Veterinary Medical Board

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MEMORANDUM

DATE	October 8, 2019
TO	Multidisciplinary Advisory Committee
FROM	Jeff Pollard, DVM, MDC Chair
SUBJECT	**Agenda Item 6. Discussion and Potential Recommendation on Guidelines for the Appropriate Administration for Use of Medicinal Cannabis on an Animal Patient**

The July 17, 2019 Veterinary Medical Board (Board) Multidisciplinary Advisory Committee (MDC) report to the Board included the list of items discussed at the MDC meeting on the previous day. For discussion purposes, the list was divided into the following categories:

1) Demonstrate efficacy & safety
Included are indications for use, effective doses, dosing intervals, therapeutic blood levels, species differences, use in patients with co-morbidities, interactions with other medications, adverse side effects, effects of long-term use, use in pregnancy & lactation. A certificate of analysis (COA) for every batch is necessary to insure accurate labeling & absence of contaminants.

2) Production & sale/delivery of product
Included are items starting with growth of the plant and continuing to the manufacturing of the final product, its percentage of CBD vs THC, its content of other cannabinoids, terpenes, & flavonoids. Also, included is the form of the product, (e.g., oil, treat, topical, suppository), and the importance of providing a consistent product.

3) Regulation
Regulatory bodies include the FDA, DEA, CDFA, CBCC, & VMB to ensure consumer & patient safety, legal labeling & advertising, guard against conflicts of interest, and provide clear parameters of use for licensees.

This list is intended as a starting point for the VMB to develop guidelines for the appropriate administration and use of medical cannabis in animal patients.

Attachments:

1. July 16, 2019 memorandum regarding the Discussion and Potential Recommendation on Defining Conditions That Must be Met for Board Approval of Providing Statutory Authority for a Veterinarian to Give Clients Cannabis Treatment Recommendations with Board and MDC edits.

2. Various journals and scholarly articles relating to cannabis usage in animals

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MEMORANDUM

DATE	July 16, 2019
TO	Multidisciplinary Advisory Committee
FROM	Jeff Pollard, DVM, MDC Chair
SUBJECT	**Agenda Item 6. Discussion and Potential Recommendation on Defining Conditions That Must be Met for Board Approval of Providing Statutory Authority for a Veterinarian to Give Clients Cannabis Treatment Recommendations**

During the April 2019 meeting, the Board opposed SB 627 (Galgiani, 2019). SB 627 would, among other things, authorize veterinarians to recommend medicinal cannabis or medicinal cannabis products for use on animal patients. It would also require the Board to issue guidelines on the appropriate administration and use of medicinal cannabis on an animal patient. The Board would be required to report to the Legislature on January 1, 2021, and every six months thereafter, on the status and progress of developing the guidelines.

The Board acknowledged that cannabis and cannabis products may have potential health benefits to animals. However, there is still a significant need for funding for cannabis research so that veterinarians and the public are informed on the possible efficacious use of cannabis to treat animals and ensure the full protection of consumers and their animals. While other medications and dangerous drugs have been provided to animal patients without significant research, those were not previously identified as Schedule I Controlled Substances, as is cannabis.

Although the Board opposed the bill, it directed the MDC to define specific conditions that must be met for Board approval of providing statutory authority for a veterinarian to give clients cannabis treatment recommendations.

In the Assembly Business and Professions Committee analysis of SB 627, multiple policy issues and recommended amendments were identified, many mirroring the Board's concerns, including the lack of research and necessary funding for the research. In addition, one of the amendments removed the Board's reporting requirement to the Legislation and replaced it with a 2022 deadline for adopting recommendation guidelines.

During the July 9, 2019 Committee hearing, the author's office accepted all amendments in the Committee analysis, the Chair provided a "Do Pass" recommendation, and the bill passed out of Committee to the Assembly Appropriations Committee.

According to Assembly Business and Professions Committee staff, the author's office will address the Committee's concern regarding the lack of research and the necessary funding.

Board staff and legal counsel are working with the Committee to propose language addressing this concern for the author's consideration.

Until SB 627 passes and research is conducted, it may be too early to discuss specific conditions that must be met in order to approve veterinarians recommending medicinal cannabis for animal use. However, once adequate research is conducted, the MDC may want to consider the following topics when developing the guidelines:

- Indications for use
- Proven alternatives
- Effective doses – dosing is ideally based on an animal patient's own endocannabinoid system (ECS), disease process, and other factors.
- Species differences (e.g., larger concentrations of CB1 receptors in the brainstem of dogs which causes them to be more susceptible to THC toxicity).
- Proper dosing intervals.
- Therapeutic blood concentrations.
- Half-life in dogs, ~~and~~ cats, and horses.
- Physiologic effects (intended) (e.g., induction of enzymes).
- Adverse side effects – real and potential.
- Interaction with other medications (e.g., pain meds, anticonvulsants, psychotropics).
- Effects of long-term use.
- Use in patients with co-morbidities (e.g., liver disease).
- Product: percentage of CBD vs. THC, Terpenes.
- Delivery: oil, treat, topical, suppositories, other.
- Certificate of Analysis.
- Toxicity - how much/what concentration is safe? Effective?
- What if the patient is pregnant or lactating?
- Monitoring.
- Liability to licensee – civil and administrative with regard to the Board (e.g., trail of plant, harvest, processing, formulation of product, sale, recommendation/prescription, storage, improper access/use (e.g., children).
- FDA Approval
- Range of dose
- Go low and go slow
- Differences between veterinary and human products
- What the specific products have been tested for – i.e. trace components, methods of extraction, etc.

