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	GREENWICH
III 2018 GREENWICH Biosciences Corporate Model Deck	2

Agenda

- Historical perspective on the use of cannabis in medicine
- Legal and regulatory status of various cannabinoids
- Differences between FDA-approved plant-derived cannabidiol, FDA- approved synthetic cannabinoids and other cannabis-derived products
- Randomized controlled data on the use of a cannabinoid in two epilepsy syndromes



APRIL 201

EENWICH Biosciences Corporate Model Dec

Historical Perspective & Regulatory Status of Cannabis Mark Bolton, JD

20th Century History & Regulations

Cannabis removed from pharmacopeias in 1932 (UK) and 1941 (USA) $\,$

- Marijuana Tax Act effectively prohibited use in 1937 by imposing onerous administrative duties
- Controlled Substance Act (CSA) 1970

Prevention of drug abuse and drug dependence: Designated as Schedule I

- High potential for abuse
- No accepted medical use
- Lack of accepted safety
- FDA Approved Products: Marinol, Syndros, Cesamet, Epidiolex
- 2018 Farm Bill - Hemp derived CBD





What does the 2018 Farm Bill do?

Defines Industrial Hemp

Defines industrial hemp as the plant *cannabis sativa* L, <u>and</u> any part of that plant, including seeds, derivatives, and extracts, with a delta-9 tetrahydrocannabinol (THC) concentration of not more than 0.3% on a dry weight basis

Excludes Hemp from CSA

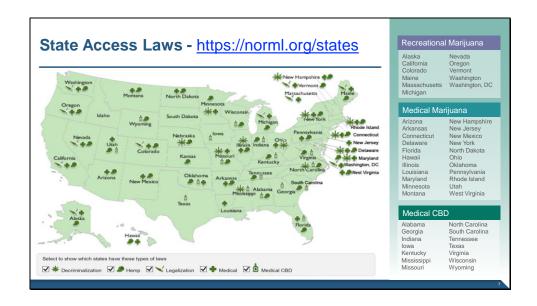
The law excludes hemp from the Controlled Substances Act (CSA) definition of "marihuana"; THC from hemp is also excluded from the CSA definition of THC, thereby making production of hemp legal

USDA Authority

Gives U.S. Department of Agriculture (USDA), State Departments of Agriculture and Tribes authority over hemp production; "production" is not defined

FDA Authority

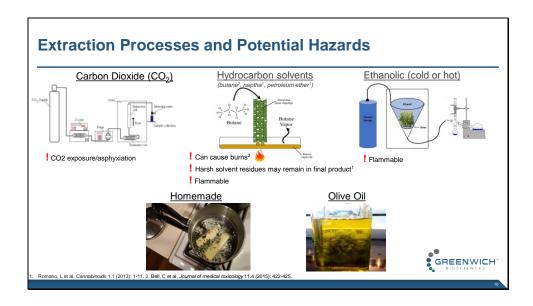
The law expressly curtails USDA's authority by preserving the FDA's authority under the Federal Food, Drug & Cosmetic Act and the Public Health Service Act.

