



## Original Research

# Efficacy and Side Effect Profile of Clobazam in Children with Different Etiologies of Epilepsy from a Single Center

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### Abstract

**Objectives:** Clobazam is a long-acting antiepileptic drug that belongs to benzodiazepines used in the polytherapy of childhood epilepsy. In this study, our aim is to retrospectively evaluate the effectiveness and side effect profile of clobazam in children with different etiologies of epilepsy, mostly drug resistant.

**Methods:** Forty patients aged 0-18 years that were admitted to Okmeydani Training and Research Hospital pediatric neurology outpatient clinic between January 2017–January 2019 and prescribed clobazam were included in this study. The data of the patients who gave informed consent were extracted retrospectively from the outpatient clinic files. The patients with no seizures over 50% reduction in seizures were classified as clobazam-responsive, whereas the patients with less than 50% reductions in seizures, patients who had no response, and who manifested side effects and stopped using the drug were classified as clobazam-unresponsive.

**Results:** Twenty-three of the patients (57.5%) were male, 17 were (42.5%) were female. The average onset age of epilepsy was 31.8±37.2 months, while the average age for the prescription of clobazam was 70.6±48.9 months. The types of seizures were focal in 23 patients (57.5%) and generalized in 17 (42.5%) patients. Thirty-three (82.5%) patients had been using double or triple combinations of eight different antiepileptic drugs when clobazam was added to their treatment and accepted as drug-resistant epilepsy. The etiology of twenty one patients (52.5%) was unknown. In the remaining 19 patients (47.5%), the most common cause was structural and others were genetic, infectious and metabolic. Thirty one of the patients (77.5%) were responsive to clobazam. Of them, fifteen (37.5%) had no seizures, and 16 had a reduction in seizures (>50%). Nine (22.5%) patients were accepted as unresponsive to clobazam. The mean dose per kg was 0.7±0.3 mg/kg/day with a median of 0.63 mg/kg/day. Side effects of clobazam were encountered in 18 patients (45%); these resulted in the cessation of administration in only six (15%) patients. The side effects that cause the cessation of clobazam were sedation, refusal to take the drug due to the taste, irritability, hypersalivation, and malaise. Four patients (10%) had their doses reduced, seven patients (17.5%) responsive to clobazam although with side effects continued taking the drug as prescribed. The most common side effects of all were hyperactivity and sedation consecutively.

**Conclusion:** Clobazam is an effective treatment for ensuring seizure freedom in pediatric epilepsy, mostly drug-resistant. The side effects are at tolerable levels in patients who are responsive to the drug.

**Keywords:** Clobazam; drug-resistant epilepsy; epilepsy; polytherapy.

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Clobazam is a benzodiazepine-derived antiepileptic that connects to the alpha-1 subunit of gamma-aminobutyric acid (GABA) receptors and shows its effects by increasing the efficacy of GABA. Studies show that the seizures persist in 30% of the epileptic patients despite the appropriate drug treatments.<sup>[1]</sup> ILAE (International League Against Epilepsy) defines drug-resistant epilepsy<sup>[2]</sup> as the continuation of the seizures despite the combined treatment with two antiepileptic drugs with appropriate and tolerated doses. In a study that included both adults and children with drug-resistant epilepsy, 77% of the patients had a reduction in seizures with the use of clobazam.<sup>[3]</sup> Unlike 1,4 benzodiazepine clonazepam, the nitrogen atoms in clobazam are located in the 1<sup>st</sup> and fifth positions, and unlike 1,4-benzodiazepines, which are non-selective receptor agonists, clobazam is believed to function as a partial agonist. Clobazam has less affinity to receptors that are believed to cause sedation and cognitive changes. Therefore, fewer side effects are observed with the use of clobazam than with the use of classic benzodiazepines.<sup>[4]</sup> However, as it is still a benzodiazepine, it may cause side effects, such as mood swings, irritability, depression, aggression, sedation, and these side effects may sometimes cause incompatibility within the treatment and result with the cessation of the drug.<sup>[5]</sup> This study aims to analyze the efficacy of clobazam in reducing seizures in pediatric patients who have different traits from adults and examine the relationship between the doses and antiepileptic responses, the side effects of clobazam and the frequency of these probable side effects.

