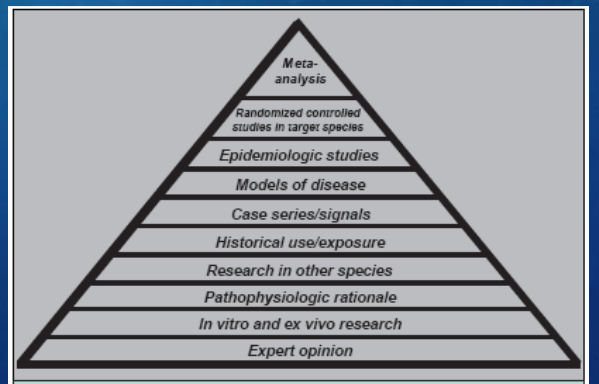
THE CHALLENGES OF MEDICAL CANNABINOIDS

PART I: UNDERSTANDING THE PRODUCTS

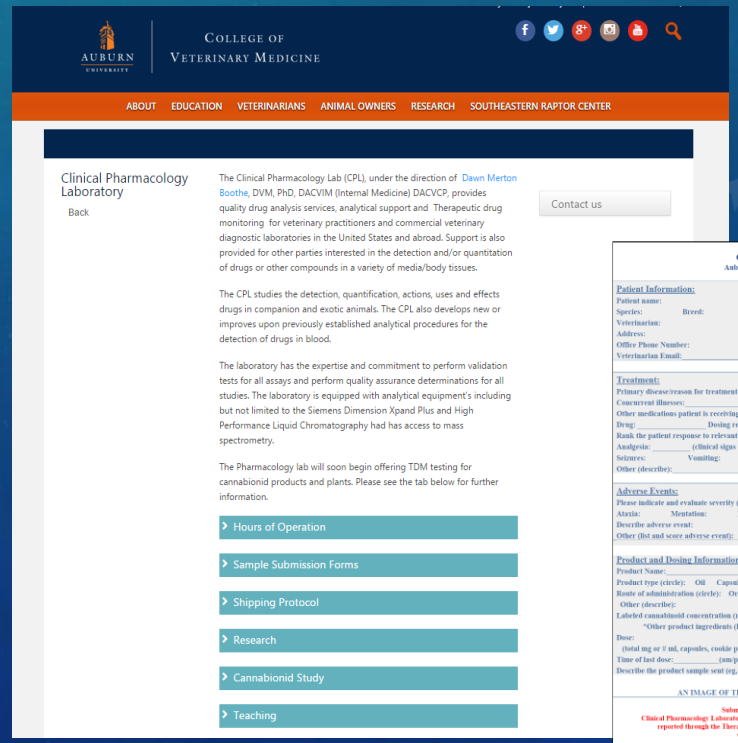


Dawn Merton Boothe, DVM, PhD
Diplomate ACVIM (Internal Med)
Diplomate ACVCP (Clinical Pharmacology)
Professor, Director Clinical Pharmacology
Auburn University

Conflict of Interest Disclosure:

I have financial interest, arrangement or affiliation with:

Name of Organization	Relationship
Dechra	Honorarium/consultant
Pegusus Labs	Consultant, product development
CannaPet ®	Gift (instrumentation, research
funds).	
Animal Nutritional Products	Gift for research
Clinical Pharmacology Laboratory-AU-CVM	Director

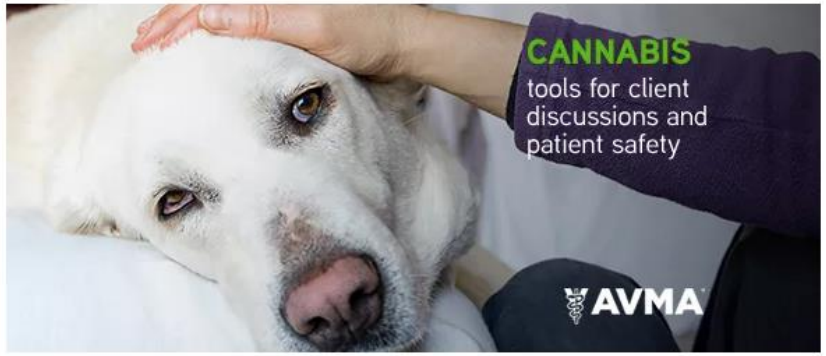


VIDEO SPOTLIGHT

Cannabis resource published for AVMA members

January 10, 2018 | AVMA@Work Editor

More tools to come



With many states allowing medicinal marijuana use in humans, and some allowing recreational use as well, it's important for veterinarians to understand both the legal status of marijuana and the risks it can pose to patients.

A new document available exclusively to AVMA members provides comprehensive background information that will **help you understand the legal aspects** of cannabis use in animals; **field questions and advise clients** who are interested in marijuana therapies for their pets; and **identify toxic exposures**.

Cannabis: What Veterinarians Need to Know addresses a broad range of important topics, including:

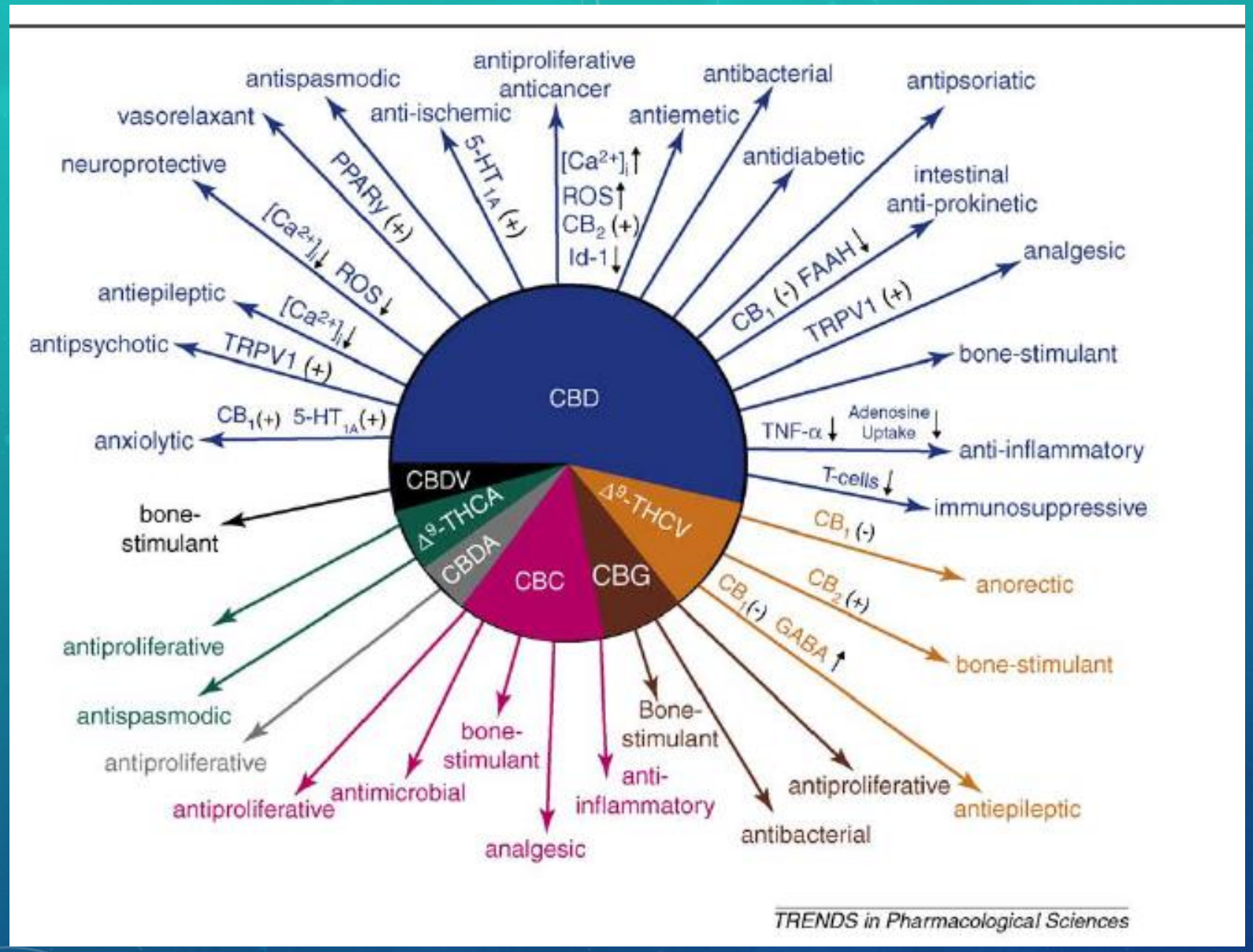
- The legal status of medicinal marijuana in veterinary medicine
- How cannabinoids function
- Marijuana risks to pets
- Clinical signs and treatment of acute marijuana toxicosis
- Effects of chronic marijuana exposure

Available on the **Cannabis Use and Pets** page of our website, the document is the first in a series of cannabis-related materials the AVMA is developing as a resource for our members. Future tools will include information on medicinal marijuana in pets, and educational materials you can share directly with clients.

POPULAR TOPICS

- AVMA Updates (560)
- Veterinarian Resources (403)
- Advocacy (396)
  - Federal Legislative Issues (355)
  - State Legislative Issues (85)
- Animal Health (359)
- AVMA Leadership (259)
  - Councils and Committees (117)
  - Board of Directors (93)
  - Future Leaders (55)

more topics



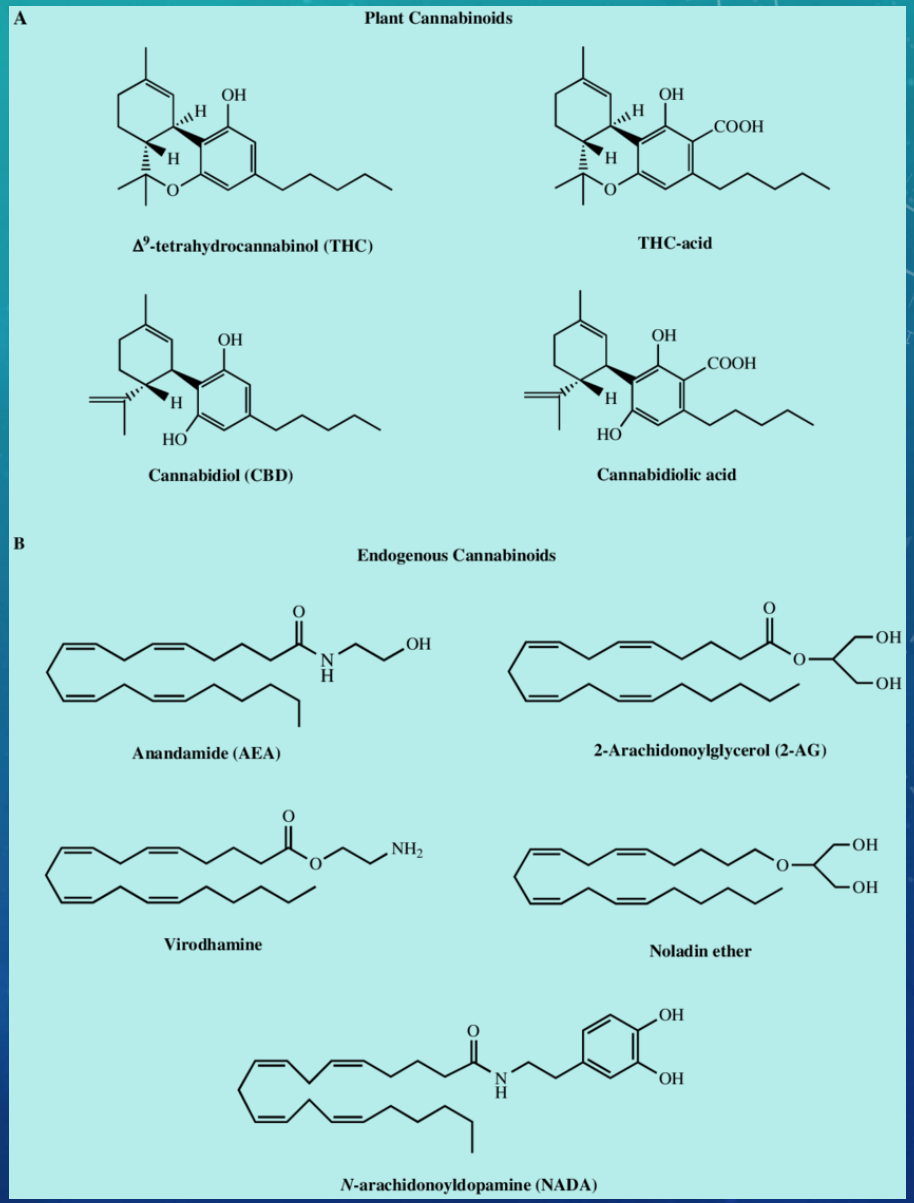
- **MEDICAL MARIJUANA**
- **It's good for what ails you! ……?**

CHALLENGES TO MEDICAL CANNABINOIDS: (BARRIERS TO) UNDERSTANDING THEIR USE

- Part I: Understanding the product
  - History: how did we get here?
  - Definitions
  - Regulatory concerns
  - Product
    - Sources
    - Quality
  - Pharmacokinetics and the dosing regimen
- Part II: Understanding the target
  - The endocannabinoid system
  - Product safety and efficacy
  - Pharmacodynamics and the dosing regime
  - Clinical trials
  - Challenges

MEDICAL MARIJUANA: A DESIGNER PRODUCT?

- Endocannabinoids
- Phytocannabinoids
- Synthetic cannabinoids



Marijuana Timeline

2727 BC - Shen Nung, the father of Chinese medicine, writes about the healing properties of "Ma" (cannabis)

1213 BC - Egyptians use cannabis for glaucoma, inflammation, and in enemas

1000 BC - Bhang, a drink of cannabis and milk, is used in India as an anesthetic

700 BC - Zoroaster proclaims cannabis the most important of 10,000 medicinal plants

200 - 70 BC - Ancient Greeks and Romans use cannabis as a remedy for earache, edema, and inflammation

79 - Pliny the Elder says 'The roots [of the cannabis plant] boiled in water ease cramped joints, gout too and similar violent pain'

1840 - Dr. William O'Shaughnessy brings cannabis to the UK, where it is reportedly used by Queen Victoria for menstrual cramps

1840s - Cannabis becomes mainstream in the west and is used to suppress headaches, increase appetite, and help people to sleep

1850 - Cannabis added to US *Pharmacopoeia*

1889 - *The Lan*... uses of cannabi... withdrawal

1930s - US p... cannabis oils ...

1937 - Cannabis made federally illegal in the U.S. with the passage of the Marihuana Tax Act, which was opposed by the American Medical Association

1941 - **1964-THC, the main psychoactive component of cannabis, is identified and synthesized**

1964

1970 - The Controlled Substance Act (CSA) places cannabis in Schedule I, claiming it has no medical value and high risk of abuse

1972 - The Nixon-appointed Shafer Commission urges decriminalization.

1988 - ...istrative Law Judge ...cannabis has ... use and should be ...scriptive...

1990 - ...over ...noid

1990-Scientists discover endogenous cannabinoid system

1992 - First endocannabinoid, anandamide, discovered. Followed by 2-AG

1996

2003 - US government obtains patent 6,630,507B1 for the therapeutic use of "cannabinoids as antioxidants and neuroprotectants"

2011 - Israeli government launches nationwide medical cannabis program

2013 - Dr. Sanjay Gupta comes out in favor of cannabis

2017 - 29 U.S. states (plus Washington DC and Guam) and 17 countries legalize medical cannabis

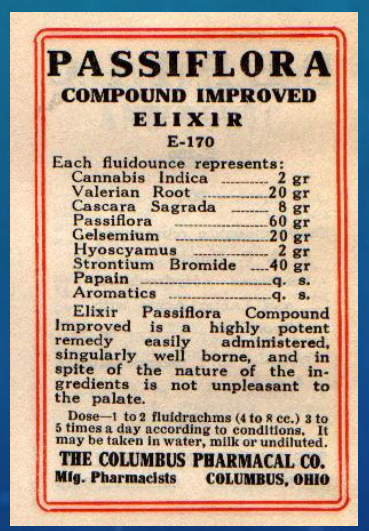
2018 - ...8 - Industrial Hemp ...ded in the 2018 Farm Bill ...h was signed by President ...p on December 20th, 2018

2727 BC | 1213 BC | 1000 BC | 700 BC | 200 - 70 BC | 79 | 1840 | 1840s | 1850 | 1889 | 1930s | 1937 | 1941 | 1964 | 1970 | 1972 | 1988 | 1990 | 1992 | 1996 | 2003 | 2011 | 2013 | 2017 | 2018

Citations:

- Boire R, Feeney K. Medical Marijuana Law. Berkeley, California: Ronin Publishing Inc; 2007.
- Booth M. Cannabis: A History. New York, New York: St. Martin's Press; 2003.
- Joy J, Watson Jr. S, Benson J. Marijuana And Medicine: Assessing The Science Base. Washington, DC: National Academy Press; 1999.
- Manniche L. An Ancient Egyptian Herbal. London, England: British Museum Press; 1999.

https://medicalmarijuana411.com/examining-medical-cannabis-treatments/

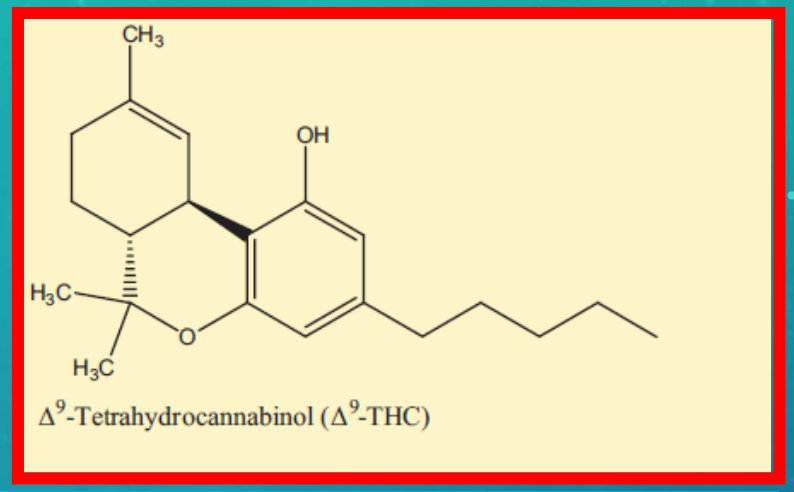


MARIJUANA

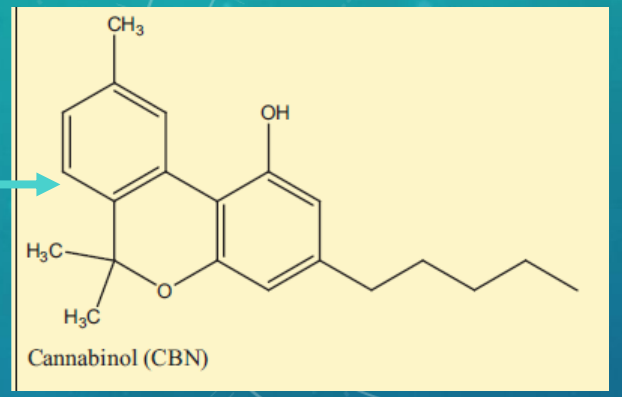
(HEMP GRASS POT WEED GANJA……)

PHYTOCANNABINOIDS

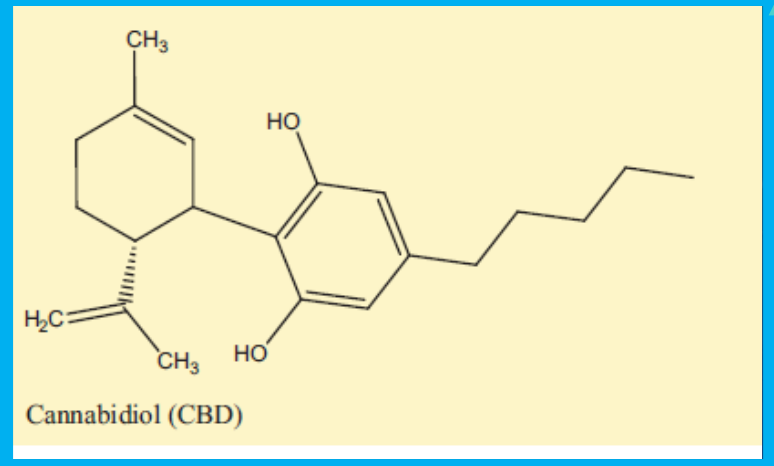
- *Cannabis* spp.
  - ≅ 500 different compounds
  - ≅ 100 cannabinoids (unique)
- Lipophilic
  - Eicosanoids
  - THC
  - CBD
  - CBC
  - CBG (source)
  - CBN (THC metabolite)



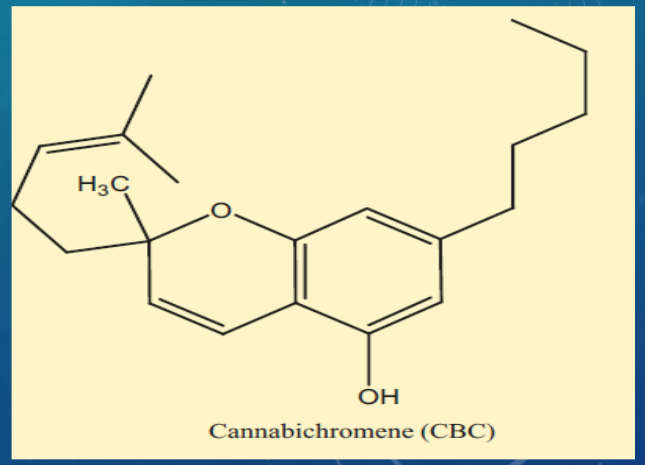
Δ9-Tetrahydrocannabinol (Δ9-THC)



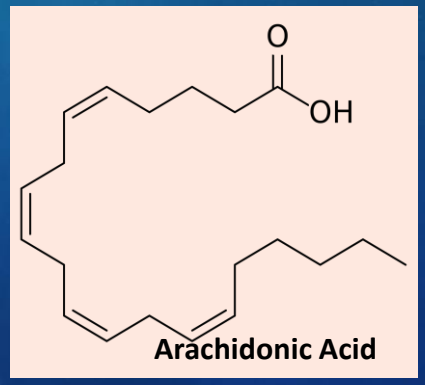
Cannabinol (CBN)



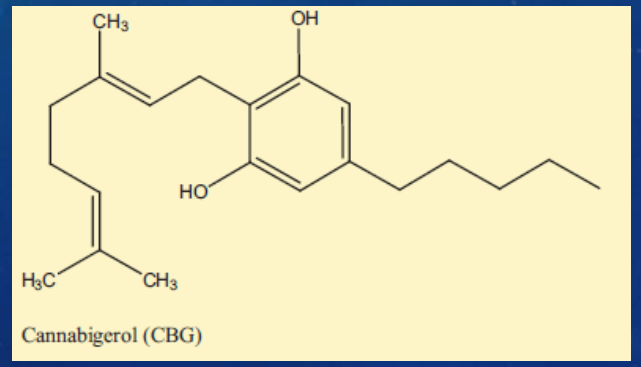
Cannabidiol (CBD)



Cannabichromene (CBC)



Arachidonic Acid

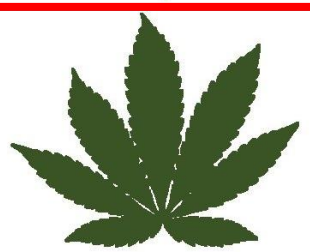


Cannabigerol (CBG)

Types Of Weed

SATIVA

Cannabis Sativa Sativa is characterized by leaflets that are more narrow, branches that are farther apart, and coloration that tends more toward spring green. Sativa Sativa plants tend to be taller and produce fewer flowers.



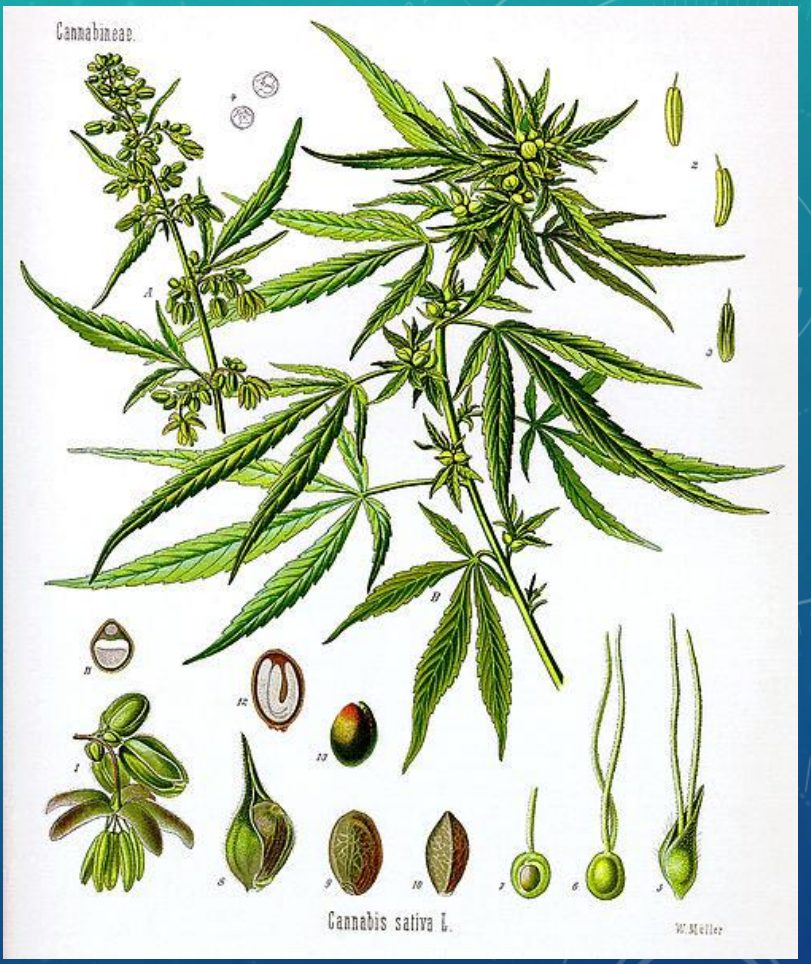
INDICA

Cannabis Sativa Indica is characterized by broad leaflets that ofter overlap, branches that are closer together, and coloration that tends more toward deep olive green. Sativa Indica plants tend to be shorter and bushier, producing fuller, denser flower buds.

RUDERALIS

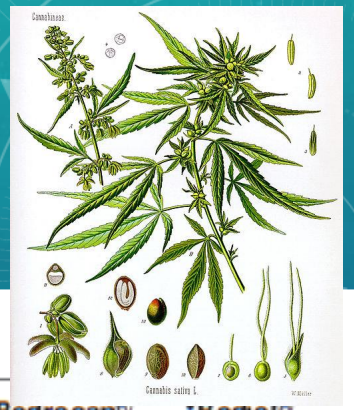
Cannabis Ruderalis is characterized by varied leaflets in the mature leaves, a shorter stature and generally small size. This subspecies is used to create S. Sativa or S. Indica hvbrids with select desired traits.

www.Types-of-Weed.ORG



MULTIPLE HEMP PLANTS

PHARMACOLOGICALLY DIVERSE



Cannabis sativa: The Plant of the Thousand and One Molecules

Christelle M. Andre, Jean-Francois Hausman and Gea Guerriero*

Environmental Research and Innovation, Luxembourg Institute of Science and Technology, Esch-sur-Alzette, Luxembourg

TABLE 1 | Summary of the concentrations in cannabinoids found in different parts of the hemp plants, *in vitro* hairy roots, and some commercial medicinal products.

Molecules	Hairy roots	Root		Seed		Stem		Leaves		Pollen		Flower		*Bedrocan®	*Bedrol®
		Fiber-type	Drug-type	Fiber-type	Drug-type	Fiber-type	Drug-type	Fiber-type	Drug-type	Fiber-type	Drug-type	Fiber-type	Drug-type	Drug-type	Drug-type
THC	1.04[a]			0–12 (<0.5 in kernel)[c] 3–29[d]	36–174 (<2 in kernel)[c] 15–70[d]	196–475[i]	3000[e]	2000[f]	60300[g] 22000[f] 8000[e]		31230[h]	76300[i]	95100[g] 34000–200000[i] 152000[e]	190000[i]	19000[i]
CBD	1.67[a]	14.3[b]		67–244[d]	4.2–78[d]	179[b] 7850–18090[i]		1790[b] 20000[f]	11200[g] 3000[f]		440[h]	8590[b] 6000[i]	10900[g] <600[i]	<600[i]	79800[i]
CBN				2–7[d]	3.4–8.4[d]	0–47[i]			800[g]		1350[h]		600[g]		
CBG	1.63[a]							2000[f]	1000[f]		1310[h]	<600[i]	1000–10000[i]	11200[i]	1700[i]
THCV											510[h]	<600[i]	(<600) – 1300[i]	1300[i]	<600[i]
CBC											3240[h]	4 600[i]	900–2200[i]	2300[i]	5400[i]

*Data are expressed in μg g^{-1} of dry weight. The most recent references have been used, when available. Abbreviations: THC, Δ^9-tetrahydrocannabinol; CBD, cannabidiol; CBN, cannabinol; CBG, cannabigerol; THCV, tetrahydrocannabivarin; CBC, cannabichromene. References: [a]Farag and Kayser, 2015; [b]Adapted from Stout et al., 2012; [c]Ross et al., 2000; [d]Petrović et al., 2015 (concentration in hempseed oil); [e]Potter, 2004; [f]Pacifico et al., 2008 (growth curve experiment, the maximum concentrations are represented); [g]Bruci et al., 2012; [h]Ross et al., 2005; [i]Fischedick et al., 2010; [j]Cappelletto et al., 2001, data from stem dust. *Commercial pharmaceutical preparations.*

U.S. DEPARTMENT OF JUSTICE ★ DRUG ENFORCEMENT ADMINISTRATION

DIVERSION CONTROL DIVISION

Search

HOME | REGISTRATION | REPORTING | RESOURCES | ABOUT US

RESOURCES > Controlled Substance Schedules > Marijuana > DEA Internal Directive Regarding the Presence of Cannabinoids in Products and Materials Made from the Cannabis Plant

Marijuana

DEA Internal Directive Regarding the Presence of Cannabinoids in Products and Materials Made from the Cannabis Plant

(May 22, 2018)

In 2004, the U.S. Court of Appeals for the Ninth Circuit enjoined DEA from enforcing certain regulations with respect to tetrahydrocannabinols (THC). *See Hemp Industries Ass'n v. DEA*, 357 F.3d 1012 (9th Cir. 2004). The government did not seek Supreme Court review of that decision. In response to various inquiries, DEA hereby issues to DEA personnel the following internal directive on how to carry out their duties in light of the Ninth Circuit's decision.

The Ninth Circuit enjoined enforcement of what is now **21 C.F.R. § 1308.11**(d)(31) (drug code 7370) with respect to products that are excluded from the definition of marijuana in the Controlled Substances Act (CSA). DEA thus does not enforce that

Products and materials that are made from the cannabis plant and which fall outside the CSA definition of marijuana (such as sterilized seeds, oil or cake made from the seeds, and mature stalks) are not controlled under the CSA. Such products may accordingly be sold and otherwise distributed throughout the United States without restriction under the CSA or its implementing regulations. The mere presence of cannabinoids is not itself dispositive as to whether a substance is within the scope of the CSA; the dispositive question is whether the substance falls within the CSA definition of marijuana.

The Controlled Substances Import and Export Act incorporates the schedules of the CSA. *See generally* **21 U.S.C. §§ 951-971**. Accordingly, any product that the U.S. Customs and Border Protection determines to be made from the cannabis plant but which falls outside the CSA definition of marijuana may be imported into the United States without restriction under the Controlled Substances Import and Export Act. The same considerations apply to exports of such products from the United States, provided further that it is lawful to import such products under the laws of the country of destination.

This directive does not address or alter DEA's previous statements regarding the drug code for marijuana extract and regarding resin. *See* **Establishment of a New Drug Code for Marihuana Extract**, 81 Fed. Reg. 90194 (Dec. 14, 2016); **Clarification of the New Drug Code (7350) for Marijuana Extract.** As DEA has previously explained, the drug code for marijuana extract extends no further than the CSA does, and it thus does not apply to materials outside the CSA definition of marijuana.

Get Email Updates:

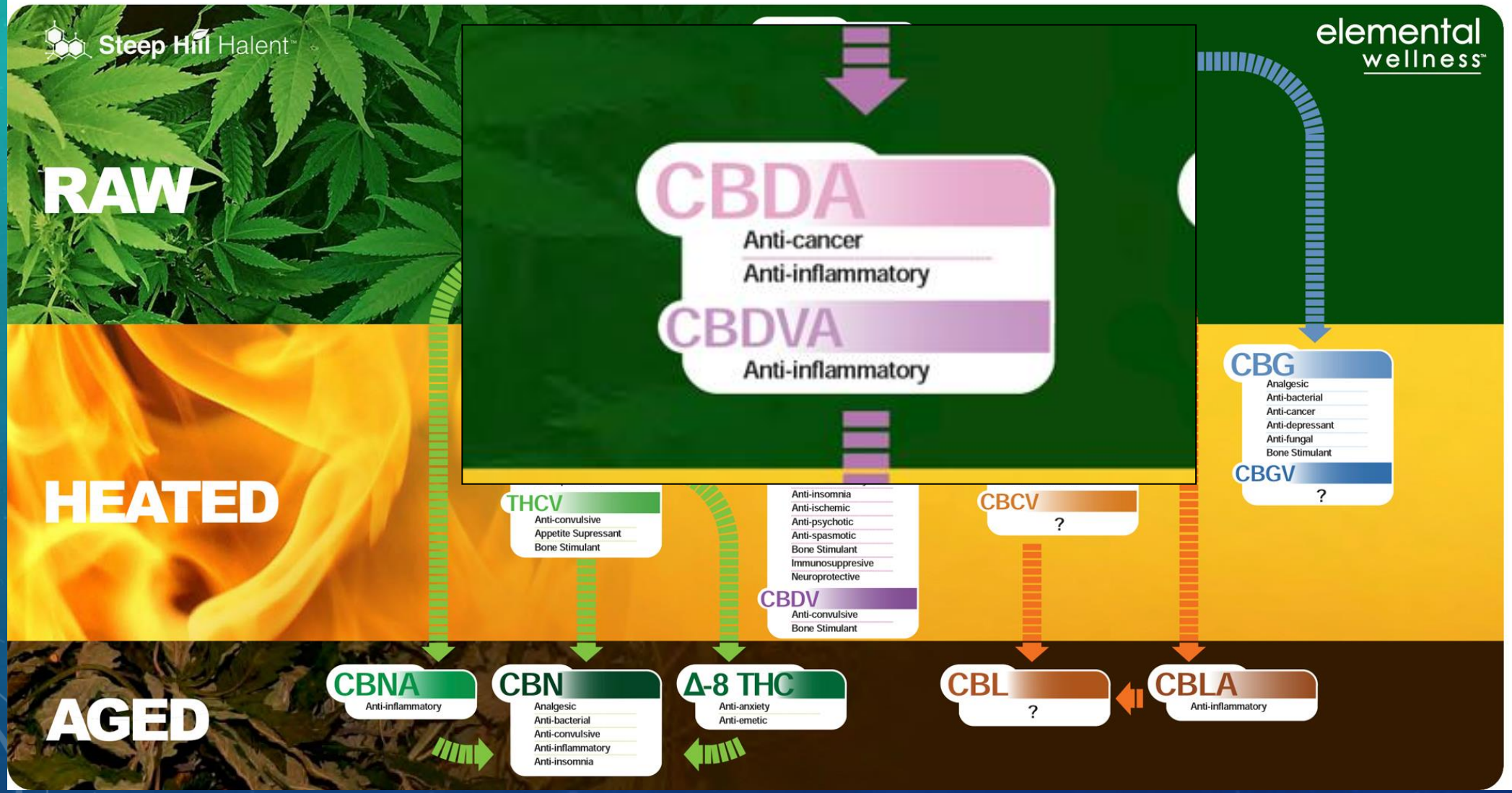
- Cases Against Doctors
- Chemical Control Program
- CMEA (Combat Meth Epidemic Act)
- Controlled Substance Schedules
- DATA Waived Physicians
- Drug Disposal Information
- Drug and Chemical Information
- Questions & Answers
- Significant Guidance Documents
- Synthetic Drugs
- Title 21 Code of Federal Regulations
- Title 21 USC Codified CSA

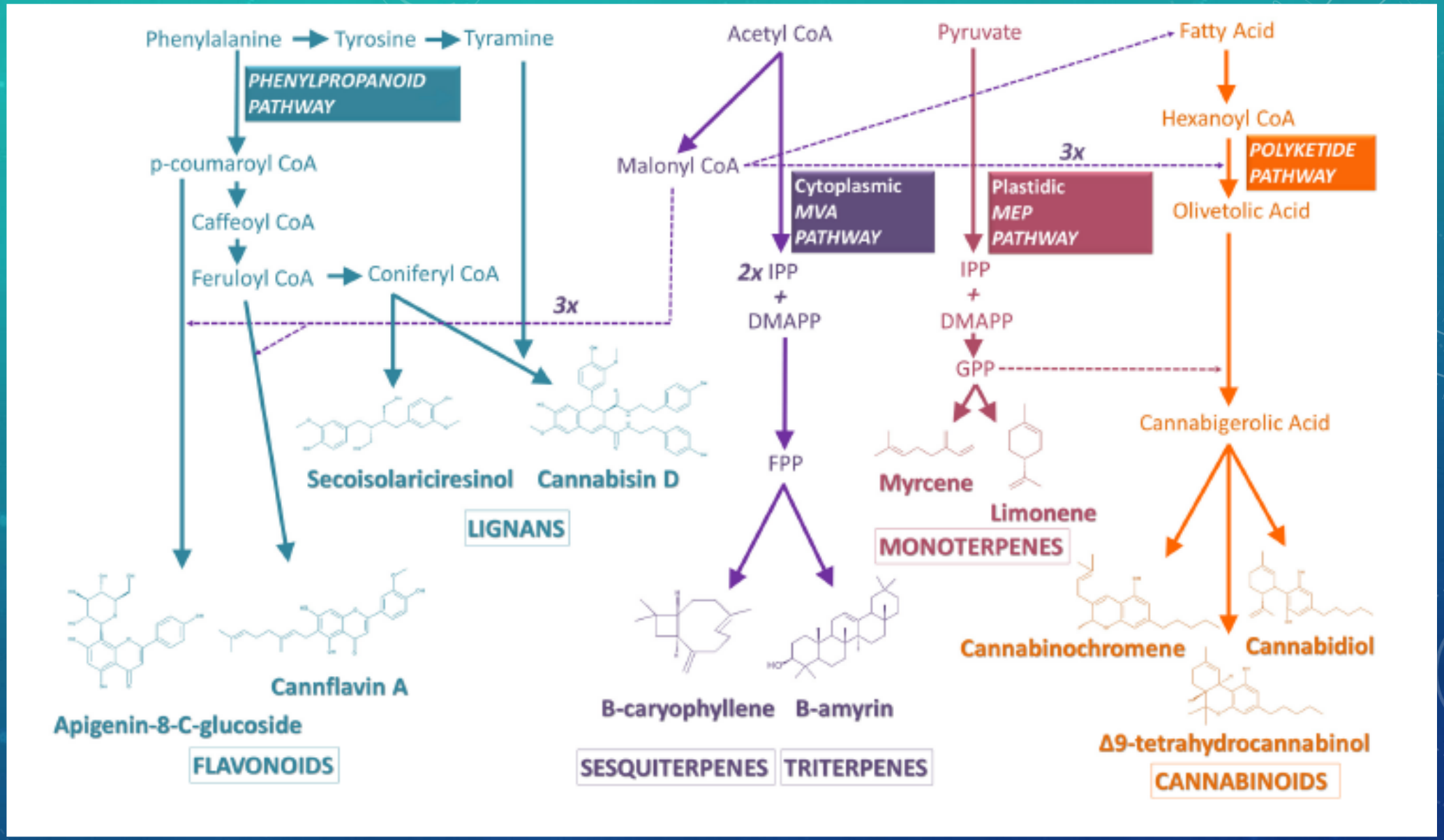
Controlled Substance Act

SCHEDULE	ABUSE POTENTIAL	MEDICAL USE	DEPENDENCY	EXAMPLE
C-I	High	None	Severe physical and psychologic	Heroin, Marijuana
C-II	High	Accepted	Severe physical and psychologic	Adderall, Codeine, Morphine, Oxycodone
C-III	Less than C-II	Accepted	Moderate to low physical or high psychologic	Codeine, Hydrocodone
C-IV	Less than C-III	Accepted	Limited physical or psychologic	Valium, Ativan
C-V	Less than C-IV	Accepted	Limited physical or psychologic	Lomotil, Codeine cough syrups

UNDERSTANDING MEDICAL CANNABIS

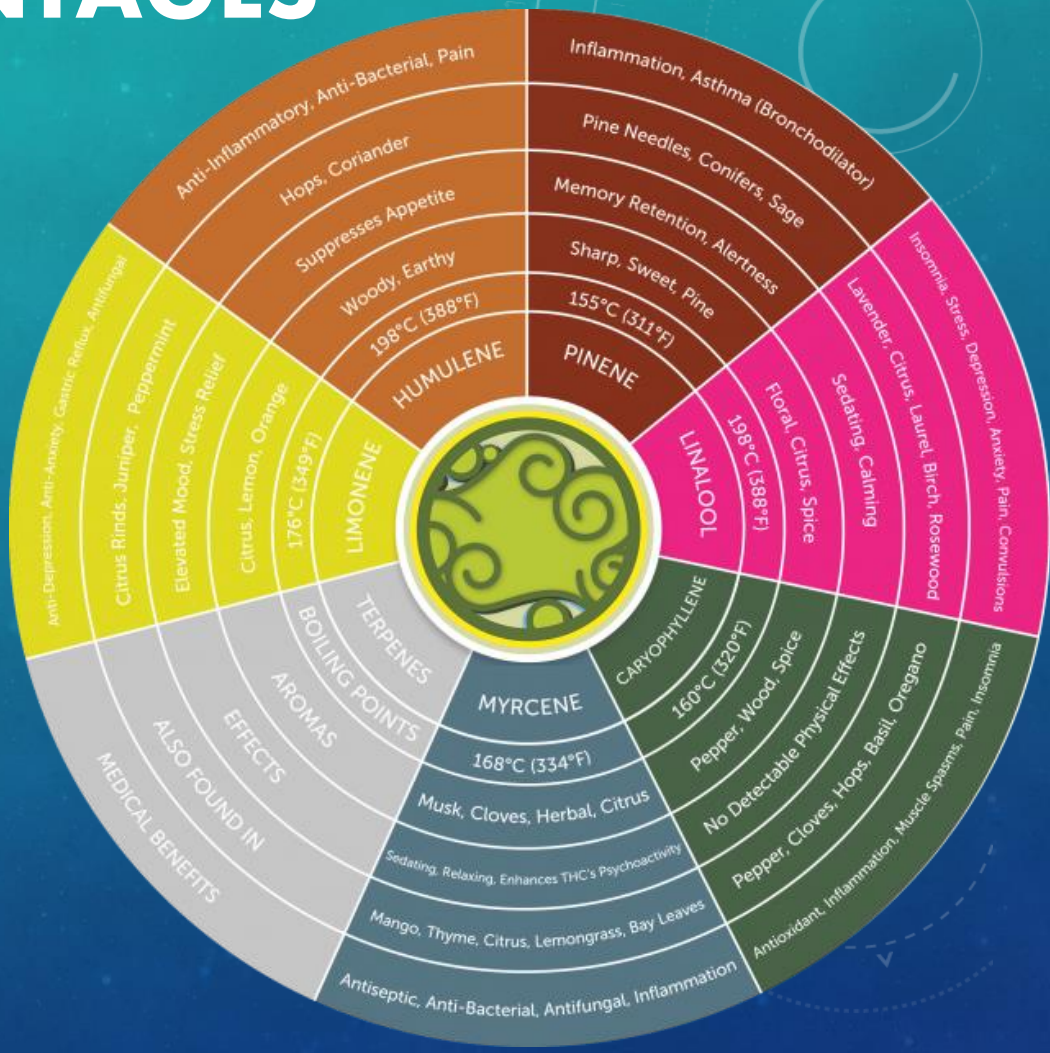
Cannabinoids and Their Therapeutic Effects

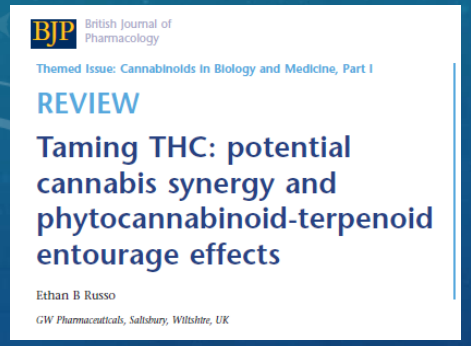



Phenylalanine
Tyrosine
Tyramine
PHENYLPROPANOID PATHWAY
p-coumaroyl CoA
Caffeoyl CoA
Feruloyl CoA
Coniferyl CoA
3x
Secoisolariciresinol
Cannabisin D
LIGNANS
Apigenin-8-C-glucoside
Cannflavin A
FLAVONOIDS
Acetyl CoA
Malonyl CoA
Cytoplasmic MVA PATHWAY
2x IPP
+
DMAPP
FPP
B-caryophyllene
B-amyrin
SESQUITERPENES
TRITERPENES
Pyruvate
Plastidic MEP PATHWAY
IPP
+
DMAPP
GPP
Myrcene
Limonene
MONOTERPENES
Fatty Acid
Hexanoyl CoA
3x
POLYKETIDE PATHWAY
Olivetolic Acid
Cannabigerolic Acid
Cannabinochromene
Cannabidiol
Δ9-tetrahydrocannabinol
CANNABINOIDS

MEDICAL MARIJUANA ADVANTAGES

- Compared to single compound
- Terpenes
- "Entourage Effect"
  - Synergism between active ingredients = enhanced efficacy
  - Antagonism of undesirable effects = enhanced safety
- Impact regarding clinical trials?




BJP British Journal of Pharmacology

Themed Issue: Cannabinoids in Biology and Medicine, Part I

REVIEW

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

Ethan B Russo

GW Pharmaceuticals, Salisbury, Wiltshire, UK

From leafly or https://emeraldviewmedia.com/terpenes-101/

MEDICAL (VARIABLE STIPULATIONS)

Federal vs. state

Human vs. veterinary?

