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Clobazam: A Novel Treatment for Lennox-Gastaut Syndrome

By: Stephanie Bass, Pharm.D.

Introduction: Lennox-Gastaut syndrome (LGS) is a type of epilepsy that generally presents during childhood, frequently persisting into adulthood.^{1,2} Lennox-Gastaut syndrome is a rare seizure disorder with a prevalence of approximately 1-2% of all patients with epilepsy or 26 people per 100,000 at 10 years of age; LGS affects boys more commonly than girls.^{2,3} The onset is typically before age 8 with peak occurrence between ages 3 and 5.^{2,4} The syndrome is characterized by three distinct features: the presence of multiple types of seizures, mental retardation, and electroencephalography abnormalities of diffuse slow spike-wave pattern. Tonic seizures are the distinguishing seizure type for LGS and are generally required for diagnosis.¹ Other types of seizures seen with LGS include atypical absence, atonic, and myoclonic seizures. Approximately 50% of patients will experience atonic or “drop seizures” which are characterized by a brief myoclonic seizure followed by a sudden loss of posture control. These seizures are responsible for the majority of injuries associated with falls seen with LGS. Prognosis for LGS is poor as most seizures are refractory to treatment and many patients experience cognitive decline. Furthermore, the mortality rate is 4-7% before age 11 due to falls from drop attack seizures.^{2,3}

Some agents used for treatment of LGS include felbamate (Felbatol[®]), lamotrigine (Lamictal[®]), and topiramate (Topamax[®]).⁵⁻⁷ All three medications

are approved by the Food and Drug Administration (FDA) for use in LGS and have been shown in studies to reduce the rate of seizures, particularly atonic or drop seizures, compared with placebo. Patients generally require several types of antiepileptics to control seizures with LGS. Additionally, benzodiazepines have a role as adjunctive therapy for LGS; these agents have shown efficacy against all types of seizures including tonic and atonic.¹

Clobazam (Onfi[™]; Lundbeck, Inc.) is a benzodiazepine that has been used in Europe since the 1970s for treatment of anxiety and epilepsy.³ Clobazam was FDA-approved in October 2011 for the adjunctive treatment of seizures associated with LGS in patients 2 years of age or older.⁸ However, clobazam has been used off-label for epileptic encephalopathy, prophylaxis of febrile seizures, and as an adjunctive therapy for the management of refractory epilepsy.⁹⁻¹³

Mechanism of Action: The precise mechanism of action for clobazam is not completely understood. Clobazam is a long-acting 1,5-benzodiazepine and is proposed to exert its anticonvulsant activity by binding at the benzodiazepine site of gamma-aminobutyric acid A (GABA_A) receptors and potentiating GABAergic neurotransmission.¹⁴ Clobazam is the first 1,5-benzodiazepine of its kind with

nitrogen occupying the first and fifth positions of the diazepine ring; this is in contrast to 1,4-benzodiazepines such as alprazolam (Xanax[®]), diazepam (Valium[®]), and lorazepam (Ativan[®]).¹⁵ It is theorized that the distinct 1,5-benzodiazepine structure of clobazam confers selective binding at the ω_2 site of the GABA_A receptor with less affinity for the ω_1 site compared with other benzodiazepines that have a 1,4-benzodiazepine structure.¹⁵ The ω_2 site primarily mediates anticonvulsant effects while the ω_1 site mediates sedation, anterograde amnesia, and some anticonvulsant activity.

Pharmacokinetics: Clobazam is rapidly absorbed after oral administration with nearly 100% bioavailability.¹⁴ Absorption is unaffected by administration with food. Clobazam is highly lipophilic with a large volume of distribution of about 100 L. Distribution is rapid throughout the body and time to peak concentration is between 0.5 to 4 hours. Clobazam is eliminated primarily through the liver by metabolism through N-demethylation which produces an active metabolite, N-desmethylclobazam. The major cytochrome P450 (CYP) enzymes responsible for metabolism of clobazam are CYP3A4 and, to a lesser extent, CYP2C19 and CYP2B6. N-desmethylclobazam has plasma concentrations three to five times higher and estimated potency 20–100% that of the parent compound.