## Methods

The study group consisted of 40 patients aged between 0-18 years-old whom admitted to Okmeydanı Training and Research Hospital, pediatric neurology outpatient clinic between January 2017 and January 2019 and were prescribed clobazam with the diagnosis of epilepsy. Patients with a progressive neurologic disease, patients who received ACTH treatment up to six months before the prescription of clobazam and the patients who had clobazam prescriptions in another facility were excluded from this study. Clobazam was the last prescribed drug; the patients who were prescribed other drugs after clobazam were removed from the study group. The clobazam dosing strategy was determined exclusively by the clinical conditions of the patients and their weight.

The data of the patients included in this study were extracted retrospectively from the pediatric outpatient files by June 2019. Informed consent was obtained from each patient for this study. The age, gender, date of birth, the age at which they first applied to the outpatient clinic, the

date when epilepsy was diagnosed, and the onset age of epilepsy were recorded. The epilepsy etiology of the patients, type of the seizures, neurological examinations, the additional neurological comorbidities, and the pathological findings in cranial MRI and EEG sessions were recorded. The initiation date of the clobazam treatment, the duration of the drug use, the maximum dose per kilogram for each patient, the observed side effects during the drug use, the need for dose reduction and termination of the drug use due to side effects were recorded. The responses after using clobazam were evaluated under five groups (no seizures, over 50% reduction in seizures, under 50% reduction in seizures, no changes, response undefined due to drug cessation because of side effects). The groups with no seizures and over 50% reduction in seizures were classified as clobazam-responsive, whereas the patients with less than 50% reductions in seizures, who showed no response, who manifested side effects and stopped medication during the drug use were classified as clobazam-unresponsive. The patients who had ongoing seizures despite the polytherapy and thus in whose polytherapy clobazam was added, were classified as drug-resistant epileptic cases. The study was approved by the Institutional Review Board of Okmeydanı Training and Research Hospital (1199/19.03.2019).

## Statistical Analysis

The data obtained in this study were analyzed using SPSS.21.0. Descriptive statistical methods (mean, standard deviation, median, first quadrant, third quadrant, frequency, percentage, minimum, maximum) were used when study data were evaluated.

## Results

### The Patients' Characteristics

Twenty-three of the patients (57.5%) were male, 17 patients (42.5%) were female in this study. The mean age that the patients admitted to the outpatient clinic was  $67.7 \pm 49.35$  months; the median age was 53 months. The youngest patient was a neonate, while the oldest was 18 years old. The patients were first diagnosed with epilepsy at  $31.8 \pm 37.2$  months of age, and the median age was 18 months. The patients first started taking clobazam at  $70.6 \pm 48.9$  months of age, with a median age of 55 months. The patients were observed for  $8.95 \pm 14.2$  months before clobazam prescription, with a median duration of four months. When the etiology of the patients was examined, 21 patients (52.5%) had unknown etiology. Structural, genetic, infectious and metabolic causes were encountered in the remaining 19 (47.5%) patients, and the most common is structural etiologies. Five patients (12.5%) were diagnosed with Lennox-

Gastaut syndrome (LGS). Of the five patients diagnosed with LGS, one patient had no seizures with clobazam, three patients had more than 50% reduction of seizures, and one stopped using the drug due to the side effects. The types of seizures were focal in 23 patients (57.5%) and generalized in 17 (42.5%) patients. The results of the muscle strength and balance examination in 8 of the patients (20%) were normal, while the other patients had neurological findings in physical examination. Three patients were diagnosed with congenital deafness, down syndrome/congenital heart disease, and congenital heart disease. The most commonly diagnosed comorbidity was intellectual impairment in 20 patients (50%) and global development delay in 14

patients (35%). Of the cranial MRI scans, 17 (42.5%) were normal, while 19 had clinically meaningful findings. MRI results of four (10%) patients were unavailable. The most common EEG findings were generalized epileptiform activity in 19 patients (47.5%), followed by focal epileptiform activity in 11 patients. The demographics are presented in Table 1.