VIEWPOINT

Should Physicians Recommend Replacing Opioids With Cannabis?

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Richard Saitz, MD, MPH
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Recent state regulations (eg, in New York, Illinois) allow medical cannabis as a substitute for opioids for chronic pain and for addiction. Yet the evidence regarding safety, efficacy, and comparative effectiveness is at best equivocal for the former recommendation and strongly suggests the latter—substituting cannabis for opioid addiction treatments is potentially harmful. Neither recommendation meets the standards of rigor desirable for medical treatment decisions.

Efficacy of Cannabis for Chronic Pain and for Opioid Use Disorder

Recent systematic reviews[1,2] identified low-strength evidence that plant-based cannabis preparations alleviate neuropathic pain and insufficient evidence for other types of pain. Studies tend to be of low methodological quality, involve small samples and short-follow-up periods, and do not address the most common causes of pain (eg, back pain). This description of evidence for efficacy of cannabis for chronic pain is similar to how efficacy studies of opioids for chronic pain have been described (except that the volume of evidence is greater for opioids with 96 trials identified in a recent systematic review[3]).

> In a sample of 84 cannabidiol extracts purchased online, 69% (n = 58) had mislabeled cannabinoid content.

The evidence that cannabis is an efficacious treatment for opioid use disorder is even weaker. 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.

Comparative Effectiveness: Substituting Cannabis for Opioids

Substituting cannabis for opioids is not the same as initiating opioid therapy. There are no randomized clinical trials of substituting cannabis for opioids in patients taking or misusing opioids for treatment of pain, or in patients with opioid addiction treated with methadone or buprenorphine. In addition to surveys of patients who use medical cannabis, the other types of studies prompting a move to cannabis to replace opioids are population-level reports stating that laws allowing medical cannabis use are followed by fewer opioid overdose deaths than expected. The methodological concern with such studies is that correlation is not causation. Many factors other than cannabis use may affect opioid overdose deaths, such as prescribing guidelines, opioid rescheduling, Good Samaritan laws, incarceration practices, and availability of evidence-based opioid use disorder treatment and naloxone. Furthermore, the aggregate population associations (eg, between medical cannabis and opioid overdose) may be opposite of those seen within individuals. In the only individual-level analysis, which included 57 146 people aged 12 and older, of a nationally representative sample, medical cannabis use was positively associated with greater use and misuse of prescription opioids.[4]

The largest prospective study of cannabis as a substitute for opioids was a 4-year cohort study of 1514 patients with chronic pain who had been prescribed opioids.[5] Cannabis use was associated with more subsequent pain, less self-efficacy for managing pain, and no reductions in prescribed opioid use. There was no substitution; rather, cannabis was simply added to the mix of addictive substances taken by patients with pain.

For opioid use disorder, there is concern that the New York State Health Commissioner has defined opioid addiction to include people being treated with US Food and Drug Administration–approved, efficacious, opioid agonist medications, as a qualifying condition for medical cannabis.[6] Methadone and buprenorphine treatment reduces illicit opioid use, blood-borne disease transmission, criminal activity, adverse birth outcomes, and mortality. Discontinuing such medications increases the risk of return to illicit opioid use, overdose, and death. The suggestion that patients should self-substitute a drug (ie, cannabis) that has not been subjected to a single clinical trial for opioid addiction is irresponsible and should be reconsidered.

These approaches reflect the stigmatized nature of people with opioid addiction that cannabis therapy might be considered reasonable with no clinical trials when no comparable provision has been made for other chronic diseases for which claims of cannabis' benefits have been made (eg, no regulations have suggested that patients with diabetes stop taking insulin and take cannabis instead). The recommendation is consistent with a history of medical professionals arguing that a different class of addictive drug will eliminate an addiction. For instance, in the past, morphine had been promoted as a cure for alcohol use disorder; cocaine as a cure for morphine addiction and alcohol use disorder; and heroin as a cure for alcohol use disorder, morphine addiction, and cocaine addiction.

Risks of Cannabis Use

Unlike opioids, cannabis appears to have no risk of fatal overdose. However, systematic reviews find increased

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risks of motor vehicle crashes, cognitive impairment, structural brain changes, and psychotic symptoms.[1,7] The risk of cannabis addiction should be mentioned, particularly when the rationale for substitution is to prevent or treat addiction in people with or at risk for cannabis and other substance addiction. In a national population-based survey of 36 309 adults, the prevalence of cannabis use disorder was 31% among those reporting any use in the past year.[8] Cannabis addiction means use that causes clinically significant impairment or distress, including use that is out of control (the person tries to reduce use and cannot); craving; and recurrent social, occupational, and physical consequences. Cannabis use is also prospectively associated with a greater risk for other substance use disorders. All of these risks must be considered in light of the lack of evidence that taking cannabis while using opioids will necessarily result in a tapering of opioid dose, ie, it is entirely possible that these risks associated with cannabis will be added to those of opioid use.

