A Veterinary Guide
to Marijuana

Lisa Parshley, DVM, PhD, DACVIM // Donna Mensching, DVM, MS, DABVT, DABT
Marijuana as medicine

Marijuana or cannabis is derived from a plant called Cannabis. Different subspecies or strains are found throughout the world. Each subspecies has differing properties and effects on the body when inhaled or ingested. Some strains have almost no obvious psychogenic effects whereas others have been almost exclusively used in the illicit or therapeutic drug trade. The non-psychogenic strains have been used for centuries to produce fiber (hemp) for clothes and rope. Some of the strains best known for their psychogenic effects have also been those used for centuries to treat a variety of maladies from nausea to pain to inflammation.

As far back as 2700 BCE use of marijuana or cannabis has been considered medicinal. First recorded reference to marijuana as a medical therapy was in an ancient Chinese medical book written by Emperor Shen-Nung, a trained pharmacist. In this Chinese medical book cannabis is mentioned as a good therapy for constipation, gout, rheumatism, and absent-mindedness. In later writings from Egypt, in the Eber Papyrus (1500 BCE) medical treaties, cannabis is listed as a remedy for pain from hemorrhoids. During this same time period in India cannabis was often used for gastrointestinal upset, pain of childbirth, for general pain, insomnia, and headaches. Writings from ancient Greece highlight yet another use of cannabis; its seeds were used for clotting of wounds. More recently in medieval times Arabic physicians used cannabis for diuresis, vomiting, pain, inflammation, and seizures. Cannabis as a medical therapy first came to the western world in 1841 when Dr. O’Shaughnessy (the father of IV fluids) introduced it as an effective therapeutic agent against the symptoms of tetanus and pain. Modern day medicinal use of cannabis has been described for, among other things, chemotherapy and cancer induced nausea and vomiting and for chronic pain. Marijuana or cannabis therapy is certainly not new, what is new is all the rational drug design research that is spinning off this very ancient therapy.

Over the last decade the search for how and why the cannabis plant works in the body, both good and bad, has led to the discovery of the endogenous cannabinoid system. This is a system that is proposed to be found in all mammals and is considered a part of normal physiology. It is a group of neuromodulatory lipids derived from the arachidonic acid pathway. These compounds are part of the family of endocannabinoids and include endocannabinoids such as anandamide (N-arachidonoylethanolamine (AEA)) and 2-arachidonylglycerol (2-AG). The enzymes that produce and degrade the endocannabinoids are fatty acid amide hydrolase or monoacylglycerol lipase. At least two receptors for endocannabinoids, CB1 and CB2, have been discovered. Remember that receptors are proteins located on the surface of cells. By binding their target molecules these proteins can cause cells to react to these compounds. Endocannabinoid receptors have been found in the nervous system (mainly CB1), on immune cells (mainly CB2 and mainly on macrophages, neutrophils, B lymphocytes, and potentially other bone marrow derived cells), and in the female and male reproductive tracts. Therefore, it is expected that these compounds will primarily involve modulating the immune and nervous systems and possibly reproduction.

Physiologically endocannabinoids have been found to be involved in a variety of processes including effects on the autonomic nervous system, memory, stress response, immune system responses, appetite, reproduction, pain, mood, thermoregulation, and metabolism. Of the over 460 compounds found in the various strains of cannabis used traditionally for medical therapy, about 80 of these are classified as phytocannabinoids. These are the plant version of the endocannabinoids found in mammals. Phytocannabinoids are the compounds which many feel are the source of both the psychogenic and medicinal effects of cannabis. They are thought to be working by binding to the endocannabinoid receptors found throughout the body. If this is true it could explain all the previously reported medical and psychogenic effects and may point to as of yet undiscovered uses or spur new drug design.

