Intérêts de la préparation magistrale pour la prise en charge de la douleur en médecine vétérinaire chez les animaux de compagnie

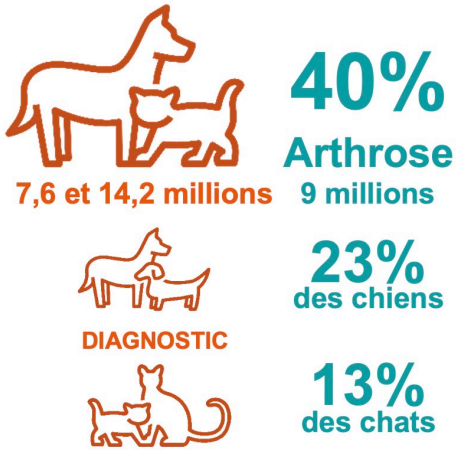
Thierry Poitte DMV - DIU Douleur - CES Chirurgie Ostéo-Articulaire

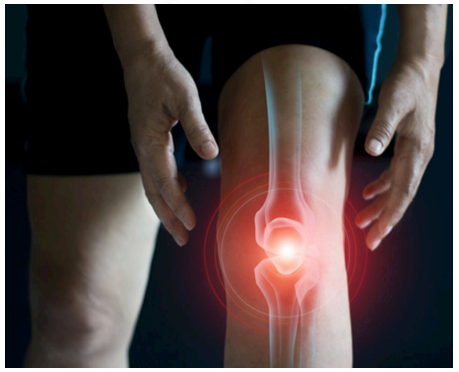
CAP douleur
CHANGE ANIMAL PAIN

Médecine vétérinaire, la douleur: 1er motif de consultation médicale

Arthrose: 1ère cause douleur chronique chez le chien

Johnston SA. Osteoarthritis: Joint anatomy, physiology, and pathobiology. Vet Clin North Am: Small Anim Pract 1997 Jul;27(4):699-723.



