

**Title:** Clinical experience of clobazam as add-on treatment in a cohort of adults with epilepsy

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**ABSTRACT**

**Objective:** Epilepsy is a common neurologic disorder affecting 1% of the world population with one-third of these patients failing to have seizure control for more than one year. Clobazam is a long-acting benzodiazepine used worldwide for the treatment of epilepsy. This antiepileptic drug has demonstrated great clinical benefits with mild side effects. The objective of this study was to better understand the efficacy of clobazam treatment on adult patients with refractory epilepsy.

**Design:** A retrospective review of 44 adult patients with diagnosis of epilepsy that were seen at our Epilepsy Clinic between January 2014 and May 2015.

**Setting:** An outpatient epilepsy clinic at the Hospital Universitario Fundación Santa Fe de Bogota, Colombia.

**Participants:** 44 adult patients with diagnosis of epilepsy.

**Measurements:** Seizure frequency, adverse effects and the use of concomitant AEDs were reviewed in each of the patient's clinical charts.

**Results:** The responder rate of patients with clobazam was 52% at 3 months, 50% at 6 months and 55% at 12 month. Seizure freedom rates at 3, 6 and 12 months were 18%, 25% and 25% respectively. Clobazam related adverse events occurred only in four patients (9%) at the end of the twelve months with somnolence being the most common.

**Conclusion:** These findings suggest that clobazam treatment in adult patients with focal or generalized epilepsy is effective and safe. Its use should be considered early when first-line agents fail to provide seizure control.

**Keywords:** Clobazam, add-on treatment, epilepsy, antiepileptic drugs.

## I. Introduction

Epilepsy affects approximately 1% of the world population and unfortunately, one-third of the patients who use antiepileptic drugs (AEDs), fail to have seizures controlled for at least one year.

[1] More effective and safe treatments for refractory epilepsy are needed, and choosing a particular AED is not always easy. The choice of an AED depends not only on efficacy, but also on tolerability, safety, drug interactions and other drug-related properties such as pharmacokinetics.

[2]

Clobazam (8-chloro-5-methyl-1-phenyl-1,5-benzodiazepine-2,4-dione), a partial agonist of gamma-aminobutyric acid type A receptor, is a long-acting benzodiazepine used worldwide for the treatment of epileptic seizures. Its anticonvulsant and anxiolytic properties arise from a unique structure with two nitrogen atoms in the first and fifth position of the diazepine ring, which distinguishes this AED from other classic 1,4-benzodiazepines. [3] Clobazam is taken orally, and it requires 1 to 4 hours to reach its highest concentration in the blood. [4] Food does not affect the extent of its absorption. It is metabolized in the liver via the cytochrome P450 pathway and has a half-life of 18 hours. [5]

Clobazam was originally used as a non-sedative agent to treat anxiety in Australia in 1970 and epilepsy in France in 1974. [6] Clobazam is approved in many countries as an adjunctive therapy for epilepsy and anxiety, however, it was only FDA approved in October 2011, as an adjunctive treatment for Lennox-Gastaut syndrome in people older than 2 years. [1]

More than 50 studies have tested clobazam on more than 3000 patients with epilepsy, and it has showed great clinical benefit with mild side effects. [7] Numerous studies have shown its efficacy

with more than 50% of seizure frequency reduction and seizure freedom in 37-61% and 9-14% of patients respectively. [8] OV-1002 and CONTAIN Trial, were the clinical studies that showed Clobazam's adequate tolerance and significant dose-dependent decrease in drop attacks and non-drop seizures. [7,9]

Although its clinical use has been shown mainly in pediatric patients, multiple studies have shown clobazam very effective in adult patients with refractory epilepsy; including those with focal (partial onset), generalized tonic-clonic, and myoclonic seizures. [10,11,12,13] In Colombia, clobazam is used as an AED for the treatment of Lennox-Gastaut Syndrome but also in the adult population as a treatment for partial seizures with or without secondary generalization, generalized epilepsy, and refractory epilepsy.

The aim of this study is to describe the use of clobazam as adjunctive treatment in an adult population with focal and generalized epilepsy at a single Epilepsy Clinic in Bogota, Colombia.

## **II. Material and Methods**

**Population.** We performed a retrospective review of 44 adult patients with diagnosis of epilepsy that visited our Epilepsy Clinic between January 2014 and May 2015.

**Clinical data.** Data collected included: demographics (age and gender), seizure type, etiology, time from diagnosis, ictal frequency 3, 6 and 12 months after beginning this medication, clobazam dose, additional AEDs, and side effects reported during the visit to the epilepsy clinic.

