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The side effects of clobazam as add-on therapy in pediatric epilepsy patients

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ABSTRACT

Objectives: Epilepsy is a long-term cerebral disorder that accompanies a lifelong predisposition to epileptic seizures, resulting in neurobiological, cognitive, psychological, and social problems. Clobazam is considered a relatively safe and effective anticonvulsant, frequently prescribed for the management of pediatric epilepsy. This study was designed to rigorously evaluate the safety profile of clobazam in pediatric epilepsy, with a particular focus on the incidence and nature of treatment-emergent side effects.

Methods: Patients aged 2 to 17 years, who received clobazam as an adjunct to valproic acid, levetiracetam, or carbamazepine therapy, who were referred to Diyarbakır Children's Hospital between December 2021 and March 2023 were included. We evaluated the safety profile of clobazam in pediatric epilepsy, with a particular focus on the incidence and nature of treatment-emergent side effects.

Results: The study included 100 patients using clobazam as an add-on anti-seizure medication. The mean age was 11.0±4.0 years, with males comprising 48% of the cohort. The average duration of clobazam use was 16.3±7.2 months. Side effects were reported in 30 patients (30%), with the most common being insomnia (10%), agitation (9%), and somnolence (6%). Allergic reactions were the least frequent. No patients experienced enuresis, ataxia, hypertension, hypotension, or constipation in our study. Clobazam was discontinued by 12% of the patients due to side effects.

Conclusions: Clobazam is regarded as safe in pediatric epilepsy patients, with minimal concerns regarding drug interactions and adverse reactions. Although it may cause some side effects, initiating low-dose treatment and gradually increasing the dosage can enhance treatment success.

Keywords: Clobazam, epilepsy, pediatric patients, side effects

Epilepsy is one of the most common neurological disorders that affect the world population. Clobazam is a widely used benzodiazepine indicated as adjunctive therapy for pediatric epilepsy with proven efficacies in reducing seizure frequency in a range of epilepsy syndromes including Lennox-Gastaut syndrome, focal epilepsy [1-3], and generalized epilepsies. However, as with other anti-seizure drugs (ASDs), clobazam use is associated with a range of side effects. Clobazam undergoes extensive hepatic metabolism via both cytochrome P450 (CYP) and non-CYP pathways. Its major metabolite, N-

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desmethyl clobazam (nor clobazam), has similar activity as clobazam at Gamma-Aminobutyric Acid (GABAA) receptors and acts as an active antiseizure drug [3, 4].

During prolonged use after 1-month being on clobazam, concentrations of norclobazam, the active metabolite of clobazam, are 8-20-fold greater than clobazam levels, with little clobazam remaining, and fully responsible for seizure control during chronic treatment [5-7]. Common side effects of clobazam in children include somnolence, fatigue, and dizziness. These effects are probably associated with its mechanism of action, which increases GABAergic inhibition in the central nervous system, leading to sedation. Some children have also shown behavioral changes including irritability, aggression, and hyperactivity [1, 6]. Clobazam can occasionally lead to serious adverse events, including severe dermatological reactions and respiratory depression, especially in children with chronic respiratory diseases, or taking other central nervous system (CNS) depressants at the same time. Between 1994 and 2004, only five cases of severe outcomes such as hepatic failure, drug-induced status epilepticus, or death have been reported in association with clobazam use [7-10], reflecting the rarity of such adverse events.

Chronic use gives rise to physical dependence, withdrawal, and tolerance, requiring dose tapering on cessation. Another rare but important side effect is the paradoxical reaction, which leads to increased seizure activity, agitation, or worsened behavior problems. Clobazam is commonly used in combination with other ASDs, which can potentiate its side effects by both pharmacodynamic and pharmacokinetic interactions. For example, co-administration with valproate or lamotrigine may enhance sedation, whereas it is metabolized through CYP3A4, as are many other drugs that could influence drug levels and side effect profiles if they are either inducers or inhibitors. Upcoming studies will prove its efficacy in use by clinicians early as an adjuvant therapy in the treatment of refractory epilepsy and may even be considered as monotherapy in a broad spectrum of epilepsy syndromes [4-7]. The purpose of this study is to investigate clobazam-related adverse effects in children with epilepsy and the parameters that may play a role in initiating these effects.