If Cannabis Is Recommended Medicine, It Should Be Held to Medical Standards

Clinical trials of opioids are of preparations of medications manufactured and regulated by national standards, which test specified doses, frequencies, and routes of administration. The known risks and benefits are derived from such studies. In clinical practice, clinicians prescribe the studied medications. These practices are not used for cannabis. Most clinical trials do not provide comparable evidence for medical cannabis. Medical cannabis regulations make unregulated products available to be inhaled in smoke or vapor, applied topically as oils and creams, eaten in edibles, or taken orally or sublingually. The demonstrated efficacy and safety of these products should not be labeled as medical. "Budtenders," not pharmacists, physicians, or other clinicians, make clinical recommendations. In a sample of 84 cannabidiol extracts purchased online, 69% (n = 58) had mislabeled cannabinoid content.[9] Ecological correlational studies and individual testimonials of benefit are not the quality of evidence typically required to recommend a medication for clinical use. Vulnerable and stigmatized patients with chronic pain and patients with addiction desperate for help are those exposed to such treatments, likely with no recourse if adverse effects occur (Food and Drug Administration–level assertions of safety and efficacy do not exist, and malpractice is likely not applicable).

Conclusions

Cannabis and cannabis-derived medications merit further research, and such scientific work will likely yield useful results. This does not mean that medical cannabis recommendations should be made without the evidence base demanded for other treatments. Evidence-based therapies are available. For chronic pain, there are numerous alternatives to opioids aside from cannabis. Nonopioid medications appear to have similar efficacy,[3] and behavioral, voluntary, slow-tapering interventions can improve function and well-being while reducing pain.

For the opioid addiction crisis, clearly efficacious medications such as methadone and buprenorphine are underprescribed. 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.

ARTICLE INFORMATION

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Disclaimer: Opinions expressed are the sole responsibility of the authors and do not necessarily reflect official Veterans Administration viewpoints.

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Letters

RESEARCH LETTER

Labeling Accuracy of Cannabidiol Extracts Sold Online

There is growing consumer demand for cannabidiol (CBD), a constituent of the cannabis plant, due to its purported medicinal benefits for myriad health conditions.[1] Viscous plant-derived extracts, suspended in oil, alcohol (tincture), or vaporization liquid, represent most of the retail market for CBD. Discrepancies between federal and state cannabis laws have resulted in inadequate regulation and oversight, leading to inaccurate labeling of some products.[2] To maximize sampling and ensure representativeness of available products, we examined the label accuracy of CBD products sold online, including identification of present but unlabeled cannabinoids.

Methods | Internet searches (keywords: *CBD*, *cannabidiol*, *oil*, *tincture*, *vape*) were performed between September 12, 2016, and October 15, 2016, to identify CBD products available for online retail purchase that included CBD content on packaging. Products with identical formulation as another product under the same brand were excluded. All unique CBD extracts that met these criteria were purchased. Products were stored according to packaging instructions, or if none were provided, in a cool, dry space. Within 2 weeks of receipt, product labels were replaced with blinded study identifiers and sent to the laboratories at Botanacor Services for analysis of cannabinoid content (cannabidiol, cannabidiolic acid, cannabigerol, cannabinol, Δ-9-tetrahydrocannabinol, Δ-9-tetrahydrocannabibolic acid [THC]) using high-performance liquid chromatography (in triplicate; lower limit of quantification, ≤0.3170% wt/wt). A 10-point method validation procedure was used to determine the appropriate sample preparation and analytical method. Triplicate test results were averaged and reported by product weight. Data were analyzed using SPSS Statistics (IBM), version 23, with descriptive analyses and a 2-tailed χ^2 (α <.05). Consistent with other herbal products in the US Pharmacopeia and emerging standards from medicinal cannabis industry leaders, a ±10% allowable variance was used for product labeling (ie, accurately labeled = 90%-110% labeled value, underlabeled >110% labeled value, and overlabeled <90% labeled value).

Results | Eighty-four products were purchased and analyzed (from 31 companies). Observed CBD concentration ranged between 0.10 mg/mL and 655.27 mg/mL (median, 9.45 mg/mL). Median labeled concentration was 15.00 mg/mL (range, 1.33-800.00). With respect to CBD, 42.85% (95% CI, 32.82%-53.53%) of products were underlabeled (n = 36), 26.19% (95% CI, 17.98%-36.48%) were overlabeled (n = 22), and 30.95% (95% CI, 22.08%-41.49%) were accurately labeled (n = 26) (**Table 1**). Accuracy of labeling depended on product type [$\chi^2(1) = 16.75$; $P = .002$], with vaporization liquid most frequently mislabeled (21 mislabeled products; 87.50% [95% CI, 69.00%-95.66%]) and oil most frequently labeled accurately (18 accurately labeled products; 45.00% [95% CI, 30.71%-60.17%]). Concentration of unlabeled cannabinoids was generally low (**Table 2**); however, THC was detected (up to 6.43 mg/mL) in 18 of the 84 samples tested (21.43% [95% CI,

Table 1. Label Accuracy by Cannabidiol Extract Type

	Cannabidiol Extract Products			
	Oil (n = 40)	Tincture (n = 20)	Vaporization Liquid (n = 24)	Total (N = 84)
Label accuracy, No. of products (%) [95% CI]				
Accurate[a]	18 (45.00) [30.71-60.17]	5 (25.00) [11.19-46.87]	3 (12.50) [4.34-31.00]	26 (30.95) [22.08-41.49]
Under[b]	10 (25.00) [14.19-40.19]	8 (40.00) [21.88-61.34]	18 (75.00) [55.10-88.00]	36 (42.85) [32.82-53.53]
Over[c]	12 (30.00) [18.07-45.43]	7 (35.00) [18.12-56.71]	3 (12.50) [4.34-31.00]	22 (26.19) [17.98-36.48]
Labeled concentration, mg/mL				
Mean (95% CI)	56.15 (14.23-98.07)	11.14 (5.60-16.60)	26.15 (12.50-39.74)	36.86 (16.21-57.51)
Median (range)	22.26 (2.50-800.00)	8.33 (1.33-50.00)	18.33 (2.00-160.00)	15.00 (1.33-800.00)
Deviation of labeled content from tested value, mg/mL				
Mean (95% CI) [% of deviation]	10.34 (4.95-15.74) [29.01]	3.94 (2.74-5.14) [220.62]	11.52 (8.10-14.94) [1098.70]	9.16 (4.96-13.36) [380.26]
Median (range) [% of deviation]	2.76 (0.13-144.73) [12.11]	1.48 (0.01-22.30) [19.12]	4.62 (0.14-66.07) [67.34]	3.17 (0.10-144.73) [20.42]