N-desmethylclobazam is also eliminated through the liver by CYP450 metabolism. The major enzyme responsible for metabolism of N-desmethylclobazam is CYP2C19, a polymorphic enzyme associated with pharmacogenomic variability.¹⁴ In poor metabolizers of CYP2C19 (those with genotype 2*/2*), the area-under-the-curve (AUC) and the maximum plasma concentration (C_{max}) of N-desmethylclobazam was found to be approximately five times higher compared with extensive metabolizers of CYP2C19. For intermediate metabolizers of CYP2C19 (those with *1/*2 genotype), the AUC and C_{max} of N-desmethylclobazam are approximately two times higher compared with extensive metabolizers. Poor metabolizers of CYP2C19 may require dosage adjustments.

After a single, radiolabeled oral dose of clobazam, about 11% was eliminated in the feces and about 82% in the urine as metabolites.¹⁴ The approximate half-life of clobazam and N-desmethylclobazam are 36-42 hours and 71-82 hours, respectively; it takes around 5-9 days to reach steady-state.

Select Clinical Trials: Conry and colleagues performed a Phase II, randomized, double-blind, dose-ranging study to determine the most effective and safe dosage of clobazam to be used as adjunctive therapy in the management of LGS.³ Patients were included in the study if they were diagnosed with LGS with an onset before the age of 11 years, had more than one type of generalized seizure (including drop seizures) for at least 6 months, weighed at least 12.5 kg, were on a stable regimen of one to three antiepileptic medications for a month prior to enrollment, and had at least two drop seizures per week. Pertinent exclusion criteria included a recent episode of status epilepticus, a history of seizures associated with progressive neurologic disease, and corticotropin use within 6 months. Sixty-eight patients were randomized to either low-dose clobazam (target dose of 0.25 mg/kg/day up to maximum dose of 10 mg/day; n=32) or high-dose clobazam (target dose of 1 mg/kg/day up to maximum dose of 40 mg/day; n=36) and stratified according to weight (12.5 kg to ≤ 30 kg or >30 kg).

Patients were followed for a total of 14 weeks in the study: a 4-week baseline period followed by a 3-week titration period, a 4-week maintenance period, and either an open-label extension period or a taper for 3 weeks. The primary efficacy endpoint was the percent reduction in the weekly rate of drop seizures (atonic, tonic or myoclonic) from baseline to the maintenance period. Secondary endpoints included the proportion of treatment responders in each group and the percent reduction from baseline in weekly rate of nondrop seizures. Adverse effects were also assessed.

Key results of this study are summarized in Table 1. The percent reduction in drop seizures from baseline was significant for both groups although the reduction in weekly drop seizures was greater in the high-dose than the low-dose group. Furthermore, there was a significantly greater reduction in nondrop seizure rates in the high-dose group compared with the low-dose group. There were significantly more patients who were treatment responders in the high-dose group compared with the low-dose group at all measured response intervals. Additionally, the high-dose group had more seizure-free patients during the maintenance period compared with the low-dose group, although this difference was not statistically significant. Adverse effects occurred with similar frequency between low-dose and high-dose clobazam groups. The authors concluded clobazam was well tolerated and decreased the rate of drop seizures overall, but that high-dose clobazam reduced the rate of drop seizures significantly more than low-dose clobazam.