The most psychoactive and one of the medically relevant phytocannabinoid found in cannabis is tetrahydrocannabinol (commonly known as THC). Other potentially important phytocannabinoids include Δ8-tetrahydrocannabinol, cannabidiol (CBD), cannabinol (CBN), cannabicyclol (CBL), cannabichromene (CBC) and cannabigerol (CBG). All of these have less psychogenic effects than THC, but may play as large a role in the overall physiologic impact of cannabis. The most studied phytocannabinoids are THC, CBD, and CBN. It is these three compounds that have been used to produce the currently approved cannabis derived therapeutic products Marinol (Dronabinol), Cesamet (Nabilone), and European Sativex (Nabiximols).
Recent work done by Dr. Palazzò and colleagues has demonstrated that the NMDA receptor (a glutamate receptor implicated in chronic pain) and the glutamate receptors (mGluRs) work in concert with CB1 to induce analgesia in mice. The detailed mechanism underlying this effect remains unclear but is being currently studied. This data may suggest a possible mechanism on how cannabis compounds and cannabis could work against chronic pain. It is work like this and from many others that will fully open our understanding of and ultimate use of cannabis based therapies in medicine.

As of 2012 over twenty cannabis derived phytocannabinoids were the focus of biomedical research and therapy development. These studies include evaluation of the various native cannabis and synthetic cannabis compounds as anti-inflammatory agents, appetite stimulants, muscle spasms therapy in multiple sclerosis, and possibly as an anticancer therapy. From these studies the three approved therapies were developed. These drugs are approved for use in intractable nausea and vomiting and in chronic pain. It is expected that other therapeutics will be discovered as research progresses on these compounds, the other compounds found in cannabis, and on the endogenous system implicated.

As encouraging as these new physiologic and therapeutic discoveries appear we still have many obstacles to overcome prior to routine prescribing of safe, effective, and predictable cannabis derived therapies. For example we have not fully mapped out mechanisms of actions, pharmacokinetics, and pharmacodynamics for most of these compounds. Without this information all the possible effective yet safe therapies remain a dream; a potentially obtainable dream but a dream none the less.

Until we are able to fill in the holes in our knowledge we will be limited to the regulatory approved products and use of whole plant or partial plant therapies. Whole or partial plant therapies while at times efficacious will forever be limited by a repeatable inaccuracy in dosing reducing reliable efficacy, varied and at times unpredictable side effects, and unregulated sourcing for the plants and product. For the three currently approved drugs we only have pharmacologic data for the human species.

As veterinarians, we especially need to remember these deficiencies in knowledge. Our clients are and will be pushing us to prescribe these therapies from anecdotal information and based solely on human studies. We need to keep in mind that not one paper has been published that describes appropriate dose ranges for the regulatory approved products much less whole or partial plant products. Only through phase I studies will we be given the data necessary for repeatedly prescribing effective and safe doses. Only through phase II and III studies will we know just how effective the therapies are in domesticated animals and for what diseases or symptoms it appears efficacious. Presently when we prescribe even Marinol we are blindly using another species (human) recommended dose range.

This leaves us open to prescribing therapies for the wrong diseases, wrong symptoms, and potentially using wrong doses. Using another species dosing range could put us too close to the toxic dose or equally as bad we may not be giving enough to achieve a therapeutic benefit.

In the future and maybe near future cannabis will provide us with safe and effective therapies for animals. Until we have done the foot work and studies necessary to evaluate their effects in animals I would recommend caution and full disclosure to your clients. Remember, we should know to the best of our ability the safety and therapeutic profile of all therapies we prescribe to our patients.

Marijuana Toxicoses

The times they are a-changin' and so are our toxicoses. Although marijuana remains a schedule I controlled substance under federal law, many states have relaxed their laws by decriminalizing cannabis possession and/or legalizing it for medical and/or recreational use.