While clobazam is an effective anticonvulsant for managing epilepsy, it is frequently prescribed alongside other ASDs to enhance therapeutic outcomes. However, the combination of clobazam with these medications can lead to a broader spectrum of side effects, some of which may be exacerbated or compounded. Valproate, for example, is known for its side effects, including weight gain, tremors, gastrointestinal discomfort, sedation, hepatotoxicity, and thrombocytopenia. Levetiracetam, though widely favored for its pharmacokinetic profile, can cause behavioral changes such as irritability, aggression, anxiety, and depression. Similarly, carbamazepine may result in dizziness, drowsiness, ataxia, hyponatremia, and, in rare cases, severe dermatological reactions like Stevens-Johnson syndrome. Many of these side effects overlap with those observed in clobazam, particularly sedation, dizziness, ataxia, behavioral disturbances, and gastrointestinal complaints [11]. Understanding these cumulative side effects is crucial in optimizing patient care, especially in pediatric populations where the management of side effects is essential for long-term treatment adherence and quality of life.

METHODS

The medical files of patients aged 2 to 17 years who were admitted to Diyarbakır Children's Hospital between December 2021 and March 2023 were evaluated retrospectively. Patients were identified by the following ICD-10 codes: G40. 0 (Epilepsy), G40. 1 (Epilepsy), G41. 2 (Complex Partial Epilepsy), G41. 8 (Other Epilepsy), and G41. 9 (Unspecified Epilepsy). Inclusion criteria were: Patients with one of these diagnoses were required to meet the medical criteria of having been prescribed clobazam an add-on ASDs [in addition to valproic acid (VPA), levetiracetam (LEV), and carbamazepine (CMZP) with a reliable seizure record]. The demographic and clinical information obtained included age, gender, weight, blood pressure, seizure type, etiology, and anti-seizure medication duration. Hematological and biochemical parameters were determined at the initiation of clobazam treatment and after one year or at cessation due to side effects (which is the routine protocol of starting any ASDs in our clinics). Magnetic Resonance Imaging (MRI) and electroencephalogram (EEG) evaluations were conducted on all participants as part

of the standard diagnostic workup to assess brain structure and electrical activity, ensuring comprehensive clinical assessment. Only those with normal hemogram and biochemical test results at the start of clobazam therapy were included. Exclusion criteria encompassed any modification in the anti-seizure medication regimen within the past year, the concomitant use of more than one additional drug alongside clobazam, the absence of side effects related to the primary medication, and the presence of systemic or psychiatric disorders. At the end of the selection, patients were divided into two groups based on their response to clobazam. Group 1 (No Side Effects): Patients who tolerated clobazam well and continued treatment without developing significant side effects. Group 2 (With Side Effects): Patients who developed side effects that led to dose adjustment or discontinuation of clobazam therapy. Based on medical records, clobazam dosing was documented as the medium dose (0.5 mg/kg/day) and high dose (1 mg/kg/day or 2×20 mg/day). The classification of epilepsy type and etiology was based on the guidelines of the International League Against Epilepsy (ILAE). The study was approved by the University of Health Sciences Gazi Yaşargil Training and Research Hospital Ethics Committee (Approval Date: 17.05.2023 & Approval No: 417).

Statistical Analysis

All analyses were performed with the IBM SPSS Statistics version 20.0 software package. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as means and standard deviations, with medians and interquartile ranges (IQRs) when appropriate. To compare categorical variables between adverse event groups, either the Pearson chi-square test or Fisher's exact test was used, depending on whether the expected value problem arose. The normality of distribution for continuous variables was confirmed using the Shapiro-Wilk test. The Student's t-test or Mann-Whitney U test was used to compare continuous variables between adverse event groups, depending on whether or not statistical hypotheses were met. To compare baseline and 1-year follow-up measurements, either the paired-sample t-test or the Wilcoxon signed-rank test was used, depending on whether or not the statistical hypotheses were met. The statistical significance level for all tests was set at 0.05.