[a] Cannabidiol content tested within 10% of labeled value.

[b] Cannabidiol content exceeded labeled value by more than 10%.

[c] Cannabidiol content tested more than 10% below labeled value.

Table 2. Observed Cannabinoid Concentration of 84 Tested Extract Products Sold Online

Cannabinoid	Average Observed Concentration Across Tests, mg/mL	
	Mean (SD)	Median (Range)
Cannabidiol[a]	30.96 (80.86)	9.45 (0.10-655.27)
Cannabidiolic acid	1.35 (6.74)	0 (0-55.73)
Cannabigerol	0.08 (0.55)	0 (0-4.67)
Cannabinol	0	0
Δ-9-Tetrahydrocannabinol	0.45 (1.18)	0 (0-6.43)
Δ-9-Tetrahydrocannabibolic acid	0	0

[a] The mean labeled concentration for cannabidiol was 36.86 mg/mL (SD, 96.56) and the median was 15.00 mg/mL (range, 1.33-800.0).

14.01%-31.35%]), cannabidiolic acid (up to 55.73 mg/mL) in 13 of the 84 samples tested (15.48% [95% CI, 9.28%-24.70%]), and cannabigerol (up to 4.67 mg/mL) in 2 of the 84 samples tested (2.38% [95% CI, 0.65%-8.27%]).

Discussion | Among CBD products purchased online, a wide range of CBD concentrations was found, consistent with the lack of an accepted dose. Of tested products, 26% contained less CBD than labeled, which could negate any potential clinical response. The overlabeling of CBD products in this study is similar in magnitude to levels that triggered warning letters to 14 businesses in 2015-2016 from the US Food and Drug Administration[3] (eg, actual CBD content was negligible or less than 1% of the labeled content), suggesting that there is a continued need for federal and state regulatory agencies to take steps to ensure label accuracy of these consumer products. Underlabeling is less concerning as CBD appears to neither have abuse liability nor serious adverse consequences at high doses[4,5]; however, the THC content observed may be sufficient to produce intoxication or impairment, especially among children.[6] Although the exclusive procurement of products online is a study limitation given the frequently changing online marketplace, these products represent the most readily available to US consumers. Additional monitoring should be conducted to determine changes in this marketplace over time and to compare internet products with those sold in dispensaries. These findings highlight the need for manufacturing and testing standards, and oversight of medicinal cannabis products.

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Author Contributions: Dr Bonn-Miller had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bonn-Miller, Loflin, Thomas, Vandrey.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bonn-Miller, Loflin, Marcu, Vandrey.
Critical revision of the manuscript for important intellectual content: Bonn-Miller, Loflin, Thomas, Hyke, Vandrey.
Statistical analysis: Loflin, Marcu.
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Supervision: Bonn-Miller.

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Association of Trial Registration With Reporting of Primary Outcomes in Protocols and Publications

A major aim of trial registration is to help identify and deter the selective reporting of outcomes based on the results.[1,2] However, it is unclear whether registered outcomes accurately reflect the trial protocol and whether registration improves the reporting of primary outcomes in publications. We evaluated adherence to trial registration and its association with subsequent publication and reporting of primary outcomes.

Methods | We conducted a cohort study of all initiated clinical trial protocols approved in 2007 by the research ethics committee for the region of Helsinki and Uusimaa, Finland. Registry records and articles published up to February 2017 were identified using keywords to search trial registries, PubMed, EMBASE, Cochrane Central, Finnish databases (Medic, ARTO, TUHAT), and Google. Trial characteristics and outcomes were extracted in duplicate from each protocol (including amendments), registry record, and publication.

Using descriptive statistics and multivariable logistic regression adjusting for characteristics in **Table 1**, we determined

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

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Abstract

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.

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US Veterinarians' Knowledge, Experience, and Perception Regarding the Use of Cannabidiol for Canine Medical Conditions.

