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

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KEYWORDS

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

KEY POINTS

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

INTRODUCTION

Over the past decade, the legal landscape of marijuana has changed dramatically in both the United States and Canada. At the time of publication, all but 4 states in the United States allowed the use of cannabis (marijuana) in some form—some strictly for medical purposes and others for recreation—even though it remains illegal at a federal level. As of October, 2018, Canadian law allows for both recreational and

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medical marijuana in all provinces. In conjunction with these trends, the incidence of marijuana exposure and intoxication in pets, especially as reported to Pet Poison Helpline, an animal poison control center, has increased dramatically. This increase is presumably due to increased accessibility. Because of this, it is imperative for veterinary professionals to understand how common types of marijuana products can affect their patients following intentional or inadvertent exposure. This article reviews marijuana-containing products along with cannabidiol (CBD), a nonpsychoactive substance with a laundry list of anecdotal and increasingly supported therapeutic benefits. Finally, synthetic marijuana products (synthetic cannabinoids [SCB]), illegal substances with a much greater affinity for cannabinoid receptors than traditional marijuana that remain accessible as a "street drug," will also be covered.

DISCUSSION

A Brief History of Cannabis (Marijuana)

Cannabis (marijuana) has been widely used for centuries in the treatment of various ailments, for its psychoactive properties in recreational use, and in religious ceremony. Use of cannabis for medical purposes dates back to 2700 BCE for treatment of various maladies, including constipation, rheumatic pain, malaria, menstrual health, venereal disease, headaches, fever reduction, appetite stimulation, and as a sleep aid. Use for these ailments continued well into the 19th century, particularly in 1839 when Irish physician W.B. O'Shaughnessy began investigating its usefulness in the treatment of seizures, tetanus, rabies, and rheumatism in animal studies. He recognized its benefits as an antispasmodic agent with antianxiety and antiemetic properties, although he consequently noted side effects including catalepsy.[1]

Although marijuana faced increasing political controversy throughout the early 1900s in the United States, it was used in veterinary medicine until 1937, at which point it was effectively abolished following the passage of the Marihuana Tax Act (marihuana is an alternative spelling of marijuana)—an act that levied taxes and excessively harsh penalties on veterinarians and other health care professionals such as physicians and dentists. Mandatory criminal sentencing for recreational possession was introduced in the 1950s. In 1970, under the Controlled Substances Act, marijuana was classified as a Schedule I controlled drug, meaning "a drug with no currently accepted medical use and a high potential for abuse" per the Drug Enforcement Agency.[2] It remains a Schedule I drug to this day. Examples of other Schedule I drugs include heroin, LSD, MDMA (Ecstasy), and peyote.

Expansive knowledge has been gained over the last half century as scientists further investigate the effects of marijuana and its cannabinoid compounds in both medical and nonmedical ways. (−) Δ^9-Tetrahydrocannabinol (THC) was identified as the major psychoactive cannabinoid from the cannabis plant in 1964.[3] The structure of CBD, the primary nonpsychoactive cannabinoid, was discovered in 1963.[4] The design of enantiomerically pure analogues or synthetic varieties of THC began in the 1960s in the pursuit of both analgesics and endogenous receptors presumed present in mammals at which THC, CBD, and other cannabinoids act.[3,5] Cannabinoid receptors were discovered in 1988, and specific receptors CB1 and CB2 were cloned in 1990 and 1993, respectively, at which time they were identified as G protein–coupled receptors affected by endogenous cannabinoids, termed endocannabinoids, during the early 1990s.[3]

Marijuana and SCBs have progressed to be the most widely used illicit drugs in the world, and most countries categorize them as drugs of abuse. In the United States,

marijuana is one of the most commonly used drugs, just behind alcohol and cigarettes.[1,6] SCB varieties developed to mimic THC have also gained popularity for their psychoactive properties, most notably since 2009.[5]

Although considered a drug of abuse, the therapeutic benefits of cannabinoids have not been ignored. Since the 1980s, synthetic THC–based medications dronabinol (Marinol) and analogue nabilone (Cesamet) have been used in treatment of inappetence and nausea in chemotherapy patients and patients with AIDS.[3,7] Cannabis—including extracts of THC and CBD—are once again at the forefront of debate with respect to potential therapeutic benefit.[1] As of early 2018, in spite of federal law, all but 4 states in the United States legally allowed the use of medical cannabis although legislation varied considerably with respect to permissible compounds (whole plant vs THC and CBD extracts vs only allowing CBD).

