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Original Article

Clobazam: Effect on Frequency of Seizures and Safety Profile in Different Subgroups of Children With Epilepsy

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ABSTRACT

BACKGROUND: Clobazam has been used in clinical practice as an adjunctive treatment for diverse seizure types and epilepsy syndromes. We evaluated the efficacy and safety of clobazam in a large sample of patients with refractory epilepsy at a tertiary pediatric center. **METHODS:** We retrospectively reviewed patients treated with clobazam between January 2001 and July 2013 who had a follow-up visit at least one month after starting clobazam. Response was defined as ≥50% reduction in seizure frequency compared with baseline seizure frequency during the 3 months before the introduction of clobazam. We examined the relationship between dose range and response rate. **RESULTS:** Four-hundred twenty-five patients were prescribed clobazam, of whom 300 (median age 9.1 years, interquartile range 4.7-13.3 years) had follow-up data greater than 1 month. Median follow-up was 5 months (interquartile range 3-11 months). Response to treatment with clobazam was observed in 203 of 300 (67.7%) patients, of whom 84 (28%) became seizure-free. The median starting dose was 0.2 (interquartile range 0.13-0.33) mg/kg/day with a target dose of 0.48 (0.26-0.80) mg/kg/day. Twenty-seven (9%) patients discontinued clobazam, 16 (59.3%) because adverse effects, 10 (37%) because of a lack of efficacy, and one (3.7%) because of a combination of adverse effects and lack of efficacy. The most common adverse effects were tiredness in 44 of 300 (14.6%) and mood or behavioral changes in 23 (7.7%). **CONCLUSIONS:** Clobazam is a well-tolerated antiepileptic drug with good response rates in pediatric patients with refractory epilepsy.

Keywords: epilepsy, refractory epilepsy, pediatric, seizure, efficacy

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Introduction

Clobazam is a 1,5-benzodiazepine with marked anxiolytic and anticonvulsant properties.[1] It acts as a partial agonist on the gamma-amino butyric (GABA) receptor complex, similar to other benzodiazepines. However, unlike 1,4-benzodiazepines, it is selective for the ω-2 subunit.[2] When clobazam binds to the $GABA_A$ receptor, it causes an influx of chloride, leading to membrane hyperpolarization and an increase in inhibitory postsynaptic potentials, a mechanism also observed with other benzodiazepines.[3-5]

Preferred epilepsy treatment consists of monotherapy with a single antiepileptic drug (AED) at the minimally effective dose, up to the maximum tolerated dose.[6] However, many patients require more than one AED, and in some reports 30% of patients continue to have seizures despite drug treatment.[6,7] Clobazam is a common

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medication choice for drug-resistant seizures. Previous studies have shown that clobazam is an effective adjunctive therapy for partial and generalized seizures and status epilepticus,[8] febrile seizures,[9,10] reflex seizures,[11] and hyperekplexia.[12]

Treatment of epilepsy may require polytherapy and high doses of medication, which frequently are associated with side effects. Clobazam has less affinity than 1,4 benzodiazepines for the ω-1 receptor and ω-5 subunit of the GABA receptor, which are known to be associated with sedation and cognitive changes.[5] The most common adverse events leading to the discontinuation of clobazam are lethargy, somnolence, aggression, ataxia, insomnia, and fatigue.[13] The prevalence of dosage-related adverse events is still unknown.[4,13] Increase in seizures, worsening of seizures, or development of new seizure types have been reported in 5% to 13% of patients.[14] Most reported adverse events due to clobazam appear to be less severe than those reported with 1,4-benzodiazepines, whereas a similar level of seizure control is obtained.[13]

Our aim is to describe the use of clobazam in a refractory epilepsy population at a single pediatric center during a long-term period. Our secondary goal is to identify subsets of patients in which clobazam emerged as an effective drug and also to try to define particular treatment regimens associated with better outcomes and/or fewer adverse events.