Table 1: Key Results from Phase II Trial³

Outcome	Low-dose Clobazam (n=32) Mean ± SD	High-dose Clobazam (n=36) Mean ± SD	P-value (between groups)
Percent Reduction in Drop Seizures from Baseline	12 ± 122% (p=0.0162)	85 ± 16.8% (p<0.0001)	0.0001
Percent Reduction in Nondrop Seizures from Baseline	9 ± 92% (p=0.1466)	59 ± 55% (p<0.0001)	0.0222

SD= Standard Deviation

Ng and colleagues evaluated the efficacy and safety of clobazam as adjunctive therapy for LGS in the CIObazam in PatieNTs with Lennox-GAstaut SyNdrome (CONTAIN) study.⁴ This was a Phase III, randomized, double-blind, placebo-controlled study. Patients were between the ages of 2 to 60 years with LGS with an onset before age of 11 years. Inclusion criteria required that LGS must involve at least two drop seizures per week and be treated with at least one antiepileptic drug during the baseline period. Patients were excluded from the study if they were receiving any benzodiazepine, felbamate or more than three concurrent antiepileptic medications, or if they had a recent episode of status epilepticus or anoxia. Patients (N=238) were stratified by weight (12.5 kg to ≤ 30 kg or >30 kg) and randomized to one of four groups: 1) placebo, 2) low-dose clobazam, 3) medium-dose clobazam, or 4) high-dose clobazam. Doses of clobazam were based on weight as shown in Table 2. The study was comprised of a 4-week baseline period followed by a 3-week titration period and then a 12-week maintenance period at which the target dose in Table 2 was maintained.

The primary outcome was the percent reduction in average weekly rate of drop seizures from 4-week baseline to the maintenance period. Some secondary outcomes were percent reduction from baseline in average weekly rate of total (drop and nondrop) and nondrop seizures and percent of treatment responders. The key results for this trial are listed in Table 3. For the primary outcome of percent reduction from baseline in average weekly rate of drop seizures, all three doses of clobazam had a significant difference in reduction compared with placebo; however the reduction in rate of drop seizures increased with increasing dose. This dose-related linear trend of increasing efficacy was shown to be statistically significant. A similar trend was seen with the percent reduction from baseline in average weekly rate of total seizures; all three doses of clobazam had significant differences compared with placebo and there was a larger difference with increasing dose. The rate of nondrop seizures increased with placebo, low-dose and medium-dose clobazam, and decreased with high-dose clobazam; however between-group differences were not statistically significant. The percentage of patients defined as treatment responders was higher with clobazam compared with placebo and increased as the dose of clobazam was increased. Adverse events were similar between groups. The authors concluded that clobazam was efficacious in decreasing the weekly rate of drop seizures in LGS and that this pharmacologic effect was dose-dependent.

Table 2: Total Daily Dose Stratified by Weight According to CONTAIN* Trial⁴

	≤30 kg Body Weight	>30 kg Body Weight
Low-dose Clobazam	5 mg daily	10 mg daily
Medium-dose Clobazam	10 mg daily	20 mg daily
High-dose Clobazam	20 mg daily	40 mg daily

*CONTAIN=CIObazam in PatieNTs with Lennox-GAstaut SyNdrome

Table 3: Key Results from CONTAIN* Trial⁴

Outcome	Placebo (n=57)	Low-dose Clobazam (n=53)	Medium-dose Clobazam (n=58)	High-dose Clobazam (n=49)
Reduction in Rate of Drop Seizures†	12.1%	41.2% (p=0.0120)	49.4% (p=0.0015)	68.3% (p<0.0001)
Reduction in Rate of Total Seizures†	9.3%	34.8% (p=0.0414)	45.3% (p=0.0044)	65.3% (p<0.0001)

*CONTAIN=CIObazam in PatieNTs with Lennox-GAstaut SyNdrome

†All comparisons to placebo

Adverse Reactions: The most common adverse reactions associated with the use of clobazam in clinical trials are somnolence, sedation, drooling, constipation, cough, urinary tract infections, aggression, insomnia, dysarthria, and fatigue.¹⁴ Side effects that occurred in at least 10% more patients compared with placebo include somnolence, pyrexia, lethargy, drooling, and constipation. The incidence of some adverse reactions (e.g., somnolence, sedation, aggression) appears to be dose-related.