DEFINITIONS OF MARIJUANA, HEMP, MEDICAL CANNABIS, AND CONCENTRATES

Marijuana is a general term that typically refers to *Cannabis sativa* and/or *cannabis indica* plants, or portions of the plants, which are used for pharmacologic effects. Cannabis is a synonym for marijuana, derived from the plants' scientific names, and more commonly used in professional settings such as health care and scientific publications. More than 500 chemical compounds and 100 cannabinoids, also termed phytocannabinoids, have been identified in *Cannabis sativa*. Of these, THC is the primary psychoactive cannabinoid (ie, responsible for inducing a "high") and the compound on which the potency of marijuana products is based.[5]

Hemp is a cultivar of *Cannabis sativa* grown mainly for fiber, seeds, oil, biofuel, etc. In the United States, "industrial hemp" cannot have more than 0.3% THC on a dry weight basis.[8] Some hemp plants are being bred to have increasing concentrations of CBD and may be referred to as "medicinal hemp."

The terms "medical marijuana" or "medical cannabis" are synonymous and can accurately be used to describe any legal cannabis formulation meant for medicinal purposes, whether or not it contains THC. The legal definition of "medical cannabis" varies widely between states with respect to allowable compounds, formulations, and qualifying health conditions. Several states allow for THC to be used medically, whereas others restrict medical use to compounds such as CBD, which have no psychoactive properties. For example, states such as California or Colorado allow human patients access to a full suite of cannabis products ranging from whole plants (live or dried) to THC-infused foods. Other states, such as Minnesota, prohibit smokable cannabis, allowing only highly purified, pharmacologic grade extracts of THC and CBD in the form of capsules, tinctures, topical creams, and oils for vaporization. In human medicine, some states allow medical cannabis to be used for an exhaustive list of complaints, whereas others limit use to a range of qualifying conditions, often including chronic or intractable pain, severe nausea/vomiting/cachexia, human immunodeficiency virus/AIDS, amyotrophic lateral sclerosis, seizures, severe/persistent muscle spasms, posttraumatic stress disorder, Tourette syndrome, inflammatory bowel disease, and terminal illness.

The other notable category of marijuana products is "concentrates" meaning products with high concentrations of THC (possibly >80%–90%). These may be used recreationally or medically and as their description implies, require smaller doses to achieve stronger and more long-lasting effects. Concentrates come in varying formulations and compositions, sometimes divided into "hash," concentrates made from dry or water-based extractions, and "solvent and CO_2-based processes."[9] Hashish is a sticky resin collected from the flowering buds that may be shaped or formed

into a cake, ball, sticks, or slabs. Hash oil is a liquid or semisolid with a higher THC concentration than hashish. Solvent-based concentrates are increasingly common and made by soaking plant material in various solvents, which are then boiled off. Such products are generally called R-S-O as an homage to the person who popularized the technique. Other names for solvent-based concentrates include BHO, "honey oil," "honeycomb," "wax," "shatter," "budder," "errl," and "CO_2 oil." Together, these may be collectively referred to as "dabs," the act of which inhaling them is called "dabbing" or "doing a dab."[9] In addition to containing THC, concentrates may be contaminated with high concentrations of solvents, pesticides, and other chemicals.

ENDOCANNABINOID SYSTEM

Similar to opioid receptors (ie, delta, kappa, mu) that are activated by endogenous opioid peptides (eg, endorphins), mammals have cannabinoid receptors in plasma membranes that are activated by endogenous ligands called endocannabinoids. The endocannabinoid system encompasses complex intracellular signaling including enzymes for ligand biosynthesis and inactivation and plays a physiologic role in several systems primarily neurologic, inflammatory, and immune.

The two best-known and well-studied endocannabinoids are anandamide (AEA) and 2-AG, which the body produces, "on demand", to stress. These bind to G protein–coupled receptors and perform several neurotransmission functions including inhibition (mostly) of adenylate cyclase, inhibition of voltage-gated calcium channels, stimulation of protein kinases, and stimulation of potassium channels.[3]

The primary targets for endocannabinoids and THC are cannabinoid receptors 1 and 2 (CB1 and CB2). These receptors are present on the postsynaptic neuron and act via retrograde synaptic signaling mechanisms to inhibit neurotransmitter release from presynaptic neurons.[10] Endocannabinoids are synthesized, as needed, from membrane phospholipids to act in an autocrine (on the same cell) or paracrine (on nearby cells) fashion and are quickly inactivated via hydrolysis after internalization into the near-by cell.[3,11]

Endocannabinoids are 4 to 20 times less potent than THC and have a significantly shorter duration of action.[1] Administration of exogenous cannabinoids such as THC or synthetic analogues disrupt the subtle endocannabinoid signaling process and may result in the common THC tetrad of delusions, hallucinations, paranoia, and sedation.[1,11]