Methods

Patient selection

We obtained approval from the Boston Children's Hospital Institutional Review Board before the acquisition of data. Patients were identified using the Informatics for Integrating Biology and the Bedside software (Partners Healthcare, https://www.i2b2.org/), using the search terms clobazam, Onfi, and epilepsy. We reviewed all patient charts, including outpatient and inpatient visits, electrophysiology, and neuroimaging examinations for patients who used clobazam for treatment of epilepsy between January 2001 and July 2013. We evaluated details regarding clobazam use, including dose, titration mode, adverse effects, and combinations with other AEDs. Patients who were already initiated on clobazam before being seen at Boston Children's Hospital or who did not return for follow-up at least 1 month after clobazam initiation were excluded from analysis.

Epilepsy classification and seizure control

Epileptic seizures were classified according to International League Against Epilepsy criteria.[15] Responders were defined as patients who experienced a reduction in overall seizure frequency ≥50% at last follow-up compared with baseline. Nonresponders were patients who experienced <50% reduction in overall seizure frequency compared with baseline. Adverse effects and efficacy were evaluated according to information provided by physicians, patients, parents, relatives, and caretakers. Seizure frequency was determined from clinic notes based on parent report at each visit and recorded as average number of seizures per month. Changes to concomitant AEDs and other treatment methods were recorded at each visit as change or no change. Patients who experienced greater than 50% seizure reduction were considered responders.

Data collection and analysis

Study data were collected and imported into REDCap (i.e., Research Electronic Data Capture, Vanderbilt University, Nashville, TN), a secure, web-based application designed to support data capture for research studies. We looked at gender, epilepsy etiology, comorbidities, concomitant AEDs, EEG characteristics, and imaging for potential predictors of response at last follow-up. Additionally, information on the titration schedule of clobazam was analyzed if documented in the patient chart. Starting dose, weeks until first dose increase, target dose, weeks until target dose reached, and dose increase were analyzed as possible predictors of response at last follow-up. We analyzed the relationship between clobazam dose and response at 1, 3, 6, 9, 12 months, and more than 12 months of follow-up. Low doses were considered ≤0.25 mg/kg/day, medium doses were 0.26-0.99 mg/kg/day, and high doses were ≥1.0 mg/kg/day.

SPSS version 21 (SPSS Institute, Chicago, IL) was used for all analyses. Mann-Whitney *U* tests, χ^2 tests, or Fisher exact tests were performed as appropriate, and a Kaplan-Meier survival analysis, including a log rank test, was performed to analyze time until discontinuation with reasons for discontinuation as group factors.

Results

Demographics

Eight-hundred fifteen charts were reviewed. Clobazam was mentioned as a potential therapy in 443 charts, 119 charts had incomplete data, 18 patients did not start clobazam, four patients received clobazam as needed, and two patients discontinued clobazam before 1-month follow-up. Three hundred patients with a median age of 9.1 (range 0.1-31.5) years were included. Demographic data and epilepsy related factors are presented in Tables 1 and 2. Two hundred ninety-two (97.3%) patients were receiving concomitant AEDs: 56 of 300 (18.7%) one additional medication, 106 (35.3%) two additional medications, and 130 (43.3%) three or more additional medications (median 2, interquartile range [IQR] 2-3). The median follow-up duration was 5 months (IQR 3-11 months). In the 3 months before the introduction of clobazam, 132 (44.0%) patients had one seizure type, 110 (36.7%) had two seizure types, 43 (14.3%) had three seizure types, 14 (4.7%) had four seizure types, and one (0.3%) patients had five seizure types. Specific seizure types are reported in Table 1.

Clobazam dose

The median starting dose was 0.2 mg/kg/day (IQR 0.13-0.33), increasing a median of 5 mg/week (IQR 2.5-5) to a median target dose of 0.48 mg/kg/day (IQR 0.26-0.80), with an average dose at last follow up of 0.73 mg/kg/day (SD = 0.53, range 0.05-3.3). There was no association between response and titration schedule (Mann-Whitney *U*-test, not significant [n.s.]). Dose increases during titration (mg/kg/week) were not correlated with seizure reduction.

