A Real-World Case Study With EPIDIOLEX® (cannabidiol): An ASM for Your Adult Patients With Lennox-Gastaut Syndrome (LGS)

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Digital Education Suite

Case Study: 32-Year-Old Male Continues to Experience Uncontrolled Seizures Despite Treatment

Past Medical History

- **Seizure onset:** Began experiencing seizures around birth
- **Seizure types:** Affected by drop, myoclonic, and generalized seizures
- **Seizure frequency:** Experiences 1 to 2 drop and generalized seizures a month, and daily myoclonic seizures (up to 20 per day)
- **EEG features:** Slow, disorganized, paroxysmal delta features
- **Other:** Developmental delay, behavioral disorder with self-injurious behavior

Treatment History

Past Treatments			Current Treatment Regimen
• Valproate • Clobazam • Lamotrigine	• Topiramate • Levitracetam • Vigabatrin	• Stiripentol • Fenfluramine • Lacosamide	• 20 mg Clobazam BID (twice a day) • 300 mg Lamotrigine BID • 200 mg Lacosamide BID

Diagnosing the Patient With LGS

- Several clinical criteria (EEG features, history of multiple seizures, developmental delays/behavioral disorder) supported a diagnosis of LGS

> "Even though pediatric neurologists may be more used to dealing with LGS, this diagnosis doesn't have to be difficult for those of us treating adult patients. In this case, the combination of multiple seizure types, abnormal EEG, history of developmental delay, and extensive ASM treatment history all pointed to LGS." **- Daniel Mattson, MD, MSc**

INDICATIONS

EPIDIOLEX (cannabidiol) oral solution is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: HYPERSENSITIVITY

EPIDIOLEX (cannabidiol) oral solution is contraindicated in patients with a history of hypersensitivity to cannabidiol or any ingredients in the product.

WARNINGS & PRECAUTIONS

Hepatic Injury:
EPIDIOLEX can cause dose-related transaminase elevations. Concomitant use of valproate and elevated transaminase levels at baseline increase this risk. Obtain transaminase and bilirubin levels prior to starting treatment, at 1, 3, and 6 months after initiation of treatment, and periodically thereafter, or as clinically indicated. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX, reduction of EPIDIOLEX and/or concomitant valproate, or without dose reduction. For patients with elevated transaminase levels, consider dose reduction or discontinuation of EPIDIOLEX or concomitant medications known to affect the liver (e.g., valproate or clobazam). Dose adjustment and slower dose titration is recommended in patients with moderate or severe hepatic impairment. Consider not initiating EPIDIOLEX in patients with evidence of significant liver injury. There have been postmarketing reports of cholestatic or mixed patterns of liver injury. Elevated ammonia levels were reported in some patients with transaminase elevations; most taking concomitant valproate, clobazam, or both. Consider discontinuation or dose adjustment of valproate or clobazam if ammonia is elevated.

Somnolence and Sedation:
EPIDIOLEX can cause somnolence and sedation that generally occurs early in treatment and may diminish over time; these effects occur more commonly in patients using clobazam and may be potentiated by other CNS depressants.

Please see Important Safety Information throughout and the full Prescribing Information.

Epidiolex® (cannabidiol)

The Decision to Add EPIDIOLEX to the Patient's Treatment Regimen

"For this patient, a change to his treatment regimen was clearly needed. EPIDIOLEX was an appropriate choice, as it is broadly indicated for the seizure types associated with LGS, several of which this patient had been experiencing."
- Daniel Mattson, MD, MSc

- Patient was started on 5 mg/kg/day (2.5 mg/kg BID) of EPIDIOLEX, which was then increased to 20 mg/kg/day over the course of 6 weeks
- Due to the potential for increased somnolence in patients taking EPIDIOLEX and concomitant clobazam, the patient's clobazam dosage was decreased to 10 mg BID
- The patient underwent liver function tests, which were found to be normal:
  - Aspartate transaminase (ASTs): 36
  - Alanine transaminase (ALTs): 38
  - Bilirubin: 1.1

There is a bidirectional pharmacokinetic interaction between EPIDIOLEX and clobazam in which each compound selectively increases exposure to the major active metabolite of the other without affecting parent drug levels.