The mean dose of clobazam administered to the patients was  $14.5 \pm 5.4$  mg/day, with a median of 15 mg/day. The minimum dose was 5 mg/day, whereas the maximum dose was 30 mg/day. The mean dose per kg was  $0.7 \pm 0.3$  mg/kg/day with a median of 0.63 mg/kg/day. The minimum dose used was 0.14 mg/kg/day, while the maximum dose was

**Table 1.** The patients' characteristics

	n	%		n	%
Gender			Hemiplegia	2	5.0
Male	23	57.5	Diplegia	1	2.5
Female	17	42.5	Concomitant diseases		
Epilepsy etiology			None	37	92.5
Unknown	21	52.5	Loss of hearing	1	2.5
Structural	10	25.0	Congenital heart disease, Down syndrome	1	2.5
Genetic	5	12.5	Congenital heart disease	1	2.5
Infectious	3	7.5	Comorbidities		
Metabolic	1	2.5	Intellectual impairment	20	60.6
Lennox-Gastaut syndrome			Global development delay	14	42.4
Yes	5	12.5	Attention deficit and hyperactivity	4	12.1
No	35	87.5	Autism	1	3.0
Specific etiology			Behavioral disorders	1	3.0
West synd.	2	5	Bilateral hearing loss	1	3.0
Neonatal hypoglycemia	4	10	MRG results		
Viral encephalitis sequela	2	9.5	Abnormal	19	47.5
Lissencephaly	2	9.5	Normal	17	42.5
Wolf-Hirschhorn syndrome	1	4.8	Not performed	3	7.5
Dravet syndrome	1	4.8	Unknown	1	2.5
2q microdeletion synd.	1	4.8	EEG findings		
Stroke from congenital heart disease	1	4.8	Generalized epileptiform activity	19	47.5
Parainfluenza encephalitis	1	4.8	Focal epileptiform activity	11	27.5
Cortical dysplasia	1	4.8	Normal	4	10.0
RCDP type 3	1	4.8	ESES	1	2.5
Hypoxia after cardiac arrest	1	4.8	Slowing EEG	1	2.5
Intraventricular bleeding, hydrocephaly	1	4.8	Unknown	4	10.0
Brain tumor	1	4.8	Antiepileptic drugs used		
Types of seizure			Levetiracetam	29	72.5
Focal onset	23	57.5	Valproic acid	22	55
Generalized onset	17	42.5	Phenobarbital	8	20
Clinical Examination			Oxcarbazepine	6	15
Quadriplegia	12	30.0	Topiramate	5	12.5
Hypotonia	11	27.5	Carbamazepine	5	12.5
Normal	8	20.0	Vigabatrin	1	2.5
Ataxia	6	15.0	Primidone	1	2.5

1.33 mg/kg/day. The mean duration of clobazam use was  $12.3 \pm 6.9$  months, with a median of 12 months. At the initiation of clobazam treatment, seven patients (17.5%) had been using only one antiepileptic drug, while the remaining 33 (82.5%) were on polytherapy.

The most commonly used antiepileptics at the time of clobazam addition were levetiracetam and valproic acid, respectively. Thirty-three patients were using double or triple combinations of eight different antiepileptic drugs when clobazam was added to their treatment. Only one patient with unknown etiology and drug-resistant seizures was using valproate, topiramate, levetiracetam, and oxcarbazepine. Oxcarbazepine was terminated during the follow-up. The side effects of clobazam were observed in 18 (45%) patients, in only six of these patients, the side effects resulted in cessation of the drug. The most frequently observed side effect was hyperactivity, while the second most frequently encountered side effect was sedation. Twenty-two patients (55%) showed no side effects of clobazam. Six of the 18 patients (39%) who encountered side effects stopped using the drug due to side effects. The side effects that caused the cessation of clobazam were sedation, refusal to take the drug due to the taste, irritability, hypersalivation in two patients, and malaise in one patient. Four patients (10%) had their dosage reduced due to hyperactivity and behavioral disorders. Of all the patients, 30 (75%) patients tolerated clobazam and continued using the drug. The patient demographics, according to the specific etiology, are presented in Table 2.

