Dr. Sarah Silcox

Canadian Association of Veterinary Cannabinoid Medicine

CAVCM

Advocate ~ Educate ~ Collaborate ~ Develop

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Cannabis in Veterinary Medicine

What You Need to Know

Cannabis Legislation

The 1930's saw the start of cannabis prohibition across North America

Early Drug Prohibition in Canada

- 1908 – Opium Act
- 1911 – Opium and Drug Act (added morphine/cocaine)
- 1920 – Opium and Narcotic Drug Act
- 1923 – Narcotics Drug Act Amendment Bill
- 1937 – First seizure of Cannabis by Canadian police
- 1960s – Surge in popularity > harsher penalties
- 1961 – Narcotics Control Act
- 1969-1972 – Le Dain Commission
- 1996 – Controlled Drugs and Substances Act
- 1998 – Industrial Hemp Regulations

Industrial Hemp Regulations (IHR) 1998

- Is an exemption to the Controlled Drug and Substances Act (CDSA)
- Hemp production requires license, regular inspections, and is limited to approved strains
- Plants must contain less than 0.3% TCH in leaves and flowers.
- Exemption only applies to seeds and stalks – *not leaves/flowers, etc.*
- Hemp is an under-utilized source of medicinal CBD
- Unlike in the US, even products derived from stalk, if they contain CBD, fall under CDSA as CBD is Schedule II drug.

Medical Cannabis Legalization

2001: MMAR
(Marihuana Med.AccessReg.)

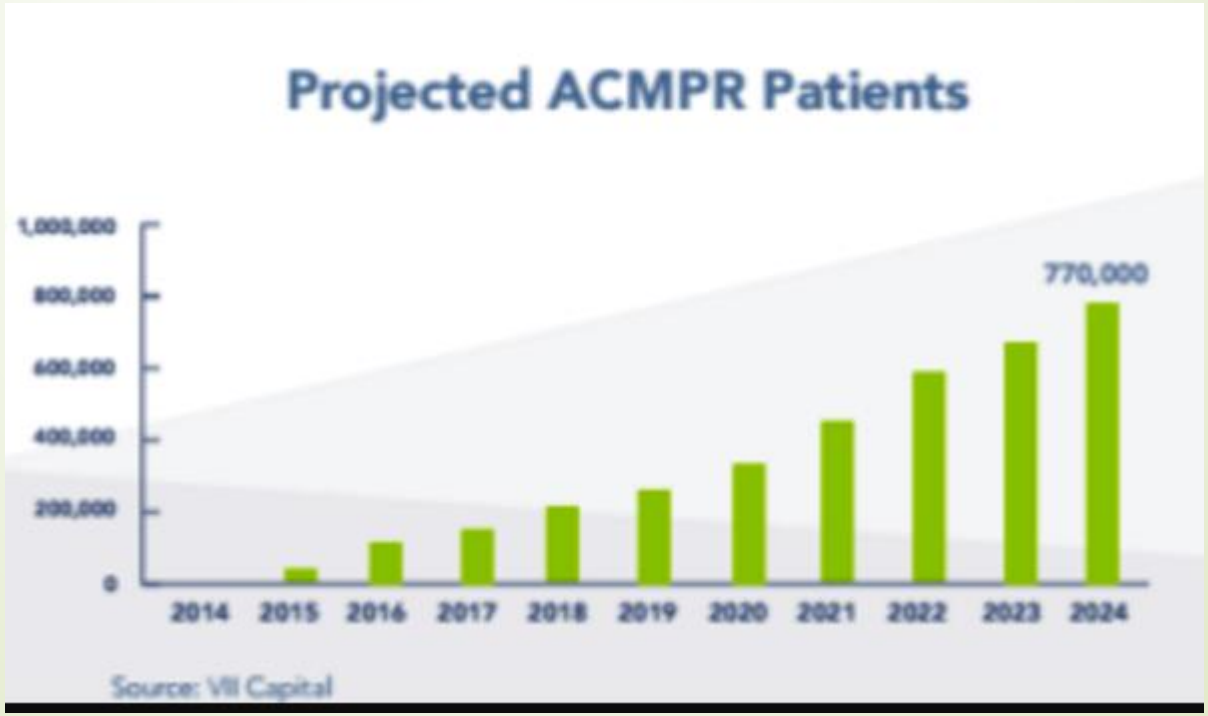
2013: MMPR
(Marihuana for Med.Purp.Reg.)

2016: ACMPR
(Access to Cannabis for Med.Purp.Reg)

Over 235,000 Canadians Accessing Medical Cannabis through the ACMPR

(as of Sept. 2017)

Growth of approx. 30% each quarter



But some important individuals were left out of all these new regulations…

…and what about these guys?

Why Should We Care About Cannabis for Animals?

- They get sick and suffer, much like we do.
- They each have an Endocannabinoid System that responds to exogenous cannabinoids – much like we do.
- They add value to our lives – in so many ways!
- Their value is reflected in the money that we spend on them.

16.4 million pet dogs & cats in Canada

(data from Canadian Animal Health Institute)

Pet Industry

*source: 2015 Canadian Pet Market Outlook prepared by consumer research firm Packaged Facts.
source: Packaged Facts' most recent report 2016. source: North American Pet Health Insurance Association

Today's Presentation

- Review of legislative issues that affect our ability to access safe and effective cannabis-based medicine for animals
- Current uses of veterinary cannabis
- Special Considerations for Animals
- New legislation and its impact on Vet. Med.
- Some potential risks and dangers of using cannabis for pets
    - * diagnostic challenges
    - * common co-toxicities
- Choosing a pet product
- Future direction of veterinary cannabinoid medicine

History of Veterinary Cannabis

* Ancient Greeks used cannabis to dress wounds on their horses.

* Cannabis was a common ingredient in many medicines (both human and animal) until the start of prohibition in the 1930's.

* Renewed interest in veterinary cannabis in last 10 years, following surge in human medical use.

ACMPR

Health Care Practitioners
Marginal note:Authorized activities
7 (1) In addition to being authorized to possess fresh or dried marihuana or cannabis oil in accordance with section 3, a health care practitioner may conduct the following activities in regard to a *person* who is under their professional treatment:

(a) transfer or administer the substance; or
(b) provide a medical document.

Marginal note:Transfer
(2) The health care practitioner may also transfer the substance to an individual who is responsible for *the person* under their professional treatment.

Marginal note:Medical document
8 (1) A medical document provided by a health care practitioner to a person who is under their professional treatment must indicate

(a) the practitioner's given name, surname, profession, business address and telephone number, the province in which they are authorized to practise their profession and the number assigned by the province to that authorization and, if applicable, their facsimile number and email address;
(b) the person's given name, surname and date of birth;
(c) the address of the location at which the person consulted with the practitioner;
(d) the daily quantity of dried marihuana, expressed in grams, that the practitioner authorizes for the person; and
(e) the period of use.

Provincial Veterinary Associations and By-Laws

College of Veterinarians of British Columbia

THE COLLEGE OF VETERINARIANS OF ONTARIO
CVO
ACCREDITED FACILITY

- No current legal routes for prescribing or access
- Risk of Professional Misconduct
- Lack of Evidence Based Medicine to support recommendations
- Medical Cannabis is not fitting with current "Standard of Care"

College of Veterinarians of British Columbia

Medical Marijuana and Cannabidiol Guidelines

Published October 2017

Veterinarians have contacted the College of Veterinarians of British Columbia (CVBC) to inquire whether they may prescribe medical marijuana and cannabidiol (CBD) to an animal. The question usually arises in one of two ways: an animal owner inquiring of a veterinarian, or a medical marijuana dispensary seeking authorization from a veterinarian.

Veterinarians may advise their clients that:

1. There is no current legal pathway for veterinarians in BC to prescribe medical marijuana to animals as the federal government legislation Access to Cannabis for Medical Purposes Regulations does not apply to veterinarians or to animals. The Regulations pertain to human health care and access for human patients only.[1]
2. There are currently no cannabidiol (CBD) products approved by Health Canada and therefore no legal pathway to obtain these products. The National Compliance Section, Office of Controlled Substances, Healthy Environments and Consumer Safety Branch of Health Canada has advised that cannabis (marijuana) and cannabidiol (CBD) are Schedule II drugs under the Controlled Drugs and Substances Act, and that there are currently no approved CBD products for animals, meaning there is no legal pathway to obtain these products for animals in Canada. It is not enough that CBD oil or related products may be offered through a licensed supplier in Canada – the supplier must also be supplying a CBD product that is approved by Health Canada.

Health Canada can be contacted for additional information on cannabis or CBD products, or on the approval process for products for animals. For more information, contact the Veterinary Drugs Directorate at Health Canada (http://www.hc-sc.gc.ca/contact/dhp-mps/hpfb-dgpsa/vdd-dmv-eng.php).

Similar information is provided to veterinarians in Ontario by the College of Veterinarians of Ontario (CVO) in the CVO e-update entitled Update on Medical Marijuana available at: https://cvo.org/About-CVO/News/Inquiries-concerning-prescribing-medical-marijuana.aspx

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[1] In 2014, the CVBC's College Matters Newsletter had provided registrants with communication from Health Canada that The Emergency Drug Release Program that the Veterinary Drugs Directorate administers does not permit access to medical marihuana for animals.

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Strategic Plan
President & Registrar
Legislation
Mission and Principles
CVO Priorities
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Update on medical marijuana

May 25, 2017

In ongoing consultation with Health Canada about the *Access to Cannabis for Medical Purposes Regulations* (federal government legislation) and how it pertains to veterinarians, the College has received further information related to this evolving topic.

The Office of Medical Cannabis has confirmed that the *Access to Cannabis for Medical Purposes Regulations* do not apply to veterinarians or animals; the regulations pertain to human healthcare practitioners and access for human patients only.

Much of the focus on this topic for veterinarians has not been on the use of medical marijuana directly with animals, but on the use of cannabidiol (CBD), specifically CBD oil. Both cannabis (marijuana) and cannabidiol are Schedule II drugs under the *Controlled Drugs and Substances Act.* As veterinarians are included in the definition of practitioner in this Act, veterinarians would be permitted to prescribe either substance if there was a legal pathway to do so. The Office of Controlled Substances at Health Canada has confirmed that there are currently no approved CBD products for animals, meaning there is no legal pathway to obtain these products for animals in Canada.