HTTPS://THECANNABISINDUSTRY.ORG/STATE-MARIJUANA-POLICIES-MAP/

17 States with Legal Cannabidiol (CBD)

(as of July 12, 2019)

While 33 stated have legalized medical marijuana, the remaining 17 states have all passed laws allowing the use of cannabidiol (CBD) extract, usually in oil form, with minimal tetrahydrocannabinol (THC), and often for the treatment of epilepsy or seizures in seriously ill children. CBD, one of the 400+ ingredients found in marijuana, is not psychoactive.

Last updated on: 7/12/2019 | Author: ProCon.org

States with Legal Cannabidiol (CBD)

(as of Apr. 14, 2020)

While 33 stated have legalized medical marijuana, the remaining 17 states have all passed laws allowing the use of cannabidiol (CBD) extract, usually in oil form, with minimal tetrahydrocannabinol (THC), and often for the treatment of epilepsy or seizures in seriously ill children. CBD, one of the 400+ ingredients found in marijuana, is not psychoactive.

ProCon.org does not consider passing a CBD-specific law to be the equivalent of making medical marijuana legal because these laws do not legalize use of the marijuana plant for medical purposes. See our resource on the legal medical marijuana states for more information.

1. Alabama

On Apr. 1, 2014, Alabama Governor Robert Bentley signed SB 174, known as "Carly's Law," which allows an affirmative defense against prosecution for CBD possession by people suffering from a debilitating epileptic condition. The law states that "a prescription for the possession or use of cannabidiol (CBD) as authorized by this act shall be provided exclusively by the UAB [University of Alabama at Birmingham] Department for a debilitating epileptic condition." Since marijuana is illegal under federal laws, doctors are not allowed to write "prescriptions" for it. The states that have legal medical marijuana allow doctors to "recommend" it.

On May 4, 2016, Gov. Bentley signed HB 61 into law. Known as Leni's Law, the bill provides an affirmative defense for possession of CBD oil "for specified debilitating conditions that produce seizures."

2. Georgia

On Apr. 16, 2015 Georgia Governor Nathan Deal signed HB 1 (*Haleigh's Hope Act*) into law, allowing the use of cannabis oil that is contains no more than 5% THC. According to the Georgia Department of Public Health, the law did "not address how low THC oil is made, purchased or shipped. The law only creates a procedure to ensure qualified persons will be protected from prosecution for having it in their possession." On Apr. 17, 2019, Gov. Brian Kemp signed a bill that permits in-state production/sale of marijuana oil and allows growing licenses for up to six private companies, effective July 1, 2019.

The Georgia Department of Public Health issues Low THC Oil Registry Cards ($25 fee) to qualifying patients with one of 16 conditions: cancer, ALS, seizure disorders, multiple sclerosis, Crohn's disease, mitochondrial disease, Parkinson's disease, sickle cell disease, Tourette's syndrome, autism spectrum disorder, when (a) patient is 18 years of age or more, epidermolysis bullosa, Alzheimer's disease, AIDS, peripheral neuropathy, hospice program patients, intractable pain, and PTSD.

3. Indiana

On Apr. 27, 2017, Gov. Eric Holcomb signed HB 1148 into law, allowing the use of cannabidiol that is at least 5% CBD and contains no more than 0.3% THC for treatment-resistant epilepsy.

On Mar. 21, 2018, Gov. Holcomb signed SB 52 into law, which allows distribution and retail sail of "low-THC hemp extract," defined as a product "(1) derived from Cannabis sativa L. that meets the definition of industrial hemp; (2) that contains not more than 0.3% delta-9-THC (including precursors); and (3) that contains no other controlled substances."

4. Iowa

On May 30, 2014, Iowa Governor Terry Branstad signed SF 2360 into law, saying "This bill received tremendous support and truly shows the power of people talking to their legislators and to their governor about important issues to them, to their families and to their children."

On May 12, 2017, Governor Branstad signed HF 524 into law. According to the Iowa Department of Health Office of Medical Cannabidiol Website (accessed Mar. 15, 2018), "a person may recommend, possess, use, dispense, deliver, transport, or administer cannabidiol if the recommendation, possession, use, dispensing, delivery, transporting, or administering is in accordance with new chapter 124E of the Iowa Code."

The Office of Medical Cannabidiol issues registration cards and the law "requires medical cannabidiol dispensaries to begin dispensing to patients in Iowa by December 1, 2018."

5. Kansas

On May 14, 2018, Governor Jeff Colyer signed SB 282 into law, which allows the

Should Recreational Marijuana Be Legal? READ MORE
Legal Medical Marijuana States and DC READ MORE
Deaths from Marijuana vs. FDA-Approved Drugs READ MORE

Sections | Browse | Search | Reader Aids | My FR | Search Documents

Sign In Sign up

FEDERAL REGISTER

The Daily Journal of the United States Government

Notice

Statement of Principles on Industrial Hemp

A Notice by the Agriculture Department, the Drug Enforcement Administration, and the Food and Drug Administration on 08/12/2016

PUBLISHED DOCUMENT

Start Printed Page 53395

AGENCY:

Office of the Secretary, USDA; Drug Enforcement Administration, DOJ; Food and Drug Administration, HHS.

ACTION:

Notice

SUMMARY:

The U.S. Department of Agriculture, in consultation with the U.S. Drug Enforcement Administration and the U.S. Food and Drug Administration, has developed a *Statement of Principles on Industrial Hemp* to inform the public how Federal law applies to activities associated with industrial hemp that is grown and cultivated in accordance with Section 7606 of the Agricultural Act of 2014. The purpose of this notice is to set forth the statement in its entirety.

DATES:

This Statement of Principles is applicable August 12, 2016.

FOR FURTHER INFORMATION CONTACT:

DOCUMENT DETAILS

Printed version: PDF

Publication Date: 08/12/2016

Agencies: Department of Agriculture, Office of the Secretary, Drug Enforcement Administration, Food and Drug Administration

Dates: This Statement of Principles is applicable August 12, 2016.

Document Type: Notice

Document Citation: 81 FR 53395

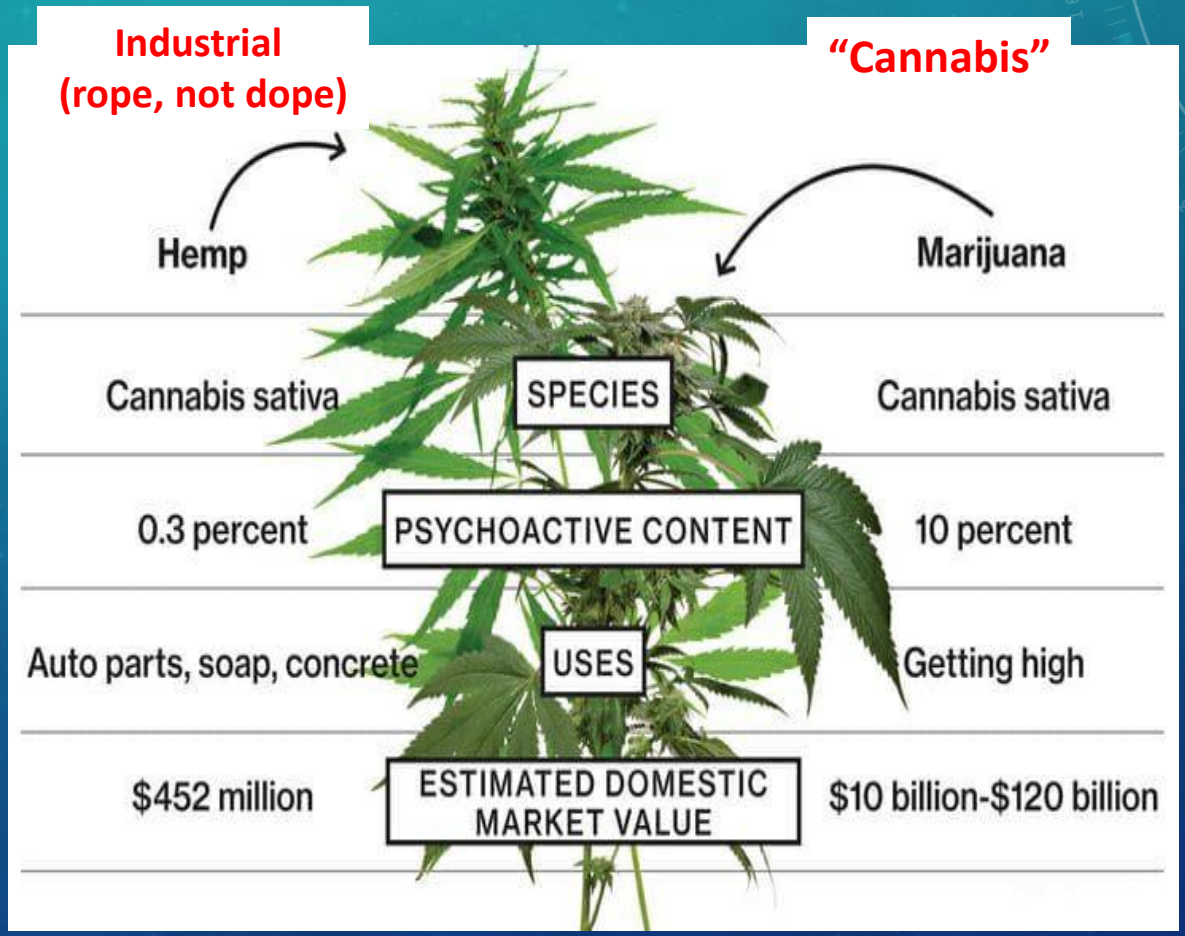
Page: 53395-53396 (2 pages)

Document Number: 2016-19146

DOCUMENT DETAILS

hemp as part of the agricultural pilot program.

- The term "industrial hemp" includes the plant *Cannabis sativa* L. and any part or derivative of such plant, including seeds of such plant, whether growing or not, that is used exclusively for industrial purposes (fiber and seed) with a tetrahydrocannabinols concentration of not more than 0.3 percent on a dry weight basis. The term "tetrahydrocannabinols" includes all isomers, acids, salts, and salts of isomers of tetrahydrocannabinols.



2014 Farm Bill

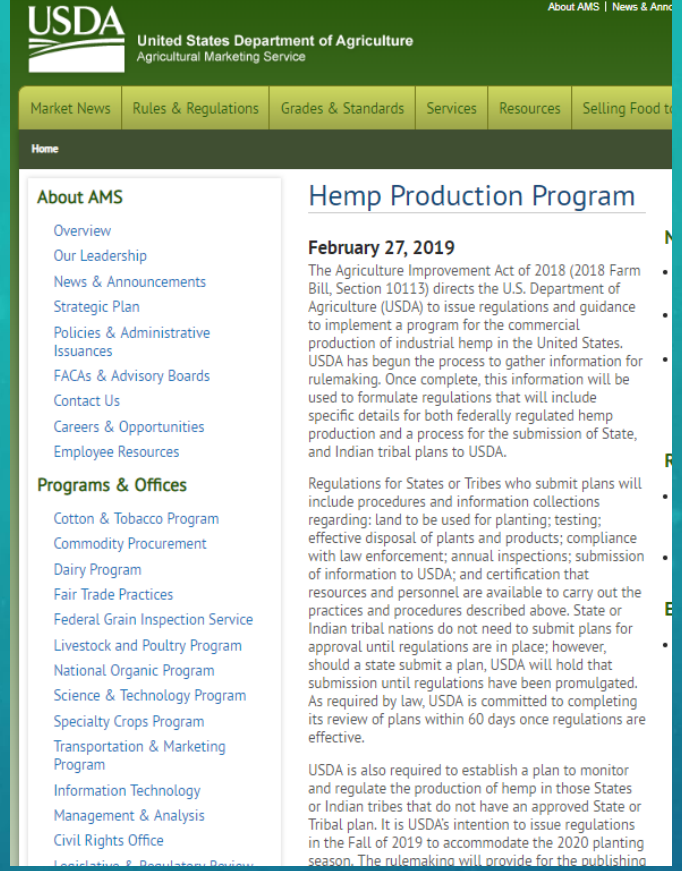
Defined Industrial Hemp and legalized growth in institutions of higher education if state approved. Notably, CBD is still a Schedule 1 substance along with all other marijuana constituents.

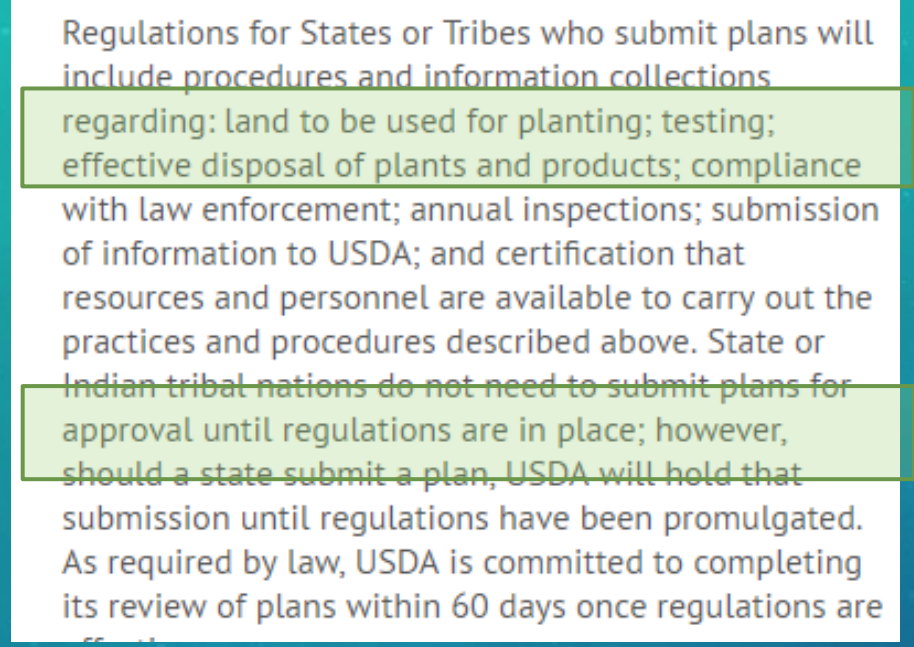
U.S. Department of Justice ★ Drug Enforcement Administration

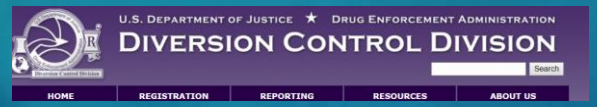
DIVERSION CONTROL DIVISION

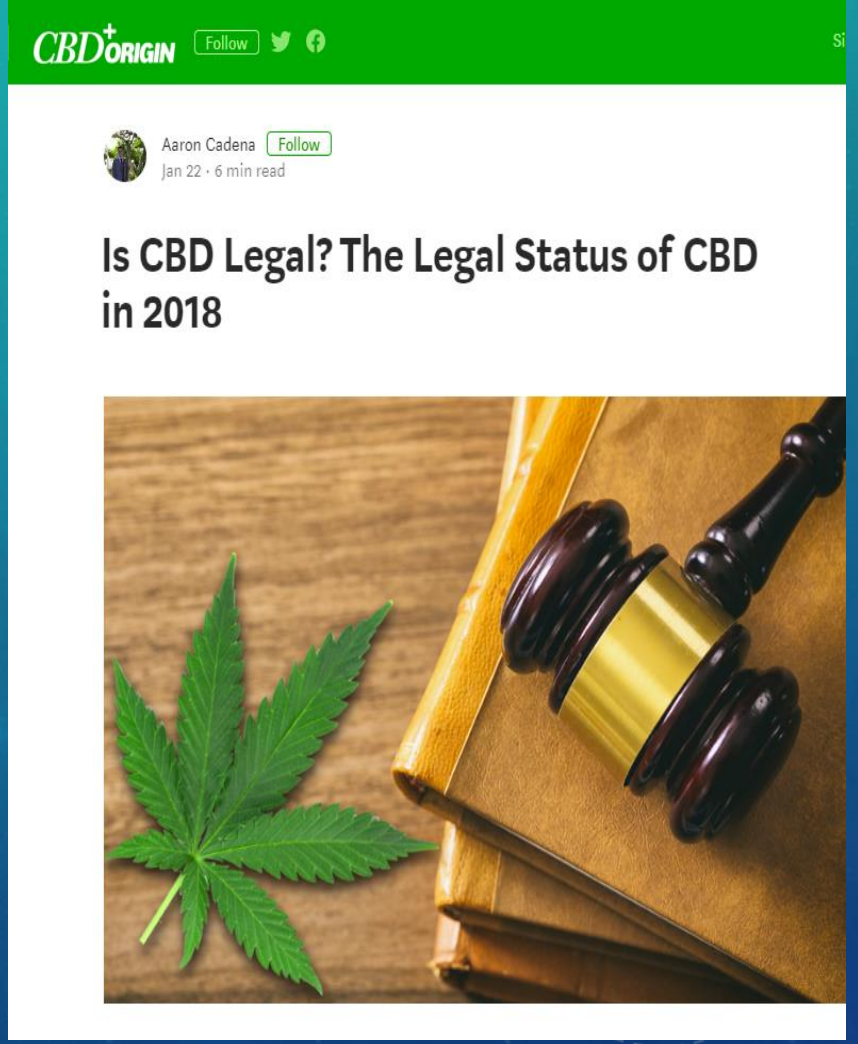
Search

HOME | REGISTRATION | REPORTING | RESOURCES | ABOUT US









2018 Farm Bill

Legalized industrial hemp throughout the US, removed it from DEA oversight, and gave the USDA regulatory oversight on state or individual "growth and distribution programs".

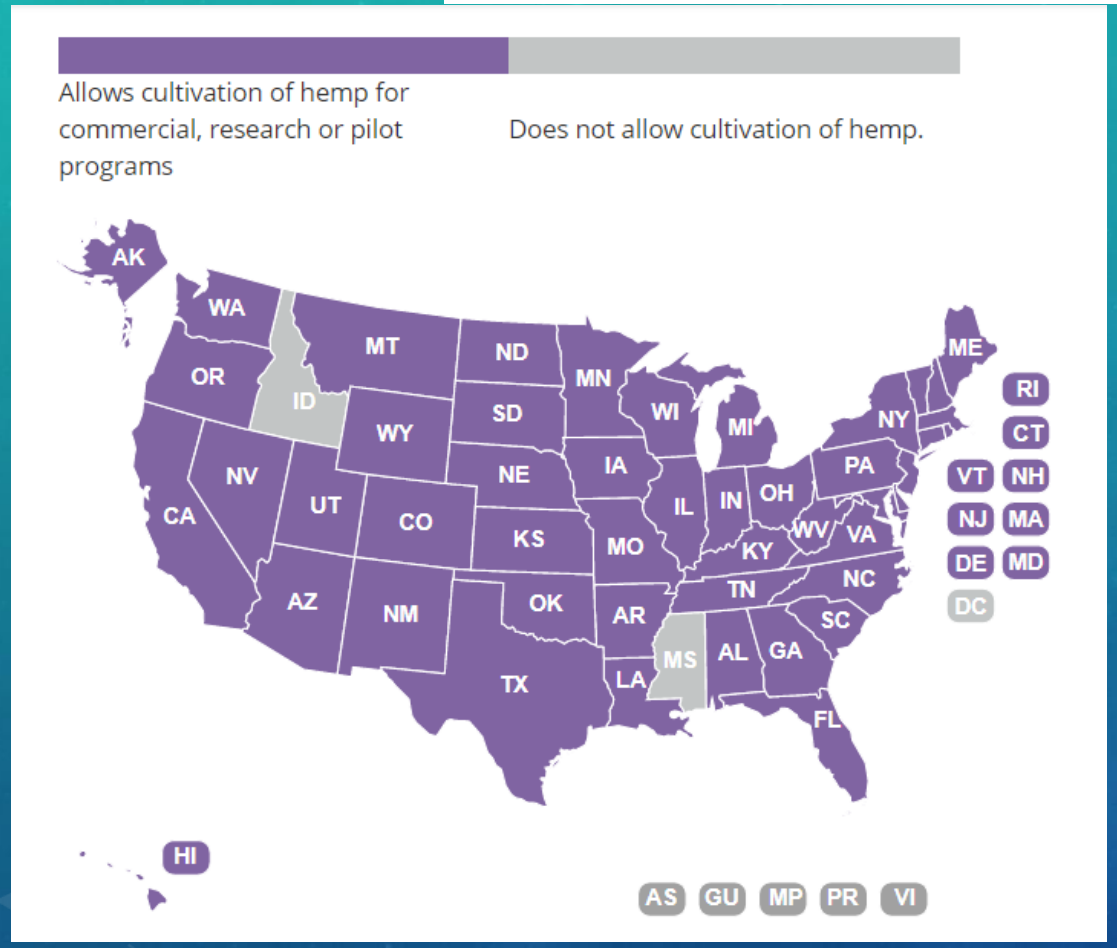
Until USDA has guidelines in place, 2014 Bill applies

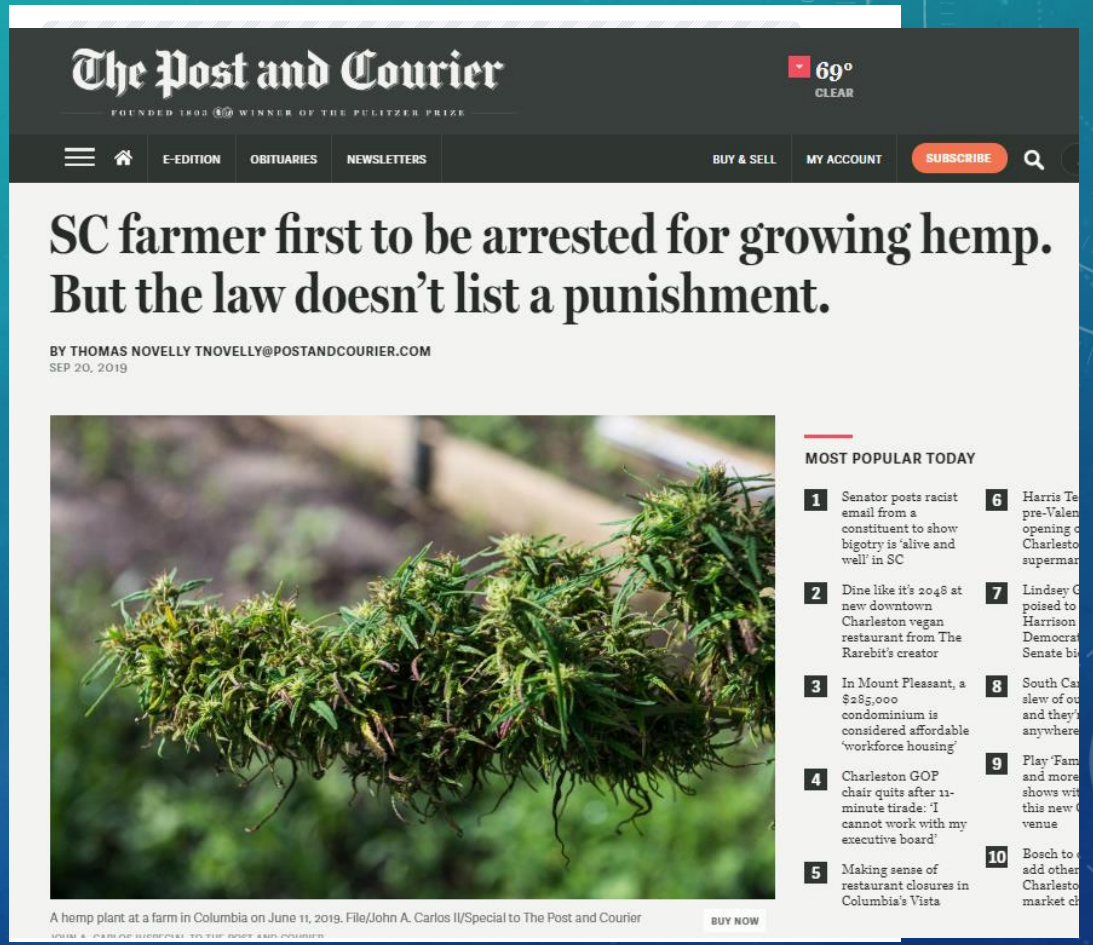
NCSL ABOUT US LEGISLATORS & STAFF RESEARCH MEETINGS & TRAINING NCSL IN D.C. NEWS

TABLE OF CONTENTS

State Industrial Hemp Statutes

4/16/2020





The Post and Courier

FOUNDED 1803 WINNER OF THE PULITZER PRIZE

69° CLEAR

E-EDITION OBITUARIES NEWSLETTERS BUY & SELL MY ACCOUNT SUBSCRIBE

SC farmer first to be arrested for growing hemp. But the law doesn't list a punishment.

BY THOMAS NOVELLY TNOVELLY@POSTANDCOURIER.COM
SEP 20, 2019

A hemp plant at a farm in Columbia on June 11, 2019. File/John A. Carlos II/Special to The Post and Courier

BUY NOW

MOST POPULAR TODAY

1 Senator posts racist email from a constituent to show bigotry is 'alive and well' in SC

2 Dine like it's 2048 at new downtown Charleston vegan restaurant from The Rarebit's creator

3 In Mount Pleasant, a $285,000 condominium is considered affordable 'workforce housing'

4 Charleston GOP chair quits after 11-minute tirade: 'I cannot work with my executive board'

5 Making sense of restaurant closures in Columbia's Vista

6 Harris Te... pre-Valen... opening ... Charlesto... superma...

7 Lindsey G... poised to ... Harrison ... Democrat... Senate bi...

8 South Ca... slew of ou... and they'... anywhere

9 Play 'Fam... and more ... shows wi... this new ... venue

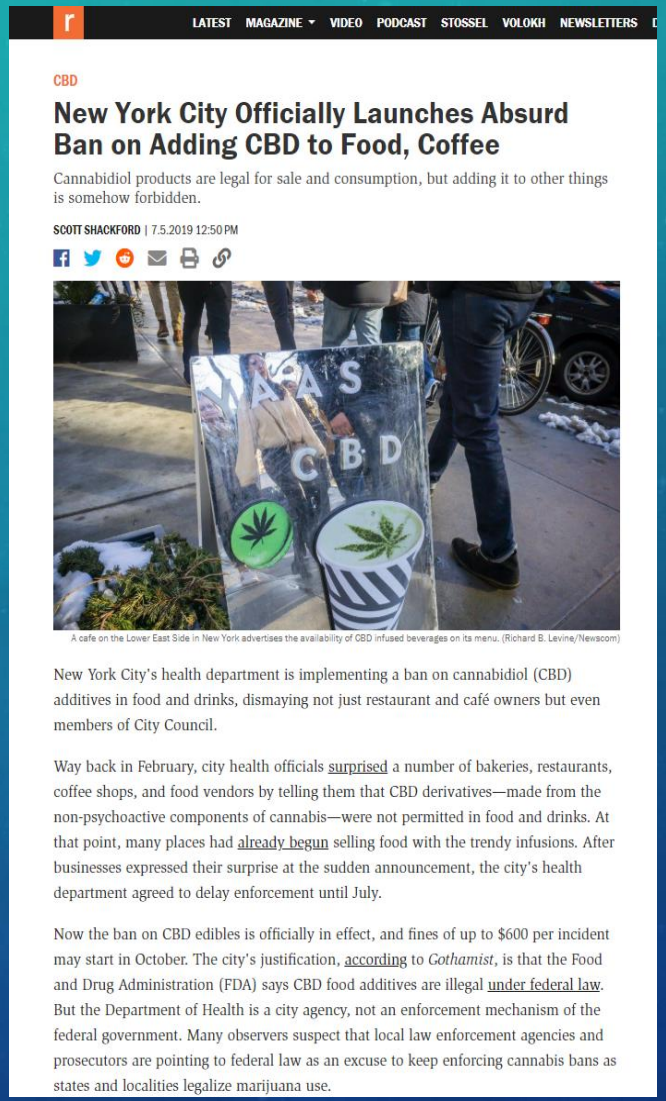
10 Bosch to ... add other ... Charlesto... market ch...

Crops approved by USDA for 2020 growing season but final rule will not be promulgated until AFTER that season

https://www.ncsl.org/research/agriculture-and-rural-development/state-industrial-hemp-statutes.aspx

REGULATION OF ‘DIETARY SUPPLEMENTS’ IS DIFFERENT FOR PEOPLE VS. ANIMALS

- **Humans**
  - Drugs
    - Regulated by FDA
  - Dietary supplements
    - Not “regulated” (no premarket assessment)
  - Food
    - Regulated by FDA
    - Must be GRAS (generally recognized as safe)
- **Animals**
  - No such thing as a “dietary supplement”
  - Either drugs (unapproved) or food which must be proven safe



LATEST MAGAZINE VIDEO PODCAST STOSSEL VOLOKH NEWSLETTERS

CBD

New York City Officially Launches Absurd Ban on Adding CBD to Food, Coffee

Cannabidiol products are legal for sale and consumption, but adding it to other things is somehow forbidden.

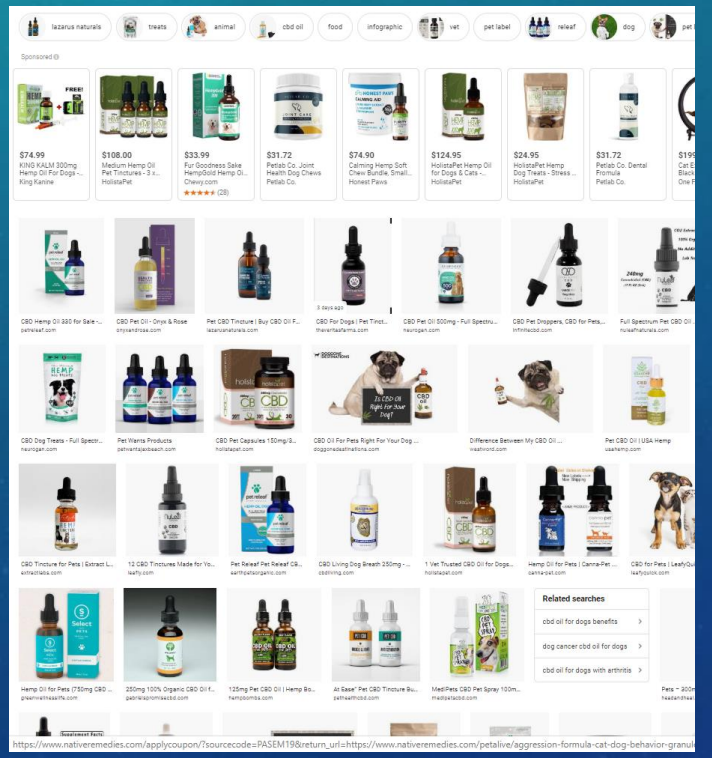
SCOTT SHACKFORD | 7.5.2019 12:50 PM

A cafe on the Lower East Side in New York advertises the availability of CBD infused beverages on its menu. (Richard B. Levine/Newscom)

New York City's health department is implementing a ban on cannabidiol (CBD) additives in food and drinks, dismaying not just restaurant and café owners but even members of City Council.

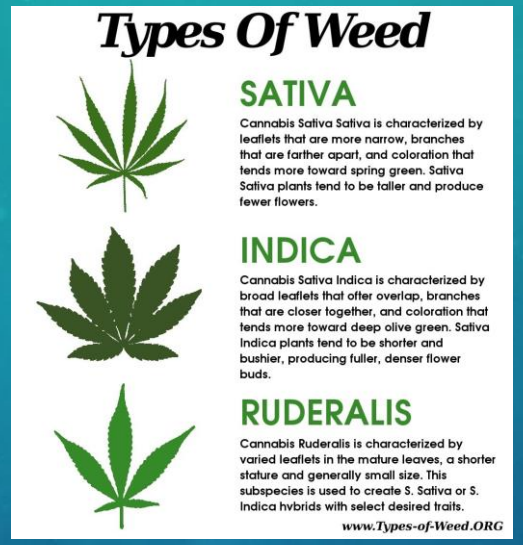
Way back in February, city health officials surprised a number of bakeries, restaurants, coffee shops, and food vendors by telling them that CBD derivatives—made from the non-psychoactive components of cannabis—were not permitted in food and drinks. At that point, many places had already begun selling food with the trendy infusions. After businesses expressed their surprise at the sudden announcement, the city's health department agreed to delay enforcement until July.

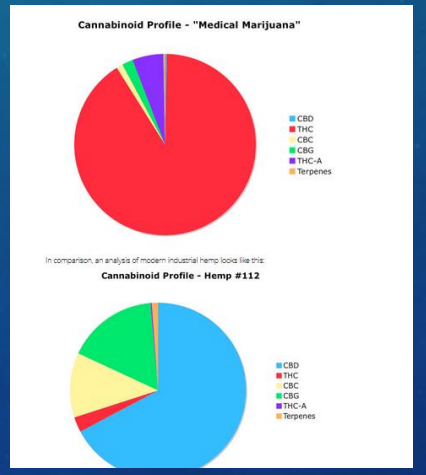
Now the ban on CBD edibles is officially in effect, and fines of up to $600 per incident may start in October. The city's justification, according to *Gothamist*, is that the Food and Drug Administration (FDA) says CBD food additives are illegal under federal law. But the Department of Health is a city agency, not an enforcement mechanism of the federal government. Many observers suspect that local law enforcement agencies and prosecutors are pointing to federal law as an excuse to keep enforcing cannabis bans as states and localities legalize marijuana use.



MEDICAL MARIJUANA: A DESIGNER PRODUCT?

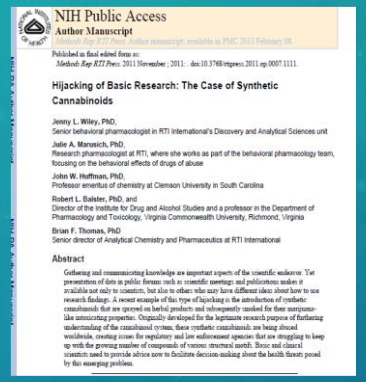
- Synthesize
- Hybridize
- Concentrate





DESIGNER SYNTHETIC CANNABINOIDS SYNTHESIZE

- Synthetic phytocannabinoids: approved drugs
- Synthetic, non-natural cannabinoids
  - Research tool
  - Substance abuse
- Substance abuse
  - "Herbal Incense", K-2, spice skunk, yukaton fire, moon rocks, etc., etc.
  - Chemical additives
    - Not on a list
    - Not detectable
    - Therefore "natural, legal, safe"
- Synthetic Drug Abuse Prevention Act 2012


NIH Public Access
Author Manuscript

Hijacking of Basic Research: The Case of Synthetic Cannabinoids

Jenny L. Wiley, PhD,
Senior behavioral pharmacologist in RTI International's Discovery and Analytical Sciences unit

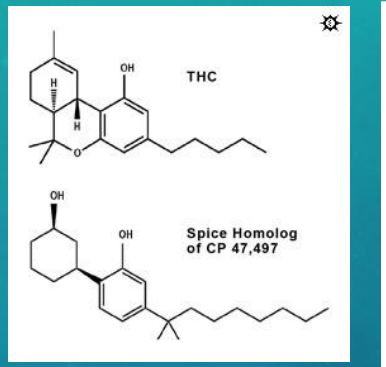
Julie A. Marusich, PhD,
Research pharmacologist at RTI, where she works as part of the behavioral pharmacology team, focusing on the behavioral effects of drugs of abuse

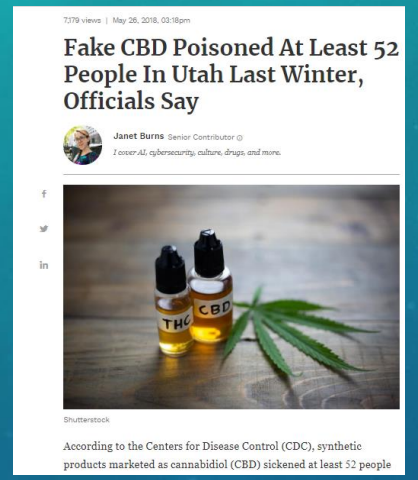
John W. Huffman, PhD,
Professor emeritus of chemistry at Clemson University in South Carolina

Robert L. Balster, PhD, and
Director of the Institute for Drug and Alcohol Studies and a professor in the Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, Virginia

Brian F. Thomas, PhD
Senior director of Analytical Chemistry and Pharmaceutics at RTI International

Abstract




7,379 views | May 26, 2016, 03:18pm

Fake CBD Poisoned At Least 52 People In Utah Last Winter, Officials Say

Janet Burns Senior Contributor
I cover AI, cybersecurity, culture, drugs, and more.

Shutterstock

According to the Centers for Disease Control (CDC), synthetic products marketed as cannabidiol (CBD) sickened at least 52 people


K-9 dies in service

Auburn clinic treated dog after he took ill during contraband search

BY SARA FALCZEWSKI

An Alabama Department of Corrections K-9 that was treated at the Auburn University Clinic died Saturday after becoming ill during a contraband search at a state corrections facility in Elmore County last Thursday.

Jake, the corrections K-9, was reported deceased at about 3 p.m. Saturday by clinical staff after developing pneumonia and suffering from abnormal vital signs, the Department of Corrections said in a Monday afternoon news release.

Sgt. Quinton Jones, Jake's handler, said Jake was performing his search at Staton Correctional Facility when he suddenly became ill after finding a substance Thursday. An initial test of the substance identified it as synthetic marijuana.

Further analysis of the narcotic discovered is pending.

Gov. Kay Ivey issued a commendation honoring Jake's service Monday and voiced her sympathy after hearing about the K-9's passing.

"I was saddened to hear that one of the corrections

and service that our four-legged friends provide."

"This K-9 died in service to public safety and in service to the state.

"Jake is an example of the goodness, the loyalty

The Incident

Corrections dispatched three emergency response teams to the prison at

about 9:10 p.m. Thursday to search a housing dorm for contraband.

Prison officials immediately evacuated the dorm

See K-9, Page 3A

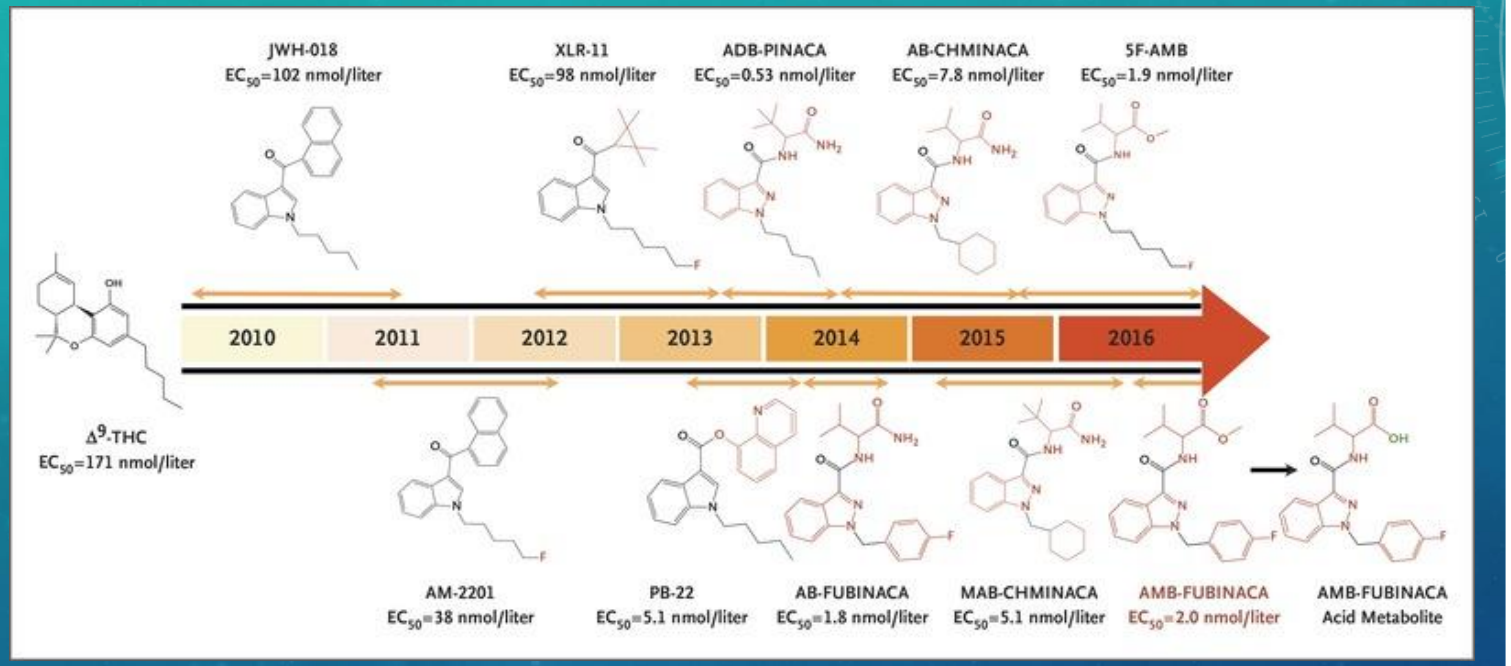
Corrections K-9 "Jake," shown with handler Sgt. Quinton Jones, died Saturday after becoming ill during a contraband search at Staton Correctional Facility on Thursday.

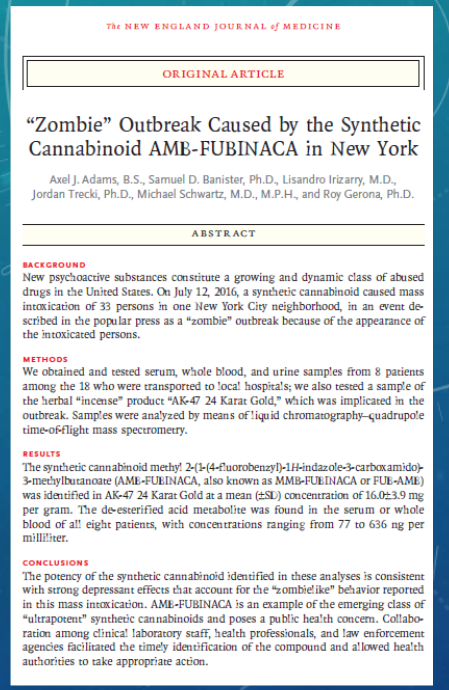
Table 1. Classification of SCs according to structure [23–28].

SC Class	Representatives	SC Class	Representatives
Aminoalkylindoles	AM-1241 JWH-018 JWH-210 JWH-081	Naphthoylindoles	WIN55,212 JWH-015 JWH-019 JWH-020 JWH-073 JWH-122 JWH-200
Adamantoylindoles	AKB48	Phenylacetylindoles	JWH-250
Benzoylindoles	RCS-4	Tetramethylcyclopropyl ketone indoles	XLR-11
Cyclohexylphenols	CP-47497 CP-47497 C8 CP55940	Quinolinyl ester indoles	PB-22
Dibenzopyrans	HU-210	Indazole carboxamide compounds	AB-FUBINACA AB-PINACA
Naphthoylpyrroles	JWH-030		

SC: Synthetic cannabinoids.

DESIGNER MEDICAL MARIJUANA: SYNTHESIZED





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

"Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York

Axel J. Adams, B.S., Samuel D. Banister, Ph.D., Lisandro Irizarry, M.D., Jordan Trecki, Ph.D., Michael Schwartz, M.D., M.P.H., and Roy Gerona, Ph.D.

ABSTRACT

BACKGROUND
New psychoactive substances constitute a growing and dynamic class of abused drugs in the United States. On July 12, 2016, a synthetic cannabinoid caused mass intoxication of 33 persons in one New York City neighborhood, in an event described in the popular press as a "zombie" outbreak because of the appearance of the intoxicated persons.

METHODS
We obtained and tested serum, whole blood, and urine samples from 8 patients among the 18 who were transported to local hospitals; we also tested a sample of the herbal "incense" product "AK-47 24 Karat Gold," which was implicated in the outbreak. Samples were analyzed by means of liquid chromatography–quadrupole time-of-flight mass spectrometry.

RESULTS
The synthetic cannabinoid methyl 2-[1-(4-fluorobenzyl)-1H-indazole-3-carboxamido]-3-methylbutanoate (AMB-FUBINACA, also known as MMB-FUBINACA or FUB-AMB) was identified in AK-47 24 Karat Gold at a mean (±SD) concentration of 16.0±3.9 mg per gram. The de-esterified acid metabolite was found in the serum or whole blood of all eight patients, with concentrations ranging from 77 to 636 ng per milliliter.

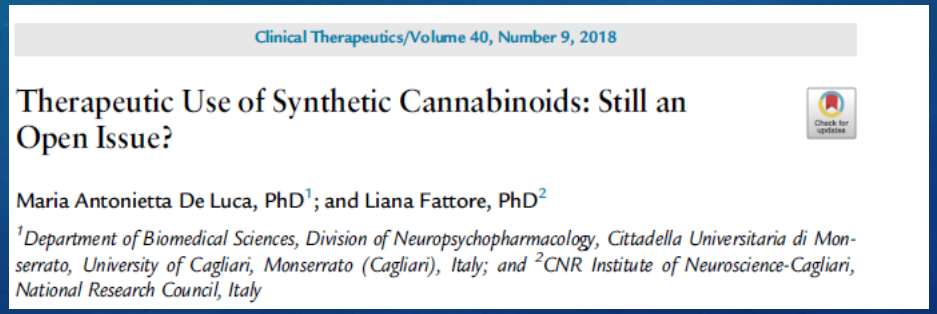
CONCLUSIONS
The potency of the synthetic cannabinoid identified in these analyses is consistent with strong depressant effects that account for the "zombie-like" behavior reported in this mass intoxication. AMB-FUBINACA is an example of the emerging class of "ultrapotent" synthetic cannabinoids and poses a public health concern. Collaboration among clinical laboratory staff, health professionals, and law enforcement agencies facilitated the timely identification of the compound and allowed health authorities to take appropriate action.

Cannabis and Cannabinoid Research

ORIGINAL RESEARCH — Open Access

Synthetic Cannabinoid Activity Against Colorectal Cancer Cells

Novel therapeutics targeting the ECS



Clinical Therapeutics/Volume 40, Number 9, 2018

Therapeutic Use of Synthetic Cannabinoids: Still an Open Issue?