Overall outcome

Median seizure reduction was 80%. Two-hundred three patients (67.7%) had ≥50% seizure reduction (Table 3), and 84 of 300 (28%) had become seizure-free by the last follow-up. There was no difference between various etiologies (χ^2 test, $P = 0.209$). Follow-up duration was not different in responders and nonresponders (Mann-Whitney *U*-test, $P = 0.777$).

TABLE 1.
Demographic and clinical data in 300 patients treated with clobazam

Characteristics	n
Girls	153 (51)
Mean age, yr (SD; IQR)	9.5 (6.0; 4.7-13.3)
Epilepsy etiology	
Genetic	52 (17.3)
Structural/metabolic	112 (37.3)
Unknown	136 (45.4)
Specific epilepsy etiology	
Hypoxic ischemic encephalopathy	33 (11.0)
Neurocutaneous syndrome	1 (0.3)
Stroke/hemorrhage	10 (3.3)
Inborn error of metabolism	9 (3.0)
Developmental encephalopathy	1 (0.3)
Malformation of cortical development	43 (14.3)
Mesial temporal sclerosis	3 (1.0)
Neoplasm	6 (2.0)
Genetic	54 (18.0)
Encephalitis	10 (34.3)
Meningitis	1 (0.3)
Tuberous sclerosis complex	2 (0.7)
Trauma	8 (2.7)
Congenital infection	2 (0.7)
CNS infection	1 (0.3)
Unknown	116 (38.7)
Seizure types at introduction of clobazam*	
Generalized tonic clonic	116 (38.7)
Generalized tonic	98 (32.7)
Generalized absence	92 (30.7)
Generalized myoclonic	90 (30.0)
Generalized atonic	42 (14.0)
Generalized clonic	35 (11.7)
Focal	33 (11.0)
Epileptic spasms	32 (10.7)
Unknown	3 (1.0)
Clinical exam*	
Normal	199 (66.3)
Quadriplegia	40 (13.3)
Diplegia	8 (2.7)
Hemiplegia	16 (5.3)
Hypotonia	35 (11.7)
Extrapyramidal	7 (2.3)
Cranial nerve abnormalities	3 (1.0)
Comorbidities*	
Autism	27 (9.0)
Mood disorders	2 (0.7)
Neurobehavioral disorders	41 (13.7)
Intellectual and developmental disabilities	240 (80.0)
ADHD	12 (4.0)
No comorbidities	42 (14.0)

Abbreviations:
ADHD = Attention deficit-hyperactivity disorder
CNS = Central nervous system
Values are n (%) unless otherwise indicated.
* Patients may have been represented in more than one category and numbers therefore do not add up to 300 (100%).

TABLE 2.
Clinical data in 300 patients treated with clobazam

MRI results (n = 225)	
Lesional	144 (64.0)
Nonlesional	81 (36.0)
EEG (n = 247)*	
Normal	15 (6.1)
Generalized slowing	80 (32.4)
Focal slowing	47 (19)
Asymmetric slowing	1 (0.4)
Generalized epileptiform activity	91 (36.8)
Focal epileptiform activity	90 (36.4)
Multifocal	69 (27.9)
Lateralized periodic discharges	8 (3.2)
Clobazam dose, mg/kg/day	
Start dose (mean; range)	0.29 (0.04-1.75)
Target dose (mean; range)	0.59 (0.08-4.0)
Weeks until first dose increase (mean; range)	1.2 (1-12)
Weeks until target dose reached (mean; range)	4.0 (1-44)
Dose increase (mean; range)	0.18 (0-2.17)
Multiple other drugs	
1 = 56	
2 = 106	
≥3 = 130*	
Concomitant antiepileptic drugs:	
Levetiracetam	141 (47.0)
Valproate	82 (27.3)
Lamotrigine	76 (25.3)
Clonazepam	74 (24.7)
Rufinamide	62 (20.7)
Zonizamide	57 (19.0)
Topiramate	40 (13.3)
Oxcarbazepine	39 (13.0)
Phenobarbital	32 (10.7)
Lorazepam	20 (6.7)
Phenytoin	20 (6.7)
Lacosamide	16 (5.3)
Diazepam	12 (4.0)
Gabapentin	12 (4.0)
Vigabatrin	7 (2.3)
Carbamazepine	7 (2.3)
Ethosuximide	5 (1.7)
Felbamate	2 (0.7)
Tiagabine	1 (0.3)
Stiripentol	1 (0.3)
Bromide	1 (0.3)

Abbreviations:
EEG = Electroencephalogram
MRI = Magnetic resonance imaging
Values are n (%) unless otherwise indicated.
* Patients may have been represented in more than one category and numbers therefore do not add up to 300 (100%).

