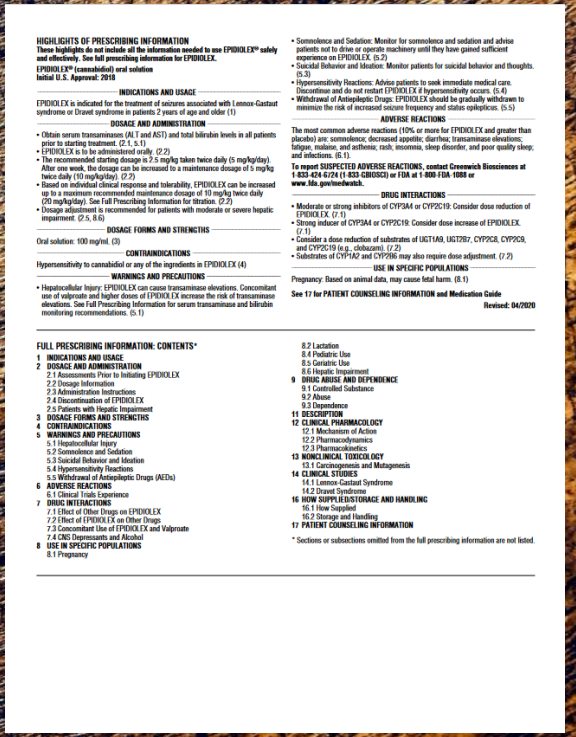
Drug Free Australia series – Media suppression of alarming cannabis harms

Episode 7 – Hemp and psychoactive metabolites

DRUG FREE AUSTRALIA

CBD side effects

- Side effects sheet for Epidiolex (CBD) treatment
  - Sleepiness
  - Decreased appetite
  - Diarrhea
  - Change in liver function
  - Fatigue/Malaise/Asthenia (weakness or lack of energy)
  - Rash
  - Insomnia/Sleep disorder/Poor quality sleep
  - Infections
  - CBD also interacts with some other seizure medicines
  - Nausea or vomiting
  - Dizziness
  - Anxiety or depression
  - Changes in appetite/weight



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPIDIOLEX® safely and effectively. See full prescribing information for EPIDIOLEX.

EPIDIOLEX® (cannabidiol) oral solution
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older (1)

DOSAGE AND ADMINISTRATION

- Obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment. (2.1, 5.1)
- EPIDIOLEX is to be administered orally. (2.2)
- The recommended starting dosage is 2.5 mg/kg taken twice daily (5 mg/kg/day). After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). (2.2)
- Based on individual clinical response and tolerability, EPIDIOLEX can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day). See Full Prescribing Information for titration. (2.2)
- Dosage adjustment is recommended for patients with moderate or severe hepatic impairment. (2.5, 8.6)

DOSAGE FORMS AND STRENGTHS

Oral solution: 100 mg/mL (3)

CONTRAINDICATIONS

Hypersensitivity to cannabidiol or any of the ingredients in EPIDIOLEX (4)

WARNINGS AND PRECAUTIONS

- Hepatocellular Injury: EPIDIOLEX can cause transaminase elevations. Concomitant use of valproate and higher doses of EPIDIOLEX increase the risk of transaminase elevations. See Full Prescribing Information for serum transaminase and bilirubin monitoring recommendations. (5.1)
- Somnolence and Sedation: Monitor for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX. (5.2)
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts. (5.3)
- Hypersensitivity Reactions: Advise patients to seek immediate medical care. Discontinue and do not restart EPIDIOLEX if hypersensitivity occurs. (5.4)
- Withdrawal of Antiepileptic Drugs: EPIDIOLEX should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus. (5.5)

ADVERSE REACTIONS

The most common adverse reactions (10% or more for EPIDIOLEX and greater than placebo) are: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections. (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Greenwich Biosciences at 1-833-424-6274 (1-833-GBIOSCI) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Moderate or strong inhibitors of CYP3A4 or CYP2C19: Consider dose reduction of EPIDIOLEX. (7.1)
- Strong inducer of CYP3A4 or CYP2C19: Consider dose increase of EPIDIOLEX. (7.1)
- Consider a dose reduction of substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19 (e.g., clobazam). (7.2)
- Substrates of CYP1A2 and CYP2B6 may also require dose adjustment. (7.2)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 04/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

