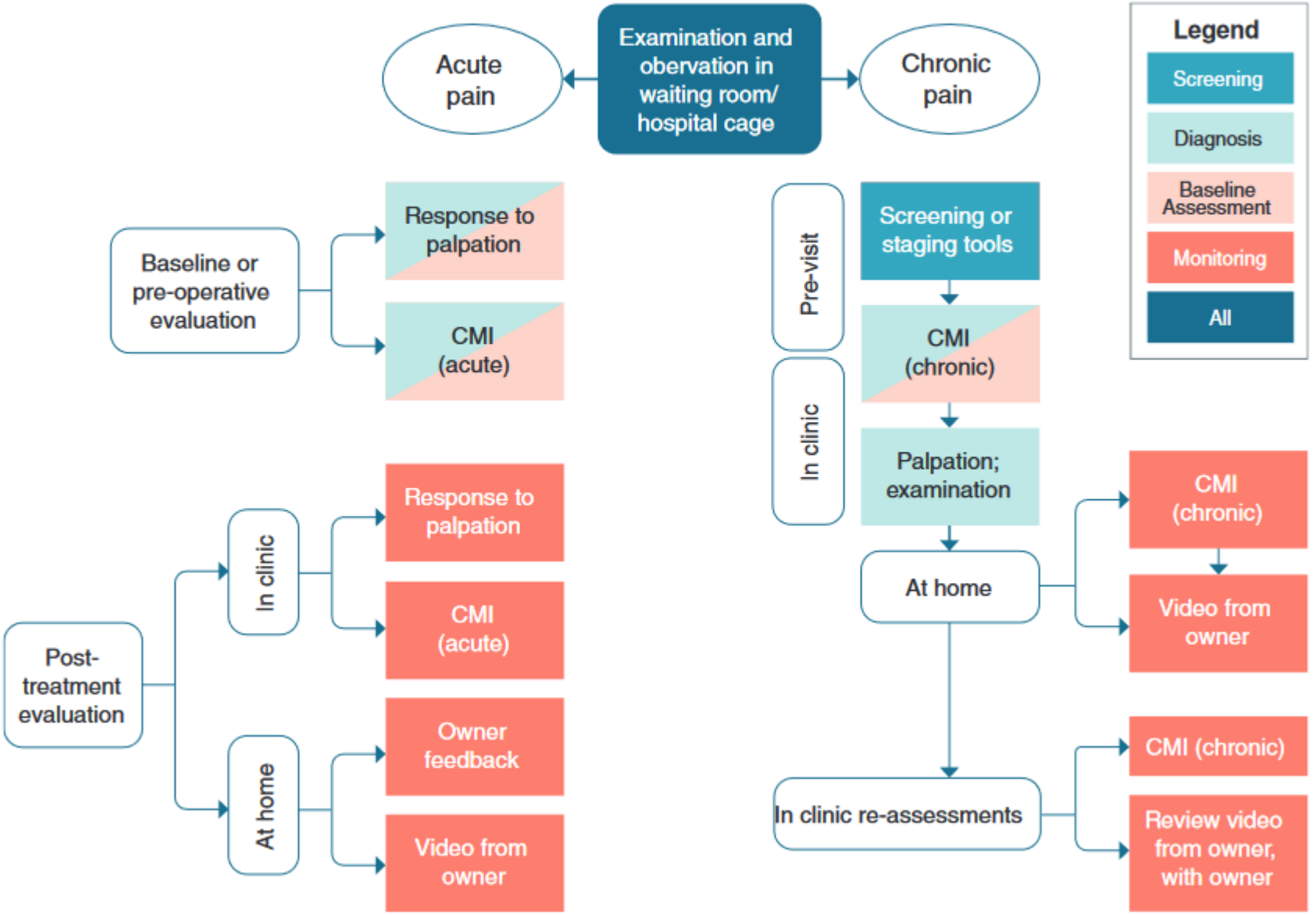
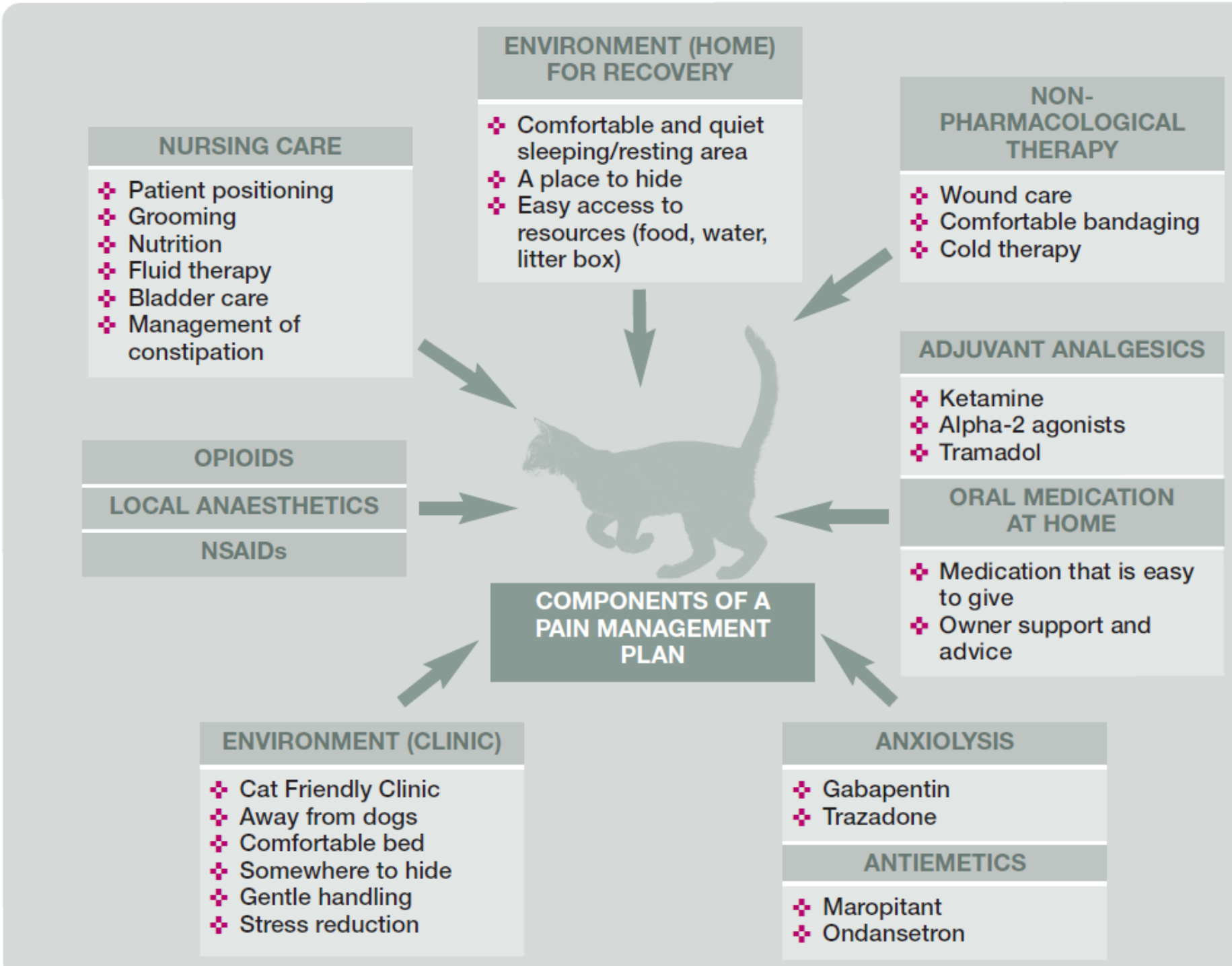
Terapia o tratamiento del dolor?

Profa. Adja. Nadia Crosignani

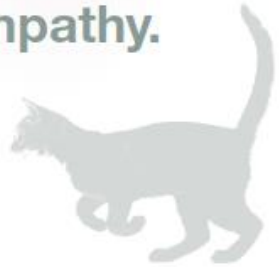
MSc. PhD.

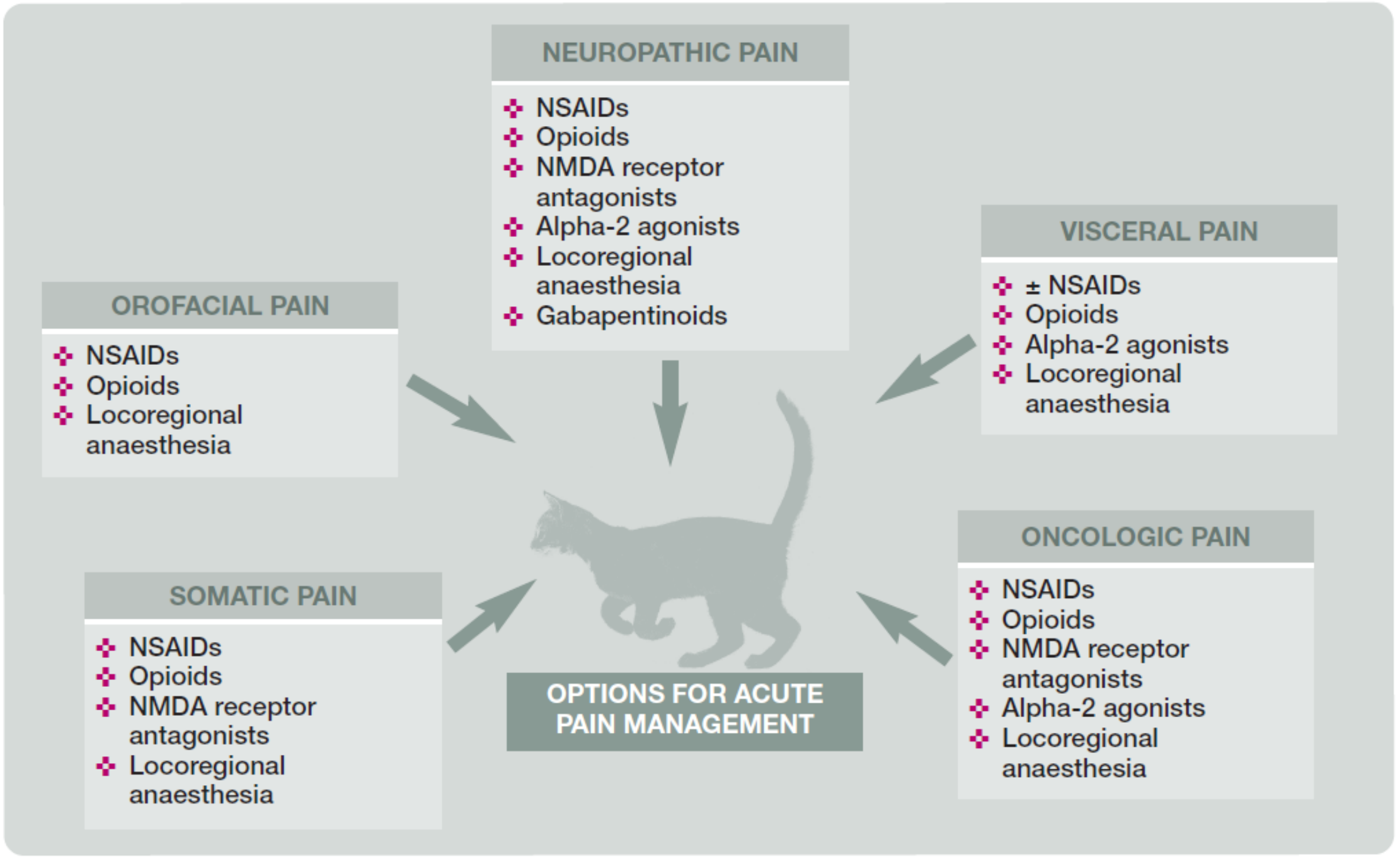

Examination and obervation in waiting room/ hospital cage
Acute pain
Chronic pain
Legend
Screening
Diagnosis
Baseline Assessment
Monitoring
All
Baseline or pre-operative evaluation
Response to palpation
CMI (acute)
Pre-visit
In clinic
Screening or staging tools
CMI (chronic)
Palpation; examination
At home
CMI (chronic)
Video from owner
In clinic re-assessments
CMI (chronic)
Review video from owner, with owner
Post-treatment evaluation
In clinic
Response to palpation
CMI (acute)
At home
Owner feedback
Video from owner

