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Cannabis Therapy in Veterinary Medicine

A Complete Guide

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Foreword

Cannabinoid Therapy in Veterinary Medicine: History and Perspective

As a human pediatric and adult neurologist, a 24-year student of cannabis and the endocannabinoid system (ECS), and the son and brother of veterinarians, I am delighted to have the opportunity to introduce this timely tome on veterinary "cannabinology."

The endocannabinoid system is a basic and fundamental homeostatic regulator of physiology (Russo 2011). It is hundreds of millions of years ancient, and has been phylogenetically widespread, including expression in all chordates from tunicates onward, notably missing a few major clades such as insects (McPartland et al. 2001; McPartland 2004), perhaps explaining why they lack a sense of humor.

In contrast, *Cannabis sativa*, the cannabis plant, is about 27.8 million years old (McPartland 2018), dispelling the anthropomorphic notion that it was placed on God's Green Earth for human diversion or veterinary applications; rather, its therapeutic utility in those areas is a happy accident of Nature for us, our pets, and domesticated work animals.

An examination of the therapeutic use of cannabis clearly reveals that, prior to its prohibition, it had always been part of the veterinary pharmacopeia. This is particularly the case in India, the archetypal base of cannabis medicine, where the ancient veterinary uses date from at least the twelfth century (Dwarakanath 1965) and have persisted into modern times (Indian Hemp Drugs Commission 1894; Russo 2005). By 1957, cannabis was still utilized to treat diarrhea in livestock, as an anthelmintic, for "footsore disease, increasing milk-flow in cows, and pacifying them, but also was administered to bullocks as a tonic, to relieve fatigue and to impart staying power" (Chopra and Chopra 1957, p. 9). The latter use of cannabis as a physical work aid parallels similar claims in human workers in Jamaica (Dreher 1982).

These traditional uses in India led directly to a watershed moment in the scientific investigation of cannabis, as William Brooke O'Shaughnessy, an Irish physician in India, applied the teachings of Ayurvedic medicine to the first modern systematic research on the plant's therapeutic properties (Russo 2017). He noted the narcotic effect of the electuary form of cannabis called majoon as reported by his informants and then proceeded to experiment on dogs and an expanded menagerie of other creatures to differentiate their reactions. The results affirmed both sedative and appetite stimulation effects of cannabis, along with static ataxia at higher doses (*vide infra*), all of which passed without notable sequelae after a few hours. He observed: "—while carnivorous animals and fish, dogs, cats, swine, vultures, crow and adjutants [military administrators], invariably exhibited the intoxicating influence of the drug, the graminivorous [grass eaters], such as the horse, deer, monkey, goat, sheep, and cow, experience but trivial effects from any dose we administered" (O'Shaughnessy 1838–1840, p. 363). These observations completed, O'Shaughnessy pressed forward with therapeutic applications of cannabis in recalcitrant human conditions ranging from rheumatism to tetanus, cholera convulsions, and even rabies. His teachings rapidly spread to Europe, where his pioneering work led to successful treatment of 4 of 5 tetanus cases in horses, provided an antidote to strychnine poisoning (Ley 1843), and subsequently set a foundation for our therapeutic cannabis knowledge base that persists after nearly two centuries.

Cannabis developed a strong foothold subsequently in veterinary practice in Europe, North America, and elsewhere. In France, the seed oil was utilized to treat chancres in dogs' ears, and as a purgative in cattle (Tabourin 1875). In Italy, the oil was suggested in veterinary practice for colic and urinary tract pain (Chiappero and Bassi 1879). In Scotland, human success with "Indian hemp" as an analgesic, hypnotic, and antispasmodic equal to opium was cited as evidence for veterinary application (Dun 1880). In South Africa, bowel inflammation, equine cough, and canine chorea were added to the indications (Gresswell et al. 1886). In England, the list expanded to include asthma, convulsions, cough, cystitis, and tetanus (Banham 1887). Across the pond in New York at Cornell University, besides tetanus and cystitis, cannabis was advanced as a treatment to control excitement in azoturia (Hassloch 1896), currently known as equine exertional rhabdomyolysis. At the University of Pennsylvania in Philadelphia, E. Stanton Muir performed extensive experiments with cannabis as a sedative in horses, finding it quite safe (Muir 1900), as well as analgesic, antispasmodic, and hypnotic (Muir 1904). In the Veterinary School of Harvard University, cannabis was observed to lead to survival in half the cases of tetanus in practice (Winslow 1901).

These same indications for cannabis persisted in the literature over the ensuing decades, with various new observations. Cannabis was noted as a powerful narcotic without constipation (Sayre 1907), as a treatment for melancholia in horses with pneumonia (Quitman 1912), as a liniment (Brumley and Snook 1913), for the relief of spasm and nervous irritability and a narcotic for equine operations (Milks 1917), for hobbling horses (Udall 1917), and for treatment of delirium associated with

parturient apoplexy (Winslow and Eichhorn 1919). Subsequent editions of these veterinary textbooks repeated similar observations in the USA (Milks and Eichhorn 1936, 1940), until the American prohibition of 1937 stopped supply. In Europe, cannabis usage continued a bit longer along traditional lines (Greig and Boddie 1942; Ironside 1946), adding indications such as volvulus and enteritis (Greig 1939).

This extensive utilization of cannabis in the veterinary context may have fallen out of vogue due to political misadventures, but supportive evidence remains not only in these moldering texts but also in preserved medicine bottles. The persistence of such products manufactured for decades is a testament to their likely efficacy: In centuries past, a farmer's good money would not likely be spent for sentimental reasons: either the medicine worked or a valuable animal was lost.

