Ciência Rural, Santa Maria, v.49:02, e20180595, 2019
http://dx.doi.org/10.1590/0103-8478cr20180595
ISSNe 1678-4596
CLINIC AND SURGERY

Perspectives in veterinary medicine on the use of cannabinoids as complementary palliative therapy for pain in cancer patients

Cláudia Sampaio Fonseca Repetti[1] **Raul José Silva Girio**[1] **Milena Friolani**[1] **Sandra Maria Barbalho**[2]

[1]Curso de Medicina Veterinária, Universidade de Marília (UNIMAR), 17.525-902, Marília, SP, Brasil. E-mail: claudiarepetti@yahoo.com.br.
*Corresponding author.
[2]Faculdade de Tecnologia de Alimentos (FATEC), Curso de Medicina, Universidade de Marília (UNIMAR), Marília, SP, Brasil.

ABSTRACT: *Pain in the cancer patient is an important clinical manifestation that results in low life expectancy and poor prognosis. Pain may be related to tumor type, invasion of adjacent tissues, metastasis, and diagnostic and therapeutic procedures with variable response to analgesic therapy. Many studies have called attention due to their potential therapeutic effect in the modulation of pain and inflammation. Cannabinoid derivatives are chemical compounds obtained from Cannabis that act on specific receptors.Several commercial products have already been approved in Europe and the USA for use in human patients. The present study aimed to review articles on the use of cannabinoids in the control of pain contributing to the well-being and quality of life in cancer patients undergoing palliative care. Although, there are few reports in the veterinary medical literature on the use of cannabinoids in the control of pain in dogs, it is believed that such patients can benefit from this therapeutic modality.*
Key words: *pain, cannabinoids, cannabidiol, oncology.*

Perspectivas sobre o uso de canabinoides como terapêutica paliativa complementar da dor em pacientes oncológicos na medicina veterinária

RESUMO: *A dor no paciente com câncer é uma manifestação clínica importante que resulta em baixa perspectiva de vida e pior prognóstico. Esta dor pode estar relacionada ao tipo de tumor, à invasão em tecidos adjacentes, metástases, procedimentos diagnósticos e terapêuticos, com resposta variável à terapêutica analgésica. Muitos estudos têm chamado atenção para os derivados canabinoides, substâncias químicas obtidas a partir da Canabis que atuam em receptores específicos, por seu potencial efeito terapêutico na modulação da dor e da inflamação. Vários produtos comerciais já tiveram seu uso aprovado na Europa e EUA para uso em pacientes humanos. Objetivou-se pesquisar artigos sobre o uso de canabinoides no controle da dor no intuito de que os mesmos possam contribuir para o bem-estar e a qualidade de vida em pacientes oncológicos sob cuidado paliativo. Apesar de ainda serem escassos os relatos na medicina veterinária sobre o uso de canabinoides no controle da dor em cães, acredita-se que tais pacientes podem ser beneficiados por esta modalidade terapêutica.*
Palavras-chave: *dor, canabinoides, canabidiol, oncologia.*

INTRODUCTION

The higher longevity associated with the prophylactic management of infectious diseases points to cancer as the main cause of morbidity and mortality in companion animals (ANTUNES et al., 2008; YASBEK, 2008). One of the difficulties encountered in treating an oncologic patient is tumor staging since most cases are diagnosed at a late stage of the disease contributing to a greater chance of relapses and metastases with unfavorable prognosis, and are often associated with obvious signs of pain (MENDES et al. al., 2014).

Despite advances in veterinary oncologic therapy, pain remains a major clinical sign in many animals which worsens prognosis and animal's quality of life (MARTINS, 2015). Cancer pain should be promptly diagnosed and treated in order to alleviate suffering and improve the animal's quality of life (LESTER & GAYNOR, 2000).

In recent years, scientific research has emphasized the study of *Cannabis sativa* which is a very popular plant (PAMPLONA,2014).

Its medicinal properties have been reported for centuries but only recently it started being prescribed for pain after the discovery of endogenous cannabinoid receptors (BONFÁ et al., 2008; LESSA et al., 2016). Cannabis-based pain medication is currently available in the international market for the use in human patients (PAMPLONA, 2014).