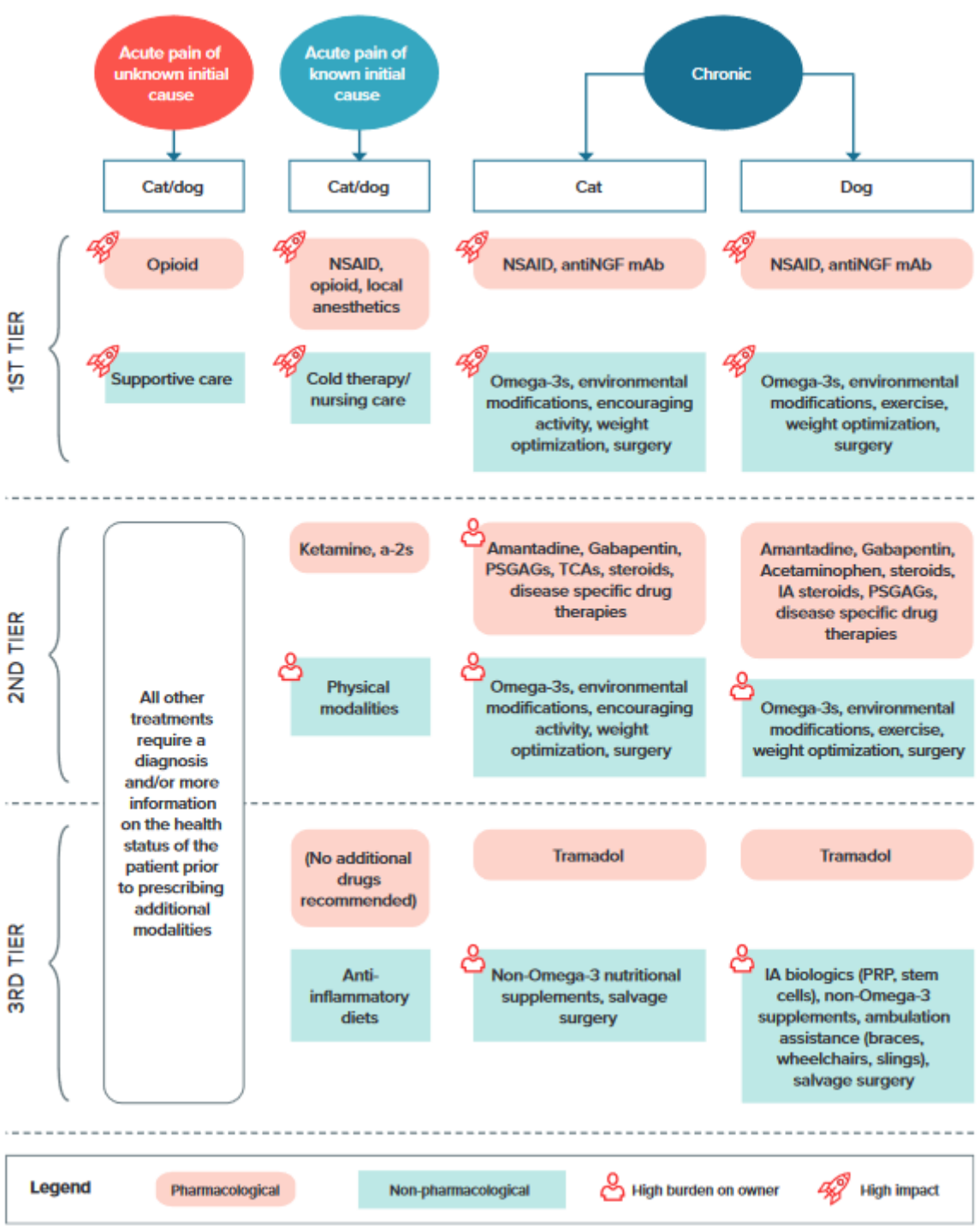

ENVIRONMENT (HOME) FOR RECOVERY
Comfortable and quiet sleeping/resting area
A place to hide
Easy access to resources (food, water, litter box)
NURSING CARE
Patient positioning
Grooming
Nutrition
Fluid therapy
Bladder care
Management of constipation
NON-PHARMACOLOGICAL THERAPY
Wound care
Comfortable bandaging
Cold therapy
ADJUVANT ANALGESICS
Ketamine
Alpha-2 agonists
Tramadol
OPIOIDS
LOCAL ANAESTHETICS
NSAIDs
ORAL MEDICATION AT HOME
Medication that is easy to give
Owner support and advice
COMPONENTS OF A PAIN MANAGEMENT PLAN
ENVIRONMENT (CLINIC)
Cat Friendly Clinic
Away from dogs
Comfortable bed
Somewhere to hide
Gentle handling
Stress reduction
ANXIOLYSIS
Gabapentin
Trazadone
ANTIEMETICS
Maropitant
Ondansetron

- Vendajes apropiados
- Frio
- Posicionamento do animal
- Fluidoterapia
- Limpieza
- Cepillado
- Espacio limpio, tranquilo, confortable
- Clinica cat Friendly (ISFM Cat Friendly Clinic accreditation and the
- AAFP Cat Friendly Practice Program

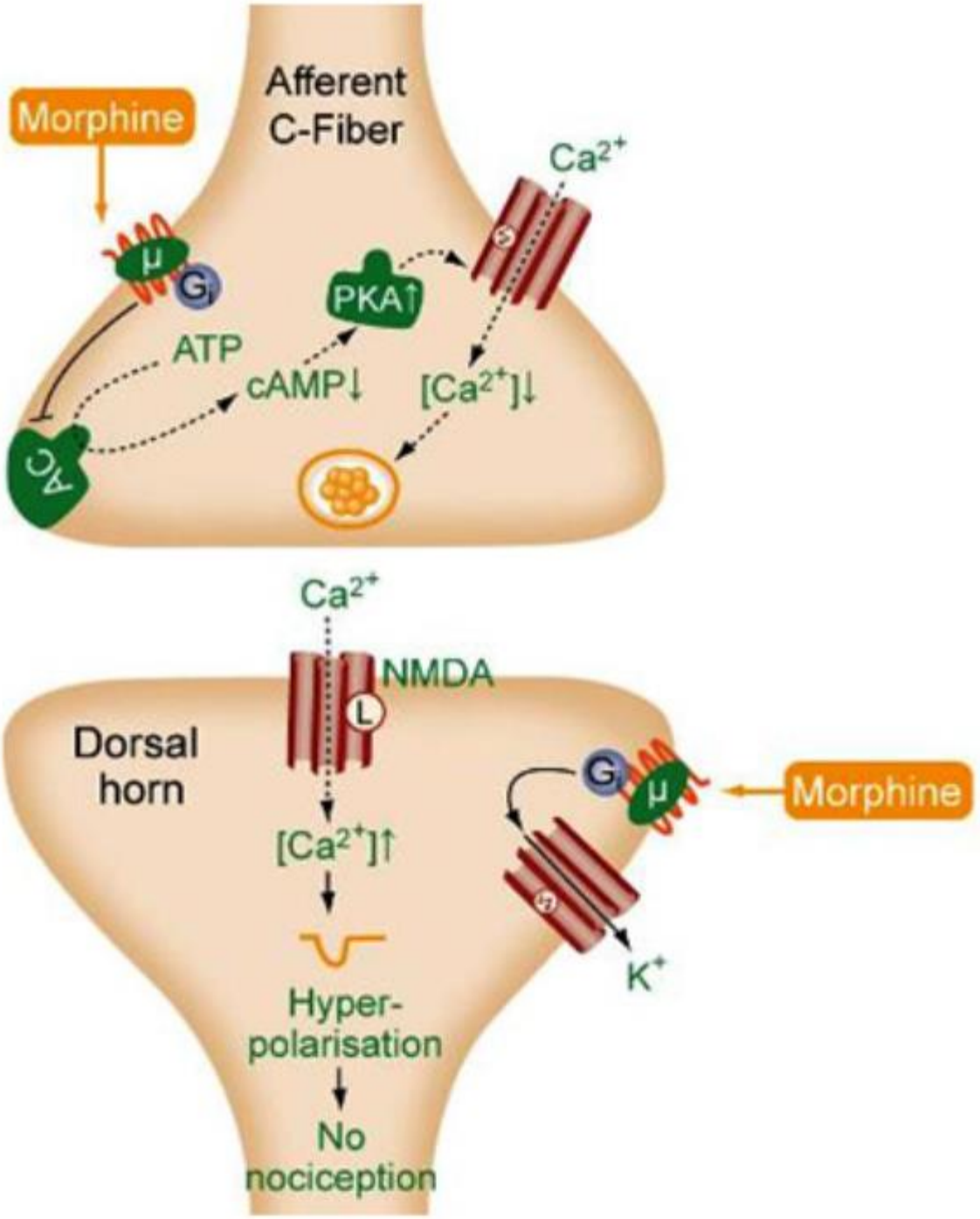
Pain management is not only about giving an analgesic drug: the emotional needs of the cat must be considered, and the patient should always be treated with respect and empathy.




NEUROPATHIC PAIN
NSAIDs
Opioids
NMDA receptor antagonists
Alpha-2 agonists
Locoregional anaesthesia
Gabapentinoids
OROFACIAL PAIN
NSAIDs
Opioids
Locoregional anaesthesia
VISCERAL PAIN
± NSAIDs
Opioids
Alpha-2 agonists
Locoregional anaesthesia
SOMATIC PAIN
NSAIDs
Opioids
NMDA receptor antagonists
Locoregional anaesthesia
ONCOLOGIC PAIN
NSAIDs
Opioids
NMDA receptor antagonists
Alpha-2 agonists
Locoregional anaesthesia
OPTIONS FOR ACUTE PAIN MANAGEMENT



AAHA Guidelines, 2022


Afferent
C-Fiber
Morphine
μ
Gi
ATP
cAMP↓
PKA↑
Ca2+
[Ca2+]↓
AC
Ca2+
NMDA
L
Dorsal
horn
[Ca2+]↑
Hyper-
polarisation
No
nociception
G
μ
Morphine
K+

OPIOIDES

MORFINA ORAL??

Clinical Trial > J Vet Pharmacol Ther. 2005 Aug;28(4):371-6.
doi: 10.1111/j.1365-2885.2005.00661.x.

Pharmacokinetics of morphine and plasma concentrations of morphine-6-glucuronide following morphine administration to dogs

B KuKanich [1], B D X Lascelles, M G Papich

Affiliations + expand

PMID: 16050817 DOI: 10.1111/j.1365-2885.2005.00661.x

5% BIODISPONIBILIDAD

Pharmacokinetics of an immediate and extended release oral morphine formulation utilizing the spheroidal oral drug absorption system in dogs

C. L. ARAGON, M. R. READ, J. S. GAYNOR, M. D. BARNHART, D. WILSON, M. G. PAPICH

First published: 06 March 2009 | https://doi.org/10.1111/j.1365-2885.2008.01011.x | Citations: 16

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Current address: Aragon C.L., Barnhart M. D. and Wilson D., MedVet Associates 300 E, Wilson Bridge Road, Worthington, OH 43085, USA
Current address: Read M. R., Western Veterinary Specialist Centre, 1802 10th Avenue SW, Calgary, AB T3C 0J8, Canada
Current address: Gaynor J. S., Animal Anesthesia and Pain Management Center, 5520 North Nevada Avenue, Suite 150, Colorado Springs, CO 80918, USA
Current address: Papich M. G., North Carolina State College of Veterinary Medicine, Molecular Biomedical Sciences, 4700 Hillsborough Street, Raleigh, NC 27606, USA

However, the low morphine plasma concentrations and high variability produced from this formulation, suggest that the clinical application of this formulation at the doses evaluated in this study are limited.