Maria Antonietta De Luca, PhD[1]; and Liana Fattore, PhD[2]

[1]Department of Biomedical Sciences, Division of Neuropsychopharmacology, Cittadella Universitaria di Monserrato, University of Cagliari, Monserrato (Cagliari), Italy; and [2]CNR Institute of Neuroscience-Cagliari, National Research Council, Italy

MEDICAL MARIJUANA :THE DESIGNER WEED

The Age of Hybridization

Hand-in-hand with the indoor grow revolution came hybridized strains, an intermixing of global indigenous varieties. This is when the sativa met the indica, beginning an ever-branching tree of hybrid offspring. Growers admired indicas for their resin-coated buds and short flowering periods, both of which are coveted traits for commercial production. The enjoyable, uplifting effects of sativa strains remain a genetic cornerstone, so mixing it with lower maintenance indicas seemed to bring out the best of both worlds.

Indica

Morphology: Short and bushy; suitable for indoor gardens

Geographical Origins: Areas between 30 to 50 degrees latitude.

Effects: Tend to be sedating and relaxing with full-body effects

Symptom Relief: Anxiety, insomnia, pain, muscle spasms

Sativa

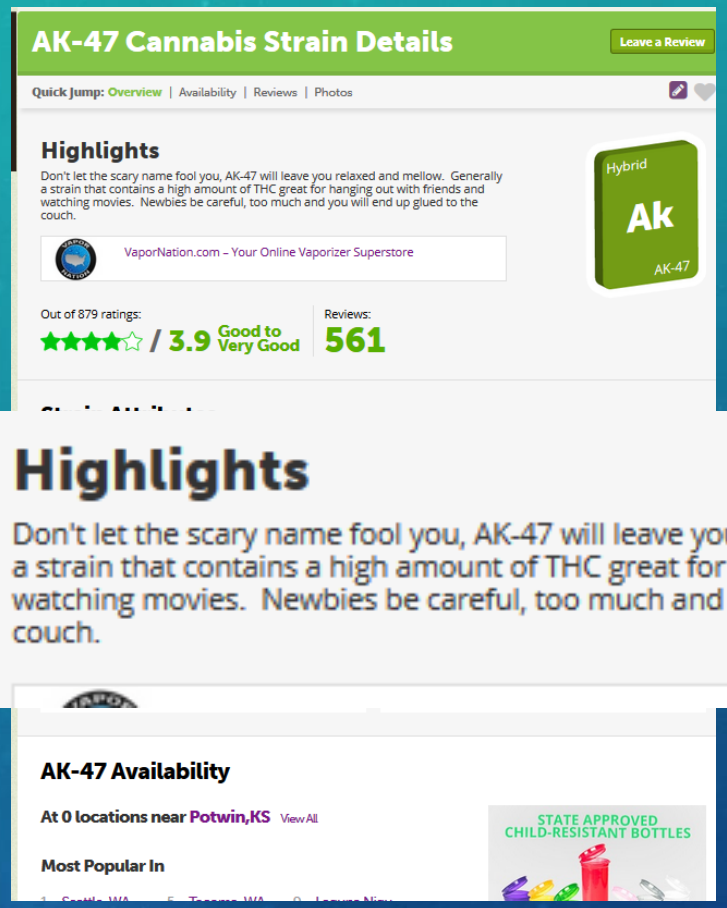
Morphology: Tall and thin; suitable for outdoor gardens

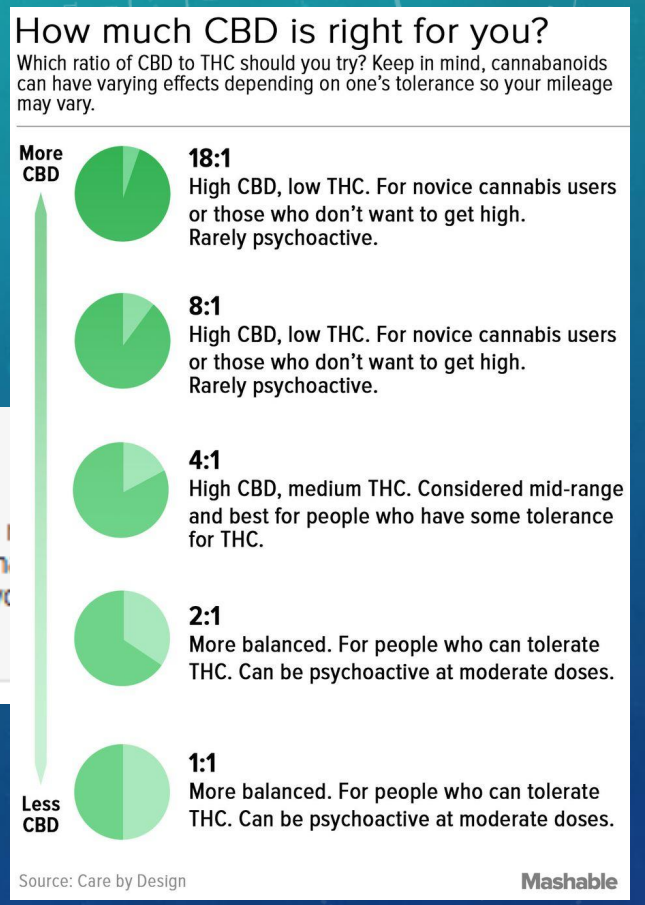
Geographical Origins: Areas between 0 and 30 degrees latitude

Effects: Tend to be uplifting and creative with cerebrally-focused effects

Symptom Relief: Depression, ADD, fatigue, mood disorders

Indica	Indica	Indica	Sativa	Sativa	Sativa
Ga	Gdp	Nl	Sd	Jh	Lh
Grape Ape	Granddaddy Purple	Northern Lights	Sour Diesel	Jack Herer	Lemon Haze



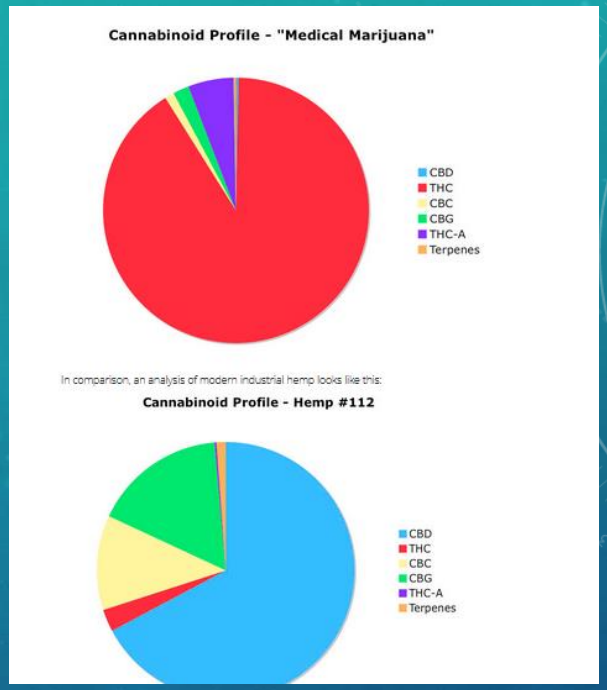


- Manipulate / concentrate
  - Terpenes/cannabinoids
  - Flavor /Taste
    - Cherry = ↑ CBD http://www.leafly.com/hybrid

CONCENTRATES DESIGNER MEDICAL MARIJUANA PRODUCTS

+

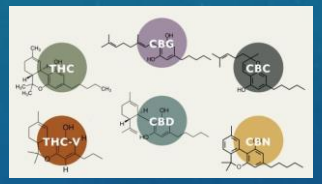
=

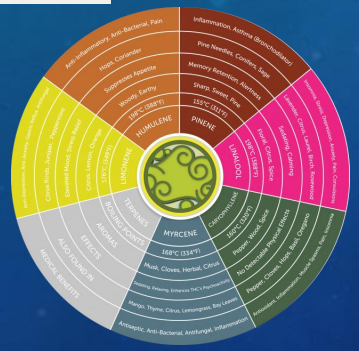


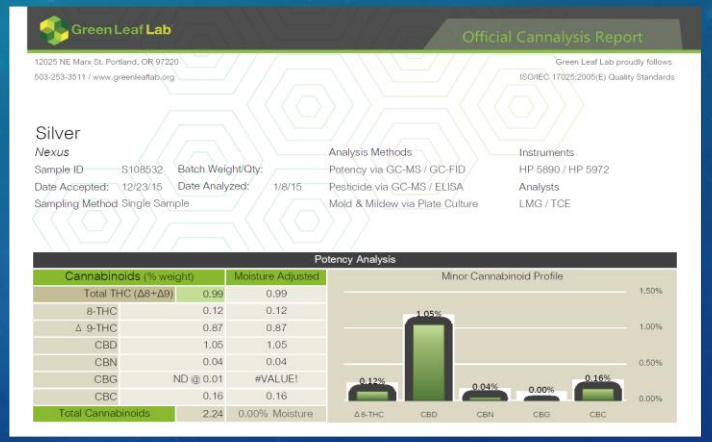
Pure/Isolate = CBD

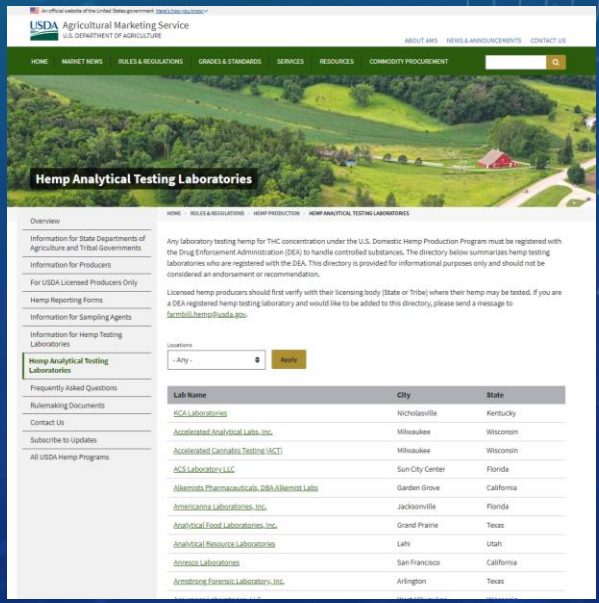
Full spectrum = all phytocannabinoids

Broad spectrum = all phytochemicals









Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

FDA's Electronic Reading Room - Warning Letters

FDA Home › Warning Letters and Responses › Warning Letters Search Results

Warning Letters Search Results

Search all warning letters

cannabi Search Advanced Search

Sort by: Go Reset

No. of Letters Found: 12

Company	Letter Issued	Issuing Office	Subject	Response Letter Posted	Closeout Date
ABC Productions	02/04/2016	Center for Food Safety and Applied Nutrition	New Drug/Labeling/Misbranded/Cannabidiol	N	
Dose of Nature	02/04/2016	Center for Food Safety and Applied Nutrition	New Drug/Labeling/Misbranded/Cannabidiol	N	
Green Garden Gold	02/04/2016	Center for Food Safety and Applied Nutrition	New Drug/Labeling/Misbranded/Cannabidiol	N	
Green Roads of Florida LLC	10/31/2017	San Juan District Office	New Drug/Misbranded/Cannabidiol(CBD) products	N	
HealthyHempOil.com	02/04/2016	Center for Drug Evaluation and Research	New Drug/Labeling/Misbranded/Cannabidiol	N	
Michigan Herbal Remedies	02/04/2016	Center for Drug Evaluation and Research	New Drug/Labeling/Misbranded/Cannabidiol	N	
Morguetorium, LLC	02/04/2016	Center for Drug Evaluation and Research	New Drug/Labeling/Misbranded/Cannabidiol	N	
Natural Alchemist	10/31/2017	Los Angeles District Office	New Drug/Misbranded/Cannabidiol(CBD) products	N	07/03/2018
PainBomb	02/04/2016	Center for Drug Evaluation and Research	New Drug/Labeling/Misbranded/Cannabidiol	N	
Sana Te	02/04/2016	Center for Food Safety and Applied Nutrition	New Drug/Labeling/Misbranded/Cannabidiol	N	
Stanley Brothers Social Enterprises, LLC	10/31/2017	Los Angeles District Office	New Drug/Misbranded/ Cannabidiol(CBD) products	N	
That's Natural	10/31/2017	Los Angeles District Office	New Drug/Misbranded/Cannabidiol(CBD) products	N	

Prev | Next | [1] | First | Last | All

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.
Language Assistance Available: Español | 繁體中文 | Tiếng Việt | 한국어 | Tagalog | Русский | العربية | Kreyòl Ayisyen | Français | Polski | Português | Italiano | Deutsch | 日本語 | فارسی | English

TREATMENT CLAM IS NOT ALLOWED

FDA WARNING LETTERS REGARDING MISBRANDING)

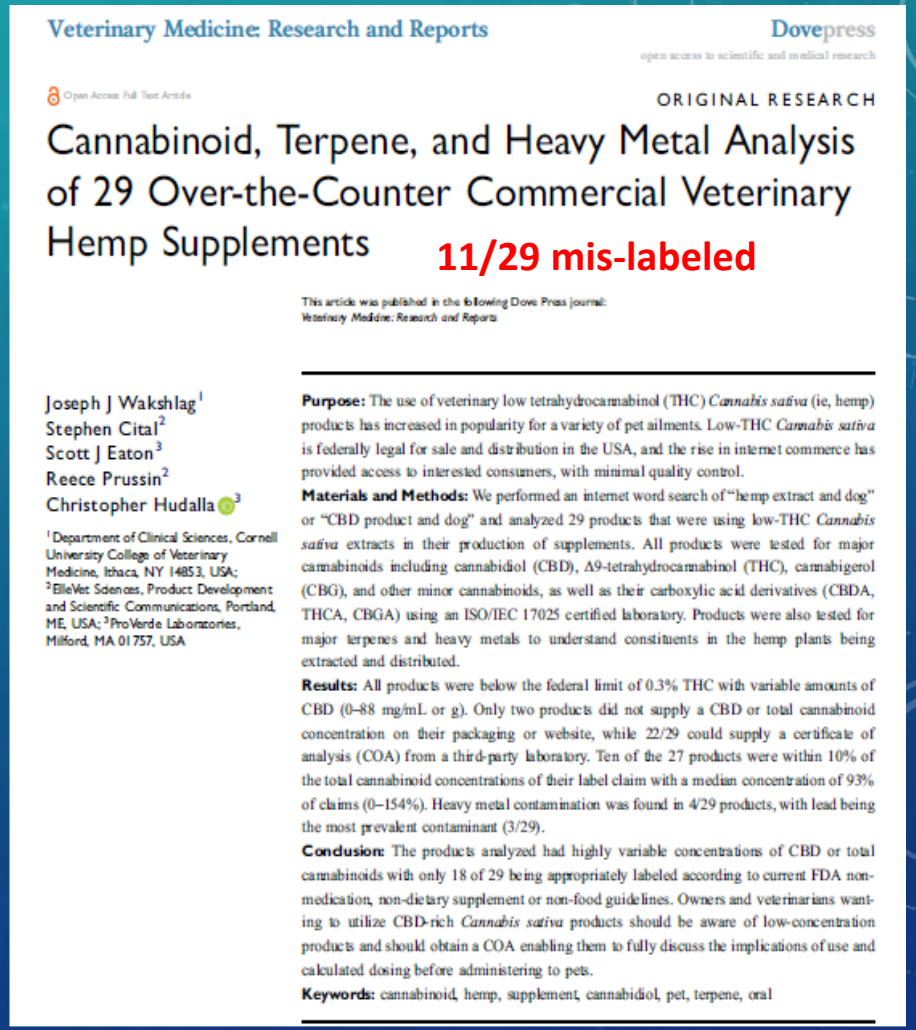
2016 Warning Letters and Test Results for Cannabidiol-Related Products

In February 2016, FDA issued eight warning letters to firms that market unapproved new drugs that allegedly contain cannabidiol (CBD). FDA had previously issued six such letters in February 2015. FDA has tested these products, and many were found to not contain the levels of CBD they claimed to contain. It is important to note that these produ are not approved by FDA for the diagnosis, cure, mitigation, treatment, or prevention of any disease. Consumers should beware purchasing and using any such products.

The links to the Warning Letters and the test results for the CBD-related products are below:

Firm	Product	State	Purchase Website	Product Size CBD Label Claim	Lab Results (mg/g)			Lab Result	
					CBD	Δ9-THC	Other Cannabinoids	CBD	Δ9-TH
Cali Stores (/ICECI/EnforcementActions/WarningLetters/2016/ucm484989.htm)	CBDy CBD Supplement Tincture	CA	0 vs 6.6	z 0mg CBD	--	0.029	THCA: 0.16	--	0.0029
Dose of Nature (/ICECI/EnforcementActions/WarningLetters/2016/ucm484970.htm)	Nano CBD Shooter *	UT	0.22 vs 1	fl oz 88mg CBD	0.22	<0.01	--	0.022%	0.001%
Michigan Herbal Remedies, LLC (/ICECI/EnforcementActions/WarningLetters/2016/ucm484979.htm)	Bluebird Botanicals Bulletproof CBD Blend	MI	8.7 vs 8	fl oz 50mg CBD	8.7	0.35	CBDA: 0.06 CBD: <0.1	0.87%	0.035%
Green Garden Gold	CBD - CBD-Oil	TX	greengardengold.com	15ml	0.79	0.02	CBDA: <0.01	0.079%	0.002%
Green Garden Gold (/ICECI/EnforcementActions/WarningLetters/2016/ucm484947.htm)	CBD - Strawberry Jam CBD-Oil	TX	greengardengold.com	6oz N/A CBD	0.96	0.03	CBDA: <0.01 CBN: <0.01	0.096%	0.003%
Healthy Hemp Oil (/ICECI/EnforcementActions/WarningLetters/2016/ucm484968.htm)	Herbal Renewals CBD Hemp Oil Supplement	TX	healthyhempoil.com	1oz 100mg CBD	2.4	0.081	CBN: <0.01	0.24%	0.008
Healthy Hemp Oil (/ICECI/EnforcementActions/WarningLetters/2016/ucm484968.htm)	Herbal Renewals 25% CBD Hemp Oil Gold Label	TX	healthyhempoil.com	3g 750mg CBD	257	8.4	CBN: 0.70	25.7%	0.84%
Healthy Hemp Oil (/ICECI/EnforcementActions/WarningLetters/2016/ucm484968.htm)	PLUS+CBD Oil Balm	TX	healthyhempoil.com	1.3oz N/A CBD	0.45	0.022	CBDA: 0.90 THCA: 0.029	0.045%	0.002
Healthy Hemp Oil (/ICECI/EnforcementActions/WarningLetters/2016/ucm484968.htm)	Hempotion Cannabidiol CBD Concentrate	TX	healthyhempoil.com	.5oz 100mg CBD	6.6	0.21	CBN: 0.017	0.66%	0.021%
Healthy Hemp Oil (/ICECI/EnforcementActions/WarningLetters/2016/ucm484968.htm)	Entourage Occam's Razor	TX	healthyhempoil.com	10ml 100mg CBD	6.8	--	--	0.68%	--
Michigan Herbal Remedies, LLC (/ICECI/EnforcementActions/WarningLetters/2016/ucm484979.htm)	Bluebird Botanicals Bulletproof CBD Blend	MI	michiganherbalremedies.com	1 fl oz 250mg CBD	8.7	0.35	CBDA: 0.06 CBD: <0.1	0.87%	0.035%

FDA WARNING LETTERS DUE TO MISBRANDING/ADULTERATION (INAPPROPRIATE CONTENT)



Veterinary Medicine: Research and Reports — Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Cannabinoid, Terpene, and Heavy Metal Analysis of 29 Over-the-Counter Commercial Veterinary Hemp Supplements

11/29 mis-labeled

This article was published in the following Dove Press journal: *Veterinary Medicine: Research and Reports*

Joseph J Wakshlag[1]
Stephen Cital[2]
Scott J Eaton[3]
Reece Prussin[2]
Christopher Hudalla[3]

[1]Department of Clinical Sciences, Cornell University College of Veterinary Medicine, Ithaca, NY 14853, USA; [2]ElleVet Sciences, Product Development and Scientific Communications, Portland, ME, USA; [3]ProVerde Laboratories, Milford, MA 01757, USA

Purpose: The use of veterinary low tetrahydrocannabinol (THC) *Cannabis sativa* (ie, hemp) products has increased in popularity for a variety of pet ailments. Low-THC *Cannabis sativa* is federally legal for sale and distribution in the USA, and the rise in internet commerce has provided access to interested consumers, with minimal quality control.

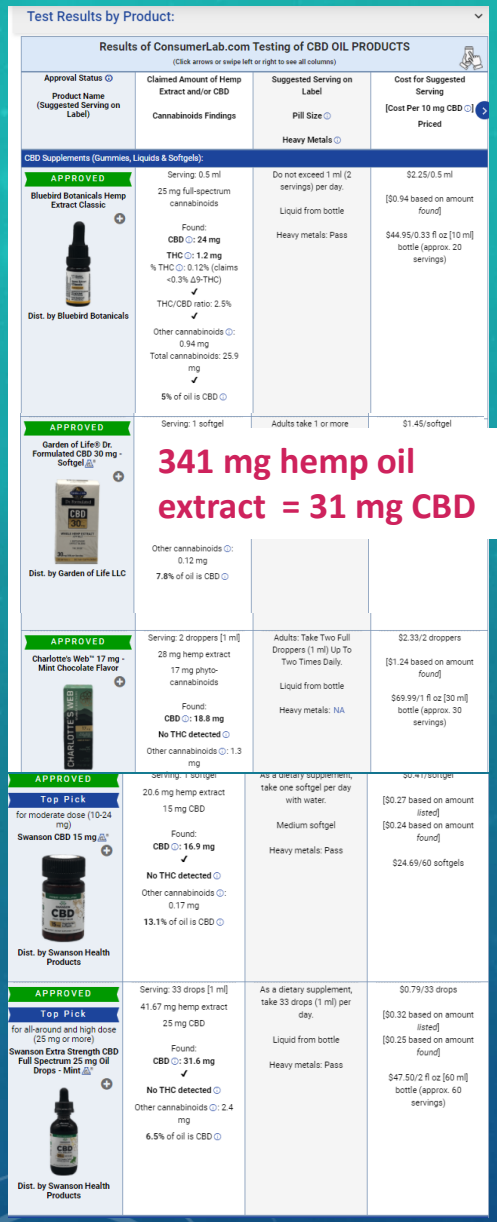
Materials and Methods: We performed an internet word search of "hemp extract and dog" or "CBD product and dog" and analyzed 29 products that were using low-THC *Cannabis sativa* extracts in their production of supplements. All products were tested for major cannabinoids including cannabidiol (CBD), Δ9-tetrahydrocannabinol (THC), cannabigerol (CBG), and other minor cannabinoids, as well as their carboxylic acid derivatives (CBDA, THCA, CBGA) using an ISO/IEC 17025 certified laboratory. Products were also tested for major terpenes and heavy metals to understand constituents in the hemp plants being extracted and distributed.

Results: All products were below the federal limit of 0.3% THC with variable amounts of CBD (0–88 mg/mL or g). Only two products did not supply a CBD or total cannabinoid concentration on their packaging or website, while 22/29 could supply a certificate of analysis (COA) from a third-party laboratory. Ten of the 27 products were within 10% of the total cannabinoid concentrations of their label claim with a median concentration of 93% of claims (0–154%). Heavy metal contamination was found in 4/29 products, with lead being the most prevalent contaminant (3/29).

Conclusion: The products analyzed had highly variable concentrations of CBD or total cannabinoids with only 18 of 29 being appropriately labeled according to current FDA non-medication, non-dietary supplement or non-food guidelines. Owners and veterinarians wanting to utilize CBD-rich *Cannabis sativa* products should be aware of low-concentration products and should obtain a COA enabling them to fully discuss the implications of use and calculated dosing before administering to pets.

Keywords: cannabinoid, hemp, supplement, cannabidiol, pet, terpene, oral

MISBRANDING/ADULTERATION
Inaccuracy in CBD vs THC content vs contaminants



341 mg hemp oil extract = 31 mg CBD

2 mg CBD / dropper full (vs. 2 mg/kg)

$1.50/10 mg

EPIDIOLEX- cannabidiol solution
Greenwich Biosciences, Inc.

3 DOSAGE FORMS AND STRENGTHS

Cannabidiol oral solution: 100 mg/mL for oral administration. Each bottle contains 100 mL of a clear, colorless to yellow solution.

Difficulty in achieving dose?
"Hemp oil extract" vs CBD content
Concentration of product
Bottle vs capsule vs dropperful
Cost of approved vs supplements?
Dosing volume of supplements vs drug

Higher than tolerable PAHs found in CBD products

Česky

16. february 2018, section News

Warning for consumers of CBD and cannabis oils sold on the EU market

In Prague, in the framework of the program *Patient Focus Certification (PFC)*, the world's first independent testing took place of a. the quality of cannabidiol available on the retail market (CBD, a non-psychotropic substance from cannabis), and b. the composition of so-called cannabis oils available in the European Union. Results have positively confirmed the need for independent certification of the quality of mass-produced products made from cannabis.

In cooperation with the first European laboratory certified by the program PFC, which works at the Department of Food Analysis and Nutrition of the University of Chemistry and Technology, Prague (VŠCHT), the International Institute for Cannabis and Cannabinoids (ICCI) headquartered in Prague assessed the quality of certain types of commercially available CBSs and so-called "cannabis oils".

The team led by professor Jana Hajšlová tested 29 oils containing the non-psychotropic biologically active substance from cannabis, CBD (cannabidiol), and 25 oils from cannabis seeds purchased on the EU market in the last quarter of 2016. *"For both categories, we are interested in the quality and authenticity of used oils and possible content of environmental contaminants, polycyclic aromatic hydrocarbons (PAH), which accumulate in oils (for protecting the health of their consumers, maximum limits have been anchored in legislation. For "CBD oils", we also examined the consistency of the determined contents of CBD with the producer's stated values and the potential content of THC" (tetrahydrocannabinol - the main psychotropic substance from cannabis),* says professor Hajšlová explaining the key points.

Director of research at ICCI Tomáš Zábranský explains the reasons why the following aspects were selected in the assessment of edible cannabis-based foods: " *Multi-core polycyclic aromatic hydrocarbons such as benzopryrene are*

APPROVED DRUGS

- Manipulations of two major cannabinoids
  - ∆9-THC, CBD
- Dronabinol (Marinol) (USA)
  - ∆9-THC
  - Appetite stimulant in AIDS/cancer patients
- Nabilone (Cesamet) (USA)
  - ∆9-THC-like
  - Antiemetic-chemotherapy
  - Extra-label: analgesic
- Epidiolex®
  - CBD
  - FDA approved June 2018
  - Pediatric drug resistant epilepsy

- Nabixomol (Sativex; UK)
  - 1:1 ratio of ∆ 9-THC and CBD
  - Spasticity of MS
  - Epilepsy

FDA News Release

FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy

For Immediate Release

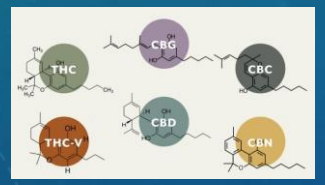
June 25, 2018

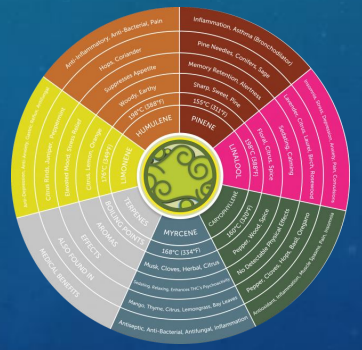
of careful scientific research and drug development," said FDA Commissioner Scott Gottlieb, M.D. "Controlled clinical trials testing the safety and efficacy of a drug, along with careful review through the FDA's drug approval process, is the most appropriate way to bring marijuana-derived treatments to patients. Because of the adequate and well-controlled clinical studies that supported this approval, prescribers can have confidence in the drug's uniform strength and consistent delivery that support appropriate dosing needed for treating patients with these complex and serious epilepsy syndromes. We'll continue to support rigorous scientific research on the potential medical uses of marijuana-derived products and work with product developers who are interested in bringing patients safe and effective, high quality products. But, at the same time, we are prepared to take action when we see the illegal marketing of CBD-containing products with serious, unproven medical claims. Marketing unapproved products, with uncertain dosages and formulations can keep patients from accessing appropriate, recognized therapies to treat serious and even fatal diseases."

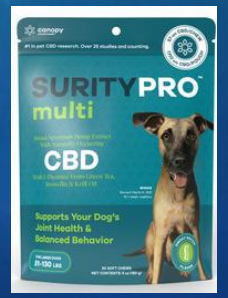
patients safe and effective, high quality products. But, at the same time, we are prepared to take action when we see the illegal marketing of CBD-containing products with serious, unproven medical claims. Marketing unapproved products, with uncertain dosages and formulations can keep patients from accessing appropriate, recognized therapies to treat serious and even fatal diseases."

MEDICAL CANNABINOIDS
PART I: UNDERSTANDING THE PRODUCT HIGH POINTS

- Emotions rather than science has driven “abuse” vs. use
- Regulations are dynamic and thus far nonsensical
  - State vs. federal
  - THC vs. CBD vs. hemp CBD
- (Unregulated) supplements are major access for clients
-







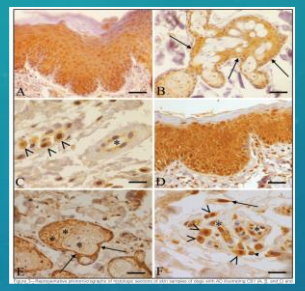
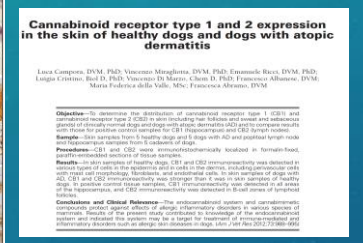
- Product quality is a major concern
  - Mislabeling: intent and content
  - Adulteration: added content?
  - Find a reputable product / manufacturer
    - Ask regarding QA
    - Peer reviewed clinical trials
- Know product content
  - Active ingredients
  - Concentration

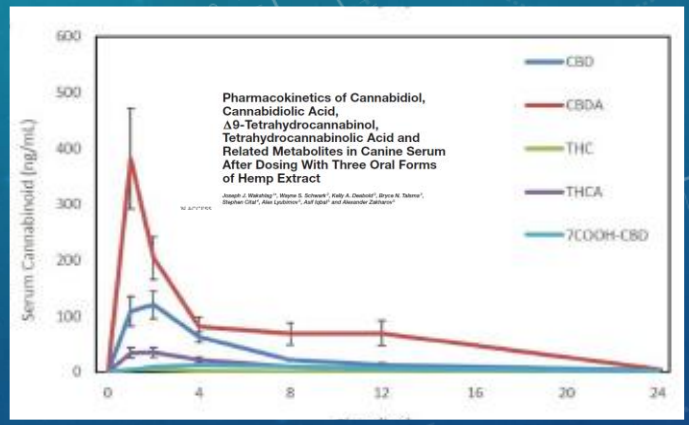
ConsumerLab.com

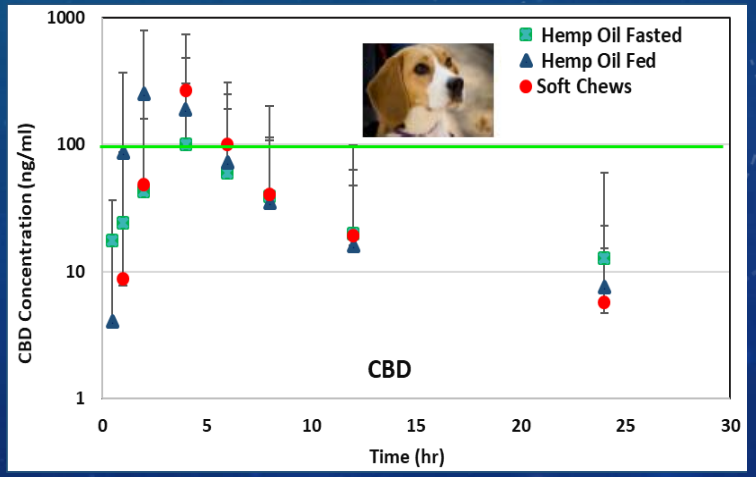
PRODUCT FORMULATION AND PHARMACOKINETICS:

- How much of the dose gets there?
  - Route
    - Transmucosal (keep in mouth)
    - Inhalation
    - Transdermal (??) vs. topical
    - Oral
  - Oral bioavailability varies
    - CBD vs. CBDA?
      - Is CBDA active?
    - Oil vs. solid vs. soft chews
    - MCT vs. others?
    - Fasted or fed?







PHARMACOKINETIC DIFFERENCES

- Species differences
  - Cats ≠ dogs ≠ small people
  - Differences in
    - Oral bioavailability
    - Metabolic profile
    - Active vs. toxic metabolites
  - Duration in body
    - Human half-life
      - THC = 1-2 DAYS
      - CBD = 3-4 DAYS
    - Dogs and cats: hours
  - Impact on dose and interval

animals

MDPI

Article

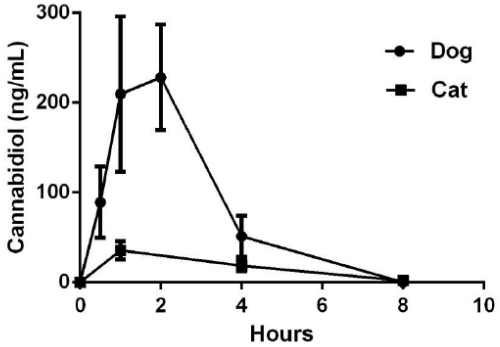
Single-Dose Pharmacokinetics and Preliminary Safety Assessment with Use of CBD-Rich Hemp Nutraceutical in Healthy Dogs and Cats

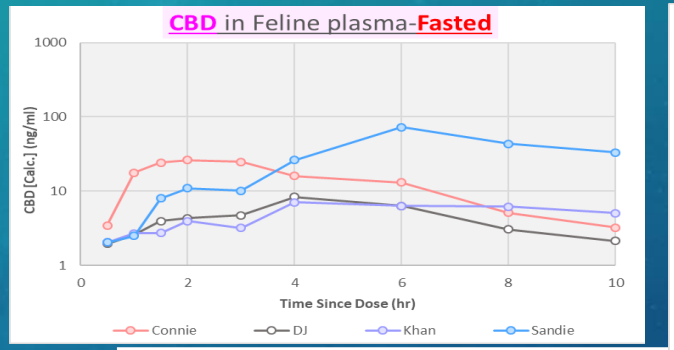
Kelly A. Deabold [1], Wayne S. Schwark [2], Lisa Wolf [3] and Joseph J. Wakshlag [4,*]

1 Department of Comparative Diagnostic Population Medicine, University of Florida College of Veterinary Medicine, Gainesville, FL 32608, USA; kdeabold@icloud.com
2 Department of Molecular Medicine, Cornell College of Veterinary Medicine, Ithaca, NY 14853, USA; wss2@cornell.edu
3 Proteomics and Metabolomics Facility, Colorado State University, Fort Collins, CO 80521, USA; Lisa.Wolfe@colostate.edu
4 Department of Clinical Sciences, Cornell College of Veterinary Medicine, Ithaca, NY 14853, USA
* Correspondence: dr.joesh@gmail.com; Tel.: +1-(607)-253-4389; Fax: +1-(607)-253-3534

Received: 30 August 2019; Accepted: 15 October 2019; Published: 19 October 2019

check for updates





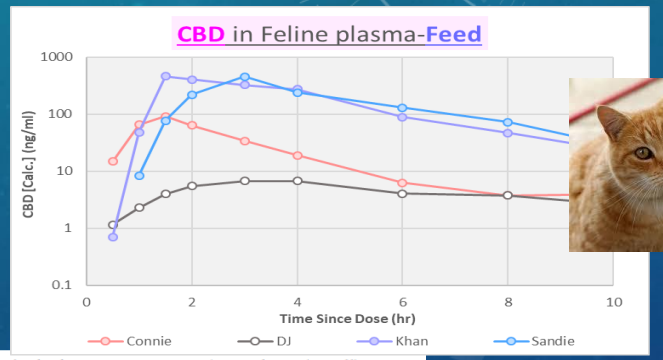


Figure 1. Mean and standard error of the mean (SEM) cannabidiol concentrations from dogs (n = 5) and cats (n = 6) at different time points after dosing.

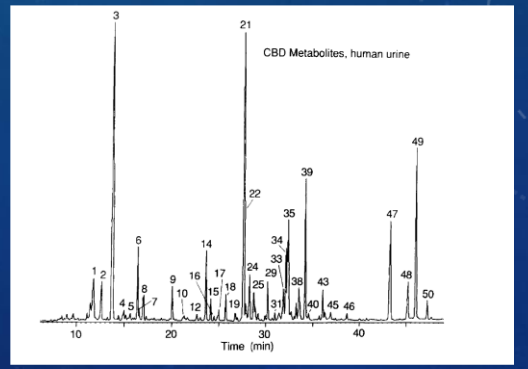
Pharmacology Biochemistry & Behavior, Vol. 40, pp. 523–532. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Comparative Metabolism of Cannabidiol in Dog, Rat and Man

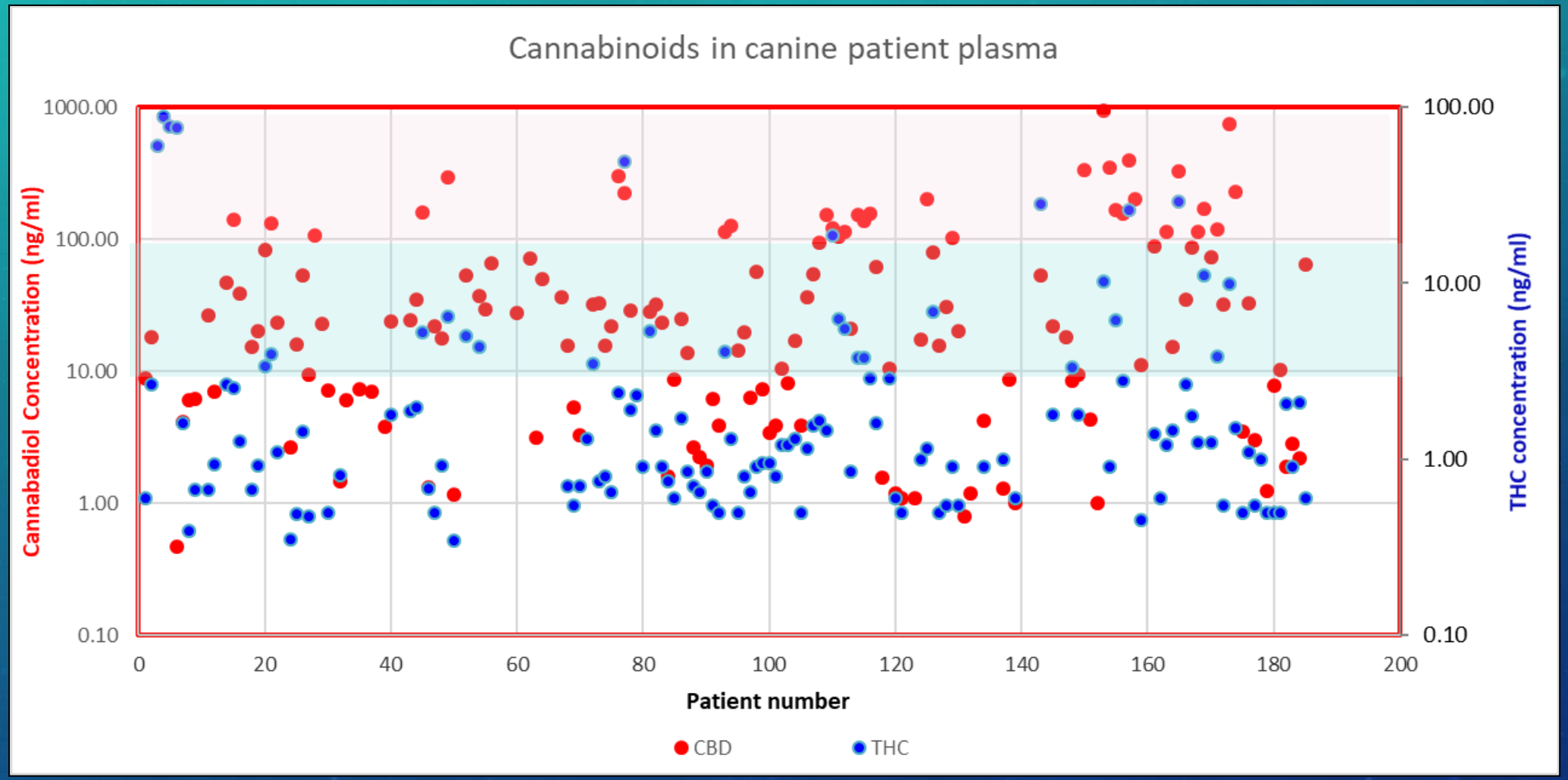
D. J. HARVEY,* E. SAMARA† AND R. MECHOULAM†

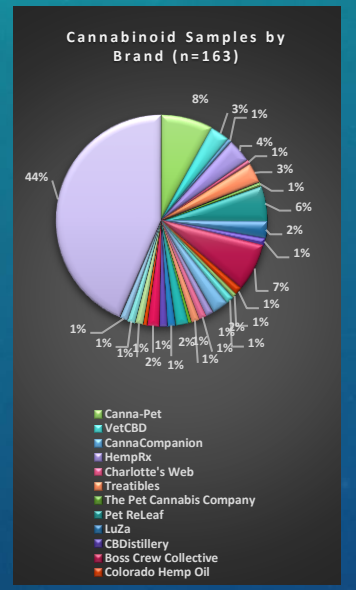
*University Department of Pharmacology, Mansfield Road, Oxford, OX1 3QT, UK
and †Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, 91 120 Israel

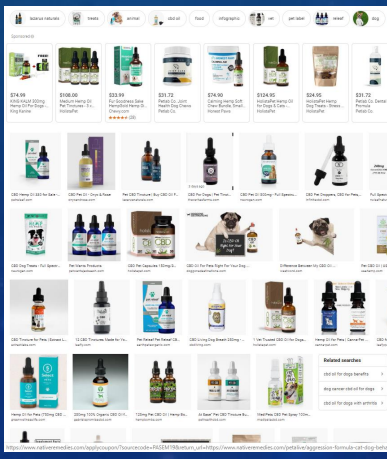
HARVEY, D. J., E. SAMARA AND R. MECHOULAM. *Comparative metabolism of cannabidiol in dog, rat and man*. PHARMACOL BIOCHEM BEHAV **40**(3) 523–532, 1991.—Urinary metabolites of cannabidiol (CBD) were extracted from human, dog and rat urine, concentrated by chromatography on Sephadex LH-20, and identified by GC/MS. Over 50 metabolites were identified with considerable species variation. CBD was excreted in substantial concentration from human urine, both in the free state and as its glucuronide. In dog, unusual glucoside conjugates of three metabolites (4''- and 5''-hydroxy and 6-oxo-CBD), not excreted in the unconjugated state, were found as the major metabolites at early times after drug administration. Other metabolites in all three species were mainly acids. Side-chain hydroxylated derivatives of CBD-7-oic acid were particularly abundant in human urine but much less so in dog. In the latter species the major oxidized metabolites were the products of beta-oxidation with further hydroxylation at C-6. A related, but undefined pathway, resulted in loss of three carbon atoms from the side-chain of CBD in man with the production of 2''-hydroxy-tris,nor-CBD-7-oic acid. Previous experiments indicate that 3'-hydroxy-metabolites are the precursors of compounds having this side-chain. Metabolism by the epoxide-diol pathway, resulting in dihydro-diol formation from the delta-8-double bond, gave metabolites in both dog and human urine. It was concluded that CBD could be used as a probe of the mechanism of several types of biotransformation, particularly those related to carboxylic acid metabolism, as intermediates of the type not usually seen with endogenous compounds were excreted in substantial concentration.



CANINE SERUM CANNABINOID CONCENTRATIONS







- **Therapeutic reference interval CBD > 100 ng/ml?**

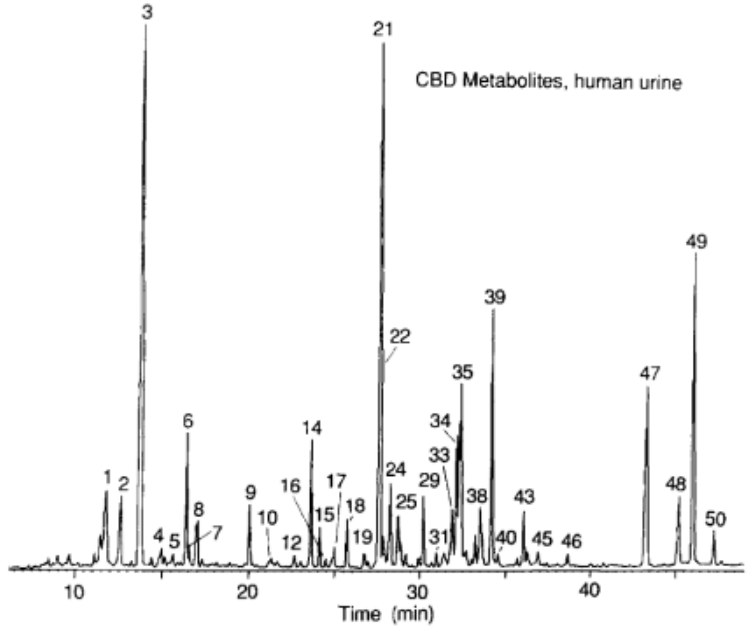
Pharmacology Biochemistry & Behavior, Vol. 40, pp. 523–532. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Comparative Metabolism of Cannabidiol in Dog, Rat and Man

D. J. HARVEY,* E. SAMARA† AND R. MECHOULAM†

**University Department of Pharmacology, Mansfield Road, Oxford, OX1 3QT, UK and †Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, 91 120 Israel*

HARVEY, D. J., E. SAMARA AND R. MECHOULAM. *Comparative metabolism of cannabidiol in dog, rat and man.* PHARMACOL BIOCHEM BEHAV **40**(3) 523–532, 1991.—Urinary metabolites of cannabidiol (CBD) were extracted from human, dog and rat urine, concentrated by chromatography on Sephadex LH-20, and identified by GC/MS. Over 50 metabolites were identi-
fi
a
e
i
n
fi
i
d
fr
p
d
n the free state
oxo-CBD), not
ther metabolites
ibundant in hu-
-oxidation with
e-chain of CBD
metabolites are
-diol formation
d be used as a
sm, as interme-



0090-9556/90/1805-0571$02.00/0
DRUG METABOLISM AND DISPOSITION
Copyright © 1990 by The American Society for Pharmacology and Experimental Therapeutics
Vol. 18, No. 5
Printed in U.S.A.