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Abstract

Due to the myriad of laws concerning cannabis, there is little empirical research regarding the veterinary use of cannabidiol (CBD). This study used the Veterinary Information Network (VIN) to gauge US veterinarians' knowledge level, views and experiences related to the use of *cannabinoids* in the medical treatment of dogs. Participants (*n* = 2130) completed an anonymous, online survey. Results were analyzed based on legal status of recreational marijuana in the participants' state of practice, and year of graduation from veterinary school. Participants felt comfortable in their knowledge of the differences between Δ9-tetrahydrocannabinol (THC) and marijuana, as well as the toxic effects of marijuana in dogs. Most veterinarians (61.5%) felt comfortable discussing the use of CBD with their colleagues, but only 45.5% felt comfortable discussing this topic with clients. No differences were found based on state of practice, but recent graduates were less comfortable discussing the topic. Veterinarians and clients in states with legalized recreational marijuana were more likely to talk about the use of CBD products to treat canine ailments than those in other states. Overall, CBD was most frequently discussed as a potential treatment for pain management, anxiety and seizures. Veterinarians practicing in states with legalized recreational marijuana were more likely to advise their clients and recommend the use of CBD, while there was no difference in the likelihood of prescribing CBD products. Recent veterinary graduates were less likely to recommend or prescribe CBD. The most commonly used CBD formulations were oil/extract and edibles. These were most helpful in providing analgesia for chronic and acute pain, relieving anxiety and decreasing seizure frequency/severity. The most commonly reported side-effect was sedation. Participants felt their state veterinary associations and veterinary boards did not provide sufficient guidance for them to practice within applicable laws. Recent graduates and those practicing in states with legalized recreational marijuana were more likely to agree that research regarding the use of CBD in dogs is needed. These same groups also felt that marijuana and CBD should not remain classified as Schedule I drugs. Most participants agreed that both marijuana and CBD products offer benefits for humans and expressed support for use of CBD products for animals.

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

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Abstract

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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%.

Idiopathic epilepsy reportedly affects 0.5% to 5.7% of the pet dog population, making it the most common neurologic condition in dogs.[1] A limited number of AEDs are licensed for the treatment of epilepsy in dogs. The most recent American College of Veterinary Internal Medicine consensus statement on seizure management in dogs[2] indicates that anticonvulsant treatment should be initiated with phenobarbital or potassium bromide. However, a combination of phenobarbital and potassium bromide is unsuccessful in controlling seizures in approximately 20% to 30% of dogs.[3] The ineffectiveness and adverse effects of these drugs have caused many dog owners to search for alternative treatments, including cannabis. Although, to the authors' knowledge, no reports have been published regarding the efficacy of cannabis products in the treatment of dogs with idiopathic epilepsy, cannabis products have been anecdotally reported to reduce seizure activity in humans and pets.[4–7]

More than 104 cannabinoids have been identified as constituents of the *Cannabis sativa* plant. The 2 most abundant cannabinoids are CBD, which is a nonpsychotropic cannabinoid, and THC, which is a psychotropic cannabinoid. Although THC is toxic to dogs, there is hope that CBD may be a safe alternative for medical use. Anticonvulsant properties of CBD have been established in vitro.[8] Cannabidiol does not bind type 1 cannabinoid receptors, but it appears to have anticonvulsant effects via other mechanisms, including binding to certain transient receptor potential channels, which leads to decreased release of glutamate (a major excitatory neurotransmitter), activation of 5-hydroxytryptophan 1A receptors, and inhibition of adenosine reuptake.[9–12] Preclinical studies[13–15] involving rats and mice with experimentally induced seizures have demonstrated the anticonvulsant effects of CBD.

Recently, a 99% pure CBD medication formulated for oral administration was approved by the US FDA for treatment-resistant epilepsy in humans.[16] During the approval process for that product, the US Drug Enforcement Administration was provided with a medical and scientific analysis of CBD so that it could reevaluate use of the product and make a scheduling determination. Subsequently, the Drug Enforcement Administration rescheduled FDA-approved CBD products as a schedule V substance.

Because of its nonpsychoactive characteristics, lack of reported adverse effects, and anticonvulsive properties, CBD has potential for use as an AED.[4,8,17,18] The purpose of the study reported here was to assess the short-term effect of addition of CBD to standard AED treatment on seizure frequency in dogs with intractable idiopathic epilepsy. Secondary objectives included evaluation of the effect of CBD on serum phenobarbital and bromide concentrations, measurement of the plasma CBD concentrations over a 12-week oral administration period, and identification of any adverse clinical and clinicopathologic effects.

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Dr. McGrath has a 5% ownership in Applied Basic Science Corporation. The authors declare that there were no other conflicts of interest.

ABBREVIATIONS

AED Antiepileptic drug
ALP Alkaline phosphatase
C-BARQ Canine Behavioral Assessment and Research Questionnaire
CBD Cannabidiol
CYP Cytochrome P450
THC Tetrahydrocannabinol

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Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs.

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Abstract

in **English**, French

The purpose of this study was to determine the pharmacokinetics of cannabidiol (CBD) in healthy dogs. Thirty, healthy research dogs were assigned to receive 1 of 3 formulations (oral microencapsulated oil beads, oral CBD-infused oil, or CBD-infused transdermal cream), at a dose of 75 mg or 150 mg q12h for 6 wk. Serial cannabidiol plasma concentrations were measured over the first 12 h and repeated at 2, 4, and 6 wk. Higher systemic exposures were observed with the oral CBD-infused oil formulation and the half-life after a 75-mg and 150-mg dose was 199.7 ± 55.9 and 127.5 ± 32.2 min, respectively. Exposure is dose-proportional and the oral CBD-infused oil provides the most favorable pharmacokinetic profile.