Clinical Trial > J Vet Pharmacol Ther. 2010 Feb;33(1):15-21.
doi: 10.1111/j.1365-2885.2009.01098.x.

Pharmacokinetics of acetaminophen, codeine, and the codeine metabolites morphine and codeine-6-glucuronide in healthy Greyhound dogs

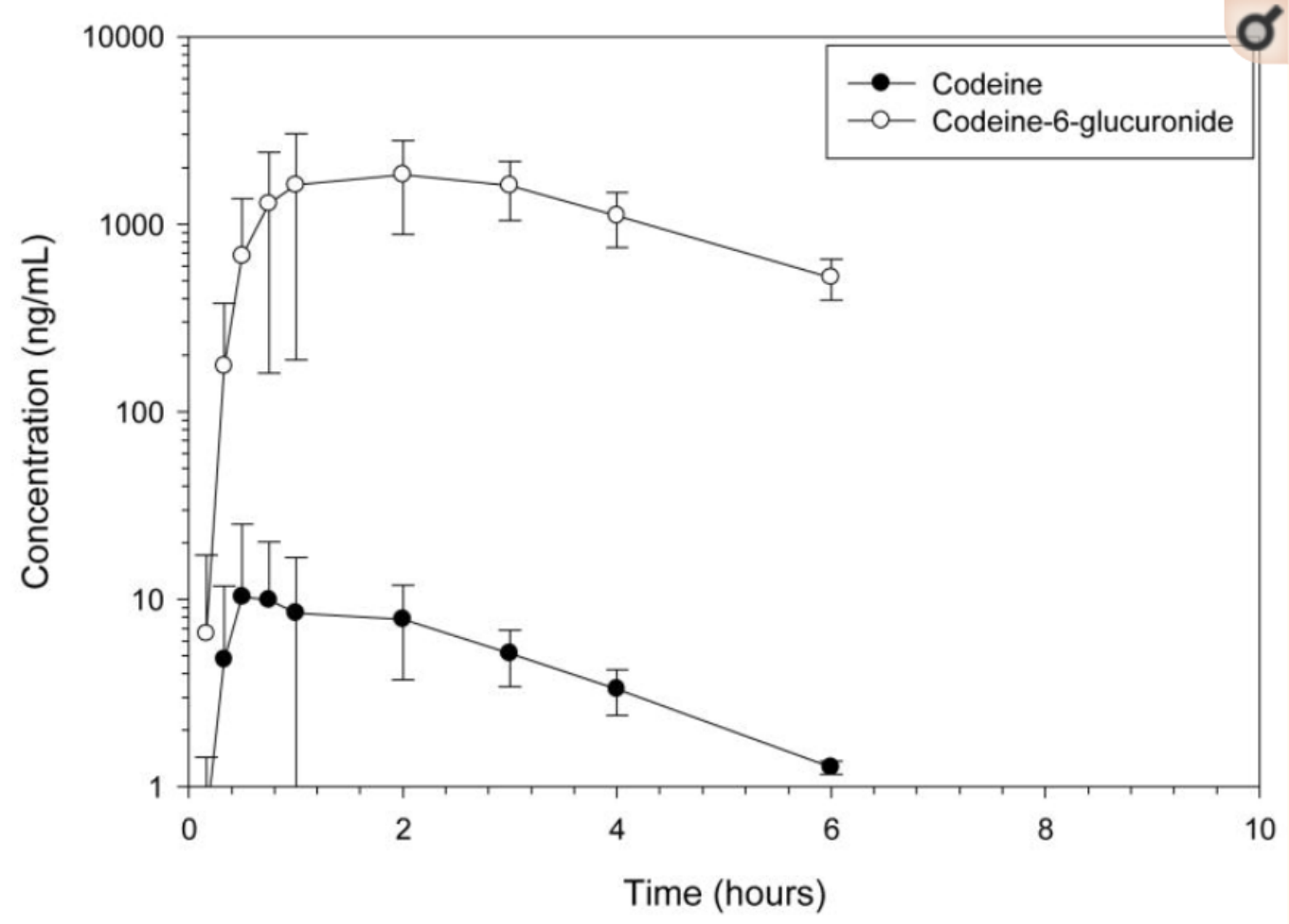
B KuKanich [1]

Affiliations + expand

PMID: 20444020 PMCID: PMC2867071 DOI: 10.1111/j.1365-2885.2009.01098.x

Free PMC article

- The oral bioavailability of codeine was 4%, morphine concentrations were negligible, but large amounts of codeine-6-glucuronide (C(max) = 1952.86 ng/mL) were detected suggesting substantial first pass metabolism.



Open in a separate window

Figure 7

Mean ± SD plasma profile of codeine and codeine-6-glucuronide after codeine 1.43 mg/kg PO (mean dose) to 6 healthy Greyhound dogs. Morphine was not detected in any dog greater than 1 ng/mL.

J Vet Pharmacol Ther. 2016 Oct;39(5):514-7. doi: 10.1111/jvp.12299. Epub 2016 Feb 20.

Pharmacokinetics and pharmacodynamics of oral acetaminophen in combination with codeine in healthy Greyhound dogs

B KuKanich [1]

Affiliations + expand

PMID: 26896302 DOI: 10.1111/jvp.12299

- Acetaminophen was administered at a dose of 600 mg (14.4-23.1 mg/kg) and codeine phosphate at 90 mg (2.1-3.3 mg/kg) equivalent to 67.5 mg codeine base (1.6-2.5 mg/kg).

- The lack of antinociception in this study could be due to a true lack of antinociception, lack of model sensitivity, or specificity.

Am J Vet Res. 2020 Aug;81(8):627-634. doi: 10.2460/ajvr.81.8.627.

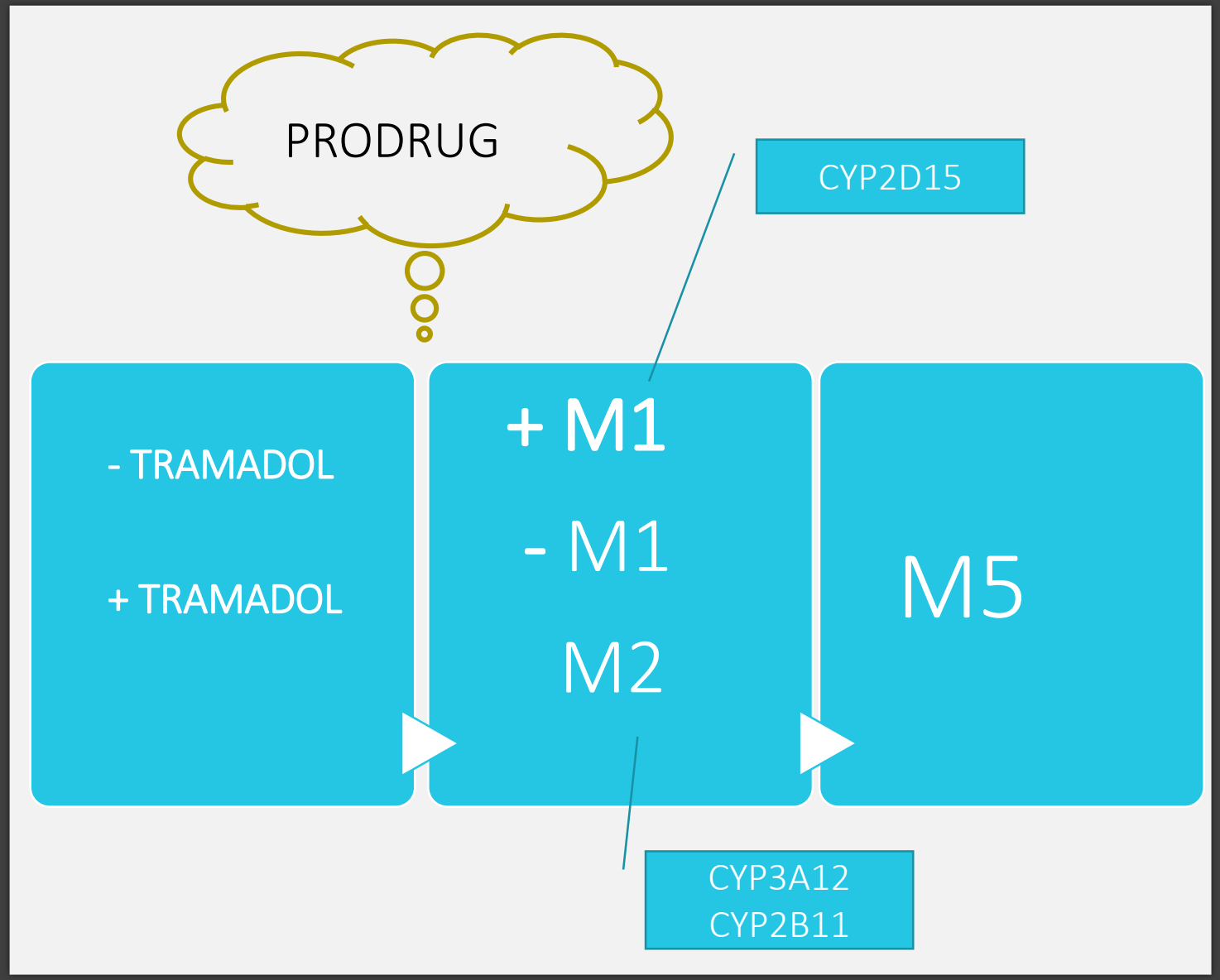
Comparison of the effects on lameness of orally administered acetaminophen–codeine and carprofen in dogs with experimentally induced synovitis

Steven C Budsberg, Stephanie A Kleine, Megan M Norton, Gabriella S Sandberg, Mark G Papich

PMID: 32701001 DOI: 10.2460/ajvr.81.8.627

- **Objective:** To compare the ability of acetaminophen-codeine (AC; 15.5 to 18.5 mg/kg and 1.6 to 2.0 mg/kg, respectively) or carprofen (4.2 to 4.5 mg/kg) administered PO to attenuate experimentally induced lameness in dogs.

- **Conclusions and clinical relevance:** Carprofen as administered was more effective than AC at attenuating SU-induced lameness in dogs.