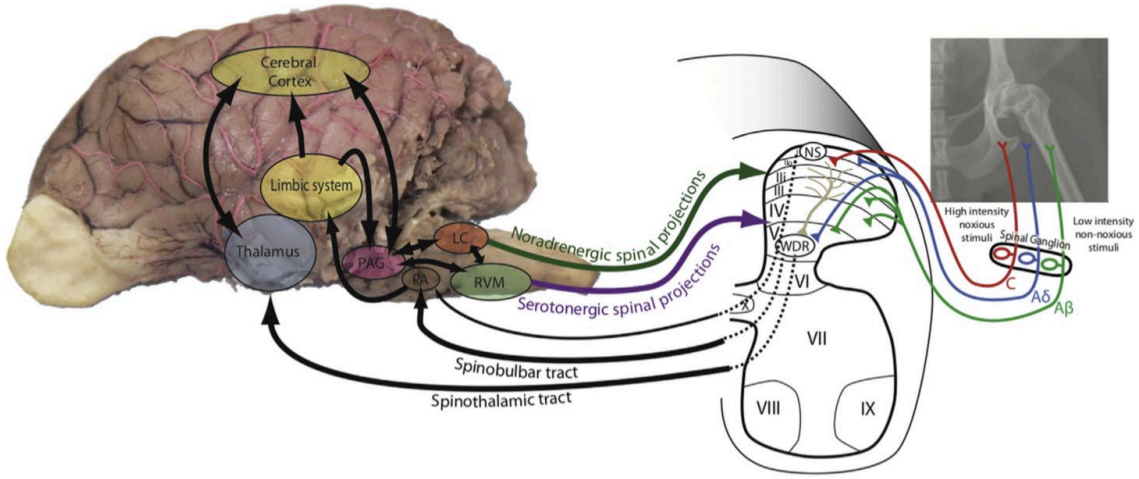


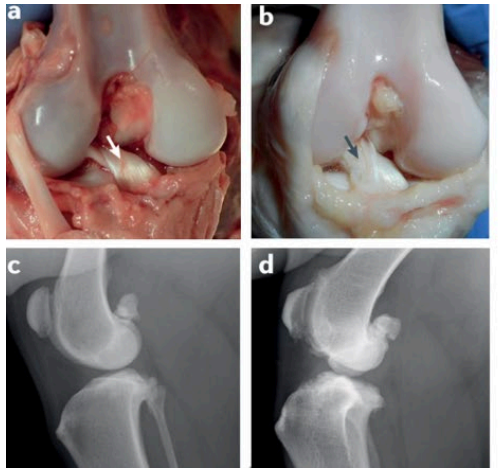
70% Ω > 75 ans
10% adultes

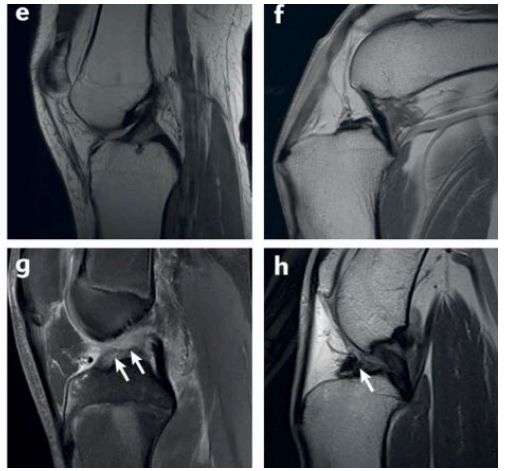
70% Chiens > 8 ans
20% (40% ?) adultes

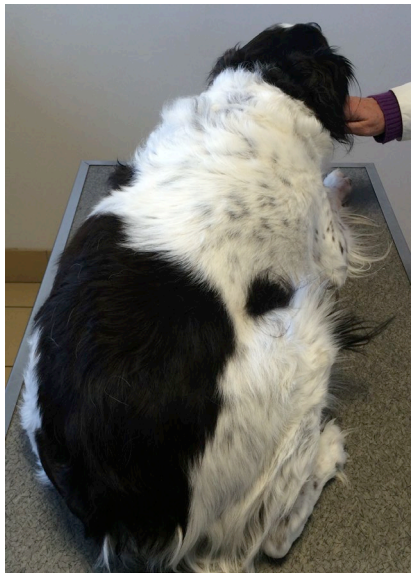
☞ 50 % douleurs associées

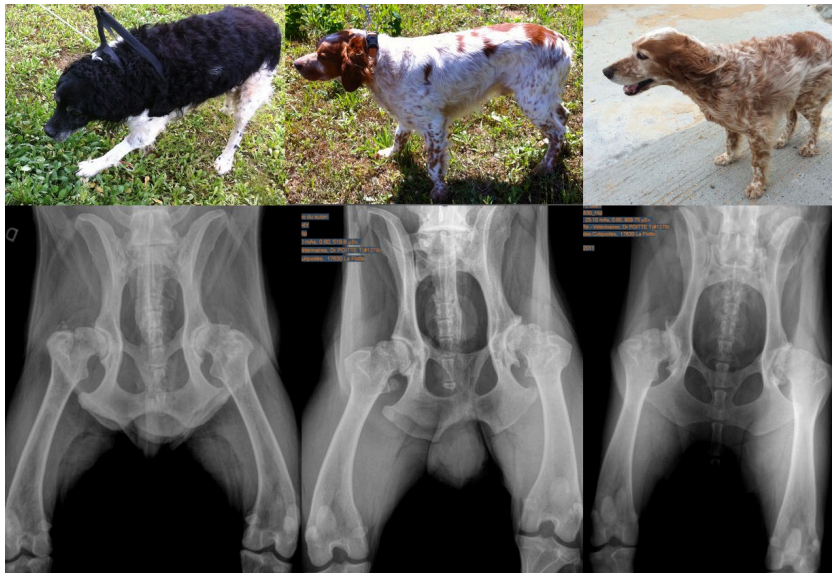
70% Chats > 11 ans
90% Chats > 12 ans

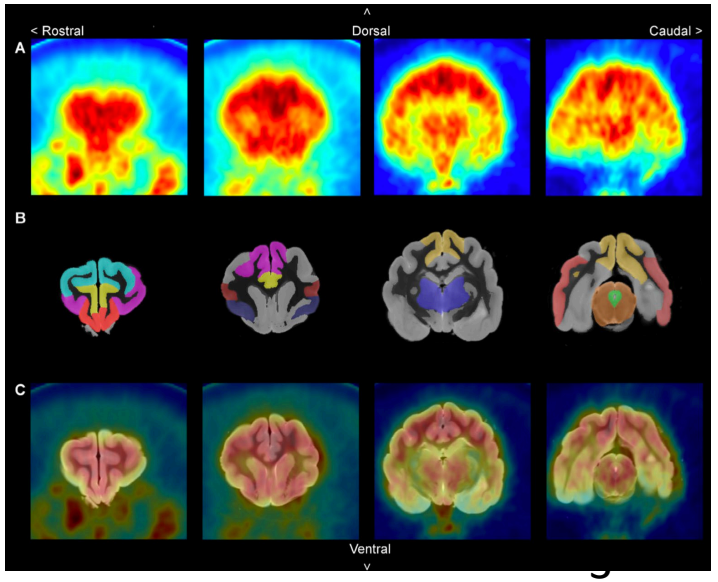

Cerebral Cortex
Limbic system
Thalamus
PAG
LC
PA
RVM
Noradrenergic spinal projections
Serotonergic spinal projections
Spinobulbar tract
Spinothalamic tract
NS
I
II
III
IV
V
WDR
VI
VII
VIII
IX
High intensity noxious stimuli
Spinal Ganglion
Low intensity non-noxious stimuli
C
Aδ
Aβ