- CB1 receptors
  - Primarily located in the central nervous system (CNS) with lower concentrations in the peripheral nervous system (PNS).
  - In the CNS, CB1 is involved in cognitive function, emotion, motion/movement, hunger, and neuroprotection in both posttraumatic events and degenerative diseases.
  - Sensory and autonomic CB1 receptors are involved in pain perception, cardiovascular, gastrointestinal, and respiratory effects.
  - CB1 is responsible for the psychotropic effects of THC.
  - Activation inhibits retrograde release of acetylcholine, dopamine, GABA, serotonin, histamine, glutamate, and/or noradrenaline, among others.
- CB2 receptors
  - Primarily located in the PNS and are nonpsychotropic.
  - Involved in reducing inflammation and chronic pain relief.[3]
  - Activation inhibits proinflammatory cytokine production and subsequent release of antiinflammatory cytokines.[12]

Cannabinoid receptors are found in abundance within the epithelial tissues of the developing embryo with highest concentrations in the nervous system, sensory organs, and thyroid tissue. CB1 is important in the normal neuronal differentiation and axonal growth during neuronal development. The developed animal has highest CB1 concentration in the basal ganglia and cerebellum.[10] Endocannabinoid signaling is required for motor learning in the cerebellum, extinction of averse memories in the amygdala, and as an aid in memory encoding.

Although CB1 and CB2 are the most prevalent receptors in the endocannabinoid system, TRPV1 (a vanilloid receptor) may be of significant importance when activated by AEA and can play roles in motor disorders; ear/skin protection; mucosal protection of the gastrointestinal, urinary, respiratory, and circulatory tracts; and can affect cognitive processes such as emotion, learning, and satiety.[4]

MARIJUANA AND THC EXPOSURE

Product Potency

The potency of THC in the cannabis plant has increased in recent decades in the United States. The average THC concentration of marijuana in the 1960s was 1.5%, rising to 3.5% by the mid 1980s.[13] As of 1995 and 2014, concentrations increased from 4% to 12%, respectively, whereas the concentration of CBD simultaneously declined from 0.28% to less than 0.15%.[13] This increase in potency correlates with a shift in production from cannabis to the more potent sinsemilla—unpollinated, sterile flowering tops from the cultivated female cannabis plant. Sinsemilla is more potent than traditional marijuana and is gaining popularity in the United States, presumably due to demand for plants with greater psychoactive effects.[1,13]

In cannabis plants, THC is most concentrated in the flowering buds, followed by the leaves, stems, and roots. The seeds do not contain notable levels of THC.[1] Marijuana joints (cigarettes) typically contain 0.5 to 1 g of plant material with THC concentrations varying from 0.4% to 20%. The average 1 g joint contains 150 mg of THC.[9] High THC concentrations in cultivated plants are thought to be a result of cross-breeding and hydroponic year-round growing operations.[1] Hashish typically contains about 10% THC and hash oil 20% to 50%.

Exposure Scenarios in Pets

The most common route of accidental exposure to marijuana in companion animal patients is via ingestion, although some are exposed via inhalation from second-hand smoke or smoke intentionally blown in their face. Approximately 66% of the marijuana exposures reported to Pet Poison Helpline involve pets ingesting homemade or commercial edible goods.[14] The second most common source of cannabis exposures involve ingestion of plant material (~19%), followed by medical cannabis preparations and/or prescription medications such as dronabinol and nabilone (~9%).[14] Edible products are most typically brownies or cookies made using "marijuana butter" or various cooking oils that had been used to extract lipid-soluble THC from plant matter. Marijuana butter/oil can contain very high concentrations of THC and poses a greater risk for poisoning than ingestion of plant material alone. In addition, chocolate present in food may also lead to intoxication and can complicate the clinical picture. Other common food products include truffles, caramels, gummy candy, lollipops, ice cream, savory baked goods, beverages, etc. There seem to be few foods or beverages to which marijuana is *not* added.

Legalization of both recreational and medical marijuana may also increase exposure to various tinctures, vaporization liquids and associated vape pens, and oral

preparations such as capsules, sublingual sprays, etc. Doses and concentrations of such products can vary widely.

Pharmacokinetics

Dogs are reported to have a larger number of cannabinoid receptors in the brain compared with humans, which may result in an increased sensitivity to the psychoactive properties of THC.[15] THC is readily and rapidly absorbed when inhaled. Absorption is slower and less predictable when ingested. Consuming THC products with a fatty meal will increase absorption due to its lipophilic nature. Most of the THC is metabolized in the liver and undergoes enterohepatic recirculation, with a small amount excreted as metabolites in the urine.[15] Because of its lipophilicity, THC is rapidly distributed into the tissues and crosses the blood-brain barrier.[6] This accounts for a short plasma but long biological half-life.[16]

The kinetic information listed pertains to dogs unless otherwise indicated.