Drug Interactions: Clobazam is a major substrate of CYP2C19 and a minor substrate of CYP2B6, CYP3A4, and P-glycoprotein.¹⁴ Clobazam is a weak inhibitor of CYP2C9, a moderate inhibitor of CYP2D6 and a weak-to-moderate concentration-dependent inducer of CYP3A4. Dosage adjustment may be required when there is concomitant use of drugs metabolized by CYP2D6. Although clobazam induces CYP3A4, this level of induction does not require dosage adjustment for drugs primarily metabolized by CYP3A4. However, some contraceptives metabolized by CYP3A4 may lose efficacy; therefore non-hormonal contraception is recommended during clobazam therapy. Due to metabolism of N-desmethylclobazam by CYP2C19, dosage adjustment of clobazam may be required with concomitant administration of strong (e.g., fluconazole [Diflucan[®]], fluvoxamine [Luvox[®]], and isoniazid) or moderate (e.g., omeprazole [Prilosec[®]]) inhibitors of CYP2C19. The blood levels of clobazam when used with alcohol may be increased by 50%. Notably, in clinical trials, the concomitant use of clobazam with antiepileptic drugs such as CYP3A4 inducers (e.g., phenobarbital, phenytoin, carbamazepine [Tegretol[®]]) and CYP2C9 inducers (e.g., valproic acid [Depakote[®]]) did not significantly affect clobazam or N-desmethylclobazam levels.

Pregnancy and Lactation: Clobazam is classified as a pregnancy-risk category C and should only be used if the benefit outweighs the risk.¹⁴ There have been no controlled studies examining the safety of clobazam in pregnant women or in animal models. The limited animal data show an association of clobazam use with developmental toxicity and fetal abnormalities. Clobazam is known to be excreted in breast milk.¹⁴ However, the risk of this exposure is unknown.

Dose and Administration: Clobazam should be started at a low dose of either 5 or 10 mg, according to body weight, and titrated weekly up to a maximum tolerable dose. The total daily dose is generally given in two divided doses daily.¹⁴ However, the 5 mg dose may be given as a single daily dose. Table 4 shows the titration schedule according to body weight. Geriatric patients, patients with mild to moderate hepatic impairment (Child Pugh score 5-9), and CYP2C19 poor metabolizers are recommended to start at 5 mg/day and titrate to half the recommended dose listed. There is no dosage adjustment for renal impairment. Clobazam may be taken without regards to meals. The tablet may be taken whole or crushed in applesauce if needed.

Table 4: Recommended Total Daily Dose Titration According to Body Weight¹⁴

	≤ 30 kg Body Weight	> 30 kg Body Weight
Starting Dose	5 mg	10 mg
Starting Day 7	10 mg	20 mg
Starting Day 14	20 mg	40 mg

Clobazam should not be abruptly discontinued to avoid withdrawal symptoms. The dose should be tapered over weeks with the total daily dose decreased by 5–10 mg/day every week until discontinued.¹⁴

Monitoring: The manufacturer’s labeling does not list specific monitoring parameters. Patients should be monitored for somnolence and sedation, particularly with concomitant use of other central nervous system (CNS) depressants. With severe CNS depression, respiratory status should be assessed.¹⁶ Due to risks with other antiepileptics, patients should also be monitored for any unusual behavior changes as these drugs have been associated with suicidal behavior and ideation.¹⁴

Availability, Cost and Formulary Status: Clobazam is listed as a Schedule IV drug under the Controlled Substances Act. It is available as 5-, 10-, and 20-mg tablets. The suggested wholesale price (SWP) of a clobazam 5 mg tablet is approximately \$3.75 and increases proportionally (e.g., clobazam 10-mg tablet cost is \$7.50 and 20-mg tablet cost is \$15.00). Therefore, the SWP for a 30-day supply of medication would be \$450–900.¹⁷ Clobazam was added to the CCHS Pediatric Formulary in March 2012; its use is restricted for continuation of home therapy. It was added to the CCHS Adult Formulary in June 2012 restricted to the Department of Neurology.