Fifteen patients (37.5%) had no seizures, 16 patients (40%) had >50% and three patients (7.5%) had <50% reduction in the number of their seizures (two had stopped medication due to side effects in this group), two patients (5%) had no changes in the number of their seizures, and four patients (10%) stopped taking the drug without waiting for the drug response due to its side effects.

## Patients Responsive to Clobazam

### Patients without Seizures

Thirty-one of the patients (77.5%) were evaluated as responsive to clobazam. Among fifteen patients (37.5%) with no seizures in the responsive group, the median age at the onset of epilepsy was 24 months, and the median age when starting clobazam was 50 months. Among the patients who were responsive to clobazam, the etiology of seven patients was unknown. The most commonly observed side effects in this group were hyperactivity, sedation, and irritability, with hyperactivity being the most common. Four patients had their dosages reduced due to hyperactivity. The median daily clobazam dose per kg was

0.55 mg/kg/day. The shortest period of drug use was seven months, while the longest period of use was 21 months. None of the patients stopped using the drug.

### >50% Reduction in Seizures

In 16 patients (40%), there was a reduction in the number of seizures, which was higher than 50%. In only eight patients who had over 50% reduction in seizures, the etiology was known. The dose of clobazam per kilogram was 0.77 mg/kg/day. The median duration for clobazam use was 15.5 months; five patients had side effects. The most commonly occurred side effect was sedation, but none of the patients stopped using the drug.

Of all 31 patients who were evaluated as responsive to clobazam (without seizures group and >50% reduction group), seven patients (22%) who had side effects could tolerate the drug, no dose reduction or cessation was needed.

### Patients Unresponsive to Clobazam

Nine patients in total (22.5%) were evaluated as unresponsive to clobazam (less than 50% reductions in seizures, who showed no response, who manifested side effects and stopped medication during the drug use). Four patients stopped using the drug due to sedation, dislike of the taste, irritability, and malaise, and the effectiveness of the drug could not be evaluated. Three patients showed <50% reduction in seizures, and two patients showed no response to the drug. The most common side effect observed in the patients who had <50% reduction in seizures was increased salivation. Two patients out of three who had <50% reduction in seizures stopped the medication due to side effects. The median clobazam dose of the two unresponsive patients was 1.2 mg/kg/day. Features of the patients responsive and unresponsive to clobazam are presented in Table 3 below.

## Discussion

Clobazam is a benzodiazepine derivative that was first used in 1975 as an anxiolytic drug.<sup>[4]</sup> Shortly after that, it was found to have antiepileptic properties. National Institute for Health and Care Excellence (NICE) recommends clobazam use for children and adults as an add-on treatment in the cases in which the first line antiepileptics fail.<sup>[6]</sup> In our study, it was used in combination with levetiracetam most commonly, as well as valproate, phenobarbital, and oxcarbazepine in other cases. In a study examining the interaction between clobazam and other antiepileptic drugs, no clinically meaningful interactions with phenytoin, phenobarbital, carbamazepine, valproate, lamotrigine, felbamate, and oxcarbazepine were detected.<sup>[7]</sup> This favorable safety profile and its pharmacokinetic properties render cloba-