In Patients Treated With EPIDIOLEX, Somnolence and Sedation Were Typically Observed Earlier in Treatment and May Diminish Over Time With Continued Treatment

	OVERALL		BY DOSE		USE OF CLOBAZAM	
	PLACEBO overall	**EPIDIOLEX** overall	**EPIDIOLEX** 10 mg/kg/day	**EPIDIOLEX** 20 mg/kg/day	**EPIDIOLEX** without clobazam	**EPIDIOLEX** with concomitant clobazam
LGS & Dravet syndrome clinical trials	11%	32%	27%	34%	16%	46%

- Somnolence and sedation generally occurs early in treatment and may diminish with continued treatment. These effects were more common in patients on concomitant clobazam
- Pneumonia was observed more frequently with concomitant use of EPIDIOLEX and clobazam
- Elevated ammonia levels have been reported in some EPIDIOLEX-treated patients who also had transaminase elevations. Most cases reported concomitant use of valproate, clobazam, or both
- Consider a reduction of dosage or discontinuation of clobazam if known clobazam adverse reactions occur
- Other CNS depressants, including alcohol, could potentiate the somnolence and sedation effect of EPIDIOLEX
- Monitor for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX

Like this patient, 49% of patients in the LGS clinical trials were on concomitant clobazam

22% of patients in the LGS studies taking concomitant clobazam with either dose of EPIDIOLEX reported a dose reduction of clobazam during the trial. For more information about the therapeutic relationship between clobazam and EPIDIOLEX, please view the "A Potential Treatment Partnership for LGS" video on the Digital Education Suite.

"EPIDIOLEX and clobazam can be effective treatment partners for patients with LGS. When starting this patient on EPIDIOLEX, I reduced his clobazam dosage to address side effects. I also spoke to his family about the possibility of somnolence, so they were aware of what to expect." **- Daniel Mattson, MD, MSc**

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS & PRECAUTIONS (CONT'D)

Suicidal Behavior and Ideation:
Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior. Inform patients, caregivers, and families of the risk and advise them to monitor and report any signs of depression, suicidal thoughts or behavior, or unusual changes in mood or behavior. If these symptoms occur, consider if they are related to the AED or the underlying illness.

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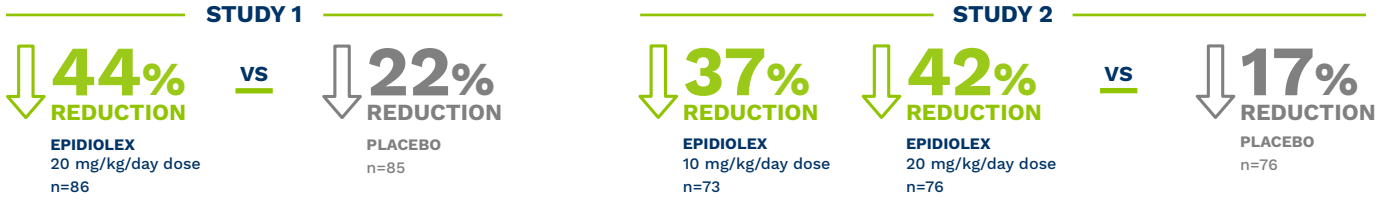
In the LGS Clinical Trials, EPIDIOLEX Significantly Reduced Frequency of Drop and Total Seizures

Median Percent Reduction in Monthly Frequency of Drop Seizures



- Additionally, in the LGS clinical trials, patients taking EPIDIOLEX 20 mg/kg/day experienced a 41% (Study 1) and 38% (Study 2) median percent reduction in monthly frequency of total seizures, patients taking EPIDIOLEX 10 mg/kg/day experienced a 36% (Study 2) reduction, compared to 14% (Study 1) and 18% (Study 2) reduction for patients taking placebo. Total seizures were defined as drop and non-drop seizures.

Most Common Adverse Events (≥10% and Greater Than Placebo) Observed During the 14-Week Treatment Period of Phase 3 Controlled Trials for LGS and Dravet Syndrome (%)

	Placebo (n=227)	EPIDIOLEX 10 mg/kg/day (n=75)	EPIDIOLEX 20 mg/kg/day (n=238)
Hepatic Disorders			
Transaminases elevated	3	8	16
Gastrointestinal Disorders			
Decreased appetite	5	16	22
Diarrhea	9	9	20
Nervous System Disorders			
Somnolence	8	23	25
Fatigue, malaise, asthenia	4	11	12
Insomnia, sleep disorder, poor-quality sleep	4	11	5
Infections			
Infection, all	31	41	40
Other			
Rash	3	7	13

Ongoing Liver Monitoring Is Recommended as EPIDIOLEX Can Cause Dose-Related Elevations of Liver Transaminases