IDENTIFICATION OF URINARY METABOLITES OF CANNABIDIOL IN THE DOG

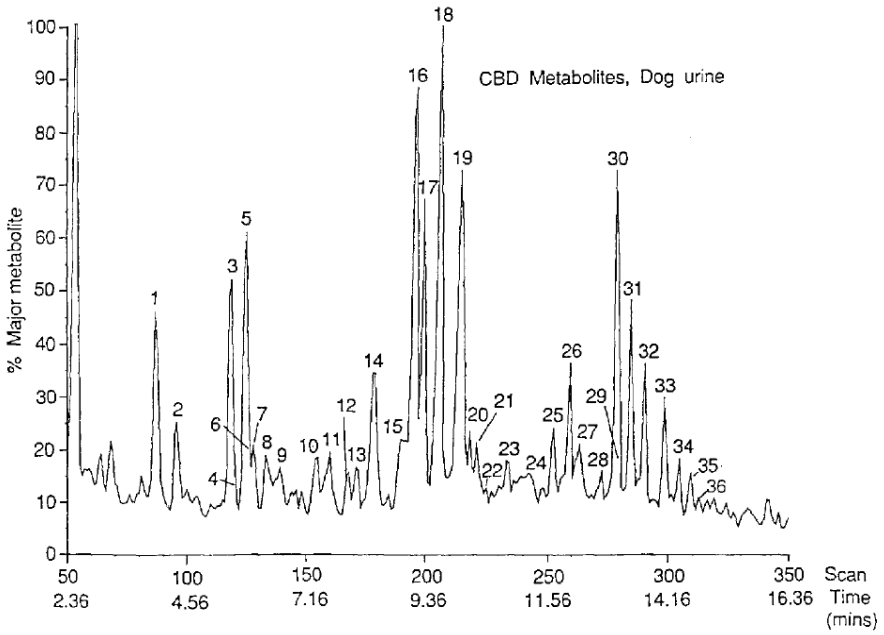
E. SAMARA, M. BIALER AND D. J. HARVEY

Department of Pharmacology, Oxford University (D.J.H.) and Department of Pharmacy, School of Pharmacy, The Hebrew University of Jerusalem (E.S., M.B.)

(Received April 18, 1989; accepted November 8, 1989)

ABSTRACT:

Three dogs were treated with cannabidiol (CBD) and urine samples were collected periodically to 30 hr. Metabolites were extracted with
ethyl acetat
examined b
a further ni
metabolites
oxidative m
β-oxidation.
hydroxy-4″,
3″-oic acid,
give 6-hydroxy-2″,3″,4″,5″-*tetrakis*,nor-CBD-1″pr-oic acid as the major metabolite. Other metabolic routes were carboxylic acid formation
and dihy-
″-hydroxy-
y times as
ose of the
metabolites
olites were
conjugated



Pharmacokinetics:

Dogs: 10% oral bioavailability for CBD

Metabolic profile of cannabidiol differs compared to humans

Table 1

Criteria Used to Evaluate Clinical Signs in Dogs Intoxicated With Eight Human Drugs/Drug Classes of Abuse

Barbiturates	CNS* depression, respiratory depression, hypothermia, arrhythmias (sinus tachycardia, ventricular bigeminy), and coma[7,8]
Benzodiazepines	Sedation, hypnotic, confusion, decreased reflexes, bradycardia, ataxia, nystagmus[9,10]
Cannabis (THC)	CNS: Ataxia, abnormal mentation, bradycardia, nystagmus, tremors, rarely hyperexcitable or vocalizing Other: vomiting, polydipsia, ptyalism, hypothermia, mydriasis[8,11-15]
Cocaine	Biphasic: Stimulation followed by depression Ptyalism, hyperesthesia, tachycardia and tachyarrhythmias, hyperpyrexia, hypertension, convulsions, mydriasis[8,16]
Methadone (synthetic opiate)	Sedation, hypothermia, skeletal muscle flaccidity[6]
Amphetamines/Methamphetamines	Excitement, stimulation, mydriasis, ptyalism, hyperthermia, hypertension, tachycardia, lactic acidosis, hypoglycemia, and seizures[8,9,13,17,18]
Opiates/Opium derivatives	Salivation, nausea, vomiting, defecation, urination, increased respiration, initial miosis followed by mydriasis[8,13]
Phencyclidines	CNS stimulation and depression, mydriasis, nystagmus, tonic-clonic convulsions, jaw snapping, opisthotonus, and death[8,15]

* CNS=central nervous system

Evaluation of a Human On-site Urine Multidrug Test for Emergency Use With Dogs

A rapid, human on-site urine multidrug test was used to screen canine urine samples for the presence of five illegal drugs and drugs from three common sample was sent to a toxicology laboratory for gas chromat (GC/MS) validation. On-site test results and GC/MS assays test kit did identify barbiturates, opiates, benzodiazepines, a mines in urine from dogs that had received these common i intravenously and/or orally. However, neither the on-site tes assays for marijuana or methadone, a synthetic opiate, wer and methadone in urine from dogs with suspected or known was seen for exposure to phencyclidines or cocaine during sures were indicated by the on-site test results. Overall, the affordable, and useful complement to the veterinarian's clini judgment. **J Am Anim Hosp Assoc 2009;45:59-66.**

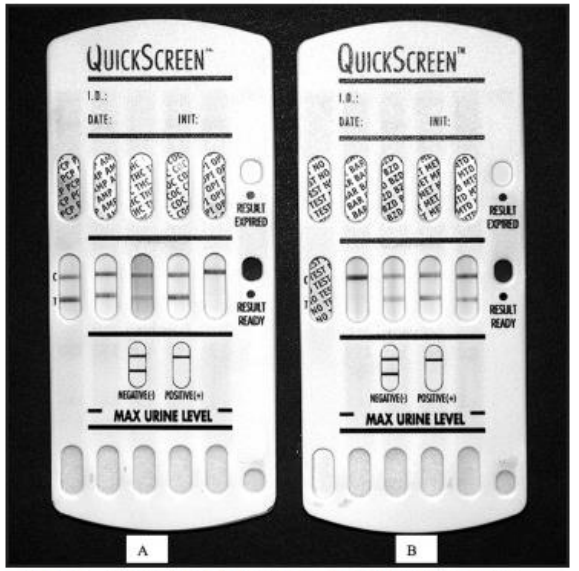
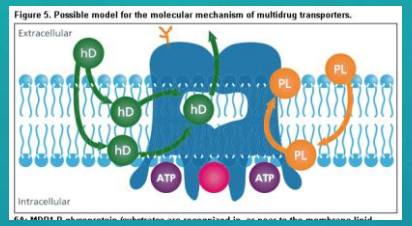


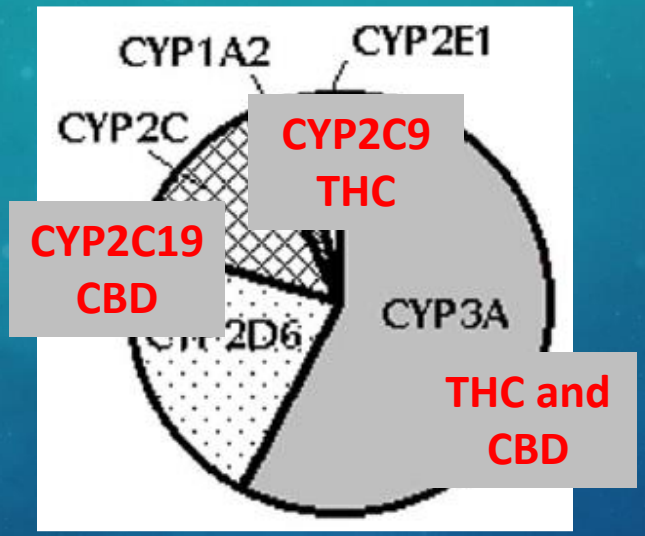
Figure 1—On-site multidrug urine test kit with positive results for opiates (A) and barbiturates (B).

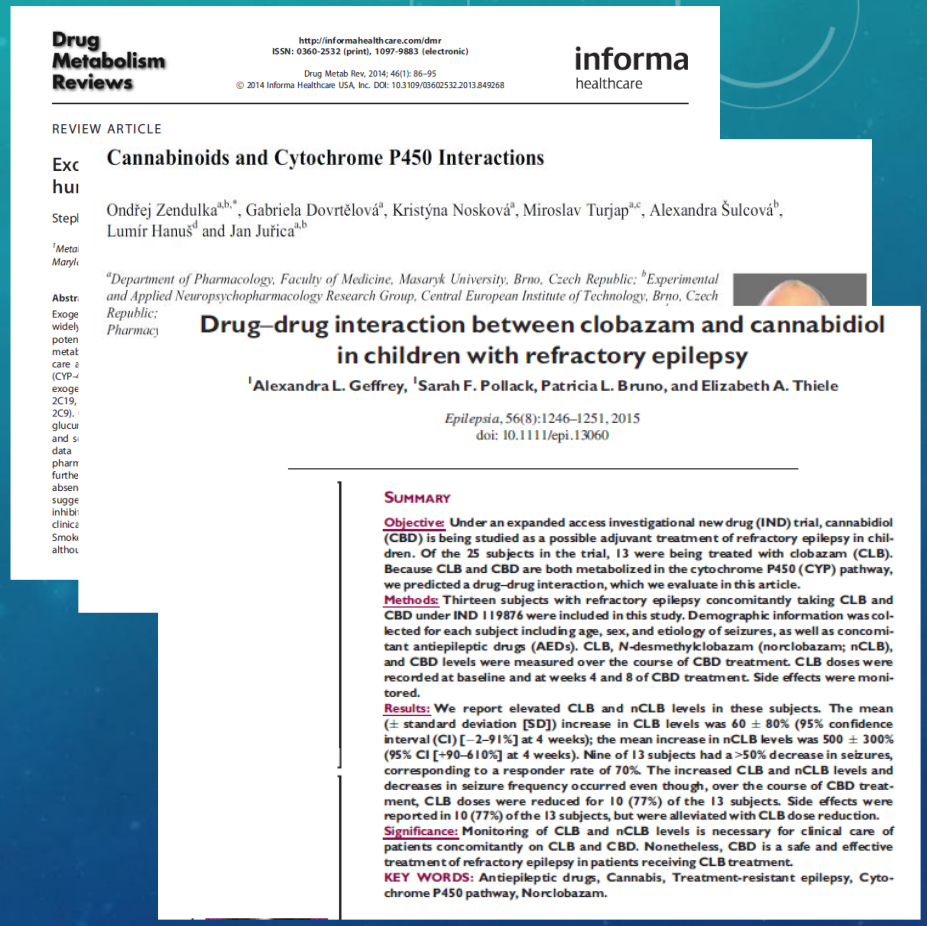
intravenously and/or orally. However, neither the on-site test kit nor the GC/MS individual assays for marijuana or methadone, a synthetic opiate, were effective in identifying marijuana

DRUG-DIET-SUPPLEMENT INTERACTIONS

- The more foreign (and lipophilic) the compound, the greater the risk
  - Foreign = Get it Out!
    - (Efflux) transport proteins: No problem for mutants?
    - Metabolite = inhibitor?
    - Cannabinoids: CYP450
      - 3A4, C29, 2C19
- Species, breed, patient variability
  - Impact on safety
  - Drug interactions
- Ask the correct questions







EPIDIOLEX- cannabidiol solution
Greenwich Biosciences, Inc.

Sensitive CYP2C19 Substrates

In vivo data show that coadministration of EPIDIOLEX increases plasma concentrations of drugs that are metabolized by (i.e., are substrates of) CYP2C19 (e.g., diazepam) and may increase the risk of adverse reactions with these substrates *[see Clinical Pharmacology (12.3)]*. Consider a reduction in dosage of sensitive CYP2C19 substrates, as clinically appropriate, when coadministered with EPIDIOLEX.

Drug Interaction Studies

In Vitro Assessment of Drug Interactions

Drug Metabolizing Enzymes *[see Drug Interactions (7.1, 7.2)]*

Cannabidiol is a substrate for cytochrome p450 (CYP) enzymes CYP3A4 and CYP2C19. Cannabidiol has the potential to inhibit CYP2C8, CYP2C9, and CYP2C19 at clinically relevant concentrations.

Cannabidiol may induce or inhibit CYP1A2 and CYP2B6 at clinically relevant concentrations.

Cannabidiol inhibits uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes UGT1A9 and UGT2B7, but does not inhibit the UGT1A1, UGT1A3, UGT1A4, UGT1A6, or UGT2B17 isoforms.

Transporters

Cannabidiol and the cannabidiol metabolite, 7-OH-CBD, are not anticipated to interact with BCRP, BSEP, MDR1/P-pg, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, OATP1B1, or OATP1B3.

The cannabidiol metabolite, 7-COOH-CBD, is not a substrate of BCRP, OATP1B1, OATP1B3, or OCT1.

However, 7-COOH-CBD is a substrate for P-gp. 7-COOH-CBD is an inhibitor of transport mediated via BCRP and BSEP at clinically relevant concentrations.

In Vivo Assessment of Drug Interactions

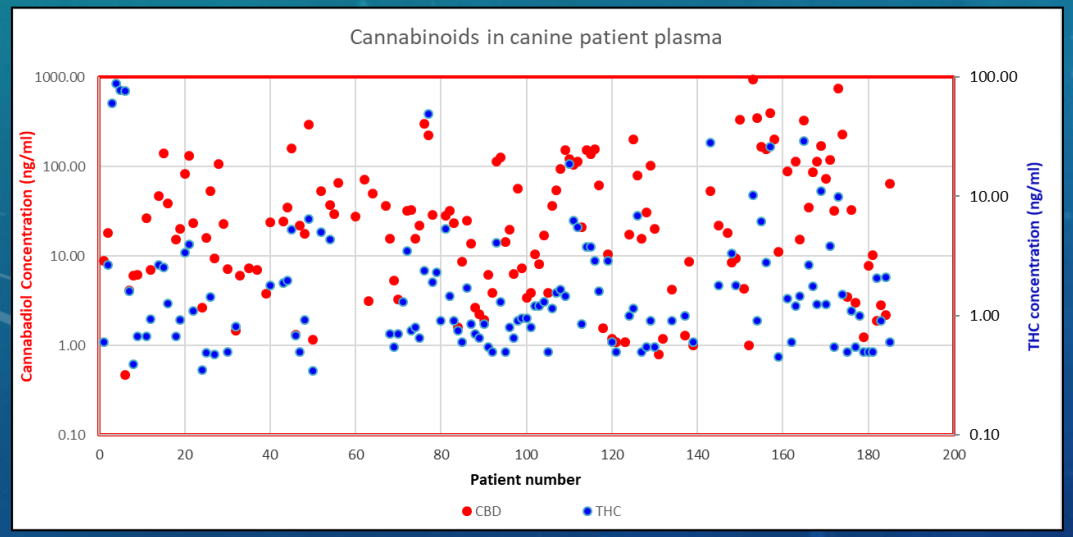
Drug Interaction Studies with AEDs

There is a risk of drug interactions at both CYP450 and transport proteins; the risk may be greater for metabolites

EPIDIOLEX- cannabidiol solution
Greenwich Biosciences, Inc.

CONCLUSIONS REGARDING PHARMACOKINETICS

- Dose
  - Variable oral absorption
    - Product
    - CBD vs. CBDA?
    - First pass metabolism increases dose and cost
    - Increased with feeding?
    - THC and CBD characterized by active metabolites

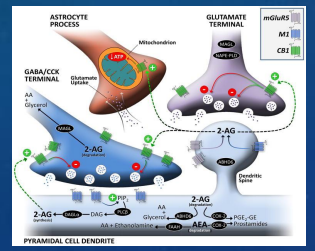


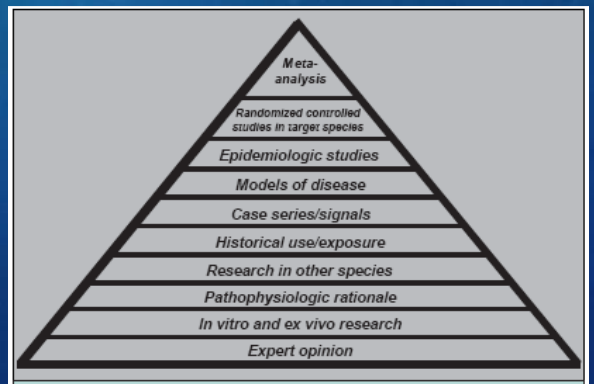
- Interval
  - Half-life much shorter in dogs and cats vs. humans
- Risk of drug interactions
  - Protein binding? (relevance?)
  - Drug metabolism (CYP3A, 2C9, 2C19)
  - P-glycoprotein

What is the dose? Should it change?
What is the target concentration?
Monitor to assure?

THE CHALLENGES OF MEDICAL CANNABINOIDS

PART II: UNDERSTANDING THE TARGET





Dawn Merton Boothe, DVM, PhD
Diplomate ACVIM (Internal Med)
Diplomate ACVCP (Clinical Pharmacology)
Professor, Director Clinical Pharmacology
Auburn University

MEDICAL CANNABINOIDS: (BARRIERS TO) UNDERSTANDING THE TARGET

Part II: Looking for Evidence

- **Product safety and efficacy**
  - Humans vs. animals
  - Pharmacodynamics
    - Receptors
    - Endocannabinoids
  - Pharmacokinetics
  - Clinical trials
- Challenges

MARINOL- dronabinol capsule
AbbVie Inc.

MARINOL- dronabinol capsule
AbbVie Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

MARINOL (dronabinol) capsules, for oral use, CIII
Initial U.S. Approval: 1985

INDICATIONS AND USAGE

MARINOL is a cannabinoid indicated in adults for the treatment of:

- Anorexia associated with weight loss in patients with AIDS. (1)
- Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. (1)

DOSAGE AND ADMINISTRATION

Anorexia Associated with Weight Loss in Adult Patients with AIDS (2.1):

- The recommended adult starting dosage is 2.5 mg orally twice daily, one hour before lunch and dinner.
- See the full prescribing information for dosage titration to manage adverse reactions and to achieve desired therapeutic effect.

Nausea and Vomiting Associated with Chemotherapy in Adult Patients Who Failed Conventional Antiemetics (2.2):

- The recommended starting dosage is 5 mg/m^2, administered 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses per day. Administer the first dose on an empty stomach at least 30 minutes prior to eating; subsequent doses can be taken without regard to meals.
- See the full prescribing information for dosage titration to manage adverse reactions and to achieve desired therapeutic effect.

EPIDIOLEX- cannabidiol solution
Greenwich Biosciences, Inc.

EPIDIOLEX- cannabidiol solution
Greenwich Biosciences, Inc.

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, CV
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

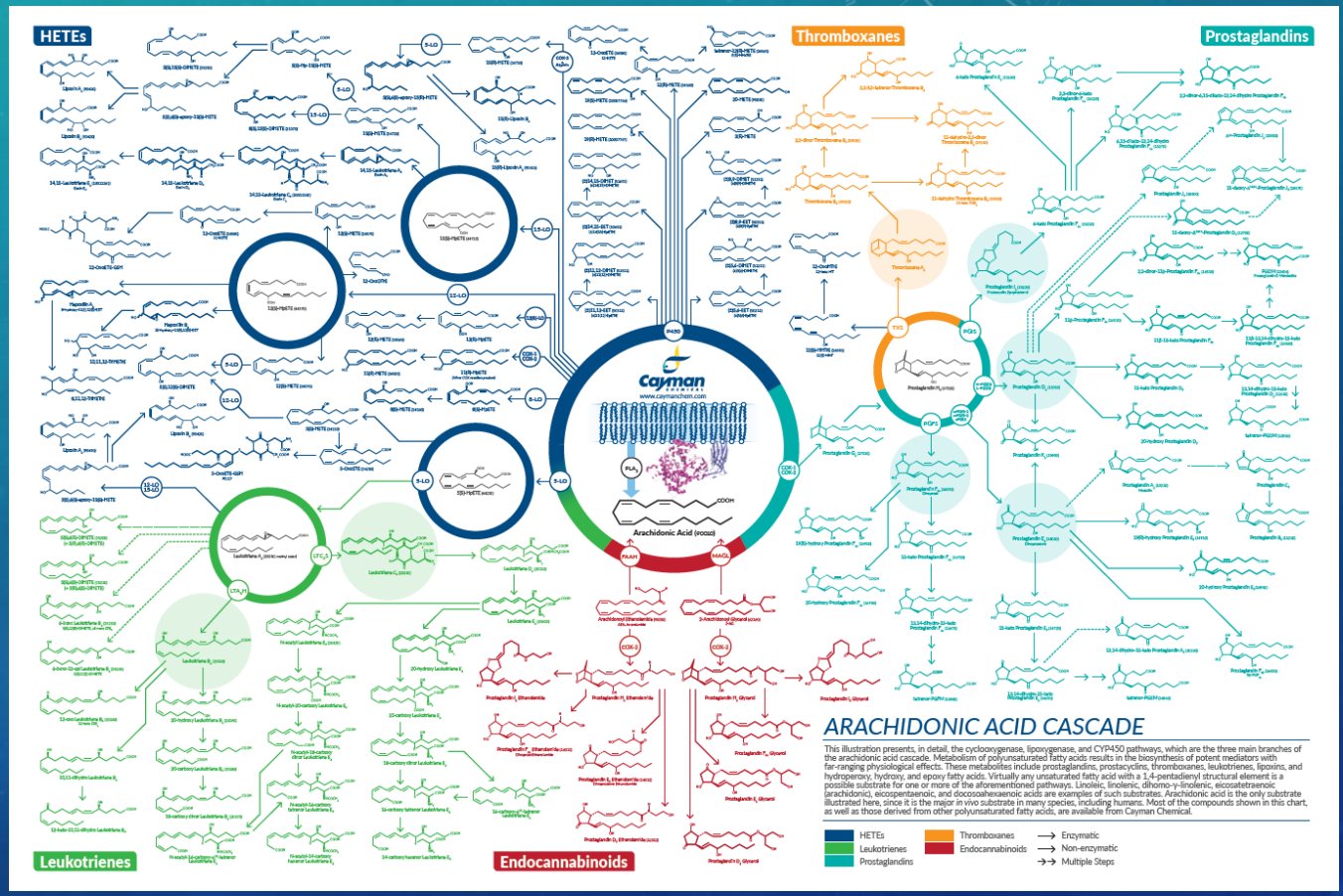
- Obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment. (2.1, 5.1)
- EPIDIOLEX is to be administered orally. (2.2)
- The recommended starting dosage is 2.5 mg/kg taken twice daily (5 mg/kg/day). After one week, the dosage can be increased to 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)

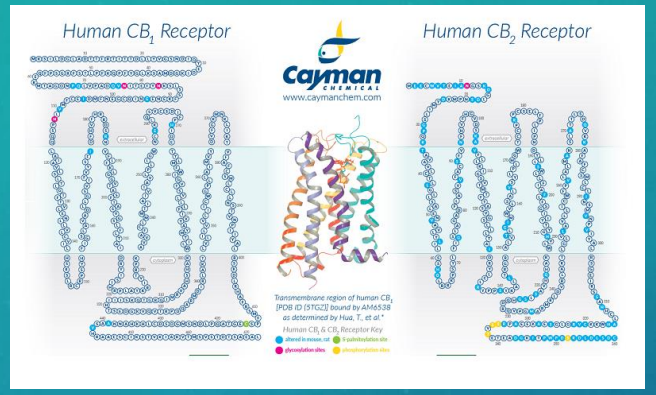
THE ENDOCANNABINOID SYSTEM

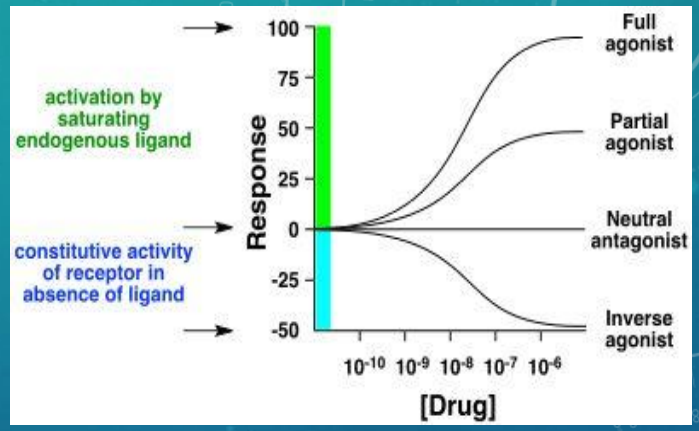
- The endogenous cannabinoid system has been described as “an ancient lipid signaling network which in mammals modulates neuronal functions, inflammatory processes, and is involved in the etiology of certain human lifestyle diseases, such as Crohn’s disease, atherosclerosis and osteoarthritis. The system is able to downregulate stress-related signals that lead to chronic inflammation and certain types of pain, but it is also involved in causing inflammation-associated symptoms, depending on the physiological context.”

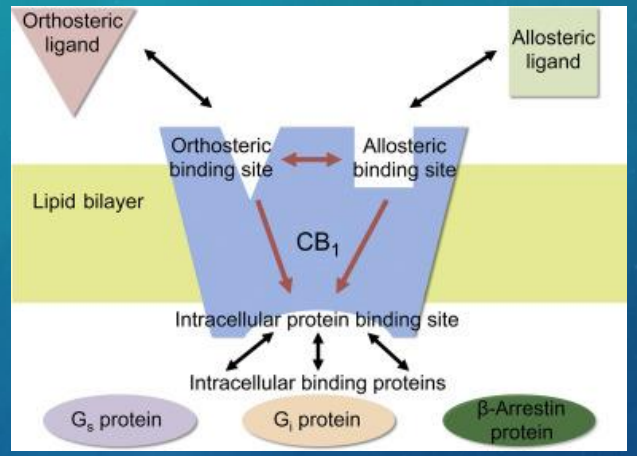


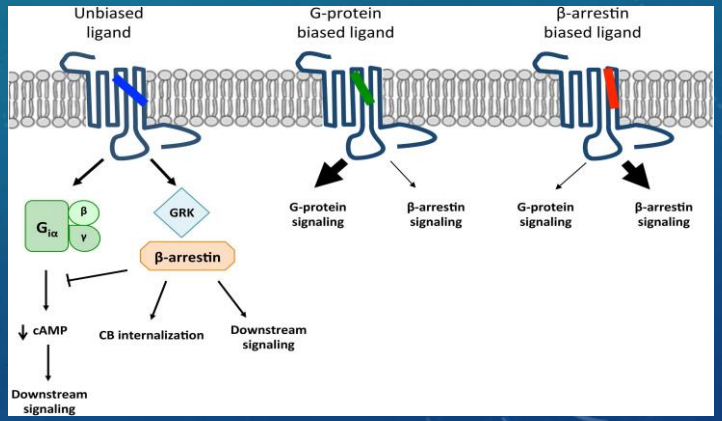
ENDOCANNABINOID RECEPTORS

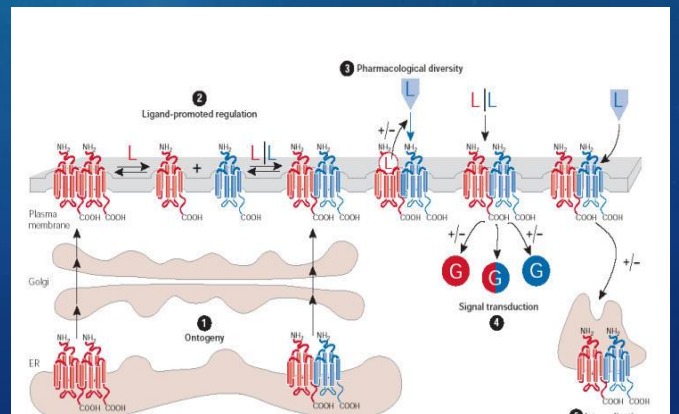
- Cannabinoid Receptors
  - CBR-1: CNS (brain [!!])
  - CBR-2: periphery (immune [!!])
  - G protein receptor
    - How
      - Agonist, antagonist, inverse (CBD)?
    - Where
      - Orthosteric vs. alloseric (CBD)
    - Which
      - Secondary messenger
    - What
      - Other receptors (opioids, GABA)
    - When
      - Immediate vs. delayed

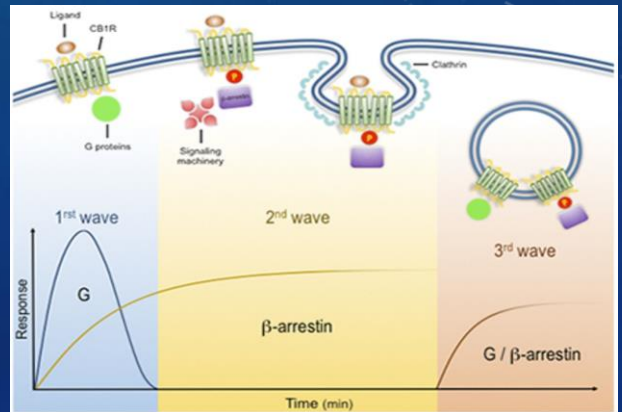












https://www.sciencedirect.com/science/article/pii/S0006295216304014
http://molpharm.aspetjournals.org/content/90/5/620
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1298963/

frontiers in
PHARMACOLOGY

REVIEW ARTICLE
published: 02 January 2014
doi: 10.3389/fphar.2013.00169

The cannabinoid receptor 1 associates with NMDA receptors to produce glutamatergic hypofunction: implications in psychosis and schizophrenia

Pilar Sánchez-Blázquez, María Rodríguez-Muñoz and Javier Garzón*

Neurofarmacología, Instituto Cajal, Consejo Superior de Investigaciones Científicas, Madrid, Spain

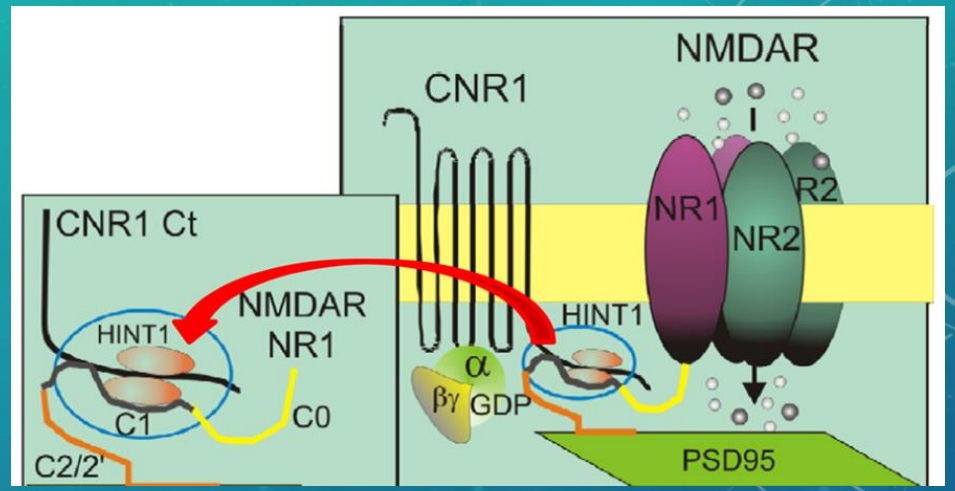
Edited by:
Maria Grazia Cascio, University of Aberdeen, UK

Reviewed by:
Caitlin Elissa McOmish, Columbia University, USA
Alline Cristina De Campos, Federal University of Minas Gerais, Brazil

Correspondence:
Javier Garzón, Neurofarmacología, Instituto Cajal, Consejo Superior de Investigaciones Científicas, Avenida Doctor Arce 37, 28002 Madrid, Spain
e-mail: jgarzon@cajal.csic.es

The endocannabinoid system is widespread throughout the central nervous system and its type 1 receptor (CB1) plays a crucial role in preventing the neurotoxicity caused by activation of glutamate *N*-methyl-D-aspartate receptors (NMDARs). Indeed, it is the activity of NMDARs themselves that provides the demands on the endogenous cannabinoids in order to control their calcium currents. Therefore, a physiological role of this system is to maintain NMDAR activity within safe limits, thereby protecting neural cells from excitotoxicity. Thus, cannabinoids may be able to control NMDAR overactivation-related neural dysfunctions; however, the major obstacles to the therapeutic utilization of these compounds are their psychotropic effects and negative influence on cognitive performance. Studies in humans have indicated that abuse of smoked cannabis can promote psychosis and even circumstantially precipitate symptoms of schizophrenia, although the latter appears to require a prior vulnerability in the individual. It is possible that cannabinoids provoke psychosis/schizophrenia reflecting a mechanism common to neuroprotection: the reduction of NMDAR activity. Cannabinoids are proposed to produce such effect by reducing the pre-synaptic release of glutamate or interfering with post-synaptic NMDAR-regulated signaling pathways. The efficacy of such control requires the endocannabinoid system to apply its negative influence in a manner that is proportional to the strength of NMDAR signaling. Thus, cannabinoids acting at the wrong time or exerting an inappropriate influence on their receptors may cause NMDAR hypofunction. The purpose of the present review is to draw the attention of the reader to the newly described functional and physical CB1–NMDAR association, which may elucidate the scenario required for the rapid and efficacious control of NMDAR activity. Whether alterations in these mechanisms may increase NMDAR hypofunction leading to vulnerability to schizophrenia will be outlined.

Keywords: cannabinoid receptors, *N*-methyl-D-aspartate receptor, HINT1 protein, glutamatergic hypofunction, cannabis abuse, schizophrenia, psychosis vulnerability, G-protein-coupled receptors



www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 3

Revie

Endocannabinoid control of glutamate NMDA receptors: the therapeutic potential and consequences of dysfunction

María Rodríguez-Muñoz[1], Pilar Sánchez-Blázquez[1], Manuel Merlos[2] and Javier Garzón-Niño[1]

[1] Department of Molecular, Cellular and Developmental Neurobiology, Laboratory of Neuropharmacology, Instituto Cajal, Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain

[2] Drug Discovery & Preclinical Development, Esteve, Barcelona, Spain

Correspondence to: María Rodríguez-Muñoz, email: mrodriguez@cajal.csic.es

Keywords: σ1R; HINT1 protein; GPCR-NMDAR coordination; convulsive disorders; mood disorders

Received: January 22, 2016 *Accepted: June 06, 2016* *Published: June 15, 2016*

ABSTRACT

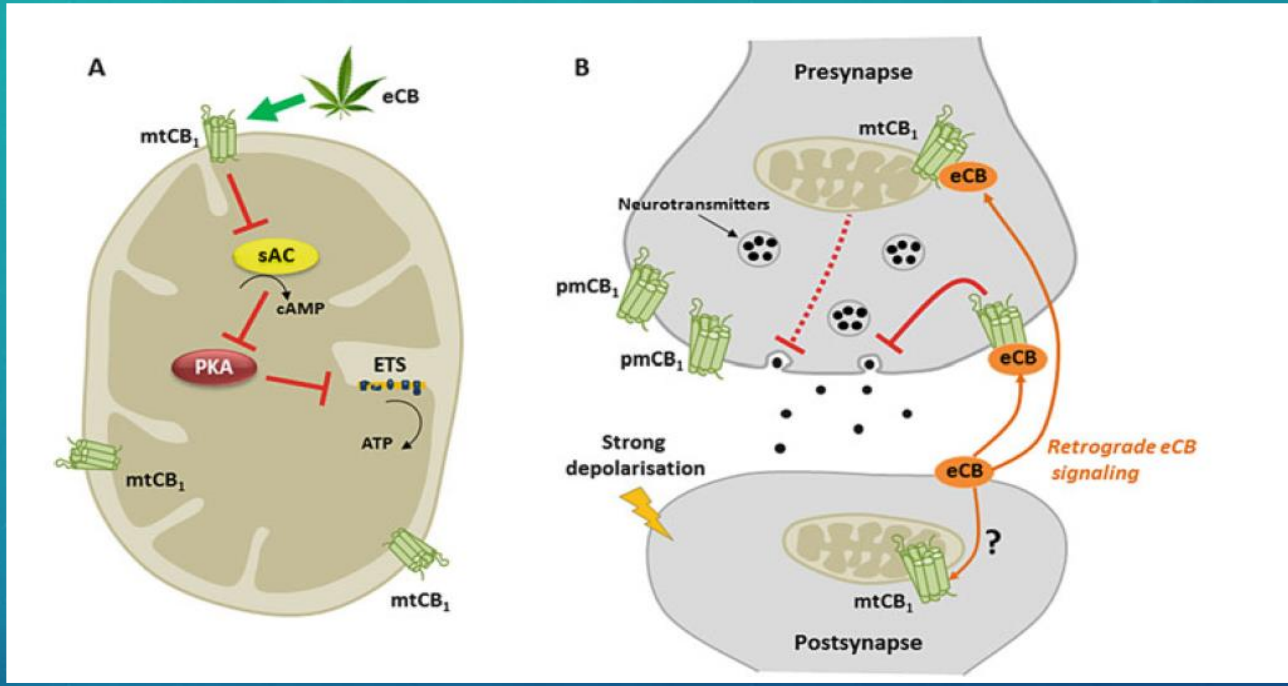
Glutamate is probably the most important excitatory neurotransmitter in the brain. The glutamate *N*-methyl-D-aspartate receptor (NMDAR) is a calcium-gated channel that coordinates with G protein-coupled receptors (GPCRs) to establish the efficiency of the synaptic transmission. Cross-regulation between these receptors requires the concerted activity of the histidine triad nucleotide-binding protein 1 (HINT1) and of the sigma receptor type 1 (σ1R). Essential brain functions like learning, memory formation and consolidation, mood and behavioral responses to exogenous stimuli depend on the activity of NMDARs. In this biological context, endocannabinoids are released to retain NMDAR activity within physiological limits. The efficacy of such control depends on HINT1/σ1R assisting in the physical coupling between cannabinoid type 1 receptors (CB1Rs) and NMDARs to dampen their activity. Subsequently, the calcium-regulated HINT1/σ1R protein tandem uncouples CB1Rs to prevent NMDAR hypofunction. Thus, early recruitment or a disproportionate cannabinoid induced response can bring about excess dampening of NMDAR activity, impeding its adequate integration with GPCR signaling. Alternatively, this control circuit can apparently be overridden in situations where bursts of NMDAR overactivity provoke convulsive syndromes. In this review we will discuss the possible relevance of the HINT1/σ1R tandem and its use by endocannabinoids to diminish NMDAR activity and their implications in psychosis/schizophrenia, as well as in NMDAR-mediated convulsive episodes.

MITOCHONDRIAL CB RECEPTORS

Endocannabinoids and Lipid Mediators in Brain Functions

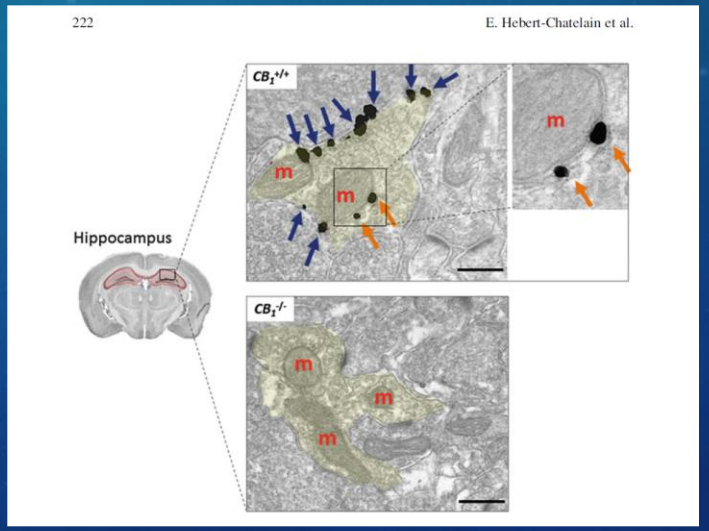
Cannabinoids and Mitochondria

Etienne Hebert-Chatelain, Giovanni Marsicano, and Tifany Desprez



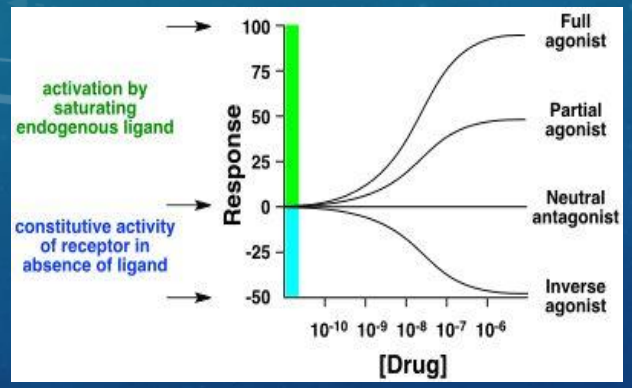
Impact on cell:

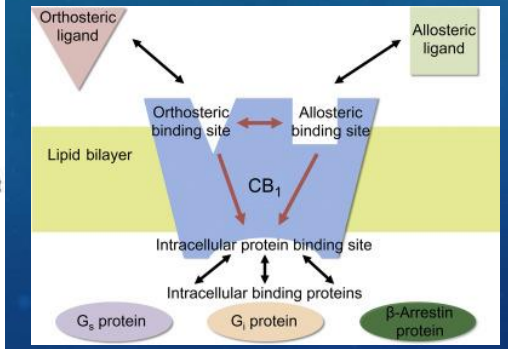
- Energy
- Production of monoamines
- Apoptosis
- Axonal / mitochondrial transport
- Calcium homeostasis



PHYTOCANNABINOIDS AND CANNABINOID RECEPTORS

- **THC: CB1 = CB2**
  - **Partial agonist**
- **CBD: ?**
  - **Poor affinity for CB1, CB2**
    - **Weak antagonist CB1**
    - **Inverse agonist CB2**
      - **Reverses endogenous activity**
  - **Allosteric binding?**
  - **Implications for safety, tolerance, physical dependence?**





RESEARCH PAPER

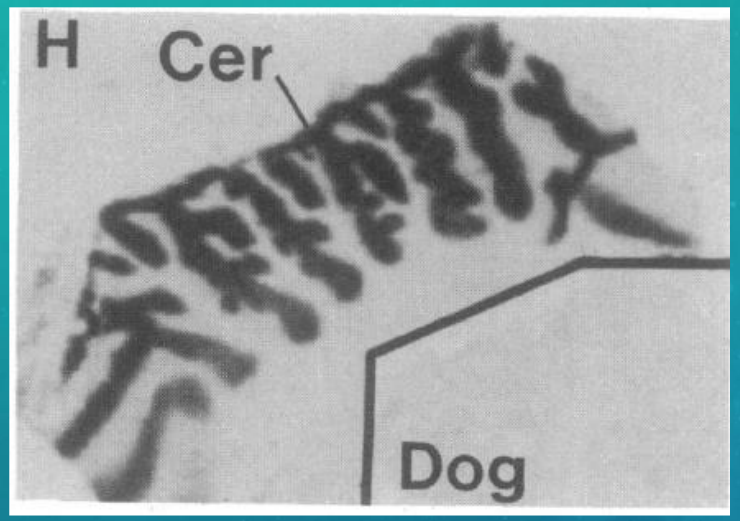
Cannabidiol displays unexpectedly high potency as an antagonist of CB_1 and CB_2 receptor agonists *in vitro*

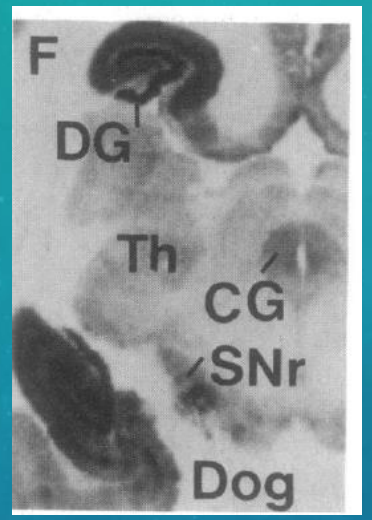
A Thomas[1], GL Baillie[1], AM Phillips[1], RK Razdan[2], RA Ross[1] and RG Pertwee[1]

[1]*School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, UK and* [2]*Organix Inc., Woburn, MA, USA*

Background and purpose: A nonpsychoactive constituent of the cannabis plant, cannabidiol has been demonstrated to have low affinity for both cannabinoid CB_1 and CB_2 receptors. We have shown previously that cannabidiol can enhance electrically evoked contractions of the mouse vas deferens, suggestive of inverse agonism. We have also shown that cannabidiol can antagonize cannabinoid receptor agonists in this tissue with a greater potency than we would expect from its poor affinity for cannabinoid receptors. This study aimed to investigate whether these properties of cannabidiol extend to CB_1 receptors expressed in mouse brain and to human CB_2 receptors that have been transfected into CHO cells.
Experimental approach: The $[^{35}S]GTP\gamma S$ binding assay was used to determine both the efficacy of cannabidiol and the ability of cannabidiol to antagonize cannabinoid receptor agonists (CP55940 and *R*-(+)-WIN55212) at the mouse CB_1 and the human CB_2 receptor.
Key results: This paper reports firstly that cannabidiol displays inverse agonism at the human CB_2 receptor. Secondly, we demonstrate that cannabidiol is a high potency antagonist of cannabinoid receptor agonists in mouse brain and in membranes from CHO cells transfected with human CB_2 receptors.
Conclusions and implications: This study has provided the first evidence that cannabidiol can display CB_2 receptor inverse agonism, an action that appears to be responsible for its antagonism of CP55940 at the human CB_2 receptor. The ability of cannabidiol to behave as a CB_2 receptor inverse agonist may contribute to its documented anti-inflammatory properties.

CANNABINOID RECEPTORS IN DOGS





Dogs have unique CBR cerebellar distribution responsible for unique ataxia behavior

Proc. Natl. Acad. Sci. USA
Vol. 87, pp. 1932–1936, March 1990
Neurobiology

Cannabinoid receptor localization in brain

(tetrahydrocannabinol/autoradiography/basal ganglia/hippocampus/cerebellum)

MILES HERKENHAM*†, ALLISON B. LYNN*, MARK D. LITTLE*, M. ROSS JOHNSON‡, LAWRENCE S. MELVIN§, BRIAN R. DE COSTA¶, AND KENNER C. RICE¶

*Unit on Functional Neuroanatomy, Building 36, Room 2D-15, National Institute of Mental Health, Bethesda, MD 20892; ‡Glaxo Inc., Research Triangle Park, NC 27709; §Central Research, Pfizer Inc., Groton, CT 06340; and ¶Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD 20892

Communicated by Walle J. H. Nauta, December 7, 1989

THC much more potent than CBD in dogs

...logs in *in vitro* and *in vivo* animal a...