Washington State is leading the way after having passed Initiative 502 in November 2012 which allows people over 21 to legally possess and use of any combination of the following:

- **1 oz.** of useable plant material
- **16 oz.** of marijuana in solid form (ex. foodstuff)
- **72 oz.** in liquid form

Pre-legalization, signs of marijuana toxicity in dogs were typically predictable with an onset from 30-90 minutes post ingestion or within minutes of inhaling smoke and resolving within 24 hours with supportive care alone. Classic signs include depression (>60%), ataxia/incipriority (~50%), vomiting (~24%), tremor (~18%), mydriasis (~11%), hyperthermia (~9%), weakness (~8.5%), bradycardia (~8%), disorientation (~6.5%), behavioral disorders (~6%), hyperesthesia (~6%), vocalizing/crying (~5%), anorexia (~5%), urinary incontinence (~5%), and tachycardia (~4%) (Janczyk et al, 2004). Serious complications could arise from trauma due to poor coordination or aspiration pneumonia potentially if vomiting occurred while sedate, but death was not expected unless these secondary complications occurred. In recent years since legalization, however, there are some notable changes in the trends in canine marijuana exposures. Meola et al (2012) report the following signs in decreasing order of occurrence in 125 dogs with marijuana toxicity: ataxia (88%), mentally dull/obtunded/disoriented (53%), mydriasis (48%), urinary incontinence (47%), hyperesthesia (47%), tremors, shaking, or twitching (30%), and vomiting (27%). Notable are the increased percentages of stimulatory signs, urinary incontinence, and hyperesthesia relative to the 2004 findings. Even more noteworthy are the reports of two fatalities in dogs exposed to baked goods made with marijuana butter in the later publication.

These changes in presentation may be a consequence of increased tetrahydrocannabinol (THC) content of modern forms of marijuana. Dried plant material has been noted to vary from 1-10% THC. Forms of marijuana such as sinsemilla (meaning “without seeds”) have been reported to contain 10-18% THC. Unsubstantiated reports of butane hash oil (BHO) claim it can contain up to 90% THC. These changes in presentation may also be due to greater access to larger amounts of THC-containing products. Especially in the solid form, such as brownies, cookies, candies, and cakes, we all know our self-respecting Labrador Retrievers will not stop at just one. And finally

---


---

"Over the next several years, if regulation of the recreational trade requires disclosure of THC content of goods sold, our knowledge of dose-related effects is likely going to skyrocket.”

---

<table>
<thead>
<tr>
<th>1 oz.</th>
<th>of useable plant material</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 oz.</td>
<td>of marijuana in solid form (ex. foodstuff)</td>
</tr>
<tr>
<td>72 oz.</td>
<td>in liquid form</td>
</tr>
</tbody>
</table>
on the list of possible differences in exposure is increased absorption of THC depending on the vehicle it may be in. Normally, THC has an oral bioavailability in people of 5-20%. Since it is highly lipophilic, ingesting THC in a high-fat vehicle such as butter can significantly increase its absorption (Truven, 2014). These exposures can result in cardiac and respiratory depression to the point of cardiorespiratory arrest. Other potential variables in reported signs of marijuana toxicosis over the years could be increased recognition of the array of previously less common signs by clinicians and increased willingness of owners to present more seriously affected patients to a hospital and to confirm exposure history post relaxation of laws.

Relatively few experimental studies have been performed with marijuana in dogs and most accidental veterinary exposures regarding recreational stashes don’t have reliable dose-related information. One study (Beaumont et al, 2009) reports an intragastric THC dosage range from 0.079 - 0.189 mg/kg that resulted in no outward clinical effect. Vomiting was seen in 1/2 of the exposed dogs in that study that received 0.252 mg/kg, however. Teitzer (2009) reported giving 2.5 mg of dronabinol (trade name Marinol; synthetic Δ9-THC) to four dogs of unknown body weight. Mild obtundation for 4-6 hours was noted in each dog. Over the next several years, if regulation of the recreational trade requires disclosure of THC content of goods sold, our knowledge of dose-related effects is likely going to skyrocket. This will give clinicians the added benefit of calculating a worst-case-scenario dosage and more reliably predicting the cases that will require significant intervention to prevent life-threatening effects. Minimum lethal dosages have not been well-established in the dog. Fitzgerald et al (2012) report the minimum lethal dosage to be >3 g/kg and reference Thompson et al (1973) who report that dosages between 3 and 9 g/kg in the dog were nonlethal. Eventually, incorporation of data regarding increased absorption with varying vehicles and plasma levels may further aid management of marijuana toxicoses. For now, clinicians should err on the side of caution and assume that any marijuana-intoxicated patient could develop life-threatening complications.