- Minimum lethal dose greater than 3 to 9 g plant material per kilogram
- LD_{50} not established[16]
- Onset of signs: minutes (inhaled), typically within 60 min (oral)
- Excretion: 85% in feces via biliary excretion; 15% renally excreted
- Half-life (biological) 30 hours; 80% of THC is excreted within 5 days[15]
- Recovery after ingestion occurs within 24 hours in most cases, potentially up to 72 hours[14,16]
- Bioavailability (inhalation, human) 10% to 27% depending on frequency of use[6]

Clinical Signs of Poisoning

Ingestion or inhalation of THC carries a high morbidity but low mortality rate. Common signs of poisoning in dogs include lethargy, CNS depression, ataxia, vomiting (especially if plant material was ingested), urinary incontinence/dribbling, increased sensitivity to motion or sound, mydriasis, hyperesthesia, ptyalism, and bradycardia.[7,14,16] Acute onset urinary incontinence is not commonly seen with other toxin exposures and can serve as a helpful clue to veterinary staff to consider marijuana/THC exposure. Less common signs include agitation, aggression, bradypnea, hypotension, tachycardia, and nystagmus.[7,14] Rare signs include seizures or comatose conditions. Seizures may also be caused by coingestants such as chocolate or other drugs. In a 2018 study investigating the susceptibility of cannabis-induced convulsions in rats and dogs, no seizures were observed in dogs given chronic daily oral doses of cannabis extracts containing concentrations as high as 27 mg/kg THC combined with 25 mg/kg CBD (1.08:1 ratio of THC to CBD) for 56 weeks; however, other CNS signs including ataxia, tremors, and hypoactivity were observed. Because dogs were not administered THC extracts without CBD, the impact of the relatively large amount of CBD. See **Fig. 1** for signs reported to Pet Poison Helpline and **Fig. 2** for the percentage of cases in which veterinary intervention was recommended.

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

CANNABIDIOL EXPOSURE

CBD is the most well-known and widely discussed nonpsychoactive phytocannabinoid with concentrations ranging from 0.3% to 4.2% in cannabis plants.[4] It is

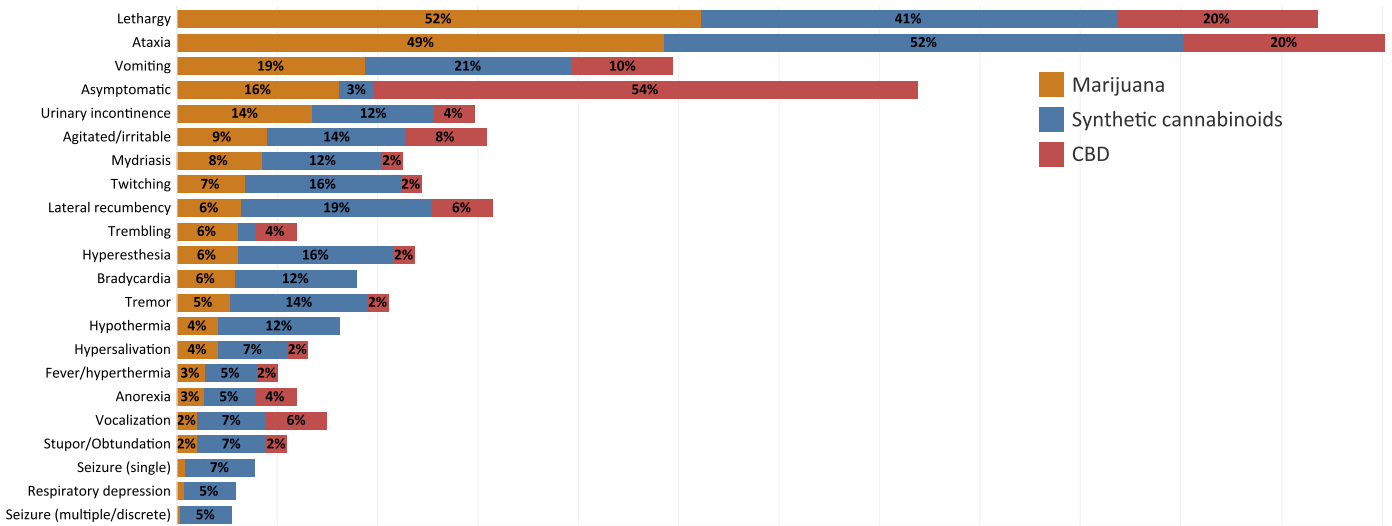

Fig. 1. Clinical signs associated with exposure to marijuana (ie, THC containing products, ~2200 cases), synthetic cannabinoids (~60 cases), and CBD (~50 cases) as reported to Pet Poison Helpline. Canines represent ~96% of the displayed data. Confirmation of exposure was not obtained in all cases, nor could co-ingestants such as chocolate or other toxicants be ruled out. Therefore, these data are meant to portray general trends only. Clinical signs reported in less than 5% of cases were excluded from this graphic.

postulated to have a variety of therapeutic benefits, such as antiseizure, antiinflammatory, analgesic, antitumor, antipsychotic, and antianxiety effects. In people, its effects may temper and counter some of the actions of THC, including reversal of THC-induced memory deficits in people.[11] Some data suggest a therapeutic synergistic effect when CBD is used in combination with THC.[4,11] For example, Sativex is a 1:1, THC:CBD oromucosal spray available in Canada for treatment of neuropathic pain in patients with multiple sclerosis (MS).[11] Likewise, many medical cannabis dispensaries offer combination CBD/THC products.