It is not enough that CBD oil or related products may be offered through a licensed supplier in Canada – the supplier must also be supplying a CBD product that is approved by Health Canada. Manufacturers would need to complete the approval process to get such a product approved for use in animals.

The College is aware that animal owners may ask their veterinarians about using products for their animals that contain active ingredients found in the cannabis plant. It is important that the public is aware that:

1. There is currently no legal pathway for veterinarians in Ontario to prescribe medical marijuana to animals.
2. There are currently no CBD products approved by Health Canada and therefore no legal pathway to obtain these products.

Health Canada can be contacted for additional information on cannabis or CBD products, or on the approval process for products for animals. For more information, contact the Veterinary Drugs Directorate at Health Canada (http://www.hc-sc.gc.ca/contact/dhp-mps/hpfb-dgpsa/vdd-dmv-eng.php).

LOOPHOLE?

Pets are considered *property* under the Criminal Code of Canada

(With some added provisions regarding neglect/cruelty)

=

But that hasn't stopped retail…

CBD vs. THC

- CBD Pet products predominate. Why?
- Spill-over from the US where CBD is 'legal' in all states
- Less enforcement even here where it is still a Scheduled II Controlled Substance
- Low toxicity; Well tolerated; Range of therapeutic effects; Media Coverage
- Perception that THC is 'toxic' to dogs

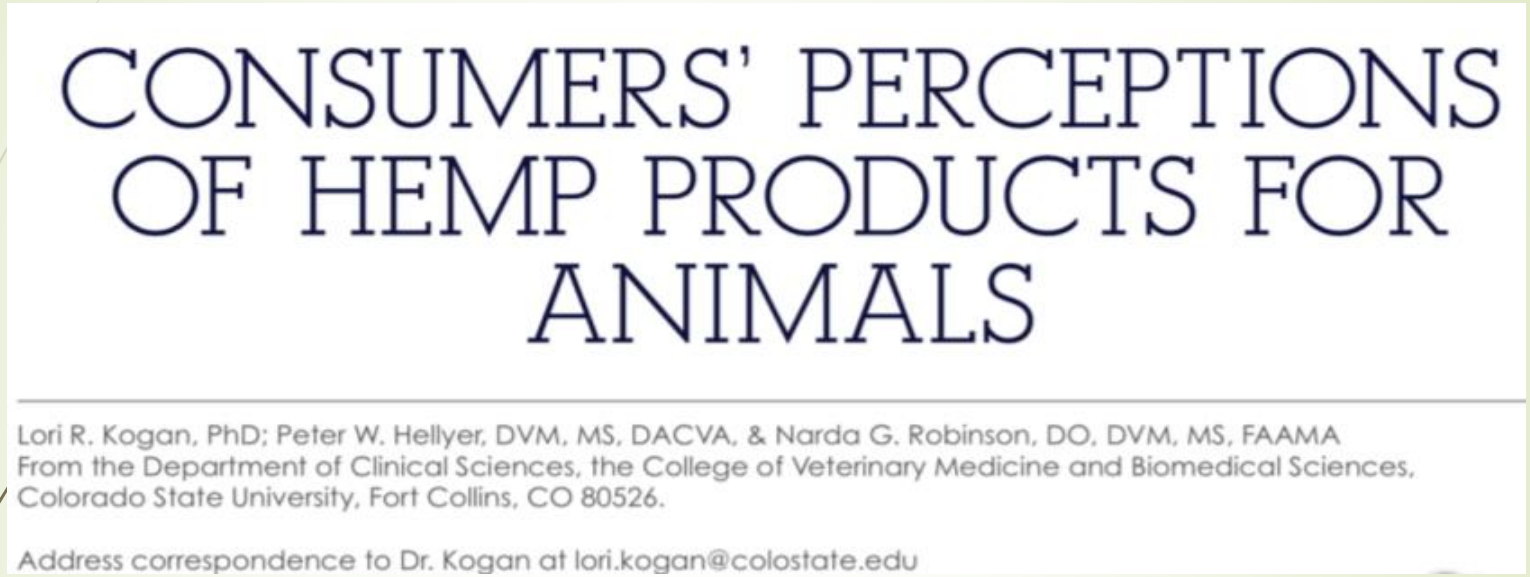
News Release

Penn Study Shows Nearly 70 Percent of Cannabidiol Extracts Sold Online Are Mislabeled

Mislabeling may lead to adverse effects for patients, including children with epilepsy

November 07, 2017

What are pet owners treating with CBD?



CONSUMERS' PERCEPTIONS OF HEMP PRODUCTS FOR ANIMALS

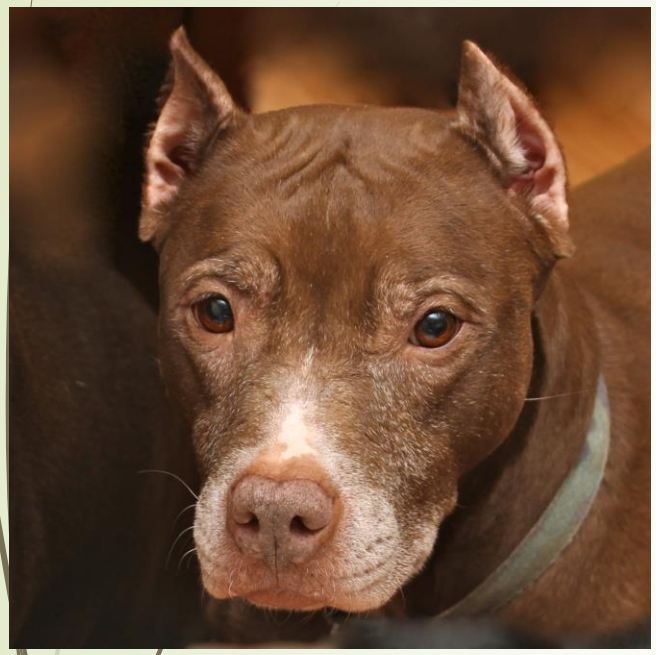
Lori R. Kogan, PhD; Peter W. Hellyer, DVM, MS, DACVA, & Narda G. Robinson, DO, DVM, MS, FAAMA
From the Department of Clinical Sciences, the College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80526.

Address correspondence to Dr. Kogan at lori.kogan@colostate.edu

According to study by CSU and published in the JAHVMA in 2016, pet owners reported that medical cannabis helped either "a moderate amount" or "a lot" for the following conditions:

JAHVMA = Journal of the American Holistic Veterinary Medical Association

For Dogs:



- Pain Relief (95%)
- Age-related behavioral changes (93%)
- Seizures (92%)
- Inflammation (92%)
- Sleep quality (89%)
- Anxiety relief (83%)
- Nausea reduction (82%)
- Muscle spasms (79%)
- Anti-cancer activity (73%)
- GI issues (71%)
- Noise phobias (65%)
- Skin conditions (62%)

For Cats:

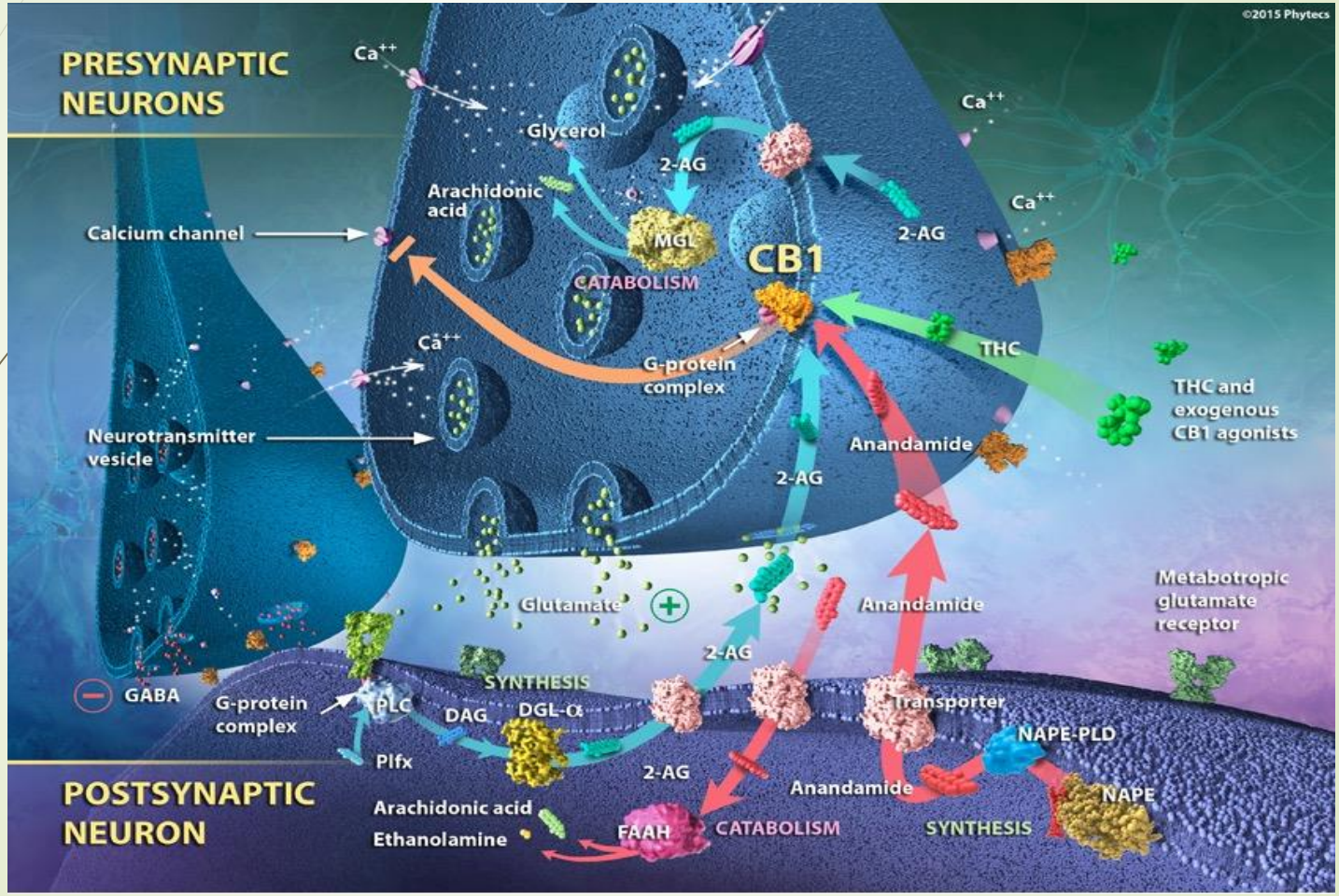
- Pain relief (100%)
- Sleep quality (96%)
- Inflammation (90%)
- Nausea reduction (86%)
- Anti-cancer activity (82%)
- Skin conditions (75%)

Compared to People?