Received 07.25.18 Approved 01.08.19 Returned by the author 02.06.19
CR-2018-0596.R1

The objective of the present study was to describe cannabinoid derivatives as promising agents for pain control aiming to improve the well-being and quality of life of patients with palliative care. Although, there are few reports on the therapeutic use of *Cannabis* derivatives in veterinary medicine, the data retrieved from the medical literature on human patients may contribute to the use of this treatment modality in animals. The present review also aimed to alert veterinarians about the use of cannabinoids as a palliative treatment of cancer pain. Specific legislation is still needed though.

Pain in the cancer patient

Pain is a clinical manifestation present in many cancer patients and confers a worse prognosis. As a result, there is a decrease in the quality of life of these animals (LOONEY, 2010). Cancer pain is a term used to refer to pain from several origins whether or not it is associated with the primary tumor or its metastatic spread in cancer patients (THOMAZ, 2010).

The control of cancer pain has been one of the goals of the World Health Organization (WHO) over the last few decades. Millions of human patients die of cancer each year without receiving adequate treatment with painkillers for the pain related to neoplasm presence (MORENO et al., 2016).

It is estimated that pain is present in 25% to 50% of cancer patients in the early stages of the disease, in 33% to 80% for cancer patients undergoing treatment, and in advanced and terminal cases of cancer this percentage rises to 55%-100% (LOONEY, 2010; LIMA et al., 2013).

Although,data on the occurrence and intensity of cancer pain in companion animals are scarce, YASBECK & FANTONI (2003) reported that 83% of dogs with neoplasms present moderate pain as reported by owners.

Pain origin cancer patient may be related to the primary tumor or to metastatic dissemination, and may be caused by diagnostic procedures such as biopsies and aspirates or therapeuticprocedures such as surgery, chemotherapy, and radiotherapy which may be uncomfortable affecting animal health and animal welfare (MARTINS, 2015).

According to ANTUNES et al. (2008), in more than 60% of veterinary patients diagnosed with cancer pain occurs due to metastasis, bone tumor infiltration, nerve compression, or extensive neoplastic growth involving adjacent tissues.

Pain may also be associated with the recommended treatment. Long-term neuropathic pain may be due to therapeutic procedures. Frequently there is pain secondary to limb amputation in patients with ostesosarcoma and peripheral neuropathy triggered by chemotherapy with platinum derivatives (cisplatin, carboplatin) and vinca alkaloids (vincristine, vinblastine) (RAHN et al., 2007; MORENO et al., 2016).

Dogs with appendicular osteosarcoma show lameness. Limb becomes non-functional due to severe pain as periosteal infiltration, bone lysis and microfractures occur in the bone affected by the tumor. Mechanisms involved in pain include concomitant activation of osteoclasts by tumor cells and of nociceptors by prostaglandins and inflammatory cytokines. Excessive osteoclastic activity is essential for the initiation and perpetuation of osteolysis and bone cancer-associated pain (GOBLIRSCH et al., 2005).

Mammary inflammatory carcinoma (MIC) in female dogs is characterized by a marked inflammatory reaction and the presence of tumor emboli in lymphatics. Clinically, there are signs of pain, inflammation and edema along the mammary chain, and cutaneous erythema and lymphedema may also be observed (DE NARDI et al., 2016). In such cases, palliative treatment is recommended and consists in the use of drugs that promote effective analgesic control and may be combined with antineoplastic chemotherapy and/or cyclooxygenase-2 inhibitors (QUEIROGA et al., 2005).

World Health Organization (WHO) has proposed some guidelines for pain management that can be extrapolated to dogs and cats with cancer in order to promote analgesia in these patients. The use of these recommendations as guidelines allows initial treatment of mild pain should be with nonsteroidal anti-inflammatory drugs. Addition of a weak opioid such as codeine or tramadol to the therapeutic protocol is recommended for the control of moderate pain. If pain is not controlled with this combination of drugs, more potent opioids are indicated. Anticonvulsants such as gabapentin and tricyclic antidepressants including amitriptyline may be used as adjuncts to analgesic therapy in cancer patients with neuropathic pain as well as in those with chronic pain (FAN, 2014).