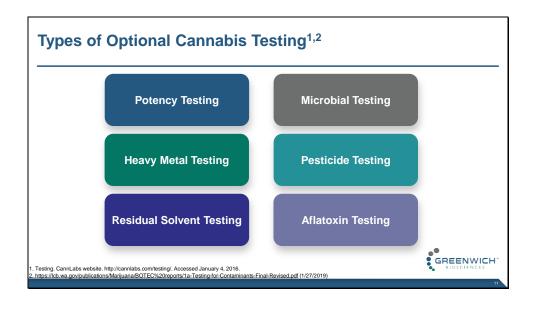


Cannabis-Based Product Categories Pharmaceutical Formulations Recreational Marijuana Hemp Medical Marijuana* Historically grown for fibrous materials found in stalks and Cannabis or cannabis products Can be plant-derived or synthetic ^{6,7} · Cannabis or cannabis used to induce pleasure, euphoria, relaxation, and to enhance sociability¹ products used to treat disease or alleviate symptoms by · Controlled preparations that patient choice Used industrially for items, such as clothing fiber³ meet Food and Drug Administration standards of Classified by intended use not There is a lack of placebocontrolled trials supporting favorable efficacy and safety of these products⁵ by chemical, botanical, or formulation-based differences² purity, consistency, stability, safety, and efficacy Contains minimal amounts (<0.3%) of delta-9 tetrahydrocannabinol (THC)³ Unevenly regulated by states and unregulated at the federal level Classified by intended use not by chemical, botanical, or Cannabinoids extracted from hemp plants are now excluded from the Controlled Substances Act as long as THC levels remain at or below 0.3%, but not legal for use as a food, drug, or supplement. formulation-based differences2 Unevenly regulated by states and unregulated at the federal level Infer's in Scientificary accepted certificant or unse Hall W, Handbook of Carnabis, Oxford, UK: Oxford University Press, 2014;645-646. 2. Mead A. Epilepsy Behav. 2017 May;70(Pt B):288-291. 3. Small E, Marcus D. Trends in New Crops and New Uses. Alexandria, VA. ASHS Press, 2012;264-326. 4. DEA; 2015, https://www.das.gov/divisions/hq/2015/hq/12/315. Accessed May 31, 2017. 5. Hazeleamp A; Pappas G. Handbook of Carnabis. Oxford, UK: Oxford University Press, 2014;319-336. 6. NIH website. https://soc.uc.in.nl...gov/divisions/hq/2015/hq/12/315. Accessed June 1, 2017. 7. FDA website https://www.das.org/disea/compliance/policyguidiancemanalulur/cur003047/hm. Accessed June 1, 2017. This compliance is a compliance of the compliance

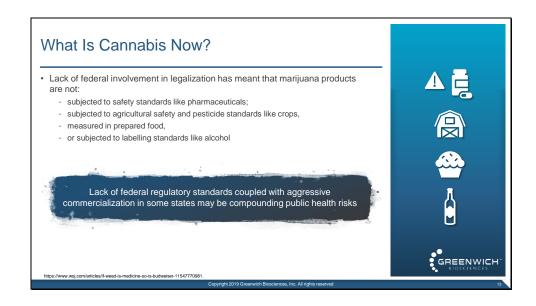
FDA-Approved vs. Non-FDA Approved Cannabinoid Products

	FDA-Approved Products: Plant-Based and Synthetic Medicines	Non-FDA Approved Products: Hemp-Derived Dispensary Products and Medical Marijuana
Clinical Testing Requirements	Randomized, placebo-controlled trials with results publicly disclosed; safety, efficacy and recommended dosing known	No randomized clinical trials. Public disclosure of smaller, informal studies not required.
Manufacturing	Produced according to regulated current good manufacturing practices (cGMP) for pharmaceutical products. Strict specifications to ensure batch consistency and stable shelf life.	Testing standards vary from state to state; some states no testing required. No federal standards. FDA does not inspect manufacturing sites for adherence to cGMP.
Quality Standards	Meet FDA standards for quality, stability, consistency. Tested to ensure they contain consistent concentrations of cannabinoids and other ingredients listed on the label.	Inconsistent regulation at the state level. No federal standards for testing to ensure accuracy and consistency.
Coverage	Eligible for insurance coverage	Insurance coverage is rare