**Outcome variables.** The primary clinical efficacy variable was the responder rate at 3, 6, and 12 months. Responders were defined as those patients with at least 50% reduction in seizure frequency compared to baseline. Basal seizure frequency (at month 0) was defined as the number of seizures reported during the three months prior to starting clobazam. Secondary efficacy variables included seizure-freedom at 3, 6, and 12 months. Seizure freedom was defined as no seizures in the three months prior to the medical visit at: 3, 6 or 12 months.

Other measures included clobazam related side effects, interruption of treatment, and other AEDs used during and after clobazam initiation; a comparison was made between the number of concomitant AEDs at baseline versus final visit.

All the patients were 17 years old or older and signed an informed consent in order to use their information. The study protocol was approved by the ethics committee and was conducted according to the code of ethics. Data was confirmed by review of clinical notes of one neurologist specialized in epilepsy.

### **III. Results**

**Clinical Characteristics.** Forty-four patients in one Epilepsy Clinic at Bogota, Colombia were treated with clobazam as adjunctive treatment. The median age was 24.5 years, 26 patients (59%) were male, and only 1 patient (2.3 %) went to surgery as a treatment (Table 1).

Most of the patients treated with clobazam in the present study had focal epilepsy with a secondary generalization (90.9%). There were 5 patients (11.7%) with more than three AED, when starting oral clobazam (table 1).

Table 1

## Patient characteristics

Data	Number of patients, N=44 (%)
Age in years, mean	30.2
Male	26 (59)
Diagnosis	
Focal Epilepsy with secondary generalization	40 (90.9)
Juvenile mioclonic Epilepsy	2 (4.5)
Generalized seizures	1 (2.2)
Partial complex seizures	1 (2.2)
Etiology	
Cryptogenic	14 (31.8)
Mesial temporal sclerosis	2 (4.6)
Perinatal hypoxia	3 (6.8)
Tumor	8 (18.1)
Brain infection	3 (6.8)
Vascular	3 (6.8)
Other*	11 (25)
Number of AED before starting clobazam	
One	21 (47.7)
Two	18 (41)
Three or more	5 (11.7)
Surgical intervention	1 (2.3)

\*Tuberous sclerosis, hydrocephaly, metachromatic leukodystrophy, Febrile infection related epilepsy syndrome

### Clobazam treatment.

The mean dosage of clobazam (mg per day) at each visit was 12.5 (basal), 13.5 (3 months), 13.01 (6 months) and 14.82 (12 months). Initial doses used were 5-10 mg per day and titration was done based on tolerability and seizure frequency response.

### Efficacy.

Initiation of adjunctive clobazam was associated with a good clinical response. The responder rate was 52% at 3 months, 50% at 6 months and 55% at 12 month. Seizure freedom rates at 3, 6 and 12 months were 18%, 25% and 25% respectively. There was no difference in efficacy between the etiologies of epilepsy at 12 months of using clobazam, although none of the patients with tuberous sclerosis or juvenile mioclonic epilepsy had a reduction of more than 50% in seizure frequency. Figure 1 illustrates how the number of AEDs the patient was on, affected the responder rate.

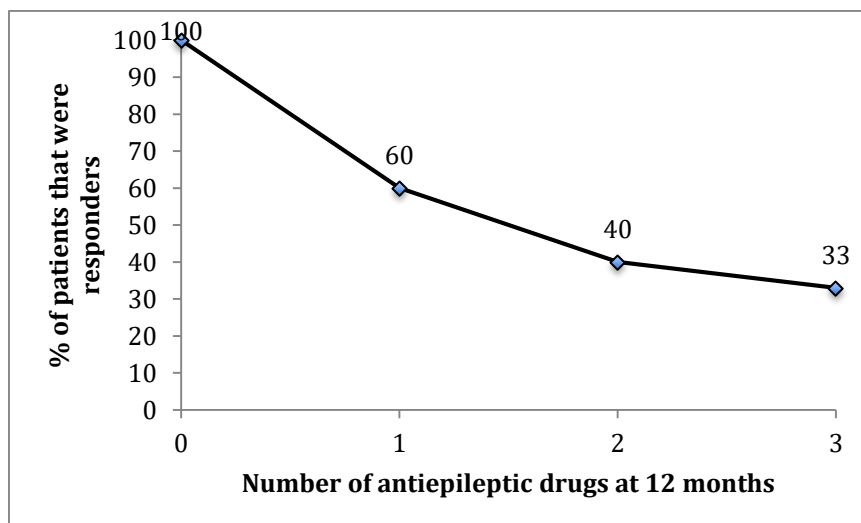


Figure 1. Response curves after initiation of add-on treatment with clobazam based on number of AEDs at 12 months

#### Clinical compliance, adverse events and concomitant AEDs.

Of the 44 patients, one patient discontinued the drug at the 12-month visit. The patient did not want to take the drug as he felt there was no effect on the seizure frequency. Clobazam related adverse events occurred only in four patients (9%) at the end of the twelve months. The most common adverse effect was somnolence, which occurred in two patients; apathy and irritability were the other adverse events. Somnolence was the cause for discontinuation in one patient. There was no serious or life-threatening disease. At the end of this study, there was no reduction in the number of AED (Table 2).