RESULTS

A total of 100 pediatric patients receiving clobazam as an add-on anti-seizure medication were included in the

Table 1. Variables in patients on clobazam anti-seizure medication

Variables	Data
Age (years)	11.0±4.0 12 (8-14)
Gender, n (%)	
Male	48 (48)
Female	52 (52)
Weight (kg)	34.4±14.9
Clobazam usage period (months)	16.3±7.2 16 (13-21.5)
Dose, n (%)	
Low-Medium	67 (67)
High	33 (33)
First drug, n (%)	
CMZP	50 (50)
LEV	25 (25)
VPA	25 (25)
Semiology, n (%)	
Focal	62 (62)
Generalized	38 (38)
Birth history, n (%)	
Normal	94 (94)
Event	6 (6)
MRI, n (%)	
Normal	84 (84)
Abnormal/Lesion	16 (16)
MRI-lesion, n (%)	
Leucomalasia	9 (57)
Arknoid kist	2 (12)
Arnold Chiari	2 (12)
Thin korpus callosum	2 (12)
Atrophy	1 (6)
Type of epilepsy, n (%)	
Symptomatic-cryptogenic	50 (50)
Idiopathic	37 (37)
Structural	13 (13)
Systolic blood pressure (mmHg)	101.3±13.9
Diastolic blood pressure (mmHg)	62.4±10.7

Data are shown as mean±standard deviation or median (IQR) or n (%). CMZP=carbamazepine, LEV=levetiracetam, MRI=magneting resonance imaging, VPA=valproic acid.

study. The mean age of the patients was 11.0±4.0 years. The cohort was almost evenly distributed by gender, with 48 males (48%) and 52 females (52%).The average duration of clobazam use was 16.3±7.2 months, with a median of 16 months. Regarding dosing, 67 patients (67%) were on a low-to-medium dose, while 33 patients (33%) were receiving a high dose. As for the first-line anti-seizure drugs used in combination with clobazam, 50 patients (50%) were on carbamazepine (CMZP), 25 (25%) on levetiracetam (LEV), and 25 (25%) on valproic acid (VPA). Sixty-two patients (62%) presented with focal seizures, while 38 (38%) had generalized seizures. Birth history was normal in 94% of the patients, with perinatal events reported in 6%. MRI findings were normal in 84% of the cohort, while 16% had abnormal findings or structural lesions (Table 1). At the 1-year follow-up, WBC counts significantly increased, while neutrophil, lymphocyte, and monocyte percentages showed a notable decrease. Other hematological and biochemical parameters, including RBC, hemoglobin, liver enzymes, and thyroid markers, remained stable over time (Table 2). Side effects associated with clobazam were observed in 30% of the pediatric epilepsy patients, with the most common being insomnia (10%), agitation (9%), and somnolence (6%). Less frequent side effects included allergic reactions (1%), visual disturbances (2%), and increased frequency of illness or pyrexia (2%). Insomnia and somnolence were most frequently reported in patients on CMZP,

Table 2. Effect of clobazam on hemogram and biochemical parameters at baseline and 1-year follow-up

Variables	Baseline	1-year follow up	P value
WBC (× 10^9/L)	7.51±2.07	8.69±2.74	**<0.001**
Neutrophil (%)	49.8±12.9	49.0±13.3	**<0.001**
Lymphocyte (%)	40.8±13.4	39.5±13.2	**<0.001**
Monocyte (%)	8.36±2.75	7.58±2.57	**<0.001**
Eosinophil (%)	3.3±2.46 2.6 (1.6-4.5)	3.37±3.03 2.35 (1.3-4.65)	**<0.001**
Basophil (%)	0.467±0.323 0.4 (0.2-0.6)	0.469±0.324 0.4 (0.2-0.6)	0.862
RBC (× 10^{12}/L)	4.67±0.7	4.7±0.73	0.855
RDW-CV (%)	14.1±1.9	14.2±2	0.933
PLT (× 10^9/L)	326.8±119.7	322.4±123.3	0.949
MPV (fL)	9.8±1.9	9.8±1.8	0.945
Hb (g/L)	12.4±1.7	12.4±1.7	0.968
Ferritin (ng/dL)	41.9±13.3	43.7±14.3	0.313
TSH (mlU/L)	2.19±0.79	2.19±0.79	0.986
T4 (µg/dL)	1.26±0.21	1.26±0.21	1.000
CK (U/L)	155.1±84.6 150.5 (78-198)	159.9±82.7 156 (89-211)	0.958
Glucose (mg/dL)	79.6±10.8	79.4±11.1	0.881
ALT (U/L)	20.3±8.1 21 (13-23)	20.1±8.1 19 (13-23)	0.743
Albumin (g/dL)	40.3±2.9	40.3±2.9	0.930