a
b
c
d


e
f
g
h

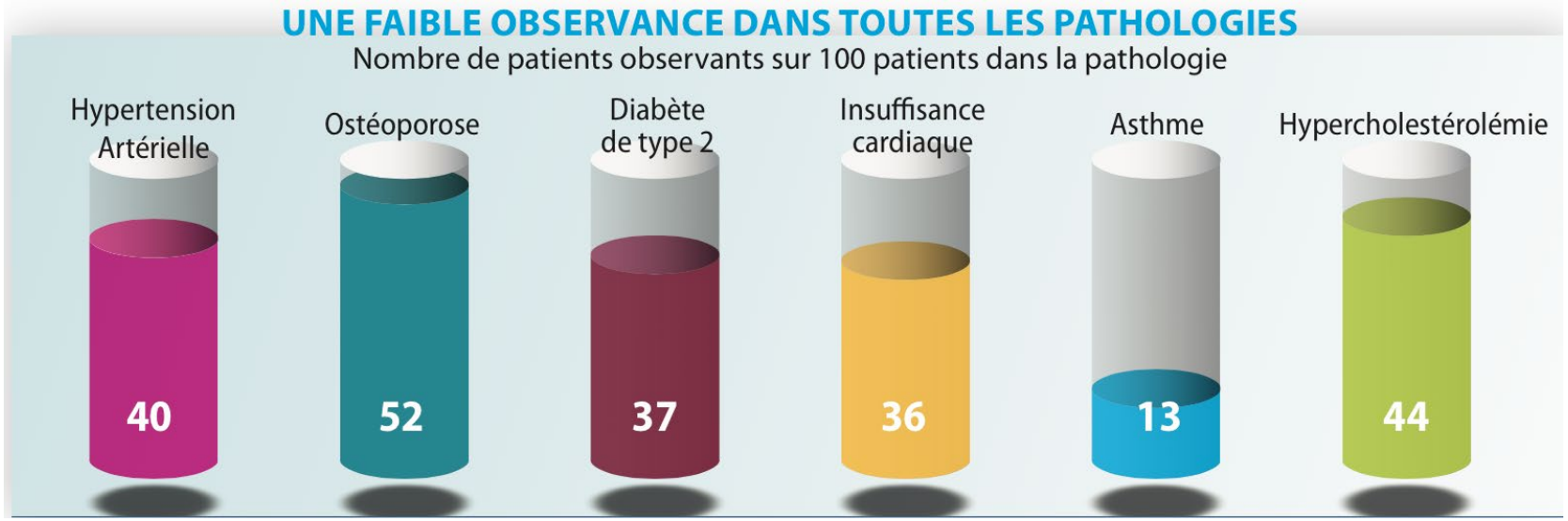


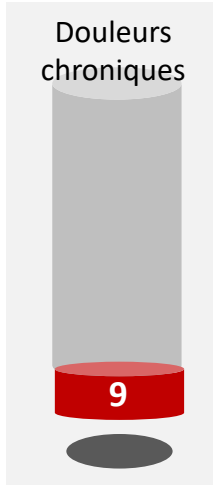


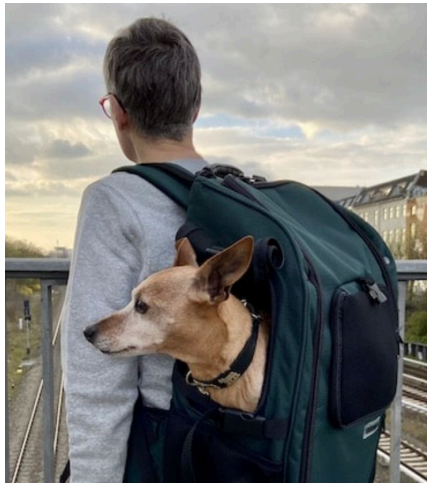

< Rostral
Dorsal
Caudal >
A
B
C
Ventral

Baudrant-Boga M 2009

Azevedo LF 2013







DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES

Observance

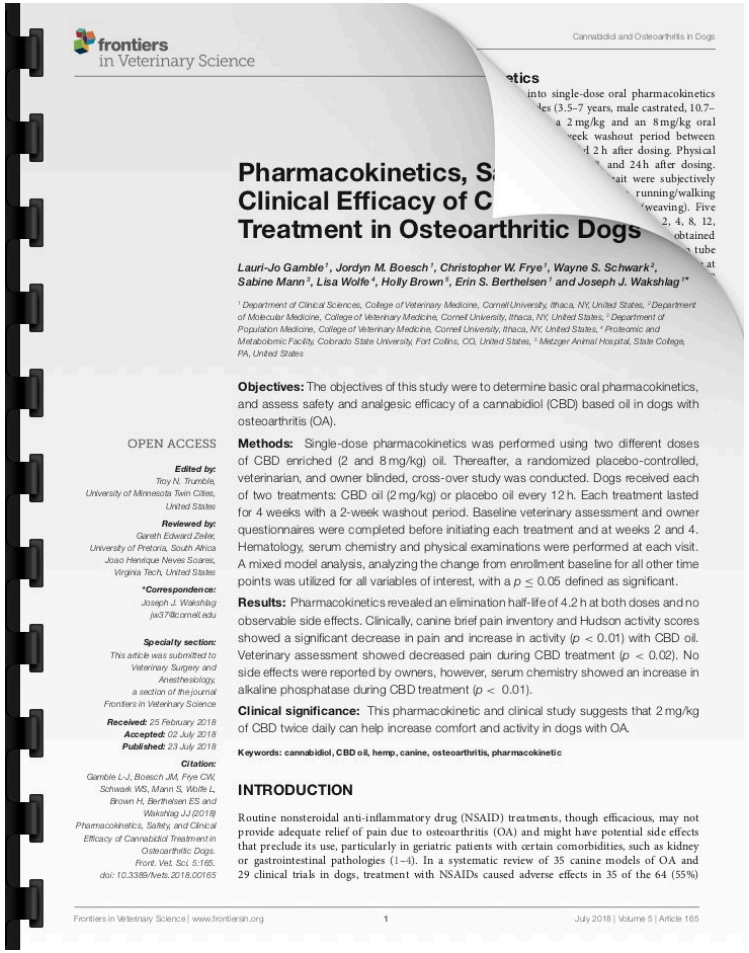
Dépistage - Évaluation

PKPD

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES

Variabilité pharmacologique

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES



frontiers in Veterinary Science

Cannabidiol and Osteoarthritis in Dogs

Pharmacokinetics, S… Clinical Efficacy of C… Treatment in Osteoarthritic Dogs

*Lauri-Jo Gamble[1], Jordyn M. Boesch[1], Christopher W. Frye[1], Wayne S. Schwark[2], Sabine Mann[3], Lisa Wolfe[4], Holly Brown[5], Erin S. Berthelsen[1] and Joseph J. Wakshlag[1]**

[1] Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY, United States, [2] Department of Molecular Medicine, College of Veterinary Medicine, Cornell University, Ithaca, NY, United States, [3] Department of Population Medicine, College of Veterinary Medicine, Cornell University, Ithaca, NY, United States, [4] Proteomic and Metabolomic Facility, Colorado State University, Fort Collins, CO, United States, [5] Metzger Animal Hospital, State College, PA, United States

Objectives: The objectives of this study were to determine basic oral pharmacokinetics, and assess safety and analgesic efficacy of a cannabidiol (CBD) based oil in dogs with osteoarthritis (OA).

Methods: Single-dose pharmacokinetics was performed using two different doses of CBD enriched (2 and 8 mg/kg) oil. Thereafter, a randomized placebo-controlled, veterinarian, and owner blinded, cross-over study was conducted. Dogs received each of two treatments: CBD oil (2 mg/kg) or placebo oil every 12 h. Each treatment lasted for 4 weeks with a 2-week washout period. Baseline veterinary assessment and owner questionnaires were completed before initiating each treatment and at weeks 2 and 4. Hematology, serum chemistry and physical examinations were performed at each visit. A mixed model analysis, analyzing the change from enrollment baseline for all other time points was utilized for all variables of interest, with a $p \leq 0.05$ defined as significant.

Results: Pharmacokinetics revealed an elimination half-life of 4.2 h at both doses and no observable side effects. Clinically, canine brief pain inventory and Hudson activity scores showed a significant decrease in pain and increase in activity ($p < 0.01$) with CBD oil. Veterinary assessment showed decreased pain during CBD treatment ($p < 0.02$). No side effects were reported by owners, however, serum chemistry showed an increase in alkaline phosphatase during CBD treatment ($p < 0.01$).

Clinical significance: This pharmacokinetic and clinical study suggests that 2 mg/kg of CBD twice daily can help increase comfort and activity in dogs with OA.