Table 2. Clobazam properties by specific etiology according to clobazam response

Age at the onset of epilepsy	Starting age of clobazam use/Sex	Specific etiology	Comorbidity	Antiepileptics used	Daily dose of clobazam mg/kg/day	Response to clobazam	Duration of clobazam use	Clobazam side effects	Cessation due to side effects
123 months	149 months/F	Hypoglycemia sequela	Intellectual impairment	Valproate Levetiracetam Oxcarbazepine	0.55 mg/kg/day	No seizures	17 months	Sedation	No
0 months	49 months/M	Past HIE	Global development delay	Valproate	0.53 mg/kg/day	No seizures	10 months	None	No
22 months	22 months/F	Status epilepticus secondary to viral encephalitis	None	Levetiracetam Levetiracetam Phenobarbital Topiramate	1 mg/kg/day	No seizures	9 months	None	No
34 months	34 months/F	Status epilepticus secondary to viral encephalitis	None	Phenobarbital Topiramate Levetiracetam	0.83 mg/kg/day	No seizures	8 months	None	No
24 months	88 months/F	2q microdeletion syndrome	Intellectual impairment	Valproate Levetiracetam	0.50 mg/kg/day	No seizures	12 months	None	No
8 months	83 months/M	Pachygyria	Intellectual impairment Global development delay	Valproate Levetiracetam	0.50 mg/kg/day	No seizures	15 months	None	No
54 months	101 months/F	Stroke secondary to cyanotic congenital heart disease	Intellectual impairment	Valproate Levetiracetam Topiramate	0.75 mg/kg/day	No seizures	12 months	None	No
24 months	36 months/M	Premature birth Intraventricular bleeding Hydrocephaly Cerebral Palsy	Intellectual impairment	Phenobarbital Valproic acid	1 mg/kg/day	No seizures	16 months	None	No
9 months	98 months/M	Cryptogenic West syndrome	Intellectual Impairment	Carbamazepine Levetiracetam	0.62 mg/kg/day	>%50 reduction	12 months	Sedation	No
6 months	47 months/M	Cryptogenic West syndrome	Behavioral disorders	Topiramate Valproate	0.95 mg/kg/day	>%50 reduction	17 months	Hyperactivity	No
105 months	106 months/F	Thalamic tumor	None	Valproic acid Levetiracetam	0.39 mg/kg/day	>%50 reduction	7 months	Sedation	No
5 months	11 months/M	Down syndrome Congenital heart disease Postoperative cardiac arrest/HIE	Global development delay	Phenobarbital Topiramate	1.05 mg/kg/day	>%50 reduction	21 months	None	No
92 months	119 months/F	Hypoglycemia sequela	None	Carbamazepine Levetiracetam	0.53 mg/kg/day	>%50 reduction	22 months	None	No

Table 2. CONT.

Age at the onset of epilepsy	Starting age of clobazam use/Sex	Specific etiology	Comorbidity	Antiepileptics used	Daily dose of clobazam mg/kg/day	Response to clobazam	Duration of clobazam use	Clobazam side effects	Cessation due to side effects
18 months	53 months/F	Encephalitis sequela	Global development delay	Oxcarbazepine Topiramate	0.83 mg/kg/day	>%50 reduction	7 months	None	No
7 months	27 months/F	Wolf-Hirschhorn syndrome	Global development delay	Levetiracetam Valproate	0.93 mg/kg/day	>%50 reduction	9 months	None	No
6 months	19 months/M	Dravet syndrome	Global development delay	Levetiracetam Valproate	0.71 mg/kg/day	>%50 reduction	17 months	None	No
124 months	131 months/M	Rhizomelic chondrodysplasia punctata type 3	Intellectual impairment Global development delay	Levetiracetam Topiramate	1.08 mg/kg/day	<%50 reduction	6 months	Increase in saliva and secretions	Yes
5 months	22 months/F	Lissencephaly	Global development delay	Vigabatrin	0.45 mg/kg/day	<%50 reduction	11 months	None	No
1 months	25 months/F	Cortical dysplasia	Intellectual impairment	Valproate Levetiracetam	1.33 mg/kg/day	No response	17 months	None	No
27 months	49 months/M	Hypoglycemia sequela	Global development delay	Carbamazepine Levetiracetam	0.50 mg/kg/day	Unknown (brief treatment period)	15 days	Refusal due to taste	Yes
84 months	151 months/F	Past HIE	Intellectual impairment	Oxcarbazepine Levetiracetam	0.4 mg/kg/day	Unknown (brief treatment period)	6 days	Sedation	Yes

zam more important in childhood epilepsies, which may require polytherapy.