Drug	K_i, nM	Dog ataxia, mg/kg	Human high % Δ^9-THC	Human high mg
CP 55,940 (−AC)	15 ± 3 (K_d)			
CP 56,667 (+AC)	470 ± 57			
CP 55,244 (−ACD)	1.4 ± 0.3			
CP 55.243 (+ACD)	18,000 ± 1100			
CP 50,556	14 ± 2		400	0.5
CP 53,870	26,000 ± 3500			
CP 54,939	14 ± 2	0.05		
Nabilone	120 ± 13	0.03	500	1
β-HHC	124 ± 17	0.1		
α-HHC	2,590 ± 360	0.5		
(−)-Δ^9-THC	420 ± 51	0.5	100	1
(+)-Δ^9-THC	7,700 ± 2100	>2.0		
Δ^8-THC	498 ± 52	0.5	75	2
11-OH-Δ^9-THC	210 ± 56	0.05	120	1
TMA-Δ^8-THC	2,300 ± 1000			
8β-OH-Δ^9-THC	4,200 ± 700		20	10
8α-OH-Δ^9-THC	8,700 ± 1800		25	10
11-OH-Cannabinol	800 ± 150			
Cannabinol	3,200 ± 450		0	>15
Cannabidiol	53,000 ± 6700	Inactive	0	>30
Cannabigerol	275,000	>7.0	0	
9-COOH-11-nor-Δ^9-THC	75,000			
9-COOH-11-nor-Δ^8-zTHC	Inactive			
Regression on K_i:R^2		0.96	0.90	
Significance (2-tailed)		$P < 0.0001$	$P < 0.0001$	

PLOS ONE

RESEARCH ARTICLE

Spatial distribution of cannabinoid receptor type 1 (CB_1) in normal canine central and peripheral nervous system

Jessica Freundt-Revilla[1,2☯*], **Kristel Kegler**[2,3☯¤], **Wolfgang Baumgärtner**[2,3], **Andrea Tipold**[1,2]

1 Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover Foundation, Hannover, Germany, 2 Center for Systems Neuroscience, Hannover, Germany, 3 Department of Pathology, University of Veterinary Medicine Hannover Foundation, Hannover, Germany

☯ These authors contributed equally to this work.
¤ Current address: Institute for Animal Pathology, Vetsuisse-Faculty, University of Bern, Bern, Switzerland
* Jessica.Freundt.Revilla@tiho-hannover.de

OPEN ACCESS

Citation: Freundt-Revilla J, Kegler K, Baumgärtner W, Tipold A (2017) Spatial distribution of

Abstract

The endocannabinoid system is a regulatory pathway consisting of two main types of cannabinoid receptors (CB_1 and CB_2) and their endogenous ligands, the endocannabinoids. The CB_1 receptor is highly expressed in the central and peripheral nervous systems (PNS) in mammalians and is involved in neuromodulatory functions. Since endocannabinoids were

of basket cell processes [21, 22]. We found identical patterns of immunoreactivity in this particular region. Higher receptor-binding levels have been found in the canine cerebellum compared to humans [3], which might induce less motor depression in humans under effects of THC [66, 67]. Interestingly, the use of THC and cannabinoid analogs in experimental studies showed ataxia and even prostration at higher dosages in dogs [67, 68]. High concentrations of cannabinoid expression in the basal ganglia and cerebellum are consistent with their involvement in the initiation and coordination of movement [3, 69] and explain this behavioural changes in dogs at high doses of THC and cannabinoid analogs.

EPIDIOLEX- cannabidiol solution
Greenwich Biosciences, Inc.

2.2 Dosage Information

- EPIDIOLEX is to be administered orally.
- The starting dosage is 2.5 mg/kg 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).
- Patients who are tolerating EPIDIOLEX at 5 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated. For patients in whom a more rapid titration from 10 mg/kg/day to 20 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day. Administration of the 20 mg/kg/day dosage resulted in somewhat greater reductions in seizure rates than the recommended maintenance dosage of 10 mg/kg/day, but with an increase in adverse reactions.

Dose starts at 2.5 mg/kg q 12 and is increased up to 10 mg/kg q 12

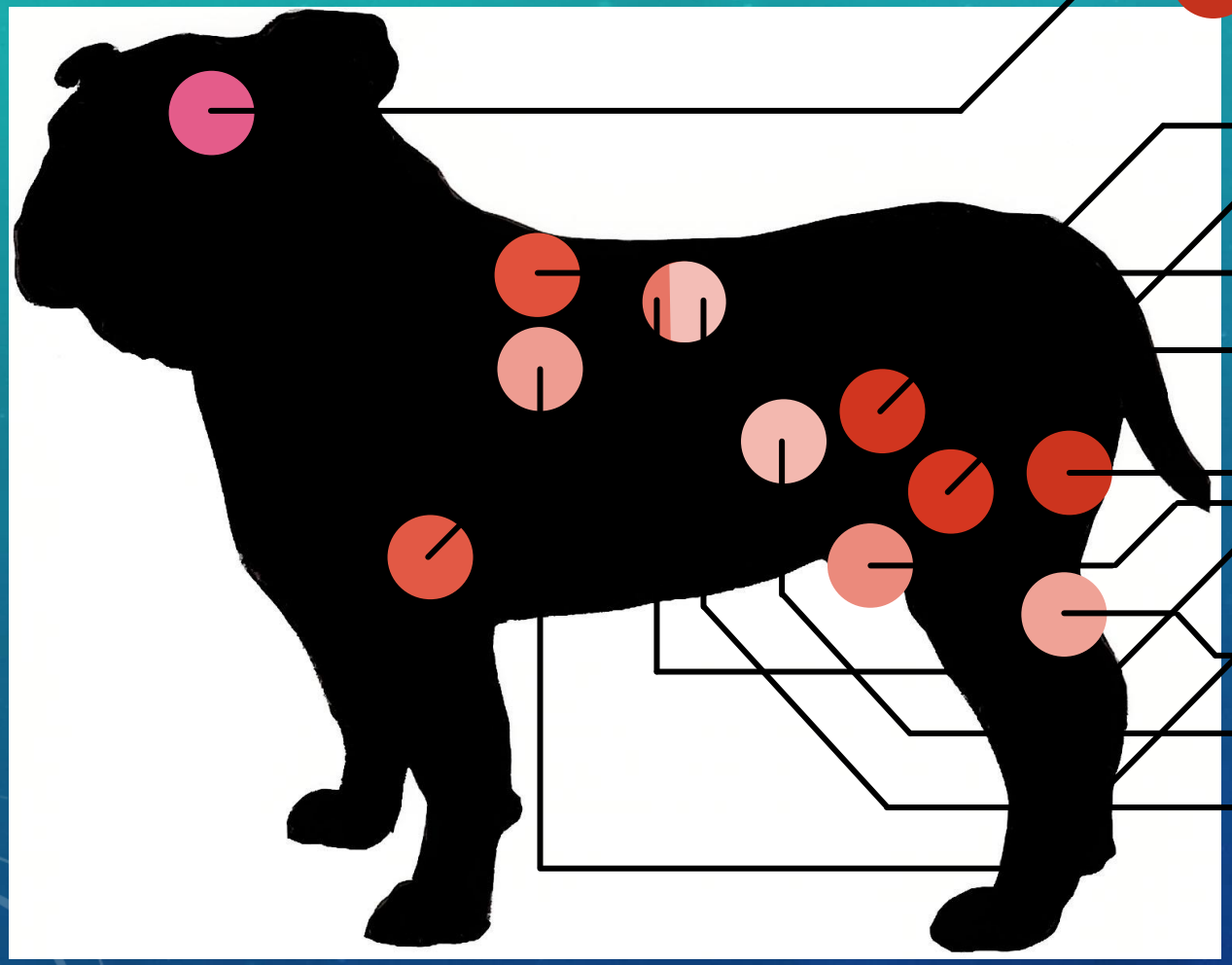
MARINOL- dronabinol capsule
AbbVie Inc.

Starting Dosage

The recommended adult starting dosage of MARINOL is 2.5 mg orally twice daily, one hour before lunch and dinner.

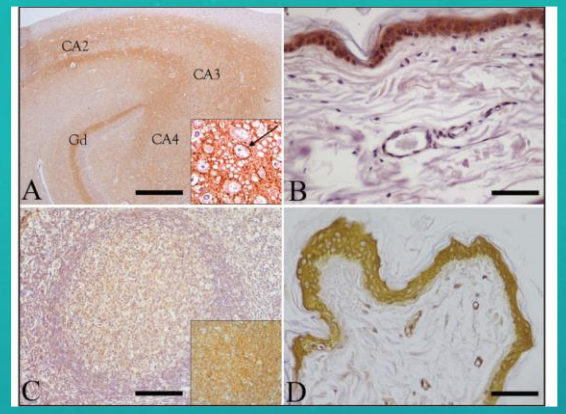
Dose starts at 2.5 mg q 12 and is increased up to 10 mg/kg q 12

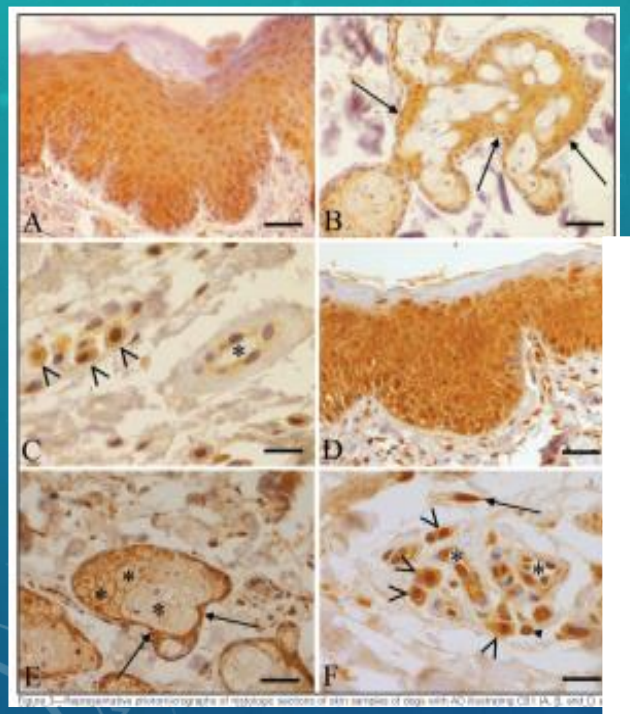
RESULTS: QUANTIFICATION



Tissue	CB1/Housekeeping
Brain	7.94E-03
Blood	6.98E-03
Testicles	5.56E-03
Fat (Visceral)	4.43E-03
Uterus	3.91E-03
Spinal Cord	1.13E-03
Fat (Lymph Node)	8.13E-04
Kidney (Pelvis)	2.81E-04
Skin	1.18E-04
Lung	5.84E-05
Lymph Node	4.79E-05
Liver	1.94E-05
Kidney (Cortex)	1.57E-05

CB1





Cannabinoid receptor type 1 and 2 expression in the skin of healthy dogs and dogs with atopic dermatitis

Luca Campora, DVM, PhD; Vincenzo Miragliotta, DVM, PhD; Emanuele Ricci, DVM, PhD; Luigia Cristino, Biol D, PhD; Vincenzo Di Marzo, Chem D, PhD; Francesco Albanese, DVM; Maria Federica della Valle, MSc; Francesca Abramo, DVM

Objective—To determine the distribution of cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) in skin (including hair follicles and sweat and sebaceous glands) of clinically normal dogs and dogs with atopic dermatitis (AD) and to compare results with those for positive control samples for CB1 (hippocampus) and CB2 (lymph nodes).

Sample—Skin samples from 5 healthy dogs and 5 dogs with AD and popliteal lymph node cadavers of dogs.

...re immunohistochemically localized in formalin-fixed, ...sue samples.

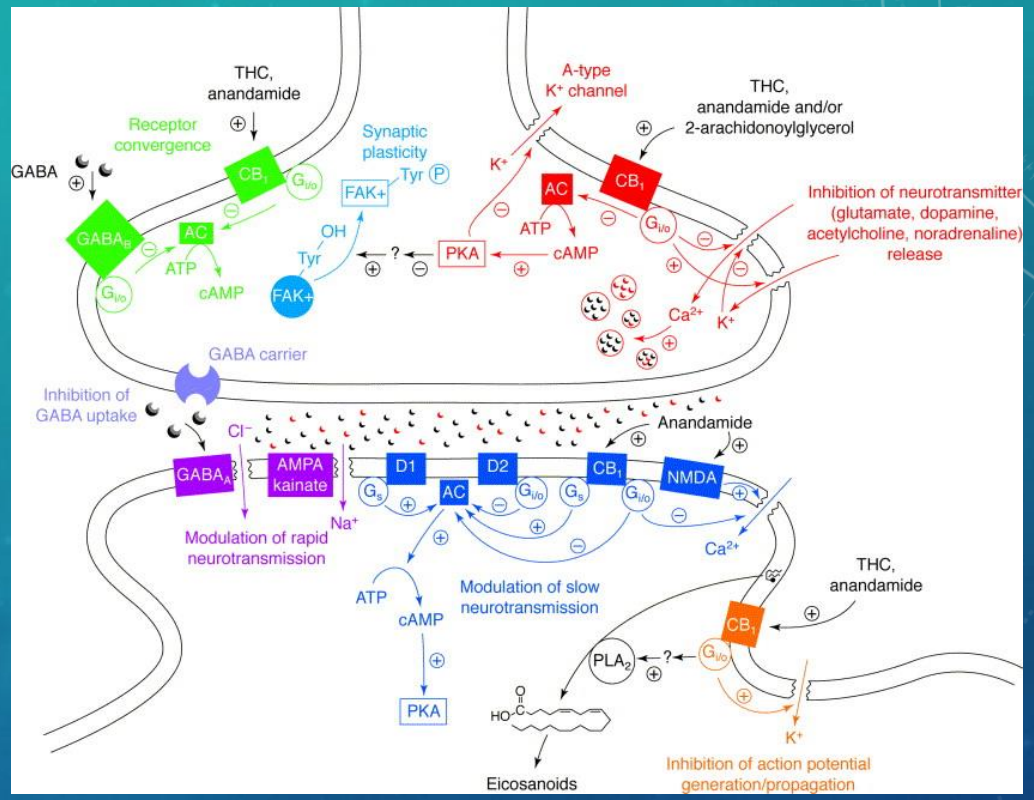
...hy dogs, CB1 and CB2 immunoreactivity was detected in ...mis and in cells in the dermis, including perivascular cells ...asts, and endothelial cells. In skin samples of dogs with ...ity was stronger than it was in skin samples of healthy ...mples, CB1 immunoreactivity was detected in all areas ...unoreactivity was detected in B-cell zones of lymphoid

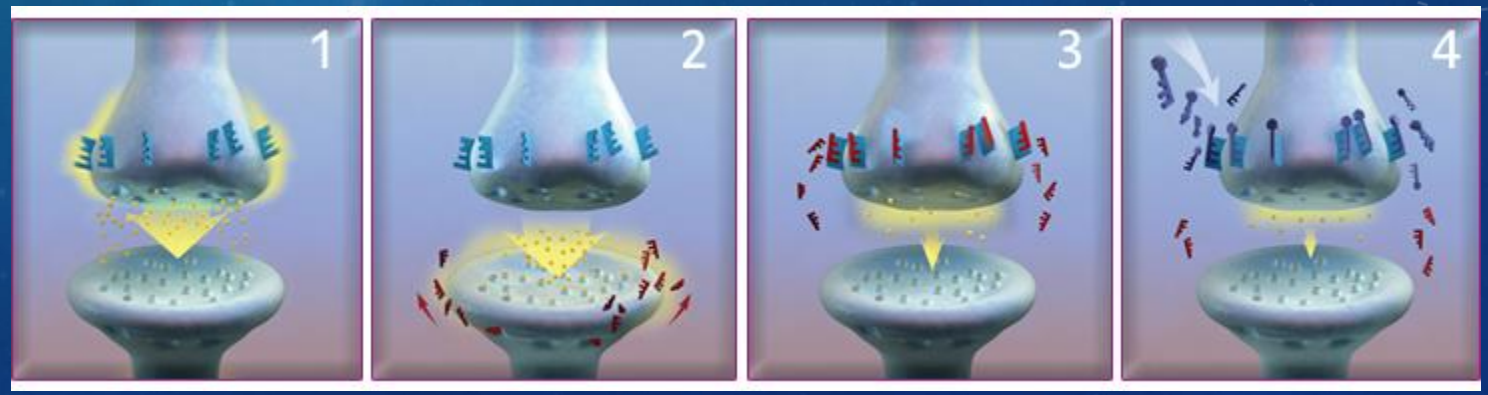
...nce—The endocannabinoid system and cannabimimetic ...s of allergic inflammatory disorders in various species of ...study contributed to knowledge of the endocannabinoid ...may be a target for treatment of immune-mediated and ...gic skin diseases in dogs. (Am J Vet Res 2012;73:989–995)

* Cost calculations based on CBD found in tests by ConsumerLab divided by price paid by ConsumerLab. For details, see Results Table below.

NON-CB RECEPTOR TARGETS

- Neurotransmitter modulation
  - Acetylcholine
  - Norepinephrine
  - Dopamine
  - Serotonin
  - Gaba (benzodiazipenes)
  - Glutamate
  - D-Aspartate
- Channels
  - N, L, P/Q calcium
  - A, M potassium
- Receptors





CHANNELS
2019, VOL. 13, NO. 1, 162–167
https://doi.org/10.1080/19336950.2019.1615824

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Cannabinoid interactions with ion channels and receptors

Abeline Rose Watkins

Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, BC, Canada

ABSTRACT

Cannabidiol (CBD), the non-psychoactive component of *Cannabis sativa*, acts on a diverse selection of membrane proteins with promising therapeutic potential in epilepsy and chronic pain. One such protein is the voltage-gated sodium channel (Na_v). CBD shows a lack of specificity for sodium channels; however, the method of interaction is still unknown. In this review, we will outline the studies that report reproducible results of CBD and other cannabinoids changing membrane channel function, with particular interest on Na_v. Na_v are implicated in fatal forms of epilepsy and are also associated with chronic pain. This makes Na_v potential targets for CBD interaction since it has been reported to reduce pain and seizures. One potential method of interaction that is of interest in this review is whether CBD affects channel function by altering lipid bilayer properties, independent of any possible direct interaction with membrane channels. CBD's ability to interact with its targets is a novel and important discovery. This discovery will not only prompt further research towards CBD's characterization, but also promotes the application of cannabinoids as potentially therapeutic compounds for diseases like epilepsy and pain.

ARTICLE HISTORY
Received 27 March 2019
Revised 29 April 2019
Accepted 30 April 2019

KEYWORDS
Cannabidiol; CBD; ion channels; review; membrane fluidity; cannabinoids

Table 1. Quantitative results of Cannabidiol's membrane protein interactions by target, cell type, and IC50 or EC50. Missing IC50 values indicate that dose–response curves were not produced, but significant effects were demonstrated.

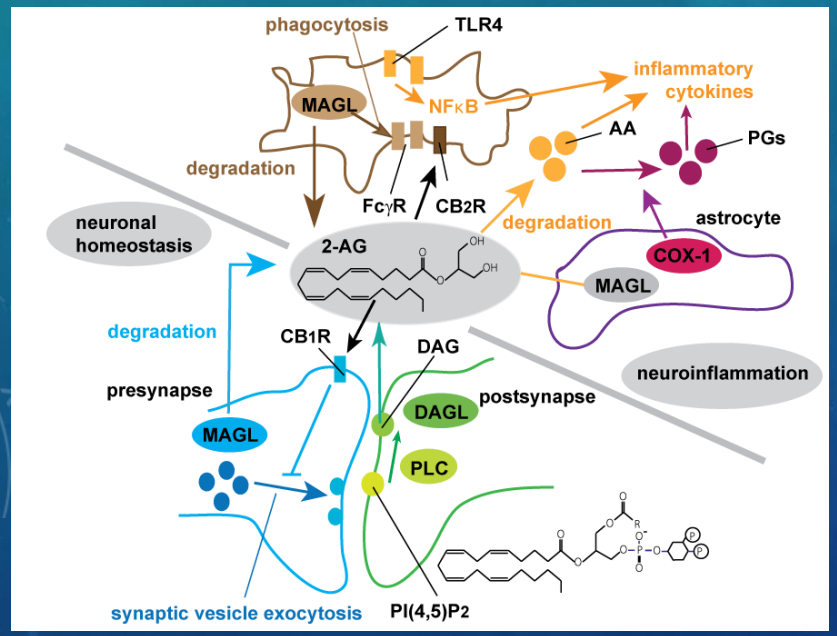
	Target	Cell type	IC50 (μM)
Channels	$Na_v1.1$	HEK-293	2.0 ± 0.1 [20]
	$Na_v1.2$	HEK-293	2.9 ± 0.1 [20]
		iPSCs	1.3 ± 0.1 [20]
	$Na_v1.3$	HEK-293	3.3 ± 0.1 [20]
	$Na_v1.4$	HEK-293	1.9 ± 0.1 [20]
	$Na_v1.5$	HEK-293	3.8 ± 0.2 [20]
	$Na_v1.6$	HEK-293	3.0 ± 0.1 [20]
	$Na_v1.7$	HEK-293	2.9 ± 0.1 [20]
	NaChBac	HEK-293	1.5 ± 0.2 [20]
	$K_v2.1$	HEK-293	3.7 ± 0.8 [20]
	TRPM8	HEK-293	0.06 ± 0.01 [26]
	$Ca_v3.1$	HEK-293	0.813* [27]
	$Ca_v3.2$	HEK-293	0.776* [27]
	$Ca_v3.3$	HEK-293	3.63* [27]
	VDAC1	Planar lipid bilayer	–[18]
Transporters	Adenosine uptake via ENT1	EOC-20 microglia	0.12 [28]
	Thymidine uptake via ENT1	EOC-20 microglia	0.19 [28]
Receptors	GPR55	HEK-293	0.445 ± 0.067 [29]
	H5-HT1aR	CHO Cells	–[30]
	5-HT2aR	CHO Cells	–[30]
	Target	Cell Type	EC50 (μM)
Channels	TRPV1	HEK-293	1.0 ± 0.1[26]
	TRPV2	HEK-293	1.25 ± 0.23[26]
	TRPA1	HEK-293	0.11 ± 0.05[26]
Receptors	α_1 homomers GlyRs	n/a	132.4 ± 12.3[25]
	$\alpha_1\beta_1$ heteromers GlyRs	n/a	144.3 ± 22.7 [25]

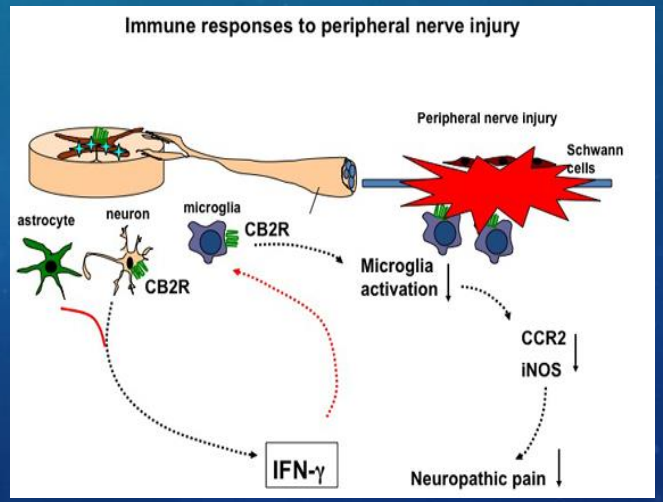
* Numbers calculated from pEC50 values

COMBINATION ANALGESIC THERAPY

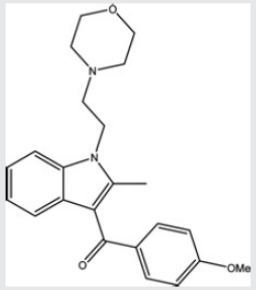
- Opioids
  - Enhanced mu agonist activity
- NSAIDs
  - Reduced dose
- Alpha-2 agonists
- TRVP-1 antagonists

- Inhibition of cannabinoid metabolism
  - Endogenous
    - Cannabidol?
  - Therapeutic
    - Particularly inflammatory pain
    - Inhibitors
      - FAAH, MAGL
      - Increases AEA/2-AG





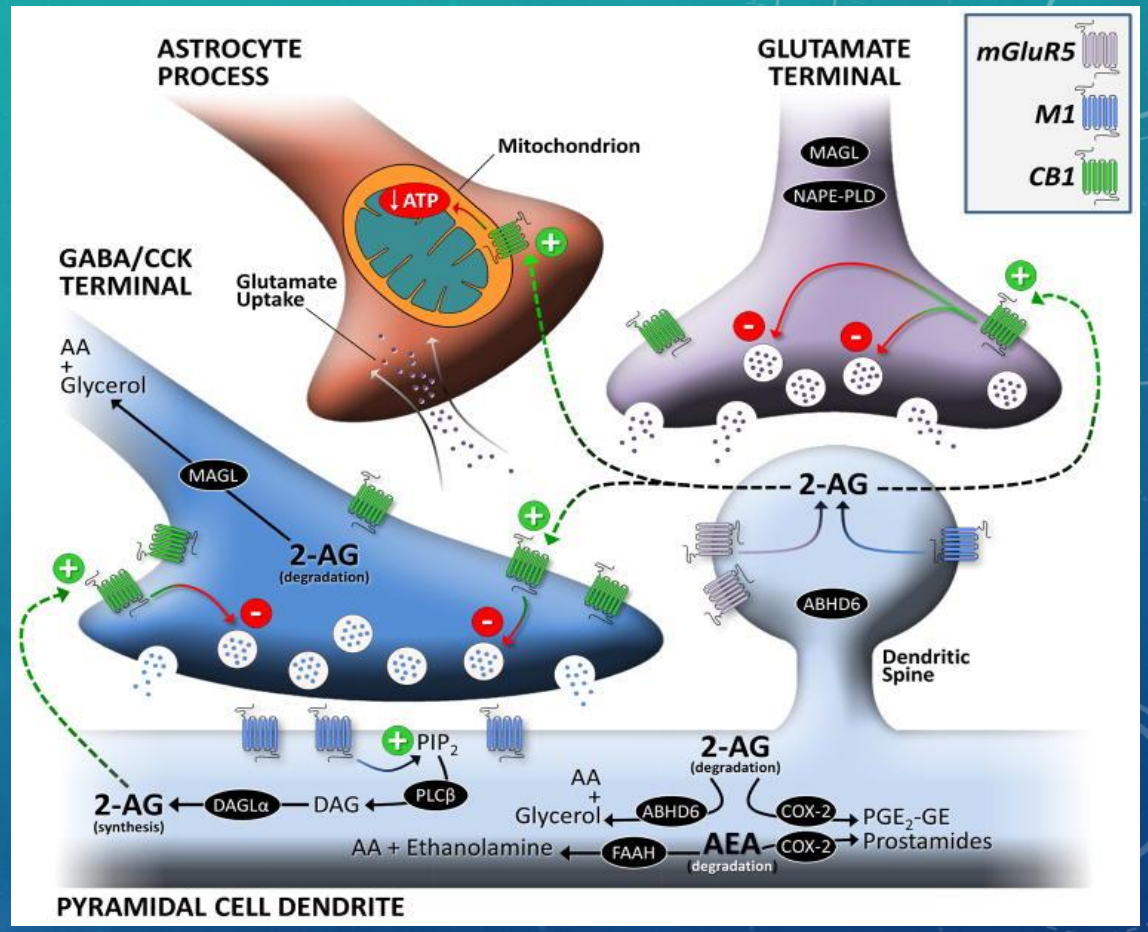
Compound
Pravadoline



Dual CB agonist/COX-inhibitory compound (D'Ambra et al., 1992).

(CLASSIC) ENDOGENOUS CANNABINOID LIGAND

- Formed in situ
- Post-synaptic neuron
- Stimulus
  - Intracellular calcium
- Endocannabinoid (eCB) synthesis
- Release into synaptic cleft
- Transported (?) to presynaptic neuron
- Uptake by neuron (proteins?)
- Modulation of neurotransmitter release
- Retrograde movement
- eCB degradation



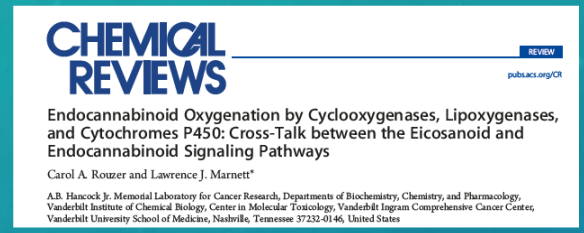
Published in final edited form as:
Biol Psychiatry. 2016 April 1; 79(7): 516–525. doi:10.1016/j.biopsych.2015.07.028.

An introduction to the endogenous cannabinoid system

Hui-Chen Lu[1,2] and Ken Mackie[1,2,*]
[1]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN USA
[2]Linda and Jack Gill Center for Biomolecular Science, Indiana University, Bloomington, IN USA

(CLASSIC) ENDOGENOUS CANNABINOID LIGANDS

- Arachidonic Acid (AA) metabolites
  - The "bliss" molecule: anandamide (AEA) (CB-1>2)
  - 2-arachidonoylglycerol (2AG) (CB1=CB2)
  - Others
  - Specific enzymes but…
  - COX, LOX and CYP 450 "cross talk"
    - Substrates for COX and LOX
  - Constitutive vs. induced
- Metabolism to AA
  - Fatty acid amide hydrolase (AEA)
  - Monoacylglycerol (MAGL) (2-AG)


CHEMICAL REVIEWS

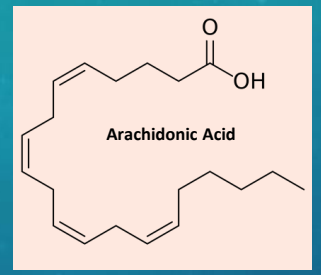
REVIEW

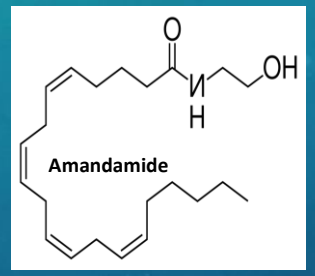
pubs.acs.org/CR

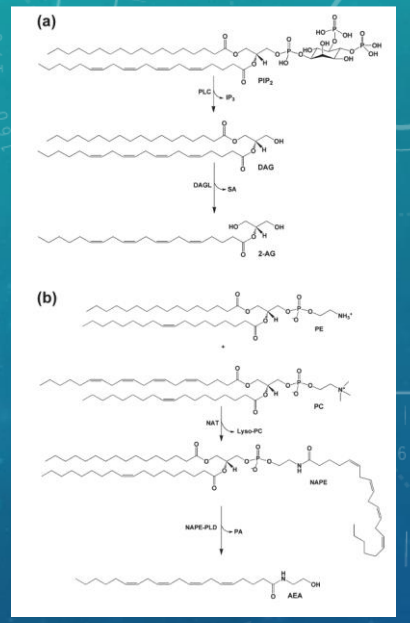
Endocannabinoid Oxygenation by Cyclooxygenases, Lipoxygenases, and Cytochromes P450: Cross-Talk between the Eicosanoid and Endocannabinoid Signaling Pathways

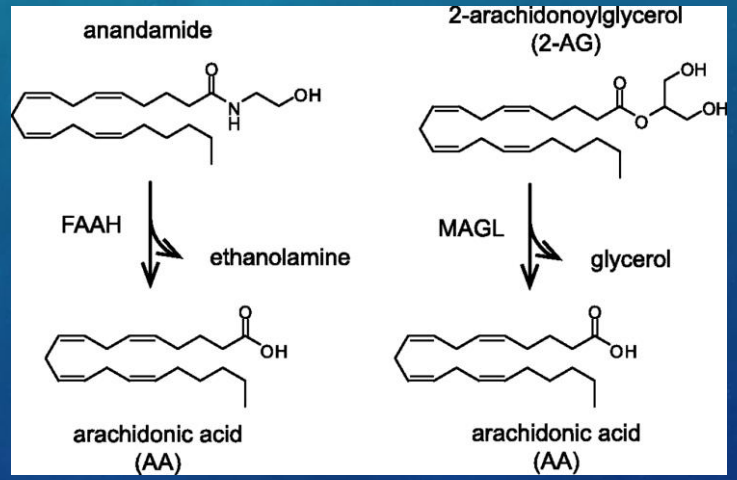
Carol A. Rouzer and Lawrence J. Marnett*

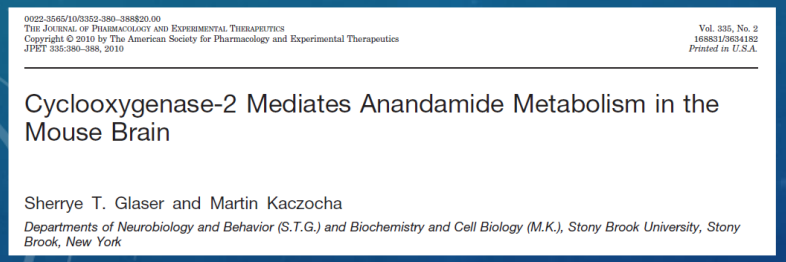
A.B. Hancock Jr. Memorial Laboratory for Cancer Research, Departments of Biochemistry, Chemistry, and Pharmacology, Vanderbilt Institute of Chemical Biology, Center in Molecular Toxicology, Vanderbilt Ingram Comprehensive Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-0146, United States










0022-3565/10/3352-380–388$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 2010 by The American Society for Pharmacology and Experimental Therapeutics
JPET 335:380–388, 2010

Vol. 335, No. 2
168831/3634182
Printed in U.S.A.

Cyclooxygenase-2 Mediates Anandamide Metabolism in the Mouse Brain

Sherrye T. Glaser and Martin Kaczocha

Departments of Neurobiology and Behavior (S.T.G.) and Biochemistry and Cell Biology (M.K.), Stony Brook University, Stony Brook, New York


nature REVIEWS DRUG DISCOVERY

Review

Nature Reviews Drug Discovery **11**, 292-310 (April 2012) | doi:10.1038/nrd3673

Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain

Bernard P. Roques, Marie-Claude Fournié-Zaluski & Michel Wurm

Chronic pain remains unsatisfactorily treated, and few novel painkillers have reached the market in the past century. Increasing the levels of the main endogenous opioid peptides — enkephalins — by inhibiting their two inactivating ectopeptidases, neprilysin and aminopeptidase N, has analgesic effects in various models of inflammatory and neuropathic pain. Stemming from the

ARTICLE TOOLS

Send to a friend
Export citation
Export references
Rights and permissions
Order commercial reprints

SEARCH PUBMED FOR

Bernard P. Roques

https://www.cell.com/trends/neurosciences/fulltext/S0166-2236(98)01283-1?code=cell-site

IMPACT AND MANIPULATION OF THE ECS

Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions that Upregulate the Endocannabinoid System

John M. McPartland[1,2]*, Geoffrey W. Guy[1], Vincenzo Di Marzo[3]

1 GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire, United Kingdom, **2** Department of Family Medicine, University of Vermont, Burlington, Vermont, United States of America, **3** Endocannabinoid Research Group, Istituto di Chimica Biomoleculare, CNR, Via Campi Flegrei, Pozzuoli, Napoli, Italy

Abstract

Background: The "classic" endocannabinoid (eCB) system includes the cannabinoid receptors CB_1 and CB_2, the eCB ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and their metabolic enzymes. An emerging literature documents the "eCB deficiency syndrome" as an etiology in migraine, fibromyalgia, irritable bowel syndrome, psychological disorders, and other conditions. We performed a systematic review of clinical interventions that enhance the eCB system—ways to upregulate cannabinoid receptors, increase ligand synthesis, or inhibit ligand degradation.

Methodology/Principal Findings: We searched PubMed for clinical trials, observational studies, and preclinical research. Data synthesis was qualitative. Exclusion criteria limited the results to 184 *in vitro* studies, 102 *in vivo* animal studies, and 36 human studies. Evidence indicates that several classes of pharmaceuticals upregulate the eCB system, including analgesics (acetaminophen, non-steroidal anti-inflammatory drugs, opioids, glucocorticoids), antidepressants, antipsychotics, anxiolytics, and anticonvulsants. Clinical interventions characterized as "complementary and alternative medicine" also upregulate the eCB system: massage and manipulation, acupuncture, dietary supplements, and herbal medicines. Lifestyle modification (diet, weight control, exercise, and the use of psychoactive substances—alcohol, tobacco, coffee, cannabis) also modulate the eCB system.

Conclusions/Significance: Few clinical trials have assessed interventions that upregulate the eCB system. Many preclinical studies point to other potential approaches; human trials are needed to explore these promising interventions.

Citation: McPartland JM, Guy GW, Di Marzo V (2014) Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions that Upregulate the Endocannabinoid System. PLoS ONE 9(3): e89566. doi:10.1371/journal.pone.0089566

Editor: Andrej A. Romanovsky, St. Joseph's Hospital and Medical Center, United States of America

Received September 8, 2013; **Accepted** January 21, 2014; **Published** March 12, 2014

Funding: This study was initially supported by an AssocPro (Associate Professor) grant, Unitec New Zealand to JM; subsequent funding by GW Pharmaceuticals. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: We have the following interests. This study was partly funded by GW Pharmaceuticals. John McPartland has received research grants from GW Pharmaceuticals and serves on its scientific advisory board. Geoffrey Guy is CEO of GW Pharmaceuticals, and Vincenzo DiMarzo has received research grants from GW Pharmaceuticals and serves as a research consultant. There are no patents, products in development or marketed products to declare. This does not alter our adherence to all the PLOS ONE policies on sharing data and materials, as detailed online in the guide for authors.

* E-mail: mcpruitt@myfairpoint.net

- Endocannabinoid (eCB) deficiency syndrome
  - Migraine, fibromyalgia, IBS, psychological disorders
- Upregulated by
  - Drugs: analgesics, glucocorticoids, antidepressants, antipsychotics, anxiolytics, anticonvulsants
  - Dietary supplements
    - PUFA, probiotics, other cannabinomimetic plants

Endocannabinoids in the dog

PLOS ONE

RESEARCH ARTICLE

The endocannabinoid system in canine Steroid-Responsive Meningitis-Arteritis and Intraspinal Spirocercosis

Jessica Freundt-Revilla[1,2]*, Franciska Heinrich[2,3], Alexander Zoerner[4], Felix Gesell[1], Martin Beyerbach[5], Merav Shamir[6], Anna Oevermann[7], Wolfgang Baumgärtner[2,3], Andrea Tipold[1,2]

1 Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover, Hannover, Germany, 2 Center for Systems Neuroscience, Hannover, Germany, 3 Department of Pathology, University of Veterinary Medicine Hannover, Hannover, Germany, 4 Institute for Clinical Pharmacology, Hannover Medical School, Hannover, Germany, 5 Institute for Biometry, Epidemiology, and Information Processing, University of Veterinary Medicine Hannover, Hannover, Germany, 6 Koret School of Veterinary Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel, 7 Department Clinical Research and Veterinary Public Health, Vetsuisse Faculty, University of Bern, Bern, Switzerland

* Jessica.Freundt.Revilla@tiho-hannover.de

OPEN ACCESS

Citation: Freundt-Revilla J, Heinrich F, Zoerner A, Gesell F, Beyerbach M, Shamir M, et al. (2018) The endocannabinoid system in canine Steroid-Responsive Meningitis-Arteritis and Intraspinal Spirocercosis. PLoS ONE 13(2): e0187197. https://doi.org/10.1371/journal.pone.0187197

Editor: Vincenzo Miragliotta, University of Pisa, ITALY

Received: November 25, 2016

Accepted: October 16, 2017

Published: February 6, 2018

Data Availability Statement: All relevant data are within the paper.

Funding: This publication was supported by Deutsche Forschungsgemeinschaft and University of Veterinary Medicine Hannover, Foundation within the funding programme Open Access Publishing. JFR recieved funding from the Deutscher Akademischer Austauschdienst (DAAD), Grant number: PKZ/12/92958 (https://www.daad.de). The funders had no role in study design, data

Abstract

Endocannabinoids (ECs) are involved in immunomodulation, neuroprotection and control of inflammation in the central nervous system (CNS). Activation of cannabinoid type 2 receptors (CB2) is known to diminish the release of pro-inflammatory factors and enhance the secretion of anti-inflammatory cytokines. Furthermore, the endocannabinoid 2-arachidonoyl glycerol (2-AG) has been proved to induce the migration of eosinophils in a CB2 receptor-dependent manner in peripheral blood and activate neutrophils independent of CB activation in humans. The aim of the current study was to investigate the influence of the endocannabinoid system in two different CNS inflammatory diseases of the dog, i.e. Steroid-Responsive Meningitis-Arteritis (SRMA) and Intraspinal Spirocercosis (IS). The two main endocannabinoids, anandamide (AEA) and 2-AG, were quantified by mass spectrometry in CSF and serum samples of dogs affected with Steroid- Responsive Meningitis-Arteritis in the acute phase (SRMA A), SRMA under treatment with prednisolone (SRMA Tr), intraspinal Spirocercosis and healthy dogs. Moreover, expression of the CB2 receptor was evaluated in inflammatory lesions of SRMA and IS and compared to healthy controls using immunohistochemistry (IHC). Dogs with SRMA A showed significantly higher concentrations of total AG and AEA in serum in comparison to healthy controls and in CSF compared to SRMA Tr ($p<0.05$). Furthermore, dogs with IS displayed the highest ECs concentrations in CSF, being significantly higher than in CSF samples of dogs with SRMA A ($p<0.05$). CSF samples that demonstrated an eosinophilic pleocytosis had the highest levels of ECs, exceeding those with neutrophilic pleocytosis, suggesting that ECs have a major effect on migration of eosinophils in the CSF. Furthermore, CB2 receptor expression was found in glial cells in the spinal cord of healthy dogs, whereas in dogs with SRMA and IS, CB2 was strongly expressed not only in glial cells but also on the cellular surface of infiltrating leukocytes (i.e. neutrophils, eosinophils, lymphocytes, plasma cells, and macrophages) at lesion sites. The

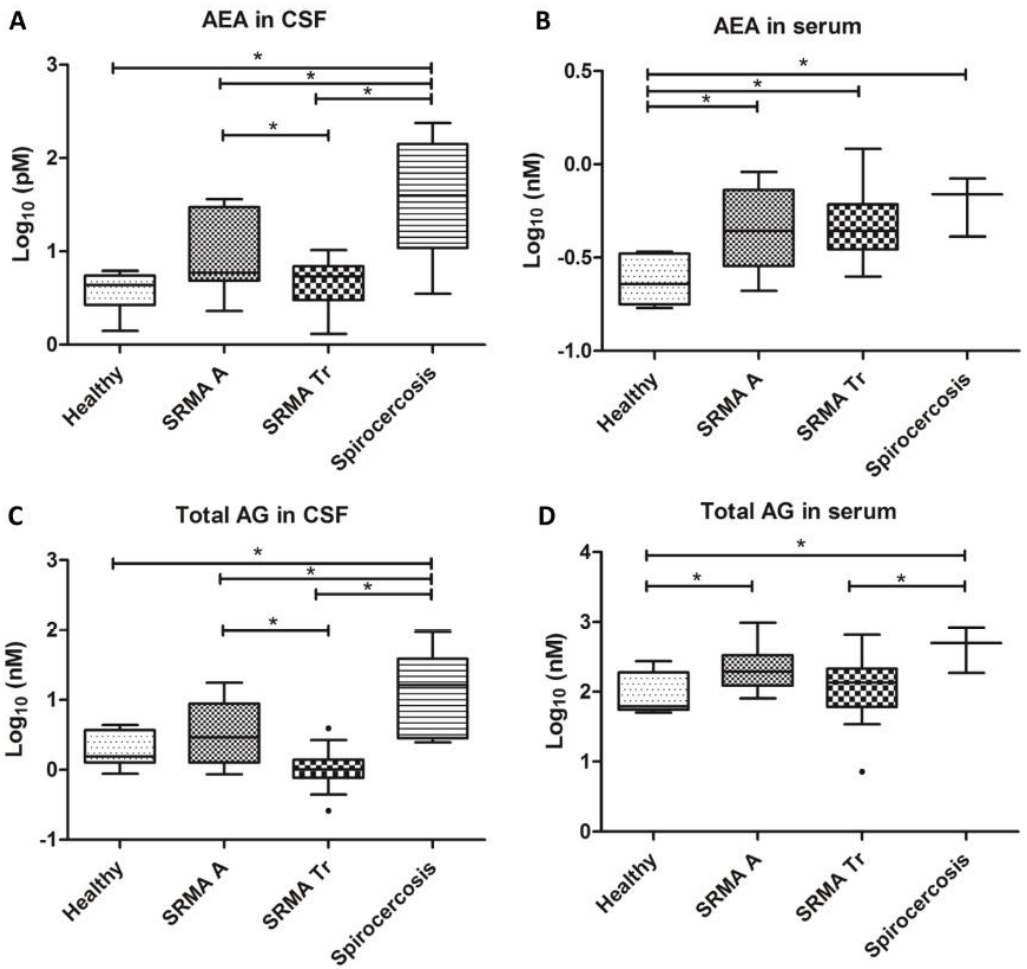


Fig 1. Concentrations of AEA and Total AG in CSF and serum samples, Log to base 10. Boxes contain values from 1st to 3rd quartile, central lines inside the boxes represent median values, and endpoints of vertical lines represent minimum and maximum values, dot (●) represent outliners. Asterisks (*) indicate statistically significant differences ($p<0.05$). AEA: Anandamide; Total AG: 1-AG (1-arachidonoylglycerol) + 2-AG (2-arachidonoylglycerol); CSF: cerebrospinal fluid; SRMA A: steroid-responsive meningitis-arteritis in acute stage; SRMA Tr: SRMA dogs under treatment; pM: picomolar; nM: nanomolar.

https://doi.org/10.1371/journal.pone.0187197.g001

The endocannabinoid system is upregulated with endocannabinoids increasing with CNS inflammatory disease

Gesell et al. BMC Veterinary Research 2013, 9:262
http://www.biomedcentral.com/1746-6148/9/262

BMC Veterinary Research

RESEARCH ARTICLE Open Access

Alterations of endocannabinoids in cerebrospinal fluid of dogs with epileptic seizure disorder

Felix K Gesell[1*], Alexander A Zoerner[2], Christina Brauer[1], Stefan Engeli[2], Dimitros Tsikas[2] and Andrea Tipold[1]

Abstract

Background: Epilepsy is one of the most common chronic neurological disorders in dogs characterized by recurrent seizures. The endocannabinoid (EC) system plays a central role in suppressing pathologic neuronal excitability and in controlling the spread of activity in an epileptic network. Endocannabinoids are released on demand and their dysregulation has been described in several pathological conditions. Recurrent seizures may lead to an adverse reorganization of the EC system and impairment of its protective effect. In the current study, we tested the hypothesis that cerebrospinal fluid (CSF) concentrations of the endocannabinoids anandamide (AEA) and 2-arachidonoyl glycerol (2AG) are altered in epileptic dogs. Concentrations of AEA and total AG (sum of 2AG and 1AG) were measured in 40 dogs with idiopathic epilepsy and in 16 unaffected, healthy control dogs using liquid chromatography combined with tandem mass spectrometry.