FAN (2014) mentioned that it is a priority in cancer therapy to maintain the quality of animals life especially with the progression of the disease as pain becomes more frequent and severe. In view of the above-mentioned, early and rational institution of analgesic protocols can be effective in maximizing the chances of improving the well-being of animals with severe and widespread neoplasm.

What are cannabinoids and what are the sites of action of these chemical compounds?

Substances isolated from plants of the genus *Cannabis* are called cannabinoids. Phytocannabinoids are natural compounds of plant origin. Endocannabinoid is the term used to cannabinoids from natural sources and non-plant origin which are produced in the body by physiological stimuli (PAMPLONA, 2014; LESSA et al., 2016; BLAKE et al., 2017).

Two types of canabinnoid receptors have been described both in humans as in animal species (ABRAMS, 2016). In 1988, the first canabinnoid receptor was identified and isolated and named endocannabinoid receptor type 1 (CB1 receptor); a second canabinnoid receptor was discovered in 1993 and named endocannabinoid receptor type 2 (CB2 receptor) (MUNRO et al., 1993). The CB1 receptors are located in areas of the cerebellum, basal ganglia, hippocampus, cerebral cortex, spinal cord, and peripheral nerves, and are responsible for the psychotropic effects of endocannabinoids. In contrast, CB2 receptors may be reported in cells of the immune system, T cells, B cells, and spleen and may be in part associated with the modulatory effects in pain and inflammatory responses (BONFÁ et al., 2008; BRUCKI et al., 2015; MURNION, 2015; ABRAMS, 2016; MAIDA & DAENINCK, 2016; TURGEMAN & BAR-SELA, 2017) (Figure 1).

Research studies have shown that the stimulation of CB1 and CB2 receptors can reduce the clinical manifestations of multiple sclerosis, neuropathic and inflammatory pain, and also reduce tumor growth and angiogenesis in some types of cancer. The activation of CB2 receptor reduces inflammation and the progression of atherosclerosis and also increases the apoptosis rate of neoplastic cells (PERTWEE, 2012).

Anandamide (N-aracuidonoyl etanolamine) and 2-aracuidonoyl glycerol both belong to the group of endocanabinnoids that are synthesized by neurons in the brain (MASSI et al., 2012; BRUCKI et al., 2015; LESSA et al., 2016) and are released by excitatory synaptic stimuli (BRUCKI et al., 2015). Endocannabinoid system encompasses endocannabinoids and their respective receptors (MASSI et al., 2012; PERTWEE, 2012; LESSA et al., 2016).

In response to algic stimuli, endocannabinoids are produced and released in the central nervous system (CNS). These neurotransmitters act in the control of central and peripheral pain by connecting to the specific receptors CB1 and CB2 (RICHARDSON et al., 1998).

Both endocannabinoids and phytocannabinoids act in receptors in the brain reducing the release of neurotransmitters; and consequently, reduces inhibition of central and peripheral awareness of nociceptive tracts. However, the effects of endocannabinoids vary according to the region of brain in which these neurotransmitters are produced. In contrast, phytocanabinnoids trigger adverse effects in any region of brain that has CB1 receptors. An important aspect to consider when using high doses of phytocannabinoids is the emergence of tetrad effects of cannabinoids; i.e., analgesia, hypothermia, sedation, and catalepsy (PAMPLONA, 2014).

However, PERTWEE (2012) described that most of the undesirable effects of agonists of cannabinoid receptors is caused by activation of CB1 receptors located in the brain. The authors also mentioned the beneficial effects of these chemicals such as pain relief and improvement of certain cardiovascular and intestinal functions. Inhibition of proliferation and dissemination of neoplastic cells can be induced by the selective activation of CB1 receptors or CB2 receptors (or both) which are expressed outside the CNS.

The CB1 receptors have neuroanatomical and pharmacological characteristics similar to those of opioid receptors. These receptors modulate nociceptive processing in the brain independently or in synergism with exogenous opioids. In contrast, CB2 receptors stimulate the release of endogenous β-endorphins and reduce the activity of the fiber C in models of neuropathic pain (TURGEMAN & BAR-SELA, 2017).