Despite its low cost and strong antiepileptic properties compared to the new generation antiepileptic drugs, clobazam is not commonly preferred in monotherapy. However, there are studies indicating that clobazam's efficiency is comparable to carbamazepine and phenytoin in the monotherapy of childhood epilepsy.<sup>[8]</sup> The most common concern regarding benzodiazepines in monotherapy is tolerance development. Tolerance to a drug can be defined as the disappearance of the antiepileptic effects sometime after seizures are put under control with an antiepileptic drug. Nevertheless, while patients can develop tolerance to clobazam, patients with short epilepsy duration and higher drug levels were reported to have long-term seizure control.<sup>[9]</sup> While clobazam levels cannot be studied in our country, it was observed in our study that the group responsive to clobazam showed long-term seizure control during the 30 month period, which was the maximum duration of observation.

Our study showed that 37.5% of the childhood epilepsy patients have no seizures upon clobazam use, while 40% of the patients have an over 50% reduction in the number of seizures. The effectiveness of clobazam on childhood epilepsy has been evaluated in many retrospective studies. One study reported that 28% of cases had no seizures, and 67.7% of cases were responsive to the drug with a daily dose of 0.73 mg/kg/day.<sup>[10]</sup> Another study reported no seizures in 12 months in 35% of patients, and the general responsiveness rate was 67% with doses of clobazam, such as 1.05 mg/kg/day. In that study, it was observed that when the patients were separated as low dosage, average dosage, and high dosage groups, the patients in the low dosage group were more responsive to the treatment.<sup>[11]</sup> In our study, the group with no seizures had a median dose of 0.55 mg/kg/day. There are studies reporting that there is no correlation between the dosages of clobazam and the treatment responsiveness.<sup>[10]</sup> In our study, no higher dosages were required for seizure control, as well.

While clobazam, a member of the class of long-acting benzodiazepines, is a broad-spectrum antiepileptic that is effective on focal, generalized, tonic-clonic, myoclonic and absence seizures,<sup>[4]</sup> it has been approved by FDA only for the treatment of the LGS in children over two years of age and adults. Lennox-Gastaut syndrome is a childhood epilepsy with multiple types of seizures, specific EEG abnormalities, and developmental delay, usually with poor prognosis.<sup>[12]</sup> Clobazam is known to be an effective treatment, especially for "drop attack" seizures observed in cases of LGS. It has been postulated that clobazam in higher

**Table 3.** Response to clobazam treatment by patient demographics

	Responsive to clobazam		Unresponsive to clobazam		Situation unknown due to cessation
	No seizures	>50% reduction in the number of seizures	<50% reduction in the number of seizures	No response	
Male (n)	8	10	2	1	2
Female (n)	7	6	1	1	2
Age at the Onset of Epilepsy (Months)	24 (0-123)	9 (4-105)	5 (0-124)	3.5 (1-6)	55.5 (0-120)
Median, range					
Start of clobazam use (months)	50 (10-149)	71.5 (10-138)	22 (18-131)	39.5 (25-54)	121.5 (49-128)
Median, range					
Specific epilepsy etiology (n)	Viral encephalitis sequela (1) Hypoglycemia sequela (1) Lissencephaly (1) 2q microdeletion syndrome (1) Stroke from congenital heart disease (1) Parainfluenza encephalitis (1) Intraventricular bleeding, hydrocephaly (1)	West syndrome (2) Viral encephalitis sequela (1) Wolf-Hirschhorn syndrome (1) Neonatal hypoglycemia sequela (1) Dravet syndrome (1) Postop cardiac arrest due to congenital heart disease (1) Brain tumor (1)	Lissencephaly (1) RCDP type 3 (1)	Cortical dysplasia (1)	West syndrome (1) Hypoglycemia sequela (1)
Side effects	Hyperactivity (4) Sedation (1) Irritability (1) None (9)	Sedation (2) Hyperactivity (1) Irritability (1) Malaise (1) None (11)	Increase in saliva (2) None (1)	Increase in saliva (1) None (1)	Sedation (1) Refusal due to taste (1) Irritability (1) Malaise (1)
Daily dose of clobazam	15 mg	15 mg	7.5 mg	17.5 mg	15 mg
Median, Range (Months)	(7.5 – 20 mg)	(7.5-30 mg)	(5-10 mg)	(15-20 mg)	(10-20 mg)
Clobazam dose per kg	0.55 mg/kg/day	0.77 mg/kg/day	0.59 mg/kg/day	1.2 mg/kg/day	0.45 mg/kg/day
Median, Range (Months)	(0.17-1.07)	(0.38 -1.1)	(0.45-1.08)	(1.07-1.33)	(0.14-0.68)
Duration of clobazam use	12	15.5	6	14.5	0.5
Median, Range (Months)	(7-21)	(6-30)	(0-11)	(12-17)	(0-3)
Cessation	None	None	Yes (2)	None	Yes (4)
Dose reduction	Dosage reduction in 4 patients due to hyperactivity	None	None	None	None