- ADD/ADHD
- Alzheimer's Disease
- Anxiety
- Arthritis
- Auto Accident(s)
- Back & Neck Problems
- Brain Injury
- Cancer
- Chronic Nausea
- Chronic Pain
- Colitis
- Crohn's Disease
- Depression
- Eating Disorders
- Epilepsy
- Fibromyalgia
- Gastrointestinal Disorders
- Hepatitis C
- HIV/AIDS
- Irritable Bowel Syndrome
- Kidney Failure/Dialysis
- Migraines
- Multiple Sclerosis
- Muscle Spasms
- Muscular Dystrophy
- Parkinson's Disease
- Post Traumatic Stress Disorder
- Severe Arthritis
- Sexual Dysfunction
- Sleep Disorders
- Spinal Cord Injury/Disease

To name a few...

Endocannabinoid System

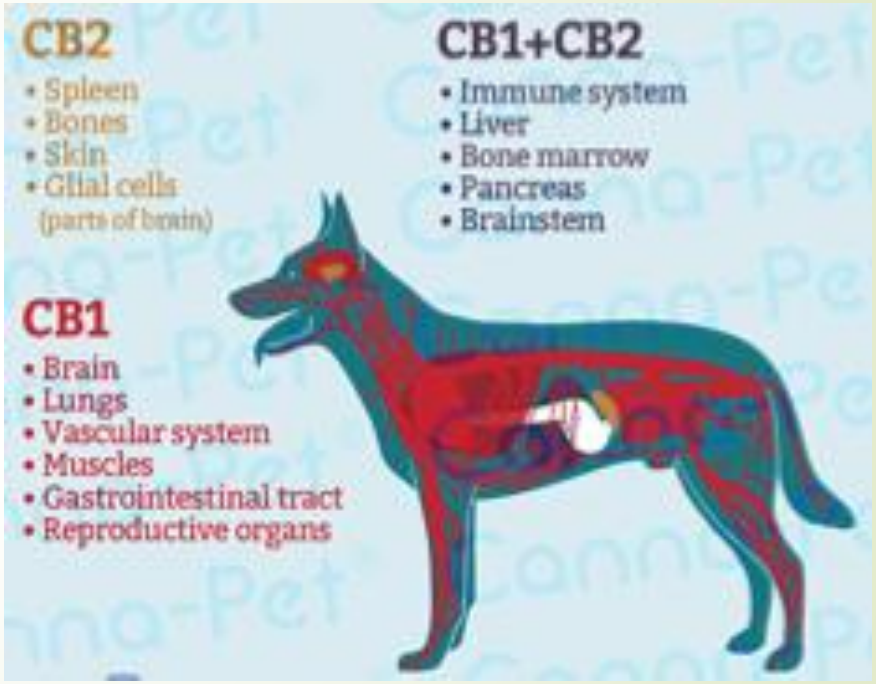


Endocannabinoid System

The ECS is an extremely complex system, and while our understanding of it has grown dramatically over the last couple decades, we have so much more to learn!

Endocannabinoid System (ECS)

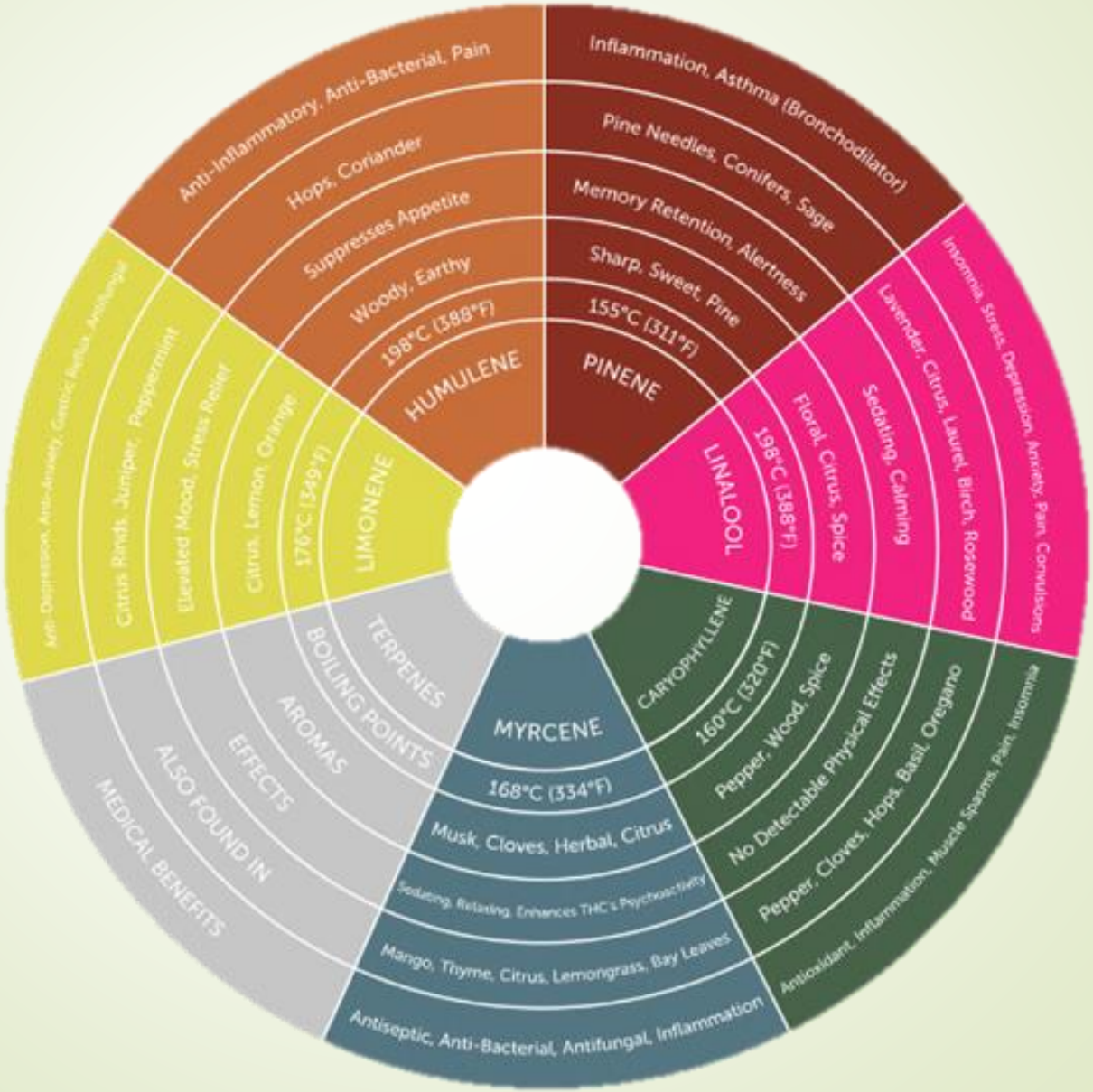
- Found in all mammals, birds, fish, reptiles, amphibians, and even some invertebrates, but *not* insects. *
- Largest receptor system in the mammalian body
- Regulates many body functions and helps to maintain *homeostasis*.



Endocannabinoid System

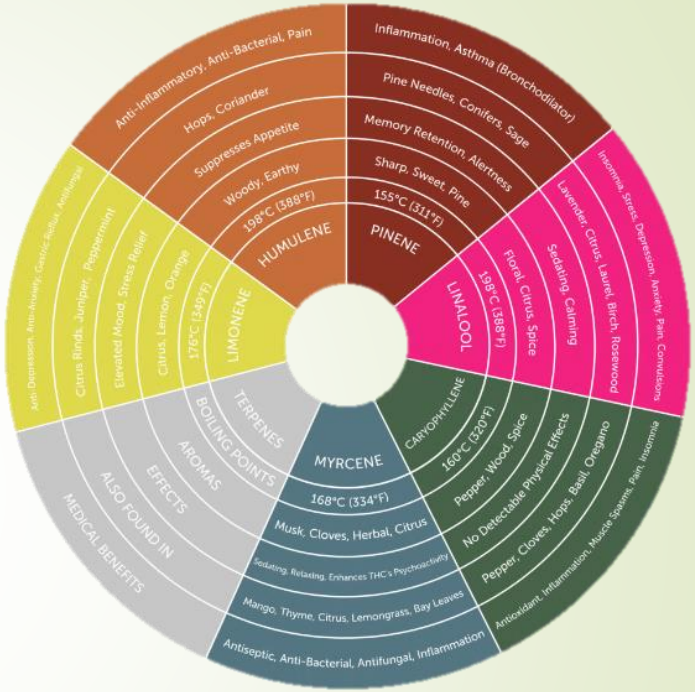
- Comprised of 2 main cannabinoid receptors +
  - CB1 & CB2
  - GPR18, GPR55, GPR12
  - 5-HT1a, TRPV1
- ECS includes receptors, neurotransmitters & enzymes (AEA, 2-AG, PEA, FAAH, MAGL, etc.)
- The ECS is modulated by both endogenous cannabinoids, as well as exogenous cannabinoids (including phytocannabinoids).