The endocannabinoid system may be explored as a therapeutic option for joint diseases as seen in studies that show the anti-nociceptive effects of agonists of cannabinoid receptors in models of osteoarthritis in rodents (SCHUELERT & MCDOUGALL, 2008).

Exogenous cannabinoids including phytocannabinoids and synthetic cannabinoids as well act similar to endocannabinoids potentiating its effects and activating CB1 and CB2 receptors (MAIDA & DAENINCK, 2016).

Large amounts of cannabidiol has been isolated from crude extract of *Cannabis sativa*. This phytocannabinoid acts as a modulator of the endocannabinoid system. In addition, it inhibits the enzymes lipoxigenase and cycloxigenase (MAIDA & DAENINCK, 2016) without psychotropic properties (MASSI et al., 2012). LESSA etal. (2016) described the effectiveness of phyitocannabinoids as adjuvants

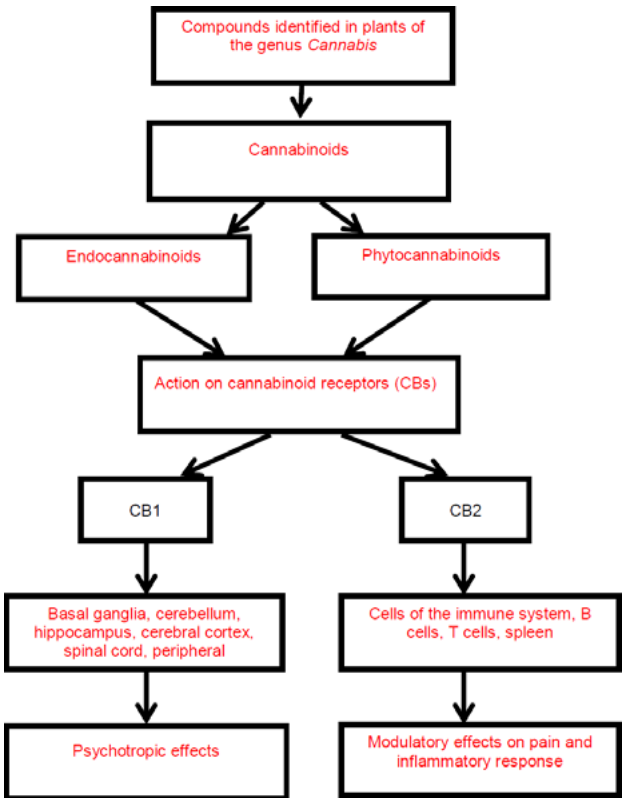

Figure 1 - Flow chart demonstrating the types of cannabinoids and their effects on specific receptors.

in the control of pain mediated by the endocannabinoid system in human patients.

Properties related to *Cannabis* toxicosis have been reported for centuries. The main psychoactive constituent of this drug is Δ-9-tetrahydrocannabinol (THC). Cannabidiol is another component of this drug but do not have psychoactive properties. It has therapeutic effects though (PAMPLONA, 2014; BRUCKI et al., 2015; MURNION, 2015; TURGEMAN & BAR-SELA, 2017). For this reason, current pharmacological strategies have used the combination of THC and cannabidiol in different concentrations instead of using pure THC only which can cause tachycardia, dysphoria, psychotic symptoms, and sedation in healthy individuals (PAMPLONA, 2014).

Synthetic cannabinoids in the treatment of cancer pain

In 1986, THC which is the main psychoactive cannabinoid of the *Cannabis* plant had its synthetic form - dronabinol - approved for the control of nausea and vomiting induced by chemotherapy. In 2006, nabilona which is another synthetic THC was approved in Europe and in the US as well (HASHIBE et al., 2005; MURNION, 2015; ABRAMS, 2016). These synthetic cannabinoids directly activate CB1 receptors and were authorized for the treatment of nausea induced by antineoplastic chemotherapy. These drugs also stimulate the appetite of debilitated patients (HASHIBE et al., 2005; PAMPLONA, 2014; ABRAMS, 2016) with minimal psychoactive effects (FATTORE & FRATTA, 2011).