Adverse events

Adverse effects were observed in 75 of 300 (25%) patients. Among these, the most common adverse events were tiredness in 44 of 75 (58.7%) and mood/behavioral changes in 23 of 75 (30.7%). Other less frequently observed adverse events included sleep problems in six (8%), appetite changes in five (6.7%), and slurred speech in four (5.3%) patients. Fifty patients (66.7%) presented with one side effect, 18 (24%) with two, and seven (9.3%) with three or more side effects. In 59 of 75 (78.7%) patients, adverse effects were considered minor and did not result in discontinuation. There was no relationship between occurrence of adverse events and response to treatment (χ^2 test, n.s.). Additionally, there was no relationship between occurrence of adverse events and dosing (Mann-Whitney *U*-test, n.s.). Time to reach low, medium, and high doses and occurrence of adverse events are detailed in Table 4.

Discontinuation

Twenty-seven patients (9%) discontinued treatment during the follow-up period. Reasons for discontinuation included adverse events in 16 (59.3%) patients, unsatisfactory response in 10 (37%) patients, and one (3.7%) patient experienced both adverse effects and unsatisfactory response. The majority of adverse events were observed in

TABLE 3.
Outcome of clobazam treatment

Total number			300
Patients <21 yr			288 (96.0%)
Median age, yr (IQR)			9.1 (4.7-13.3)
Mean follow-up, mo (range)			11.4 (1-133)
Overall Outcome	**N**	**Median % Seizure Reduction (IQR)**	**N (%) of Responders**
Response		80.0 (33.0-100.0%)	203 (67.7)
General etiology			
Genetic	54	77.5 (45.8-99.8%)	41 (75.9)*
Structural/metabolic	124	78.5 (5.0-100.0%)	81 (65.3)*
Unknown	109	80.0 (45.6-100.0%)	81 (74.3)*

Abbreviations:
IQR = Interquartile range
n.s. = Not significant.
* χ^2 test, n.s.

the early phase of treatment (within the first 3 months). The most frequent side effects leading to discontinuation were tiredness in 9 of 16 (56.3%) and mood/behavioral changes in 5 of 16 (31.3%). Discontinuation because of unsatisfactory response or adverse events was observed within the first year, with sooner discontinuation after adverse events (log rank test, $P = 0.031$). There was loss of efficacy in 24 patients over a median of 9.5 months (IQR 6-15).

Discussion

Summary

We examined a large group of patients with refractory epilepsy at a single tertiary pediatric hospital with an epilepsy division to verify the efficacy and safety of clobazam within this population. The median seizure reduction was 80%. Sixty-eight percent of patients were responders, of whom 28% achieved complete seizure freedom. After the initial titration step 27 of 300 (9%) patients discontinued clobazam because of adverse effects or inefficacy. We found clobazam an effective and safe treatment option for refractory pediatric epilepsy.

Efficacy

Our sample had a high response rate (67.7%) in all epilepsy etiologies, with no statistical significance among the various subgroups. Retrospective and prospective studies have shown good response rates (≥50% seizure control) with the use of clobazam as an add on-therapy in different seizures types and epilepsies. In retrospective studies with refractory epilepsy, including Lennox-Gastaut syndrome and tuberous sclerosis complex, responder rates from 25% to 83% have been observed, with greater rates linked to shorter follow-up.[3,4,16-22] This finding indicates the effect of tolerance with longer clobazam use, as seen with other benzodiazepines. Prospective studies in patients with refractory epilepsies have revealed similar responder rates (26.5-92.3%), with especially high rates of response in drop seizures in patients with Lennox-Gastaut syndrome (details in Table 5).[3,4,16-35] Use of clobazam as monotherapy has also shown similar efficacy compared with carbamazepine and phenytoin.[23] Some authors assessed predictors but did not find any correlations.[6,19,20] This finding is concordant with our findings that there is no specific subset of patients for whom clobazam provides better results.