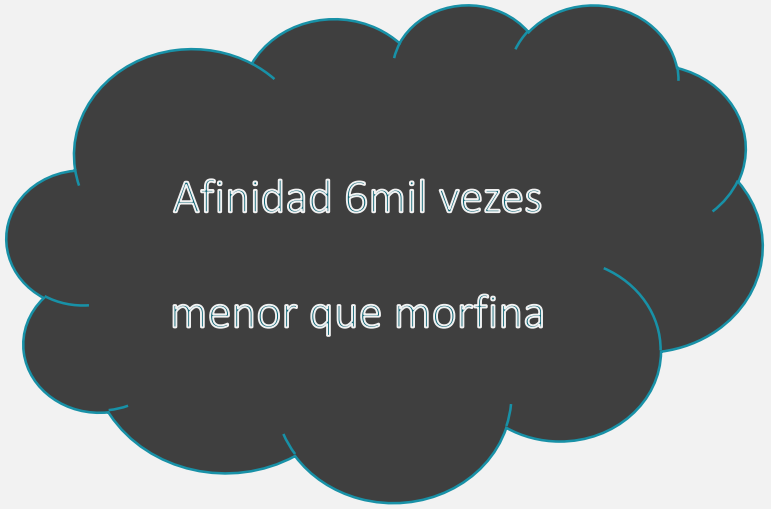

PRODRUG
CYP2D15
- TRAMADOL
+ TRAMADOL
+ M1
- M1
M2
M5
CYP3A12
CYP2B11

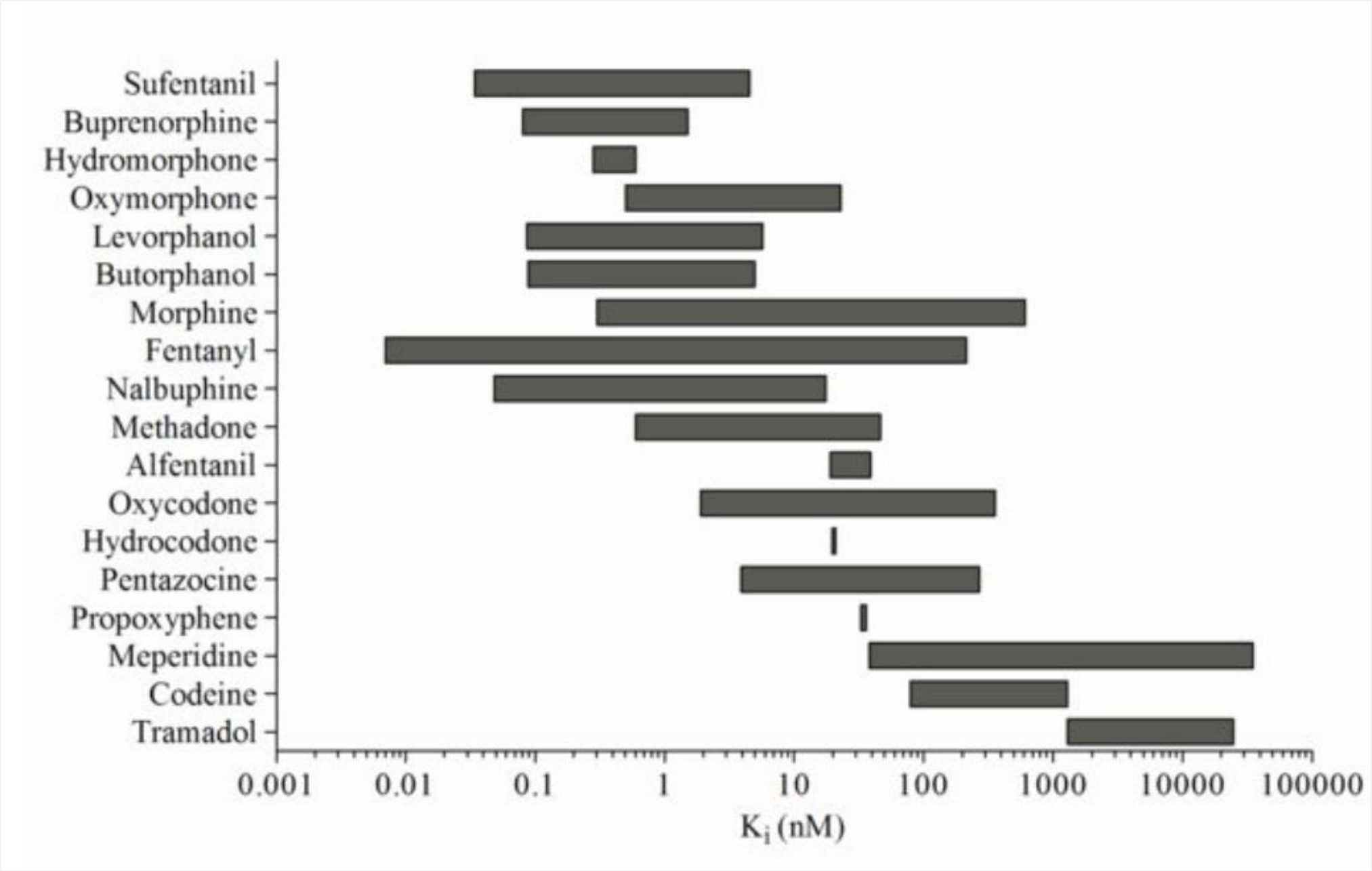
PKPD

MECANISMOS DE ACCIÓN DEL TRAMADOL

- ✓Agonista receptor μ (Hennies et al. 1988)

- ✓Inhibidor receptación monoaminas (Reimann and Hennies 1994)
  - ✓Serotonina (+) y noradrenalina (-)
- ✓Receptores acoplado a Proteina G (GPCR)
- ✓Agonista alfa2adrenérgico
- ✓Receptor Subst. P




Sufentanil
Buprenorphine
Hydromorphone
Oxymorphone
Levorphanol
Butorphanol
Morphine
Fentanyl
Nalbuphine
Methadone
Alfentanil
Oxycodone
Hydrocodone
Pentazocine
Propoxyphene
Meperidine
Codeine
Tramadol
0.001
0.01
0.1
1
10
100
1000
10000
100000
K_i (nM)

J. vet. Pharmacol. Therap. 27, 239–246, 2004. DRUGS ACTING ON THE CENTRAL AND PERIPHERAL NERVOUS SYSTEMS

Pharmacokinetics of tramadol and the metabolite *O*-desmethyltramadol in dogs

B. KUKANICH &
M. G. PAPICH

Department of Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA

KuKanich, B., Papich, M. G. Pharmacokinetics of tramadol and the metabolite *O*-desmethyltramadol in dogs. *J. vet. Pharmacol. Therap.* 27, 239–246.

Tramadol is an analgesic and antitussive agent that is metabolized to *O*-desmethyltramadol (M1), which is also active. Tramadol and M1 exert their mode of action through complex interactions between opiate, adrenergic, and serotonin receptors. The pharmacokinetics of tramadol and M1 were examined

Veterinary Anaesthesia and Analgesia 2017, 44, 309–316 http://dx.doi.org/10.1016/j.vaa.2016.02.003

RESEARCH PAPER

Influence of tramadol on acute thermal and mechanical cutaneous nociception in dogs

Alexandra F Schütter, Julia Tünsmeyer & Sabine BR Kästner
Clinic for Small Animals, University of Veterinary Medicine, Hannover Foundation, Germany

Correspondence: Alexandra Schütter, Small Animal Clinic, University of Veterinary Medicine, Hannover Foundation, Bünteweg 9, 30559 Hannover, Germany. Email: Alexandra.friederike.schuetter@tiho-hannover.de

Conclusion and clinical relevance Tramadol was metabolized marginally to O-desmethyltramadol and failed to produce clinically relevant acute antinociception. Therefore, the use of tramadol for acute nociceptive pain is questionable in dogs.

Lack of effectiveness of tramadol hydrochloride for the treatment of pain and joint dysfunction in dogs with chronic osteoarthritis

Steven C. Budsberg DVM, MS

Bryan T. Torres DVM, PhD

Stephanie A. Kleine DVM

Gabriella S. Sandberg BS

Amanda K. Berjeski BS

From the Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, Athens, GA 30602. Dr. Torres' present address is Department of Veterinary Medicine and Surgery, College of Veterinary Medicine, University of Missouri, Columbia, MO 65211.

Address correspondence to Dr. Budsberg (budsberg@uga.edu).

OBJECTIVE

To investigate the effectiveness of tramadol for treatment of osteoarthritis in dogs.

DESIGN

Randomized, blinded, placebo-controlled crossover study.

ANIMALS

40 dogs with clinical osteoarthritis of the elbow or stifle joint.

PROCEDURES

Dogs orally received 3 times/d (morning, midday, and night) for a 10-day period each of 3 identically appearing treatments (placebo; carprofen at 2.2 mg/kg [1 mg/lb], q 12 h [morning and night], with placebo at midday; or tramadol hydrochloride at 5 mg/kg [2.3 mg/lb], q 8 h) in random order, with treatment sessions separated by a minimum 7-day washout period. Vertical ground reaction forces (vertical impulse [VI] and peak vertical force [PVF]) were measured and Canine Brief Pain Inventory (CBPI) scores assigned prior to (baseline) and at the end of each treatment period. Repeated-measures ANOVA was performed to compare VI and PVF data among and within treatments, and the χ^2 test was used to compare proportions of dogs with a CBPI-defined positive response to treatment.

- Placebo
- 2,2 mg/kg Carprofeno BID
- 5 mg/kg Tramadol TID

CONCLUSIONS AND CLINICAL RELEVANCE

10 days of treatment with tramadol as administered (5 mg/kg, PO, q 8 h) provided no clinical benefit for dogs with osteoarthritis of the elbow or stifle joint. (*J Am Vet Med Assoc* 2018;252:427–432)

Randomized Controlled Trial > Can J Vet Res. 2016 Oct;80(4):323-328.

Tramadol does not enhance sedation induced by acepromazine in dogs

Eduardo R Monteiro [1], Renan B Lobo [1], Juarez S Nunes Jr [1], Julia P P Rangel [1], Flavia S Bitti [1]

Affiliations + expand

PMID: 27733788 PMCID: PMC5052885

Free PMC article

Under the conditions of this study, sedation induced by acepromazine with tramadol was similar to that of acepromazine alone.

The main adverse effects of the combination were a decrease in blood pressure and HR, without clinical significance.

Review > Br J Anaesth. 2015 Mar;114(3):384-95. doi: 10.1093/bja/aeu414. Epub 2014 Dec 16.

Effect of combining tramadol and morphine in adult surgical patients: a systematic review and meta-analysis of randomized trials

V Martinez [1], L Guichard [2], D Fletcher [3]

Affiliations + expand

PMID: 25516276 DOI: 10.1093/bja/aeu414

Free article

We found no significant clinical benefit from the combination of i.v. tramadol and morphine after surgery.

Review > Vet Clin North Am Small Anim Pract. 2019 Nov;49(6):1127-1141.
doi: 10.1016/j.cvsm.2019.07.005. Epub 2019 Aug 30.

Adjuvant Analgesics

Hélène L M Ruel [1], Paulo V Steagall [2]

Affiliations + expand

PMID: 31474414 DOI: 10.1016/j.cvsm

Box 7
Species-specific differences in the metabolism of tramadol

- Tramadol is catalyzed by CYP2D6 and CYP3A4 in humans, whereas the CYP2D15 is responsible for the production of (+)-M1 metabolites in dogs.
- Both (+)-M1 and (+)-M2 metabolites are transformed into (+)-M5 metabolite in dogs, which is the major by-product of tramadol found in plasma and urine in this species. The complex metabolism of tramadol in dogs has been recently described.[56]
- Oral, epidural, and parenteral administration of tramadol does not lead to significant concentrations of the (+)-M1 metabolites (eg, *O*-desmethyltramadol) in dogs.[57–60] On the other hand, cats produce *O*-desmethyltramadol,[61,62] and opioid-induced adverse effects may be observed.
- The formation of the *O*-desmethyltramadol is produced at much faster rate (3.9-fold) and elimination half-life is longer with higher concentrations of *O*-desmethyltramadol in cats when compared with dogs.[62,63]
- The half-life of tramadol and the (+)-M1 metabolite is considerably shorter in dogs when compared with humans (2 hours vs 7 hours, respectively). Therefore, intervals of administration would be much shorter in canine individuals than in humans (ie, 4–6 times a day),[64,65] making treatment difficult and limiting clinical use.