Data are shown as mean±standard deviation or median (IQR). WBC=White blood cells, RBC=Red blood cell, RDW-CV=Red cell distribution width-coefficient of variation, PLT=Platelet, MPV=Mean platelet volume, Hb=Hemoglobin, CK=Creatine kinase, ALT=Alanine transaminase, AST=Aspartate transferase, TSH=Thyroid Stimulating Hormone, T4=Thyroxine

Table 3. Percentage and variation of side effects of clobazam

Variables	Data
Side Effect, n (%)	30 (30)
First drug	
CMZP	12 (40)
LEV	8 (27)
VPA	10 (33)
Agitation, n (%)	9 (9)
First drug	
CMZP	1 (11)
LEV	2 (22)
VPA	6 (66)
Insomnia, n (%)	10 (10)
First drug	
CMZP	5 (50)
LEV	2 (20)
VPA	3 (30)
Allergy, n (%)	1 (1)
First drug	
LEV	1 (100)
Visual (Accommodation), n (%)	2 (2)
First drug	
CMZP	2 (100)
Pyrexia/Increased frequency of illness, n (%)	2 (2)
First drug	
CMZP	1 (5)
LEV	1 (50)
Somnolence, n (%)	6 (6)
First drug	
CMZP	3 (50)
LEV	2 (33)
VPA	1 (17)
Stop side effect, n (%)	12 (12)
Agitation	4 (4)
Insomnia	4 (33)
Increased frequency of illness	1 (8)
Somnolence	3 (25)

Data are shown as n (%). CMZP=carbamazepine, LEV=levetiracetam, VPA=valproic acid.

while agitation was predominantly observed in those receiving VPA, accounting for 66% of cases. Notably, 12% of the cohort discontinued clobazam due to side effects, with insomnia and agitation being the primary reasons for cessation (Table 3). A comparison between Group 1 (patients without clobazam-related side effects) and Group 2 (patients experiencing side effects) revealed that those in Group 2 had significantly higher mean body weight (P<0.001). No significant differences were observed between the groups regarding age, gender, clobazam dose, seizure semiology, epilepsy type, birth history, or MRI findings (Table 4). A comparison of hematological and biochemical parameters at baseline and after 1-year follow-up in relation to side effects of clobazam revealed no significant differences in most blood parameters, including WBC, neutrophils, RBC, and ferritin between the groups. However, an increase in ALT was observed (P<0.001) (Table 5).

DISCUSSION

Clobazam, a benzodiazepine frequently prescribed for epilepsy and anxiety disorders, can lead to several side effects, particularly those related to its sedative properties. As a central nervous system (CNS) depressant, clobazam enhances the effects of GABA, a neurotransmitter that inhibits neural activity. This action results in sedative and hypnotic effects, commonly leading to somnolence (excessive sleepiness), which may manifest as daytime drowsiness, lethargy, and a decline in alertness. These effects can impair daily functioning and cognitive performance, especially during the initiation of therapy or when adjusting the dose. In the long term, tolerance to the sedative effects of clobazam may develop, meaning that the calming effect decreases over time. This can lead to an escalation in dosage and an increased risk of dependence. Conversely, some individuals may experience insomnia as a paradoxical side effect, particularly after they have developed tolerance to the drug's sedative properties. Moreover, rebound insomnia characterized by difficulty falling asleep, frequent awakenings, and reduced sleep quality can occur when clobazam is suddenly discontinued or its dose is rapidly reduced. This is due to the neuroadaptive changes that occur in the brain with chronic use, where the cessation of the drug creates a temporary imbalance in neurotransmitter activity [7].