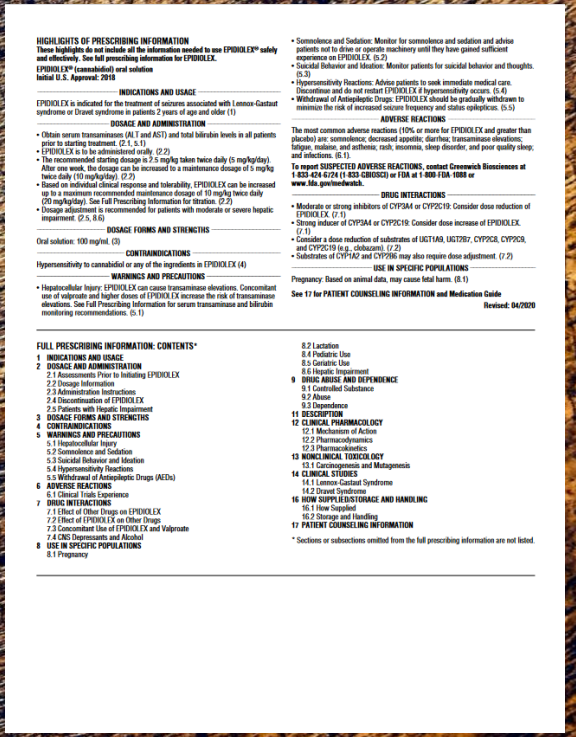
https://www.epidiolex.com/sites/default/files/pdfs/EPIDIOLEX_Full_Prescribing_Information_04_16_2020.pdf

CBD adverse events

- Epidiolex (CBD) medication prescribing info sheet

5 WARNINGS AND PRECAUTIONS

5.1 Hepatocellular Injury
5.2 Somnolence and Sedation
5.3 Suicidal Behavior and Ideation
5.4 Hypersensitivity Reactions
5.5 Withdrawal of Antiepileptic Drugs (AEDs)



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https://www.epidiolex.com/sites/default/files/pdfs/EPIDIOLEX_Full_Prescribing_Information_04_16_2020.pdf

CBD converts to THC

- 2003 Japanese study found that CBD metabolises to THC

"Cannabidiol (CBD), another major component, was biotransformed to two novel metabolites . . . . Both metabolites have some pharmacological effects comparable to Δ^9-THC."

Journal of Toxicology: Toxin Reviews

Volume 22, 2003 - Issue 4

Pharmacology and Toxicology of Major Constituents of Marijuana—On the Metabolic Activation of Cannabinoids and Its Mechanism

Ikuo Yamamoto, Kazuhito Watanabe, Tamihide Matsunaga, Toshiyuki Kimura, Tatsuya Funahashi & Hidetoshi Yoshimura