Box 8
The controversy involving the analgesic effects of tramadol in dogs

- Dogs produce much lower concentrations of *O*-desmethyltramadol than other species. This metabolite is responsible for the opioid analgesic effect after the administration of tramadol.
- There is usually high individual variability in resulting plasma concentrations of the metabolites of tramadol in dogs and cats.
- Tramadol has failed to provide analgesia and antinociception in dogs in several studies (see evidence of tramadol in veterinary medicine).
- Other studies have shown an analgesic effect in the treatment of canine acute pain. However, it must be considered that pain assessment was not always performed by experienced individuals or using validated pain scoring tools, and tramadol was often given in combination with another analgesic drug.
- Some studies on the use of tramadol in dogs and cats have been criticized because of poor study methodology, inappropriate dosage regimens, lack of control groups and valid models for evaluating clinical pain or antinociception, low sample size, and factors that could have biased the results.
- Beyond all the controversy, the question remains: does tramadol have a place in canine pain management when administered in combination with NSAIDs or other nonopioid analgesic techniques when compared with these drugs administered alone?[68] The serotoninergic and noradrenergic analgesic effects produced by tramadol might produce some level of clinical analgesia that investigators have not been able to address yet. Until then, the administration of tramadol should be very judicious in dogs, with clear understanding of these limitations, and the drug should never be administered alone for pain management in dogs.

Ruel and Steagall 2019

Review > Vet Clin North Am Small Anim Pract. 2019 Nov;49(6):1127-1141.
doi: 10.1016/j.cvsm.2019.07.005. Epub 2019 Aug 30.

Adjuvant Analgesics in Acute Pain Management

Hélène L M Ruel [1], Paulo V Steagall [2]

Affiliations + expand

PMID: 31474414 DOI: 10.1016/j.cvsm.2019.07.005

The use of tramadol in dogs should be judicious. Veterinarians should know the potential for analgesic failure and the clinical limitations of the drug in pain management.

VETERINARY ANAESTHESIA AND ANALGESIA

REVIEW ARTICLE | VOLUME 48, ISSUE 3, P283-296, MAY 01, 2021

Efficacy of tramadol for postoperative pain management in dogs: systematic review and meta-analysis

Pablo A. Donati • Lisa Tarragona • Juan V.A. Franco • ... Alfredo Diaz • Natali Verdier • Pablo E. Otero •

Show all authors

Published: February 09, 2021 • DOI: https://doi.org/10.1016/j.vaa.2021.01.003

- Tramadol administration probably results in a lower need for rescue analgesia *versus* no treatment or placebo, and may result in a lower need for rescue analgesia *versus* buprenorphine, codeine and nalbuphine
- However, tramadol administration may result in an increased requirement for rescue analgesia *versus* methadone and COX inhibitors
- Compared with multimodal therapy, tramadol administration may make minimal to no difference in the requirement for rescue analgesia
- The overall CoE (certainty of evidence) of the analgesic efficacy of tramadol for postoperative pain management in dogs was low or very low, and the main reasons for downgrading the evidence were risk of bias and imprecision.

Directrices de WSAVA para el reconocimiento, evaluación y tratamiento del dolor, 2022

AUTORES:

B. P. Monteiro [1,*], B. D. X. Lascelles [†], J. Murrell [‡], S. Robertson [§], P. V. M. Steagall [¶,**] and B. Wright [‖]

Ketamine	Dolor preoperatorio	Perros: 0.2-0.5 mg/kg IV (bolos) luego 2-10 µg/kg/min (CRI)	Bolus (dosis de carga antes de la cirugía) luego CRI por hasta 72h	Se usan tasas de infusión más altas durante la cirugía y luego se reducen gradualmente después de la cirugía.
		Gatos: 0.2-0.5 mg/kg IV (bolos) luego 2-10 µg/kg/min (CRI)	Bolus (dosis de carga antes de la cirugía) luego CRI por hasta 72h	Se usan tasas de infusión más altas durante la cirugía y luego se reducen gradualmente después de la cirugía; algunos gatos pueden mostrar signos de anestesia en dosis más altas
Tramadol	Dolor preoperatorio	Gatos: 2-4 mg/kg PO, IV o IM	Se utiliza para la premedicación en combinación con sedantes.	No administrar concomitantemente con otros fármacos serotoninérgicos..
	Dolor crónico	Gatos: 2-4 mg/kg PO	Cada 8 a 12h	Sabor desagradable; puede no ser una opción si la administración se vuelve estresante o forzada. No administrar concomitantemente con otros fármacos serotoninérgicos.

Directrices WSAVA, Monteiro et al., 2022.

Tramadol

Modo de acción: Tramadol es un analgésico de acción central con un mecanismo de acción dual (agonista opioide μ débil e inhibición de la recaptación de serotonina y norepinefrina), entre otros mecanismos.

Indicaciones: Para el tratamiento del dolor agudo (formulación inyectable) o crónico (formulación oral) en gatos en combinación con otros analgésicos (Evangelista et al. 2014, Monteiro et al. 2017, Guedes et al. 2018).

Diferencias entre perros y gatos: El metabolito más importante del tramadol, el O-desmetil tramadol (M1), está relacionado con los efectos agonistas μ opioides. Este metabolito se produce a tasas mucho más rápidas con una vida media más prolongada y una eliminación más lenta en gatos en comparación con perros (Pérez Jiménez *et al*. 2016). Los perros no pueden producir concentraciones significativas de O-desmetil tramadol y no se observaron efectos analgésicos en perros con OA (Budsberg *et al*. 2018) o dolor posoperatorio (Donati *et al.* 2021). Existe buena evidencia para el uso de tramadol en gatos (aunque el sabor amargo puede impedir la administración oral en algunos casos). El nivel de evidencia para el uso de tramadol en perros es bajo. Por lo tanto, el tramadol solo debe usarse como analgésico adyuvante en perros cuando la disponibilidad de medicamentos es limitada (es decir, aunque no se esperan efectos opioides en perros, podría existir un efecto analgésico potencial por la inhibición de la recaptación de serotonina y norepinefrina).

Directrices WSAVA, Monteiro et al., 2022.

RESEARCH ARTICLE

Analgesic efficacy of tramadol in cats with naturally occurring osteoarthritis

Beatriz P. Monteiro[1☯], Mary P. Klinck[1,2☯], Maxim Moreau[1,2☯], Martin Guillot[1,2], Paulo V. M. Steagall[3], Jean-Pierre Pelletier[2], Johanne Martel-Pelletier[2], Dominique Gauvin[1], Jérôme R. E. del Castillo[1], Eric Troncy[1,2]*

1 GREPAQ (Animal Pharmacology Research Group of Quebec), F... Veterinar... de Montréal, Saint-Hyacinthe, QC, Canada, **2** Osteoarthritis Research ... University of Montreal Hospital Centre, Montreal, QC, Canada, **3** Departm... Veterinary Medicine–Université de Montréal, Saint-Hyacinthe, QC, Cana...

☯ These authors contributed equally to this work.
* eric.troncy@umontreal.ca

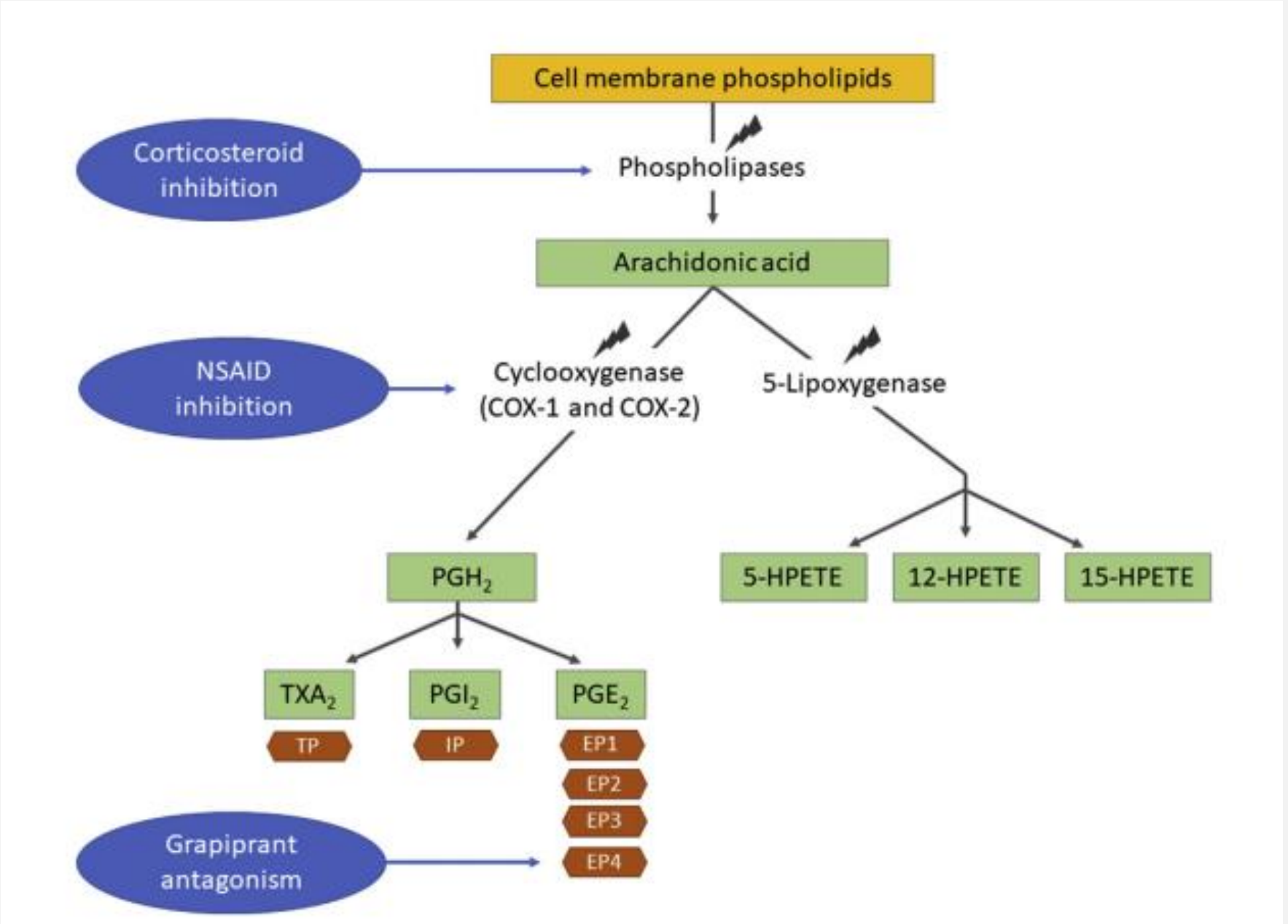
3 mg/kg BID

Treatment with tramadol increased weight-bearing, mobility and decreased central sensitisation based on PVF, NMA and RMTS in cats with naturally occurring OA.