TABLE 4.
Dose timing in relation to adverse events

Dose, mg/kg/day	Months to Reach Dose Median (IQR)
Low (≤0.25)	
AE	0 (0-0)
No AE	0 (0-0)
Medium (0.26-0.99)	
AE	6 (0-6)
No AE	3 (1-6)
High (≥1.0)	
AE	12 (3-10.5)
No AE	10.5 (3-9)

Abbreviations:
AE = Adverse event
IQR = Interquartile range
n.s. = Not significant.
Mann-Whitney *U*-test, n.s.

Dosing/safety

In agreement with the literature, we found no correlation between the average dose of clobazam at the last follow-up and response rate. To compare our response rate (67.7%) and average final dose (0.73 mg/kg/day), we reviewed similar studies. In one retrospective pediatric study investigators found a greater rate of seizure freedom of 35% at 12 months but lower overall responder rate (33%) compared with our study on a higher average dose of clobazam.[19] Another retrospective study with a similar average dose of clobazam found both lower seizure freedom and responder rates at 12 months.[22] The Canadian Study Group for Childhood Epilepsy conducted a prospective, double-blind, controlled study in 235 pediatric patients (mean age 9.5 years) with 1-year follow-up. They found the same seizure freedom rate (23%) on a lower average dose (0.6 mg/kg/day). Another prospective study with 63 pediatric patients (age 3-20 years) revealed a similar responder rate of 65% at a greater dose of 0.8 mg/kg/day.[24] This wide ranging response rate at varying doses is likely the result of differences in patient populations.

Three retrospective studies that reported titration schedules of 5 mg/week increase had greater discontinuation rates than that found in our study.[6,17,20] Compared with our findings, a similar responder rate (69%) was reported in one study[20] and a similar seizure freedom rate (23%) in another study[17] with the five mg/week titration schedule.

In our series, treatment was discontinued in 9% of patients, and in 59.3% of those because of adverse events. Discontinuation rates in retrospective studies ranged from 0% to 42% (Table 4). Retrospective studies have revealed similar adverse events of sleepiness and behavioral changes.[3,19,22] The adverse effects associated with clobazam are often less severe than those associated with 1,4-benzodiazepines, phenytoin, and carbamazepine.[2,23] The sedative effects of clobazam are less than with 1,4-benzodiapines.[36] Clobazam has been associated with less neurotoxicity than clonazepam and nitrazepam.[25] In one study in pediatric patients with febrile seizures, researchers reported that patients experienced less sedation with clobazam than diazepam.[10] Mills et al.[3] revealed similar withdrawal rates because of adverse events in patients on