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PHARMACOKINETICS OF CANNABIDIOL IN DOGS

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ABSTRACT:

Cannabidiol (CBD) is one of the major nonpsychoactive cannabinoids produced by *Cannabis sativa L.* Recent studies have shown that CBD has a high protective index, comparable to that of phenobarbital and phenytoin. Because CBD has been reported to possess both anticonvulsant and antiepileptic activity, its pharmacokinetics were studied in dogs after the administration of two iv doses (45 and 90 mg) and one oral dose (180 mg) to dogs. After iv administration, CBD was rapidly distributed, followed by a prolonged elimination. It has a terminal half-life of 9 hr. CBD plasma levels declined in a triphasic fashion. The total body clearance of CBD was 17 liters/hr (after the 45-mg dose) and 16 liters/hr (after the 90-mg dose). This clearance value, after its normalization to blood clearance using mathematical equations, approaches the value of the hepatic blood flow; the extraction ratio in the liver is 0.74. CBD was observed to have a large volume of distribution, approximately 100 liters. In the dose range of 45 to 90 mg, the increase in the AUC was proportional to the dose, a fact that indicates that the pharmacokinetic profile of CBD in this dose range was not dose dependent. In three of the six dogs studied, CBD could not be detected in the plasma after oral administration. In the other three, the oral bioavailability ranged from 13 to 19%. The results of this study show that CBD is barely absorbed after oral administration to dogs. This low bioavailability may be due to a first pass effect.

CBD[1] is one of the major cannabinoids produced by *Cannabis sativa L.* (1) and, although it was first isolated in 1940, its structure was elucidated only 23 years later (2). In contrast to the highly psychoactive major compound, THC, CBD has virtually no psychoactive propeties in humans (3–5). Nevertheless, CBD possesses anticonvulsant activity in both animals and man (6, 7). Recent studies have shown that CBD has a high protective index, comparable to that of phenobarbital and phenytoin (6–8). Despite the fact that CBD is one of the main constituents of cannabis and the recent surge of interest in its medical applications, few reports have been published on its pharmacokinetics (9, 10).

The present study was undertaken to investigate the pharmacokinetics of CBD in dogs after the administration of two iv doses (45 and 90 mg) and one oral dose (180 mg).

Materials and Methods

The experiments were conducted in six dogs (mongrels), three males and three females, all weighing between 16 and 24 kg. Each dog received, at separate times and in a crossover design, iv injections of CBD (45 or 90 mg in 1.5 ml of 70% alcohol) into the cephalic vein and an oral gelatin capsule containing 180 mg of CBD (in raw material form). Venous blood samples (8 ml) were collected via an indwelling catheter from the other cephalic vein at 0, 2, 5, 10, 15, 20, 30, 40, and 50 min and 1.0, 1.25, 1.5, 2.0, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 24 hr after each of the two iv injections. After oral administration, the sampling times were the same except for the first hour, in which blood was first withdrawn only 30 min after drug administration. A washout period of 3 weeks was allowed between any two consecutive studies. Plasma was immediately separated by centrifugation at 7000 rpm for 15 min and stored at −20°C. Before assaying, the plasma was allowed to reach room temperature and the residual clot was removed. Plasma levels of CBD were assayed by an HPLC assay that we have already reported in detail (11).

The linear terminal slope of log C (CBD plasma concentration) *vs.* t (time) was calculated by the method of least squares. The terminal $t_{1/2}$ of CBD was calculated from the quotient: (0.69)/(terminal slope). The AUC (area under the C *vs.* t curve) was calculated by using the trapezoidal rule with extrapolation to infinity, by dividing the last experimental plasma concentration by the terminal slope (12).

The total body clearance of CBD (CL) was calculated from the dose-quotient and the AUC. The volume of distribution (V) was calculated from the ratio of the clearance and the linear terminal slope. The volume of distribution at steady state (V_{ss}) and the mean residence time (MRT) were calculated by using equations 1 and 2 (13–15).

$$V_{ss} = \frac{D \cdot \text{AUMC}}{(\text{AUC})^2} \quad (1)$$

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}} \quad (2)$$

AUMC is the area under the curve of the product of t (time) and C (plasma drug concentration) *vs.* (t), from time zero to infinity. AUMC was calculated by the trapezoidal rule with extrapolation to infinity. All pharmacokinetic parameters were calculated in a noncompartmental manner, based on the statistical moment theory (15, 16).

The blood-plasma concentration ratio (17) of CBD (partition study) was determined at room temperature by spiking known various amounts of CBD in seven samples of fresh blood taken from a dog before drug administration. CBD concentration ranged from 50 to 1000 ng/ml. Each blood sample was centrifuged immediately after spiking and the plasma was separated according to the procedure mentioned above. Plasma levels of CBD were determined by HPLC assay (11). The mean blood cell plasma concentration ratio was calculated by means of the following formula:

$$\frac{C_b}{C_p} = \frac{C_{bc}}{C_p} \times \text{HCT} + (1 - \text{HCT}) \quad (3)$$

where C_b/C_p is the blood-plasma concentration ratio, C_{bc}/C_p is the blood cell-plasma concentration ratio, and HCT is the hematocrit.

This paper is taken from the doctoral dissertation of Mr. Emil Samara, submitted in partial fulfillment of the Ph.D. requirements of the Hebrew University of Jerusalem.

[1] Abbreviations used are CBD, cannabidiol; THC, Δ^1-tetrahydrocannabinol; MFO, mixed function oxidases.

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A blood stability study of CBD was carried out by incubating 500 ng/ml of CBD in 20 ml of dog blood (placed in heparinized test tubes) at 37°C with continuous shaking. Blood samples (2 ml) were collected at the following times: 0, 1, 2, 3, 4, 5, 6, and 7 hr. Plasma was immediately separated and CBD concentration in the plasma was assayed by HPLC.