AINEs

Antiinflamatorios

- AINES
- AIEs
- Ketamina
- Lidocaina
- Métodos Físicos
- Arnica



Monteiro, 2019

BSAVA BRITISH SMALL ANIMAL VETERINARY ASSOCIATION

CAPSULE REVIEW

Long-term use of non-steroidal anti-inflammatory drugs in cats with chronic kidney disease: from controversy to optimism

B. Monteiro,[1,*] P. V. M. Steagall,[*] B. D. X. Lascelles,[†] S. Robertson,[‡] J. C. Murrell,[§] P. W. Kronen,[¶] B. Wright[‖] and K. Yamashita[**]

Table 1. Summary of studies evaluating the renal effects after long-term administration of non-steroidal anti-inflammatory drugs (NSAIDs) in cats with chronic kidney disease (CKD)

Study type	NSAID	Population included	Treatment protocol	Main findings	References
Retrospective case–control	Meloxicam	All cats: older than 7 years old and with evidence of OA. CKD cats of IRIS stages 1, 2 and 3. • Group A: CKD (n=22) • Group B: no CKD (n=16) • Group C: CKD (n=22) • Group D: no CKD (n=16)	Groups A and B: meloxicam (0.015 to 0.033 mg/kg PO) once daily for >6 months Groups C and D: no treatment (age- and renal status-matched controls)	• No detectable deleterious effect on renal function in groups A and B • Serum creatinine concentrations increased more slowly over time in cats in group A than group C and were not different between groups B and D • No significant differences in urine concentration ability between groups	Gowan *et al.* 2011
Retrospective	Meloxicam	All cats: older than 7 years old and with evidence of OA. CKD cats of IRIS stages 1, 2 and 3. • Group A: CKD (n=47) • Group B: no CKD (n=35)	Groups A and B: meloxicam (0.01 to 0.05 mg/kg PO) once daily for >6 months	• Cats with CKD had shorter survival than cats without CKD. However, survival after diagnosis of CKD in group A was longer than previous studies • Treatment did not appear to reduce the lifespan of cats with CKD • Most common cause of death was neoplasia for both groups	Gowan *et al.* 2012
Prospective randomised placebo-controlled	Robenacoxib	All cats: median age of 15 years old (range 6 to 20) with evidence of OA. CKD cats of IRIS stages 2 and 3. • Group A: CKD (n=18) • Group B: CKD (n=22)	Group A: robenacoxib (1 to 2 mg/kg PO) once daily for 28 days Group B: placebo (lactose) once daily for 28 days	• Bodyweight was not different from baseline or between groups • Serum creatinine or urea nitrogen concentrations were not different from baseline or between groups • Incidence of adverse effects was similar in both groups	King *et al.* 2016

OA Osteoarthritis, IRIS International Renal Interest Society

RESEARCH PAPER | VOLUME 48, ISSUE 1, P7-16, JANUARY 01, 2021

Cyclooxygenases 1 and 2 inhibition and analgesic efficacy of dipyrone at different doses or meloxicam in cats after ovariohysterectomy

Marco AA. Pereira • Karina D. Campos • Lucas A. Gonçalves • ... Júlia M. Matera • Cristina OMS. Gomes • Denise T. Fantoni • Show all authors

Published: November 02, 2020 • DOI: https://doi.org/10.1016/j.vaa.2020.10.004

- D25 (dipyrone 25 mg kg^{-1} every 24 hours), D12.5 (dipyrone 12.5 mg kg^{-1} every 12 hours) and M (meloxicam 0.1 mg kg^{-1} every 24 hours).
- Dipyrone at both doses and meloxicam provided a nonselective inhibition of COX-1 and -2 activities and effective analgesia without causing significant adverse effects or laboratory tests alterations.

Randomized Controlled Trial > J Vet Emerg Crit Care (San Antonio). Jul-Aug 2015;25(4):512-20.
doi: 10.1111/vec.12336. Epub 2015 Jun 25.

Effects of dipyrone, meloxicam, or the combination on hemostasis in conscious dogs

Felipe S Zanuzzo [1], Francisco J Teixeira-Neto [2], Camila M Thomazini [3], Regina K Takahira [3], Bobbi Conner [4], Miriely S Diniz [1]

Affiliations + expand

PMID: 26112345 DOI: 10.1111/vec.12336

Conclusions: While meloxicam does not alter hemostasis by the methods evaluated, dipyrone inhibits platelet aggregation for up to 3 hours. Meloxicam-dipyrone combination causes more prolonged inhibition of platelet function than dipyrone alone. Decreased platelet aggregation induced by dipyrone and dipyrone-meloxicam does not appear to impact the viscoelastic properties of the blood clot nor increase the risk of bleeding in dogs without preexisting hemostatic disorders.

AINEs

Droga	Indicación	Especies, Dosis‡, Vía	Frecuencia
Carprofeno	Dolor quirúrgico	Perros: 4 o 4.4 mg/kg SC, IV, PO	Cada 24h hasta por 4 días
		Perros: 2 o 2.2 mg/kg SC, IV, PO	Cada 12h hasta por 4 días
		Gatos: 2 a 4 mg/kg SC, IV	Solo 1 dosis. No continuar con ninguna dosis adicional
	Dolor crónico	Perros: 4 o 4.4 mg/kg PO	Cada 24h; use la dosis efectiva más baja
		Perros: 2 o 2.2 mg/kg PO	Cada 12h; use la dosis efectiva más baja
Cimicoxib	Dolor quirúrgico	Perros: 2 mg/kg PO	Cada 24h por 4 a 8 días
	Dolor crónico	Perros: 2 mg/kg PO	Cada 24h; use la dosis efectiva más baja
Deracoxib	Dolor quirúrgico	Perros: 3–4 mg/kg PO	Cada 24h hasta por 7 días
	Dolor crónico	Perros: 1–2 mg/kg PO	Cada 24h; use la dosis efectiva más baja
Enflicoxib	Dolor por osteoartritis	Perros: dosis de carga de 8 mg/kg seguido de 4 mg/kg PO	Una vez a la semana
Firocoxib	Dolor quirúrgico	Perros: 5 mg/kg PO	Cada 24h hasta por 3 días
	Dolor crónico	Perros: 5 mg/kg PO	Cada 24h; use la dosis efectiva más baja
Flunixin meglumine	Fiebre	Perros y Gatos: 0.25 mg/kg SC	Una vez
	Procedimientos quirúrgicos y oftálmicos	Perros y Gatos: 0.25-1.0 mg/kg SC	Cada 12 a 24h for 1 o 2 tratamientos

Directrices WSAVA, Monteiro et al., 2022.

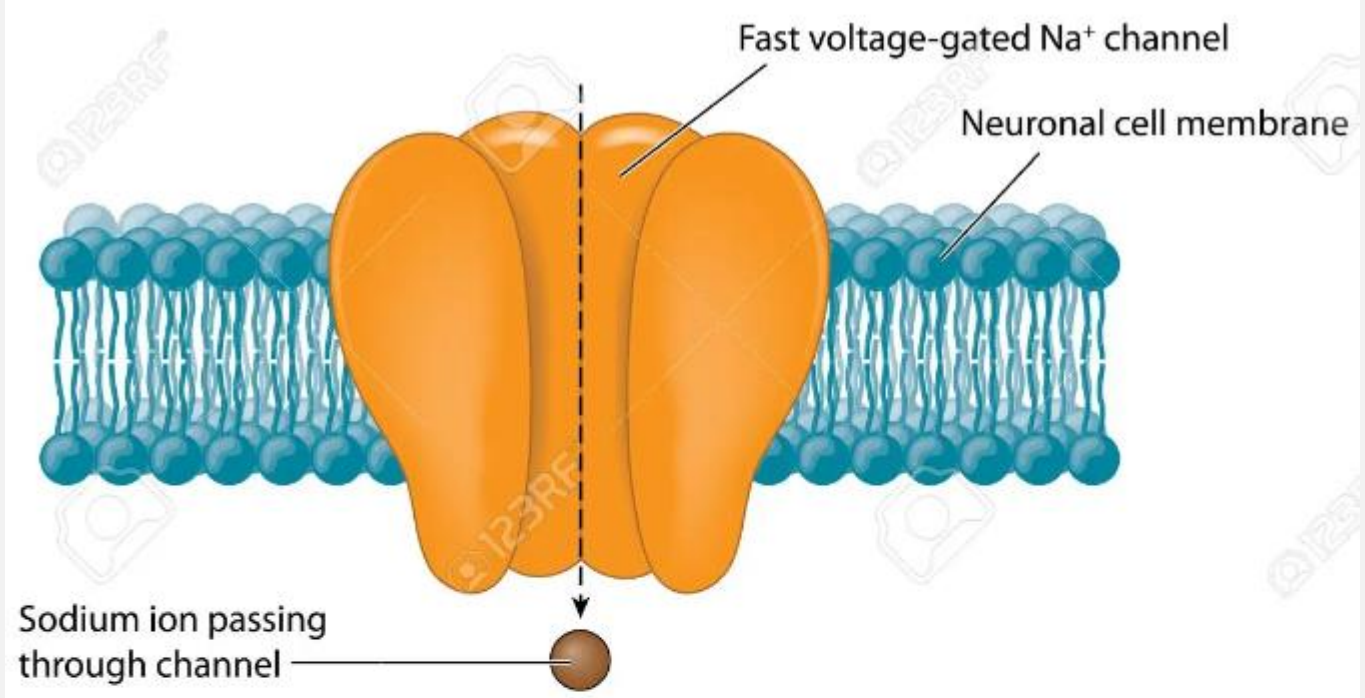
Droga	Indicación	Especies, Dosis‡, Vía	Frecuencia
Grapiprant	Dolor por osteoartritis	Perros: 2 mg/kg PO	Cada 24h
Ketoprofeno	Dolor quirúrgico y crónico	Perros: 2.0 mg/kg, IV, SC, IM	Una vez en el posoperatorio
		Perros: 1.0 mg/kg PO	Cada 24 horas hasta por 4 días
		Gatos: igual que en perros	
Mavacoxib	Dolor crónico	Perros: 2 mg/kg PO	Una vez en el día 0 y otra en el día 14. Luego, 1 vez al mes por 5 tratamientos adicionales
Meloxicam	Dolor quirúrgico/	Perros: 0.2 mg/kg IV, SC	Una vez
	dolor musculoesquelético agudo	Perros: 0.1 mg/kg PO	Cada 24h
		Gatos: 0.2-0.3 mg/kg SC	Solo 1 dosis
		Gatos: 0.05 mg/kg PO	Cada 24 horas hasta por 5 días
	Dolor crónico	Perros: 0.2 mg/kg PO	Una vez en el día 1
		Perros : 0.1 mg/kg PO	Cada 24h después del día 1; use la dosis efectiva más baja
		Gatos: 0.1 mg/kg PO	Una vez en el día 1
		Gatos: 0.05 mg/kg PO	Cada 24h después del día 1; use la dosis efectiva más baja
Metamizole (dipirona)	Dolor agudo	Perros y Catos: 25 mg/kg IV	Cada 8-12h
Paracetamol (acetaminofeno)	Dolor quirúrgico/agudo o crónico	SOLO PERROS: 10-15 mg/kg PO	Cada 8-12h. ***NO USAR EN GATOS***
		SOLO PERROS: 10 mg/kg IV durante 15 min	Cada 8-12h. ***NO USAR EN GATOS***

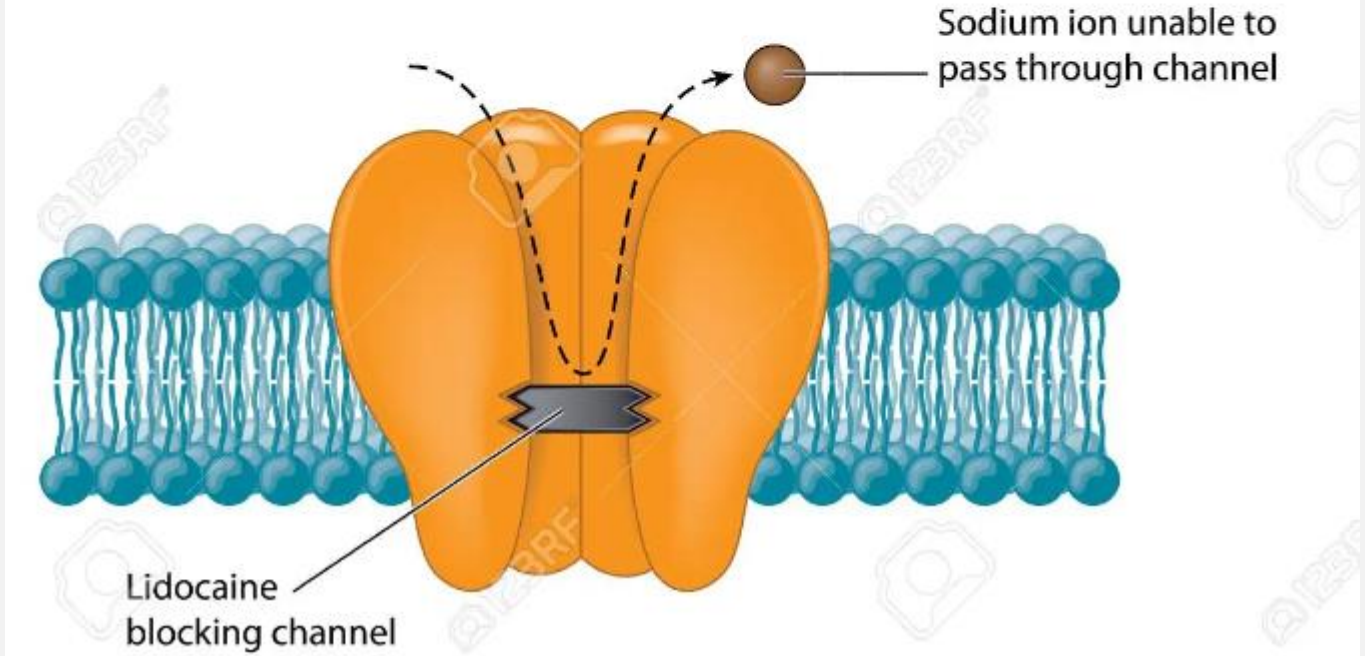
Directrices WSAVA, Monteiro et al., 2022.