Terpenes

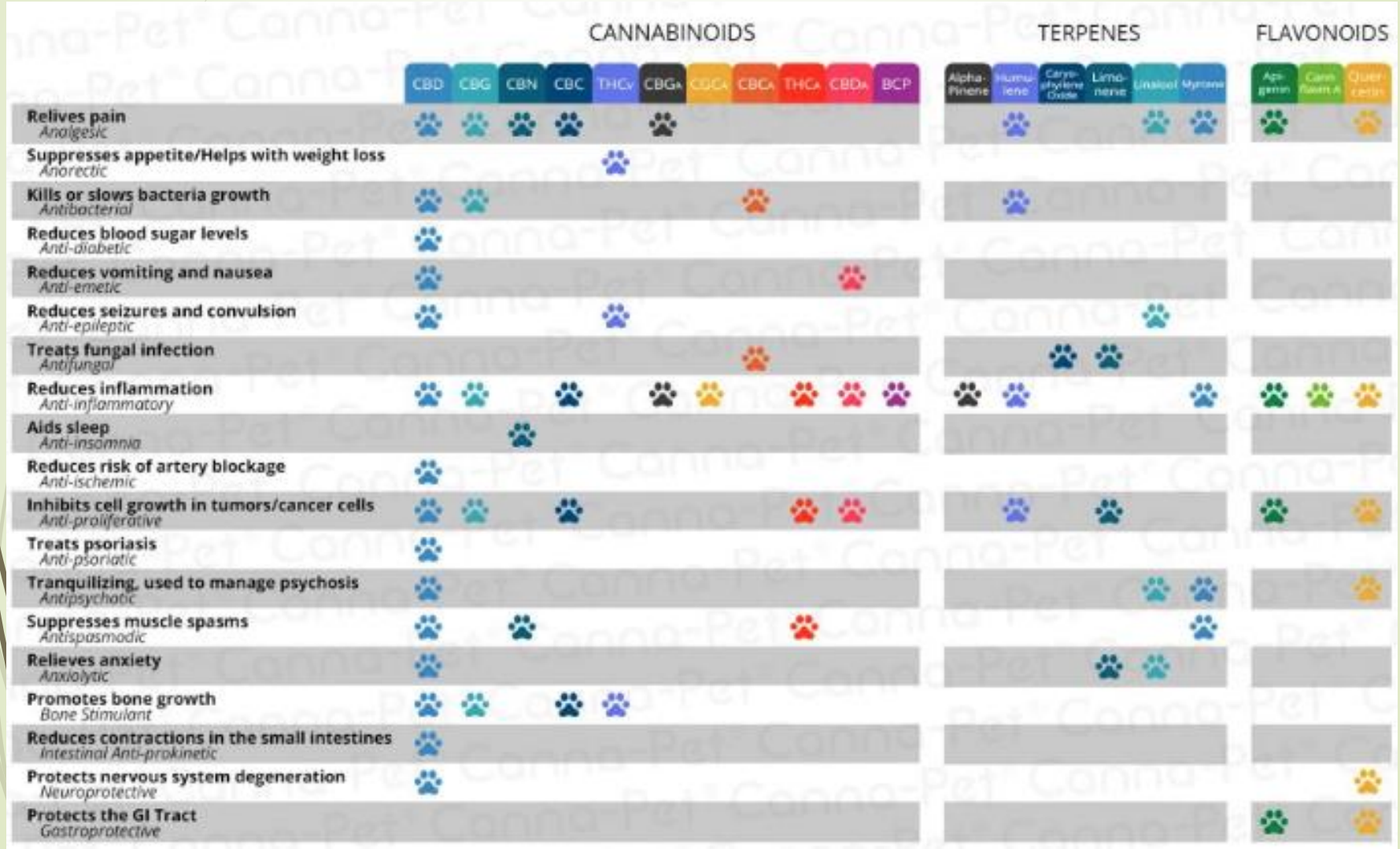

HUMULENE
198°C (388°F)
Woody, Earthy
Suppresses Appetite
Hops, Coriander
Anti-Inflammatory, Anti-Bacterial, Pain
PINENE
155°C (311°F)
Sharp, Sweet, Pine
Memory Retention, Alertness
Pine Needles, Conifers, Sage
Inflammation, Asthma (Bronchodilator)
LINALOOL
198°C (388°F)
Floral, Citrus, Spice
Sedating, Calming
Lavender, Citrus, Laurel, Birch, Rosewood
Insomnia, Stress, Depression, Anxiety, Pain, Convulsions
LIMONENE
176°C (349°F)
Citrus, Lemon, Orange
Elevated Mood, Stress Relief
Citrus Rinds, Juniper, Peppermint
Anti-Depression, Anti-Anxiety, Gastric Reflux, Antifungal
CARYOPHYLLENE
160°C (320°F)
Pepper, Wood, Spice
No Detectable Physical Effects
Pepper, Cloves, Hops, Basil, Oregano
Antioxidant, Inflammation, Muscle Spasms, Pain, Insomnia
MYRCENE
168°C (334°F)
Musk, Cloves, Herbal, Citrus
Sedating, Relaxing, Enhances THC's Psychoactivity
Mango, Thyme, Citrus, Lemongrass, Bay Leaves
Antiseptic, Anti-Bacterial, Antifungal, Inflammation
TERPENES
BOILING POINTS
AROMAS
EFFECTS
ALSO FOUND IN
MEDICAL BENEFITS

Terpenes

- Responsible for the aromatic properties of cannabis as well as other plants
- Secreted by the plants resin glands
- Also bind to receptors in the body to produce a range of physical effects
- Monoterpenes may be metabolized in cats by glucosidation (vs. glucuronidation in many other species)



Endocannabinoid System



Drug Metab Dispos. 1988 May-Jun;16(3):469-72.

Pharmacokinetics of cannabidiol in dogs.

Samara E[1], Bialer M, Mechoulam R.

Author information

Abstract

J Pharm Sci. 1977 Mar;66(3):395-407.

Pharmacokinetics of delta9-tetrahydrocannabinol in dogs.

Garrett ER, Hunt CA.

Abstract

The pharmacokinetics of intrave
in three dogs at two doses each
sampled in the other. The time
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PMID: 84580

Curr Pharm Biotechnol. 2017;18(10):821-827. doi: 10.2174/1389201018666171122115815.

Simple and Fast Gas-chromatography Mass Spectrometry Assay to Assess Delta 9-Tetrahydrocannabinol and Cannabidiol in Dogs Treated with Medical Cannabis for Canine Epilepsy.

Rotolo MC[1], Graziano S[1], Pellegrini M[1], Corlazzoli D[2], Antinori L[2], Porcarelli L[2], Pichini S[1].

Author information

J Chromatogr. 1991 Jan 2;562(1-2):299-322.

Urinary metabolites of cannabidiol in dog, rat and man and their identification by gas chromatography-mass spectrometry.

Harvey DJ[1], Samara E, Mechoulam R.

Author information

Abstract

Urinary metabolites of cannabidiol (CBD), a non-psychoactive cannabinoid of potential therapeutic interest, were extracted from dog, rat and human urine, concentrated by chromatography on Sephadex LH-20 and examined by gas chromatography-mass spectrometry as trimethylsilyl (TMS), [2H9]TMS, methyl ester-TMS and methyloxime-TMS derivatives. Fragmentation of the metabolites under electron-impact gave structurally informative fragment ions; computer-generated single-ion plots of these diagnostic ions were used extensively to aid metabolite identification. Over fifty metabolites were identified with considerable species variation. CBD was excreted in substantial concentration in 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 production of 2"-hydroxy-tris,nor-CBD-7-oic acid. 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.

PMID: 2026700

[Indexed for MEDLINE]

Res Commun Chem Pathol Pharmacol. 1977 Jul;17(3):457-70.

3H-delta9-tetrahydrocannabinol distribution in pregnant dogs and their fetuses.

Martin BR, Dewey WL, Harris LS, Beckner JS.

Abstract

Pregnant dogs were administered intravenously 0.5 mg/kg of 3H-delta9-tetrahydrocannabinol and sacrificed at 30 minutes, the time of peak behavioral effects. The distribution of radioactivity in mothers and fetuses was quantified in many peripheral tissues and in major

Br J Pharmacol. 1977 Apr;59(4):561-3.

Cardiovascular effects of delta9-tetrahydrocannabinol in conscious and anaesthetized dogs.

Friedman E, Gershon S, Hine B, Torrelio M.

Abstract

1. Temporal effects of delta9-tetr
anaesthetized dogs. 2. In consci
respectively, and in no significan
peak reduction in heart rate of 3
bradycardia in response to THC
heart rate response to THC in d

PMID: 858008 PMCID: PMC1667768

Res Commun Chem Pathol Pharmacol. 1978 Jun;20(3):489-508.

Effects of prolonged administration of delta 9-tetrahydrocannabinol on the autonomic and cardiovascular function and regional hemodynamics in mongrel dogs.

Jandhyala BS.

Abstract

Cardiovascular and autonomic functions of the dogs treated with delta 9-Tetrahydrocannabinol (delta 9-THC) 2 mg/kg/day for 35 days, were evaluated under pentobarbital anesthesia. Treated animals required significantly less pentobarbital in comparison with that of the placebo group. However, the interaction between delta 9-THC and pentobarbital at central vagal structures noted in the 7-day chronic study was not evident in the present study. Similarly, vagolytic effects of THC reported in acute studies could not be demonstrated following 35-day treatment. Reflex bradycardia responses to intravenous norepinephrine and phenylephrine were potentiated in the

Br J Pharmacol. 1973 Sep;49(1):1-10.

Cardiovascular and respiratory effects of cannabis in cat and rat.

Graham JD, Li DM.

Abstract

1. In anaesthetized rats, intravenous administration of cannabis extract (10 mg/kg), Delta(1)-tetrahydrocannabinol (THC) (0.5 mg/kg) and Delta(6)-THC (0.5 mg/kg) caused a reduction in systemic blood pressure, pulse rate and respiratory rate.2. Neither cannabinol (1 mg/kg, i.v.) nor cannabidiol (1 mg/kg, i.v.) had any observed effects on the cardiovascular and respiratory systems of the rat.3. Pretreatment of rats with atropine (1 mg/kg, i.v.) reduced the hypotension and bradycardia caused by Delta(1)-THC or the extract.4. In anaesthetized cats with autoperfused hindquarters, cannabis extract (10 mg/kg, i.v.) and Delta(1)-THC (0.2 mg/kg, i.v.) caused hypotension, bradycardia, depression of respiratory rate and reduction of hindlimb perfusion pressure.5. Both cannabis extract and Delta(1)-THC potentiated reflex vasodilation and direct vasoconstriction in the hindlimb induced by intravenous noradrenaline in the cat; they reduced reflex hindlimb vasoconstriction elicited by histamine, acetylcholine or bilateral carotid occlusion.6. Tolerance to these cardiovascular and respiratory effects of cannabis extract developed in rats which had been treated i.p. with the extract at (50 mg/kg) per day for 14 days.