In a study by Uzunhan *et al*. [12], side effects of clobazam were observed in 18 patients (45%). Among

Table 4. Effects of variables on the side effects of clobazam

	Side effects		P value
	No (Group 1)	Yes (Group 2)	
Age (years)	10.8±3.5 12 (8-14)	11.5±4.9 14 (6-16)	0.477
Gender, n (%)			0.541
Male	35 (%)	13 (43)	
Female	35 (50)	17 (57)	
Weight (kg)	32.4±14.8	39.1±14.4	**0.040**
Clobazam period (months)	17.9±5.4 16.5 (14-22)	12.5±9.4 13.5 (1-18)	**0.022**
Dose, n (%)			0.150
Low-Medium	50 (71)	17 (57)	
High	20 (29)	13 (43)	
First drug, n (%)			0.351
KMZP	38 (54)	12 (40)	
LEV	17 (24)	8 (27)	
VPA	15 (21)	10 (33)	
Semiology, n (%)			0.787
Focal	44 (63)	18 (60)	
Generalized	26 (37)	12 (40)	
Birth history, n (%)			0.361
Normal	67 (96)	27 (90)	
Event	3 (4)	3 (10)	
MRI, n (%)			0.771
Normal	58 (83)	26 (87)	
Lesion	12 (17)	4 (13)	
MRI-lesion, n (%)			0.155
Leucomalasia	8 (67)	1 (25)	
Arknoid kist	2 (17)	0 (0)	
Arnold Chiari	0 (0)	2 (50)	
Thin korpus kallosum	1 (8)	1 (25)	
Atrophy	1 (8)	0 (0)	
Type of epilepsy, n (%)			0.350
Symptomatic-cryptogenic	32 (46)	18 (60)	
Idiopathic	29 (41)	8 (27)	
Structural	9 (13)	4 (13)	
Systolic blood pressure (mmHg)	100.3±13.3	103.8±15.1	0.240
Diastolic blood pressure (mmHg)	63.7±10.7	59.4±10.2	0.066
Stop side effect, n (%)			**<0.001**
No	70 (100)	18 (60)	
Yes	0 (0)	12 (40)	

Data are shown as mean±standard deviation or median (IQR) or n (%). CMZP=carbamazepine, LEV=levetiracetam, MRI=magneting resonance imaging, VPA=valproic acid.

Table 5. Hematological and biochemical variables at baseline and 1-year follow-up

	Baseline values			1-year follow-up values		
	Side effects		P value	Side effects		P value
	No (Group 1)	Yes (Group 2)		No (Group 1)	Yes (Group 2)	
WBC (× 10^9/L)	7.59±2.19	7.32±1.77	0.556	8.77±2.99	8.52±2.07	0.675
Neutrophil (%)	48.9±11.6	51.9±15.6	0.289	48.1±11.9	51.3±16.2	0.281
Lymphocyte (%)	41.8±11.9	38.4±16.4	0.243	40.4±11.7	37.3±16.2	0.283
Monocyte (%)	8.28±2.8	8.54±2.66	0.672	7.5±2.77	7.77±2.04	0.633
Eosinophil (%)	3.21±2.44 2.6 (0.1-12.5)	3.51±2.56 2.6 (0.7-10.2)	0.892	3.29±3.1 2.3 (0.1-14.6)	3.57±2.91 3.05 (0.6-11.9)	0.649
Basophil (%)	0.47±0.33 0.4 (0.02-1.4)	0.46±0.31 0.4 (0.1-1.4)	0.909	0.46±0.3 0.4 (0.02-1.4)	0.5±0.38 0.3 (0.2-1.4)	0.973
RBC (× 10^{12}/L)	4.73±0.6	4.51±0.87	0.152	4.68±0.58	4.74±1.01	0.670
RDW-CV (%)	13.9±1.4	14.7±2.8	0.151	14.1±1.8	14.2±2.3	0.853
PLT (× 10^9/L)	330±114.9	319.7±131.5	0.699	330.4±120.9	303.7±128.8	0.324
MPV (fL)	9.93±2.18	9.42±0.86	0.099	9.82±2	9.61±1.08	0.586
Hb (g/L)	12.4±1.8	12.3±1.3	0.659	12.4±1.7	12.5±1.7	0.704
Ferritin (ng/dL)	42.9±13.2	39.6±13.3	0.266	43.6±14.9	44±13	0.876
TSH (mlU/L)	2.11±0.78	2.39±0.79	0.102	2.16±0.79	2.25±0.8	0.609
T4 (µg/dL)	1.24±0.2	1.31±0.22	0.100	1.26±0.23	1.26±0.17	0.942
CK (U/L)	163.29±86.04 160 (45-453)	136.1±79.16 117 (54-345)	0.115	164.9±85.4 160 (54-453)	148.4±76.3 150.5 (45-324)	0.402
Glucose (mg/dL)	79.8±11.7	79±8.7	0.742	80.8±11.4	76.1±9.7	0.053
ALT (U/L)	20.87±8.25 21.5 (9-45)	19.03±7.64 17.5 (11-45)	0.224	18.9±7.3 17 (9-44)	23.0±9.2 23 (12-45)	**0.026**
Albumin (g/dL)	40,5±2,6	40±3,5	0,421	40.6±1.4	39.4±4.8	0.178