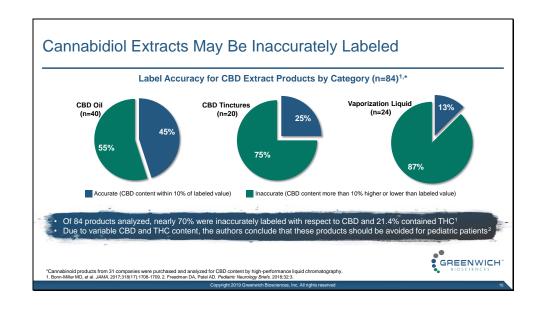




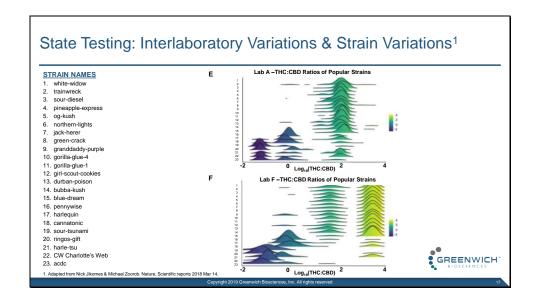


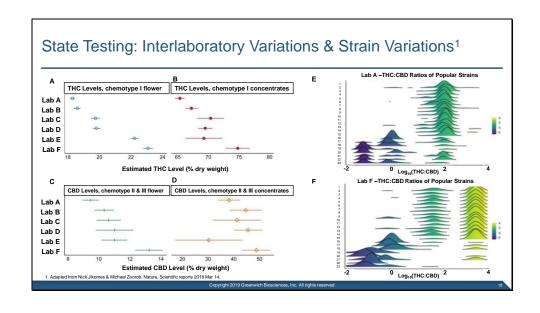




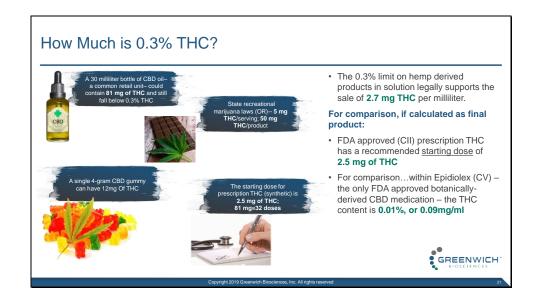


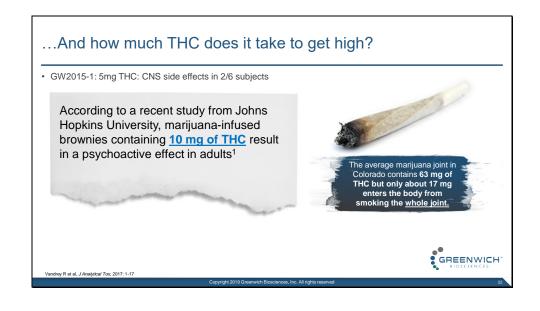
Current Issues Associated with Cannabis Testing¹ Lack of Standardized · Varying results across different labs Inaccurate information from labs regarding potency, **Testing Labs** cannabinoid content, and contaminants Lack of Standardized Variation from batch to batch, leading to issues with dosing, residual THC levels, contaminants, etc **Testing Processes** Lack of Federal Ability of cannabis companies to report results most favorable for their business Testing Regulations for Cannabis Ability of companies to publish results that may not accurately reflect true results of cannabinoid compounds Companies Lack of understanding of issues and risks that currently exist under the current system (eg, dosing, THC levels, contaminants, etc) General Lack of Understanding GREENWICH* Difficulty in discerning credible results from non credible results





"Natural" Cannabis May Be Contaminated - Hemp is a bio-accumulator, meaning the plant draws toxins from the soil; "2 cannabis also naturally draws toxins from soil, so it can become contaminated with heavy metals, including lead, arsenic, mercury and cadmium¹ - Testing shows cannabis crops have been treated with agricultural chemicals even though EPA has not approved any pesticides for cannabis - California, Sept 2015: Pesticide - Independent cannabis facility tests 57 state legal products: 83% contained unsafe solvents (propane, butane, isopentane) 40% contained unsafe solvents (propane, butane, isopentane) 40% contained pesticide - 1 of the 5 died due to the infection - 20 products tested in investigation with 100% having mold and 90% fungus - 1 of the 5 died due to the infection of the in