PMID: 4787563 PMCID: PMC1776461

[Indexed for MEDLINE] **Free PMC Article**

Br J Pharmacol. 2009 Jan;156(1):153-62. doi: 10.1111/j.1476-5381.2008.00010.x. Epub 2008 Dec 6.

Effect of delta9-tetrahydrocannabinol, a cannabinoid receptor agonist, on the triggering of transient lower oesophageal sphincter relaxations in dogs and humans.

Beaumont H[1], Jensen J, Carlsson A, Ruth M, Lehmann A, Boeckxstaens G.

Author information

Abstract

BACKGROUND AND PURPOS
oesophageal reflux and are a p
delta(9)-tetrahydrocannabinol (
volunteers.

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humans.

PMID: 190

J Pharmacol Exp Ther. 1978 Sep;206(3):567-73.

A study of the effect of delta 9-tetrahydrocannabinol (delta 9-THC) on mammalian salivary flow.

McConnell WR, Dewey WL, Harris LS, Borzelleca JF.

ated salivary flow of the
lation of the chorda
ubmaxillary gland of the
chorda tympani. The
e synthesis of ACh could
ansmurally stimulated
electrically stimulated
to the submaxillary

Format: Abstract Send to

Br J Pharmacol. 2018 Feb 19. doi: 10.1111/bph.14165. [Epub ahead of print]

Species-specific susceptibility to cannabis-induced convulsions.

Whalley BJ[1,2], Lin H[1], Bell L[3], Hill T[4], Patel A[2], Gray RA[2], Elizabeth Roberts C[2], Devinsky O[5], Bazelot M[2], Williams CM[3], Stephens GJ[1].

Author information

Abstract

BACKGROUND AND PURPOSE: Numerous claims are made for cannabis' therapeutic utility upon human seizures, but concerns persist about risks. A potential confounder is the presence of both Δ^9 -tetrahydrocannabinol (Δ^9 -THC), variously reported to be pro- and anti-convulsant, and ca
Δ^9 -THC/CBD can

EXPERIMENTAL A
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KEY RESULTS: Pr
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CONCLUSION AN
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This article is protect

PMID: 29457829 DO

Endokrinologie. 1977;69(3):299-305.

Testicular degeneration and necrosis induced by chronic administration of cannabis extract in dogs.

Dixit VP, Gupta CL, Agrawal M.

Abstract

1. Daily administration of cannabis extract (12.5 mg/kg body wt. for 30 days) produced a complete arrest of spermatogenesis in dogs. Distinct degenerative effects were produced in the form of extensive fibrosis and exfoliation of the seminiferous elements. 2. RNA, protein and sialic acid contents of the testis and epididymides were reduced after cannabis extract administration, whereas, testicular cholesterol and enzyme phosphatase were elevated. 3. Serum transaminases were slightly elevated, whereas the alkaline phosphatase and haemoglobin/haematocrit values were in normal range. 4. Histophysiological examination of the liver did not show any damage. 5. Reduced androgen production was reflected in low levels of sialic acid in the testis and epididymides, and shrunken Leydig cell nuclei and luminal epididymal epithelium. 6.

IN CONCLUSION: Cannabis extract at 12.5 mg/kg body wt. dose level did not cause severe damage to the vital organs but it produced an effective inhibition of spermatogenesis in male dogs in 30 days and thus induces an antifertility state. The possibility of an adverse effect of frequent marihuana use on male reproductive organ functioning in man is alarming.

PMID: 913356

Lack of Species-Specific Research

Current Studies in Veterinary Cannabinoid Medicine

Cornell University
College of Veterinary Medicine

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

Colorado State University
Veterinary Teaching Hospital

Efficacy of Cannabidiol for the Treatment of Epilepsy in Dogs

Efficacy of Cannabidiol for the Treatment of Osteoarthritis in Dogs

canopy health
INNOVATIONS

Animal Health

Canopy Animal Health is a wholly-owned subsidiary of Canopy Health, focused on creating cannabis-based healthcare products for companion animals. Our goal is to provide family pets with specialized cannabinoid medicines to maintain, improve or extend their quality of life.

TETRA
BIO-PHARMA

- Tetra Bio-Pharma accelerates its clinical research program in the veterinary market by entering into agreement with Dr. Louis-Philippe de Lorimier
- Tetra Bio-Pharma Continues Forward into the Veterinary Ophthalmology Market by Entering into an Agreement with Drs. Cullen and Webb

13 October, 2017

Lauri-Jo Gamble, DVM, CCRP
lg497@cornell.edu

Institution and Location	Degree	Year
Montreal University, St-Hyacinthe, Canada	DVM	2014
Carolina Veterinary Specialists, Charlotte, North Carolina	Internship	2015
VOSM, Annapolis Junction, Maryland	Spec. Internship	2016
Cornell University, Ithaca, New York	Residency	2016-Present

Current Position
Resident, Sports Medicine and Rehabilitation, 2nd Year

Abstract Title:
Pilot Study on Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol Treatment in Osteoarthritic Dogs

Authors Names:
Lauri-Jo Gamble[1], Christopher W. Frye[1], Erin S. Berthelsen [1], Sabine Mann[1], Jordyn M. Boesch[1], Joseph J. Wakshlag[1]

[1]Cornell University, College of Veterinary Medicine, Ithaca, New York

Project Mentor(s):
Joseph J. Wakshlag, DVM, PhD, ACVN, ACVSMR; Department of Clinical Sciences (Mentor)
Christopher W. Frye, DVM; Department of Clinical Sciences (Co-mentor)
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Abstract:
In the absence of an ideal treatment for chronic pain associated with osteoarthritis, there is an interest for cannabinoid derivatives, yet minimal scientific evidence regarding efficacy or safety in dogs. The objectives of this ongoing study were to determine the (1) basic oral pharmacokinetics, (2) general short term safety, and (3) efficacy of a novel cannabidiol extract (CBD) in dogs with multi-joint osteoarthritis.

A basic 24-hour oral pharmacokinetic study was performed at 2 different dosages (2mg/kg and 8mg/kg). Thereafter, sixteen client-owned dogs completed a placebo-controlled double-blind cross-over study. Dogs were randomly receiving CBD oil (2mg/kg ml/kg q12) or placebo oil for 4 weeks with 2 weeks washout period before cross-over. Veterinary assessments as well as owner questionnaires were completed at weeks 0, 2, and 4 for both oils.

Oral pharmacokinetics showed that half-life of elimination was 4.7 ± 1.2 hours with a 2 mg/kg dose. No obvious psychoactive properties were observed on neurological evaluation at any time point. On the clinical assessment, CBPI and Hudson scores showed a significant decrease in pain and increase in activity ($p \leq 0.01$) at week 2, while only Hudson activity indices were improved at week 4 for CBD oil ($p \leq 0.01$). ALP increased over time for 8 dogs while receiving CBD oil, reaching significance at week 4 ($p \leq 0.01$). We conclude that dogs with osteoarthritis receiving CBD oil are perceived to be more comfortable and active with very few undesirable side effects detected when compare to a placebo oil.

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Dear Colleague,

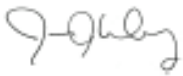
Over the past 8 months we have conducted a pharmacokinetic and clinical trial on the efficacy of ElleVet Sciences CBD preparation on Osteoarthritis. To date our findings have confirmed that their product is safe and efficacious for pain in dogs with osteoarthritis, chronic joint pain and geriatric pain and soreness; with dramatic beneficial effects in our more geriatric patients.

Considering these very promising initial results we are continuing our work with Ellevet examining post-surgical pain, and oncology pain at Cornell University College of Veterinary Medicine.

Our soon to be published clinical study was done at 2 mg/kg, but follow up at 1 mg/kg after completion of the study suggested that 1 mg/kg was also effective. We are currently suggesting the following dosing recommendation: 1 mg/kg twice daily for two weeks, if effective and then ½ mg/kg twice daily thereafter. If the initial 1 mg/kg dose does not work well, then increasing the dose to 2 mg/kg would be indicated.

It is our belief that this product is an efficacious and safe method of treatment, and can be used with routine NSAIDS. This is a new and exciting modality in the area of pain relief for dogs and hope you feel similarly once you try the product.

Sincerely,



Joseph J. Wakshlag

Associate Professor of Clinical Nutrition, Sports Medicine and Rehabilitation

2E | Assessment of Safety, Toxicity and Pharmacokinetics of Cannabidiol in Healthy Dogs

Stephanie McGrath, Colorado State University-Ft. Collins, *Lisa Bartner*, Colorado State University-Ft. Collins, *Sangeeta Rao*, Colorado State University-Ft. Collins, and *Luke Wittenburg*, University of California, Davis

Epilepsy is a serious and prevalent disease in both human and canine patients, with drug resistance occurring at an estimated 20-30%. The phytocannabinoid cannabidiol (CBD), has anecdotally shown promise for use as an antiepileptic drug. Here we present the pharmacokinetic analysis and safety of CBD in healthy dogs.

30 healthy dogs were assigned to receive one of three CBD delivery routes (oil, capsules, or transdermal cream) at two different dosages. The medication was continued in each dog for a total of six weeks, during which time examinations, routine bloodwork, and CBD levels were assessed.

Pharmacokinetic analysis demonstrated that the oil formulation resulted in higher Cmax and systemic exposure than the other two routes. The oil appeared to have the smallest amount of intra-individual variability in plasma concentrations and provided equal or greater plasma CBD exposures than the other two routes at each time point. CBD levels were adequately maintained over the course of the study. The most common adverse effect was diarrhea. Mild liver enzyme elevations were present in some of the dogs, but the bile acids remained normal.

This is the first scientific canine study to demonstrate that CBD blood levels were measurable after a single dose of all three delivery methods, and that side effects, when present, were minimal and nonspecific. Further studies in a clinical population of dogs is warranted to assess efficacy but our results demonstrate adequate absorption and maintenance of CBD levels with few adverse effects.