AINEs

Droga	Indicación	Especies, Dosis‡, Vía	Frecuencia
Paracetamol (acetaminofeno)	Dolor quirúrgico/agudo o crónico	SOLO PERROS: 10-15 mg/kg PO	Cada 8-12h. ***NO USAR EN GATOS***
		SOLO PERROS: 10 mg/kg IV durante 15 min	Cada 8-12h. ***NO USAR EN GATOS***
Piroxicam	Inflamación del tracto urinario bajo	Perros: 0.3 mg/kg PO	Cada 24h para 2 tratamientos, luego, cada 48h
Robenacoxib	Dolor quirúrgico/ dolor musculoesquelético agudo	Perros: 2 mg/kg SC	Cada 24h hasta por 3 días
		Perros: 1-2 mg/kg PO	Cada 24h
		Gatos: 2 mg/kg SC	Cada 24h hasta por 3 días
		Gatos: 1-2 mg/kg PO	Cada 24h
	Dolor crónico	Perros: 1 mg/kg PO	Cada 24h; use la dosis efectiva más baja
		Gatos: 1 mg/kg PO	Cada 24h; use la dosis efectiva más baja
Ácido tolfenámico	Dolor agudo y crónico	Perros: 4 mg/kg SC, IM, PO	Cada 24h por 3 a 5 days. Repetir 1 vez por semana
		Gatos: igual que en perros	
	Dolor crónico	Perros: 5 mg/kg PO	Cada 24h; use la dosis efectiva más baja

Directrices WSAVA, Monteiro et al., 2022.





Anestésicos Locais

Otras opciones en la prevención y tratamiento del dolor: ANESTÉSICOS LOCALES

- Lidocaina, bupivacaina y ropivacaina
  - Interrumpen la conducción de nervios periféricos
    - Previenen la sensibilización central
  - Bloqueos
  - Epidural
  - Infiltrativa
  - Uso pré/trans/pós-operatorio

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EXPAREL, a liposome injection of bupivacaine, reduces the need for postsurgical opioids and devices

8 16 24 32 40 48 56 64 72 HOURS

EXPAREL (bupivacaine liposome injectable suspension)

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266 mg/20 mL (13.3 mg/mL)

For Infiltration Only. Not for Any Other Route of Administration

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9

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WOUND SOAKER CATHETERS

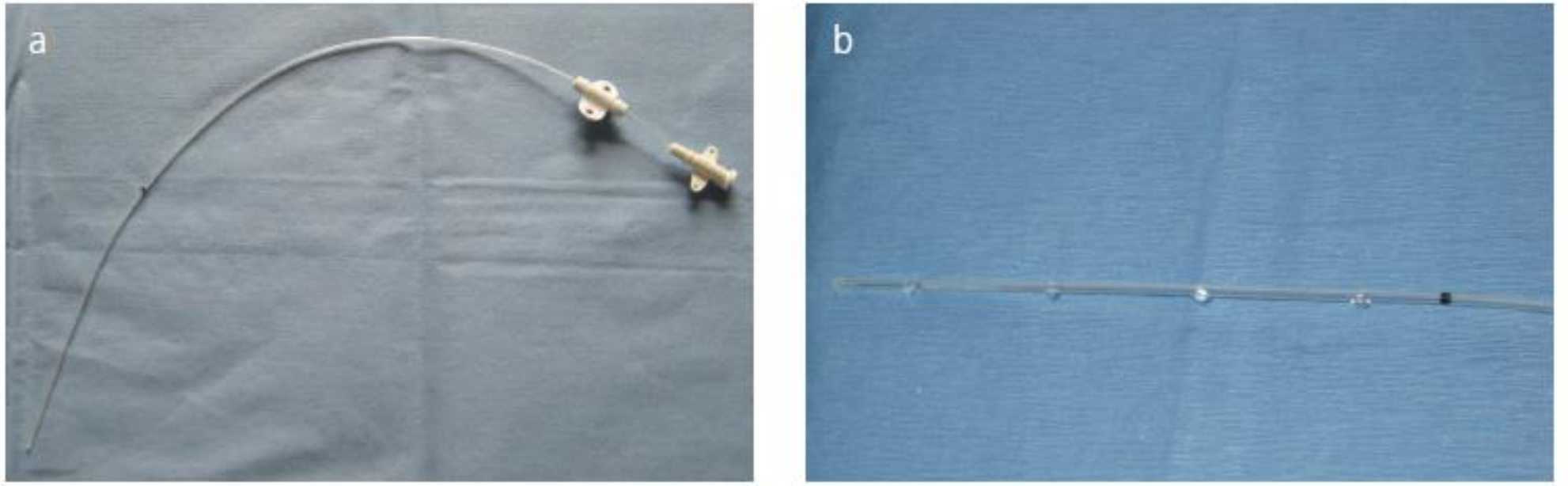


Fig 1: (a) A veterinary wound diffusion catheter, in this case a Mila diffusion catheter. (b) Dispersal of local anaesthetic droplets during drug injection

- *Dogs – lidocaine* continuous infusion rates of 2.0 mg/kg/hour, and the dilution of lidocaine (from 1 – 2%), adjusted so that the following approximate volumes are used:
  - 30 – 40 kg, limb amputation wound: 3 - 4 mls/hour
  - 5 – 25 kg, limb amputation wound: 1 – 3 mls/hour
  - 30 – 40 kg, thoracotomy wound: 2 – 3 mls/hour
  - 5 – 25 kg, thoracotomy wound: 0.75 – 2 mls/hour
- *Dogs – bupivacaine* diluted to 0.25% with saline, intermittent injection every 4 – 6 hours:
  - 30 – 40 kg, limb amputation wound: 4 – 8 mls/dose
  - 5 – 25 kg, limb amputation wound: 1.5 – 6 mls/dose
  - 30 – 40 kg, thoracotomy wound: 2 – 3.5 mls/dose
  - 5 – 25 kg, thoracotomy wound: 0.75 – 2 mls/dose
- *Cats - intermittent bupivacaine* diluted to 0.25% with injection of 0.5 mg/kg every 4 – 6 hours.

Table 4
Local anesthetics used for the treatment of acute pain in the dog and cat

Drug	Onset	Duration	Dosage in the Dog	Dosage in the Cat
Lidocaine (Lidocaine)	5–10 min	1–3 h	2 mg/kg IV 0.025–0.05 mg/kg/min IV CRI 4.4 mg/kg epidural Maximum recommended dose: 8 mg/kg	Constant rate infusion not recommended in the cat[52] 4.4 mg/kg epidural Maximum recommended dose: 6 mg/kg
Mepivacaine (Carbocaine V)	3–10 min	2–4 h	Maximum recommended dose: 4.5 mg/kg	Maximum recommended dose: 3 mg/kg
Bupivacaine (Marcaine)	10–20 min	3–6 h	1–1.5 mg/kg epidural Maximum recommended dose: 2 mg/kg	1 mg/kg epidural Maximum recommended dose: 1 mg/kg
Etidocaine (Duranest)	3–5 min	5–10 h	Maximum recommended dose: 8 mg/kg	Maximum recommended dose: 4 mg/kg
Ropivicaine (Naropin)	15–20 min	1.5–6 h	0.5 mg/kg epidural Maximum recommended dose: 3 mg/kg	0.5 mg/kg epidural Maximum recommended dose: 1.5 mg/kg

