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From the Department of Pharmacy

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Cannabidiol (Epidiolex®) for Lennox-Gastaut and Dravet Syndrome

By: Ana Simonyan, Pharm.D.

Background: Lennox-Gastaut Syndrome (LGS) is characterized by severe tonic seizures and cognitive dysfunction usually occurring in children < 8 years of age.[1] Approximately 56% of patients with LGS experience sudden tonic or atonic falls known as drop seizures. Dravet Syndrome (DS) is characterized by prolonged, convulsive seizures.[2] Lennox-Gastaut Syndrome is estimated to account for 1%-10% of childhood epilepsies, whereas DS has a reported incidence of 1 in 15,700.[2,3] Frequently accompanied by a poor prognosis these rare and severe forms of epilepsy are difficult to manage and are often refractory to most conventional anti-seizure therapies.[1,3] Fortunately, a new medication, cannabidiol (CBD) oral solution (Epidiolex®; Greenwich Biosciences), was approved by the Food and Drug Administration (FDA) in June 2018 for the treatment of seizures in patients ≥ 2 years of age with LGS or DS.[4]

Mechanism of Action: Cannabidiol is a chemical component of the *Cannabis sativa* plant.[5] Since it does not contain tetrahydrocannabinol (THC), CBD does not exert the same psychoactive effects seen with THC. The exact antiepileptic mechanism of action of CBD is not known.[4,6] However, it is theorized that CBD's anti-seizure activity may be associated with its interactions with various receptors (e.g., opioid, serotonin, glycine, GPR55).[5]

Key Clinical Trials: Cannabidiol oral solution received FDA approval based on three randomized, double-blind, placebo-controlled trials in patients with either LGS or DS.[4] Study 1 (N=171) evaluated CBD solution at a dose of 20 mg/kg/day compared with matching placebo for 14 weeks in patients with LGS.[7] The primary endpoint was the percentage change from baseline in the monthly frequency of drop seizures

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Stiripentol (Diacomit®) for Dravet Syndrome

By: Amber Daley, Pharm.D.

Background: Dravet Syndrome (DS) is often refractory to the off-label use of conventional antiepileptic therapy (e.g., valproate, clobazam, topiramate, and levetiracetam) which in some cases may actually exacerbate DS associated seizures.[1-3] The lack of effective therapeutic options highlights the importance of the June 2018 approval of cannabidiol solution (Epidiolex®) by the Food and Drug Administration (FDA) for the treatment of DS. Shortly afterwards in August 2018, the FDA approved another agent, stiripentol (Diacomit®; Biocodex), for the treatment of seizures associated with DS in patients ≥ 2 years of age concurrently receiving clobazam.[4,5] There are no data to support stiripentol as a monotherapy for this disease state.[5]

Mechanism of Action: Stiripentol's exact mechanism of action is unknown.[5] One proposed mechanism is an indirect anticonvulsant effect involving inhibition of Cytochrome P450 (CYP 450) activity and clobazam metabolism. This

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during the treatment period. The median percent reduction in monthly drop seizure frequency from baseline was 44% in patients receiving CBD solution compared to 22% in those receiving placebo ($p<0.0135$). Study 2 (N=225) evaluated CBD solution at 10 mg/kg/day and 20 mg/kg/day compared to placebo in patients with LGS for 14 weeks.[8] The primary outcome was the percentage change from baseline in the frequency of drop seizures. The median reduction in drop seizure frequency from baseline during the treatment period was 38% in the 10 mg/kg/day group, 42% in the 20 mg/kg/day group, and 17% in the placebo group ($p<0.005$ for the 20 mg group vs. placebo and $p=0.002$ for the 10 mg group vs. placebo). Study 3 (N=120) compared CBD solution 20 mg/kg/day with placebo in patients with DS.[9] The primary endpoint was the change in convulsive seizure frequency after 14 weeks of treatment compared with a 4 week baseline period. The percentage of patients who experienced at least a 50% reduction in convulsive seizure frequency from baseline was 43% in the CBD group versus 27% in the placebo group ($p=0.08$).

Dosing and Administration: The recommended starting dose of CBD solution is 2.5 mg/kg twice daily (5 mg/kg/day) taken on an empty stomach.[4,6] After 1 week of treatment, patients can be titrated to 5 mg/kg twice daily (10 mg/kg/day). Patients who would benefit from further seizure reduction can be titrated to a maximum dose of 10 mg/kg twice daily (20 mg/kg/day). Abrupt discontinuation of CBD oral solution should be avoided to minimize the risk of status epilepticus. If CBD solution is to be discontinued, the dose should be decreased gradually.