dosages is more effective in controlling drop attack seizures observed in LGS, in contrast to the dosage response relations reported for other types of seizures.<sup>[3]</sup> In our study, the few patients with LGS diagnosis had a high treatment response rate, and the dosages were similar to effective dosages that are used for the other types of seizures.

The most frequently reported side effects of clobazam are sedation, pyrexia, ataxia, hypersalivation, constipation, malaise, and behavioral changes.<sup>[13, 14]</sup> The relevant literature mentions low to medium level side effects in 40% of patients, but severe side effects are rare.<sup>[14]</sup> In our study, the side effects were observed in 22% of the clobazam responsive patients, but due to its effects on seizure control, both families and patients were able to tolerate the side effects and did not terminate or reduce the drug. None of the patients who took part in our study reported ataxia, pyrexia, or constipation as side effects of the drug. In the group of patients responsive to clobazam in our study, only four patients had their doses reduced due to hyperactivity. Some patients reported sedation, but a few other patients reported hyperactivity/behavioral changes. This situation is known as the paradoxical (disinhibitory) reaction, which is explained with the capability of benzodiazepines to inhibit the control of cortical centers.<sup>[15]</sup>

The behavioral and cognitive side effects of clobazam in the monotherapy of school-age children have been reported to be comparable to standard treatments like carbamazepine in various studies.<sup>[16]</sup> However, as mainly clobazam is used in polytherapy, it can be inferred that the behavioral side effects of clobazam manifest more frequently in patients who require multiple drug use on the grounds of latent cognitive and behavioral problems. Sedation by clobazam occurs less frequently than 1-4 benzodiazepines like clonazepam.<sup>[17]</sup> In a study performed on healthy volunteers, less sedation and psychomotor side effects were observed in people who used 10-20 mg/day of clobazam compared to 0.5-1mg/day of clonazepam.<sup>[18]</sup> In our study, four patients stopped using the drug due to the side effects, such as sedation, irritability and hypersalivation even before the effectiveness of the drug could be evaluated.

We evaluated the effectiveness of clobazam as an add-on treatment for both focal and generalized seizures and its side effect profile on children with varying epilepsy etiologies in a single medical center for a short period, such as two years. Our study did not use a control group. The selection of the patients and the collection of the data were performed retrospectively. The effectiveness of clobazam was evaluated observationally with local application methods without a fixed protocol on a small group of patients. The side effects were determined without a systematic check-

list and may have been affected by the side effects of other drugs and the high rate of neurological and behavioral comorbidities of this population.

## Conclusion

Our study was performed on a group of patients who were mostly drug-resistant. We observed that clobazam is effective at stopping seizures. Side effects were generally well-tolerated, and no severe side effects were encountered. Clobazam will remain as an important option for all childhood epilepsy cases that may require polytherapy including the Lennox-Gastaut syndrome. It is essential to evaluate the effectiveness and the reliability of clobazam in monotherapy and in combined treatment for childhood epilepsies with prospective large scale studies, which include a more extended follow-up period and in which the compatibility with the drug is tracked closely.