Although CBD lacks psychoactive properties, it remains a Schedule 1 controlled substance in the United States as of August, 2018. In spite of this, a rapidly increasing number of "CBD-containing" products are sold for use in both dogs and cats, including oils, treats, capsules, etc. These products can be found at some cannabis dispensaries (select states) and are readily available online. They are not approved by Food and Drug Administration (FDA), nor do they have any regulatory quality oversight. In 2015, FDA tested various "CBD-containing products," including those marketed specifically for pets, and found many did not contain the amount of CBD stated on the label (if any), whereas others also contained unlabeled THC.[18] The lack of regulation for pet products

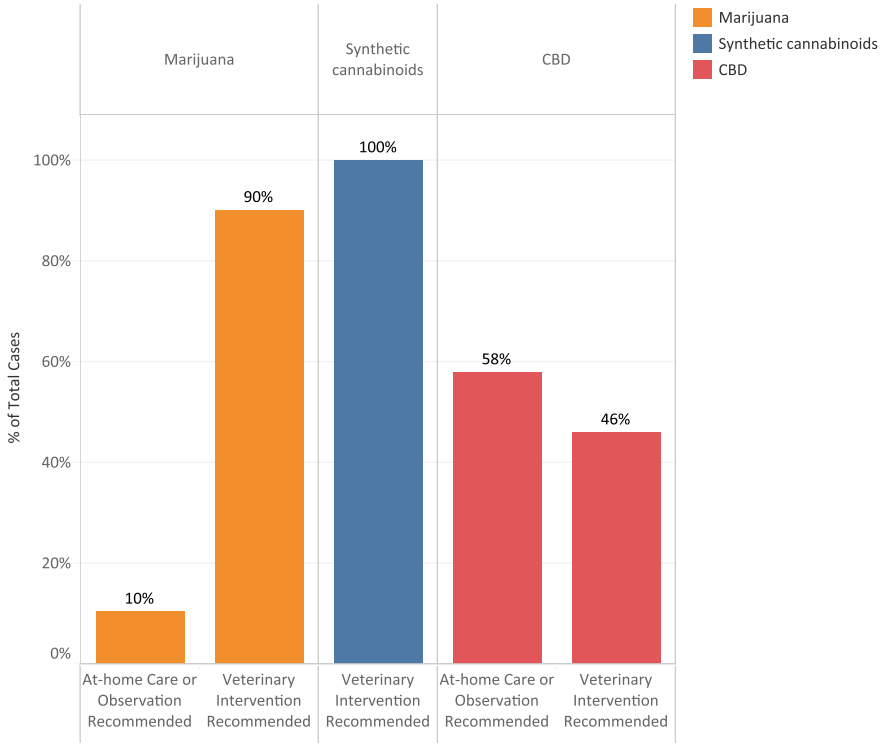

Fig. 2. Comparison amongst the ultimate recommended management site for dogs and cats exposed to marijuana (ie, THC containing products), synthetic cannabinoids, and CBD-only containing products for Pet Poison Helpline cases. Referral for veterinary intervention is based on a thorough, individual risk evaluation including but not limited to patient signalment, dose, expected or current clinical signs, current and prior medical history, and co-ingestants or concomitant medications.

leaves consumers vulnerable to unscrupulous manufacturers and poor-quality products.

Clinical Effects and Drug-Drug Interactions

There is emerging data regarding the pharmacokinetics, safety, and efficacy of CBD in pets, particularly for epilepsy and osteoarthritis (OA). In 2018, researchers at Colorado State University published a Phase I study examining the pharmacokinetics of CBD in 30 healthy, purpose bred beagle dogs.[19] Dogs received CBD via one of three formulations–transdermal cream applied to the pinnae, oral capsules containing microencapsulated CBD oil, or oral CBD infused oil at ~10 mg/kg and ~20 mg/kg daily for 6 weeks. The highest systemic absorption was observed with the infused oil product. Pharmacokinetic data is reported below. Adverse effects were not reported in this publication but are forthcoming in a subsequent paper; they included nonspecific mentions of liver enzyme elevation without corresponding clinical evidence of disease and diarrhea.[20] The investigators concluded the CBD formulation they used to be "tolerable and measureable."[20]

The first North American study investigating the efficacy of CBD for OA in client owned dogs (n = 16) demonstrated a statistically significant decrease in pain and increase in activity in dogs dosed with 2 mg/kg CBD q 12 hours for 4 weeks. While no observable adverse clinical effects were displayed, 9 of 16 dogs had a statistically significant increase in alkaline phosphatase (ALP). The reason for the increase may be due to chronic CBD dosing but other causes cannot be ruled out.[21]