Results: AEA and total AG were measured at 4.94 (3.18 – 9.17) pM and 1.43 (0.90 – 1.92) nM in epileptic dogs and at 3.19 (2.04 – 4.28) pM and 1.76 (1.08 – 2.69) nM in the control group, respectively (median, 25 – 75% percentiles in brackets). The AEA difference between epileptic and healthy dogs was statistically significant ($p < 0.05$). Values correlated with seizure severity and duration of seizure activity. Dogs with cluster seizures and/or status epilepticus and with seizure activity for more than six months displayed the highest EC concentrations.

Conclusion: In conclusion, we present the first endocannabinoid measurements in canine CSF and confirm the hypothesis that the EC system is altered in canine idiopathic epilepsy.

Keywords: Endocannabinoids, Anandamide, 2-arachidonyl glycerol, Epilepsy, Cerebrospinal fluid, Canine

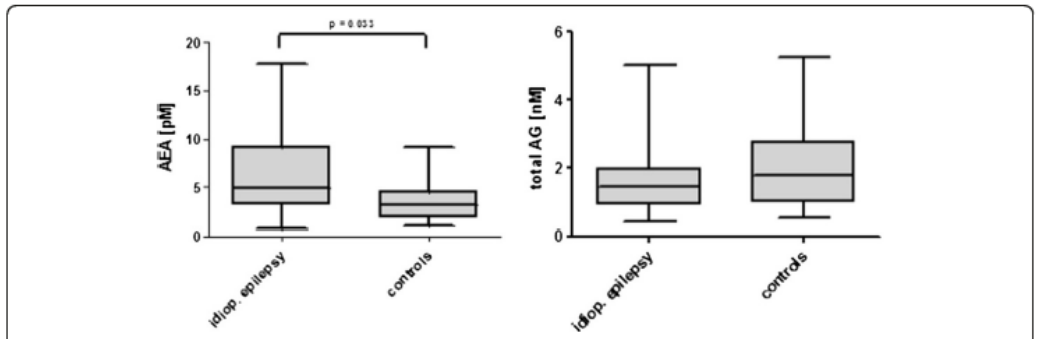


Figure 1 AEA and total AG concentrations of 40 dogs with idiopathic epilepsy and 16 control dogs, statistic was calculated using the Wilcoxon-Test, central lines of the box represent the median, upper and lower limits of the box represent the 75 th and 25 th percentiles.

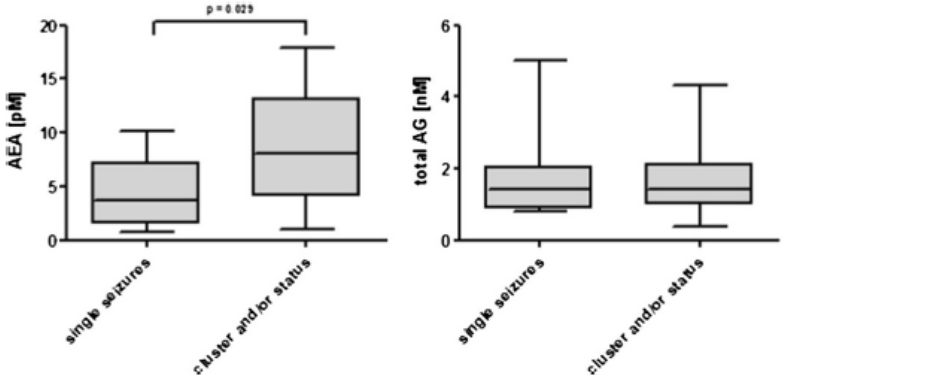
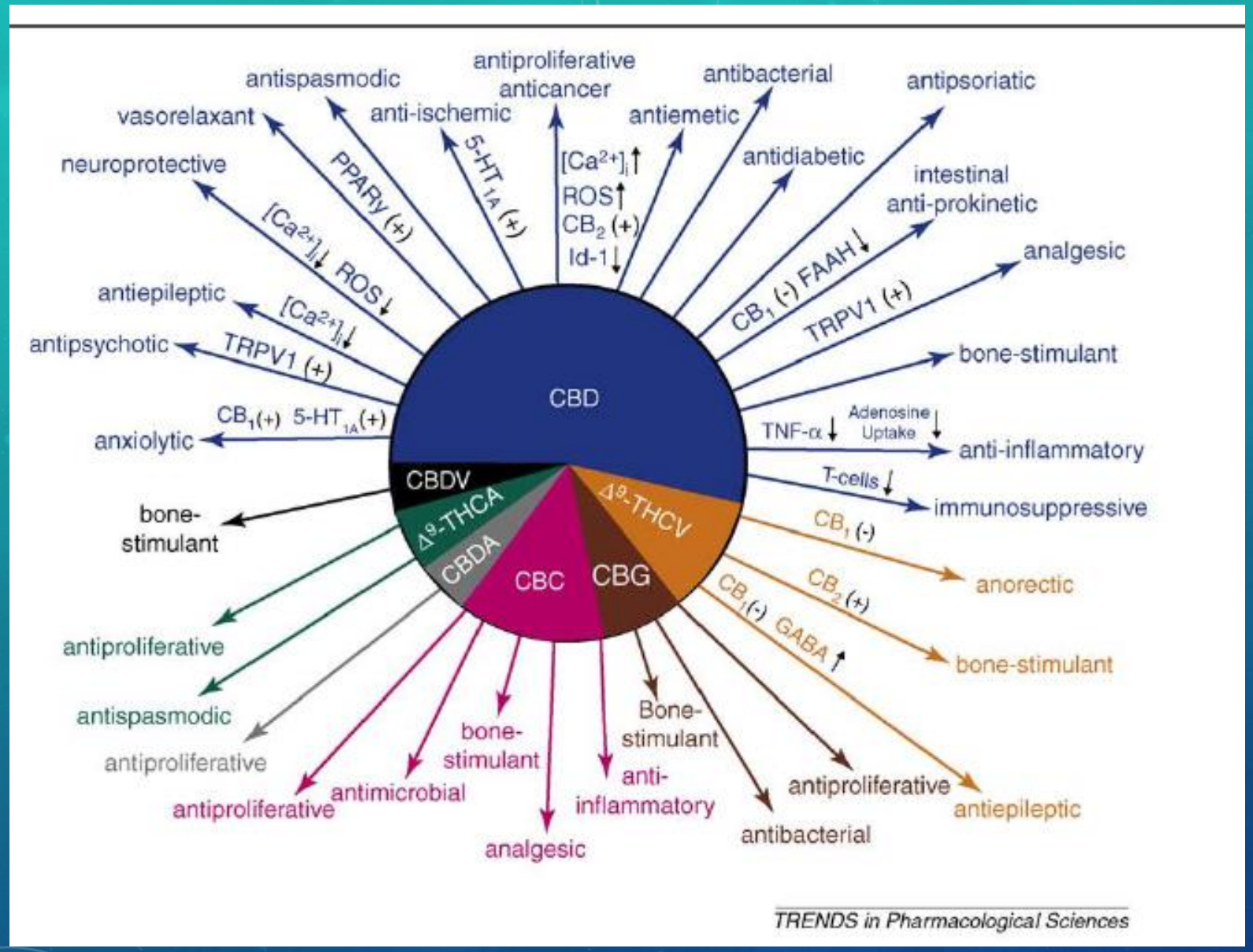


Figure 2 AEA and total AG concentrations of 16 dogs with single seizures and 23 dogs with cluster seizures and/or status epilepticus, statistic was calculated using the Wilcoxon-Test, central lines of the box represent the median, upper and lower limits of the box represent the 75 th and 25 th percentiles.

Endocannabinoid concentrations increase with severity of seizures in epileptic patients



- **MEDICAL MARIJUANA**
- **It's good for what ails you! ……?**

Peer-reviewed studies on medical marijuana, listed by condition treated	# of studies		
	Pro	Con	Not Clearly Pro or Con
ALS	1	0	0
Bipolar Disorder	2	0	0
Cancer	5	1	1
General Use	2	0	0
Glaucoma	0	0	1
HIV/AIDS	5	1	2
Huntington's Disease	0	0	1
IBD/Crohn's	1	0	1
Multiple Sclerosis	11	4	4
Nausea	1	0	0
Pain	6	0	1
Parkinson's Disease	2	0	1
PTSD	1	0	0
Psychosis / Schizophrenia	1	0	1
Rheumatoid Arthritis	1	0	0
Tourette's Syndrome	2	0	0
TOTALS	41 (68%)	6 (10%)	13 (22%)

6. A review does not find persuasive evidence to recommend marijuana for preventing vomiting in cancer patients

CON

Richard H. Schwartz, MD, Clinical Professor of Pediatrics at Georgetown University, Eric A. Voth, MD, Chairman of the Institute on Global Drug Policy, et al., wrote the following in their Feb. 1997 article titled "Marijuana to Prevent Nausea and Vomiting in Cancer Patients: A Survey of Clinical Oncologists" in the *Southern Medical Journal*:

> "Marijuana, if rescheduled by the Drug Enforcement Agency, would be the only Food and Drug Administration (FDA)-approved drug to be administered by smoking. American physicians need timely, factual information about probable usage patterns and potential adverse effects of medical marijuana, and a factual complete review of the literature on the subject.
>
> We mailed a survey to 1,500 American clinical oncologists. Of particular interest was whether and how often in the past 24 months these physicians recommended smoked marijuana, synthetic tetrahydrocannabinol, or 5-HT3 (serotonin) antagonists (ondansetron [Zofran], granisetron [Kytril]) for their patients. We also inquired whether and how often the oncologists would prescribe marijuana in the form of cigarettes, were it to be FDA-approved. Completed surveys were received from 1,122 (75%) of the oncologists.
>
> The percentages of oncologists who prescribed or recommended selected antiemetics more than five times between 1992 and 1994 were 98% for 5-HT, antagonists, 6% for dronabinol (Marinol), and 1% for smoked marijuana. We also found that 332 (30%) of the oncologist-respondents to this nationwide survey supported rescheduling of marijuana for medical purposes; however, two thirds (67%) of the 332 respondents who were in favor of rescheduling estimated that they would write less than one prescription per month for marijuana cigarettes. A comprehensive literature review failed to provide persuasive evidence to recommend marijuana as a needed antiemetic medicine."

Feb. 1997 - Richard H. Schwartz, MD ☆☆☆☆ Eric Voth, MD ☆☆☆☆

7. Oncologists have favorable opinions on the use of marijuana to prevent vomiting in cancer chemotherapy patients

PRO

Rick Doblin, PhD, President of the Multidisciplinary Association for Psychedelic Studies (MAPS), and Mark A. R. Kleiman, PhD, Professor of Public Policy at the UCLA School of Public Affairs, wrote in a July 1991 article titled "Marijuana as Antiemetic Medicine: A Survey of Oncologists' Experiences and Attitudes" in the *American Journal of Clinical Oncology*:

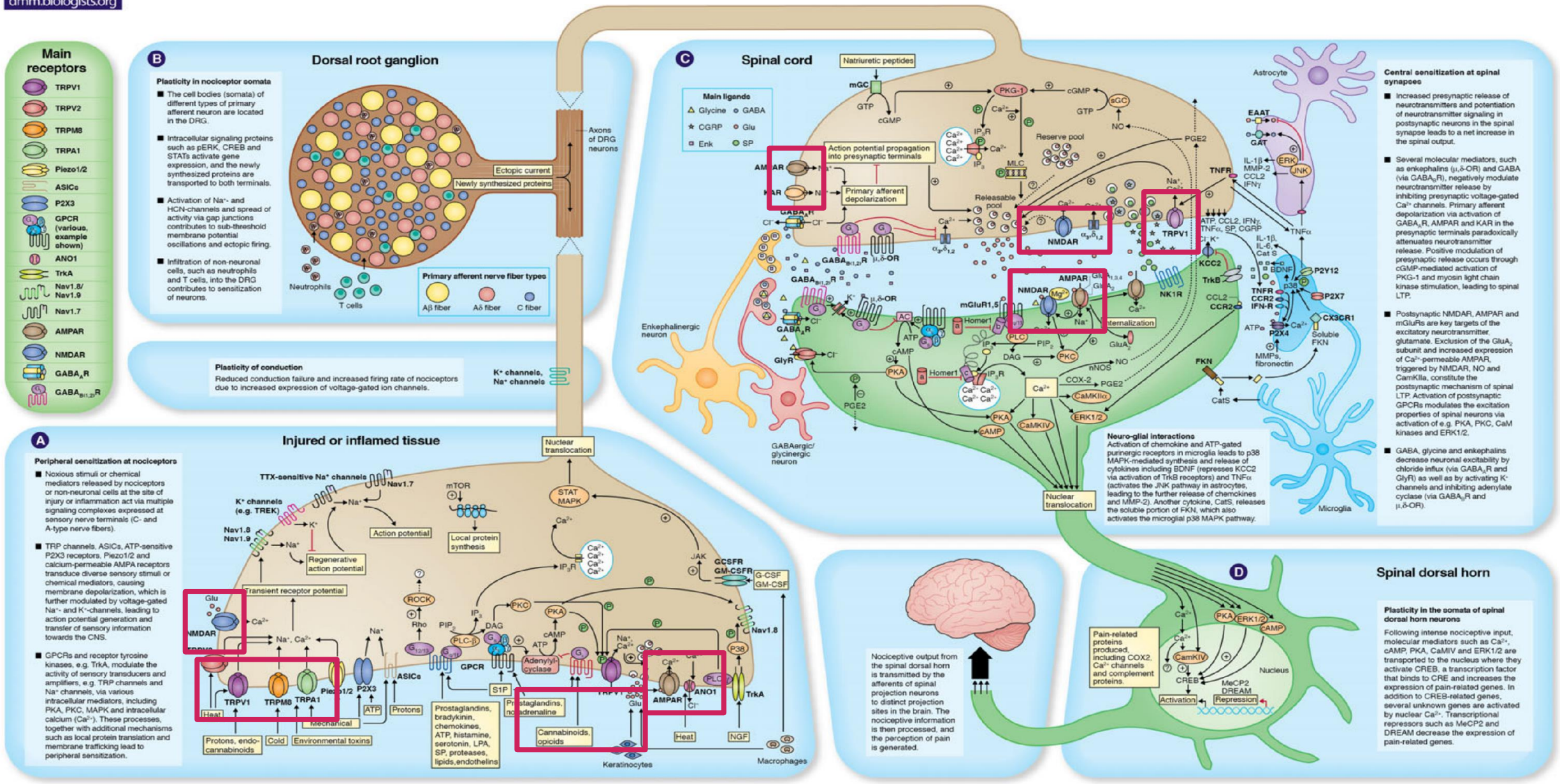
> "A random-sample, anonymous survey of the members of the American Society of Clinical Oncology (ASCO) was conducted in spring 1990 measuring the attitudes and experiences of American oncologists concerning the antiemetic use of marijuana in cancer chemotherapy patients. The survey was mailed to about one third (N = 2,430) of all United States-based ASCO members and yielded a response rate of 43% (1,035).
>
> More than 44% of the respondents report recommending the (illegal) use of marijuana for the control of emesis to at least one cancer chemotherapy patient. Almost one half (48%) would prescribe marijuana to some of their patients if it were legal. As a group, respondents considered smoked marijuana to be somewhat more effective than the legally available oral synthetic dronabinol ([THC] Marinol; Unimed, Somerville, NJ) and roughly as safe. Of the respondents who expressed an opinion, a majority (54%) thought marijuana should be available by prescription.
>
> These results bear on the question of whether marijuana has a 'currently accepted medical use,' at issue in an ongoing administrative and legal dispute concerning whether marijuana in smoked form should be available by prescription along with synthetic THC in oral form. This survey demonstrates that oncologists' experience with the medical use of marijuana is more extensive, and their opinions of it are more favorable, than the regulatory authorities appear to have believed."

July 1991 - Rick Doblin, PhD ☆☆☆ Mark A. R. Kleiman, PhD ☆☆☆

DMM Disease Models & Mechanisms
dmm.biologists.org

Pain hypersensitivity mechanisms at a glance

Vijayan Gangadharan and Rohini Kuner



J Neuroimmune Pharmacol (2015) 10:293–301
DOI 10.1007/s11481-015-9600-6

INVITED REVIEW

Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials

M. E. Lynch[1,3] · Mark A. Ware[2]

Received: 29 January 2015 / Accepted: 5 March 2015 / Published online: 22 March 2015

Abstract An updated systematic review of randomized controlled trials examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to PRISMA guidelines for systematic reviews reporting on health care outcomes. Eleven trials published since our last review met inclusion criteria. The quality of the trials was excellent. Seven of the trials demonstrated a significant analgesic effect. Several trials also demonstrated improvement in secondary outcomes (e.g., sleep, muscle stiffness and spasticity). Adverse effects most frequently reported such as fatigue and dizziness were mild to moderate in severity and generally well tolerated. This review adds further support that currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.

Introduction

Chronic pain is a growing public health problem affecting approximately one in five people and predicted to increase to one in three over the next two decades (Blyth et al. 2001; Moulin et al. 2002; Breivik et al. 2006). The prevalence of chronic pain is likely to increase as the population ages and as medical advances continue to improve survival related to cancer, serious injury and diseases that previously would have been fatal, such as HIV, but have left the survivors with serious neuropathic pain conditions (Lynch 2011). Currently available agents

verse effects most frequently reported such as fatigue and dizziness were mild to moderate in severity and generally well tolerated. This review adds further support that currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.

The Effectiveness of Cannabinoids in the Management of Chronic Nonmalignant Neuropathic Pain: A Systematic Review

Darrell G. Boychuk, DDS, MSc
Clinician
TMD Clinic
Health Partners
Minneapolis/St Paul, Minnesota, USA

Greg Goddard, DDS
Professor
School of Dentistry
University of California, San Francisco
San Francisco, California, USA

Giovanni Mauro, MD, DDS
Visiting Professor
Dental Center
University of Parma
Parma, Italy

Maria F. Orellana, DDS, PhD, MSc
Associate Clinical Professor
School of Dentistry
University of California, San Francisco
San Francisco, California, USA

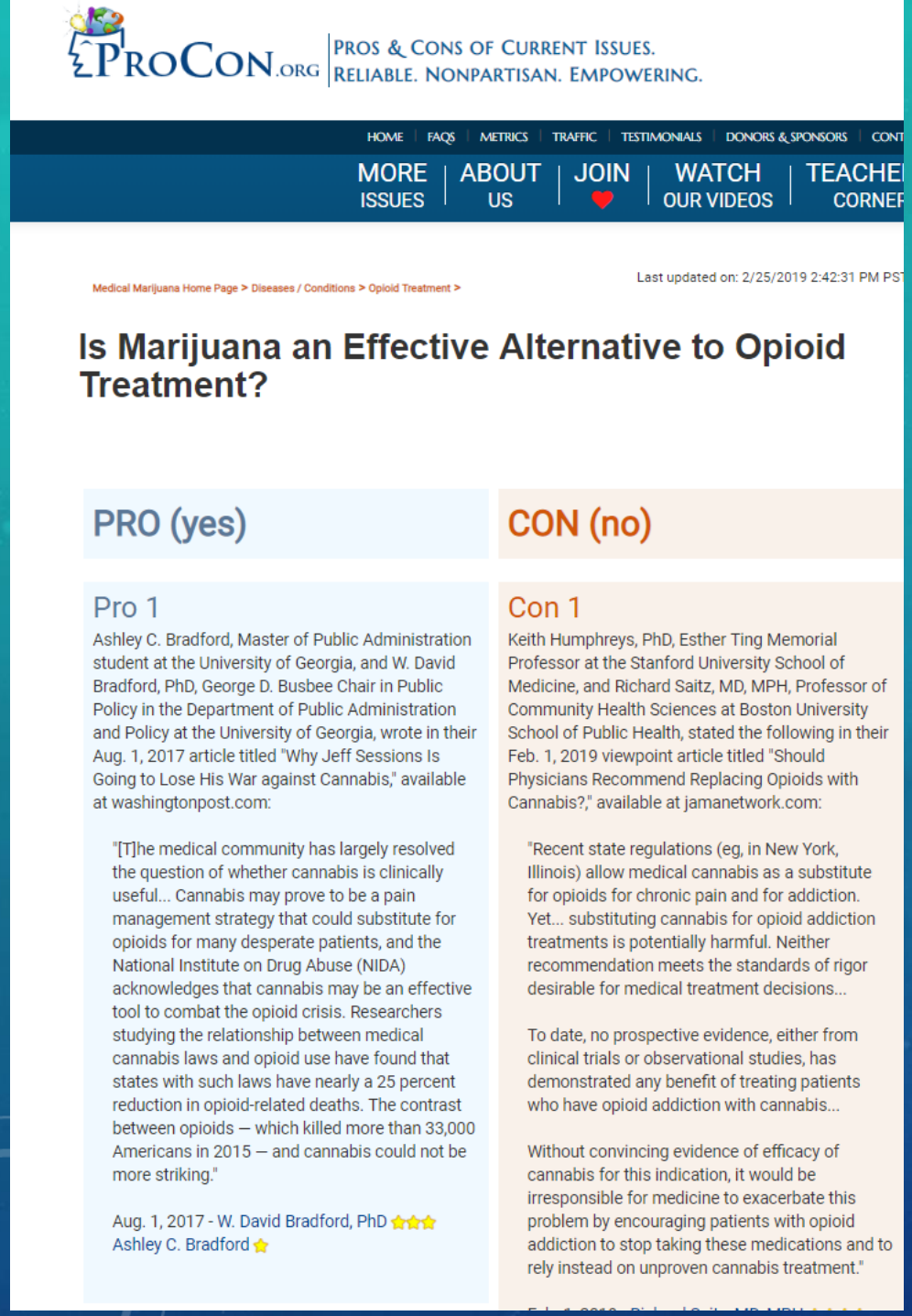
Correspondence to:
Dr Darrell Boychuk
UCSF School of Dentistry
Box 0438
San Francisco, CA 94143, USA
Email: dgboychuk@gmail.com

Aims: To carry out a systematic review to assess the effectiveness of cannabis extracts and cannabinoids in the management of chronic nonmalignant neuropathic pain. **Methods:** Electronic database searches were performed using Medline, PubMed, Embase, all evidence-based medicine reviews, and Web of Science, through communication with the Canadian Consortium for the Investigation of Cannabinoids (CCIC), and by searching printed indices from 1950. Terms used were marijuana, marihuana, cannabis, cannabinoids, nabilone, delta-9-tetrahydrocannabinol, cannabidiol, ajulemic acid, dronabinol, pain, chronic, disease, and neuropathic. Randomized placebo-controlled trials (RCTs) involving cannabis and cannabinoids for the treatment of chronic nonmalignant pain were selected. Outcomes considered were reduction in pain intensity and adverse events. **Results:** Of the 24 studies that examined chronic neuropathic pain, 11 studies were excluded. The 13 included studies were rated using the Jadad Scale to measure bias in pain research. Evaluation of these studies suggested that cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments. **Conclusion:** Cannabis-based medicinal extracts used in different populations of chronic nonmalignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments. Further high-quality studies are needed to assess the impact of the duration of the treatment as well as the best form of drug delivery. *J Oral Facial Pain Headache 2015;29:7–14. doi: 10.11607/ofph.1274*

Key words: *cannabinoids, chronic nonmalignant pain, management, neuropathic pain, systematic review*

conditions that are refractory to other treatments. **Conclusion:** Cannabis-based medicinal extracts used in different populations of chronic nonmalignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments. Further high-quality studies are needed to assess

Treatment for opioid addiction versus alternative to opioids for control of pain?



ProCon.org | Pros & Cons of Current Issues. Reliable. Nonpartisan. Empowering.

HOME | FAQS | METRICS | TRAFFIC | TESTIMONIALS | DONORS & SPONSORS | CONT

MORE ISSUES | ABOUT US | JOIN ♥ | WATCH OUR VIDEOS | TEACHE CORNE

Medical Marijuana Home Page > Diseases / Conditions > Opioid Treatment >

Last updated on: 2/25/2019 2:42:31 PM PST

Is Marijuana an Effective Alternative to Opioid Treatment?

PRO (yes)

Pro 1

Ashley C. Bradford, Master of Public Administration student at the University of Georgia, and W. David Bradford, PhD, George D. Busbee Chair in Public Policy in the Department of Public Administration and Policy at the University of Georgia, wrote in their Aug. 1, 2017 article titled "Why Jeff Sessions Is Going to Lose His War against Cannabis," available at washingtonpost.com:

"[T]he medical community has largely resolved the question of whether cannabis is clinically useful... Cannabis may prove to be a pain management strategy that could substitute for opioids for many desperate patients, and the National Institute on Drug Abuse (NIDA) acknowledges that cannabis may be an effective tool to combat the opioid crisis. Researchers studying the relationship between medical cannabis laws and opioid use have found that states with such laws have nearly a 25 percent reduction in opioid-related deaths. The contrast between opioids — which killed more than 33,000 Americans in 2015 — and cannabis could not be more striking."

Aug. 1, 2017 - W. David Bradford, PhD ★★★
Ashley C. Bradford ★

CON (no)

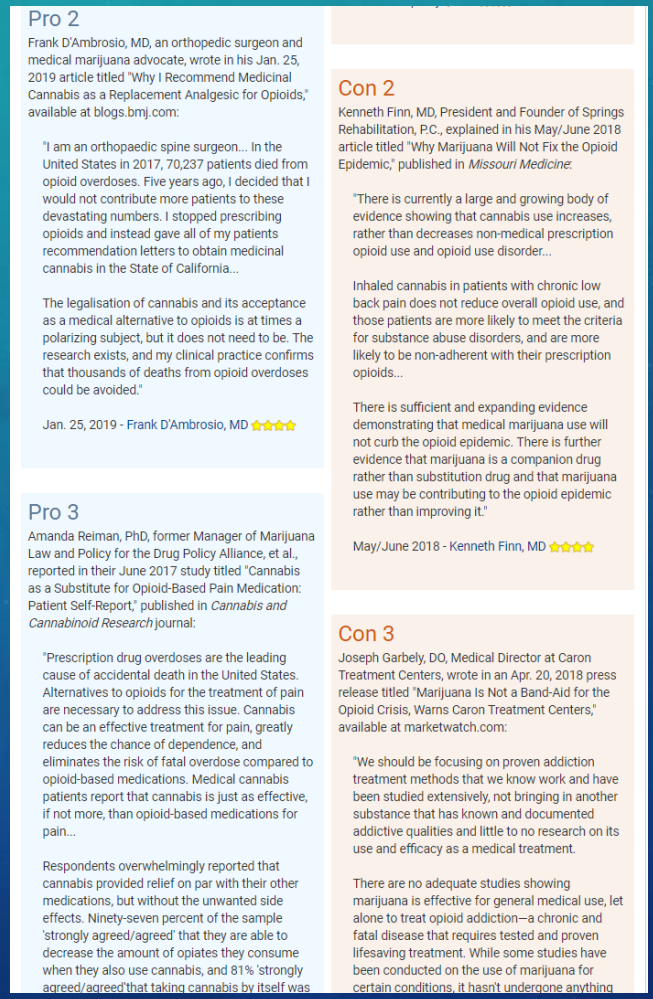
Con 1

Keith Humphreys, PhD, Esther Ting Memorial Professor at the Stanford University School of Medicine, and Richard Saitz, MD, MPH, Professor of Community Health Sciences at Boston University School of Public Health, stated the following in their Feb. 1, 2019 viewpoint article titled "Should Physicians Recommend Replacing Opioids with Cannabis?," available at jamanetwork.com:

"Recent state regulations (eg, in New York, Illinois) allow medical cannabis as a substitute for opioids for chronic pain and for addiction. Yet... substituting cannabis for opioid addiction treatments is potentially harmful. Neither recommendation meets the standards of rigor desirable for medical treatment decisions...

To date, no prospective evidence, either from clinical trials or observational studies, has demonstrated any benefit of treating patients who have opioid addiction with cannabis...

Without convincing evidence of efficacy of cannabis for this indication, it would be irresponsible for medicine to exacerbate this problem by encouraging patients with opioid addiction to stop taking these medications and to rely instead on unproven cannabis treatment."



Pro 2

Frank D'Ambrosio, MD, an orthopedic surgeon and medical marijuana advocate, wrote in his Jan. 25, 2019 article titled "Why I Recommend Medicinal Cannabis as a Replacement Analgesic for Opioids," available at blogs.bmj.com:

"I am an orthopaedic spine surgeon... In the United States in 2017, 70,237 patients died from opioid overdoses. Five years ago, I decided that I would not contribute more patients to these devastating numbers. I stopped prescribing opioids and instead gave all of my patients recommendation letters to obtain medicinal cannabis in the State of California...

The legalisation of cannabis and its acceptance as a medical alternative to opioids is at times a polarizing subject, but it does not need to be. The research exists, and my clinical practice confirms that thousands of deaths from opioid overdoses could be avoided."

Jan. 25, 2019 - Frank D'Ambrosio, MD ★★★★

Pro 3

Amanda Reiman, PhD, former Manager of Marijuana Law and Policy for the Drug Policy Alliance, et al., reported in their June 2017 study titled "Cannabis as a Substitute for Opioid-Based Pain Medication: Patient Self-Report," published in *Cannabis and Cannabinoid Research* journal:

"Prescription drug overdoses are the leading cause of accidental death in the United States. Alternatives to opioids for the treatment of pain are necessary to address this issue. Cannabis can be an effective treatment for pain, greatly reduces the chance of dependence, and eliminates the risk of fatal overdose compared to opioid-based medications. Medical cannabis patients report that cannabis is just as effective, if not more, than opioid-based medications for pain...

Respondents overwhelmingly reported that cannabis provided relief on par with their other medications, but without the unwanted side effects. Ninety-seven percent of the sample 'strongly agreed/agreed' that they are able to decrease the amount of opiates they consume when they also use cannabis, and 81% 'strongly agreed/agreed'that taking cannabis by itself was

Con 2

Kenneth Finn, MD, President and Founder of Springs Rehabilitation, P.C., explained in his May/June 2018 article titled "Why Marijuana Will Not Fix the Opioid Epidemic," published in *Missouri Medicine*:

"There is currently a large and growing body of evidence showing that cannabis use increases, rather than decreases non-medical prescription opioid use and opioid use disorder...

Inhaled cannabis in patients with chronic low back pain does not reduce overall opioid use, and those patients are more likely to meet the criteria for substance abuse disorders, and are more likely to be non-adherent with their prescription opioids...

There is sufficient and expanding evidence demonstrating that medical marijuana use will not curb the opioid epidemic. There is further evidence that marijuana is a companion drug rather than substitution drug and that marijuana use may be contributing to the opioid epidemic rather than improving it."

May/June 2018 - Kenneth Finn, MD ★★★★

Con 3

Joseph Garbely, DO, Medical Director at Caron Treatment Centers, wrote in an Apr. 20, 2018 press release titled "Marijuana Is Not a Band-Aid for the Opioid Crisis, Warns Caron Treatment Centers," available at marketwatch.com:

"We should be focusing on proven addiction treatment methods that we know work and have been studied extensively, not bringing in another substance that has known and documented addictive qualities and little to no research on its use and efficacy as a medical treatment.

There are no adequate studies showing marijuana is effective for general medical use, let alone to treat opioid addiction—a chronic and fatal disease that requires tested and proven lifesaving treatment. While some studies have been conducted on the use of marijuana for certain conditions, it hasn't undergone anything

ARE CANNABINOIDS A REASONABLE ALTERNATIVE TO OPIOIDS?

- Sole
  - Mild and chronic pain
- Sole to adjuvant
  - Moderate to severe pain
- Effective adjuvant for severe (acute?) pain
- Dose? Product? Monitor?
  - Product issues
  - Individual response

Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol Treatment in Osteoarthritic Dogs

*Lauri-Jo Gamble[1], Jordyn M. Boesch[1], Christopher W. Frye[1], Wayne S. Schwark[2], Sabine Mann[3], Lisa Wolfe[4], Holly Brown[5], Erin S. Berthelsen[1] and Joseph J. Wakshlag[1]**

[1] Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY, United States, [2] Department

CBD oil (2 mg/kg) or placebo oil every 12 h.

Objectives: The objectives of this study were to determine basic oral pharmacokinetics, and assess safety and analgesic efficacy of a cannabidiol (CBD) based oil in dogs with osteoarthritis (OA).

Methods: Single-dose pharmacokinetics was performed using two different doses of CBD enriched (2 and 8 mg/kg) oil. Thereafter, a randomized placebo-controlled, veterinarian, and owner blinded, cross-over study was conducted. Dogs received each of two treatments: CBD oil (2 mg/kg) or placebo oil every 12 h. Each treatment lasted for 4 weeks with a 2-week washout period. Baseline veterinary assessment and owner questionnaires were completed before initiating each treatment and at weeks 2 and 4. Hematology, serum chemistry and physical examinations were performed at each visit. A mixed model analysis, analyzing the change from enrollment baseline for all other time points was utilized for all vari

Results: Pharmacokinetics
observable side effects. Clini
showed a significant decrea
Veterinary assessment shov
side effects were reported b
alkaline phosphatase during

Clinical significance: This
of CBD twice daily can help

Keywords: cannabidiol, CBD oil, her

OPEN ACCESS

Edited by:
Troy N. Trumble,
University of Minnesota Twin Cities, United States

Reviewed by:
Gareth Edward Zeiler,
University of Pretoria, South Africa
Joao Henrique Neves Soares,
Virginia Tech, United States

***Correspondence:**
Joseph J. Wakshlag
jw37@cornell.edu

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *25 February 2018*
Accepted: *02 July 2018*
Published: *23 July 2018*

SOME EVIDENCE OF EFFICACY FOR CONTROL OF OA PAIN WHEN USED WITH NSAIDS IN DOGS (2 mg/kg)

Response at 2 wks = 4 wks

	CBD oil		Placebo oil	
	Week 0	Week 2	Week 0	Week 2
CBPI Pain (0–40)	21 ± 8	14 ± 6*	17 ± 7	19 ± 9
CBPI activity interference (0–60)	35 ± 15	25 ± 15*	27 ± 15	29 ± 15
Hudson (0–110)	54 ± 13	67 ± 15*	65 ± 14	64 ± 16
Veterinary lameness§	3 (1–4)	3 (1–4)	3 (2–4)	3 (2–4)
Veterinary pain ∫	3 (3–4)	3 (2–4)*	3 (2–4)**	3 (2–4)
Veterinary weight-bearing =	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)

TABLE 1 | Serum pharmacokinetic of single oral dosing (2 mg and 8 mg/kg) of CBD oil in dogs.

	Cmax (ng/mL)	Tmax (h)	T1/2 elim (h)	AUC 0-t (ng-hr/mL)	MRT (h)
DOSE (2 mg/kg)					
Dog 1	61	1	4.4	183	6.0
Dog 2	132	1	3.9	351	4.2
Dog 3	102	2	3.8	382	5.1
Dog 4	101	2	6.8	437	9.1
Median (Range)	102 (61–132.0)	1.5 (1.0–2.0)	4.2 (3.8–6.8)	367 (183–437)	5.6 (4.2–9.1)

Research Paper

PAIN

A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain

Chris D. Verrico[a,b], Shonda Wesson[c], Vanaja Konduri[d], Colby J. Hofferek[d], Jonathan Vazquez-Perez[d], Emek Blair[e], Kenneth Dunner Jr[f], Pedram Salimpour[g], William K. Decker[d,h,i], Matthew M. Halpert[d,*]

Abstract

Over the last 2 decades, affirmative diagnoses of osteoarthritis (OA) in the United States have tripled due to increasing rates of obesity and an aging population. Hemp-derived cannabidiol (CBD) is the major nontetrahydrocannabinol component of cannabis and has been promoted as a potential treatment for a wide variety of disparate inflammatory conditions. Here, we evaluated CBD for its ability to modulate the production of proinflammatory cytokines in vitro and in murine models of induced inflammation and further validated the ability of a liposomal formulation to increase bioavailability in mice and in humans. Subsequently, the therapeutic potential of both naked and liposomally encapsulated CBD was explored in a 4-week, randomized placebo-controlled, double-blinded study in a spontaneous canine model of OA. In vitro and in mouse models, CBD significantly attenuated the production of proinflammatory cytokines IL-6 and TNF-α while elevating levels of anti-inf
decreased pain and increased mobility in a dose-dependent fashion amo
CBD (20 mg/day) was as effective as the highest dose of nonliposomal CB
comprehensive metabolic profile, and clinical chemistry indicated no signif
week analysis period. This study supports the safety and therapeutic pot
suggests follow-up investigations in humans are warranted.

Keywords: Osteoarthritis, Cannabidiol, Randomized trial, Liposomal e

Owner perspective: Quality of Life Score
Placebo vs. oil or liposome at 1.2 mg/kg oil or oil at 3 mg/kg.

N (5/group) = large breed (>20 kg) dogs with osteoarthritis

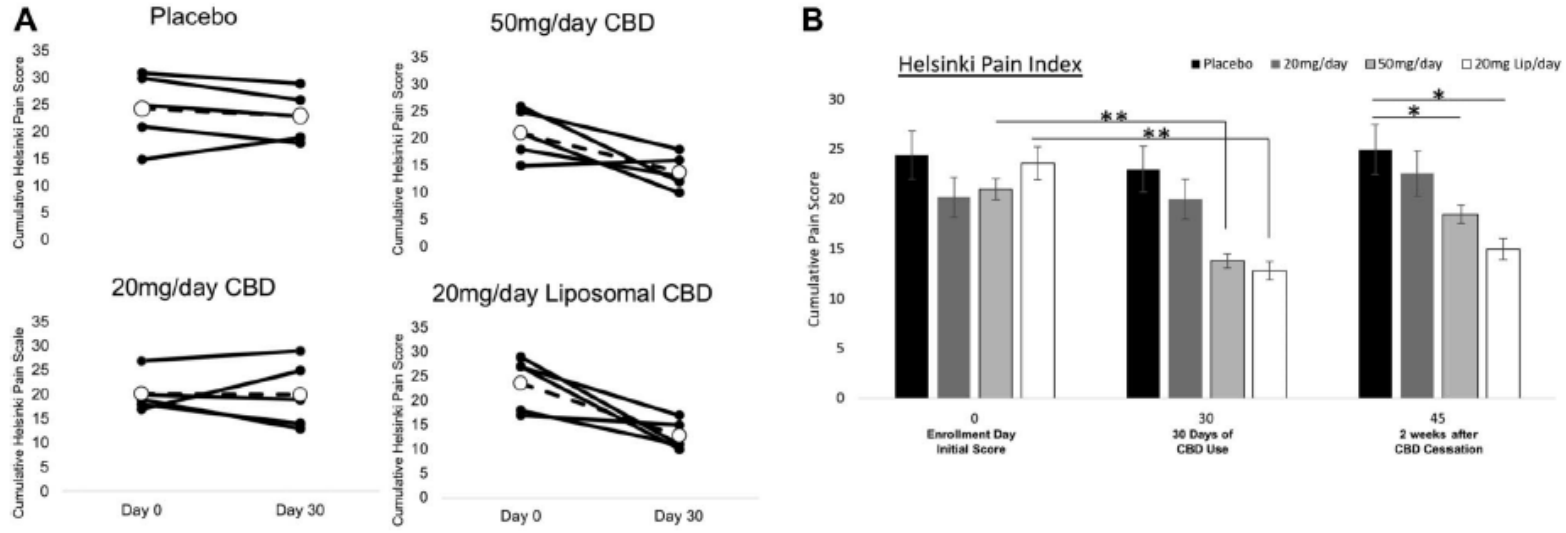


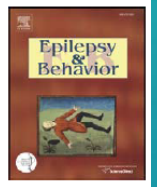
Figure 4. Daily administration of CBD for 30 days improves owner-perspective quality of life scores among large dogs with affirmative diagnosis of osteoarthritis. Twenty large domestic canines with affirmative diagnosis of osteoarthritis were enrolled in a double-blind, placebo-controlled randomized study. Animals were administered coconut oil placebo, 20-mg/day naked CBD, 50-mg/day naked CBD, or 20-mg/day liposomal CBD. Owners assessed their animals by means of the Helsinki Chronic Pain Index (HPCI) on days 0, 30, and 45. (A) Individual HPCI values were plotted for each study cohort on days 0 and 30. (B) Cohort HPCI values were plotted on days 0, 30, and 45. Error bars ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$ by Student's two-tailed t test. CBD, cannabidiol.

CANNABINOIDS AND EPILEPSY

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh



Brief Communication

Report of a parent survey c treatment-resistant epileps

Brenda E. Porter, Catherine Jacobs

[a] Department of Neurology, Stanford University, USA

ARTICLE INFO

Article history:
Received 24 May 2013
Revised 23 July 2013
Accepted 30 August 2013

Keywords:
Epilepsy
Pediatric
Intractable
Cannabidiol
Side effects
Medically refractory seizures
Treatment-resistant
Dravet syndrome

Epilepsy & Behavior 69 (2017) 59–68

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Association between antiepileptic drug dose and long-term response patients with refractory epilepsy

Nicholas P. Poolos [a,*], Christina E. Castagna [a], Stephen Williams [b], Alison B. Miller [c], Tyler J

[a] Department of Neurology and Regional Epilepsy Center, University of Washington, Seattle, WA, United States
[b] Rainier Residential Habilitation Center, Buckley, WA, United States
[c] Fircrest Residential Habilitation Center, Shoreline, WA, United States
[d] UCB Pharma, SA, Smyrna, GA, United States

ARTICLE INFO

Article history:
Received 13 September 2016
Revised 11 October 2016
Accepted 11 October 2016
Available online 23 February 2017

Keywords:
Refractory epilepsy
Dose-response
Lamotrigine
Valproate
Pharmacodynamic synergy

ABSTRACT

Seizures in patients with medically refractory epilepsy remain a substantial clinica
the dearth of evidence-based guidelines as to which antiepileptic drug (AED) r
and what doses of these drugs to employ. We sought to determine whether th
range of commonly used AEDs that were associated with superior efficacy in pa
We retrospectively analyzed treatment records from 164 institutionalized, dev
with refractory epilepsy, averaging 17 years of followup per patient. We determ
quency in within-patient comparisons during treatment with the most comm
AEDs, and then analyzed the response to treatment by quartile of the dose rang
mazepine (CBZ), lamotrigine (LTG), valproate (VPA), or phenytoin (PHT), and
found that of the 26 most frequently used AED regimens, only LTG/VPA yielded
earlier study. For the monotherapies, patients who were treated in the lowest qu
nificantly better long-term reduction in seizure frequency compared to those trea
of the dose range. Patients with paired exposures to CBZ in both the lowest quart
range experienced an increase in seizure frequency at higher doses, while patient
improved response with escalation of LTG dosage. We conclude that in this popul
epilepsy, LTG/VPA was the most effective AED combination. The best response to
observed at low dosage. This suggests that routine exposure to maximally tolera
essary to identify those patients with drug-resistant seizures who will have a
Rather, responders to a given AED regimen may be identified with exposure to lo
uation of the response to subsequent titration to identify non-responders or tho
frequency at higher doses.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 25, 2017 VOL. 376 NO. 21

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

ABSTRACT

BACKGROUND

The Dravet syndrome is a complex childhood epilepsy disorder that is associated with

From the New York University Langone
ve Epilepsy Center, New York
University College London
nd Street Institute of Child
.) and GW Pharmaceuticals
h in London; Lurie Children's
ter, Ann and Robert H. Lurie
ospital of Chicago, Chicago
ildren's Hospital of Philadel-
phia (E.M.); Miami Children's
ami (I.M.); Hôpital Necker–
des, Paris (R.N.); Florey Insti-
Health and Royal Children's
iversity of Melbourne, Mel-
Australia (I.E.S.); and Massa-
eral Hospital, Boston (E.A.T.).
int requests to Dr. Devinsky
rtment of Neurology, NYU
ool of Medicine, 223 E. 34th
, NY 10016, or at od4@nyu

list of investigators in the
l in Dravet Syndrome Study
ovided in the Supplementary
vailable at NEJM.org.

and Cross contributed equal-
cle.

2017;376:2011-20.
NEJMoa1611618

The Utility of Cannabidiol in the Treatment of Refractory Epilepsy

DS Reddy[1]

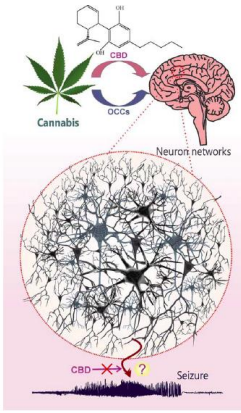
Cannabis-derived cannabinoids such as cannabidiol (CBD) have anticonvulsant properties. Recently, there has been an emerging interest in the use of CBD-enriched products for treatment of drug-resistant epilepsy. Some pilot trials of CBD have proved beneficial for refractory epilepsy, but its efficacy is yet to be confirmed by standard placebo-controlled trials. However, the mechanisms underlying the seizure protection efficacy claims of CBD remain unclear. This review briefly describes the clinical utility of CBD in the treatment of refractory epilepsy.

Epilepsy affects an estimated 65 million people worldwide. Antiepileptic drugs are used for symptomatic control of seizures; however, only two-thirds of epilepsy patients can be successfully treated with current medications. As many as 30% of people with epilepsy—or about 20 million people worldwide—still have seizures while on antiepileptic treatments. People with medication-resistant or refractory epilepsy suffer from consequences of recurrent seizures, which could damage the brain and adversely impact quality of life. This is commonly observed in children with certain types of devastating pediatric epilepsies, such as Lennox-Gastaut, Doose, and Dravet syndromes. Thus, there is a large unmet need for novel drugs for many treatment-resistant types of epilepsy. Recently, medical marijuana or cannabis has been suggested as a potential therapy for refractory epilepsy.[1] The cannabis plant contains over 100 compounds, referred to as cannabinoids. Among these are tetrahydrocannabinol (THC)

on social media, with special focus being placed on the rationa
of cannabis products for children. This article briefly discuss
the translational and clinical pharmacology of cannabidiol pro
ucts for treatment-resistant epilepsy.