## Disclosures

**Ethics Committee Approval:** Okmeydanı Training and Research Hospital (1199/19.03.2019).

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## References

1. Chu-Shore CJ, Thiele EA. New drugs for pediatric epilepsy. *Semin Pediatr Neurol* 2010;17:214–23.
2. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;51:1069–77.
3. Ng YT, Conry J, Mitchell WG, Buchhalter J, Isojarvi J, Lee D, Drummond R, Chung S. Clobazam is equally safe and efficacious for seizures associated with Lennox-Gastaut syndrome across different age groups: Post hoc analyses of short- and long-term clinical trial results. *Epilepsy Behav* 2015;46:221–6.
4. Pernea M, Sutcliffe AG. Clobazam and Its Use in Epilepsy. *Pediatr Rep* 2016;8:6516.
5. Joshi R, Tripathi M, Gupta P, Gupta YK. Effect of clobazam as add-on antiepileptic drug in patients with epilepsy. *Indian J Med Res* 2014;140:209–15.
6. National Clinical Guideline Centre (UK). *The Epilepsies: The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care*. London: Royal College of Physicians (UK); 2012.
7. Walzer M, Bekersky I, Blum RA, Tolbert D. Pharmacokinetic drug



- interactions between clobazam and drugs metabolized by cytochrome P450 isoenzymes. *Pharmacotherapy* 2012;32:340–53.
8. Clobazam has equivalent efficacy to carbamazepine and phenytoin as monotherapy for childhood epilepsy. Canadian Study Group for Childhood Epilepsy. *Epilepsia* 1998;39:952–9.
  9. Singh D, Kumar P, Narang A. A randomized controlled trial of phenobarbital in neonates with hypoxic ischemic encephalopathy. *J Matern Fetal Neonatal Med* 2005;18:391–5.
  10. Klehm J, Thome-Souza S, Sánchez Fernández I, Bergin AM, Bolton J, Harini C, et al. Clobazam: effect on frequency of seizures and safety profile in different subgroups of children with epilepsy. *Pediatr Neurol* 2014;51:60–6.
  11. Perry MS, Bailey L, Malik S, Gilson C, Kotecha A, Hernandez A. Clobazam for the treatment of intractable epilepsy in children. *J Child Neurol* 2013;28:34–9.
  12. Conry JA, Ng YT, Paolicchi JM, Kernitsky L, Mitchell WG, Ritter FJ, et al. Clobazam in the treatment of Lennox-Gastaut syndrome. *Epilepsia* 2009;50:1158–66.
  13. Mudigoudar B, Weatherspoon S, Wheless JW. Emerging Antiepileptic Drugs for Severe Pediatric Epilepsies. *Semin Pediatr Neurol* 2016;23:167–79.
  14. Gauthier AC, Mattson RH. Clobazam: A Safe, Efficacious, and Newly Rediscovered Therapeutic for Epilepsy. *CNS Neurosci Ther* 2015;21:543–8.
  15. Paton C. Benzodiazepines and disinhibition: a review. *Psychiatr Bull* 2002;26:460–2.
  16. Bawden HN, Camfield CS, Camfield PR, Cunningham C, Darwish H, Dooley JM, et al. The cognitive and behavioural effects of clobazam and standard monotherapy are comparable. Canadian Study Group for Childhood Epilepsy. *Epilepsy Res* 1999;33:133–43.
  17. Sankar R. GABA(A) receptor physiology and its relationship to the mechanism of action of the 1,5-benzodiazepine clobazam. *CNS Drugs* 2012;26:229–44.
  18. Wildin JD, Pleuvry BJ, Mawer GE, Onon T, Millington L. Respiratory and sedative effects of clobazam and clonazepam in volunteers. *Br J Clin Pharmacol* 1990;29:169–77.