Cannabidiol which is also a phytocannabinoid has aroused interest due to its potential therapeutic effect (MASSI et al., 2012). Nabiximol is an extract obtained from *Cannabis* which has a THC: cannabidiol ratio of 1:1. It was originally approved in Europe for the control of pain associated with multiple sclerosis. It has also been studied in the therapy of pain associated with cancer in humans (ABRAMS, 2016).

The pharmacological compounds cannabinoids are usually administered per os as capsules or spray (JOHNSON et al., 2013; BLAKE et al., 2017). Oral spray with active ingredients of THC and cannabidiol (Sativex®) underwent clinical trials and was approved for medical prescription. Its use is only allowed in individualized dosage regimens to patients with cancer pain and neuropathic pain (BONFÁ et al., 2008; PAMPLONA, 2014).

Advances in pharmacological research pointed out that the association of cannabinoids and opioids in pain control is promising. Both the cannabinoids and the endocannabinoid system interact with the endogenous opioid system. This synergism helps to amplify the effects of each of these two components reducing drug concentration decreasing side effects without affecting the efficacy of medications (LESSA et al., 2016; BLAKE et al., 2017).

JOHNSON et al. (2013) conducted a clinical trial to evaluate the analgesic effects of Δ9-THC/cannabidiol containing formulations in patients with opioid-refractory cancer pain. These researchers observed pain relief in individuals with breast, lung, and prostate câncer and in other individuals treated with Δ9-THC/cannabidiol when compared to those treated only with Δ9-THC or placebo.

Current studies demonstrated a synergistic analgesic effect between cannabinoids and opioids suggesting that these two drugs act through different pathways and receptors (ABRAMS, 2016; BLAKE et al., 2017). In a study involving 359 cancer patients subjected to opioid-sparing analgesic therapy, it was observed that analgesic supplementation with nabiximol for 5 weeks resulted in reduced pain and improved sleep quality (PORTENOY et al., 2012) due to lessening in the severity of symptoms and not as a result of the hypnotic action of the drug (LESSA et al., 2016).

Pain of neuropathic origin is common in cancer patients. Experimental studies with rodents have demonstrated that cannabinoids may be more effective in suppressing peripheral neuropathic pain induced by vincristine chemotherapy when compared to the use of opioids (RAHN et al., 2007).

Sativex® is indicated in cancer patients with pain that does not respond to conventional protocols including opioids, and in those individuals with chronic pain. Side effects reported are mild and include fatigue, nausea, and sour taste in the mouth (LESSA et al., 2016).

THOMPSON et al. (1973) carried out a study on the acute toxicity of cannabinoids in various animal species including dogs. These authors reported that THC has a wide safety margin in the canine species. The doses used varied between 3000mg/kg and 9000mg/kg in a single dose per os. Predominant clinical signs and toxicity included somnolence, ataxia, prostration, tremors, mild hypothermia, salivation, vomiting, and anorexia.

VALASTRO et al. (2017) reported that synthetic agonists of cannabinoid receptors represent an innovative tool in the treatment of joint disease in dogs.However, more studies are needed in order to evaluate the efficacy of cannabinoids in veterinary medicine.

Brazilian legislation related to the commercialization of *Cannabis* derivatives is complex and a work in prpgress (MURNION, 2015). In Brazil, the use of cannabidiol was authorized by the Regional Medical Council of the State of São Paulo in October 2014. In some cases, the National Sanitary Surveillance Agency (ANVISA) allows the importation of the drug. A prescription, medical reports, a signed document, and a term of responsibility are requested upon the purchase of this drug (BRUCKI et al., 2015).

A resolution of the Collegiate Board of Directors (RDC) n.66 was published on March 18, 2016 and provides an the update of Annex I which has a list of narcotic and psychotropic substances, Decree-Law SVS/MS n.344, published on May 12, 1998. According to the RDC, Article 61, plants included in list “E” (plants that may be used to prepare narcotic and/or psychotropic substances) can not be prescribed or manipulated to obtain allopathic and homeopathic medicines except for the prescription of ANVISA’s registered medicines containing in its composition the plant *Cannabis* sp., its parts or substances obtained from it including THC as well as the prescription of products that have cannabidiol and/or THC to be imported exceptionality for own use of a patient for medical treatment with medical prescription (BRASIL, 2018).