Conclusion: Clobazam is a 1,5-benzodiazepine which is FDA-approved for the treatment of seizures associated with LGS in patients 2 years and older. Although clobazam has recently been approved in the United States, it has been used in Europe since the 1970s. Clobazam is the first 1,5-benzodiazepine of its kind with proposed selectivity for GABA_A receptors that promote anticonvulsant activity. The adverse effect profile of clobazam supports this selectivity; the primary adverse effects are somnolence and sedation. Clobazam has demonstrated efficacy for adjunctive treatment of seizures associated with LGS in two large clinical trials. Its place in therapy remains to be determined, however the current literature demonstrate clobazam is an effective adjunctive therapy for reducing the rate of drop seizures associated with LGS in patients 2 years and older.

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Formulary Update

The CCHS Medical Staff P&T Committee met on October 2, 2012, and the Cleveland Clinic Local P&T Committee met on October 30, 2012, and the following decisions were made:

Adults:

Additions to the CCHS Formulary:

Critical Care/Surgery/Anesthesia:

1) **Benzocaine metered-dose topical spray (Topex®):**

- a) It is a 20% benzocaine metered-dose spray for oral mucosal application. Topex® is dispensed as a multi-use container with disposable extension tubes or “straws” that should be used for each patient. Topex® will be the preferred oral mucosal topical anesthetic spray on the CCHS Formulary for patient safety reasons; to decrease risk of methemoglobinemia; and to standardize benzocaine topical spray for CCHS. The Main Campus has been using Topex® exclusively for many years. This change was intended for the rest of the CCHS Hospitals (i.e., standardization). No other benzocaine topical sprays should be ordered, stocked, or dispensed.

Internal Medicine:

1) **Etonogestrel Implant (Nexplanon®):**

- a) It is a reversible, long-acting (up to 3 years), progestin-only contraceptive FDA-approved for use by women to prevent pregnancy. Nexplanon® is inserted subdermally by a healthcare provider just under the skin at the inner side of the non-dominant upper arm. The advantage of Nexplanon® as compared to other contraceptive implants is that it can be visualized on X-rays and CT scan and it also has a special applicator which is designed to reduce insertion errors. Implanon®, another contraceptive implant with similar efficacy and safety, can only be visualized on ultrasound and MRI. The Committee will re-evaluate the need for both medications on the CCHS Formulary at a later time.

Hematology and Medical Oncology:

1) **Carfilzomib (Kyprolis®):**

- a) It is a second generation proteasome inhibitor indicated for the treatment of patients with relapsed or refractory multiple myeloma who have received at least two prior therapies including bortezomib (Velcade®) and an immunomodulatory agent. Compared to bortezomib, it exhibits selective and irreversible inhibition of the 20S proteasome. It is recommended to administer carfilzomib intravenously over 2 to 10 minutes, on 2 consecutive days each week for 3 weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered one treatment cycle. In cycle 1, the recommended dose is 20 mg/m²/day, and if tolerated, increases during Cycle 2 and subsequent cycles to 27 mg/m²/day. The maximum dose should not exceed 59.4 mg (2.2 m² x 27 mg/m²).
- b) Carfilzomib is *restricted* to the Department of Hematology/Oncology for outpatient use only.

Transplant:

1) **Telaprevir (Incivek™):**

- a) It is a viral protease inhibitor that inhibits the NS3/4A serine protease of the hepatitis C virus (HCV). It is FDA-approved for use with the current standard of care (SOC), peginterferon alfa-2a and ribavirin, for the treatment of chronic hepatitis C genotype 1 in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated with interferon-based treatment, including prior null responders, partial responders, and relapsers. Telaprevir must not be used as monotherapy and must only be used in combination with **peginterferon alfa-2a** and **ribavirin**.
- b) The recommended dose of telaprevir tablets is 750 mg (two 375-mg tablets) taken orally 3 times a day (7-9 hours apart) with food containing approximately 20 grams of fat. Patients should be advised that the fat content of the meal or snack is critical for the absorption of telaprevir. Food that is taken with telaprevir should be ingested within 30 minutes prior to each dose. Examples of some foods that could be taken with telaprevir include: a bagel with cream cheese, ½ cup nuts, 3 tablespoons peanut butter, 1 cup ice cream, 2 ounces American or cheddar cheese, 2 ounces potato chips, or ½ cup trail mix. **Please note that due to its metabolism through the CYP 3A4 system, telaprevir is associated with several significant drug interactions; therefore, a heightened awareness regarding potential drug interactions between telaprevir and concurrent drug therapy is warranted.**
- c) Telaprevir is *restricted* to Hepatology or Transplant Services for continuation of therapy from home.