TRANSLATIONAL ASPECTS OF CANNABIDIOL FOR EPILEPSY

CBD is a major phytocannabinoid in cannabis extracts, and i
levels vary greatly in diffe
psychoactive properties a
CBD is considered to h
epilepsy when compared
antiinflammatory, and an
ments have tested the efl
many animal models of
anticonvulsant effects, in
py.[3] CBD and its varia
animal epileptic models, s
tetrazol, pilocarpine, peni
razol threshold test, and
of these experimental stu
vulsant effects, with an E
anticonvulsant doses of C
and behavioral impairme
additive or synergistic el
there is strong evidence i



2.2 Dosage Information

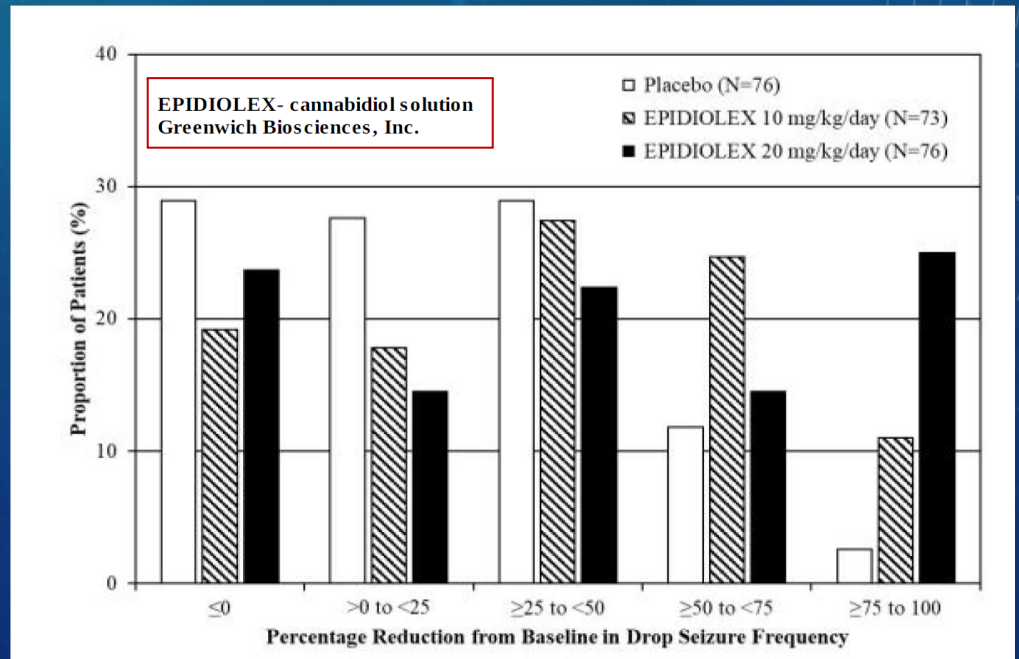
- EPIDIOLEX is to be administered orally.
- The starting dosage is 2.5 mg/kg twice daily (5 mg/kg/day).
- After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day).
- Patients who are tolerating EPIDIOLEX at 5 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated. For patients in whom a more rapid titration from 10 mg/kg/day to 20 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day. Administration of the 20 mg/kg/day dosage resulted in somewhat greater reductions in seizure rates than the recommended maintenance dosage of 10 mg/kg/day, but with an increase in adverse reactions.

Dose starts at 2.5 mg/kg q 12 and is increased up to 10 mg/kg q 12

Table 8 Pharmacokinetic parameters of cannabidiol and metabolites for the food effect arm of the trial

Pharmacokinetic parameter (unit)	1500 mg CBD, fasted ($n = 12$)	1500 mg CBD, fed ($n = 12$)
CBD		
C_{max} (ng/mL)[a]	335.4 (81.3)	1628 (51.4)

EPIDIOLEX- cannabidiol solution
Greenwich Biosciences, Inc.



Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy

Stephanie McGrath DVM, MS
Lisa R. Bartner DVM, MS
Sangeeta Rao BVSc, PhD
Rebecca A. Packer DVM, MS
Daniel L. Gustafson PhD

From the Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523.

Address correspondence to Dr. McGrath (stephanie.mcgrath@colostate.edu).

OBJECTIVE
To assess the effect of oral cannabidiol (CBD) administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with idiopathic epilepsy.

DESIGN
Randomized blinded controlled clinical trial.

ANIMALS
26 client-owned dogs with intractable idiopathic epilepsy.

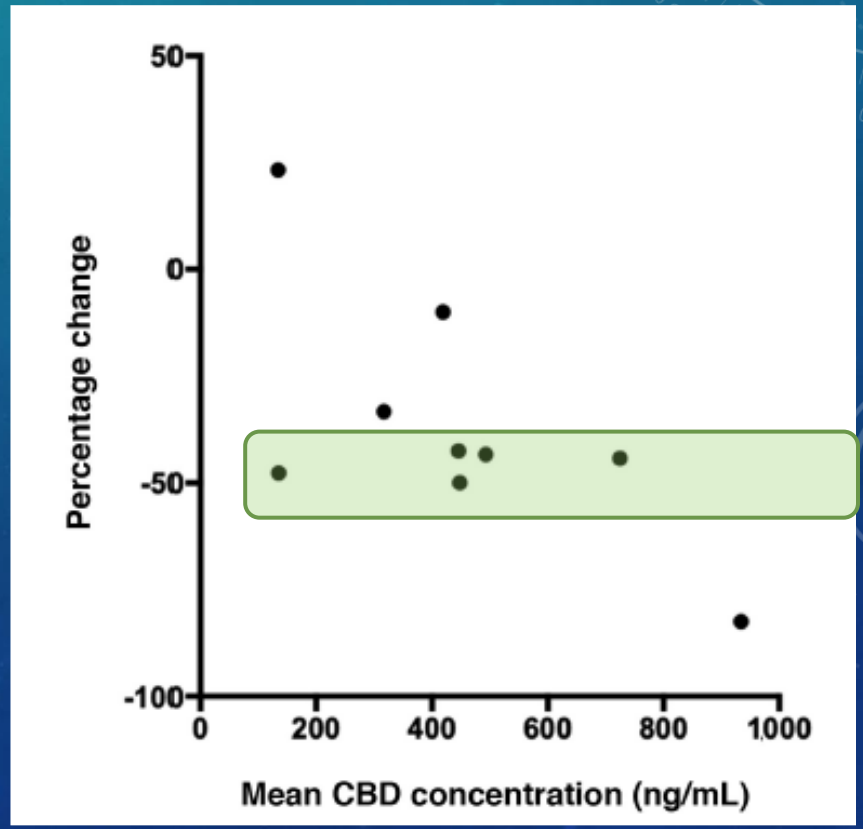
PROCEDURES
Dogs were randomly assigned to a CBD (n = 12) or placebo (14) group. The CBD group received CBD-infused oil (2.5 mg/kg [1.1 mg/lb], PO) twice daily for 12 weeks in addition to existing antiepileptic treatments, and the placebo group received noninfused oil under the same conditions. Seizure activity, adverse effects, and plasma CBD concentrations were compared between groups.

RESULTS
2 dogs in the CBD group developed ataxia and were withdrawn from the study. After other exclusions, 9 dogs in the CBD group and 7 in the placebo group were included in the analysis. Dogs in the CBD group had a significant (median change, 33%) reduction in seizure frequency, compared with the placebo group. However, the proportion of dogs considered responders to treatment (≥ 50% decrease in seizure activity) was similar between groups. Plasma CBD concentrations were correlated with reduction in seizure frequency. Dogs in the CBD group had a significant increase in serum alkaline phosphatase activity. No adverse behavioral effects were reported by owners.

CONCLUSIONS AND CLINICAL RELEVANCE
Although a significant reduction in seizure frequency was achieved for dogs in the CBD group, the proportion of responders was similar between groups. Given the correlation between plasma CBD concentration and seizure frequency, additional research is warranted to determine whether a higher dosage of CBD would be effective in reducing seizure activity by ≥ 50%. (*J Am Vet Med Assoc* 2019;254:1301–1308)

Table 2—Mean (SD) serum phenobarbital (µg/mL) and bromide (mg/mL) concentrations in the dogs of Table 1 before (week 0) and after (week 12) study treatment and percentage change in values between assessment points for dogs with increases or decreases.

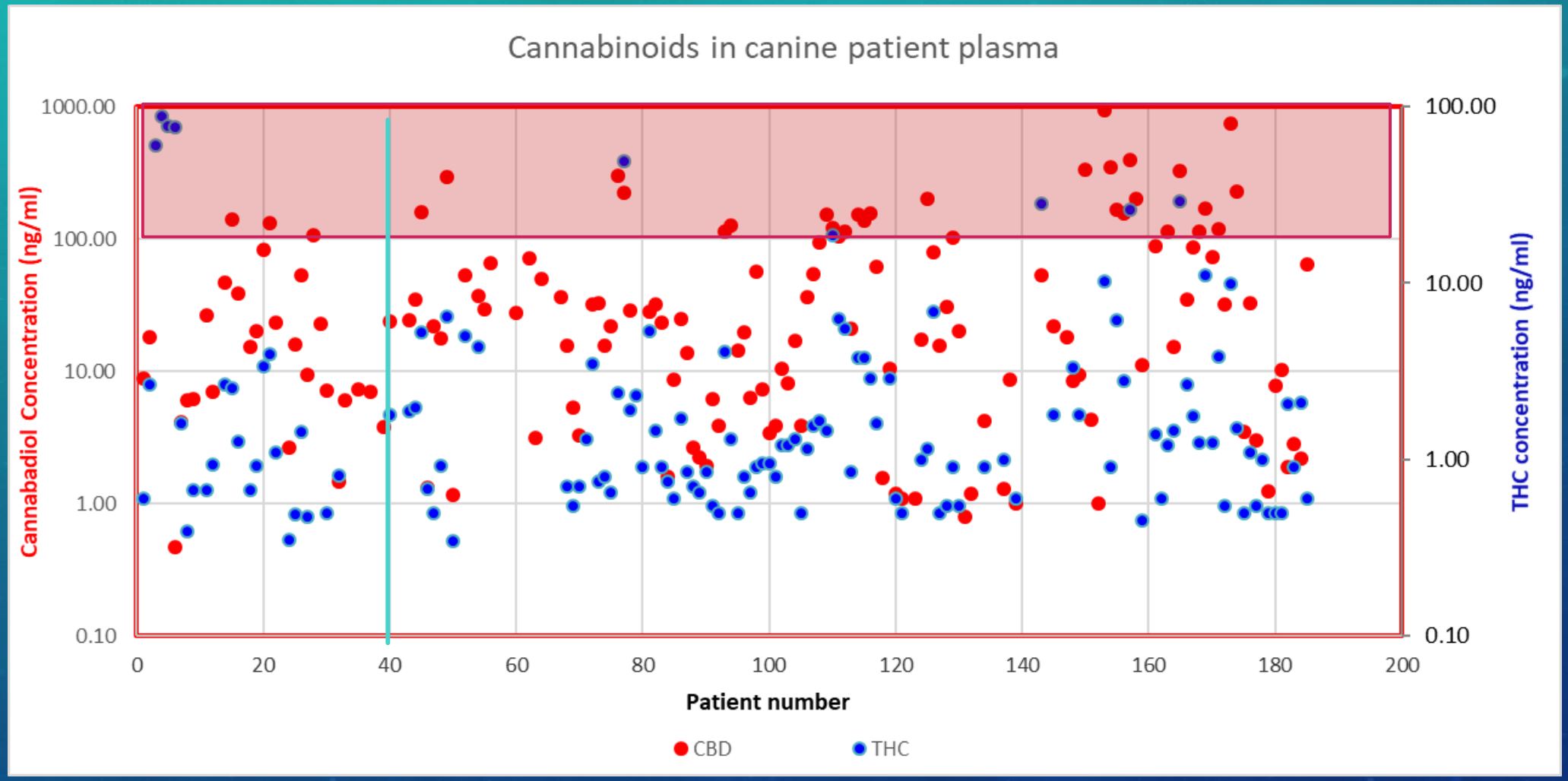
AED and group	Week 0	Week 12	*P* value	Percentage increase from week 0 (No. of dogs with increase)	Percentage decrease from week 0 (No. of dogs with decrease)
Phenobarbital					
CBD (n = 7)	28.4 (4.7)	31.5 (7.8)	0.30	22 (5)	14 (2)
Placebo (n = 4)	33.4 (4.2)	29.5 (6.9)	0.25	16 (1)	26 (3)
Bromide					
CBD (n = 3)	1.2 (0.5)	1.2 (0.5)	1.00	77 (1)	26 (2)
Placebo (n = 2)	1.5 (0.6)	2.0 (0.4)	1.00	112 (1)	10 (1)



Reduction in # > with CBD
Reduction correlated with CBD concentrations
AED concentrations did not change

CANINE SERUM CANNABINOID CONCENTRATIONS

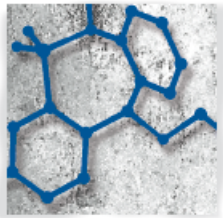
Target Plasma Drug Concentrations (?)
20 mg/kg CBD = 350 ng/ml ? (Human epilepsy)
2 mg/kg CBD = 100 ng/ml (Dogs OA)



- **Therapeutic reference interval > 100 ng/ml ?**

Cannabis, cannabinoids, and health

Genevieve Lafaye, MD; Laurent Karila, MD, PhD; Lisa Blecha, MD; Amine Benyamina, MD, PhD



Cannabis (also known as marijuana) is the most frequently used illicit psychoactive substance in the world. Though it was long considered to be a "soft" drug, studies have proven the harmful psychiatric and addictive effects associated with its use. A number of elements are responsible for the increased complications of cannabis use, including the increase in the potency of cannabis and an evolution in the ratio between the two primary components, Δ⁹-tetrahydrocannabinol (Δ⁹-THC) and cannabidiol (toward a higher proportion of Δ⁹-THC). Synthetic cannabinoid (SC) use has rapidly progressed over the last few years, primarily among frequent cannabis users, because SCs provide similar psychoactive effects to cannabis. However, their composition and pharmacological properties make them dangerous substances. Cannabis does have therapeutic properties for certain indications. These therapeutic applications pertain only to certain cannabinoids and their synthetic derivatives. The objective of this article is to summarize current developments concerning cannabis and the spread of SCs. Future studies must further explore the benefit-risk profile of medical cannabis use.

 Dialogues Clin Neurosci. 2017;19:309-316.

Keywords: *cannabis; cannabidiol; medical cannabis; psychosis; synthetic cannabinoid; tetrahydrocannabinol*

Introduction

Cannabis (also known as marijuana) is a psychoactive plant that contains more than 500 components, of which 104 cannabinoids have presently been identified.[1] Two of these have been the subject of scientific investigation into their pharmacological properties: Δ⁹-tetrahydrocannabinol (Δ⁹-THC) and cannabidiol (CBD). Cannabis potency is primarily evaluated according to a sample's THC concentration. This is the primary psychoactive cannabinoid in cannabis. The adverse effects after acute or regular cannabis use are in direct relation to THC concentrations in the product.[2]

Over the last few years, many studies have shown that CBD levels may also have an important impact. CBD may have a protective effect against certain negative psychological effects from THC. It may also be capable of antagonizing at least some of the adverse effects related to THC.[3]

Various cannabis preparations are available on the illicit drug market: hashish, herbal cannabis (leaves and flowers), and oils. Real-time monitoring of confiscated cannabis preparations has enabled scientists to measure the potency of currently used products. Changes can then be compared with the prevalence of negative health consequences in users. Certain authors speculate that an increase in cannabis potency and in the ratio of

Author affiliations: AP-HP, GH Paris-Sud, Hôpital Paul Brousse, Dpt Addictologie, F94800 Villejuif, France; INSERM U1178, F94800 Villejuif, France

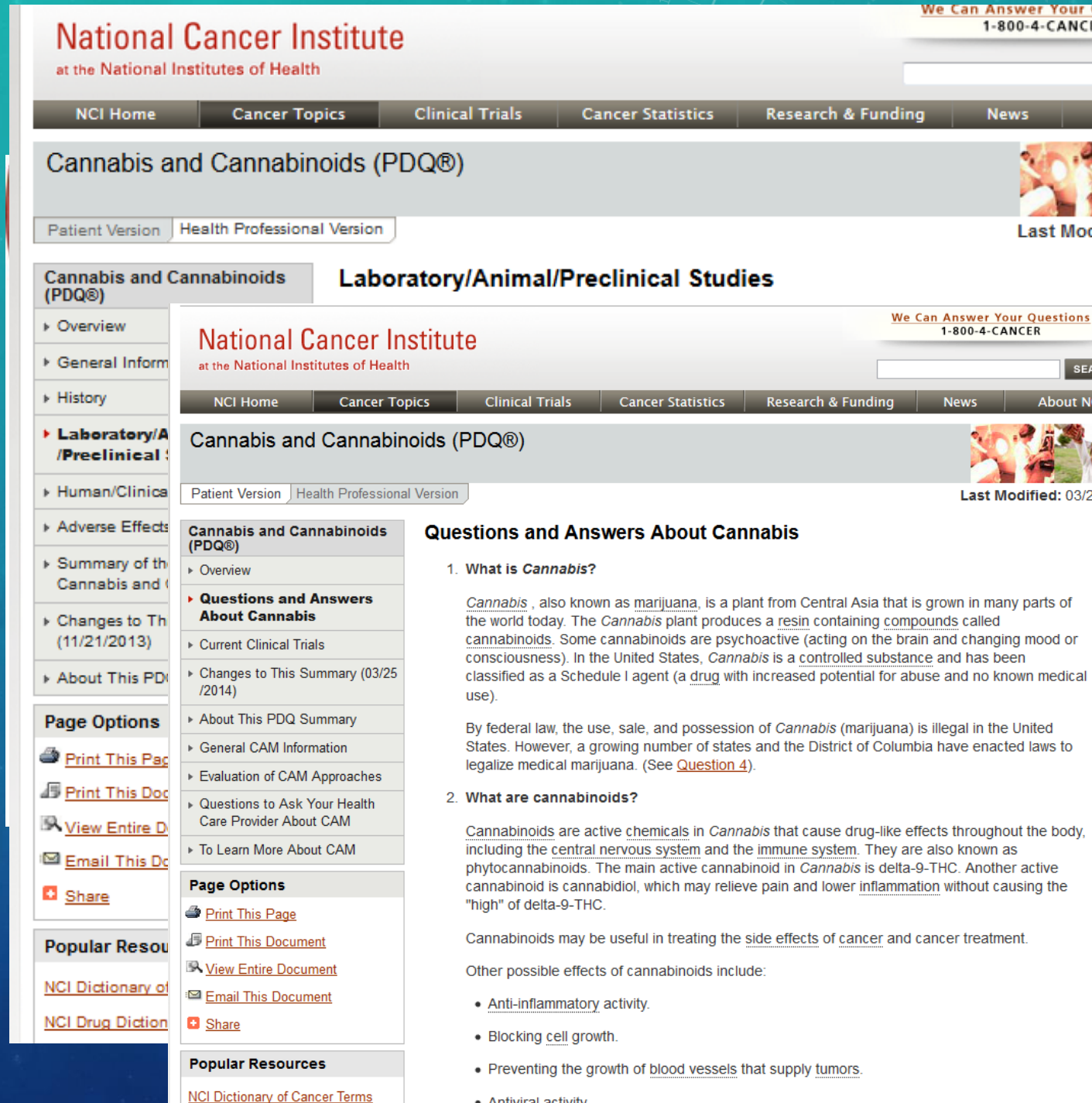
Address for correspondence: Dr Genevieve Lafaye, Hôpital Paul Brousse, Dpt Addictologie, F94800 Villejuif, France
(email: genevieve.lafaye@aphp.fr)

Only THC or CBD had sufficient level of proof for treating spasticity of MS

A systematic review by the American Academy of Neurology examined publications from 1948 through November 2013 concerning the use of cannabinoids in the treatment of multiple sclerosis, movement disorders, and epilepsy.[58] Only oral cannabis extracts (combined THC/CBD or CBD alone) had a sufficient level of proof in treating spasticity from multiple sclerosis and central pain. The other formulations seemed to be effective in these indications, but with lower levels of proof. Proof was insufficient to conclude as to the efficacy of smoked cannabis. In other neurological indications, such as Huntington disease and Tourette syndrome, proofs were judged insufficient.

ANTICANCER

- Prevention of certain cancers (benign and malignant
- Induced apotosis
- Inhibited angiogenesis
- (Indirect?) cytotoxic while protecting normal cells
  - Not all actions through CB-R

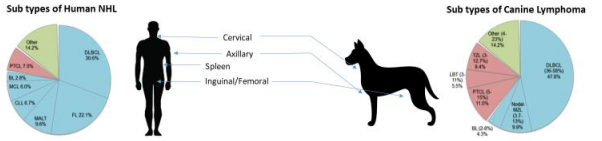


http://www.cancer.gov/cancertopics/pdq/cam/cannabis/patient/page2

Anti-Cancer Effects of Cannabinoids in Canine Lymphoma

Saba Omer[1], Mahmoud Mansour, Satyanarayana Pondugula, Dawn Boothe
[1]PhD Student, Biomedical Sciences, Auburn University, AL
Department of Anatomy, Physiology, and Pharmacology, Biomedical Sciences, Auburn University, AL

Similarities in Canine and Human Lymphoma



Similarities in canine and human lymphoma:
- One of the most common cancer in human and canine.
- Similar morphological, histopathological and molecular presentation.
- 95% of dogs and 30% of human show drug resistance following CHOP based chemotherapy.

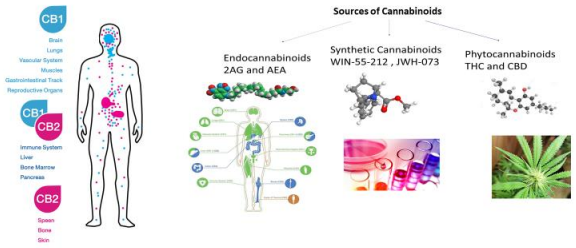
Advantages of canine as a model:
- Spontaneous disease occurring without an isogenic background or genetic engineering
- Chronology of disease adapted to lifespan
- Shared environment and societal status

PLoS ONE 13(12): e0208147 (2018) *BMC Cancer* volume 18, Article number: 522 (2018)

Cannabinoids

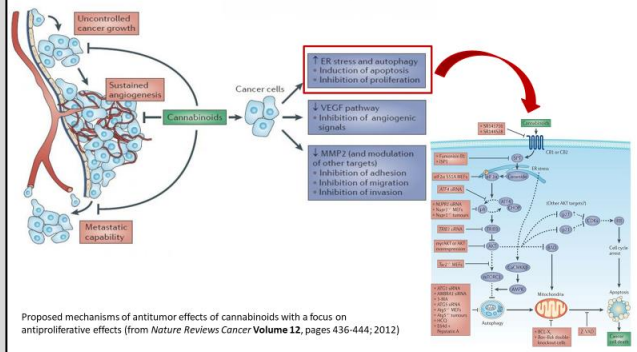
A cannabinoid is a class of diverse chemical compounds that acts on cannabinoid receptors (CB1 and CB2) in the body. Endocannabinoids and their receptors have diverse physiologic roles in the mammalian body.

Cannabinoid Receptors



Sources of Cannabinoids

Cannabinoids and Cancer



Proposed mechanisms of antitumor effects of cannabinoids with a focus on antiproliferative effects (from *Nature Reviews Cancer* **Volume 12**, pages 436-444; 2012)

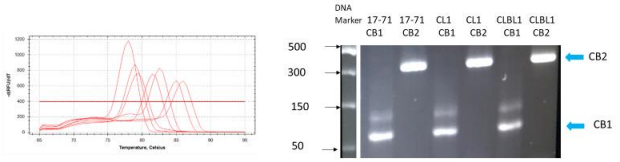
Anti-Cancer Effects of Cannabinoid In Canine Lymphoma Cell Lines

- **To establish base-line expression of CB1 and CB2 cannabinoid receptors in canine B and T cell lymphoma cell lines**
- **To investigate the antiproliferative effects of cannabinoids receptor agonists on canine B and T cell lymphoma cell lines.**

Cannabinoid Receptor Expression in Canine Lymphoma Cell Lines

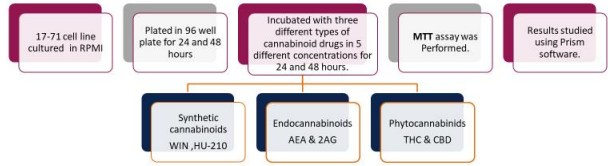
Cell line	Ct GAPDH	Ct CB_1	Δ Ct CB1	Ct CB_2	Δ Ct CB2
1771 B Cell	16.44	25.21	9	26.31	10
CLBL1 B Cell	17.28	22.45	5.5	25.7	7
CL1 T Cell	19.05	24.45	5	23.44	6

qPCR results showing positive expression of both CB1 and CB2 endocannabinoid receptors in untreated 17-71, CLBL1 and CL1 canine B and T cell lymphoma cell lines.

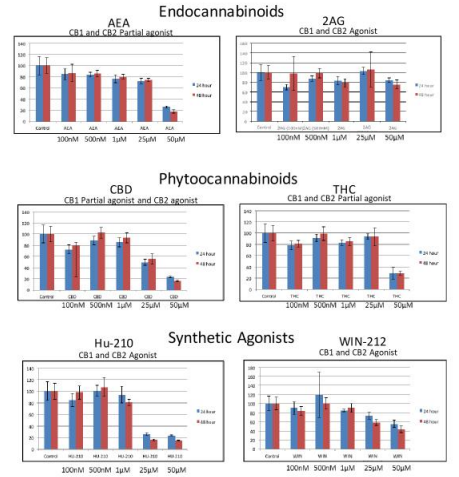


Conventional PCR analysis of CB1 and CB2 receptors expression in canine lymphoma cell lines. Blue arrows point to expected PCR products

Anti-Proliferative Effect of Cannabinoids on Canine B-cell Lymphoma Cell line



Time and Dose Dependent Effect of Cannabinoids Canine Lymphoma Cells



MTT Cell proliferation assay results showing effect of endo, phyto and synthetic cannabinoids on 17-71 lymphoma cell line. Cell proliferation was inhibited in a dose dependent manner by AEA, CBD, THC, WIN-212 and Hu-210 but not 2AG.

Conclusion

We found positive expression of CB1 and CB2 receptor genes in all three canine lymphoma cell lines

We found dose dependent inhibition by 5 of the 6 cannabinoid CB1 and CB2 agonists on one B cell lymphoma cell line.

Future Goals

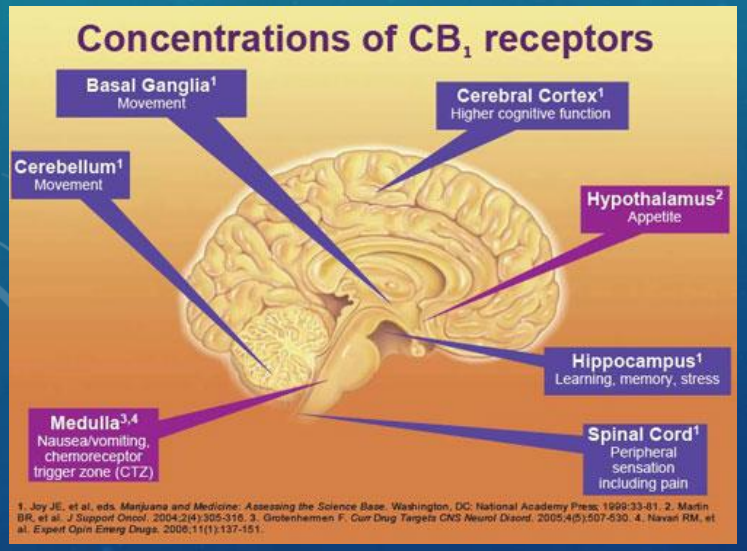
- To study the effect of cannabinoids on canine lymphoma cells when combined with doxorubicin.
- Biochemical analysis of ROS, Nitrite and caspases upon exposure to cannabinoids in order to confirm apoptosis and its mechanism.
- Cell migration assay to study the effect of cannabinoids on cell migration.
- Cell cycle flow cytometry to identify the cycle stage that is most impacted.
- To study the anti-tumor effects of cannabinoid on tumor samples of canine lymphoma using live organ incubator.

Acknowledgements

We are grateful to:
- Steven Suter, North Carolina State University for sharing canine lymphoma cell lines.
- Auburn University Research Initiatives in Cancer (AURIC) for travel funding.

CANNABINOID PHARMACODYNAMICS EFFECTS: SAFETY

- Cannabinoids are able to disrupt short-term memory, impair cognition and time perception, alter mood while enhancing body awareness, discoordination, sleepiness, and reduce attention focus and the ability to “filter” irrelevant information.



- Neuroprotectant
  - ↓ glutamate, etc.
- Dopaminergic reward system
  - Eating, smoking and substance abuse
- Regulation of food intact
- Fat accumulation
- Lipid and glucose metabolism

- Protecting itself:
  - Tolerance
  - Withdrawal
  - Minimized by long half-life

CANNABINOIDS IN DOGS

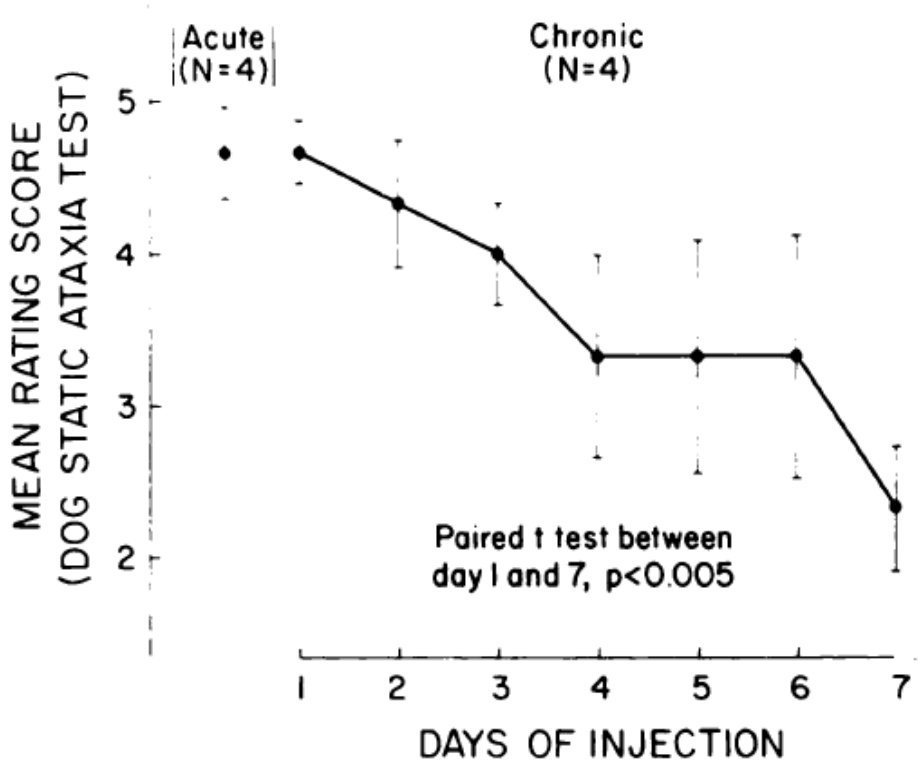


FIG. 1. Development of tolerance to the behavioral effects of Δ⁹-THC. Seven daily i.v. injections of Δ⁹-THC to dogs caused a 50% decrease in response by day 7. Paired *t* test between day 1 and day 7 showed significant difference at $P < .005$. The results are expressed as the means ± S.E.

THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 1976 by The Williams & Wilkins Co.
Vol. 196, No. 1
Printed in U.S.A.

³H-Δ⁹-TETRAHYDROCANNABINOL TISSUE AND SUBCELLULAR DISTRIBUTION IN THE CENTRAL NERVOUS SYSTEM AND TISSUE DISTRIBUTION IN PERIPHERAL ORGANS OF TOLERANT AND NONTOLERANT DOGS[1, 2, 3]

BILLY R. MARTIN, WILLIAM L. DEWEY, LOUIS S. HARRIS AND JACQUELINE S. BECKNER

TABLE 1

Quantification of the behavioral effects produced by cannabinoids[a]

Score	Behavioral Effects
0	No effect
1	Slight depression of activity, slight static ataxia seen only after dog has been standing in one position for 3–5 min
2	Walks with a prance-like placement of feet, exaggerated reflex to a swinging hand and static ataxia after standing in one position for 2–3 min
3	Tail is often tucked, some loss of tone in hind legs as evidenced by a semisquatting position, static ataxia more pronounced and seen after dog stands in one position for 1–2 min, and nodding may be observed 30–60 min after injection
4	Marked static ataxia, sways forward and backward and/or side-to-side, and almost falls after standing in one position for 1 min
5	Cannot stand for longer than 30 sec without almost falling and frequently plunges about
6	Lies prostrate on the floor

[a] Presented here is a slight modification of the rating scales described by Walton *et al.* (1938) and Dewey *et al.* (1972).

Arch. int. Pharmacodyn. **198**, 118–131 (1972)

The effects of Chronic Administration of *Trans*-Δ^9-Tetrahydrocannabinol on Behavior and the Cardiovascular System of Dogs [1]

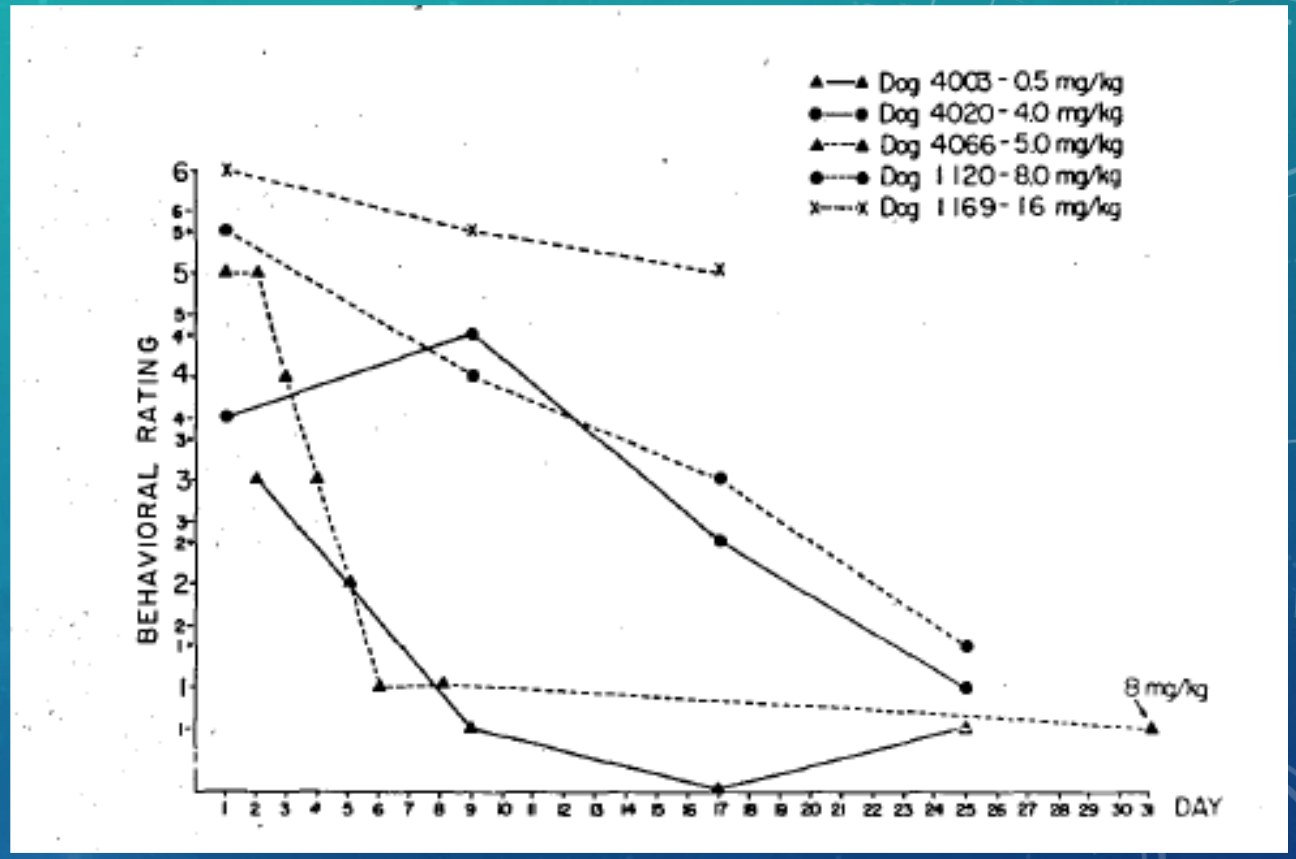
W. L. Dewey, J. Jenkins, T. O'Rourke and L. S. Harris

Department of Pharmacology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina 27514, U.S.A.

Abstract—The daily intravenous administration of Δ^9-tetrahydrocannabinol (Δ^9-THC) produced a marked tolerance to the behavioral effects of this compound in six mongrel dogs. Similar results were obtained with Δ^8-THC in the only dog tested. The minimal effective acute I.V. dose of Δ^9-THC to produce ataxia and other behavioral changes is 0.5 mg/kg. In one dog, the effects of 161 mg/kg Δ^9-THC given intravenously after chronic treatment were less than those observed following 0.5 mg/kg in a drug naive dog. There were no behavioral responses which would indicate a withdrawal syndrome following abrupt stopping of the medications. Tolerance to the behavioral effects of Δ^9-THC developed over a range of doses when the injections were made only once every 8 days. Behavioral tolerance could still be observed 23 days after the last injection of Δ^9-THC in a tolerant dog. Initially Δ^9-THC produced bradycardia in four of seven dogs tested but this changed to tachycardia at higher doses of Δ^9-THC on approximately day 6 or 8 of treatment. There was no significant change in blood pressure in these dogs after either acute or chronic administration.

Bradycardia transitioned to tachycardia at day 6

Minimum effective dose of THC IV = 0.5 mg/kg
Chronic dosing (q 8 days X 80 Days): 161 mg/kg IV had LESS impact
Tolerance still present 23 days after last dose



The production of tolerance to the behavioral effects of *l-trans*-Δ^9-THC given only once every eight days to dogs. The numbers on the ordinate represent the readings on the behavioral rating scale described in methods. Plus and minus signs are used to indicate the behavioral effect observed was somewhat more or less than described. Injections of Δ^9-THC were given only on those days where the character is presented. The animals were drug free on the other days and had food and water presented *ad libitum*. (*Ann. N. Y. Acad. Sci.* **191**, 83, 1971).

Last updated on: 7/8/2009 10:40:00 AM PST

Deaths from Marijuana vs. 17 FDA-Approved Drugs

(Jan. 1, 1997 to June 30, 2005)

I. Background

Much of the medical marijuana discussion has focused on the safety of marijuana compared to the safety of FDA-approved drugs. On June 24, 2005 ProCon.org sent a Freedom of Information Act (FOIA) request to the US Food and Drug Administration (FDA) to find the number of deaths caused by marijuana compared to the number of deaths caused by 17 FDA-approved drugs. Twelve of these FDA-approved drugs were chosen because they are commonly prescribed in place of medical marijuana, while the remaining five FDA-approved drugs were randomly selected because they are widely used and recognized by the general public.

We chose Jan. 1, 1997 as our starting date as it is the beginning of the first year following the Nov. 1996 approval of the first state medical marijuana laws (such as California's Proposition 215). The FDA reports we read from Sep. 13, 2005 to Oct. 14, 2005 included drug deaths "to present", which was the date each report was compiled for our request. We cut off the counting as of June 30, 2005 to provide a uniform end-date to the various reports.

On Aug. 25, 2005 the FDA sent us 12 CDs and five printed reports containing copies of their Adverse Event Reporting System (AERS) report on each drug requested. These reports included all adverse events

Medical Marijuana Homepage

Top Pro & Con Quotes

Top 10 Pro & Con Arguments

Historical Timeline

RECOMMENDED to you...

1. Did You Know?
2. Readers' Comments
3. HOT 33 Legal Medical Marijuana States and DC
4. 17 States with Laws Specifically about Legal Cannabidiol (CBD)
5. Deaths from Marijuana vs. 17 FDA-Approved Drugs

VI. Sources & Disagreement on Marijuana Deaths

Has marijuana caused any deaths?	
General Reference (not clearly pro or con) The Substance Abuse and Mental Health Services Administration's (SAMHSA) 2003 report Mortality Data from the Drug Abuse Warning Network, 2001 (1.5 MB) stated: "Marijuana is rarely the only drug involved in a drug abuse death. Thus... the proportion of marijuana-induced cases labeled as 'One drug' (i.e., marijuana only) will be zero or nearly zero." 2003 - Substance Abuse and Mental Health Services Administration	
PRO (Yes)	**CON (No)**
Thomas Geller, MD, Associate Professor of Child Neurology at the Saint Louis University Health Sciences Center, et al., wrote the following in their Apr. 4, 2004 article titled "Cerebellar Infarction in Adolescent Males Associated with Acute Marijuana Use," published in the journal Pediatrics: "Each of the 3 cannabis-associated cases of cerebellar infarction was confirmed by biopsy (1 case) or necropsy (2 cases)... Brainstem compromise caused by cerebellar and cerebral edema led to death in the 2 fatal cases." Apr. 4, 2004 - Thomas Geller, MD	Stephen Sidney, MD, Associate Director for Clinical Research at Kaiser Permanente, wrote the following in his Sep. 20, 2003 article titled "Comparing Cannabis with Tobacco -- Again," published in the British Medical Journal: "No acute lethal overdoses of cannabis are known, in contrast to several of its illegal (for example, cocaine) and legal (for example, alcohol, aspirin, acetaminophen) counterparts... Although the use of cannabis is not harmless, the current knowledge base does not support the assertion that it has any notable adverse public health impact in relation to mortality." Sep. 20, 2003 - Stephen Sidney, MD
Liliana Bachs, MD, Senior Medical Officer at the Norwegian Institute of Public Health, et al., wrote the following in their Dec. 27, 2001 article titled "Acute Cardiovascular Fatalities Following Cannabis Use," published in the journal Forensic Science International: "Cannabis is generally considered to be a drug with very low toxicity. In this paper, we report six cases where recent cannabis intake was associated with sudden and unexpected death. An acute cardiovascular event was the probable cause of death. In all cases, cannabis intake was documented by blood analysis... Further investigation of clinical, toxicologial and epidemiological aspects are needed to enlighten causality between cannabis intake and acute cardiovascular events." Dec. 27, 2001 - Liliana Bachs, MD	Joycelyn Elders, MD, former US Surgeon General, wrote the following in her Mar. 26, 2004 editorial published in the Providence Journal: "Unlike many of the drugs we prescribe every day, marijuana has never been proven to cause a fatal overdose." Mar. 26, 2004 - Joycelyn Elders, MD
[Editor's Note: Dr. Bachs clarified the findings from her Dec. 27, 2001 study reported above in a Nov. 28, 2005 email to ProCon.org, as quoted below. "Causality is a difficult assessment in	

ASPCA reports 765% increase in calls about pets being poisoned by marijuana

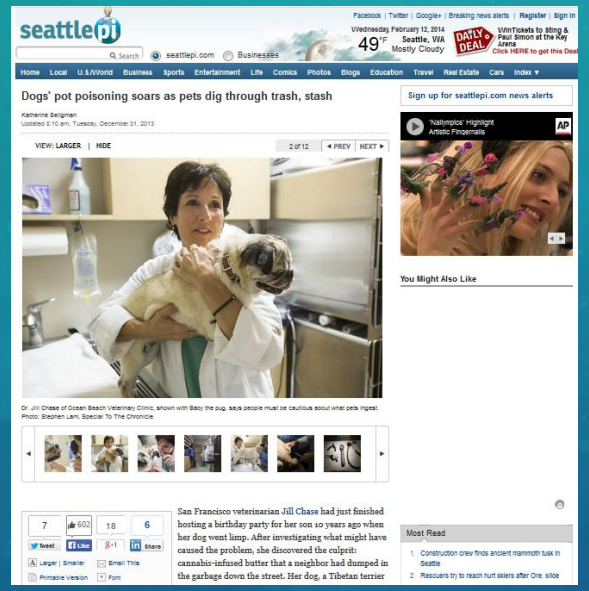
IMAGE: GETTY IMAGES

The last ten years have seen a massive spike in dogs getting accidentally stoned. Tom Shell's dog Stella is one of them — a few weeks ago, he came home to find her on a real wild ride.