Safety: Cannabidiol oral solution is associated with dose-related elevations in liver enzymes.[4,6-9] This may occur within the first 2 months of treatment, especially in patients taking other antiepileptic medications. Prior to initiating CBD oral solution, serum transaminases and total bilirubin levels should be obtained.[4] Monitoring for liver injury should continue at 1 month, 3 months, and 6 months after initiation, and as clinically indicated thereafter. Common adverse reactions associated with CBD 20 mg/kg/day dosage include somnolence (25%), sedation (6%), sleep disturbances (5%), decreased appetite (22%), weight loss (5%) diarrhea (20%), and infections (40%). As with any anti-epileptic treatment, patients taking CBD should be aware of the increased risk for suicidal thoughts or behavior and be monitored appropriately. A dosage adjustment should be made if CBD solution is administered concomitantly with strong inhibitors or inducers of Cytochrome P450 (CYP)3A4 and CYP2C19, as well as clobazam and valproate. Patients should also be told that they may test positive for cannabis during urine drug screening.

Availability and Storage: Cannabidiol 100 mg/mL is available in an amber glass bottle with a child-resistant closure containing 100 mL of strawberry flavored solution (NDC 70127-100-01) and also packaged in a carton containing two 5 mL calibrated oral dosing syringes and a bottle adapter (NDC 70127-100-10).[4] Pharmacies are instructed to provide a 1 mL calibrated oral syringe for doses less than 1 mL. The bottle of cannabidiol oral solution should be stored at room temperature 20°C to 25°C (68°F to 77°F) and used within 12 weeks of opening. Cannabidiol oral solution is designated as a CV Controlled Substance.

Formulary Status: Cannabidiol oral solution is not currently on the CCHS Formulary.

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results in an increase in serum concentrations of clobazam and its active metabolite, thereby potentiating their anti-seizure activity.[1,5] Stiripentol may also have a direct antiepileptic effect as a weak partial agonist of the gamma-amino butyric acid $(GABA)_A$ receptor.[5,6]

Key Clinical Trials: Stiripentol received FDA approval based on two randomized, double-blind, placebo-controlled trials in patients with DS.[1,5,7] Both Study 1 (STICLO-France) (N=42) and Study 2 (STICLO-Italy) (N=23) compared the efficacy and safety of stiripentol with placebo added to a clobazam and valproate regimen in patients with DS. These studies featured a 1-month baseline period in which subjects were observed for seizure activity while on clobazam (0.5 mg/kg/day; maximum 20 mg/day) and valproate (30 mg/kg/day) alone, followed by randomization to either 50 mg/kg/day of stiripentol in two or three divided doses or placebo taken for a 2-month period. All participants received a concurrent clobazam and valproate regimen. The primary outcome for both studies was the percentage of responders experiencing at least a 50% reduction of generalized clonic or tonic-clonic seizure frequency from baseline to month 2. In Study 1 the percent of responders was 71% in patients receiving stiripentol compared to 5% in those receiving placebo ($p<0.00002$). In Study 2 the percent of responders was 67% in patients receiving stiripentol compared to 9% in those receiving placebo (p value was not reported).

Safety: Adverse reactions occurring in at least 10% of those treated with stiripentol include somnolence, decreased appetite, agitation, ataxia, weight loss hypotonia, nausea, tremor, dysarthria, and insomnia.[5,8] Due to the potential for decreased appetite and weight loss, the growth of pediatric patients treated with stiripentol should be carefully monitored. Roughly 13% of those treated with stiripentol experienced neutropenia and thrombocytopenia; therefore, hematologic testing is recommended at baseline and every 6 months.

Drug Interactions: Stiripentol increases the plasma concentration of clobazam and its active metabolite norclobazam through inhibition of the CYP3A4 and CYP2C19.[5,8] Dose reductions of clobazam should be considered in cases of drug-induced adverse reactions. Substrates of CYP2C8, CYP2C19 (e.g., diazepam), P-gp (e.g., carbamazepine), and BCRP (e.g., methotrexate) may require dose reductions, while substrates of CYP1A2 (e.g., theophylline), CYP2D6 (e.g., sertraline), and CYP3A4 (e.g., midazolam) may require dose adjustments. A dosage increase of stiripentol should be considered when used concomitantly with strong inducers of CYP1A2, CYP3A4 or CYP2C19 (e.g., rifampin, phenytoin, phenobarbital, and carbamazepine).

Dosing and Administration: The recommended starting dose of stiripentol is 50 mg/kg/day divided in two or three doses with a maximum of 3000 mg/day.[5,8] Stiripentol capsules should be swallowed whole with a glass of water during a meal. Stiripentol powder for oral suspension should be mixed with 100 mL of water and taken immediately after mixing during a meal. The drug should not be given with milk or other dairy products, carbonated drinks, fruit juice, or liquids containing caffeine. Use in patients with moderate to severe renal or hepatic impairment is not recommended. Stiripentol should not be abruptly discontinued as it may lead to increased seizure frequency and status epilepticus. If immediate cessation of therapy is necessary, the patient should be carefully monitored.

Availability and Storage: Stiripentol is not yet commercially available. It will be supplied as 250 mg and 500 mg capsules as well as packaged powder packets containing 250 mg or 500 mg of stiripentol.[5] The drug should be stored at room temperature 20°C to 25°C (68°F to 77°F) and protected from light.

Formulary Status: Stiripentol is not currently on the CCHS Formulary.