Incidence of ALT Elevations >3x the ULN in Patients With LGS and Dravet Syndrome Treated With EPIDIOLEX

	LGS and Dravet Syndrome Clinical Trials
EPIDIOLEX + clobazam and valproate	30%
EPIDIOLEX + valproate (without clobazam)	21%
EPIDIOLEX + clobazam (without valproate)	4%
EPIDIOLEX (without clobazam and valproate)	3%

Overall Population of Patients With LGS, Dravet Syndrome, and TSC

Elevations resolved in 2/3 of patients following:
- Discontinuation of EPIDIOLEX, or
- Reduction of EPIDIOLEX and/or concomitant valproate

And in 1/3 of patients:
- With no change in EPIDIOLEX treatment

Elevations typically occurred within the first 2 months of treatment; however, there were some cases observed up to 18 months after initiation
- There were cases of transaminase elevations associated with hospitalization

Risk factors for elevated transaminases include:

1. Increased EPIDIOLEX dose
2. Concomitant use of valproate and, to a lesser extent, clobazam*
3. Baseline transaminase elevations

Less than 1% of EPIDIOLEX patients had ALT or AST >20x the ULN.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS & PRECAUTIONS (CONT'D)

Withdrawal of Antiepileptic Drugs:
As with most AEDs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

Please see Important Safety Information throughout and the full Prescribing Information.

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Ongoing Liver Monitoring Is Recommended as EPIDIOLEX Can Cause Dose-Related Elevations of Liver Transaminases

Obtain Serum Transaminases (ALT and AST) and Total Bilirubin Levels

- Prior to starting treatment with EPIDIOLEX, obtain serum transaminases (ALT and AST) and total bilirubin levels
  - Serum transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after initiation of treatment with EPIDIOLEX, and periodically thereafter or as clinically indicated
- Consider more frequent monitoring of serum transaminases and bilirubin in patients who are taking valproate or who have elevated liver enzymes at baseline
  - Monitor within 1 month following changes in EPIDIOLEX dosage and addition of or changes in medications that are known to impact the liver
- Consider discontinuation or dose reduction of EPIDIOLEX or concomitant medications known to affect the liver (eg, valproate or clobazam) if liver enzyme elevations occur (transaminase levels >3x the ULN and bilirubin levels >2x the ULN, or sustained transaminase elevations >5x the ULN)

Patient Experienced Reduction in Seizures on EPIDIOLEX

As of January 2023:

- Patient continues to take 20 mg/kg/day (10 mg/kg BID) of EPIDIOLEX
- Like many patients in the LGS clinical trials, this patient's seizure frequency significantly reduced after treatment with EPIDIOLEX. This patient's drop seizures and convulsive activity has reduced to just one per month, and the frequency of his myoclonic seizures has reduced significantly
- Continual liver monitoring is ongoing for this patient and has so far yielded normal results
- In addition to significant seizure reduction, the patient has experienced an increase in his appetite since his seizures have reduced

Case Study Summary

"I like to emphasize that epilepsy treatment is a marathon, not a sprint. Like my patient, other adult patients may benefit from a slower approach to EPIDIOLEX titration that can help manage side effects while maximizing benefits to seizure reduction. EPIDIOLEX was both effective and well tolerated for this patient, resulting in a significant reduction in his seizure burden." **- Daniel Mattson, MD, MSc**

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS:
The most common adverse reactions in patients receiving EPIDIOLEX (≥10% and greater than placebo) include transaminase elevations; somnolence; decreased appetite; diarrhea; pyrexia; vomiting; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder and poor-quality sleep; and infections. Hematologic abnormalities were also observed.

PREGNANCY:
EPIDIOLEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the EPIDIOLEX Pregnancy Surveillance Program and the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

DRUG INTERACTIONS:
Strong inducers of CYP3A4 and CYP2C19 may affect EPIDIOLEX exposure. EPIDIOLEX may affect exposure to CYP2C19 substrates (e.g., clobazam, diazepam, stiripentol), orally administered P-gp substrates, or other substrates (see full Prescribing Information). Consider dose reduction of orally administered everolimus, with appropriate therapeutic drug monitoring, when everolimus is combined with EPIDIOLEX. A lower starting dose of everolimus is recommended when added to EPIDIOLEX therapy. Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations. Pneumonia was observed more frequently with concomitant use of EPIDIOLEX and clobazam. Dosage adjustment of EPIDIOLEX or other concomitant medications may be necessary.

Please read the EPIDIOLEX full Prescribing Information for additional important information.

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