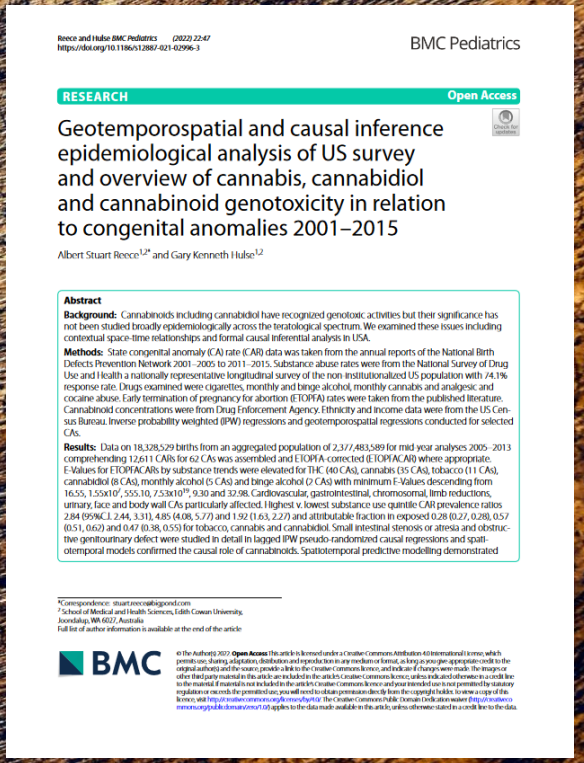
Abstract

Many oxidative metabolites of tetrahydrocannabinols (THCs), active components of *Cannabis sativa* L. (*Cannabinaceae*), were pharmacologically potent, and 11-hydroxy-THCs, 11-oxo-Δ^{8}-THC, 7-oxo-Δ^{8}-THC, 8β,9β-epoxyhexahydrocannabinol (EHHC), 9α,10α-EHHC and 3′-hydroxy-Δ^{9}-THC were more active than THC in pharmacological effects such as catalepsy, hypothermia and barbiturate synergism in mice, indicating that these metabolites are active metabolites of THCs. Cannabidiol (CBD), another major component, was biotransformed to two novel metabolites, 6-hydroxymethyl-Δ^{8}-THC and 3-pentyl-6, 7, 7a, 8, 9, 11a-hexahydro-1, 7-dihydroxy-7,10-dimethyldibenzo[b,d]oxepin (PHDO) through 8R,9-epoxy-CBD and 8S, 9-epoxy-CBD as intermediates, respectively, identified by us. Both metabolites have some pharmacological effects comparable to Δ^{9}-THC. Cannabinol (CBN), the other major component, was mainly metabolized to 11-hydroxy-CBN by hepatic microsomes of animals including humans. The pharmacological effects of the metabolite were higher than those of CBN demonstrating that 11-hydroxylation of CBN is an activation pathway of the cannabinoid as is the case in THCs. Tolerance developed to catalepsy, hypothermia and pentobarbital-induced sleep prolonging effects of Δ^{8}-THC and its active metabolite, 11-hydroxy-Δ^{8}-THC. Reciprocal cross-tolerance also developed to pharmacological effects and the magnitude of tolerance development produced by the metabolite was significantly higher than that by Δ^{8}-THC indicating that 11-hydroxy-Δ^{8}-THC has important role not only in the pharmacological effects but also its tolerance development of Δ^{8}-THC. THCs and their metabolites competed with the specific binding of CP-55,940, an agonist of cannabinoid receptor, to synaptic membrane from bovine cerebral cortex. The Ki value of THCs and their metabolites were closely parallel to their pharmacological effects in mice. A novel cytochrome P450 (cyp2c29) was purified and identified for the first time by us as a major enzyme responsible for the metabolic activation of Δ^{8}-THC at the 11-position in the mouse liver. cDNA of cyp2c29 was cloned from a mouse cDNA library and its sequence was determined. All of major P450s involving the metabolic activation of Δ^{8}-THC at the 11-position are belonging to CYP2C subfamily in mammalian liver.

https://www.tandfonline.com/doi/abs/10.1081/TXR-120026915

US population

- Results for birth defects
  - tobacco 11
  - alcohol 5
- Cannabis constituents (cannabinoids)
  - THC 40
  - Cannabidiol (CBD) 8
- Cannabis causal in 45 of 62 birth defects in all in the US data



Reece and Hulse *BMC Pediatrics* (2022) 22:47
https://doi.org/10.1186/s12887-021-02996-3

BMC Pediatrics

RESEARCH Open Access

Geotemporospatial and causal inference epidemiological analysis of US survey and overview of cannabis, cannabidiol and cannabinoid genotoxicity in relation to congenital anomalies 2001–2015

Albert Stuart Reece[1,2*] and Gary Kenneth Hulse[1,2]

Abstract

Background: Cannabinoids including cannabidiol have recognized genotoxic activities but their significance has not been studied broadly epidemiologically across the teratological spectrum. We examined these issues including contextual space-time relationships and formal causal inferential analysis in USA.

Methods: State congenital anomaly (CA) rate (CAR) data was taken from the annual reports of the National Birth Defects Prevention Network 2001–2005 to 2011–2015. Substance abuse rates were from the National Survey of Drug Use and Health a nationally representative longitudinal survey of the non-institutionalized US population with ⁄4.1% response rate. Drugs examined were cigarettes, monthly and binge alcohol, monthly cannabis and analgesic and cocaine abuse. Early termination of pregnancy for abortion (ETOPFA) rates were taken from the published literature. Cannabinoid concentrations were from Drug Enforcement Agency. Ethnicity and income data were from the US Census Bureau. Inverse probability weighted (IPW) regressions and geotemporospatial regressions conducted for selected CAs.