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Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction/ Comments**
Eculizumab (Soliris®)	Monoclonal Antibody	aHUS TMA gMG PNH	Modified restrictions to add Department of Nephrology for outpatient use only
Infliximab-abda (Renflexis®)	Biosimilar Monoclonal Antibody	Severe, persistent steroid refractory immune checkpoint inhibitor reactions*	Modified restrictions to allow for use for severe, persistent steroid refractory immune-related adverse effects from immune checkpoint inhibitor cancer therapy*
Intravenous immune globulin (Gammagard Liquid®)	Blood Product Derivative	Autoimmune Encephalitis	Modified restrictions to allow use for the treatment of auto-immune encephalitis
N-acetylcysteine (NAC, Acetadote®)	Antidote	Acetaminophen overdose Acute alcoholic hepatitis NAI-ALF	Modified restrictions to allow for use in: 1) Acetaminophen overdose 2) Acute alcoholic hepatitis 3) NAI-ALF
Tocilizumab (Actemra®)	Interleukin-6 Receptor Antagonist	CRS	Modified restrictions to add the Department of Hematology/Oncology for management of CRS

*Immune check-point inhibitors such as ipilimumab, nivolumab, pembrolizumab
aHUS= Atypical hemolytic uremic syndrome TMA=Thrombotic microangiopathy gMG=Generalized myasthenia gravis
PNH=Paroxysmal nocturnal hemoglobinuria NAI-ALF=Non-acetaminophen induced acute liver failure CRS=Cytokine release syndrome

Removal from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Promethazine Injection (Phenergan®)	Phenothiazine Derivative	Antiemetic	Rationale for removal: The ISMP recommended the removal of promethazine injection from in-patient formularies due to risk of serious tissue injuries and amputations which can occur after extravasation or accidental arterial administration

ISMP=The Institute for Safe Medication Practices

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Bezlotoxumab (Zinplava™)	Monoclonal Antibody	Recurrent CDI	Restricted to Infectious Disease physicians for the prevention of recurrent CDI in patients with at least three risk factors for recurrence for outpatient use only Risk factors include: 1) ≥ 65 years of age 2) History of CDI 3) Immunocompromised status 4) Severe CDI (Zar score ≥2) 5) C. difficile with ribotypes 027, 078, or 244
Cemiplimab-rwlc (Libtayo®)	Monoclonal Antibody	Metastatic CSCC Locally advanced CSCC ineligible for curative surgery or curative radiation	Restricted to Hematology/Oncology for outpatient use only
Epoetin alfa-epbx (Retacrit®)	Biosimilar Colony Stimulating Factor	Anemia due to CKD or Chemotherapy	Restricted to outpatients whose insurance mandates the use of Retacrit®
Macimorelin (Marcrilen®)	Diagnostic Agent	Diagnosis of AGHD	Restricted to the Department of Endocrinology for outpatient use only in patients whose insurance covers this diagnostic agent (i.e., pre-authorization is required)
Meropenem Inhalation	Antibiotic	BC infections in patients with CF or bronchiectasis from other causes	Restricted to Pulmonary and Critical Care Medicine
Mogamulizumab-kpkc (Poteligeo®)	Monoclonal Antibody	Relapsed or refractory mycosis fungoides or Sézary syndrome	Restricted to Hematology/Oncology for outpatient use only
Pegfilgrastim-jmdb (Fulphila™)	Biosimilar Colony Stimulating Factor	Prevention of chemotherapy-induced neutropenia	Restricted to Hematology/Oncology for outpatients whose insurance mandates the use of Fulphila™

CDI=Clostridium difficile infection C. difficile= Clostridium difficile CSCC=Cutaneous squamous cell carcinoma CKD=Chronic kidney disease
AGHD=Adult growth hormone deficiency BC=Burkolderia cepacia CF=Cystic fibrosis

Product Standardizations on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Atracurium	Non-depolarizing Neuromuscular Blocker	Neuromuscular Blockade	Cisatracurium has been removed and replaced with atracurium as the formulary Cost-savings measure
Temsirolimus	Antineoplastic Agent	Renal Cell Carcinoma	Switching to generic temsirolimus (Accord Healthcare) Cost-savings measure

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions**
Long-acting Reversible Contraceptives	Contraceptive	Pregnancy Prevention	Added: Restricted to outpatient use and for inpatient use in the immediate post-partum period: 1) Mirena®(levonorgestrel-releasing IUD, 52 mg) 2) Nexplanon®(etonogestrel implant, 68 mg) 3) ParaGard®(intrauterine copper contraceptive) Restricted to outpatient use only: 1) Kyleena®(levonorgestrel-releasing IUD, 19.5 mg) 2) Skyla®(levonorgestrel-releasing IUD, 13.5 mg)

IUD=Intrauterine device

Removal from the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Promethazine Injection (Phenergan®)	Phenothiazine Derivative	Antiemetic	Rationale for removal: The ISMP recommended the removal of promethazine injection from inpatient formularies due to risk of serious tissue injuries and amputations which can occur after extravasation or accidental arterial administration

ISMP=The Institute for Safe Medication Practices