CBD can inhibit certain cytochrome P450 enzymes, specifically CYP450 2C19 in people, resulting in inhibition or slowed metabolism of certain medications.[22] Dogs and cats also express CYP450 2C19 although data regarding interaction with CBD are lacking.[23]

Clinical Signs of Poisoning

Because of the lack of psychoactive properties and interaction with CB1 receptors, less severe effects are expected in case of pet exposure/overdose compared with that of THC-containing products; however, exposure can be complicated by poor-quality CBD products which may contain unlabeled THC or other agents. Of the CBD exposures reported to Pet Poison Helpline, most of the cases remained asymptomatic but those that developed signs seemed similar to marijuana exposures, including lethargy/CNS depression, ataxia, and agitation (see **Fig. 1**). See **Fig. 2** for the percentage of CBD exposure cases in which Pet Poison Helpline recommended veterinary intervention.

Other risks of accidental CBD product ingestion include exposure to carriers such as oils (aspiration), alcohols, or a massive amount of treats or novel food sources that could result in gastrointestinal upset, or other issues. Although significant systemic health effects are unlikely when ingested, intravenous (IV) dosing of 150 to 200 mg/kg in rhesus macaques did lead to tremors, hypopnea, respiratory arrest, and cardiac arrest in a dose-dependent nature.[24] Such severe signs would not be anticipated following oral exposure in small animals.

Pharmacokinetics

CBD undergoes enterohepatic recirculation but also faces extensive first-pass metabolism, which affects oral bioavailability. In spite of this, oral CBD oils appear to have better systemic uptake transdermal preparations.[19] Like other cannabinoids, CBD is

highly lipophilic and rapidly distributed into the tissues.[26] Available pertinent kinetic information listed pertains to dogs:

- Cmax, median or mean (single oral dose of CBD oil): 102 ng/mL (2 mg/kg), 591 ng/mL (8 mg/kg), 625 ng/mL (~10 mg/kg), 846 ng/mL (~20 mg/kg).[19,21]
- Tmax, median (single oral dose of CBD oil): 1.5 hours (2 mg/kg), 2 hours (8 mg/kg).[19]
- Half-life, median or mean (single oral dose of CBD oil, 2-20 mg/kg): 2-4 hours.[19,21]
- Volume of distribution: 6.9 to 10.4 L/kg following 45 mg IV dose[25]

SYNTHETIC CANNABINOID EXPOSURE

SCBs manufactured for recreational purposes became popular in the United States starting in the 2000s when they were initially marketed as a "legal high." These compounds are dissolved in solvents and applied to dried plant material, intended to be smoked as an alternative to marijuana.[27] They are sold under a multitude of names including K2, Spice, Skunk, Wild Greens, Purple Haze, etc. They may also be labeled as "incense" or "potpourri" and carry a "warning" stating "not for human consumption." These products may also be laced with other chemicals/drugs such as caffeine or other stimulants. Although initially legally available in gas stations, head shops, and tattoo parlors, many of these products have been banned with the 2011 Synthetic Drug Control Act.

Clinical Effects

SCBs are designed for potent psychotropic effects and have a higher affinity for cannabinoid receptors than traditional marijuana, resulting in more severe clinical effects.[27,28] In people, SCBs are 2 to 3 times more likely to cause sympathomimetic effects including tachycardia and hypertension, 5 times more likely to cause hallucinations, and cause a higher incidence of seizures in comparison to marijuana.[29] Other signs may include cyclical agitation, aggression, and incontinence.[28] Rare but significant cases of acute kidney injury have been reported in humans as well.[29]

Clinical effect data in animals exposed to SCBs is limited, although similar signs as those seen in humans have been reported. Exposure may occur via inhalation or ingestion. A case report involving both a pet owner and a dog affected by SCBs reported hyperesthesia, tremors, miosis, hyperresponsiveness to stimuli, ataxia, seizurelike activity, aggression, and mild respiratory acidosis in the dog.[28] Similar signs were observed in the pet owner. Another case report involving presumptive SCB intoxication detailed signs of progressive ataxia, inappropriate mentation, hypothermia, stupor, and intermittent aggression with rapid progression to comatose condition, apnea, tremors, and opisthotonos.[27] Cases reported to Pet Poison Helpline are more likely to involve severe signs such as tremors and seizures, compared with marijuana, and all cases were deemed serious enough to warrant veterinary evaluation (see **Figs. 1** and **2**). These data seem to mirror the increase in severity of signs described in human medicine.

