorpromazine equivalent dose, M ± SD | 808.7±386.6 | 551.6±273.4 | **0.002** |
| Suicide attempt, n (%) | 9 (8.4) | 22 (71.0) | **<0.001** |
| NSSI, n (%) | 19 (38.8) | 29 (93.5) | **<0.001** |
| Smoking, n (%) | 25 (51.0) | 20 (64.5) | 0.236 |
| Alcohol, n (%) | 16 (33.3) | 14 (45.2) | 0.290 |
| Substance, n (%) | 10 (20.4) | 4 (12.9) | 0.389 |

CGI-S: Clinical Global Impression- Symptom, NSSI: Non-Suicidal Self-Injury, SD: Standard deviation, M: Mean

used to collect comprehensive information on psychotropic drug side effects[39]. The data of 80 patients who were under follow-up and treated with lamotrigine or valproate at our center were retrospectively reviewed. The patients' demographic and diagnostic characteristics, treatments, and UKU[40] and Clinical Global Impression- Symptom (CGI-S) scale results from their files were retrospectively evaluated. The dose of lamotrigine was increased by 25 mg/day every 3 days, and the dose of valproate was increased by 500 mg/week, titrated to maintain blood levels between 80-100 µg/mL. The average duration of medication use was 45 days. Patients were followed up at a tertiary psychiatric hospital between January 2022 and January 2023. The study protocol was reviewed and approved by the Bakırköy Sadi Konuk Trainig and Research Hospital Clinical Research Ethics Committee under (decision no: 2023/59, date: 23.01.2023). Both the patients and the parents of the patients involved in the study provided written informed consent.

Exclusion criteria included patients with head trauma, epilepsy, or other neurological or chronic medical conditions (liver, kidney, and pancreas diseases etc.). Patients with severe sensory impairments or who were unable to cooperate during assessments were also excluded. Defining the number of excluded patients is important for emphasizing the point of widespread use of the medication. A patient with an epilepsy diagnosis using lamotrigine and another patient using valproate after electroconvulsive therapy were excluded from the study.

### Statistical Analysis

The skewness and kurtosis values were examined to determine whether the data pertaining to the patients exhibited a normal distribution. The independent t-test was applied to analyze continuous variables with a normal distribution concerning patients' sociodemographic data. These variables were represented as mean ± standard deviation in the table. For categorical variables, The chi-square test was utilized. Descriptive statistics were employed to present the data on medication side effects among patients, which were presented as frequencies and percentages (%). Additionally, descriptive statistics were included in the table for diagnosis and medication usage. Statistical analyses were performed using the SPSS, version 26. A significance level of 0.05 was adopted for all analyses.

## RESULTS

Eighty adolescents (aged 13-18 years, with a mean age of 16.1±1.4 years) treated with lamotrigine and valproate were identified. 49 patients were using valproate, and 31 were using lamotrigine. Patient data were summarized in Table 2. Among the diagnoses, 30 had unipolar depression, 23 had bipolar disorder, 14 had conduct disorder, eleven had early-onset schizophrenia, and two had autism spectrum disorder. The indications for the use of lamotrigine and valproate are shown in Table 3. Forty-eight-point eight percent (n=39) of the sample was female. The average daily dose of lamotrigine was 99.1±62.1 mg, and the average daily dose of valproate was 1166.6±429.9 mg. The mean duration of lamotrigine treatment was 108.4±101.3 days, and for valproate, it was 171.4±123.1 days. The mean CGI-S score decreased from 4.5±1.0 at baseline to 2.4±0.6 at the endpoint.

In our study, side effects were observed in 74.2% (n=23) of patients using lamotrigine and 75.5% (n=37) of patients using valproate. The most reported side effects after lamotrigine and valproate drug treatment were sedation and easy fatigue. The rate of easy fatigue in patients receiving valproate (44.9%) was higher than those receiving lamotrigine (35.5%). However, there was no statistically significant difference (p=0.405). Sedation rates between valproate and lamotrigine were similar (34.7% and 38.7%, respectively), with no statistically significant difference (p=0.716). After valproate use, tremor occurred in 20.4% (n=10) of patients, and one patient developed polycystic ovary syndrome. After lamotrigine use, pruritus occurred in 22.6% (n=7) of patients, and rash occurred in 6.5% (n=2). The rash appeared in the first week of lamotrigine treatment and resolved after the discontinuation of the drug. Data on side effects are summarized in Table 4.

## DISCUSSION

This study evaluates the indications and side effect profiles of lamotrigine and valproate in children and adolescents with mood disorders, including MDD and bipolar disorder, as well as common symptoms such as irritability during adolescence. There is limited literature on the effects of these drugs on children and adolescents. The results of the study indicate that these drugs may be effective and well-tolerated in the young population.

The effects of lamotrigine and valproate on clinical global impression scores were significant in some studies, including ours[18,21], but not significant in other studies[19,41]. This discrepancy can be explained by the different mood episode periods in which the patient groups were. This supports that lamotrigine may be particularly beneficial in patients experiencing a depressive episode.