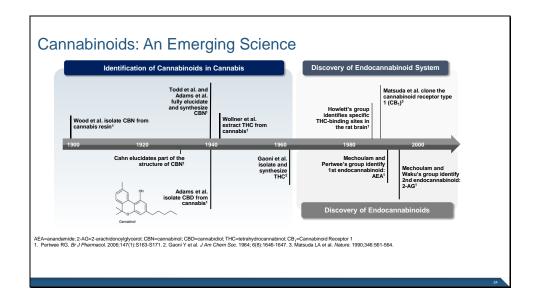


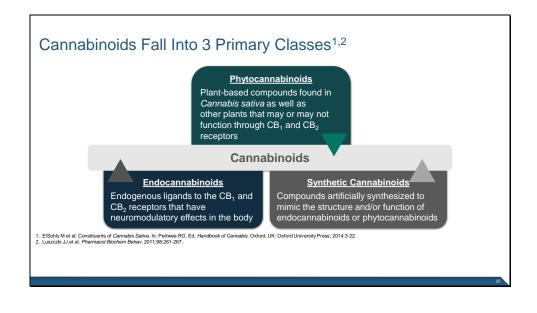


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Therapeutic Potential of Cannabinoids: An Emerging Science

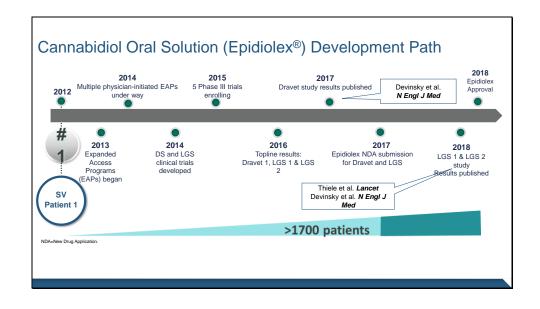
Elise Conlee, PhD

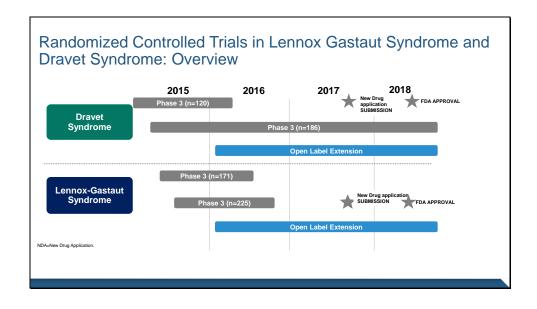


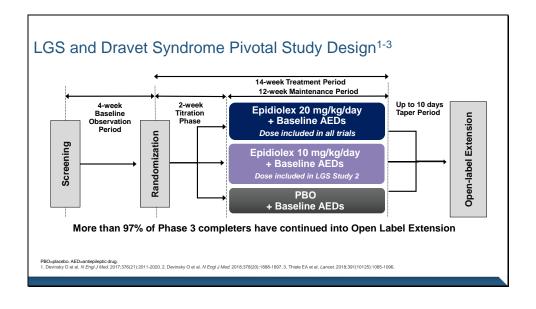


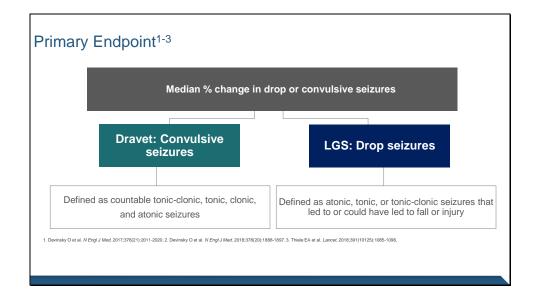
Randomized Controlled Clinical Trial Data: Cannabidiol Oral Solution (Epidiolex®)