CONCLUSION

Cannabinoids have therapeutic efficacy in the control of pain especially chronic pain caused by neoplasia. Despite the scarcity of data in the veterinary literature on the use of cannabinoids in the treatment of pain of oncological origin in dogs, it is believed that such patients may also benefit from the use of this therapeutic modality, which would improve the well-being and quality of life of these animals lessening the severity of the symptoms that

the therapies currently available are unable to control. In addition, with regard to the limitations imposed by the current Brazilian legislation for the importation of cannabidiol-containing drugs by individuals, it is believed that the present review article may provide authorities with evidence that shows the importance of this pharmacological group of drugs in the control of pain in animals with cancer given the high caseload of neoplasms in small animal clinical practice.

BIOETHICS AND BIOSECURITY COMMITTEE APPROVAL

This study was approved by the Ethics Committee on the Use of Animals in Research (CEUA-UNIMAR), Universidade de Marília (UNIMAR), SP, Brazil, according to Protocol 04/2018.

DECLARATION OF CONFLICTING INTERESTS

The authors declare no conflict of interest. The founding sponsors had no rele in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

REFERENCES

ABRAMS, D.I. Integrating cannabis into clinical cancer care. **Current oncology**, v.23, supp.2, p.8-14, 2016.Disponível em: <http://www.current-oncology.com/index.php/oncology/article/view/3099/2051>. Accessed: Oct. 17, 2017. doi: 10.3747/co.23.3099.

ANTUNES, M.I.P.P. et al. Avaliação e manejo da dor em cães e gatos com câncer – revisão. **Arquivos de ciências veterinárias e zoologia**, v.11, n.2, p.113-119, 2008. Disponível em: <http://revistas.unipar.br/index.php/veterinaria/article/view/2567>. Accessed: Oct. 24, 2017. doi: 10.25110/arqvet.v11i2.2008.2567.

BLAKE, A. et al. A selective review of medical cannabis in cancer pain management. **Annals of palliative medicine,** p.1-8, 2017. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/28866904>. Accessed: Oct. 17, 2017. doi: 10.21037/apm.2017.08.05.

BONFÁ, L. et al. Use of cannabinoids in chronic pain and in palliative care. **Revista brasileira de anestesiologia**, v.58, n.3, p.267-279, 2008. Disponível em: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0034-70942008000300010>. Accessed: Oct. 17, 2017. doi: 10.1590/S0034-70942008000300010.

BRASIL. Resolução diretoria colegiada – RDC n.66, de 18/03/2016. **Anvisa: Agência nacional de vigilância sanitária**. Disponível em: <http://portal.anvisa.gov.br/legislacao>. Accessed: May 15, 2018.

BRUCKI, S.M.D. et al. Cannabinoids in neurology – Brazilian academy of neurology. **Arquivo neuropsiquiatria**, v.73, n.4, p.371-374, 2015. Disponível em: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-282X2015000400371>. Accessed: Oct. 17, 2107. doi: 10.1590/0004-282X20150041.

DE NARDI, A.B. et al. Neoplasias mamárias. IN: DALECK, C.R.; DE NARDI, A.B. **Oncologia em cães e gatos**. 2ed. Rio de Janeiro: Roca, p.499-516, 2016.

FAN, T.M. Pain management in veterinary patients with cancer. **Veterinary clinics of north America: small animal practice**,v.44, n.5, p.989-1001, 2014.Disponível em: <https://www.sciencedirect.com/science/article/pii/S0195561614000837?via%3Dihub>. Accessed: Nov. 29, 2017. doi: 10.1016/j.cvsm.2014.05.005.

FATTORE, L.; FRATTA, W. Beyond THC: the new generation of cannabinoid designer drugs. **Frontiers in behavioral neuroscience**, v.5, p.1-12, 2011. Disponível em: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3187647/pdf/fnbeh-05-00060.pdf>. Accessed: Dec. 12, 2017. doi: 10.3389/fnbeh.2011.00060.