Results

The mean plasma levels of CBD, as obtained after the two iv administrations to the six dogs, are presented in fig. 1. Fig. 1 outlines the initial rapid decline of CBD plasma levels followed by a prolonged elimination, with a mean $t_{1/2}$ of 7 to 9 hr. Upon oral administration of 180 mg, CBD was not detected in three dogs over the 24-hr collection period. In the other three dogs CBD plasma levels were low and could only be determined over limited periods of time. These low plasma concentrations produced individual bioavailability values of 13, 13, and 19% respectively.

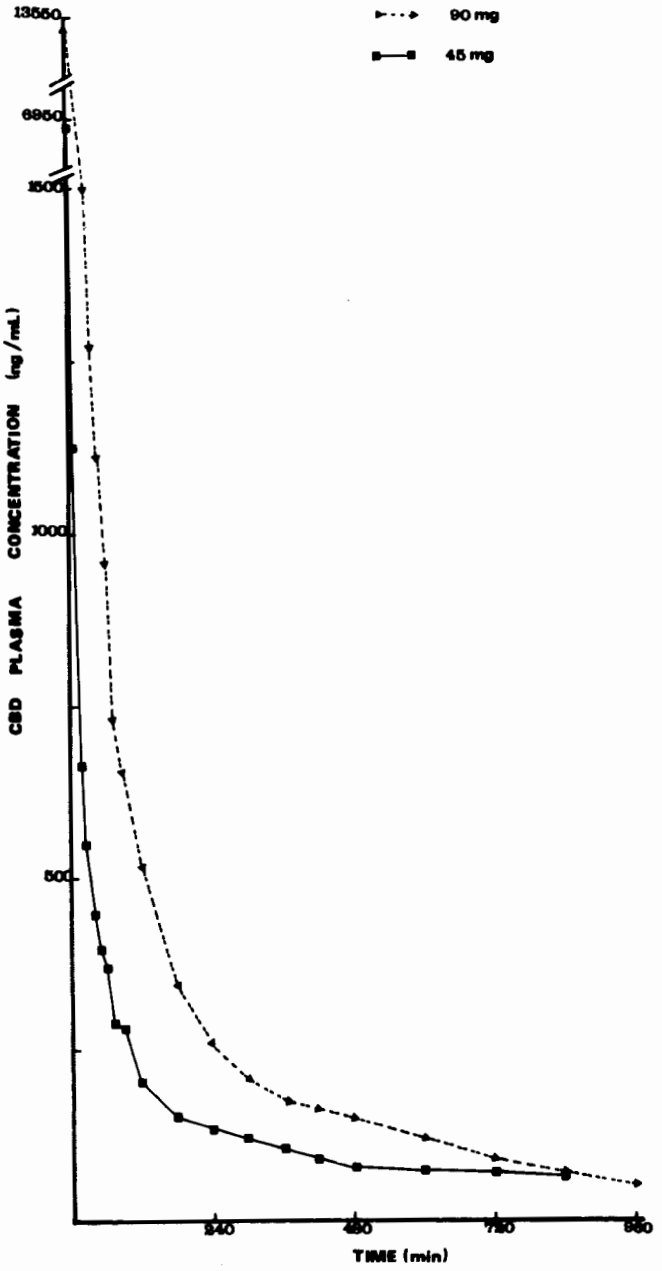

FIG. 1. *Mean plasma concentrations of CBD obtained after two iv (45 and 90 mg) to six dogs.*

Table 1 summarizes the individual and mean pharmacokinetic parameters of CBD as obtained after the two iv administrations. Table 1 shows that there were no significant differences in any of the parameters calculated except AUC, which increased proportionally. This observation indicates no dose dependency in the dose range used in this study.

In relation to the partition study carried out in dog blood, the CBD blood/plasma ratio was calculated and the mean value (± SD) was found to be 0.67 ± 0.02. The hematocrit of the same dog's blood was 48%, giving a mean blood cell/plasma ratio of 0.31. The partition study indicates that there is a low uptake of CBD by the blood cells. Furthermore, the stability study carried out with CBD in blood showed that CBD is stable in blood.

Discussion

Upon iv administration, a rapid CBD distribution occurs, followed by a prolonged elimination with a terminal $t_{1/2}$ of 7–9 hr. CBD plasma levels decline in a triphasic fashion and its $t_{1/2}$ as determined in this study was not significantly dependent upon the dose administered. At a dose range of 45–90 mg the increase in AUC was proportional to the dose, a fact that indicates that the pharmacokinetic profile of CBD at this dose range was not dose dependent.

The large volume of distribution of CBD indicates the presence of a "deep compartment," due to the fact that CBD was sequestered out of the plasma into various organs and tissues.

The low uptake of CBD by blood cells, along with its stability in blood, indicates that blood cells and/or plasma are not among its metabolic sites. The mean total body clearance of CBD was 17.3 liters/hr (after the 45-mg dose) and 15.9 liters/hr (after the 90-mg dose) or 288 and 265 ml/min, respectively. CBD is mainly eliminated from the body by a metabolic process that occurs primarily in the liver (18). Thus, its high metabolic clearance value is not due to multisite metabolism but due to its high affinity in the eliminating organ. This leads to its high extraction ratio in the liver. The calculated hepatic blood flow for dogs ranges from 372 to 747 ml/min or 30 to 45 ml/min/kg (19). To compare CBD plasma clearance with the hepatic blood flow, CBD blood clearance has to be calculated. This is carried out by using equations 3 and 4 (17):

$$\frac{\text{Plasma clearance}}{\text{Blood clearance}} = \frac{\text{blood concentration}}{\text{plasma concentration}} \qquad (4)$$

The blood clearance of CBD was 1.5 times greater than its plasma clearance; mean values were 405 and 384 ml/min. Dividing the blood clearance by the average dog hepatic blood flow of 560 ml/min gave an extraction ratio of 0.74, which means that the metabolic clearance of CBD was within the range of its hepatic blood flow. Thus, CBD has a high extraction ratio in the liver, a fact that indicates that CBD is suceptible to a first pass effect upon oral administration. The high extraction ratio of CBD indicates that CBD clearance will be affected by changes in blood flow but will not be affected by changes in plasma protein binding (17).