Patent medicines also existed for dogs, including "Security Cough, Cold and Distemper Remedy" which cost $1 in 1906 (equivalent to $28 today) containing *Cannabis indica*: "Will relieve the worst cough, chill or fever, Influenza or mucous membranes affections of the animal's throat, nose, eyes, mouth or air passages" (Wirtshafter 2016, p. 26). In some areas of the world, hemp seed persists as fish bait/fish food and remains a favorite seed of songbirds.

In 1938, Robert P. Walton published the definitive tome of the era on cannabis and its medical and veterinary applications (Walton 1938), citing many of the uses described above, just in time for the initiation of cannabis prohibition. He also summarized and expanded on the veterinary bioassays available to assess cannabis potency, most particularly in dogs. A gradual sedation without distress was an initial sign, followed by a progressive static ataxia that foreshadowed later knowledge of cannabinoid receptor density data (*vide infra*), and eventual sleep. When subjects were exposed too often or at elevated doses, tolerance to the intoxication was observed. The same phenomenon was observed later by a Greek veterinarian writing in French (Cardassis 1951) who related the case of a lamb that seemingly developed a compulsion to graze on cannabis presented after each feeding with gaiety and panic but repeating the exposure it continued developing and fattening normally. Readers may question how cannabis plants in the field would be psychoactive at all, since most would harbor non-intoxicating cannabinoid acids, but modern liquid chromatography techniques always show at least some neutral cannabinoids such as THC in fresh flower material (Lewis et al. 2018).

Beyond the patent medicines of the previous era, many mainstream pharmaceutical companies including Upjohn, Lilly, and Sharp and Dohme marketed their own products of *Cannabis americana*, a spurious appellation for a hybrid species of domestic agriculture (Wirtshafter 2016). These companies typically utilized canine subjects to titrate medicine batches and judge product consistency. United States Pharmacopoeia (USP) standard doses were developed (Walton 1938) but cannot be quantified with certainty today given our ignorance of the original concentrations of the preparations.

Walton also described effects of corneal anesthesia in rabbits, swaying and decreased tonus in cats, and profound and prolonged narcosis in frogs (Walton 1938). Finally, effects in mice included corneal anesthesia (analgesia), catalepsy, and hypnosis, providing three of the four components of the cannabinoid tetrad

(along with hypothermia) utilized today in that species for assaying cannabinoid activity of test compounds (Smith et al. 1994). Ultimately, Walton opined that lethal doses in animals were more likely attributable to alcohol content, stating, "When considered in terms of the minimally active doses, the drug has an extraordinarily high range of safety" (Walton 1938, p. 175).

The latter statement is supported by more recent reports of accidental poisonings with cannabis, particularly a review of 213 cannabis toxicosis cases after oral ingestion in dogs (Janczyk et al. 2004). Doses ranged from 0.5 to 90 g, with virtually all the patients demonstrating neurological effects such as sedation, ataxia and coordination impairment, and emesis in about 5% within 3 h, and lasting variable durations up to 4 days. With decontamination, fluid replacement, and diazepam (in some instances), all the animals completely recovered, however.

In all, aside from their increased susceptibility to ataxia, the effects of cannabis in dogs are closely related to those in humans. This is highlighted by the findings of one of the landmark studies of cannabinoid receptor CB_1 distribution in the brain shortly after the discovery of the endocannabinoid system (Herkenham et al. 1990). Throughout mammalian species, binding of cannabinoid ligands was greatest in the basal ganglia, hippocampus, and the cerebellum, the latter being particularly prevalent in the cerebellar molecular layer in dogs, highlighting their sensitivity to ataxia after exposure to tetrahydrocannabinol with doses as low as 0.5 mg/kg. As in humans, a paucity of receptor density in lower brainstem centers mediating cardiovascular and respiratory functions explains the relative safety of cannabis in even extreme overdoses. Observed K_i values and potencies of cannabinoid agonists in tests of canine ataxia and human subjective reports were highly correlated, supporting the similar effects of such drugs in the two species.

Considering this brief survey, what trends and suggestions may be put forward? Firstly, from the earliest modern scientific studies of cannabis, analogous conditions should be quite amenable to cannabis therapeutics across mammalian species. An examination of recent reviews (National Academies of Sciences Engineering and Medicine (U.S.). Committee on the Health Effects of Marijuana: an Evidence Review and Research Agenda 2017; MacCallum and Russo 2018), foremost among these indications would be treatment of chronic pain, whether neuropathic or cancer-related, emesis associated with chemotherapy, spasticity, sleep disorders, and epilepsy, especially with cannabidiol in the instance of the latter. However, the possibilities do not end there. The weight of history, basic research, and a considerable body of anecdotal evidence support many additional indications for cannabis in autoimmune conditions, obesity, neurobehavioral disorders, degenerative neurological conditions, and obstetrics and gynecology (Russo 2002, 2016, 2018).

American families spent $61.4 billion on their pets in 2011, 1% of total expenditures, or about $500 per household (Henderson 2013). This author and many of his cohorts expend considerably more in veterinary bills than on their own medical care. Modern trends indicate that cannabis has a large and increasingly important role to play in such treatment. It is equally clear that the disciplines of veterinary and human medicine have valuable insights to share and that a proper course of action would be a coordination of basic and applied clinical research efforts to produce a mutual

synergy that will expedite therapeutic advances and bring cannabis-based medicines of high quality, safety, efficacy, and consistency to our companion animals and the people who love them.

Ethan Russo

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