GOBLIRSCH, M.J. et al. Advances in understanding bone cancer pain. **Journal of Cellular biochemistry**, v.96, p.682-688, 2005. Disponível em: <http://onlinelibrary.wiley.com/doi/10.1002/jcb.20589/full>. Accessed: Dec. 12, 2017. doi: 10.1002/jcb.20589.

HASHIBE, M. et al. Epidemiologic review of marijuana use and cancer risk. **Alcohol**, v.35, p.265-275, 2005. Disponível em: <https://s3.amazonaws.com/academia.edu.documents/43559148/Epidemiologic_review_of_marijuana_use_an20160309-14170-qr35vb.pdf?AWSAccessKeyId=AKIAIWOWYYGZ2Y53UL3A&Expires=1520255689&Signature=R1f%2Bpbb18Tbt%2BbohB4MaIwpZc18%3D&response-content-disposition=inline%3B%20filename%3DEpidemiologic_review_of_marijuana_use_an.pdf>. Accessed: Dec. 12, 2017. doi: 10.1016/j.alcohol.2005.04.008.

JOHNSON, J.R. et al. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. **Journal pain symptom management**, v. 46, n.2, p.207-218, 2013. Disponível em: https://www.ncbi.nlm.nih.gov/pubmed/23141881. Accessed: Oct. 20, 2017. doi: 10.1016/j.jpainsymman.2012.07.014.

LESSA, M.A. et al. Cannabinoid derivates and the pharmacological management of pain. **Revista dor**, v.17, n.1, p.47-51, 2016. Disponível em: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1806-00132016000100047>. Accessed: Oct. 22, 2017. doi: 10.5935/1806-0013.20160012.

LESTER, P.; GAYNOR, J.S. Management of cancer pain. **Veterinary clinics of north America: small animal practice**, v.30, n.4, p.951-966, 2000. Disponível em: <https://www.sciencedirect.com/science/article/pii/S0195561608700172>. Accessed: Nov. 22, 2017. doi: 10.1016/S0195-5616(08)70017-2.

LIMA, A.D. et al. Evaluation of pain in cancer patients hospitalized in a school hospital in Northeastern Brazil. **Revista dor**,v.14, n.4, p.267-271, 2013. Disponível em: <http://www.scielo.br/pdf/rdor/v14n4/v14n4a07.pdf>. Acesso: Oct.17, 2017. doi: 10.1590/S1806-00132013000400007.

LOONEY, A. Oncology pain in veterinary patients. **Topics in companion animal medicine**, v.25, n.1, p.32-44, 2010.Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/20188337>. Accessed: Oct. 17, 2017. doi: 10.1053/j.tcam.2009.10.008.

MAIDA, V.; DAENINCK, P.J. A user's guide to cannabinoid therapies in oncology. **Current oncology**, v. 23, n.6, p.398-406,

2016. Disponível em: <http://www.current-oncology.com/index.php/oncology/article/view/3487>. Accessed: Oct. 17, 2017. doi: 10.3747/co.23.3487.

MARTINS, T.L. Controle da dor e cuidados paliativos em cães e gatos com câncer. É possível? **Clínica veterinária**,v.20, n.115, p.76-91, 2015.

MASSI, P. et al.Cannabidiol as a potente anticancer drug. **British journal of clinical pharmacology**, v.75, p.303-312, 2012.Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/22506672>. Accessed: Dec. 14, 2017. doi: 10.1111/j.1365-2125.2012.04298.x

MENDES, T.R. et al. Ocorrência da dor nos pacientes oncológicos em cuidado paliativo. **Acta paulista de enfermagem**,v.27, n.4, p.356-361, 2014. Disponível em: <http://www.scielo.br/scielo.php?pid=S0103-002014000400011&script=sci_abstract&tlng=pt>. Accessed: Oct. 22, 2017. doi: 10.1590/1982-0194201400059.

MORENO, J.C.D. et al. Manejo da dor no paciente com câncer. IN: DALECK, C.R.; DE NARDI, A.B. **Oncologia em cães e gatos**. 2ed., Rio de Janeiro: Roca, p.305-324, 2016.