CBD, like THC, is a highly lipophilic drug (20, 21), with its water solubility being in the range of only several milligrams per liter. This low water solubility may lead to incomplete absorption. In addition, as THC is unstable at acidic gastric pH (21), a similar phenomenon may occur with CBD. The low systemic availability of CBD upon oral administration may thus be due

TABLE 1

Summary of the pharmacokinetic parameters of CBD obtained after two iv administrations (45 and 90 mg) to six dogs

Dose	Terminal slope	Terminal $t_{½}$	MRT[a]	AUC[b]	CL[c]	V[d]	V_{ss}[e]
mg	*1/hr*	*hr*	*hr*	*μg·hr/liter*	*liters/hr*	*liters*	*liters*
Dog 2							
45	0.14	5.0	5.0	2331	19.3	136	46
90	0.14	4.9	2.8	5018	17.9	128	96
Dog 3							
45	0.14	5.0	4.7	1960	23.0	164	108
90	0.11	6.4	7.0	9414	9.6	87	67
Dog 6							
45	0.09	8.0	8.0	3008	15.0	174	113
90	0.05	14.8	11.4	5956	15.1	321	173
Dog 8							
45	0.14	5.1	5.1	3435	13.1	97	67
90	0.06	11.4	7.5	6917	13.0	217	98
Dog 9							
45	0.11	5.8	4.9	2366	19.0	173	93
90	0.10	7.6	6.7	3911	22.9	252	153
Dog 10							
45	0.06	12.3	14.4	3134	14.3	255	201
90	0.07	10.4	9.6	5355	16.8	251	160
Mean ± SD							
45	0.11 ± 0.03	6.8 ± 2.7	7.0 ± 3.5	2706 ± 519	17.3 ± 3.4	167 ± 47	113 ± 42
90	0.09 ± 0.04	9.3 ± 3.3	7.5 ± 2.7	6095 ± 1741	15.9 ± 4.1	209 ± 79	117 ± 48

[a] MRT, mean residence time.
[b] AUC, area under the plasma concentration *vs.* time curve.
[c] *CL*, total body clearance.
[d] *V*, volume of distribution.
[e] V_{ss}, volume of distribution at steady state.

to a first pass effect and incomplete absorption. In a previous report the bioavailability of CBD was 6% upon oral administration (20 mg) to humans (9, 10); however, no detailed data were presented. In another report (22) 900 mg of CBD were administered orally to a monkey and extremely low levels of CBD were detected over the entire course of the experiment. This observation corroborates our evidence that the low oral bioavailability of CBD in dogs is similar to that observed in humans and monkeys.

CBD has been administered orally to epileptic patients and has been found to cause "a beneficial effect in those patients suffering from secondary generalized epilepsy with a temporal focus and who did not benefit from known antiepileptic drugs" (8). The question raised by the present results is whether the low oral bioavailability is compatible with the reported antiepileptic activity in patients. No definite answer can be given until a clinical study has been carried out in which CBD is administered alone and its pharmacokinetics are analyzed. We must, however, point out that all 15 patients who participated in the study (8) were under polytherapy. They received other antiepileptic drugs such as phenytoin, phenobarbital, primidone, and carbamazepine, drugs that are metabolized by the MFO. CBD is known to be a potent inhibitor of the MFO system (23–26) and, as such, can inhibit the metabolism of the above-mentioned antiepileptic drugs, thus potentiating their antiepileptic activity. From our observation it would appear that, due to its low bioavailability upon oral administration, CBD is not a potent antiepileptic agent alone but only when combined in a therapeutic regimen with other antiepileptic drugs. It thus appears that, after CBD is absorbed, upon oral administration, it undergoes a first pass metabolism that may lead to the metabolic inhibition of MFO and the potentiation of the activity of the other antiepileptic drugs administered with it.

The fact that CBD has been demonstrated to possess antiepileptic activity in rats and mice can be explained by its mode of administration in those experiments. On iv or ip administration CBD does not undergo first pass metabolism.

To date, no report has appeared that states that CBD possesses antiepileptic or anticonvulsant activity in humans or animals upon oral administration when it is the only drug administered.

The following conclusions have been drawn from this study:

1) After iv administration, CBD is rapidly distributed, followed by a prolonged elimination with a mean terminal $t_{½}$ of 7 to 9 hr.

2) CBD was found to have a large volume of distribution, a total body clearance of 17 liters/hr and a liver extraction ratio of 74%.

3) In the dose range of 45 to 90 mg, the pharmacokinetic profile of CBD was non-dose dependent.

4) No significant changes were observed in the major pharmacokinetic parameters of CBD such as $t_{½}$, mean residence time, total body clearance, volume of distribution, and steady-state volume of distribution after the administration of the two iv doses (45 and 90 mg).

5) After oral administration, CBD has a low bioavailability due to its high extraction ratio in the liver, leading to a first pass effect.

6) Because of the low oral bioavailability of CBD, clinical studies with this cannabinoid should be monitored for plasma levels.

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