Pharmacokinetics

The pharmacokinetics of SCBs are likely similar to the non-SCBs, although limited information is available. The oral bioavailability of various SCB products is likely low and similar to that of THC and CBD, because case reports in people have indicated milder signs of shorter duration after inadvertent ingestion of baked goods laced with SCBs.[5]

- Half-life: 72 to 96 hours in dogs and people[27]
- Recovery typically occurs within 24 hours in people, perhaps shorter in duration if ingested (4–10 hours)[5,27]
- LD_{50} and minimum toxic dose have not been established[25]

CANNABINOIDS: THERAPEUTIC CONSIDERATIONS

CBD, THC, combinations thereof, and analogues have been suggested in therapy for many different disease processes and maladies. Therapeutic targets in past and recent years have included the CB receptors, fatty acid amide hydrolases (responsible for breakdown of endocannabinoids), and in encouraging an "entourage effect" to enhance effect and duration of endocannabinoids within the body. CB1 receptor agonists and even antagonists have been developed in recent years with hopes for therapeutic benefit. The 1980s brought dronabinol and nabilone to the market to aid in controlling nausea and inappetence in chemotherapy and AIDS patients. Sativex, a 1:1 THC:CBD medication, has been available since 2005 in Canada to aid in control of neuropathic pain in patients with MS. CB1 antagonists have also been developed to aid in controlling nicotine addiction in Europe, although this is not yet available in North America given concerns for side effects that include depression and suicidal thoughts.[11]

Cannabinoids have been considered in treatment or supportive care of many different medical conditions, including the following[11,12]:

- Alzheimer's disease
- Anxiety
- Arrhythmias
- Asthma
- CNS injury
- Depression
- Diabetes
- Epilepsy
- Feeding-related disorders
- Glaucoma
- Hypertension
- Inflammation, inflammatory bowel disease
- Multiple sclerosis
- Myocardial infarct
- Nausea
- Pain
- Parkinson's disease
- Rheumatoid arthritis
- Some cancers
- Tourette syndrome

The potential for therapeutic use of cannabinoids in veterinary medicine may best be supported by human medical research studies and, less commonly, in veterinary directed studies in animals. In researching antiepileptic properties, for instance, THC was investigated and found to be relatively promising in treatment of seizures in a small population of cats.[30] Perhaps some of the most promising research into use of cannabinoid-type products in veterinary medicine has been shown with use of palmitoylethanolamide (PEA), an analogue to the endocannabinoid AEA. AEA is synthesized during inflammatory processes and in instances of tissue damage. PEA

is suspected to enhance function of AEA at the TRPV1 receptor and downregulate mediator release from various inflammatory cells. It has shown promise for treatment of pain, inflammation, and pruritus associated with eosinophilic granuloma complex in cats and mast cell–mediated disorders and skin disease in dogs.[31] To date there are no FDA-regulated cannabinoid products for use in pets, but nonregulated CBD supplements or nutraceuticals can be purchased from several companies in the form of treats, oils, capsules, and liquids for use in dogs and cats.

DIAGNOSIS

Specific Diagnostics

There is no reliable patient-side test available for diagnosis of cannabis or SCB exposure in veterinary patients. The readily available human urine drug screen immune assays designed to detect marijuana exposure are ineffective for SCB detection in both people and animals and often yield false negatives in veterinary patients exposed to marijuana/THC.[32] Liquid chromatography mass spectrometry (LC/MS) remains the gold standard for drug screening in both humans and animals. Because of the wide variability of SCBs, clinicians wishing to submit samples for testing are advised to consult with the diagnostic laboratory before sending.

Potential reasons for false-negative results using urine drug screens:

- Sample run too soon after exposure
- Large number of nondetectable metabolites of THC unique to dog urine
- Secondary to poor handling (THC binds to glass and rubber stoppers)[15]
- Increased patient water consumption resulting in dilute urine[16]
- SCB exposure, because these do not test positive[5,28]

Potential reasons for false-positive results using urine drug screens:

- In people, nonsteroidal antiinflammatory drugs, such as ibuprofen, naproxen, and niflumic acid, and efavirenz (antiviral drug) may cause false positives depending on the brand of test. Whether or not these agents could affect testing with dog or cat urine is unknown.[33]

Nonspecific Diagnostics

The following routine diagnostics can guide supportive care and alert clinicians to secondary intoxications or unrelated medical problems.

- Radiographs: monitor for evidence of ingested foil, other packaging materials, or batteries in the instance of a vaporizer pen ingestion and the rare risk for foreign body obstruction if baggies, pipes, or vape pens are consumed.
- CBC/chemistry/prefluid urinalysis: rule out primary underlying causes and establish normal baselines.
- Minimally: packed cell volume/total protein to monitor hydration status, electrolytes (monitor sodium if multidose-activated charcoal is given and monitor potassium if severely symptomatic), blood glucose (monitor intermittently in severely affected patients), and renal profile (in the event hypotension occurs and causes perfusion concerns).

DIFFERENTIAL DIAGNOSES

The clinical signs for marijuana and SCBs are nonspecific and differential diagnoses must be considered if exposure cannot be confirmed. Differentials may include but are not limited to alcohols (ethanol, methanol, ethylene glycol, diethylene glycol, propylene glycol), opiates, benzodiazepines, muscle relaxants, tranquilizers, bromethalin

(rodenticide), macrocyclic lactones (ivermectin, milbemycin), and other illicit drugs (LSD, PCP, and hallucinogenic mushrooms).