Results: Data on 18,328,529 births from an aggregated population of 2,377,483,589 for mid year analyses 2005–2013 comprehending 12,611 CARs for 62 CAs was assembled and ETOPFA-corrected (ETOPFACAR) where appropriate. E-Values for ETOPFACARs by substance trends were elevated for THC (40 CAs), cannabis (35 CAs), tobacco (11 CAs), cannabidiol (8 CAs), monthly alcohol (5 CAs) and binge alcohol (2 CAs) with minimum E-Values descending from 16.55, 1.55×10^{7}, 555.10, 7.53×10^{19}, 9.30 and 32.98. Cardiovascular, gastrointestinal, chromosomal, limb reductions, urinary, face and body wall CAs particularly affected. Highest v. lowest substance use quantile CAR prevalence ratios 2.84 (95%CI. 2.44, 3.31), 4.85 (4.08, 5.77) and 1.92 (1.63, 2.27) and attributable fraction in exposed 0.28 (0.27, 0.28), 0.57 (0.51, 0.62) and 0.47 (0.38, 0.55) for tobacco, cannabis and cannabidiol. Small intestinal stenosis or atresia and obstructive genitourinary defect were studied in detail in lagged IPW pseudo-randomized causal regressions and spatiotemporal models confirmed the causal role of cannabinoids. Spatiotemporal predictive modelling demonstrated

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Full list of author information is available at the end of the article

BMC

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8767720/pdf/12887_2021_Article_2996.pdf

THC accumulation

- THC accumulates in the body
  - THC is stored in the fat deposits of the brain and body
  - THC lasts for months
  - CBD Hemp is legally allowed to contain 0.3% THC
  - consistent use of CBD keeps THC accumulating
  - CBD metabolised to THC also contributes to accumulation
  - the harms presented by THC could affect CBD users as well

"THC has a half-life of about seven days, meaning that one-half of the THC ingested or inhaled stays in the brain and body tissue for seven days. Traces can stay in body tissues for a month or more. The only important substance that exceeds THC in fat solubility is DDT."

DrugWatch INTERNATIONAL

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Cannabis Hemp THC in the Food–Cosmetic Supply

Details | Category: Articles | Published: 01 August 2000

By Jeanette McDougal, MM, CCDP, Chair
William R. Walluks, Member
Hemp Committee, Drug Watch Intl.
August 2000

Fiber Cannabis hemp seed, though containing tetrahydrocannabinol (THC, the main psychoactive ingredient in hemp/marijuana) and other cannabinoid residue, is being heavily marketed and promoted by the hemp industry as a source of food, nutraceuticals, and cosmetics. The harmful effects of THC on humans and other animals is well documented. Hemp advocates, however, mimicking the tactics of tobacco industry apologist, challenge and "call into question" every statement substantiating harm caused by the use of Cannabis sativa L. hemp. (Where used in this paper, the term hemp refers to cannabis sativa, aka marijuana, and not to any of the numerous other plant fibers also commonly referred to as hemp.)

The campaign to use hemp fiber for paper, biomass, textiles, etc. has largely failed because hemp is neither economically viable nor technically feasible. However, because the handling, storage, and processing of hemp seed is more adaptable to present technologies than for hemp fiber, hemp seed production and products are now being aggressively promoted.

Low THC Cannabis sativa hemp that contains less than .3% (w/w) THC became legal to grow in Canada in March, 1998. THC and the other cannabinoids are found in food and other products made from fiber hemp seed. According to Canada's national health department, Health Canada, "In theory the ripened seeds of Cannabis contain no detectab quantity of THC. However, because of the nature of the material it is almost impossible to obtain the seeds free from extraneous THC in the form of residues arising from other parts of the plant which are in close proximity to the seeds. Although it is required for the seeds to be cleaned before any subsequent use, the resinous nature of some of the material makes complete cleaning extremely difficult." [1]

Since THC and the over 60 other cannabinoids are fat-soluble, i.e., store themselves in the fatty tissues of the brain and body, even a very small amount may be damaging, especially if ingested regularly. Fat-soluble substances accumulate in the body.