MUNRO, S. et al. Molecular characterization of a peripheral receptor for cannabinoids. **Nature**, v.365, n.6441, p.61-65, 1993. Disponível em: <https://www.researchgate.net/profile/Sean_Munro/publication/15508867_Munro_S_Thomas_KL_Abu-Shaar_M_Molecular_characterization_of_a_peripheral_receptor_for_cannabinoids_Nature_365_61-65/links/571610d708ae730bc5ae1daa/Munro-S-Thomas-KL-Abu-Shaar-M-Molecular-characterization-of-a-peripheral-receptor-for-cannabinoids-Nature-365-61-65.pdf?origin=publication_detail>. Accessed: Oct. 20, 2017. doi: 10.1038/365061a0.

MURNION, B. Medical cannabis. **Australian prescriber**, v.38, n.6, p.212-215, 2015.Disponível em: <https://www.nps.org.au/australian-prescriber/articles/medicinal-cannabis>. Accessed: Oct. 23, 2017. doi: 10.18773/austprescr.2015.072.

PAMPLONA, F.A. Quais são e pra que servem os medicamentos à base de Cannabis? **Revista da biologia**, v.13, n.1, p.28-35, 2014. Disponível em: <htpp://www.ib.usp.br/revista/system/files/05_Pamplona.pdf>: Accessed: Oct. 26, 2017. doi: 10.7594/revbio.13.01.05

PERTWEE, R.G.; Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies ant therapeutic possibilities. **Philosophical transactions of the royal society Biological sciences**, v.367, p.3353-3363, 2012.Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/23108552>. Accessed: Dec. 14, 2017. doi: 10.1098/rstb.2011.0381.

PORTENOY, R.K. et al. Nabiximols for opiod-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. **Journal of pain**, v.13, p.438-449, 2012. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/22483680>. Accessed: Dec. 14, 2017. doi: 10.1016/j.jpain.2012.01.003.

QUEIROGA, F.L. et al. Cox-2 levels in canine mammary tumors, including inflammatory mammary carcinoma: clinicopathological features and prognostic significance. **Anticancer research**, v.25, n.6B, p.4269-4275, 2005.

RAHN, E.J. et al. Activation of cannabinoid CB1 and CB2 receptors suppressers neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats. **British journal pharmacology**, v.152, p.765-777, 2007. Disponível em: <https://www.researchgate.net/publication/6263828_Activation_of_cannabinoid_CB1_and_CB2_receptors_suppresses_neuropathic_nociception_evoked_by_the_chemotherapeutic_agent_vincristine_in_rats>. Accessed: Dec. 14, 2017. doi: 10.1038/sj.bjp.0707333.

RICHARDSON, J.D. et al. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. **Pain**, v.75, n.1, p.111-119, 1998. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/9412521>. Accessed: Dec. 14, 2017. doi: 10.1016/S0304-3959(97)00213-3.

SCHUELERT, N.; McDOUGALL, J.J. Cannabinoid-mediated antinociception is enhanced in rat osteoartthritic knees. **Arthritis rheumatology**, v.58, p.145-153, 2008. Disponível em: http://onlinelibrary.wiley.com/doi/10.1002/art.23156/pdf. Accessed: Oct. 20, 2017. doi: 10.1002/art.23156.

THOMAZ, A. Dor oncológica: conceitualização e tratamento farmacológico. **Onco&**.,ago/set., p.24-29, 2010.

THOMPSON, G.R. et al. Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys. **Toxicology applied pharmacology**, v.25, n.3, p.363-372, 1973.

TURGEMAN, I.; BAR-SELA, G. Cannabis use in palliative oncology: a review of the evidence for popular indications. **Israel medical association journal**, v. 19, p.85-88, 2017. Disponível em: <https://www.ima.org.il/FilesUpload/IMAJ/0/228/114215.pdf>. Accessed: Oct. 20, 2017.

VALASTRO, C. et al. Characterization of endocannabinoids and related acylethanolamides in the synovial fluido f dogs with osteoarthritis: a pilot study. **BMC veterinary research**, v.13, n.309, p.1-5, 2017. Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/29110674>. Accessed: Oct. 20, 2017. doi: 10.1186/s12917-017-1245-7.

YASBEK, K.V.B. Avaliação da dor e da qualidade de vida em cães com câncer. **Revista dor**,v.9, n.3, p.1297-1304, 2008.