GENERAL TREATMENT PLAN

Decontamination

A. Emesis can be performed if a toxic dose was ingested, exposure was within the last 30 to 60 minutes or a significant amount of material remains in the stomach, the patient is asymptomatic and thus low risk for aspiration, and spontaneous vomiting has not occurred.
   a. The preferred emetics in dogs are apomorphine (0.03 mg/kg IV) or hydrogen peroxide, 3% (1–2 mL/kg PO, food in the stomach increases chance of success).
   b. The preferred emetics in cats are dexmedetomidine (7–10 mcg/kg intramuscularly [IM]) or xylazine (0.44 mg/kg IM). Reverse as needed with atipamezole.
B. Multidose activated charcoal may be considered in asymptomatic patients who are at low risk for aspiration.
   a. Administer one dose of activated charcoal (1–4 g/kg PO) with sorbitol to start the series
   b. Administer a half dose of activated charcoal (or 0.5–1 g/kg PO) without sorbitol every 6 to 8 hours $\times$ 1 to 2 additional doses
   c. Do not administer if the patient is at increased risk for aspiration, hypernatremic, dehydrated, or not passing stool before redosing.
C. Massive ingestions may benefit from gastric lavage with the patient under anesthesia and airway secured. A dose of activated charcoal with sorbitol may be placed through the stomach tube.
D. If suspect material is noted on rectal examination, enemas may expedite clearance.

Supportive Care

A. Antiemetics as needed. Do not use maropitant or antiemetics with a prokinetic effect if the patient is at risk for a foreign body obstruction.
B. IV fluids 1 to 1.5 x maintenance, adjust as needed for perfusion changes. IV fluids are not expected to expedite or enhance excretion of cannabinoids to a great degree.
C. Thermoregulation and nursing care
   a. Warming or cooling therapy as needed. Hypothermia is more common with marijuana exposure, whereas hyperthermia is more commonly associated with SCB exposure.
   b. Generalized nursing care should be provided to obtunded or profoundly sedate patients including body rotation, ocular lubrication q 4 to 6 hours, etc.
   c. Keep the patient clean and dry. Although rarely necessary, an incontinent patient may benefit from a temporary urinary catheter.

Monitoring

A. Mildly affected cases may be monitored at home if kept in a safe environment with no fall risk.
B. Monitor vitals and blood pressure q 1 to 6 hours depending on patient status.

Medications

A. For agitation: butorphanol (0.1–0.4 mg/kg IM or IV) +/– acepromazine (0.01–0.2 mg/kg slow IV, IM, or subcutaneous, titrate dose for effect). Avoid acepromazine in hypotensive patients.
B. Tremors: methocarbamol (44–220 mg/kg slow IV to effect, select dose based on severity of signs). Re-dose PRN.

C. Seizures: diazepam (0.5–1.0 mg/kg IV), phenobarbital, propofol, levetiracetam
D. Bradycardia: atropine

Intravenous lipid emulsion

Intravenous lipid emulsion (ILE) has been suggested for marijuana and SCB intoxications in pets and used with varied success.[15,17,27] The potential therapeutic benefit of ILE is based on the knowledge that THC and cannabinoids are extremely lipophilic. All pharmacologically active cannabinoid compounds have a LogP greater than 4.5.[34] Please see Sharon Gwaltney-Brant and Irina Meadows's article, "Intravenous Lipid Emulsions in Veterinary Clinical Toxicology," in this issue for additional information on ILE.

- THC[35]:
  - LogP = 7.68
  - LogD at pH 7.4 = 7.25
- CBD[36]:
  - LogP = 7.03
  - LogD at pH 7.4 = 6.43

The veterinary toxicologists at Pet Poison Helpline do not routinely recommend the use of ILE in cases of marijuana or SCB exposure, in part because of scant supportive data, both in the literature and from the Pet Poison Helpline database, but also because ILE may negatively affect the effect of therapies such as sedatives or anticonvulsants.

PROGNOSIS

Most companion animals recover from marijuana exposures within 24 to 36 hours. Severe cases may be affected for up to 72 hours. Prognosis is generally good with supportive care.

SUMMARY

Marijuana, THC, CBD, and SCB exposures and intoxications have been increasing in frequency in both human and veterinary medicine. As therapeutic benefits of cannabinoids come to light and societal perceptions change, veterinary professionals are likely to see a continued increase in legalization and decriminalization of marijuana and individual cannabinoids and thus likely to see an increase in inadvertent companion animal exposure and intoxication. Vigilant and careful physical examinations with attentive and empathetic history taking skills devoid of judgment are imperative to help in diagnosing and best treating our companion animal patients.

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