Data are shown as mean±standard deviation or median (IQR). WBC=White blood cells, RBC=Red blood cell, RDW-CV=Red cell distribution width- oefficient of variation, PLT=Platelet, MPV=Mean platelet volume, Hb=Hemoglobin, CK=Creatine kinase, ALT=Alanine transaminase, AST=Aspartate transferase, TSH=Thyroid Stimulating Hormone, T4=Thyroxine

them, only six (33%) discontinued the drug due to adverse effects. The most commonly reported side effect was hyperactivity, followed by sedation. The remaining 22 patients (55%) experienced no side effects. Reasons for discontinuation included sedation, refusal to take the drug due to its taste, irritability, hypersalivation (in two patients), and malaise in one patient [12]. In our study, 30% of the patients had side effects, 10% insomnia, 6 % Somnolence, and 9% agitation. Twelve percent of patients discontinued clobazam due to side effects. (These adverse effects were dose-dependent, and approximately 18% of patients experienced them in mild to moderate severity, while 12% experienced them in heavy severity that the family and doctors had to stop clobazam). Initiating high doses led to expressing more frequent or heavier side effects. No cases of clobazam-induced ataxia, pyrexia, hypertension, worsening of seizures, and nocturnal, enuresis in our pediatric epilepsy study have been seen. Our results were in line with the findings of the study by Uzunhan *et al*. [12].

Although clobazam has a safe profile, it can in-

duce side effects affecting visual functions but is less frequently reported than other side effects such as sedation. Some patients may also experience visual disturbances. These side effects include blurred vision, decreased vision, light sensitivity (photophobia), and eye fatigue. One study reported a four-year-old boy with symptomatic generalized epilepsy who had also been treated with clobazam at a dosage of 0.75 mg/kg/day, developed eye-rolling with episodes of ataxia and back arching, but these were of non-epileptic origin [13-15]. Our two patients experienced blurred vision/accommodation disorders which were reversible while using clobazam, this may be secondary to the muscle relaxant properties of clobazam as a benzodiazepine. Like other drugs in this class, clobazam increases the effect of GABA, the brain's main inhibitory neurotransmitter. This results in sedation, anxiolysis, anticonvulsant effects , and relaxation of muscle. None of our patients experienced eye-rolling as a side effect.

Hematologic adverse effects may occur in patients using clobazam. While infrequent, these adverse impacts could entail changes in blood cell counts, as well as potential modifications in hematological parameters. Joshi *et al*. [16] witnessed an increase in WBC and hemoglobin and a decrease in all other blood count parameters but they were not statistically significant, which needs more extensive evaluation and further monitoring guidelines. Our study observed an increase in WBC, monocyte, and eosinophile, and a decrease in neutrophile, and lymphocyte, but despite both changes being statistically significant, both values were in the normal range. Basophile, RBC, Hg, and PLT values did not change. Pyrexia and an increased frequency of illness were observed in only 2% of the patients. While these changes in neutrophil and lymphocyte counts may suggest a potential association with a higher incidence of illness, further investigation through larger studies is required to confirm this relationship. Patients who reported side effects have higher values of ALT at the end of 1-year follow-up control, this can raise the suspicion of abnormal metabolism of clobazam through cytochrome CYP450 which can be due to genetic factors.