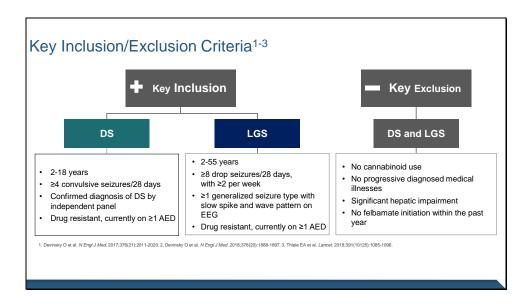
FDA Approved June 2018









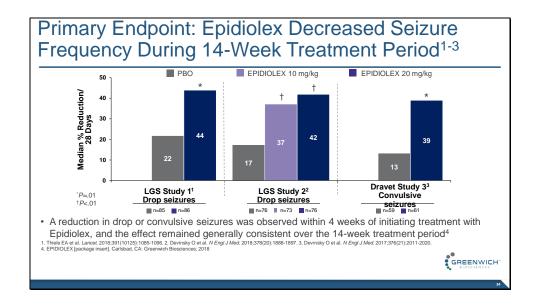


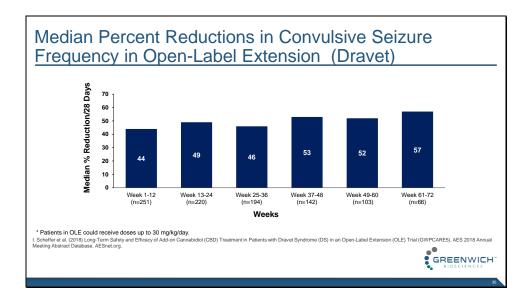
Patient Characteristics 1-4

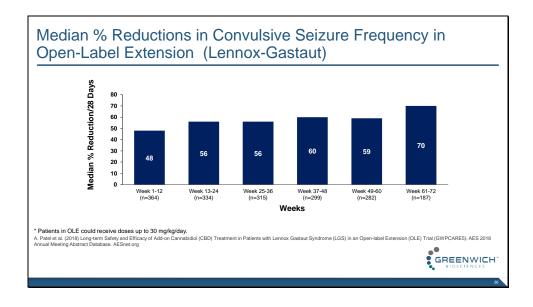
Variable	LGS Study 1 (N=171)	LGS Study 2 (N=225)	Dravet Study 3 (N=120)
Age,* %			
2-5 years	13.5	11.6	29.2
6-11 years	31.0	32.4	39.2
12-17 years	21.6	26.2	31.7
18-55 years	33.9	29.8	N/A
Seizure types at baseline, %			
Generalized tonic-clonic	59.6	49.8	89.2
Tonic	79.9	76.4	24.2
Atonic	62.0	58.2	13.3
Clonic	11.1	7.1	20.8
Primary seizure types at baseline, median/28 days (range)			
Convulsive seizures	_	_	13.0 (3.7-1716.7)
Drop seizures	73.8 (10.3-3174.6)	85.0 (8.7-7494.0)	_

Patient Characteristics

Variable	LGS Study 1 (N=171)	LGS Study 2 (N=225)	Dravet Study 3 (N=120)
Number of previous AEDs, median (range)	6 (0–28)	6 (0–22)	4 (0–26)
Number of current AEDs, median (range)	3 (1–5)	3 (0–5)	3 (1–5)
Number of AEDs patient currently taking, %			
0	_	0.4	-
1	5.8	5.8	6.7
2	27.5	26.7	25.0
3	38.0	39.6	44.2
4	27.5	26.2	17.5
5	1.2	1.3	6.7
Most common concomitant AEDs at baseline	CLB, VPA, LTG	CLB, VPA, LEV	CLB, VPA, STP
Current nonpharmacologic antiepileptic therapies, %	38.0	28.9	20.0
Ketogenic diet	8.2	8.0	8.3
Vagus nerve stimulation	29.8	23.6	12.5







Discontinuation Rates Due to Adverse Reactions in Controlled Trials

Patients discontinued, %	РВО	Epidiolex 10 mg/kg/day	Epidiolex 20 mg/kg/day
Any adverse reaction	1.3	2.7	11.8
Transaminase elevation	0.4	1.3	5.9
Somnolence, sedation, and lethargy	0	0	3