THC has a half-life of about seven days, meaning that one-half of the THC ingested or inhaled stays in the brain and body tissue for seven days. Traces can stay in body tissues for a month or more. The only important substance tha exceeds THC in fat solubility is DDT. [2]

A risk assessment done for Health Canada states that, "New food products and cosmetics made from hemp – the marijuana plant – pose an unacceptable risk to the health of consumers. It also says that hemp products may not be safe because even small amounts of THC may cause developmental problems. "Those most at risk," the study says, "are children exposed in the womb or through breast milk, or teen-agers whose reproductive systems are developing." [3]

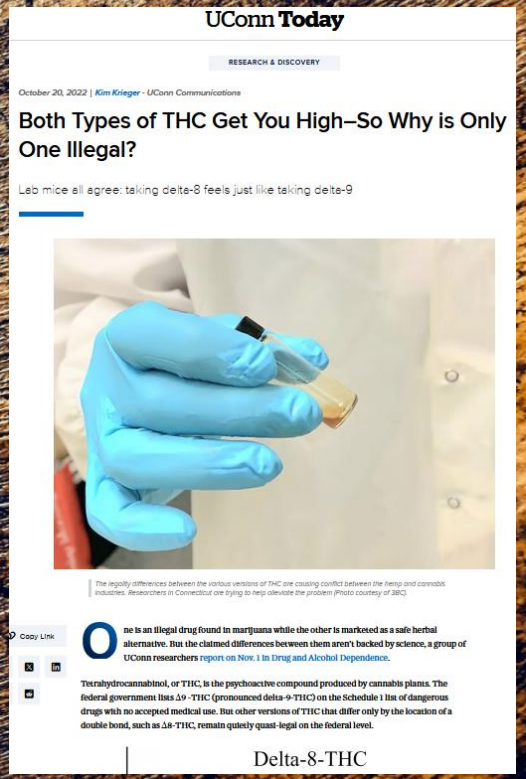
https://www.drugwatch.org/resources/publications/articles/161-cannabis-hemp-thc-in-the-food-cosmetic-supply.html

In the lab

- CBD can be converted in the lab to Δ8-THC

From the University of Connecticut, commenting on Δ8-THC, which is equally as psychoactive as Δ9-THC, being produced from hemp, and the differing legalities across US states. This is just another way that unregulated CBD can produce an illicit recreational product.

"Tetrahydrocannabinol, or THC, is the psychoactive compound produced by cannabis plants. The federal government lists Δ9 -THC (pronounced delta-9-THC) on the Schedule 1 list of dangerous drugs with no accepted medical use. But other versions of THC that differ only by the location of a double bond, such as Δ8-THC, remain quietly quasi-legal on the federal level."



UConn Today

RESEARCH & DISCOVERY

October 20, 2022 | Kim Krieger - UConn Communications

Both Types of THC Get You High–So Why is Only One Illegal?

Lab mice all agree: taking delta-8 feels just like taking delta-9

The legality differences between the various versions of THC are causing conflict between the hemp and cannabis industries. Researchers in Connecticut are trying to help alleviate the problem (Photo courtesy of 3BIO).

Copy Link

One is an illegal drug found in marijuana while the other is marketed as a safe herbal alternative. But the claimed differences between them aren't backed by science, a group of UConn researchers report on Nov. 1 in Drug and Alcohol Dependence.

Tetrahydrocannabinol, or THC, is the psychoactive compound produced by cannabis plants. The federal government lists Δ9 -THC (pronounced delta-9-THC) on the Schedule 1 list of dangerous drugs with no accepted medical use. But other versions of THC that differ only by the location of a double bond, such as Δ8-THC, remain quietly quasi-legal on the federal level.

Delta-8-THC

https://today.uconn.edu/2022/10/191210/

Next episode

- More detail in future episodes:
  - Cannabis and cancer
  - Cannabis and birth defects
  - Cannabidiol (CBD), cancer and birth defects
  - Cannabis and pain
  - Cannabis and driving
  - Hemp and psychoactive metabolites
  - Cannabis and psychosis
  - Cannabis and violence/homicide
  - Cannabis and suicide
  - Cannabis – its other harms