TABLE 5.
Clinical studies conducted with clobazam in the pediatric population

Author, Year	N	Age, yr Range (Median)	Epilepsy/Seizure	Dose	Seizure Reduction (>50%)	Seizure Free	DR/AE	Follow-Up, mo (Median)
Retrospective studies								
Buchanan, 1993[16]	56	6-59 (29.3)	PS and or GS	10-30 mg/d (median 15.6)	48.2%	25%	DR: (50%); AE: (25%)	1-96
Montenegro et al., 2001[21]	97	15-70 (35.8)	HA, MCD, and others	10-60 mg/d (median 29.7)	49.4%	7.2%	DR (2.1%); AE (30.9%)	1-93 (16.7)
da Silveira et al., 2006[17]	100	0.5-18 (8)	Refractory focal epilepsy	Tit.: 5 mg/d weekly, 5→ 60 mg/d (median 23.6); ≥75% resp. 18.6 m/d	≥75% (11%)	26%	DR (25%); AE (22%)	0.5-78 (18.6)
Silva et al., 2006[18]	97	1-17 (9.9)	LGS, MAE, WS, other EP	5-60 mg/d (median 37.5)	27.8%	11.3%	DR: (11.3%); AE: (41%)	12
Montenegro et al., 2008[6]	193	7-88 (48.1)	PS and or GS	Tit.: 5 or 10 mg/each time range: 5-60 mg/d (median 23.9)	N/A	6mo (11.3%); 18 mo (3.2%)	DR (39%); AE (16.5%)	18
Mills et al., 2011[3]	73	0.3-16.2 (9.9)	Intractable epilepsy	0.12-3.5 mg/kg/d (max. 7.1)	6 mo (48%) >12 mo (25%)	4.2%	DR (42%); AE (60%)	12
Conry et al., 2009[4]	68	2-26	LGS (DS)	LD: 0.25 mg/kg/d HD:1.0 mg/kg/d	LD: 38%; HD: 83%	LD: 6%; HD: 22%	DR (15.0%); AE (85%)	3.5
Lee et al., 2013[22]	46	1.1-21 (3)	LGS	0.16-1.60 mg/kg/d (median 0.7)	12 mo (19.3%)	12 mo (16.1%)	DR 12 mo (32.6%); AE (15.2%)	12
Perry et al., 2013[19]	108	0.6-17.9 (8.7)	PS and or GS	0.23-2.17 mg/kg/d (median 0.88)	12 mo: 33%, >12 mo: 29%	12 mo (35%) >12 mo (44%)	DR (25%); AE (10.8%)	6 mo-4.5 y (16 mo)
Jennesson et al., 2013[20]	29	0.3-27	TSC (ES and PS)	Tit. 5 mg/day weekly	69%		DR 12 mo/24 mo (18% and 32%); AE (44.8%)	12-24 (17.3)
Prospective studies								
Shimizu et al., 1981[26]	36	1-16.4 (8)	PS and or GS	0.1-0.83 mg/kg/d (median 0.33)	26.5%	29%	AE: (47%)	12
Allen et al., 1983[27]	26	18-60 (34)	Refractory seizure	30 mg/night	92.3%	23.1%	AE (50%)	2.1
Vajda et al., 1985[28]	14	6-38	Refractory epilepsy	15-60 mg/d	42.9%	N/A	DR (28.6%)	0.25-11 (6)
Farrell, 1986[29]	50	16	LGS	5-40 mg/d	54%	34%	20%	3
Schmidt et al., 1986[30]	20	18-54 (38)	PS and or GS	0.24-0.74 m/kg/d (median 0.54)	3 mo: 54%	20%	AE (85%)	4
Keene et al., 1990[31]	21	2-19 (11)	Refractory epilepsy	0.25-1.0 mg/kg/d	54%	N/A	DR: (9.5%)	8
Munn and Farrell, 1993[25]	115	1.3-17 (8.4)	PS and or GS	0.36-3.8 mg/kg/d (median 0.9)	46%	16%	AE: (11.3%)	18
Sheth et al., 1995[24]	63	3-20	Refractory epilepsy	0.8 m/k/d	24%	41%	DR: (35%)	15-64
Canadian Study Group for Childhood Epilepsy, 1998[23]	119	2-16 (115 mo)	PS and or GS	0.37-1.1 mg/kg/d (median 0.6)	N/A	23%	DR (45%); AE (41%)	12
Jan and Shaabat, 2000[32]	31	0.17-15 (4.6)	Refractory epilepsy	5-40 mg/d	83.9%	35.5%	DR (16.1%); AE: (22.5%)	3-12
Rose et al., 2005[9]	39	0.5-3	Febrile seizure	5 mg ≤5 kg, 5 mg BD 6-10 kg, 7.5 mg BD 11-15 kg, 10 mg BS > 15 kg	Recurrence, CLB: 1.7%, Placebo: 12.5%		Drowsiness 46.8%, weakness 4.8%, ataxia 8.3%	14
Kalra et al., 2010[33]	88	0.58-12	Refractory epilepsy	0.3-2.0 m/k/d	85.2%	60.2%	DR: (3.4%); AE: (26%)	6-36
Khosroshahi et al., 2011[10]	40	6 mo-5 yr	Simple febrile seizure	5 mg/d ≤ 5 kg; 5 mg BD 6-10 kg; 7.5 mg BD 11-15 kg, 10 mg BD > 15 kg	Recurrence (oral CBL and oral DZP) $P = 0.474$	94%	DR (12.5%); AE (14.2%)	12