• The most frequent cause of discontinuations was transaminase elevation

Epidiolex [package insert], Carlsbad, CA: Greenwich Biosciences: 2018



Pooled Safety From Controlled Trials: Most Common Adverse Reactions (>10%) DS & LGS

Adverse events were similar across LGS and DS in pediatric and adult patients

Patients reporting, %	PBO (n=227)	Epidiolex 10 mg/kg/day (n=75)	Epidiolex 20 mg/kg/day (n=238)
Somnolence	8	23	25
Decreased appetite	5	16	22
Diarrhea	9	9	20
Transaminase elevations	3	8	16
Fatigue, malaise, asthenia	4	11	12
Rash	3	7	13
Insomnia, sleep disorder, poor quality sleep	4	11	5
Infection, all	31	41	40

1.3% EPIDIOLEX 10 mg/kg/day, 0.4% PBO) and somnolence, sedation, and lethargy (3% Epidiolex 20 mg/kg/day, 0% EPIDIOLEX 10 mg/kg/day, 0% PBO)

Discontinuation Rates Due to Adverse Events in Oper Label Extension

Patients Reporting, %	Dravet Syndrome (n=278)	Lennox-Gastaut Syndrome (n=366)
Any adverse events	7%	11%
Increased alanine aminotransferase (ALT)	3%	1%
Increased aspartate aminotransferase (AST)	3%	
Convulsion	1%	2%
Abnormal liver function test	1%	
Diarrhea		1%
Vomiting		1%

Most Common Adverse Events (≥10% of patients) in Open Label Extension

Patients Reporting, %	Dravet Syndrome (n=278)	Lennox-Gastaut Syndrome (n=366)
Diarrhea	37%	32%
Pyrexia	33%	25%
Decreased appetite	27%	21%
Somnolence	26%	26%
Nasopharyngitis	21%	12%
Upper respiratory tract infection	18%	18%
Convulsion	17%	27%
Vomiting	17%	22%
Status epilepticus	13%	
Cough	11%	10%
Fatigue	11%	
Weight decreased		11%

Safety: Transaminase Elevations Elevations of ALT/AST (>3X ULN) were observed in the clinical trials (LGS and DS) • Typically presented in the first 2 months of treatment; some cases observed up to 18 months after initiation · Risk factors for transaminase elevations: concomitant valproate and clobazam, higher dose of Epidiolex, and baseline transaminase elevations Resolution occurred in approximately 2/3 of cases with discontinuation of Epidiolex, or reduction of Epidiolex and/or concomitant valproate; about 1/3 of cases resolved during continued Epidiolex treatment without dose reduction · Periodically thereafter or as clinically indicated Within 1 month following changes in EPIDIOLEX dosage and addition of Obtain serum transaminases (ALT and AST) and total bilirubin levels: or changes in medications that are known to impact the liver Consider more frequent monitoring of serum transaminases and bilirubin in patients who are taking valproate or who have elevated liver enzymes Draw 2 Draw 4 Month 6 Month 15

Dosing and Practical Use

Epidiolex® (cannabidiol) Indications and Dosing

INDICATIONS AND USAGE

Epidiolex* (cannabidiol) is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.

DOSAGE & ADMINISTRATION

Starting dose	Maintenance Dose	Maximum Recommended Dose
Week 1	Week 2	Week 3 and On
2.5 mg/kg taken twice daily	Increase dosage to maintenance dose of 5 mg/kg twice daily	If tolerated and required, increase dose weekly by 2.5 mg/kg (5 mg/kg/day) to max recommended dose of 10 mg/kg twice daily
5 mg/kg/day	10 mg/kg/day	20 mg/kg/day

- * Food may affect Epidiolex levels.
- Dose adjustment is recommended in patients with moderate or severe hepatic impairment. A slower dose titration may also be necessary for
- these patients.