Keywords: cannabidiol, CBD oil, hemp, canine, osteoarthritis, pharmacokinetic

OPEN ACCESS

Edited by:
Troy N. Trumble, University of Minnesota Twin Cities, United States

Reviewed by:
Gareth Edward Zeiler, University of Pretoria, South Africa
Joao Henrique Neves Soares, Virginia Tech, United States

****Correspondence:***
Joseph J. Wakshlag
jjw37@cornell.edu

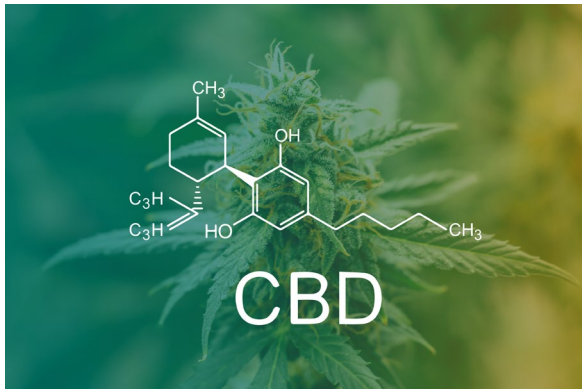
Specialty section:
This article was submitted to Veterinary Surgery and Anesthesiology, a section of the journal Frontiers in Veterinary Science

Received: *25 February 2018*
Accepted: *02 July 2018*
Published: *23 July 2018*

Citation:
Gamble L-J, Boesch JM, Frye CW, Schwark WS, Mann S, Wolfe L, Brown H, Berthelsen ES and Wakshlag JJ (2018) Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol Treatment in Osteoarthritic Dogs. Front. Vet. Sci. 5:165. doi: 10.3389/fvets.2018.00165

INTRODUCTION

Routine nonsteroidal anti-inflammatory drug (NSAID) treatments, though efficacious, may not provide adequate relief of pain due to osteoarthritis (OA) and might have potential side effects that preclude its use, particularly in geriatric patients with certain comorbidities, such as kidney or gastrointestinal pathologies (1–4). In a systematic review of 35 canine models of OA and 29 clinical trials in dogs, treatment with NSAIDs caused adverse effects in 35 of the 64 (55%)



- 1er passage hépatique
- Biodisponibilité faible et variable 0 à 19%
- Forte lipophilie
- ½ vie CBD 2 mg/kg: 4,2h
- Catabolisme / Cytochrome P450
- Forte variabilité génétique
- Interactions médicamenteuses

Variabilité pharmacologique

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES

Research Paper

PAIN

A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain

Chris D. Verrico[a,b], Shonda Wesson[c], Vanaja Konduri[d], Colby J. Hofferek[d], Kenneth Dunner Jr[f], Pedram Salimpour[g], William K. Decker[d,h,i], Matthew M. Halpert[d,e]

Abstract

Over the last 2 decades, affirmative diagnoses of osteoarthritis (OA) in the United States have tripled due to increasing rates of obesity and an aging population. Hemp-derived cannabidiol (CBD) is the major nontetrahydrocannabinol component of cannabis and has been promoted as a potential treatment for a wide variety of disparate inflammatory conditions. Here, we evaluated CBD for its ability to modulate the production of proinflammatory cytokines in vitro and in murine models of induced inflammation and further validated the ability of a liposomal formulation to increase bioavailability in mice and in humans. Subsequently, the therapeutic potential of both naked and liposomally encapsulated CBD was explored in a 4-week, randomized placebo-controlled, double-blinded study in a spontaneous canine model of OA. In vitro and in mouse models, CBD significantly attenuated the production of proinflammatory cytokines IL-6 and TNF-α while elevating levels of anti-inflammatory IL-10. In the veterinary study, CBD significantly decreased pain and increased mobility in a dose-dependent fashion among animals with an affirmative diagnosis of OA. Liposomal CBD (20 mg/day) was as effective as the highest dose of nonliposomal CBD (50 mg/day) in improving clinical outcomes. Hematocrit, comprehensive metabolic profile, and clinical chemistry indicated no significant detrimental impact of CBD administration over the 4-week analysis period. This study supports the safety and therapeutic potential of hemp-derived CBD for relieving arthritic pain and suggests follow-up investigations in humans are warranted.

Keywords: Osteoarthritis, Cannabidiol, Randomized trial, Liposomal encapsulation, TNF-α, IL-6

1. Background

Arthritis is a leading cause of pain, disfigurement, and disability in the United States where nearly one-quarter of all adults have received an affirmative diagnosis.[2] Although the incidence of rheumatoid arthritis has remained constant, osteoarthritis (OA) diagnoses have tripled since 2000 due to an aging population, increasing levels of obesity, and greater physician recognition of its prevalence. Accordingly, OA is a leading cause of chronic pain and disability among the elderly.[23] Irrespective of the precipitating cause, the pathology of joint destruction in arthritis is driven by an overlapping profile of pathologic inflammatory cytokines including TNF-α, IL-1β, IL-6, IL-17, and IL-21.[26,46,49] In addition, pain, inflammation, and joint destruction among both etiologies are mediated by overlapping subsets of innate cell types, most prominently neutrophils.[16,45] Treatment of rheumatoid arthritis consists of both targeted and nonspecific immunosuppressive drug regimens (disease-modifying antirheumatic drugs), whereas treatment of OA consists of analgesics, nonsteroidal anti-inflammatory drugs, glucocorticoids, and joint replacement supplemented by a weight loss regimen, if applicable. In either case, pharmacomodulation is not curative and often accompanied by severe side-effects.[6,9,36] Because pain is the predominant symptom of OA, it is also the primary target of intervention. Recent reviews comparing the efficacy of pharmacotherapies for reducing OA pain conclude opioids are most effective, however, abuse potential limits utility. Overall, the effect size across all pharmacotherapies is small (0.39), signaling a need for additional treatments with novel and complementary mechanisms of action.[1,32,54,61]

The ubiquitous endocannabinoid system plays a role in many physiological and pathophysiological processes. Consistent with this, cannabis and its constituents are increasingly being recognized as bona fide pharmacologic agents with significant therapeutic potential. For example, cannabidiol (CBD), the major nontetrahydrocannabinol (THC) constituent of cannabis, can exert numerous biological effects through several different receptor and signaling pathways, including anti-inflammatory

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

C.D. Verrico, S. Wesson, W.K. Decker, and M.M. Halpert contributed equally to the preparation of this manuscript.