Incoming Legislation and Proposed Changes

First Session, Forty-second Parliament,
64-65-66 Elizabeth II, 2015-2016-2017

HOUSE OF COMMONS OF CANADA

BILL C-45

An Act respecting cannabis and to amend the Controlled Drugs and Substances Act, the Criminal Code and other Acts

AS PASSED

BY THE HOUSE OF COMMONS

NOVEMBER 27, 2017

Legislative Assembly of Ontario

Assemblée législative de l'Ontario

2ND SESSION, 41ST LEGISLATURE, ONTARIO
66 ELIZABETH II, 2017

Bill 174

An Act to enact the Cannabis Act, 2017, the Ontario Cannabis Retail Corporation Act, 2017 and the Smoke-Free Ontario Act, 2017, to repeal two Acts and to make amendments to the Highway Traffic Act respecting alcohol, drugs and other matters

Proposed Approach to the Regulation of Cannabis

8.6.1 Proposed framework for NHPs with cannabis

The approximately 220 NHPs with cannabis that are currently authorized for sale will continue to be available to Canadians. These NHPs contain parts of the cannabis plant that fall outside of the legal definition of cannabis in the CDSA (or are exempted from the CDSA by virtue of the Industrial Hemp Regulations) and contain no more than 10 ppm THC. It is proposed that new NHPs similar to these would also be permitted under the Cannabis Act and its regulations if authorized by Health Canada.

A new pathway is proposed for NHP submissions containing parts of the cannabis plant subject to the proposed Cannabis Act, such as products derived from cannabis flowers containing cannabinoids such as CBD. To minimize the risk of psychoactivity, the same 10 ppm THC limit would be applied to such products. These submissions would be required to demonstrate robust safety and efficacy evidence under the NHP regulatory framework.

The 10 ppm THC limit applicable to all NHPs with cannabis would be established in the Natural Health Product Regulations.

8.8 Veterinary Drugs

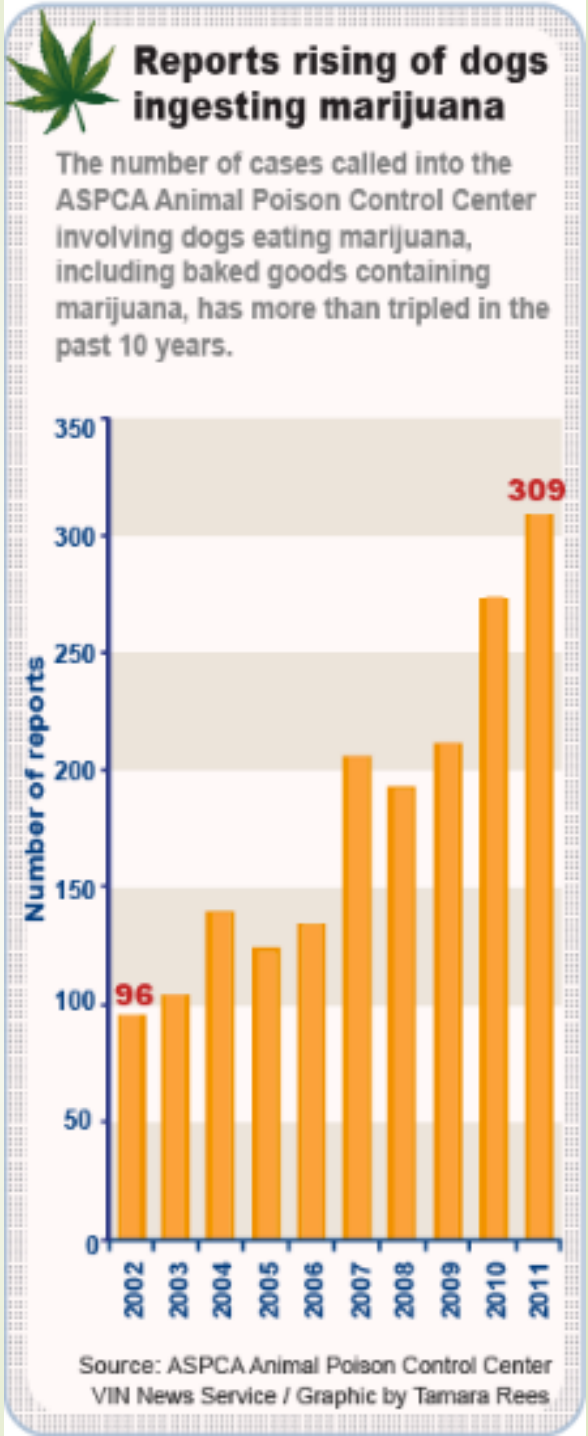
Similar to drugs for human use, veterinary drugs must undergo Health Canada's drug review process before they can be sold. As part of the review process to ensure they are safe, effective, and of high quality for their intended animal use, applications are reviewed against the factors for requiring health practitioner oversight. Any submission for a new veterinary drug with cannabis would be examined through this review process.

8.9 Veterinary Health Products

Veterinary health products are used to maintain or promote the health and welfare of animals. They are low-risk drugs in dosage form, such as vitamins, minerals, and traditional medicines. Like NHPs for humans, VHPs can contain ingredients such as hemp seed derivatives containing no more than 10 ppm THC, which will be exempt from the proposed Cannabis Act. These products will remain available as they are now, limited to a maximum of 10 ppm THC.

Risks/Dangers of Cannabis for Pets

Increased access to cannabis, combined with reduced stigma attached to its use, means more potential for pets to be exposed to cannabis.



THC Toxicity in Dogs

- Minimal dose required to see side effects/signs of toxicity on *initial* exposure: 0.25mg/kg - 0.5mg/kg of THC
- (Ex. 10kg/22lb dog ingesting 2.5mg of THC = <0.1 gram of a typical high THC strain of dried material)

- Minimal Lethal Dose: >3g/kg (controversial based on differing studies).
- (Ex. 10kg dog = 1.5kg of dry flower @ 20mg/g)

- Symptoms seen within 30min of ingestion, and can last up to 72hrs.

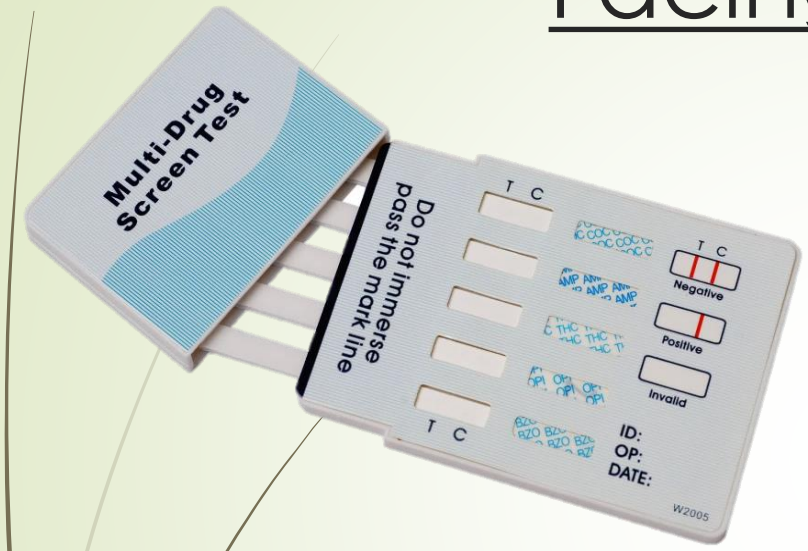
THC Toxicity – Common Signs

	JVECC 2012
*Ataxia (loss of balance)	88%
*Lethargy (or agitation)	75% (25%)
*Disorientation	53%
*Dilated pupils	48%
*Urinary Incontinence	47%
*Hyperesthesia	47%
Tremors/Seizures	30%
Vomiting	27%

Low heart rate, low body temperature, low BP, coma

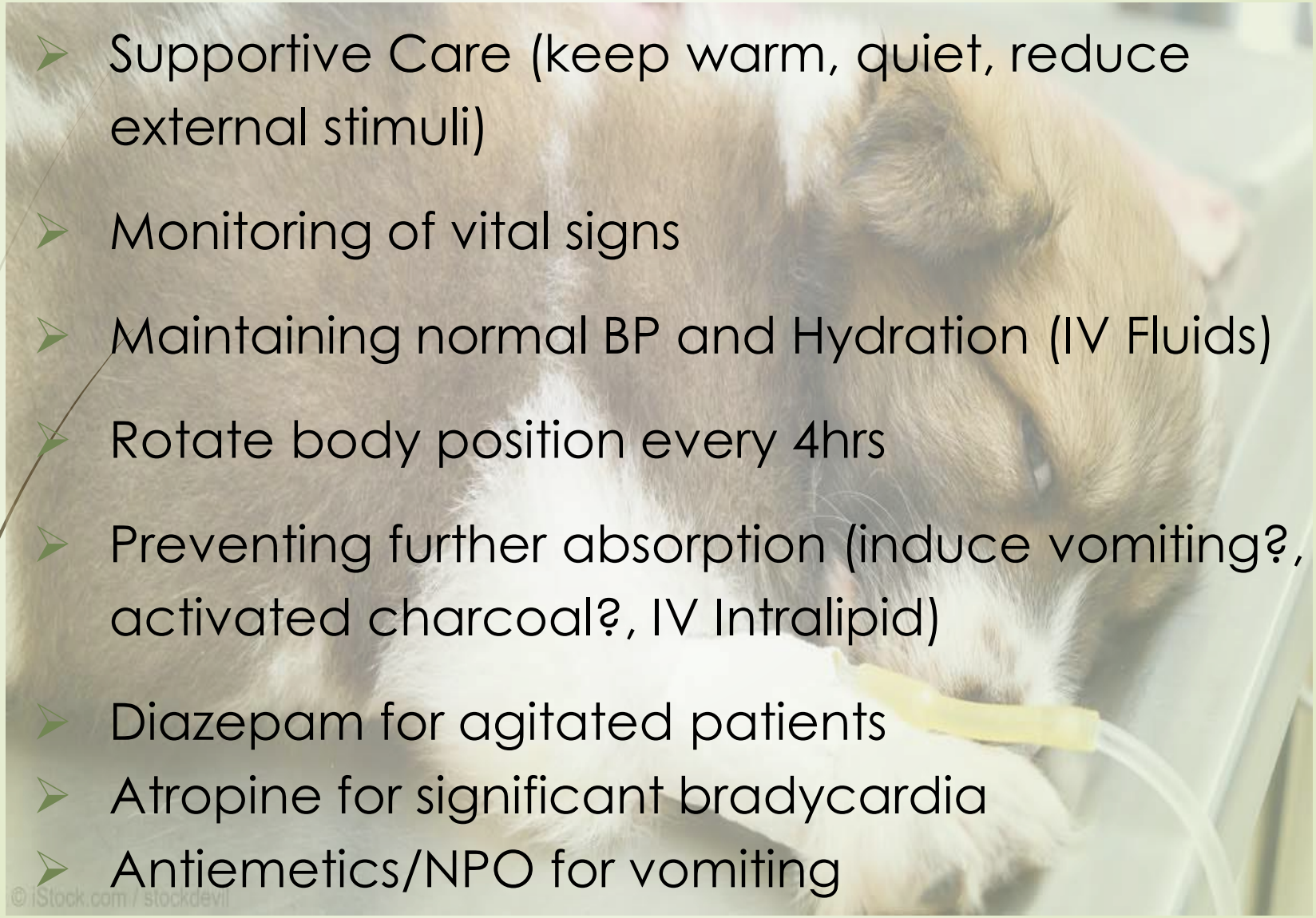
*JVECC = Journal of Veterinary Emergency and Critical Care