**Table 3. Indications for the use of medications**

| Indications, n (%) | Valproate (n=49) | Lamotrigine (n=31) |
|---|---|---|
| Irritability | 30 (61.2) | 1 (3.2) |
| Treatment resistant depressive disorder | 2 (4.1) | 25 (80.6) |
| Bipolar disorder, manic episode | 17 (34.7) | 2 (6.5) |
| Bipolar disorder, depressive episode | - | 3 (9.7) |

| Tablo 4. Mood stabilizers side effects | | | |
|---|---|---|---|
| **Side effects** | **Valproate (n=49)** | **Lamotrigine (n=31)** | **p-value** |
| Difficulty in concentrating, n (%) | 2 (4.0) | 5 (16.1) | 0.051 |
| Fatigue, n (%) | 22 (44.9) | 11 (35.5) | 0.405 |
| Sedation, n (%) | 17 (34.7) | 12 (38.7) | 0.716 |
| Forgetfulness, n (%) | 4 (8.2) | 0 (0.0) | 0.103 |
| Inner restlessness, n (%) | 6 (12.2) | 0 (0.0) | 0.128 |
| Increased sleep duration, n (%) | 9 (18.4) | 8 (25.8) | 0.428 |
| Decreased sleep duration, n (%) | 2 (4.1) | 0 (0.0) | 0.523 |
| Tremor, n (%) | 10 (20.4) | 2 (6.5) | 0.089 |
| Nausea n (%) | 9 (18.4) | 6 (19.4) | 0.912 |
| Diarrhea, n (%) | 7 (14.3) | 3 (9.7) | 0.544 |
| Rash, n (%) | 0 (0.0) | 2 (6.5) | 0.072 |
| Photosensitivity, n (%) | 1 (2.0) | 1 (3.2) | 0.741 |
| Pruritus, n (%) | 1 (2.0) | 7 (22.6) | **0.003** |
| Pigmentation, n (%) | 0 (0.0) | 1 (3.2) | 0.206 |
| Weight gain, n (%) | 8 (16.3) | 9 (29.0) | 0.176 |
| Amenorrhea, n (%) | 2 (4.1) | 1 (3.2) | 0.844 |
| Headache, n (%) | 13 (26.5) | 8 (25.8) | 0.943 |
| Polycystic ovary syndrome, n (%) | 1 (2.0) | 0 (0.0) | 0.875 |

No serious side effects were observed with lamotrigine or valproate in our patient group, and the most common side effects were sedation (n=29) and easy fatigability (n=33). The tolerability of these medications has been well-documented in prior research[5,8,12,16,21]. Fatigue is less frequently reported for lamotrigine and valproate in the literature compared to our findings, which may be due to concurrent antipsychotic use[42,43].

The widespread and dose-dependent side effect of valproate is postural tremor, which occurred in 20.4% of our patients in this study[44]. Mild itching and rash were observed with lamotrigine, which resolved after discontinuing the medication. No serious side effects, such as Stevens-Johnson syndrome, have been observed, as found in several studies in the literature[7-9,11,12]. Similar to our study, in a study by Carandang et al.[8] with demographically similar participants, benign rash developed in one out of a total of 9 adolescents with mood disorders (%11) who were using lamotrigine. No serious side effects related to valproate and lamotrigine were observed in any of our patients. Rash occurred in two patients at the initiation of lamotrigine treatment, and as a precaution, the medication was discontinued. The absence of serious side effects is likely due to gradual dose escalation (25 mg/day increase every three days) and close monitoring. Initiating medications of concern under close observation for potential side effects is an important option. The absence of serious side effects in our study aligns with the literature, which highlights the safety and tolerability of valproate and lamotrigine in clinical practice[8,13,16,45]. Weight gain has been reported in 10-70% of patients treated with valproate[46-50]. In our study, 16.3% of patients using valproate experienced weight gain. Contrary to the findings in the literature, 29% of those using lamotrigine showed weight gain[20]. This is noteworthy because lamotrigine is generally associated with a lower likelihood of weight gain or no weight gain[14]. This finding may be attributed to the concurrent use of antipsychotics in these patients. Polycystic ovary syndrome was observed in one patient receiving valproate, but the treatment was continued. However, it should be noted that the presence of side effects and individual response to treatment can vary from one person to another. Therefore, this is significant to assess the characteristics of patients and the risk of side effects before the use of medications.

## Study Limitations

The study has limitations, including the use of various medications in combination and a small sample size. Methodological issues include highly variable treatment durations and types, heterogeneous samples, and the uncertain effect of comorbid conditions. Determining whether the side effects are caused by lamotrigine, the placebo effect, or concurrent medications is challenging. These intricate elements constrain the validity and reliability of the results.

## CONCLUSION

In conclusion, the study's findings suggest that lamotrigine and valproate may be viable options for managing mood disorders and irritability in adolescence. Nonetheless, additional investigation is warranted to ascertain their prolonged effects. This research highlights the potential of lamotrigine and valproate as safe and effective treatments for mood disorders in adolescents, though further studies are needed to confirm these findings.

### Ethics

**Ethics Committee Approval:** The study protocol was reviewed and approved by the Bakırköy Sadi Konuk Trainig and Research Hospital Clinical Research Ethics Committee under (decision no: 2023/59, date:23.01.2023).

**Informed Consent:** Both the patients and the parents of the patients involved in the study provided written informed consent.

### Footnotes

### Authorship Contributions

Concept: Y.S., Design: Y.S., Data Collection or Processing: K.T., Ş.A., Analysis or Interpretation: G.K., Literature Search: K.T., Ş.A., G.K., Writing: Y.S., G.K.

### Footnotes

**Conflict of Interest:** No conflict of interest was declared by the authors.

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