When Shell walked through the front door, his 13-year-old mini Australian shepherd was

MARIJUANA TOXICITY

- Accidental ingestion
  - Oral > inhalant (1st and 2nd hand)
- Preclinical (human studies)
  - 0.5 to 2 mg/kg THC IV
  - Ataxia
    - Unique cerebellar CR distribution?
    - Tolerance within 5 days
- No fatalities in 213 cases (2004)
- LD_{50} not determinable
  - 3 g/kg THC
    - 1000 X behavioral dose
- 2 deaths/76 cases
  - Chocolate chip cookies/brownies



Journal of Veterinary Emergency and Critical Care

Retrospective Study

Journal of Veterinary Emergency and Critical Care **22**(6) 2012, pp 690–696
doi: 10.1111/j.1476-4431.2012.00818.x

Evaluation of trends in marijuana toxicosis in dogs living in a state with legalized medical marijuana: 125 dogs (2005–2010)

Stacy D. Meola, DVM, MS; Caitlin C. Tearney, DVM; Sharlee A. Haas, DVM, MS; Timothy B. Hackett, DVM, MS, DACVECC and Elisa M. Mazzaferro, MS, DVM, PhD, DACVECC

Abstract

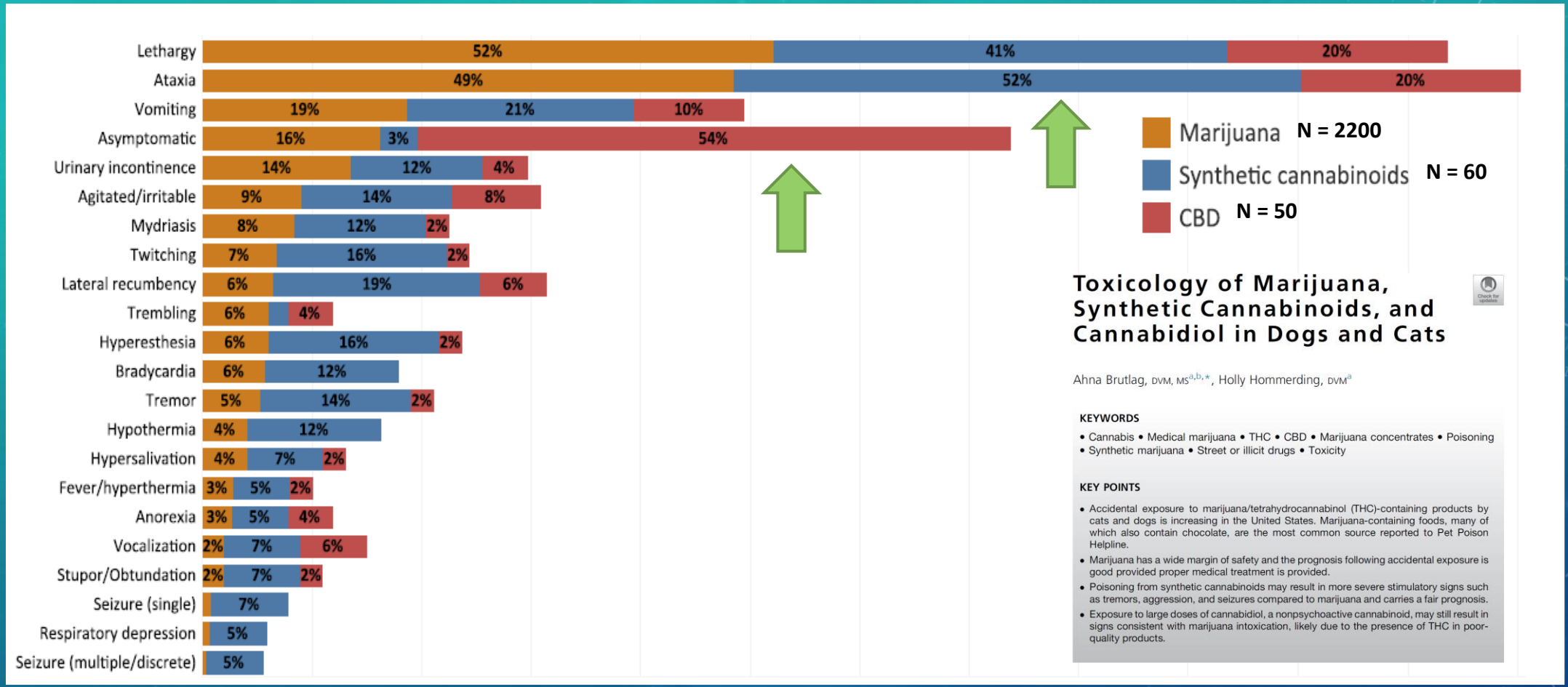
Objective – To report a correlation between the increased number of medical marijuana licenses and marijuana toxicosis in dogs in a state with legalized marijuana for medical use.
Design – Retrospective case series from January 1, 2005 to October 1, 2010.
Setting – Private specialty referral hospital and a university teaching hospital.
Animals – A total of 125 client-owned dogs presenting for known or suspected marijuana toxicosis with or without a urine drug screening test (UDST).
Interventions – None.
Measurements and Main Results – During the study period, 125 dogs were evaluated including 76 dogs with known marijuana exposure or a positive UDST (group 1), 6 dogs with known marijuana ingestion and a negative UDST (group 2), and 43 dogs with known marijuana ingestion that were not tested (group 3). The incidence of marijuana toxicosis presenting to both hospitals increased 4-fold, while the number of people registered for medical marijuana in the state increased 146-fold in the last 5 years. A significant positive correlation was detected between the increase in known/suspected marijuana toxicosis in dogs (groups 1–3) and the increased number of medical marijuana licenses (correlation R coefficient = 0.959, P = 0.002). Two dogs that ingested butter made with medical grade marijuana in baked products died.
Conclusions – A significant correlation was found between the number of medical marijuana licenses and marijuana toxicosis cases seen in 2 veterinary hospitals in Colorado. Ingestion of baked goods made with medical grade tetrahydrocannabinol butter resulted in 2 deaths. UDST may be unreliable for the detection of marijuana toxicosis in dogs.

(J Vet Emerg Crit Care 2012; 22(6): 690–696) doi: 10.1111/j.1476-4431.2012.00818.x

Keywords: canine, elicit drug, intoxication, THC

The Pet Poison Hotline, which takes calls from around the country and Canada, noted a 200 percent increase in reported incidents of poisoning in the past five years. Dr. Lori Green, a

and died of cardiac arrest 14 hours after ingesting the brownies. The interac
the chocolate with the THC may have exacerbated the toxic effects of the TH



Toxicology of Marijuana, Synthetic Cannabinoids, and Cannabidiol in Dogs and Cats

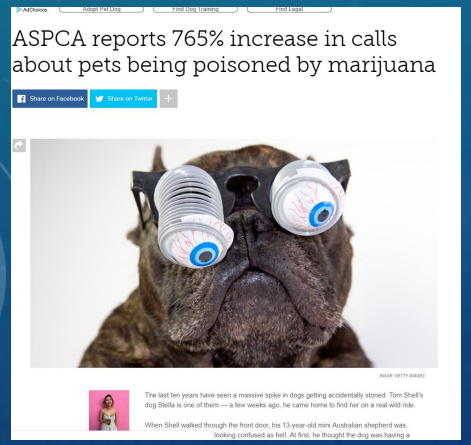
Ahna Brutlag, DVM, MS[a,b,*], Holly Hommerding, DVM[a]

KEYWORDS

• Cannabis • Medical marijuana • THC • CBD • Marijuana concentrates • Poisoning • Synthetic marijuana • Street or illicit drugs • Toxicity

KEY POINTS

- Accidental exposure to marijuana/tetrahydrocannabinol (THC)-containing products by cats and dogs is increasing in the United States. Marijuana-containing foods, many of which also contain chocolate, are the most common source reported to Pet Poison Helpline.
- Marijuana has a wide margin of safety and the prognosis following accidental exposure is good provided proper medical treatment is provided.
- Poisoning from synthetic cannabinoids may result in more severe stimulatory signs such as tremors, aggression, and seizures compared to marijuana and carries a fair prognosis.
- Exposure to large doses of cannabidiol, a nonpsychoactive cannabinoid, may still result in signs consistent with marijuana intoxication, likely due to the presence of THC in poor-quality products.



ASPCA reports 765% increase in calls about pets being poisoned by marijuana

Share on Facebook Share on Twitter

The last ten years have seen a massive spike in dogs getting accidentally stoned. Tom Shell's dog Stella is one of them — a few weeks ago, he came home to find her on a real wild ride.

When Shell walked through the front door, his 13-year-old mini Australian shepherd was looking confused as hell. At first, he thought the dog was having a

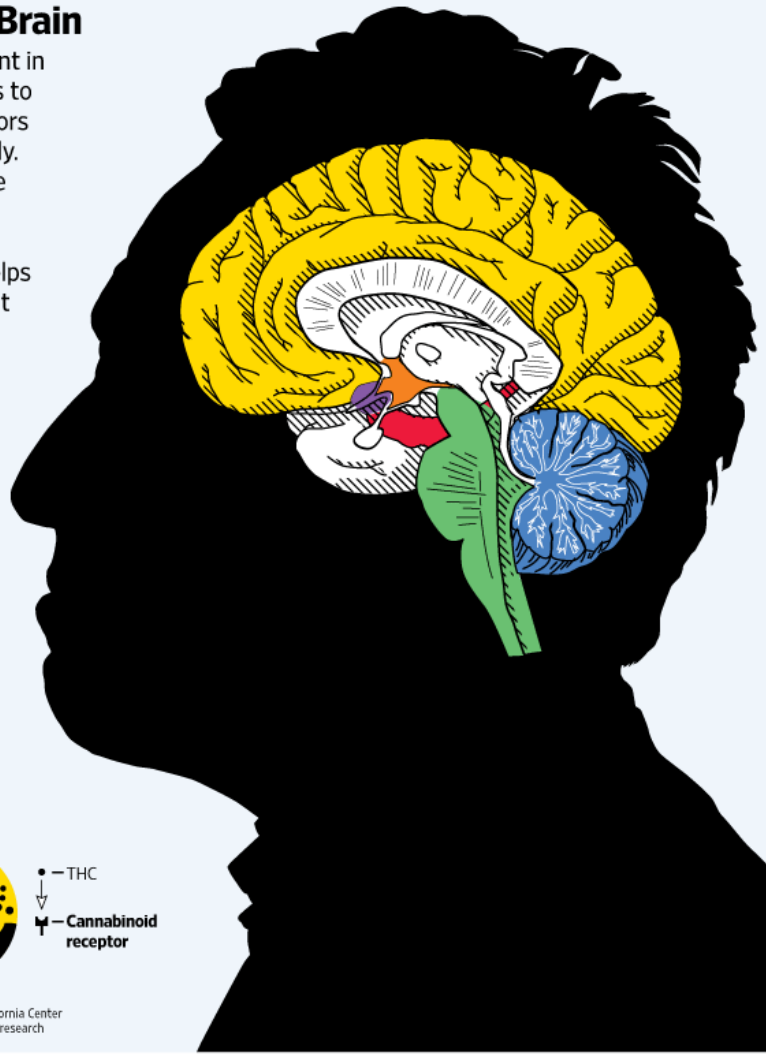
Clinical Signs of Poisoning

Ingestion or inhalation of THC carries a high morbidity but low mortality rate.

Fatality in pets from marijuana intoxication is extremely rare. Two canine fatalities were reported in conjunction with the ingestion of baked goods made with marijuana butter although the cases became complicated and the exact cause of death was not determined.[17] No deaths associated with marijuana have been reported to Pet Poison Helpline.[14]

How Marijuana Affects the Brain

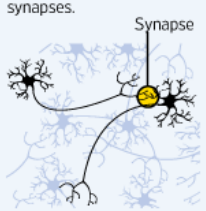
THC, a key ingredient in marijuana, attaches to cannabinoid receptors throughout the body. Several areas of the brain have high densities of these receptors, which helps explain the different effects of the drug.



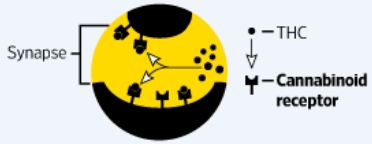
Some areas with high concentrations of cannabinoid receptors:	Corresponding effects of marijuana:
Cerebral cortex	
Plays a role in memory, thinking, perceptual awareness and consciousness	**Altered consciousness; perceptual distortions; memory impairment; occasional delusions and hallucinations**
Hypothalamus	
Governs metabolic processes such as appetite	**Increased appetite**
Brain stem	
Controls many basic functions including arousal, the vomiting reflex, blood pressure and heart rate	**Nausea relief; rapid heart rate; reduced blood pressure; drowsiness**
Also plays a role in pain sensation, muscle tone and movement	**Pain reduction; reduced spasticity; reduced tremor**
Hippocampus	
Is key to memory storage and recall	**Impairment in memory**
Cerebellum	
Governs coordination and muscle control	**Reduced spasticity; impaired coordination**
Amygdala	
Plays a role in emotions	**Anxiety and panic in some cases; reduced anxiety and blocking of traumatic memories in other cases; reduced hostility**

How the receptors work

Nerve cells communicate by passing chemical messages across contact points called synapses.



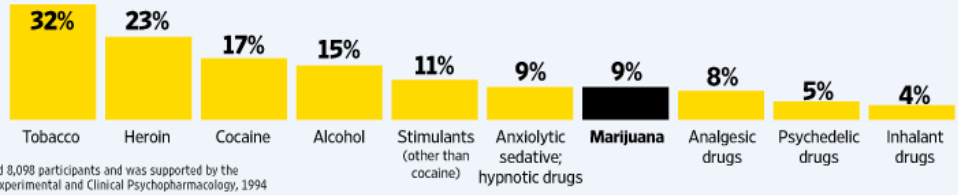
The most active ingredient in marijuana, THC, attaches to cannabinoid receptors and modifies nerve action.



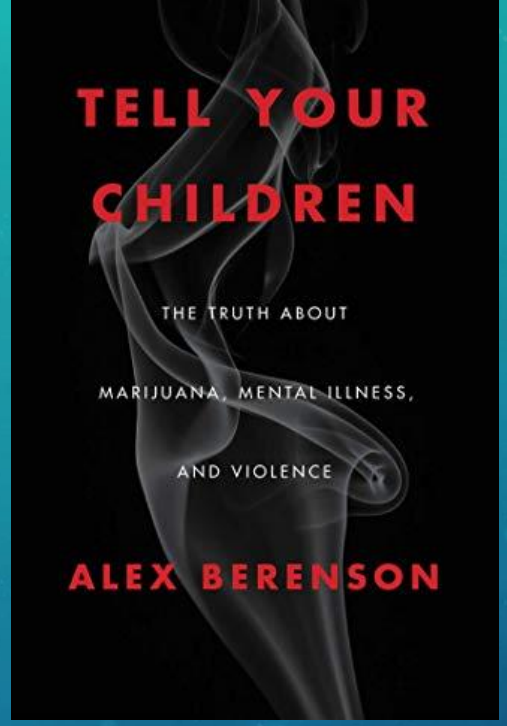
Sources: Igor Grant, University of California Center for Medicinal Cannabis Research; WSJ research

Maryanne Murray/WSJ

Estimated percentage of people in a national survey who used a substance at least once and became dependent



Source: The National Comorbidity Survey, which included 8,098 participants and was supported by the National Institute on Drug Abuse; results published in Experimental and Clinical Psychopharmacology, 1994



the reduction of NMDAR activity. Cannabinoids are proposed to produce such effect by reducing the pre-synaptic release of glutamate or interfering with post-synaptic NMDAR-regulated signaling pathways. The efficacy of such control requires the endocannabinoid

frontiers in
PHARMACOLOGY

REVIEW ARTICLE
published: 02 January 2014
doi: 10.3389/fphar.2013.00169

The cannabinoid receptor 1 associates with NMDA receptors to produce glutamatergic hypofunction: implications in psychosis and schizophrenia

Pilar Sánchez-Blázquez, María Rodríguez-Muñoz and Javier Garzón*

Neurofarmacología, Instituto Cajal, Consejo Superior de Investigaciones Científicas, Madrid, Spain

Edited by:
Maria Grazia Cascio, University of Aberdeen, UK

Reviewed by:
Caitlin Elissa McOmish, Columbia University, USA
Alline Cristina De Campos, Federal University of Minas Gerais, Brazil

***Correspondence:**
Javier Garzón, Neurofarmacología, Instituto Cajal, Consejo Superior de Investigaciones Científicas, Avenida Doctor Arce 37 28002 Madrid, Spain
e-mail: jgarzon@cajal.csic.es

The endocannabinoid system is widespread throughout the central nervous system and its type 1 receptor (CB1) plays a crucial role in preventing the neurotoxicity caused by activation of glutamate *N*-methyl-D-aspartate receptors (NMDARs). Indeed, it is the activity of NMDARs themselves that provides the demands on the endogenous cannabinoids in order to control their calcium currents. Therefore, a physiological role of this system is to maintain NMDAR activity within safe limits, thereby protecting neural cells from excitotoxicity. Thus, cannabinoids may be able to control NMDAR overactivation-related neural dysfunctions; however, the major obstacles to the therapeutic utilization of these compounds are their psychotropic effects and negative influence on cognitive performance. Studies in humans have indicated that abuse of smoked cannabis can promote psychosis and even circumstantially precipitate symptoms of schizophrenia, although the latter appears to require a prior vulnerability in the individual. It is possible that cannabinoids provoke psychosis/schizophrenia reflecting a mechanism common to neuroprotection: the reduction of NMDAR activity. Cannabinoids are proposed to produce such effect by reducing the pre-synaptic release of glutamate or interfering with post-synaptic NMDAR-regulated signaling pathways. The efficacy of such control requires the endocannabinoid system to apply its negative influence in a manner that is proportional to the strength of NMDAR signaling. Thus, cannabinoids acting at the wrong time or exerting an inappropriate influence on their receptors may cause NMDAR hypofunction. The purpose of the present review is to draw the attention of the reader to the newly described functional and physical CB1–NMDAR association, which may elucidate the scenario required for the rapid and efficacious control of NMDAR activity. Whether alterations in these mechanisms may increase NMDAR hypofunction leading to vulnerability to schizophrenia will be outlined.

Keywords: cannabinoid receptors, *N*-methyl-D-aspartate receptor, HINT1 protein, glutamatergic hypofunction, cannabis abuse, schizoph

medicines

MDPI

Perspective

The Role of Cannabis within an Emerging Perspective on Schizophrenia

Jegason P. Diviant [1], Jacob M. Vigil [1,*] and Sarah S. Stith [2]

1 Department of Psychology, University of New Mexico, Albuquerque, NM 87131, USA; diviantj@unm.edu
2 Department of Economics, University of New Mexico, Albuquerque, NM 87131, USA; ssstith@unm.edu
* Correspondence: vigilj@unm.edu; Tel.: +1-505-277-0374

Received: 10 June 2018; Accepted: 31 July 2018; Published: 8 August 2018

check for updates

Abstract: Background: Approximately 0.5% of the population is diagnosed with some form of schizophrenia, under the prevailing view that the pathology is best treated using pharmaceutical medications that act on monoamine receptors. **Methods:** We briefly review evidence on the impact of environmental forces, particularly the effect of autoimmune activity, in the expression of schizophrenic profiles and the role of *Cannabis* therapy for regulating immunological functioning. **Results:** A review of the literature shows that phytocannabinoid consumption may be a safe and effective treatment option for schizophrenia as a primary or adjunctive therapy. **Conclusions:** Emerging research suggests that *Cannabis* can be used as a treatment for schizophrenia within a broader etiological perspective that focuses on environmental, autoimmune, and neuroinflammatory causes of the disorder, offering a fresh start and newfound hope for those suffering from this debilitating and poorly understood disease.

Keywords: schizophrenia; cannabis; marijuana; autoimmunity; monoamine therapy; mental illness; cannabidiol; tetrahydrocannabinol; endocannabinoid system

option for schizophrenia as a primary or adjunctive therapy. **Conclusions:** Emerging research suggests that *Cannabis* can be used as a treatment for schizophrenia within a broader etiological perspective that focuses on environmental, autoimmune, and neuroinflammatory causes of the

Acute Effects of a Single, Oral dose of d9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) Administration in Healthy Volunteers

Authors: Martin-Santos, R.; A. Crippa, J.; Batalla, A.; Bhattacharyya, S.; Atakan, Z.; Borgwardt, S.; Allen, P.; Seal, M.; Langohr, K.; Farre, M.; Zuardi, AW.; K. McGuire, P.
Source: Current Pharmaceutical Design, Volume 18, Number 32, 2012, pp. 4966-4979(14)
Publisher: Bentham Science Publishers
DOI: https://doi.org/10.2174/138161212802884780

Rationale: Animal and humans studies suggest that the two main constituents of cannabis sativa, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have quite different acute effects. However, to date the two compounds have largely been studied separately.

Objective: To evaluate and compare the acute pharmacological effects of both THC and CBD in the same human volunteers.

Methods: A randomised, double-blind, cross-over, placebo controlled trial was conducted in 16 healthy male subjects. Oral THC 10 mg or CBD 600 mg or placebo was administered in three consecutive sessions, at one-month interval. Physiological measures and symptom ratings were assessed before, and at 1, 2 and 3 hours post drug administration. The area under the curve (AUC) between baseline and 3 hours, and the maximum absolute change from baseline at 2 hours were analysed by one-way repeated measures analysis of variance, with drug condition (THC or CBD or placebo) as the factor.

Results: Relative to both placebo and CBD, administration of THC was associated with anxiety, dysphoria, positive psychotic symptoms, physical and mental sedation, subjective intoxication (AUC and effect at 2 hours: $p<0.01$), an increase in heart rate ($p<0.05$). There were no differences between CBD and placebo on any symptomatic, physiological variable.

Conclusions: In healthy volunteers, THC has marked acute behavioural and physiological effects, whereas CBD

How much CBD is right for you?

Which ratio of CBD to THC should you try? Keep in mind, cannabanoids can have varying effects depending on one's tolerance so your mileage may vary.

More CBD

18:1
High CBD, low THC. For novice cannabis users or those who don't want to get high. Rarely psychoactive.

8:1
High CBD, low THC. For novice cannabis users or those who don't want to get high. Rarely psychoactive.

4:1
High CBD, medium THC. Considered mid-range and best for people who have some tolerance for THC.

2:1
More balanced. For people who can tolerate THC. Can be psychoactive at moderate doses.

1:1
More balanced. For people who can tolerate THC. Can be psychoactive at moderate doses.

Less CBD

Source: Care by Design

Mashable

no differences between CBD and placebo on any symptomatic, physiological variable.

CONCLUSIONS: In healthy volunteers, THC has marked acute behavioural and physiological effects, whereas CBD has proven to be safe and well tolerated.

5.1 Neuropsychiatric Adverse Reactions

MARINOL- dronabinol capsule
AbbVie Inc.

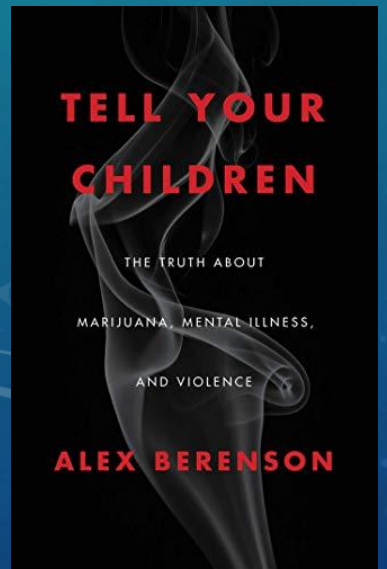
Psychiatric Adverse Reactions

Dronabinol has been reported to exacerbate mania, depression, or schizophrenia. Significant CNS symptoms followed oral doses of 0.4 mg/kg (28 mg per 70 kg patient) of MARINOL in antiemetic studies.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatocellular Injury

EPIDIOLEX- cannabidiol solution
Greenwich Biosciences, Inc.



frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 11 February 2020
doi: 10.3389/fvets.2020.00051

Preliminary Investigation of the Safety of Escalating Cannabinoid Doses in Healthy Dogs

Dana Vaughn, Justyna Kulpa and Lina Paulionis*

Canopy Animal Health, Canopy Growth Corporation, Toronto, ON, Canada

Objective: To determine the safety and tolerability of escalating doses of three cannabis oil formulations, containing predominantly CBD, THC, or CBD and THC (1.5:1) vs. placebo in dogs.

Design: Randomized, placebo-controlled, blinded, parallel study.

Animals: Twenty healthy Beagle dogs (10 males, 10 females).

Methods: Dogs were randomly assigned to one of five treatment groups (n = 4 dogs per group balanced by sex): CBD-predominant oil, THC-predominant oil, CBD/THC-predominant oil (1.5:1), sunflower oil placebo, medium-chain triglyceride oil placebo. Up to 10 escalating doses of the oils were planned for administration via oral gavage, with at least 3 days separating doses. Clinical observations, physical examinations, complete blood counts, clinical chemistry, and plasma cannabinoids were used to assess safety, tolerability, and the occurrence of adverse events (AEs). AEs were rated as mild, moderate, or severe/medically significant.

Results: Dose escalation of the CBD-predominant oil formulation was shown to be as safe as placebo and safer than dose escalation of oils containing THC (CBD/THC oil or THC oil). The placebo oils were delivered up to 10 escalating volumes, the CBD oil up to the tenth dose (640.5 mg; ~62 mg/kg), the THC oil up to the tenth dose (597.6 mg; ~49 mg/kg), and the CBD/THC oil up to the fifth dose (140.8/96.6 mg CBD/THC; ~12 mg/kg CBD + 8 mg/kg THC). AEs were reported in all dogs across the five groups and the majority (94.9%) were mild. Moderate AEs (4.4% of all AEs) and severe/medically significant AEs (0.8% of all AEs) manifested as constitutional (lethargy, hypothermia) or neurological (ataxia) symptoms and mainly occurred across the two groups receiving oils containing THC (CBD/THC oil or THC oil).

Conclusions and clinical significance: Overall, dogs tolerated dose escalation of the CBD oil well, experiencing only mild AEs. The favorable safety profile of 10 escalating doses of a CBD oil containing 18.3–640.5 mg CBD per dose (~2–62 mg/kg) provides comparative evidence that, at our investigated doses, a CBD-predominant oil formulation was safer and more tolerated in dogs than oil formulations containing higher concentrations of THC.

Keywords: cannabinoids, CBD—cannabidiol, THC—tetrahydrocannabinol, safety, adverse events, canine

OPEN ACCESS

Edited by:
Deirdre P. Campion, University College Dublin, Ireland

Reviewed by:
Colm B. Collins, University College Dublin, Ireland
Mario Giorgi, University of Pisa, Italy

****Correspondence:***
Dana Vaughn
dana.vaughn@canopygrowth.com

Specialty section:
This article was submitted to Veterinary Pharmacology and Toxicology, a section of the journal Frontiers in Veterinary Science

Received: *29 October 2019*
Accepted: *21 January 2020*
Published: *11 February 2020*

Citation:
Vaughn D, Kulpa J and Paulionis L (2020) Preliminary Investigation of the Safety of Escalating Cannabinoid Doses in Healthy Dogs. Front. Vet. Sci. 7:51. doi: 10.3389/fvets.2020.00051

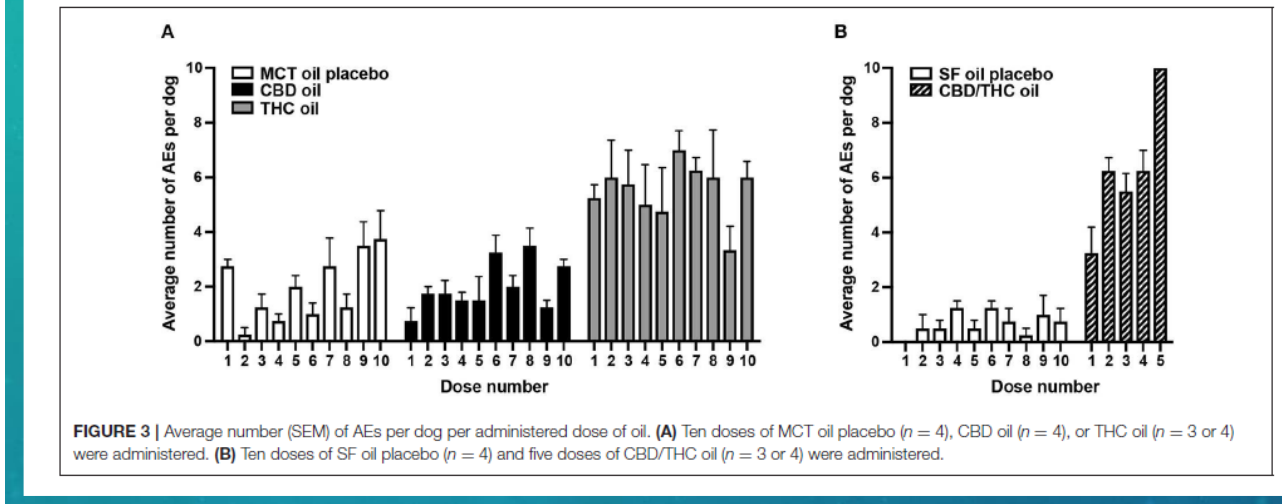
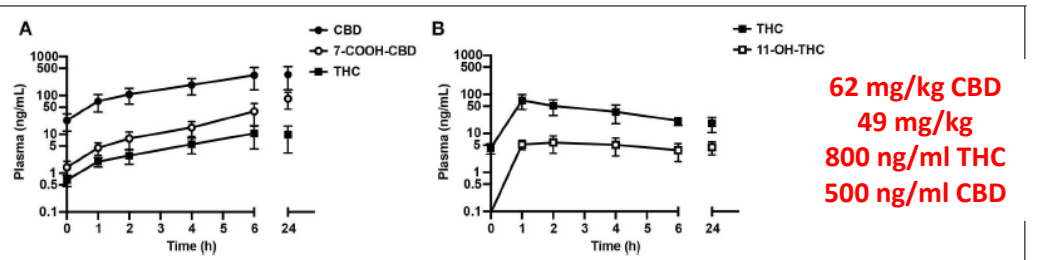
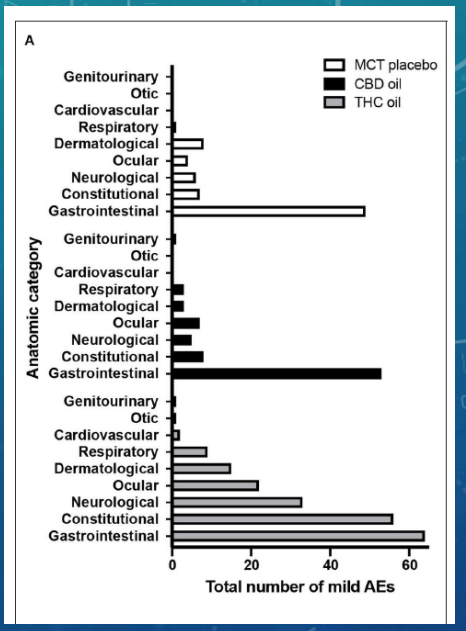


FIGURE 3 | Average number (SEM) of AEs per dog per administered dose of oil. **(A)** Ten doses of MCT oil placebo (n = 4), CBD oil (n = 4), or THC oil (n = 3 or 4) were administered. **(B)** Ten doses of SF oil placebo (n = 4) and five doses of CBD/THC oil (n = 3 or 4) were administered.



62 mg/kg CBD
49 mg/kg
800 ng/ml THC
500 ng/ml CBD



THC oil). The placebo oils were delivered up to 10 escalating volumes, the CBD oil up to the tenth dose (640.5 mg; ~62 mg/kg), the THC oil up to the tenth dose (597.6 mg; ~49 mg/kg), and the CBD/THC oil up to the fifth dose (140.8/96.6 mg CBD/THC; ~12 mg/kg CBD + 8 mg/kg THC). AEs were reported in all dogs across the five groups and the majority (94.9%) were mild. Moderate AEs (4.4% of all AEs) and severe/medically significant AEs (0.8% of all AEs) manifested as constitutional (lethargy, hypothermia) or neurological (ataxia) symptoms and mainly occurred across the two groups receiving oils

Original Article

Journal of Feline Medicine and Surgery 1–14

Safety and tolerability of escalating cannabinoid doses in healthy cats

Justyna E Kulpa[1,2], Lina J Paulionis[1], Graham ML Eglit[2] and Dana M Vaughn[1,2]

Abstract

Objectives The aim of this study was to determine the safety and tolerability of escalating doses of cannabis oils predominant in cannabidiol (CBD), tetrahydrocannabinol (THC), or both CBD and T

Methods In this placebo-controlled, blinded study, 20 healthy adult cats were randomized to o groups (n= 4 per group): two placebo groups (sunflower oil [SF] or medium-chain triglyceride plant-derived cannabinoid oil groups (CBD in MCT, THC in MCT or CBD/THC [1.5:1] in SF). L doses of each formulation were delivered orally via syringe to fasted subjects, with at least doses. Safety and tolerability were determined from clinical observations, complete blood c clinical chemistry. Plasma cannabinoids (CBD, THC) and metabolites (7-COOH-CBD, 11-OH-TH

Results Titration to maximum doses of 30.5 mg/kg CBD (CBD oil), 41.5 mg/kg THC (THC oil CBD/THC (CBD/THC oil) was safely achieved in all subjects. All observed adverse events (AEs) and resolved without medical intervention. Gastrointestinal AEs were more common with form MCT. Constitutional (lethargy, hypothermia), neurologic (ataxia) and ocular (protrusion membr were more common with oils containing THC (CBD/THC and THC oils). There were no clinically s in CBC or clinical chemistry across treatment groups. Higher plasma levels of the cannabinoids a following administration of the CBD/THC combination product are suggestive of a pharmacokin

Conclusions and relevance This is the first feline study to explore the safety and tolerability of C and in combination, in a controlled research setting. These findings will inform veterinarians of cannabinoids, particularly when considering the potential therapeutic use of CBD in cats or r signs associated with accidental exposure to THC-containing products.

Keywords: Cannabidiol; tetrahydrocannabinol; safety; cannabinoid adverse effects; cannabinc and dosage

Accepted: 10 February 2021

Table 2 Cannabidiol (CBD) and tetrahydrocannabinol (THC) quantities per kilogram body weight delivered to cats across the cannabinoid treatment groups (n = 4/group)

	CBD oil		THC oil		CBD/THC oil	
Carrier oil	MCT		MCT		SF	
BSN weight range (kg)	3.5–5.5		3.2–5.0		3.8–5.2	
Dose number	CBD (mg/kg)	THC (mg/kg)	CBD (mg/kg)*	THC (mg/kg)	CBD (mg/kg)	THC (mg/kg)
1	2.8	0.1	–	3.8	1.2	0.8
2	5.5	0.21	–	7.6	2.4	1.5
3	8.3	0.31	–	11.3	3.5	2.3
4	11.1	0.42	–	15.1	4.7	3.0
5	13.9	0.52	–	18.9	5.9	3.8
6	16.6	0.62	–	22.6	7.1	4.6
7	19.4	0.73	–	26.4	8.3	5.3
8	22.2	0.84	–	30.2	9.4	6.1
9	24.9	0.94	–	34.0	10.6	6.9
10	27.7	1.0	–	37.7	11.8	7.6
11	30.5	1.1	–	41.5	13.0	8.4

*CBD was not detected in the cannabinoid analysis (mg/ml) of the THC oil formulation; CBD quantities at higher volumes (>1 ml) of the formulation are unknown
MCT = medium-chain triglyceride; SF = sunflower; BSN = baseline

Adverse Reactions	EPIDIOLEX		Placebo
	10 mg/kg/day	20 mg/kg/day	
	N=75 %	N=238 %	N=227 %
Hepatic Disorders			
Transaminases elevated	8	16	3
Gastrointestinal Disorders			
Decreased appetite	16	22	5

EPIDIOLEX- cannabidiol solution
Greenwich Biosciences, Inc.

Hepatic Impairment	Starting Dosage	Maintenance Dosage	Recommended Dosage
Mild	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)	10 mg/kg twice daily (20 mg/kg/day)
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 mg/kg twice daily (2 mg/kg/day)	2 mg/kg twice daily (4 mg/kg/day)

Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy

Stephanie McGrath DVM, MS
Lisa R. Bartner DVM, MS
Sangeeta Rao BVSc, PhD
Rebecca A. Packer DVM, MS
Daniel L. Gustafson PhD

From the Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523.

Address correspondence to Dr. McGrath (stephanie.mcgrath@colostate.edu).

OBJECTIVE
To assess the effect of oral cannabidiol (CBD) administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with idiopathic epilepsy.

DESIGN
Randomized blinded controlled clinical trial.

ANIMALS
26 client-owned dogs with intractable idiopathic epilepsy.

PROCEDURES
Dogs were randomly assigned to a CBD (n = 12) or placebo (14) group. The CBD group received CBD-infused oil (2.5 mg/kg [1.1 mg/lb], PO) twice daily for 12 weeks in addition to existing antiepileptic treatments, and the placebo group received noninfused oil under the same conditions. Seizure activity, adverse effects, and plasma CBD concentrations were compared between groups.

RESULTS
2 dogs in the CBD group developed ataxia and were withdrawn from the study. After other exclusions, 9 dogs in the CBD group and 7 in the placebo group were included in the analysis. Dogs in the CBD group had a significant (median change, 33%) reduction in seizure frequency, compared with the placebo group. However, the proportion of dogs considered responders to treatment (≥ 50% decrease in seizure activity) was similar between groups. Plasma CBD concentrations were correlated with reduction in seizure frequency. Dogs in the CBD group had a significant increase in serum alkaline phosphatase activity. No adverse behavioral effects were reported by owners.

CONCLUSIONS AND CLINICAL RELEVANCE
Although a significant reduction in seizure frequency was achieved for dogs in the CBD group, the proportion of responders was similar between groups. Given the correlation between plasma CBD concentration and seizure frequency, additional research is warranted to determine whether a higher dosage of CBD would be effective in reducing seizure activity by ≥ 50%. (*J Am Vet Med Assoc* 2019;254:1301–1308)

Treatment effects

Following study treatment, a significant ($P = 0.01$) reduction was identified in the group median for

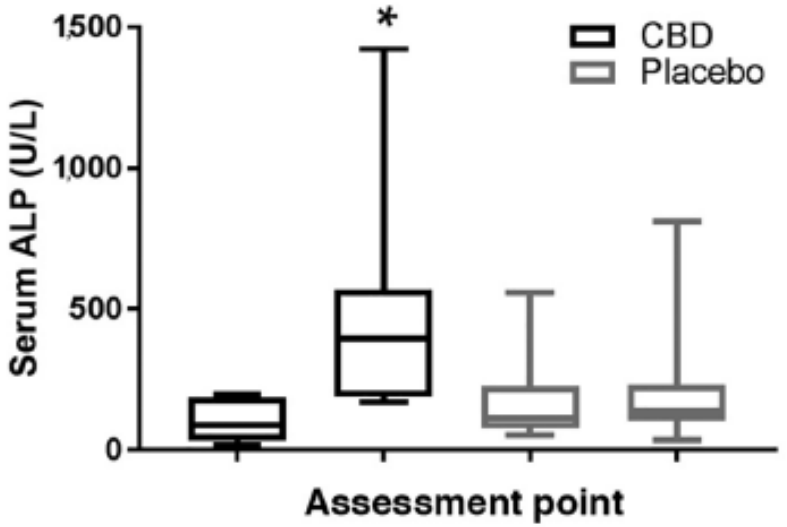


Figure 1—Box-and-whisker plots of serum ALP activity at week 0 (before study treatment) and week 12 for client-owned dogs with intractable idiopathic epilepsy that were randomly assigned to receive CBD-infused oil (2.5 mg/kg [1.1 mg/lb], PO, twice daily for 12 weeks; n = 9; black boxes) or a placebo at a similar dosage (7; gray boxes), in addition to currently prescribed conventional AEDs. The top and bottom of each box represent the 75th and 25th percentiles, respectively; the central horizontal line within each box represents the median; and the whiskers represent the minimum and maximum values. *Values differ significantly ($P = 0.004$) between assessment points for dogs in the CBD group.

Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol Treatment in Osteoarthritic Dogs

*Lauri-Jo Gamble[1], Jordyn M. Boesch[1], Christopher W. Frye[1], Wayne S. Schwark[2], Sabine Mann[3], Lisa Wolfe[4], Holly Brown[5], Erin S. Berthelsen[1] and Joseph J. Wakshlag[1]**

[1] Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY, United States, [2] Department of Molecular Medicine, College of Veterinary Medicine, Cornell University, Ithaca, NY, United States, [3] Department of Population Medicine, College of Veterinary Medicine, Cornell University, Ithaca, NY, United States, [4] Proteomic and Metabolomic Facility, Colorado State University, Fort Collins, CO, United States, [5] Metzger Animal Hospital, State College, PA, United States

Objectives: The objectives of this study were to determine basic oral pharmacokinetics, and assess safety and analgesic efficacy of a cannabidiol (CBD) based oil in dogs with osteoarthritis (OA).

Methods: Single-dose pharmacokinetics was performed using two different doses of CBD enriched (2 and 8 mg/kg) oil. Thereafter, a randomized placebo-controlled, veterinarian, and owner blinded, cross-over study was conducted. Dogs received each of two treatments: CBD oil (2 mg/kg) or placebo oil every 12 h. Each treatment lasted for 4 weeks with a 2-week washout period. Baseline veterinary assessment and owner questionnaires were completed before initiating each treatment and at weeks 2 and 4. Hematology, serum chemistry and physical examinations were performed at each visit. A mixed model analysis, analyzing the change from enrollment baseline for all other time points was utilized for all variables of interest, with a $p \leq 0.05$ defined as significant.

Results: Pharmacokinetics revealed an elimination half-life of 4.2 h at both doses and no observable side effects. Clinically, canine brief pain inventory and Hudson activity scores showed a significant decrease in pain and increase in activity ($p < 0.01$) with CBD oil. Veterinary assessment showed decreased pain during CBD treatment ($p < 0.02$). No side effects were reported by owners, however, serum chemistry showed an increase in alkaline phosphatase during CBD treatment ($p < 0.01$).

Clinical significance: This pharmacokinetic and clinical study suggests that 2 mg/kg of CBD twice daily can help increase comfort and activity in dogs with OA.

Keywords: cannabidiol, CBD oil, hemp, canine, osteoarthritis, pharmacokinetic

OPEN ACCESS

Edited by:
Troy N. Trumble, University of Minnesota Twin Cities, United States

Reviewed by:
Gareth Edward Zeiler, University of Pretoria, South Africa
Joao Henrique Neves Soares, Virginia Tech, United States

****Correspondence:***
Joseph J. Wakshlag
jw37@cornell.edu

Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *25 February 2018*
Accepted: *02 July 2018*
Published: *23 July 2018*

- **Is the increase in SALP induction, or is it hepatopathy?**

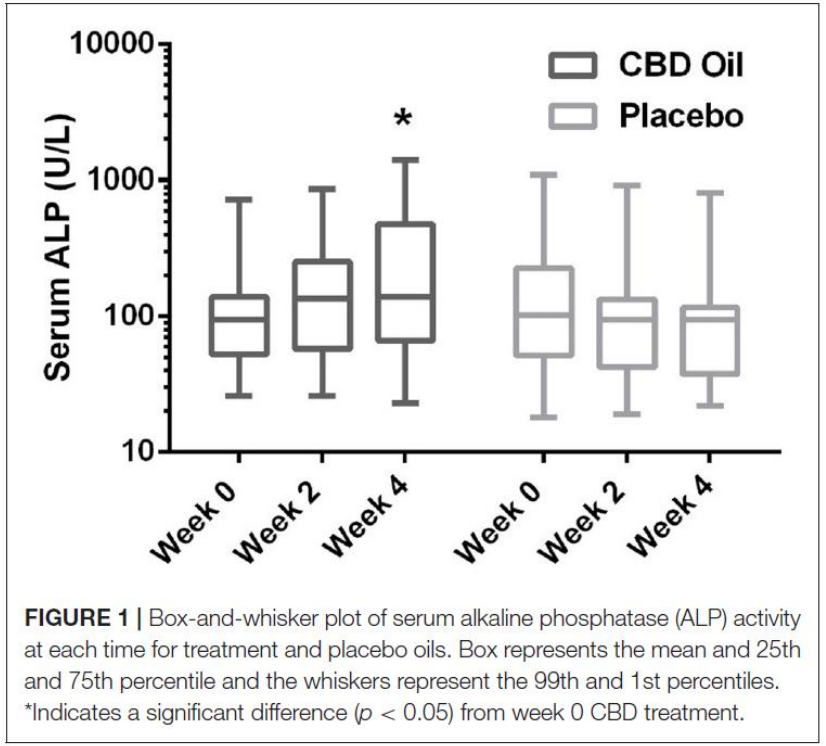


FIGURE 1 | Box-and-whisker plot of serum alkaline phosphatase (ALP) activity at each time for treatment and placebo oils. Box represents the mean and 25th and 75th percentile and the whiskers represent the 99th and 1st percentiles. *Indicates a significant difference ($p < 0.05$) from week 0 CBD treatment.

TABLE 4 | Clinical chemistry plasma parameters indicative of liver function as measured in healthy Beagle dogs administered cannabinoid oils.

	AST (U/L)			ALT (U/L)			ALP (U/L)			GGTP (U/L)			Total Bilirubin (μmol/L)		
	RR = 15–66 U/L			RR = 12–118 U/L			RR = 5–131 U/L			RR = 1–12 U/L			RR = 0.0–5.1 μmol/L		
	BSN	24 h post FD	7 d post FD	BSN	24 h post FD	7 d post FD	BSN	24 h post FD	7 d post FD	BSN	24 h post FD	7 d post FD	BSN	24 h post FD	7 d post FD
CBD OIL															
Mean (SD)	23.3 (1.7)	21.0 (2.8)	21.0 (2.2)	24.3 (3.4)	29.8 (10.6)	26.0 (5.0)	53.8 (17.6)	93.3 (24.7)	90.5 (24.3)	4.0 (1.4)	4.0 (1.4)	3.8 (0.5)	2.5 (0.5)	1.7 (0.5)	1.7 (0.4)
THC OIL															
Mean (SD)	20.3 (5.1)	19.0 (4.0)	17.0 (3.6)	20.3 (1.5)	22.3 (1.5)	22.0 (1.7)	30.5 (8.6)	35.3 (9.7)	39.0 (10.0)	3.8 (1.3)	3.7 (0.6)	3.0 (1.0)	2.4 (0.4)	1.8 (0.2)	1.6 (0.2)
CBD/THC OIL															
Mean (SD)	24.5 (2.6)	20.3 (3.2)	18.0 (1.7)	29.8 (7.8)	44.0 (21.1)	36.3 (6.4)	43.3 (15.7)	95.0 (81.7)	55.7 (28.1)	2.8 (0.5)	3.7 (1.2)	3.3 (2.1)	2.7 (0.7)	2.0 (0.3)	2.1 (0.2)

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 11 February 2020
doi: 10.3389/fvets.2020.00051

Check for updates

Preliminary Investigation of the Safety of Escalating Cannabinoid Doses in Healthy Dogs

Dana Vaughn, Justyna Kulpa and Lina Paulionis*

Canopy Animal Health, Canopy Growth Corporation, Toronto, ON, Canada

CONCLUSIONS / CHALLENGES

- Product variability
  - Adulteration/misbranding
  - Buyer beware
  - Content
    - Cannabinoids plus?
    - CBDA vs CBD
    - Vehicle? Feed
- Know your cannabinoid
  - THC / cannabis vs. hemp/CBD
  - Safety, efficacy CBD>THC
- Sole versus add-on
  - Target disease dependent?
- Needs to know:
- Proper dose
  - Concentration? (hemp vs CBD?)
- Tolerance: anticipate the need to increase dose
- Drug interactions (watch carefully)
- Well designed controlled clinical trials (multiple)
- Monitoring to establish your patient's therapeutic range?


MEDICAL
MARIJUANA
OPEN
TOP SHELF