Diagnostic Challenges Facing Veterinarians



- Fear of judgement/legal action
- Test kits measure 11-OH-delta9-THC (human metabolite) vs. 8-OH-delta9-THC (produced by dogs)
- Dogs require relatively low levels to show symptoms
- Time to produce positive urine test?

THC Toxicity - Treatment



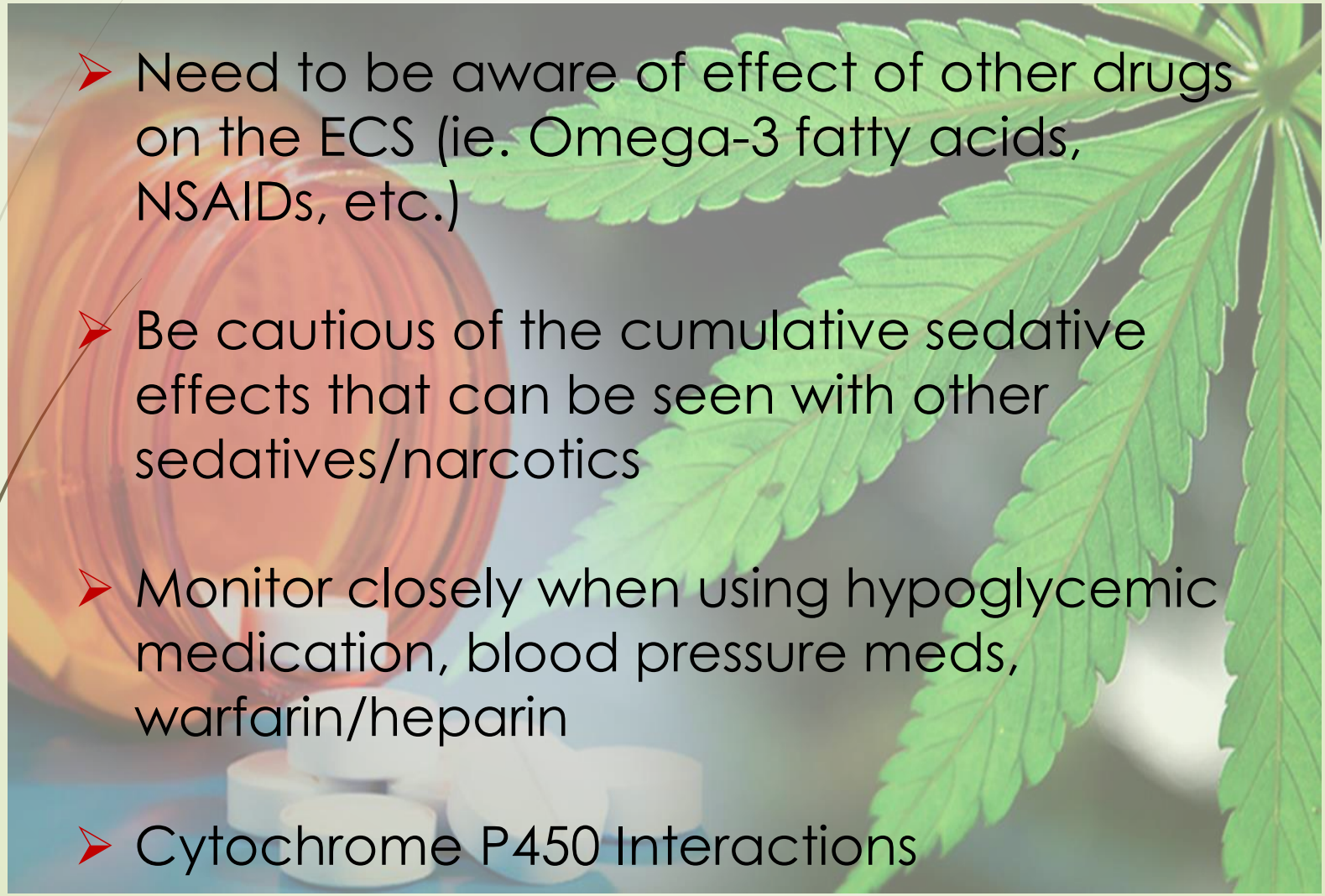
- Supportive Care (keep warm, quiet, reduce external stimuli)
- Monitoring of vital signs
- Maintaining normal BP and Hydration (IV Fluids)
- Rotate body position every 4hrs
- Preventing further absorption (induce vomiting?, activated charcoal?, IV Intralipid)
- Diazepam for agitated patients
- Atropine for significant bradycardia
- Antiemetics/NPO for vomiting

OR….

Confounding Issues

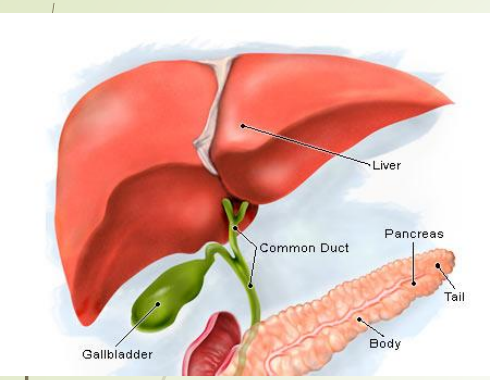
- Other toxins commonly found in edibles (fats, chocolate, raisins, macadamia nuts, etc.)
- Ingestion of synthetic marijuana (Spice, K2, Skunk, etc.) can have more pronounced effects on heart and increased risk of seizures.
- Presence of pesticides, solvents, fungal contamination, etc.
- Other recreational drug ingestion
- Pre-existing medical conditions/medications

Potential Drug Interactions



- Need to be aware of effect of other drugs on the ECS (ie. Omega-3 fatty acids, NSAIDs, etc.)
- Be cautious of the cumulative sedative effects that can be seen with other sedatives/narcotics
- Monitor closely when using hypoglycemic medication, blood pressure meds, warfarin/heparin
- Cytochrome P450 Interactions

CYTOCHROME P450

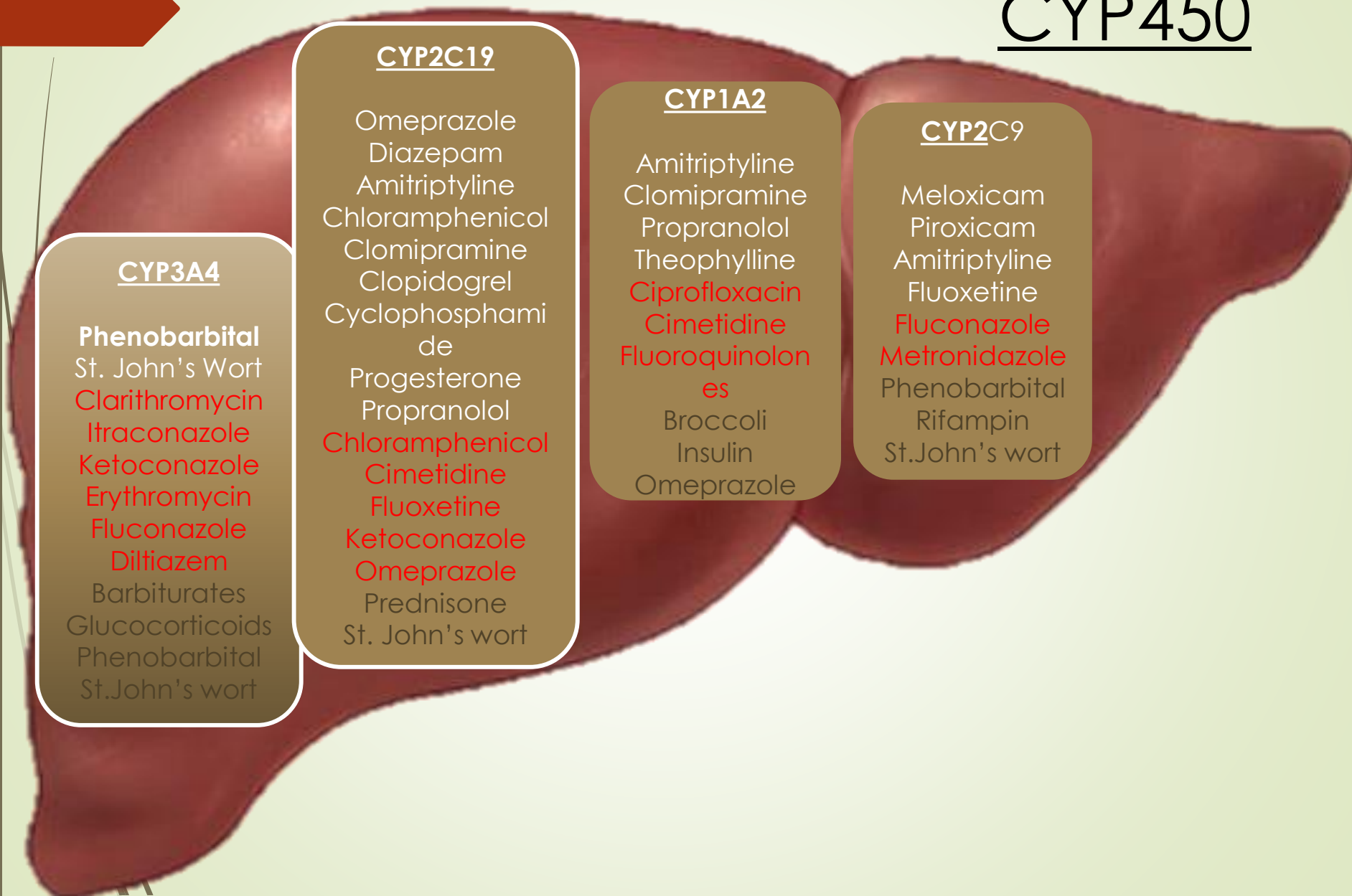


A family of 6 main enzymes that occur primarily in liver cells where drug metabolism occurs.