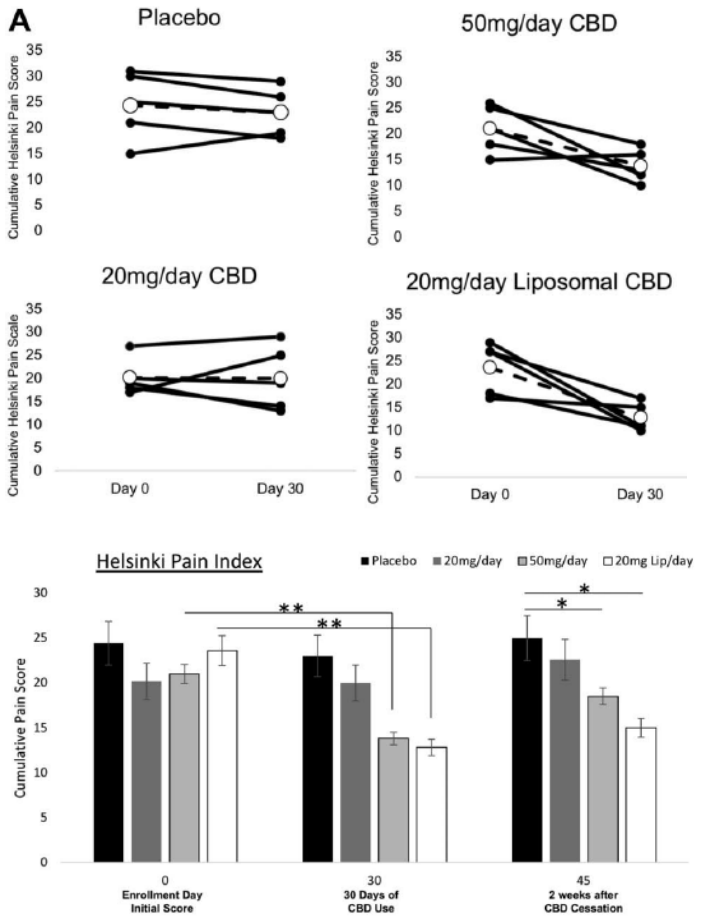
[a] Department of Psychiatry, [b] Department of Pharmacology, Baylor College of Medicine, Houston, TX, United States, [c] Sunset Animal Hospital, Houston, TX, United States, [d] Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX, United States, [e] Vallmenta Labs, Fort Collins, CO, United States, [f] Department of Cancer Biology, University of Texas MD Anderson Cancer Center, Houston, TX, United States, [g] Boston University School of Medicine, Boston, MA, United States, [h] Center for Cell and Gene Therapy, [i] Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX, United States

*Corresponding author. Address: Tel.: 713-798-1560; fax: 713-798-3700. E-mail address: halpert@bcm.edu (M.H. Halpert).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 161 (2020) 2191–2202

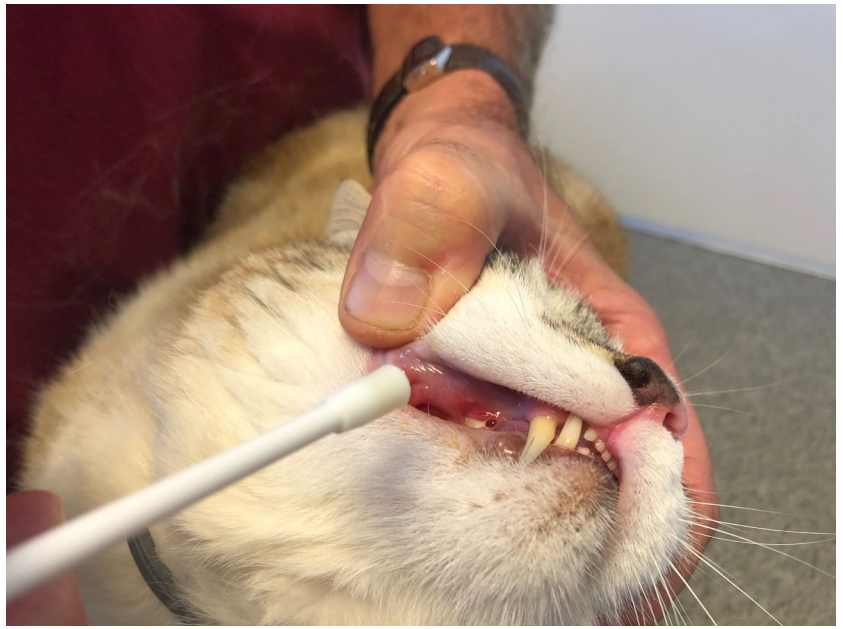
http://dx.doi.org/10.1097/j.pain.0000000000001896