 Administration of 20mg/kg/day resulted in somewhat greater reductions in seizure rates than 10mg/kd/day, but with an increase in

Additional Labeling Information: Pharmacokinetic Overview ABSORPTION T_{max}: 2.5-5 hr, absorption affected by high-fat meal (-4-fold increase in AUC) DISTRIBUTION CBD is highly lipophilic; >94% protein bound; large apparent steady-state volume of distribution (20,963L – 42,849L) METABOLISM Primary metabolites: y-OH-CBD active metabolite has a 38% lower AUC than the parent drug; half-life is 56 to 61 hours after twice daily dosing for 7 days ELIMINATION Primarily fecal excretion of parent drug and metabolites; moderate to severe hepatic impairment can lead to increased exposure. Renal elimination is a minor pathway; no changes in exposure based on renal impairment AUC-area under the curvic Communication of parent drug and metabolites; moderate to severe hepatic impairment can lead to increased exposure. Renal elimination is a minor pathway; no changes in exposure based on renal impairment AUC-area under the curvic Communication of parent drug and metabolites; moderate to maximum concentration; UST-UDP apparent metabolites; moderate to maximum concentration; UST-UDP apparent metabolites; Distribution (20,963L – 42,849L)

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

Hepatocellular Injury:

- EPIDIOLEX can cause dose-related transaminase elevations. Concomitant use of valproate and elevated transaminase levels at baseline increase this risk.
- Transaminase and bilirubin levels should be obtained prior to starting treatment, at one, three, and six 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 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.

Somnolence and Sedation:

EPIDIOLEX can cause somnolence and sedation that occurs early in treatment and may diminish over time; these effects occur in the second patients using clobazam and may be potentiated by other CNS depressants.

Reference: EPIDIOLEX (package insent). Carlobad, CA: Greenwich Biosolences, 2018.

Important Safety Information (cont)

Warnings & Precautions (cont)

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 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.

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.

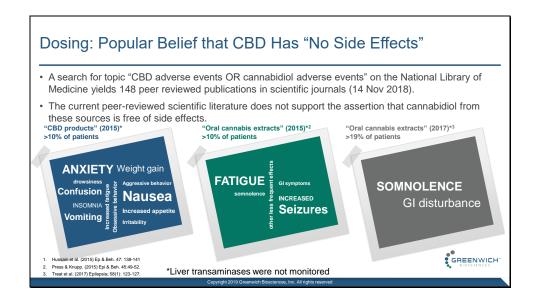
Adverse Reactions

- The most common adverse reactions in patients receiving EPIDIOLEX (≥10% and greater than placebo) include somnolence; decreased appetite; diarrhea; transaminase elevations; 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 North American Antiepileptic Drug (NAAED) Pregnancy English Reference: EPIDIOLEX (package insert). Carlabad, CA: Greenwich Biosciences; 2018.

Important Safety Information (cont) Drug Interactions: • Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations. EPIDIOLEX may affect exposure to CYP3A4 and CYP2C19 substrates (e.g., clobazam, diazepam, ketoconazole, erythromycin) or others. Dosage adjustment of EPIDIOLEX or other concomitant medications may be necessary. Drug Abuse: ■ EPIDIOLEX is a Schedule V (CV) controlled substance and has a low potential for abuse. GREENWICH* Reference: EPIDIOLEX [package insert]. Carlsbad, CA: Greenwich Biosciences; 2018.



"Natural" Is Not Always Safe

Water Hemlock (Cicuta maculata)

 Deemed "the most violently toxic plant in North America." A large wildflower in the carrot family. Will rapidly generate potentially fatal symptoms including painful convulsions, abdominal cramps, nausea, and death; those who survive are often afflicted with amnesia or lasting tremors¹

White Snakeroot (Ageratina altissima)

North American herb contains a toxic alcohol known as trematol. The meat and milk from
poisoned livestock can pass the toxin to human consumers. Symptoms of "milk poisoning"
include loss of appetite, nausea, weakness, abdominal discomfort, reddened tongue,
abnormal acidity of the blood, and death²

Arsenic

 One of many natural elements found in air, water, and soil, and virtually all crop plants take up arsenic.