Table 5 (*continued*)

Author, Year	N	Age, yr Range (Median)	Epilepsy/Seizure	Dose	Seizure Reduction (>50%)	Seizure Free	DR/AE	Follow-Up, mo (Median)
Ng et al., 2011[34]	238	2-60	LGS (DS/non DS)	LD: 0.25 mg/kg/d: MD: 0.5 mg/kg/d; HD: 1.0 mg/kg/d	(DS/nDS): LD: 57.6%/52.5%; MD: 65.4%/62.5%; HD: 85.1%/83.5%	41.2%	DR (8.9%); AE: LD (6.9%); MD (12.9%); HD: (20.3%)	5
Ng et al., 2012[35]	267	2-54 (11)	LGS (DS and total of seizure)	0.94 mg/kg/d (mean modal); 1.22 mg/kg/d (mean max.)	Total: 4.8% (3 mo); 81.5% (24 mo). DS: 71.1% (3 mo); 91.6% (24 mo)	N/A	DR (79.8%); AE (82%)	24

Abbreviations:
AE = Adverse event
BD = Bi-daily
DR = Discontinuation rate
DS = Drop seizure
DZP = Diazepam
EP = Encephalopathy
ES = Epileptic spasm
GS = Generalized seizure
HA = Hippocampal atrophy
HD = High dose
LD = Low dose
LGS = Lennox-Gastaut syndrome
MAE = Myoclonic astatic epilepsy
MCD = Malformation of cortical development
MD = Medium dose
N/A = Not available
nDS = Non-drop seizure
PS = Partial seizure
Tit = Titration
TSC = Tuberous sclerosis complex
WS = West syndrome

clobazam, topiramate, and lamotrigine of 11%, 15%, and 12%, respectively. The most common adverse effect in patients on clobazam was sleepiness in 27%, which is slightly greater than the 14.6% found in our study. Clobazam may be associated with fewer adverse events because of its partial agonist activity. We found a relationship between the development of adverse events and the titration schedule of clobazam, as well as greater doses at first follow-up. Adverse events of sleepiness and behavioral changes during the introduction/titration phase on low doses of clobazam may be related to individual patients' baseline characteristics, known as a paradoxical (disinhibitory) reaction.[37] There is not a clear explanation for this phenomenon. Some postulate that the disinhibitory action of the medication could be caused by a loss of cortical restraint.[37] Others believe it is due to a reduction of serotonin transmission (*5-hydroxytryptamine*).[38,39]

In general, clobazam is well tolerated. Side effects most commonly observed in our study include tiredness, mood/behavioral changes, sleep problems, appetite changes, and slurred speech. Side effects may be sufficiently severe to require treatment discontinuation in only a minority of patients, as seen in 6% of our series and a comparable percentage in other trials.

Challenges

Our findings need to be interpreted in the setting of data acquisition. Our study approach was retrospective, with inherent information and selection bias. Because of the retrospective nature of our study, it was not possible to report data on seizure frequency by seizure type because this information was not available in the clinical charts. Additionally, medication compliance was not consistently monitored. This is difficult to monitor as pill bottle sensors are not usually available and clobazam levels are not routinely checked. The focus of our study was on seizure reduction and not seizure freedom, as patients with refractory epilepsy do not tend to remain seizure free for an extended period of time due to the nature of the disease. In general, this subset of patients is on polytherapy. In an attempt to achieve better seizure control, clinicians try different drug combinations and treatment with multiple medications makes it difficult to attribute adverse effects to one single agent. However, we present a large series of pediatric patients treated with clobazam.

Conclusions

Our experience suggests that clobazam is well tolerated and provides good seizure reduction in patients with refractory epilepsy, with 28% of patients becoming seizure free. In addition, it appears to have a good safety profile with relatively low rates of discontinuation due to adverse effects. Clobazam appears to be a valuable drug for children with refractory epilepsy.

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