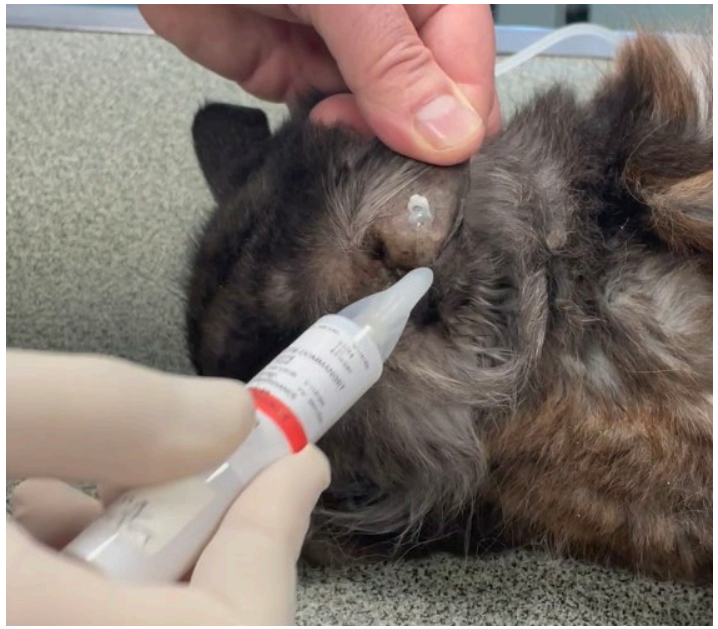
Encapsulage CBD
bulles liposomes

- ↑ biodisponibilité VO
- ↓ Scores Helsinki CBD 50mg/j et CBD lipos. 20mg/j

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES

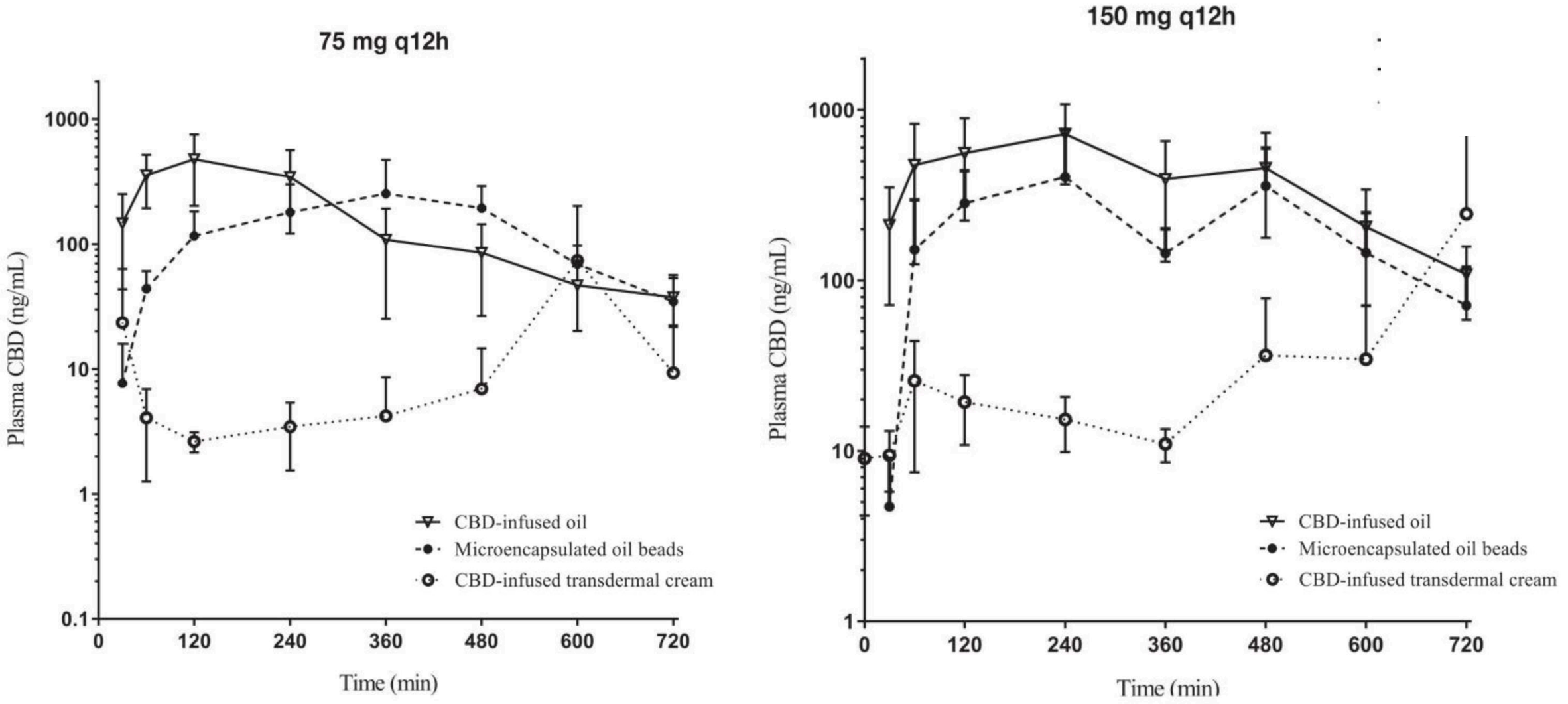


Voie transmucosale



Voie transdermique

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES



Bartner et al. Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. Can J Vet Res. 2018 Jul; 82(3): 178–183.

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES

Forme galénique non adaptée

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES

Gabapentine

Amantadine

Principe actif non disponible
en médecine vétérinaire

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES

Mirtazapine

Principe actif non disponible
en médecine vétérinaire

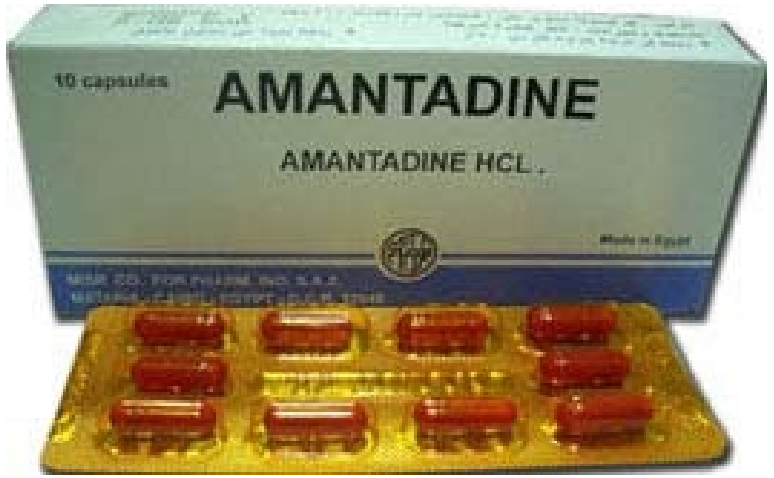
DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES

Mirtazapine

Principe actif non disponible
en médecine vétérinaire

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES

5 – 10 mg/kg BID TID



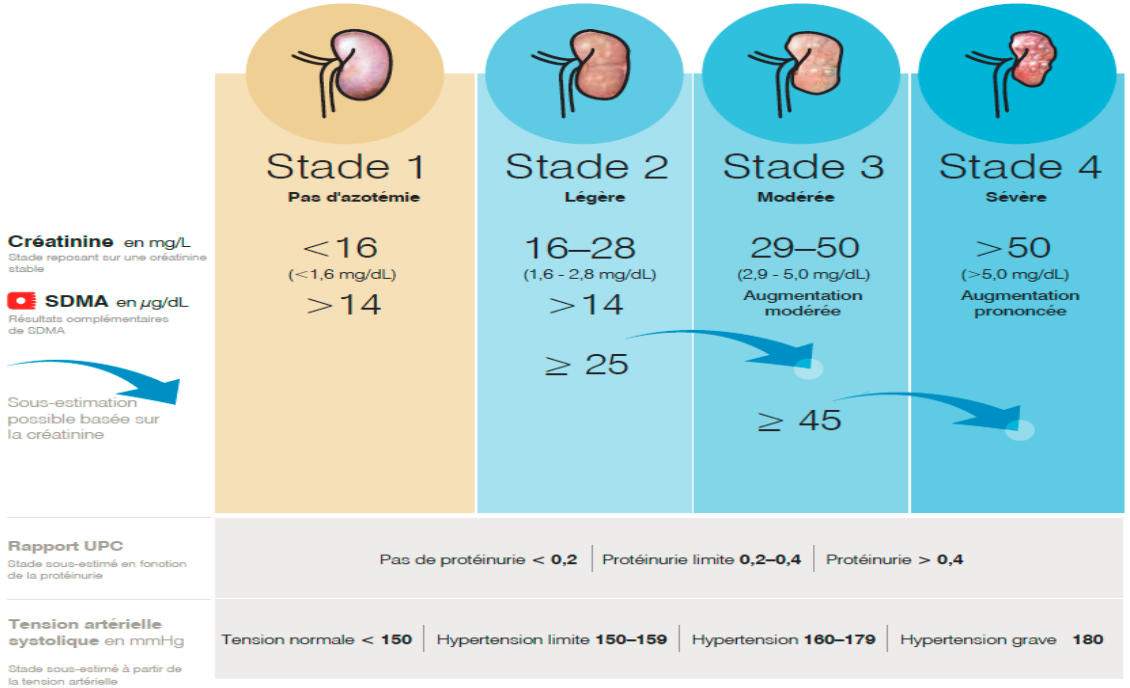
3 -5 mg/kg SID

Dosage non adapté au format

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES
et de leurs comorbidités

Meloxicam

Telmisartan



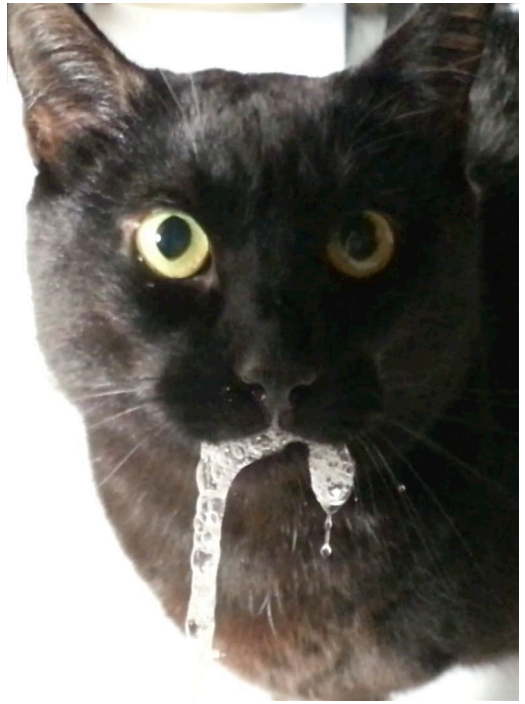
RUPTURE DE STOCK

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES

Suspension buvable 250mg/5mL (flacon de 470mL) Excipients : Glycérine, **xylitol,** eau purifiée, arôme artificiel fraise-anis

Excipient inadapté

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES



Excipient inadapté

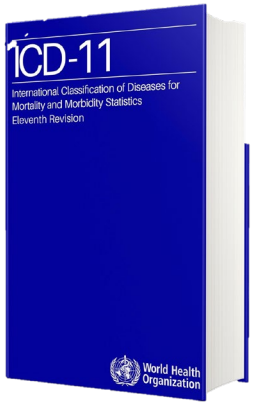
L.A. Aldrich; James Roush and Butch KuKanich . American Journal of Veterinary Research, 2021, Vol. 82, No. 10, Pages 840-845

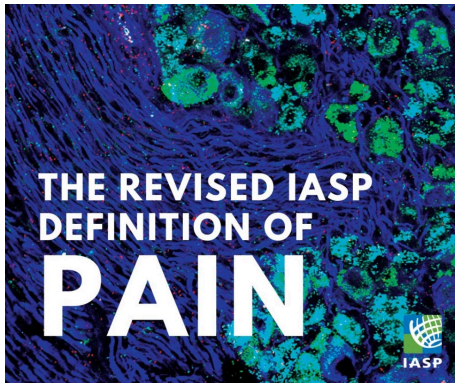
Objectifs :
Comparer les concentrations plasmatiques de tramadol chez le chat à la suite d'une prescription unique par voie orale ou par application transdermique. Evaluer la pharmacocinétique du tramadol appliqué par voie transdermique et déterminer sa concentration au sein du gel appliqué.

Résultats :
Les concentrations plasmatiques de tramadol sont indétectables ou bien plus faibles dans le cadre de l'utilisation de la voie transdermique (<1 à 4,3ng/ml), en comparaison à la forme orale (concentration plasmatique maximale de 261,3ng/ml).
La pharmacocinétique du tramadol appliqué par voie transdermique n'a pas pu être évaluée.