Skin change can be seen in most anti-seizure drugs. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is reported while using clobazam. It is estimated that more than 750,000 prescriptions of clobazam were filled in 2022 in the United States. Exploring cases of DiHS/DRESS related to clobazam in the Food and Drug Administration Adverse Event Reporting System (FAERS) database and current literature yielded 10 cases associated with clobazam [17, 18]. In addition, four cases of pedal, pitting nonpainful edema, with one of the patients developing anasarca were reported due to clobazam use. Edema was completely regressed 6 weeks after stopping clobazam in all four patients. Another case of edema in the lower extremities was reported by İncecik *et al*. [19]. In our study, allergy was seen in 1% of the patients which was reversible, we think that DiHS/DRESS due to clobazam is under-reported.

Clobazam is also an ASD that is relatively safe and mainly has sedative and anxiolytic effects [15]. However, paradoxical reactions have been reported including agitation, aggression, irritability, and hyperactivity. These effects are more frequent in children, older patients, or people with previous psychiatric disorders. Mechanisms are unclear but may involve GABAergic dysregulation, genetic factors, or dose-dependent excitatory effects. Agitation can also occur as a result of tolerance, withdrawal, or drug interactions [20-22]. Management consists of dose adjustment, slow titration, and alternative therapies. Uzunhan TA *et al*. [12] reported that four patients (10%) had their clobazam dosage reduced due to hyperactivity and behavioral disorders, and irritability was seen as a cause for clobazam cessation in that study. In our study, 6% of the patients experienced agitation. Further research is needed to understand individual susceptibility and optimize treatment strategies to mitigate these adverse effects. In our study, it was found that MRI, EEG findings, age gender, final given dose of clobazam, associated drug (CMZP, VPA, LEV), semiology, birth history, type of epilepsy, didn't play a role in creating side effects. Weight had a role in initiating side effects, which might be due to starting a high dose of clobazam from the first day can lead to having more side effects than starting a low dose and titering it slowly till reaching a high dose over some time.

Limitations

Our study is retrospective. Agitation, insomnia,

and somnolence disturbance were based on family and patient reports and could not be assessed by a valid and reliable scale.

CONCLUSION

In conclusion, while clobazam is generally effective and well-tolerated in pediatric epilepsy, common side effects such as agitation, insomnia, and somnolence may still occur. To mitigate the risk of adverse effects and optimize therapeutic outcomes, it is advisable to initiate clobazam therapy at a lower dose, followed by a gradual dose titration. This cautious approach should be adopted as standard practice when incorporating clobazam into pediatric epilepsy management.

The side effect was seen in people with higher weight. Clobazam was also used for a shorter period in those who had side effects (naturally due to the side effects).

Ethics Approval and Consent to Participate

The study was approved by the University of Health Sciences Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (Decision no.: 417 and date: 26.05.2023). It was conducted in accordance with the ethical standards established in the Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all the participants and/or legal guardians.

Data Availability

All data generated or analyzed during this study are included in this published article. The data that support the findings of this study are available on request from the corresponding author, upon reasonable request.

Authors' Contribution

Study Conception: SB; Study Design: SB; Supervision: SB; Funding: SB, NB, SNT; Materials: SB, NB, SNT; Data Collection and/or Processing: NB, SNT; Statistical Analysis and/or Data Interpretation: NB, SNT; Literature Review: SB, NB, SNT; Manuscript Preparation: SB and Critical Review: SB, NB, SNT.

Conflict of interest

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Generative Artificial Intelligence Statement

The author(s) declare that no artificial intelligence-based tools or applications were used during the preparation process of this manuscript. The all content of the study was produced by the author(s) in accordance with scientific research methods and academic ethical principles.

Editor's note

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