Lead, Cadmium, Mercury

- · Metals found naturally in the earth's crust found or in ores with other metals.
- Schep LJ, Slaughter RJ, Becket G, Beasley DM. Poisoning due to water hemicol. Clin Toxicol (Phila). 2009 Apr;47(4):270-8. doi: 10.1080/1556850902904332.
 Lee ST, Davis TZ, Gardner DR, Colegate SM, Cook D, Gireen BT, Meyerholtz KA, Wilson CR, Stepsimieire IE, Evens TJ. Tremetione and structurally related compound in white snakeroot (Ageratina altissima): a plant associated with trembles and milk sickness. J Ager Food Chem. 2010 Jug 11;58(15):8569-5. doi: 10.1021/jf1012456.
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Trainso (Phila), 2009, Apr.47 (4) 279-8, doi: 10.1001/15833600002004322

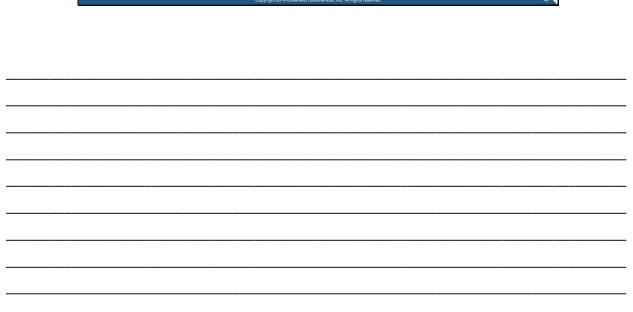
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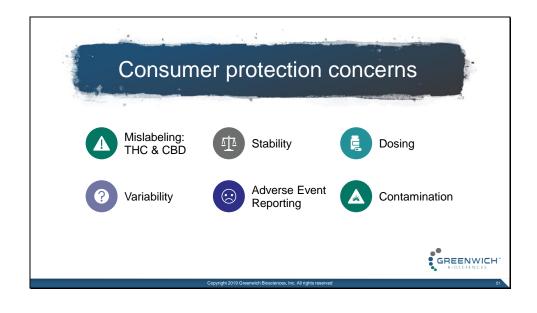
Trainso (Phila), 2009, Apr.47 (4) 279-8, doi: 10.1001/159360000004322

BIOSCIENCES

BIOSCIENCES



Medically Fragile Patients / Vulnerable Populations - Cannabis products are sometimes marketed as a "supplement," but supplements are intended to maintain good health, not treat disease. - The concerns with cannabinoid labeling are of great public health concern in general, but these concerns may be exacerbated in vulnerable patient populations. - Taking multiple drugs; - Having sensitivity to concentrations of medications - With multiple comorbidities & complex health concerns



Practical considerations for the use of cannabinoid products

- There are practical differences between dispensary products and FDA approved Epidiolex.
- If using an over-the-counter or dispensary product, there may be differences batch to batch; strict testing of these products is not typically done.
- Monitoring of liver enzymes should be considered for all CBD products, both prior to starting and periodically
 after initiation.
- Dosing parameters are not known for the non-FDA products
- Know the laws in your state, but remember that state law and federal law may not be the same.

Key Take Home Points

While use of cannabis for medicinal purposes has been written about for centuries, scientific data are sparse

There are significant differences in regulation and manufacturing between FDA-approved products and the many products now available without prescription

Epidiolex @ (cannabidiol) decreased median drop or convulsive seizure frequencies relative to placebo when added to existing AED regimens in three Phase 3 clinical trials in patients with LGS or DS

The most common adverse reactions that occurred in patients treated with Epidiolex (incidence at least 10% and greater than placebo) were somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections

The safety profile was consistent across studies and across adult and pediatric patients

Discussion with patients and families regarding the use cannabinoid products in the treatment of epilepsy is essential for their health and safety

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