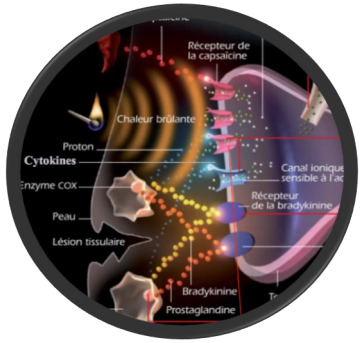
Conclusions et interprétation clinique :
L'application d'une dose unique par le propriétaire de tramadol par voie transdermique ne permet pas d'atteindre des concentrations plasmatiques efficaces chez le chat

LA PRISE EN CHARGE DES DOULEURS CHRONIQUES: DE MULTIPLES RÉVOLUTIONS





NOSOGRAPHIQUE -SÉMANTIQUE

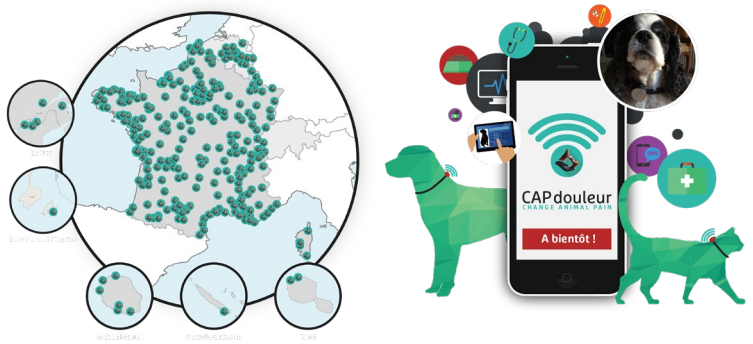


MÉCANISMES

ÉVALUATION

THÉRAPEUTIQUE

RELATIONNELLE



STRUCTURATION / DATA

Intérêts de la préparation magistrale pour la prise en charge de la douleur en médecine vétérinaire

↑ pharmacocinétique
↑ biodisponibilité

↑ observance: formulations adaptées

↓ risques : excipients

↑ disponibilité: rupture de stock

DÉFIS DE LA PRISE EN CHARGE DES DOULEURS CHRONIQUES

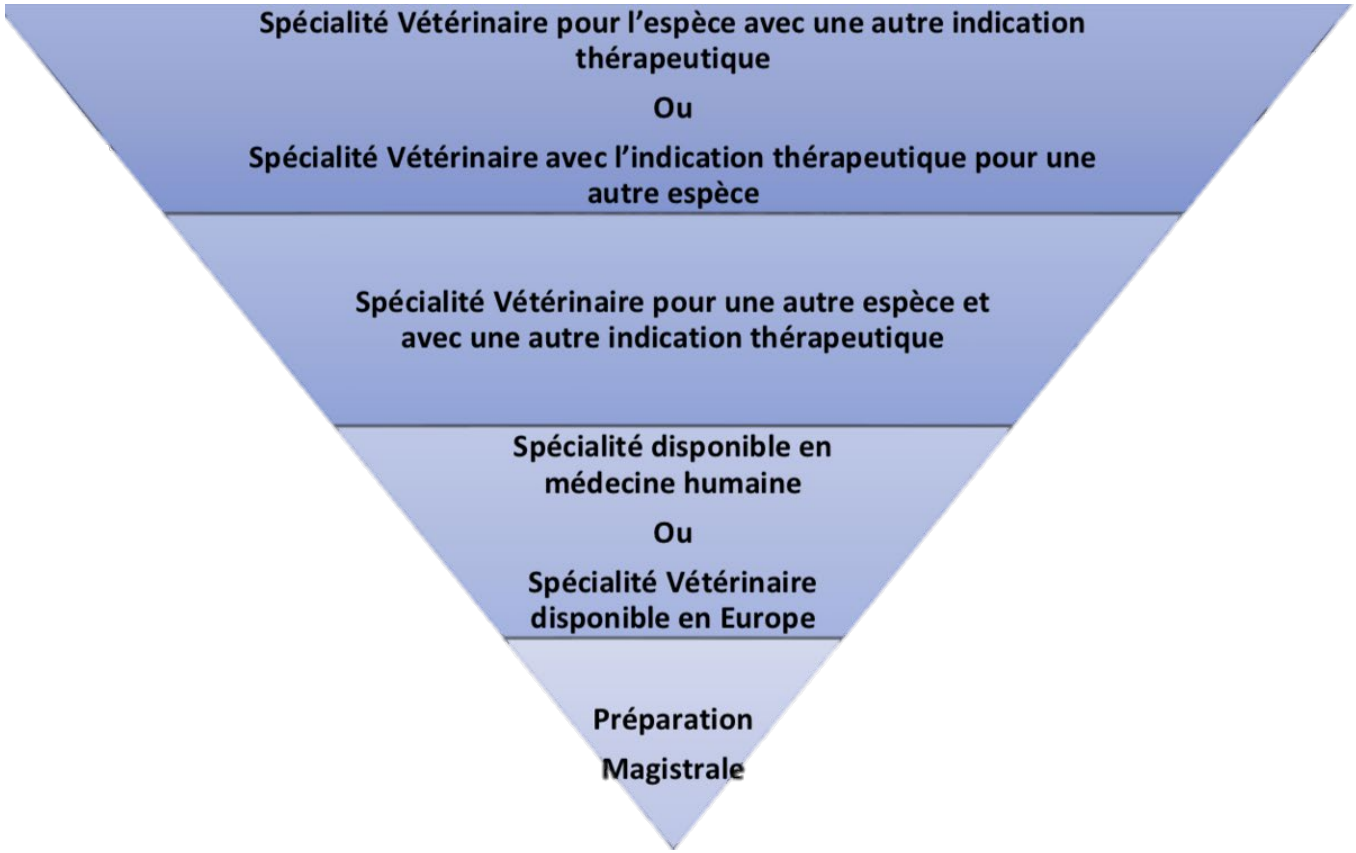
Préparations magistrales vétérinaires

Suspensions buvables
(+/- aromatisées)

Gélules :de taille adaptée
+/-appétantes

Formes transdermiques

Le vétérinaire doit satisfaire aux dispositions dites de la **cascade décisionnelle**
La préparation magistrale vétérinaire a un **statut de médicament vétérinaire**
art L-5143-4 et art L 5111-1 du CSP



Contrat de sous-traitance avec un laboratoire ou une pharmacie ayant une autorisation de l'ARS
Traçabilité - registre


CAPdouleur
CHANGE ANIMAL PAIN
Etablissement membre du réseau CAPdouleur