2) **Boceprevir (Victrelis®):**

- a) It is a viral protease inhibitor that inhibits the NS3/4A protease of the hepatitis C virus (HCV). It is FDA-approved for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with **peginterferon alfa-2b** and **ribavirin**, in adult patients (18 years of age or older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy. Boceprevir **must** be administered in combination with **peginterferon alfa-2b** and **ribavirin**. The dose of boceprevir is 800 mg (four 200-mg capsules) three times daily (every 7 to 9 hours) with food [a meal or light snack]. **Please note that due to its metabolism through the CYP 3A4/5 system, boceprevir is associated with several significant drug interactions; therefore, a heightened awareness regarding potential drug interactions between boceprevir and concurrent drug therapy is warranted.**
- b) Boceprevir is *restricted* to Hepatology or Transplant Services for continuation of therapy from home.

Did Not Add to the CCHS Formulary:

- 1) **Intravenous temozolomide (Temodar® Injection):** This agent was not added because use of IV temozolomide may not be appropriate in all patients, and it is significantly more expensive than oral temozolomide.
- 2) **Belatacept (Nulojix®):** This agent was not added because of cost and also need for frequent intravenous infusion that could potentially lead to issues with patient adherence.

Changes in Current CCHS Formulary Restrictions:

- 1) **Intravenous acetaminophen (Ofirmev®):**
 - a) The adult restrictions for use of intravenous acetaminophen have been modified and the drug is now **approved to be placed in PACU Pyxis machines only** to allow for quicker access to the medication once the order is verified by pharmacy. **Intravenous acetaminophen will still not be permitted in any pediatric PACU areas to avoid potential for dosing errors.**
- 2) **Eltrombopag (Promacta®) and romiplostim (Nplate®):** Due to removal of the Risk Evaluation and Mitigation Strategies (REMS) programs by the FDA (which required prescribers to be certified), it was determined that both these medications will be **restricted** to the Department of Hematology/Oncology.

Therapeutic Interchanges:

- 1) More information will be forthcoming regarding a therapeutic interchange for **inhaled corticosteroids (ICS)** in which all ICS will be converted at equipotent doses to mometasone (Asmanex® Twisthaler; Merck) in non-ventilated patients and fluticasone (Flovent®; GSK) in ventilated patients.
- 2) More information will be forthcoming regarding a therapeutic interchange for **ICS/Long-Acting Beta Agonists (LABA) Combinations** in which all ICS/LABA combinations will be converted at equipotent doses to fluticasone/salmeterol (Advair®).

Practice Guidelines:

The CCHS Medical Staff P&T Committee supports the CCHS Hypertonic Saline Use Guidelines. The hypertonic saline EPIC drug files have been updated and reconfigured to reflect the guidelines. In addition, a link to the CCHS Hypertonic Saline Use Guidelines will be available within the EPIC order composer and EMAR.

Practice Change:

- 1) Ideal body weight (IBW) will be used as the dosing weight for **Antithymocyte Globulin (Rabbit) (Thymoglobulin®)** and doses should be rounded to the nearest vial size (25 mg).

Cleveland Clinic Children's Hospitals (Pediatrics):

Changes in Current CCHS Pediatric Formulary Restrictions:

- 1) The current restrictions for infliximab (Remicade®; Janssen) will be expanded to include bone marrow transplant patients with graft versus host disease who are refractory to steroids.

Practice Change:

- 1) The practice of adding lidocaine injection to IV potassium infusions in order to decrease infusion-related pain/burning will no longer be permitted.