Classic decontamination measures such as induction of emesis and administration of activated charcoal are appropriate for asymptomatic patients exposed to marijuana. Monitoring parameters thereafter include heart rate, rhythm, blood pressure, temperature, oxygenation, and central nervous system status. Garrett and Hunt (1977) report that 10-15% of THC is enterohepatically recirculated. Multiple doses of activated charcoal, in theory, would be indicated with a significant ingestion, but concerns for aspiration in a sedate patient must be weighed heavily against the potential benefit. For potentially life-threateningly clinical patients, a course of intravenous lipid emulsion therapy would be preferable to taking the risk associated with multiple doses of activated charcoal.

Additional treatment recommendations include the following:

• Intravenous fluid support with crystalloids.
• Thermoregulation (warm fluids and ambient temperature if hypothermic; cooling fluids or bath to 103°F if hyperthermic).
• Benzodiazepines to effect for significant tremors or seizures (rare).
• Antiemetic therapy/NPO status PRN for vomiting.
• Supportive care (rotation, padded bedding) to prevent pressure sores if severely depressed.
• Atropine (0.02 mg/kg IV) to effect for significant bradycardia.
• Minimize external stimuli (sound, movement, light) if hyperesthetic.
• Minimize external stimuli (sound, movement, light) if hyperesthetic.
• Confine disoriented and ataxic animals to prevent secondary trauma.
• Supplemental oxygen (+/-ventilation) if difficulty oxygenating.
Diagnosis of marijuana toxicity in dogs classically has been based on the presence of clinical signs consistent with exposure and a reluctant confession by the owner that the dog was exposed to someone else’s recreational stash. State legalization of medicinal and recreational marijuana is breaking down barriers to admission of exposure, but a reliable point-of-care test would be beneficial in cases of unknown or unconfessed exposure. Particularly in light of exposure, but a reliable point-of-care test would be beneficial in cases of unknown or unconfessed exposure. In dogs, 11-hydroxy-Δ9-THC is reported to be further oxidized to 8-hydroxy-Δ9-THC, which has been hypothesized as the cause of the urinary incontinence commonly seen in our canine patients (Meola et al., 2012). A recent visit to a medical marijuana dispensary, however, provided anecdotal confirmation that urinary incontinence occurs in overdose situations in people as well, so the frequency seen in our canine patients may be more a function of dosage rather than differences in metabolism.

In addition to novel metabolites not being detected, other theories for false negative canine results include interference of additional metabolites with test antibodies and inappropriately low detection limits. Given the relatively higher percentage of fecal metabolites versus urinary metabolites, use of urine as the preferred sample medium has been questioned. In support of the suggestion to utilize feces as a test medium, Coles et al. (2005) reported an extraction method for analyzing THC metabolites from human meconium. Teitler (2009) even reports that gold standard validation with GC-MS was also unreliable in dogs. Despite these inconsistencies, several UDSTs have been anecdotally suggested by veterinarians to be more reliable in detecting THC exposures in dogs (Table 1). No large-scale, controlled studies have been performed to validate these findings in dogs, however. Current recommendations remain to include marijuana on the differential diagnosis list when clinical signs are consistent with exposure, to attempt to rule in exposure with appropriate history-taking, and to attempt to confirm exposure with both a point-of-care urine drug screen test and the gold standard GC-MS analysis.

— Dr. Donna Mensching is the Veterinary Medical Director at the WA Poison Center. She can be reached at dmensching@wapc.org.