CYP1A2, CYP3A4, CYP2C9, and CYP2C19 enzymes, are known to be affected by cannabis, **specifically CBD**.

- The CYP3A4 enzyme is involved in the metabolism of both THC & CBD.
- CYT3A4 Inhibitors (such as ketoconazole) have been shown to increase concentrations of both CBD and THC.
- CYT3A4 inducers (such as rifampin) have been shown to reduce THC levels by 20-40% and CBD levels by 50%-60%.
- However, in one study, omeprazole (a 2C19 inhibitor) did not increase serum concentrations of CBD.
- Even with these unexpected results, 2C19 inhibitors and inducers should be assumed to have similar effects on CBD concentrations as the 3A4 inhibitors and inducers until further studies provide a better understanding.

Common Vet Drugs Involved with CYP450



CYP3A4

Phenobarbital
St. John's Wort
Clarithromycin
Itraconazole
Ketoconazole
Erythromycin
Fluconazole
Diltiazem
Barbiturates
Glucocorticoids
Phenobarbital
St.John's wort

CYP2C19

Omeprazole
Diazepam
Amitriptyline
Chloramphenicol
Clomipramine
Clopidogrel
Cyclophosphamide
Progesterone
Propranolol
Chloramphenicol
Cimetidine
Fluoxetine
Ketoconazole
Omeprazole
Prednisone
St. John's wort

CYP1A2

Amitriptyline
Clomipramine
Propranolol
Theophylline
Ciprofloxacin
Cimetidine
Fluoroquinolones
Broccoli
Insulin
Omeprazole

CYP2C9

Meloxicam
Piroxicam
Amitriptyline
Fluoxetine
Fluconazole
Metronidazole
Phenobarbital
Rifampin
St.John's wort

Special Considerations for Pets

- Animals can't tell us how they're feeling, so close observation and record keeping is essential.
- Cannabis (particularly THC) can enhance the senses. Theirs are already hypersensitive compared to ours. Further enhancement may be unsettling for them.
- Dogs in particular, as less likely to take it easy when feeling 'high', and may therefore be more likely to stumble and fall if overdosed.
- Many pets (particularly dogs) have atopic dermatitis – cannabis may be a potential allergen as well.
- Pets groom themselves, and other pets. Topical applications should be applied with this in mind to avoid unintended oral ingestion/risk of toxicity
- THC can, and has been, used in pets. "The poison is in the dose."

Administering to Pets

Tinctures	Hash oils/RSO	Smoke
Commercial Oils (mg/ml)	Keif	Vaporizing
Capsules	Hash/Shatter/Wax	Edibles containing xylitol, chocolate, raisins, etc.
Treats for pets	Butters	
Fresh greens/Juice/Tea	Transdermals and Patches?	

Administering to Pets

As with people, if you choose to use cannabis for your pets,

START LOW, GO SLOW!

Remember: Dogs seem particularly sensitive to THC on *initial* exposure, but will develop tolerance to adverse effects with continued low-dose use, allowing dose adjustments.

Stay *well below* 0.5mg/kg of THC when starting.

Doses below 0.2mg/kg unlikely to produce any outward clinic effects.

Administering to Pets

- CBD Dosing: Anecdotal reports suggest CBD doses as low as 0.05-0.1mg/kg once daily can be effective, but can increase as high as 1-5mg/kg twice daily.
- The "Entourage Effect": Products that utilize a complete range of compounds from the whole plant may be safer and more therapeutic than those that utilize a single compound.
- Keeping records of what you try and the relative effects are important for human patients, but even *more so* for animals!

Choosing a Product for Pets:

- Legal
- Manufacturer Reputation
- Provides actual amounts/potential amounts of THC/CBD
- Provides source of original product
- Safe extraction techniques
- Provides laboratory analysis including:
  - cannabinoids,
  - terpene profile,
  - testing for pesticides, microbes, and solvent residuals
- Lists all ingredients (avoid additives such as colouring, preservatives, and *particularly* Xylitol)

Laboratory Analysis

ANANDIALABS Certificate of Analysis

Client: Aurora
Strain: CBD Drops

Anandia Sample ID: 2018030905-007

Lot #: 18-034

Authorized By:
Leo Law, BSc
Laboratory Manager

CoA Prepared: 17-Mar-18

Potency		wt %	mg/mL
Total THC equivalents	(Δ9-THC + Δ9-THCA x 0.877)	0.14%	1.3
Total CBD equivalents	(CBD + CBDA x 0.877)	3.33%	31.3

Most abundant minor cannabinoids

	wt %		wt %
CBC	0.17%	CBDV	0.01%
CBG	0.06%	CBGA	0.01%

Terpenes

Most abundant of the 39 terpenes quantified

	wt %		wt %
alpha-Bisabolol	0.030	alpha-Humulene	0.003
Guaiol	0.029	beta-Myrcene	0.002
trans-Caryophyllene	0.010	Fenchyl Alcohol	0.001
alpha-Terpineol	0.006	Limonene	BLQ
Linalool	0.004	alpha-Pinene	BLQ

Contaminant Analysis

Residual Solvents		
Limits for residual solvents below ICH Q3C guidelines		pass
Microbial Quality		
Total aerobic microbial counts		pass
Total yeast and mold counts		pass
Bile-tolerant gram-negative bacteria		pass
E coli		absent
Salmonella spp		absent
Aflatoxins	Aflatoxin B1, B2, G1, G2	pass
Heavy Metals	Arsenic, Cadmium, Lead, Mercury	pass
Pesticides		None detected

Details of Testing

Cannabinoid Profile
Quantification of 14 cannabinoids by ultra-high-performance liquid chromatography and mass spectrometry detection (UHPLC-MS). LOQ for flower and formulated oils is 0.064% (w/w) and for concentrates is 0.128% (w/w). [STM-401]

Terpene Profile
Quantification of 39 terpenes by gas chromatography and mass-spectrometry detection (GC-MS). [STM-406]

Loss On Drying
Percent loss on drying using modified United States Pharmacopoeia method <731> under vacuum at 40 degrees C. [STM-

Residual Solvents
Quantification of 11 extraction solvents using headspace sampling, gas chromatography, and mass spectrometry detection (HS-GC-MS) compliant to ICH Q3C. [STM-410]

Microbial Quality
Microbiological screening using European Pharmacopoeia methods 2.6.12, 2.6.13, and 2.6.31. [STM-402]

Aflatoxins
Aflatoxins B1, B2, G1, and G2 quantification using immunoaffinity column chromatography followed by ultra-high-performance liquid chromatography with tandem mass-spectrometry (UHPLC-MS/MS) detection to meet criteria in European Pharmacopoeia method 2.8.18. [STM-405]

Heavy Metals
Microwave digestion and inductively-coupled plasma mass-spectrometry detection (ICP-MS) (USEPA 6020A R1 2007) to test for arsenic, cadmium, lead, and total mercury. ICP-MS analysis performed by ISO 17025 accredited 3rd party lab. [STM-

Pesticides
Screening of 51 pesticide residues and plant growth regulators specifically identified as prevalent contaminants to cannabis production. Analysis performed ultra-high-performance liquid chromatography with tandem mass-spectrometry detection (UHPLC-MS/MS). [STM-407]

Pesticides and Plant Growth Regulators tested for:

Abamectin	Diazinon	Imidacloprid	Pyrethrin I
Acephate	Dichlorvos	Kresoxim-methyl	Pyrethrin II
Acetamiprid	Dimethoate	Malathion	Pyridaben
Aldicarb	Ethoprophos	Metalaxyl	Spinosad A
Azoxystrobin	Etofenprox	Methiocarb	Spinosad D
Bifenazate	Etoxazole	Methomyl	Spiromesifen
Boscalid	Fenoxycarb	Myclobutanil	Spirotetramat
Carbaryl	Fenpyroximat	Oxamyl	Spiroxamine
Carbofuran	Fipronil	Paclobutrazol	Tebuconazole
Chlorantraniliprole	Flonicamid	Phosmet	Thiacloprid
Chlorpyrifos (ethyl)	Fludioxonil	Piperonyl butoxide	Thiamethoxam
Clofentezine	Hexythiazox	Propiconazole	Trifloxystrobin
Daminozide	Imazalil	Propoxur	

Tips for Pet Parents

- Cautions: Although cannabis is remarkably safe, if an animal that is taking other medications, please be sure to discuss your animal's cannabis plan with your veterinarian.
- Do not use cannabis in immature or pregnant animals.
- Set Up for Success: Arrange the home environment so your animal feels safe and comfortable at all times. An animal that receives an inappropriate dose of cannabis, they may be overly sensitive to bright lights and loud sounds.
- Keep a journal. Record all symptoms, better and worse.

What's on the Horizon?

- Concerns regarding increased toxicities, lack of regulation/control of pet products, lack of veterinary guidance.
- Potential for explosion of new CBD pet products on the market – liquids, capsules, treats, food additives, etc.
- Development of new protocols for treating pets with whole plant/plant-derived cannabinoid medicines

What's on the Horizon?

- Development of veterinary pharma-ceutical products derived from cannabis
- New delivery systems for pets (intranasal, transdermal, patches, topical products, etc.)
- Public pressure to drive the profession to become better educated, and hopefully encourage changes in legislation
- Rapid increase in cannabinoid research for pets

QUESTIONS?

cavcm.com