Table 2. Number of AED before and after initiation of clobazam treatment.

Number of AED	Baseline (%)	12 months (%)
One	21 (47.7)	1 (2.3)
Two	18 (41)	26 (59.1)
Three or more	5 (11.7)	17 (38.6)

#### IV. Discussion

We described an adult population (N = 44) treated with clobazam during a one-year period and found out that 55% of the patients had a seizure frequency reduction of >50% after 12 months of follow up. This was higher than the response rate of the Canadian Clobazam Cooperative group where 40% of the patients with a single seizure type had a 50% or greater reduction in seizure frequency. [11] There was also a good seizure freedom rate at the end of the twelve-month with 25% of the patients being seizure free at that time; result that differ with the rates found in the literature. In one retrospective clinical trial in a tertiary US epilepsy center, sixty-two patients with refractory epilepsy were evaluated for seizure-free for at least six months after the introduction of clobazam. [13] They concluded that 7 patients (11.3%) became seizure free for at least six months and only 4 remained seizure free after 18 months of follow-up. Joshi et al. reported a 36.2% of seizure freedom (defined as no seizure in the previous 12 months) and no improvement in 7.7%. [14]

The mean dose of clobazam used in this study was lower than the used by the Canadian Clobazam Cooperative group where the average dose for adults was 30.8 mg. [11] This is important because in this study, there was a good response rate achieved with a lower dose when compared to other studies.

Clobazam is generally considered safe to use, with only mild side effects when compared to other AEDs. Data collected from 50 clinical studies from more than 3000 epileptic adult and pediatric patients revealed that the most common side effects that may lead to drug's discontinuation are: lethargy, somnolence, aggression, ataxia, insomnia, and fatigue. [10,15] In the present study, the most common adverse effect was somnolence. More over, somnolence was the cause for discontinuation in only one patient after a one year of follow-up. Other adverse effects described

in the literature were not seen in this study. We believe the lower dose used in our patients might explain the minor side effects and better compliance to clobazam.

Three systemic reviews have concluded that clobazam may be a useful treatment for epilepsy as intermittent or short-term add-on therapy and may reduce seizure in partial onset seizures. [16,17,18] The results of the present study are a proof of the ability of clobazam as adjunctive treatment due to its clinical efficacy and lower rate of side effects. Although there was no change in the number of AEDs at the end of the twelve-month period, the dose of most of the antiepileptic in each patient were reduced significantly. The number of AEDs is important before starting clobazam. As shown in figure 1, the more antiepileptic drugs the patient has, there will be a less reduction in seizure frequency, as the probability of being seizure free is less as you add a second and third antiepileptic drug to the patient.

A major limitation of the current study is its retrospective nature and its small sample size. Many patients in this study received adjunctive treatment with multiple antiepileptic drugs and surgical intervention (e.g. tumor resection) occurred in one patient. Even though we recorded the number of antiepileptic drug used by each patient, the duration or serum levels were not obtained. Therefore, we cannot exclude the chance that other interventions led to clinical improvement or seizure freedom. Study strengths include the low dose used of clobazam as add-on treatment, the high compliance of clobazam and low adverse events, the long follow-up period (12 months) and the usefulness of real-life efficacy and safety data.

## V. Conclusions

Clobazam is a unique AED highly effective and safe in the treatment of a broad spectrum of epilepsies. This 1,5 benzodiazepine has shown remarkable efficacy as adjunctive therapy for adults with refractory epilepsy. Although it is only approved for Lennox-Gastaut syndrome since 2011 in the USA, we here demonstrate its efficacy and safety in patients with other types of epilepsy at our Epilepsy Clinic in Colombia.

This retrospective study suggests that clobazam is a safe and well-tolerated AED in adults with refractory focal (partial onset) and generalized epilepsy. With 44 patients, this is the largest cohort with clobazam described in Latin America and the only one including patients with epilepsy other than Lennox-Gastaut syndrome.

Future Clobazam trials are needed to further evaluate its clinical efficacy and tolerability. There is need for additional studies and hopefully clinical guidelines for the use of this AED in focal and generalized epilepsy worldwide, particularly in the United States where it is FDA approved for Lennox-Gastaut syndrome. Because it causes less sedation than other benzodiazepines, and its anxiolytic properties may be an added benefit, clobazam should be considered early when first-line agents fail to provide seizure control in patients with refractory epilepsy.

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