Berry, 2015

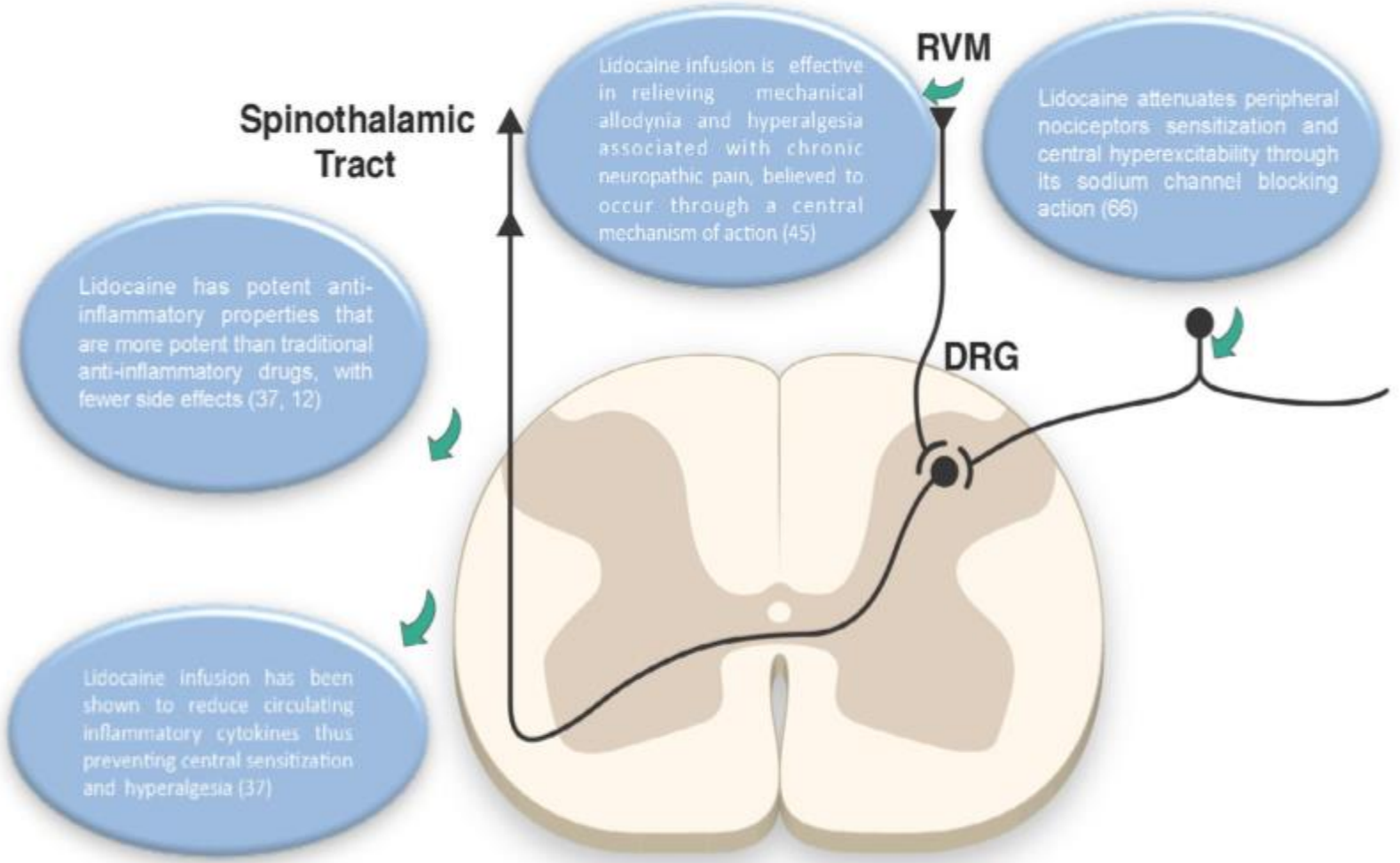
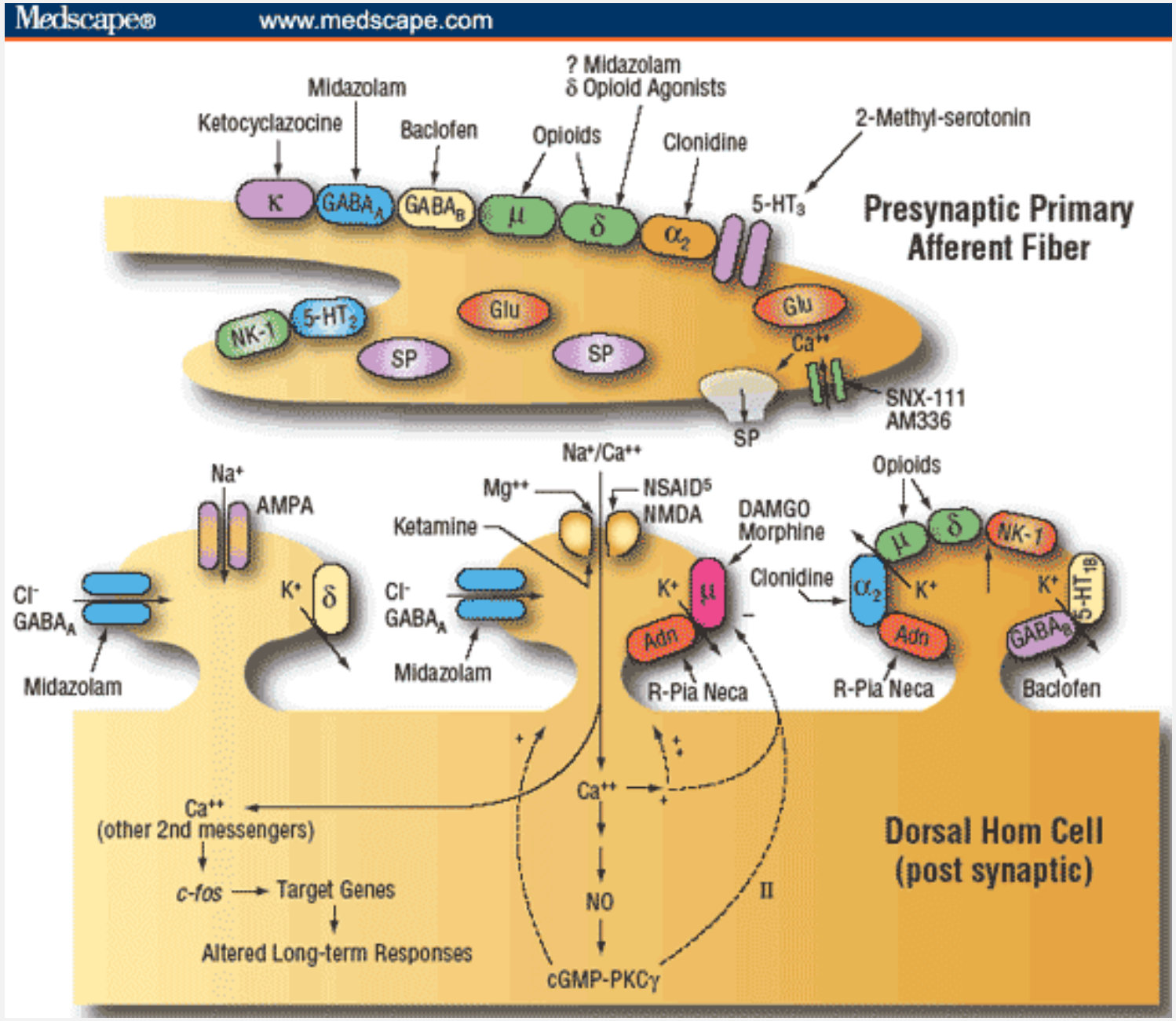
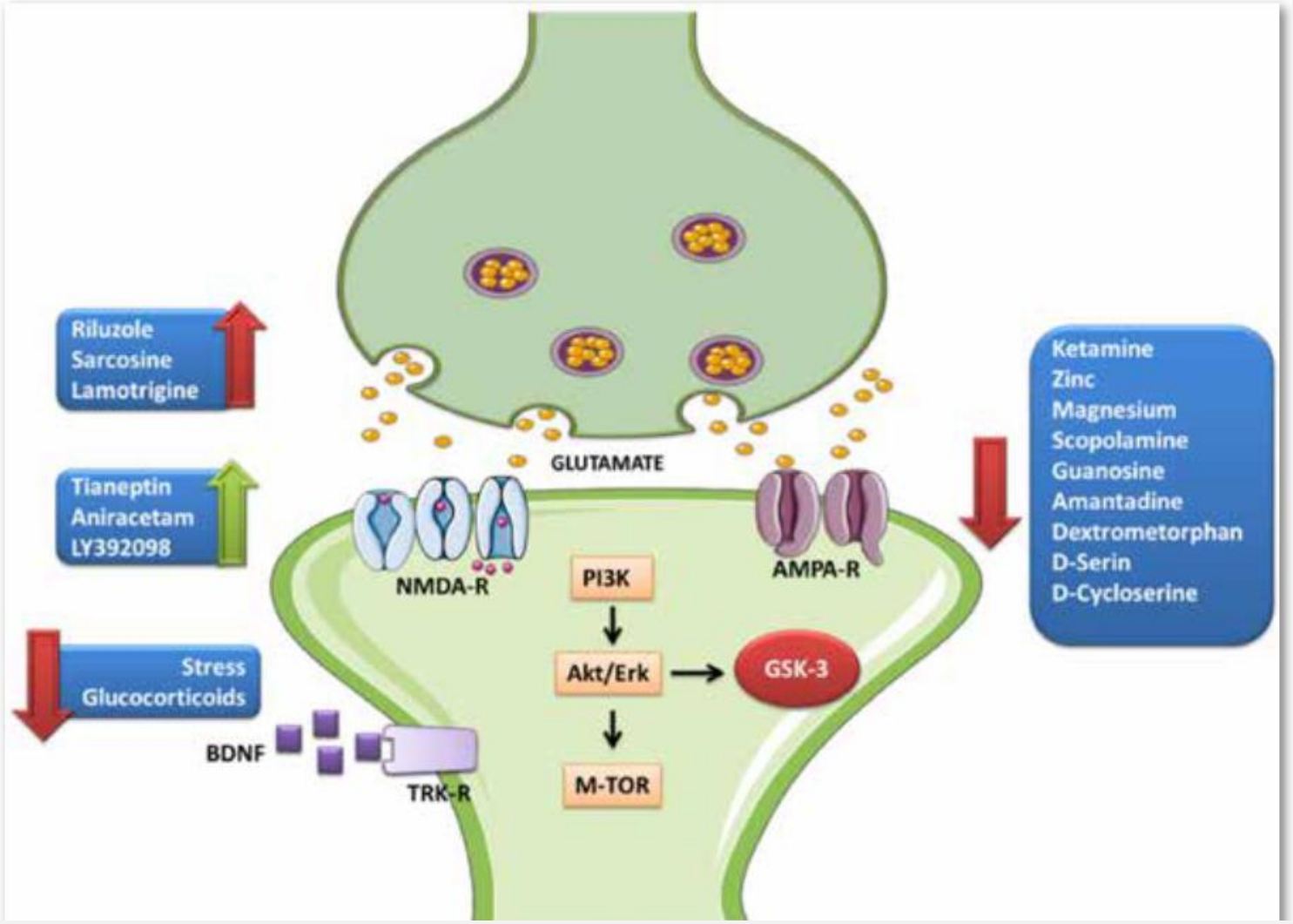


Figure 2.
Role of lidocaine in prevention of central sensitization.



Alfa2agonistas


Riluzole
Sarcosine
Lamotrigine
Tianeptin
Aniracetam
LY392098
Stress
Glucocorticoids
BDNF
TRK-R
GLUTAMATE
NMDA-R
AMPA-R
PI3K
Akt/Erk
GSK-3
M-TOR
Ketamine
Zinc
Magnesium
Scopolamine
Guanosine
Amantadine
Dextrometorphan
D-Serin
D-Cycloserine

Ketamina

Ketamina

- Antagonista de receptor NMDA

- Dosis subanestésicas producen analgesia
  - Usada para inducción de anestesia (0,5 mg.kg)
  - Infusión en trans y pos-operatorio (2-30 µg/kg/min)
  - Dor irruptiva oncológica, dor neuropática: 2-10 µg/kg/min

Table 1. Summary of Pharmacological Actions of Ketamine

Action	Potency	Reference
NMDA receptor block	Ki 0.4–46 μM	Fisher et al.[5]
	IC_{50} 1.6–6.2 μM	Chiz et al.[11]
Opioid receptors (ORs)		Smith et al.[24]
μ-ORs	Ki 27 μM	
δ-ORs	Ki 101 μM	
κ-ORs	Ki 85 μM	
Block of monoamine uptake		
Noradrenaline transporter	Ki 67 μM	Kohrs and Durieux[23]
Dopamine transporter	Ki 63 μM	
Serotonin transporter	Ki 162 μM	Nishimura et al.[25]
Receptors actions		
Block of muscarinic, nicotinic cholinergic receptors	IC_{50} 10–80 μM	Kohrs and Durieux[23]
Receptor binding		
Dopamine D_2	Ki 0.5 μM	
Serotonin 5-HT_2	Ki 15 μM	Kapur and Seeman[26]
Ion channels		
Block of Na^+, Ca^{2+} channels	Ki >50 μM or >100 μM	Eide et al.[20] Hirota and Lambert[21]
Block of Na^+, voltage-gated K^+ channels	IC_{50} 130–270 μM	Meller[22]
Block of Ca^{2+}-activated K^+ channels	100 μM	Schnoebel et al.[27] Hayashi et al.[28]
Functional effects		
Decreased activation, migration of microglia	100 μM	Hayashi et al.[28]
Inhibition of production of inflammatory mediators	≥ 2 μM, ≥ 50 μM, ≥100 μM depending on mediator and test system	DeKoch and Loix[41] See also Liu et al.[40]

Ki refers to binding studies, IC_{50} to functional effects. See references for further details.

STEAGALL, 2020

Box 5
The clinical use of ketamine infusion in cats

- Ketamine has been used as an adjunctive analgesic agent within multimodal analgesia protocols in 3 cats with major injury.[57] The drug should never be used as a stand-alone analgesic.
- Ketamine is given by the intravenous route of administration with appropriate pain assessment and monitoring during hospitalization.
- Administer an intravenous loading dose (0.15–0.7 mg/kg) followed by a CRI (2–10 μg/kg/min). The administration of a single bolus without an infusion is uncommon due to the rapid clearance of ketamine.
- The author uses ketamine in cats undergoing major surgery or after major trauma to prevent or treat hyperalgesia and allodynia commonly associated with central sensitization. These cats are often transferred to an intermediate or intensive care unit after surgery where the infusion is continued for 24 to 72 hours postoperatively.[55]
- The administration of intravenous remifentanil and ketamine (bolus of 0.5 mg/kg followed by 30 μg/kg/min infusions) provided greater reductions in isoflurane requirements when compared with a control group or remifentanil alone after ovariohysterectomy in cats.[58]

Data from Refs.[55,57,58]

Box 3
A practical approach to ketamine infusion in clinical practice.

- 60 mg of ketamine (0.6 mL of ketamine 10%) can be mixed in 0.5 L of a crystalloid solution. The patient will receive an infusion of 10 μg/kg/min if the infusion is administered at 5 mL/kg/h in the intraoperative period.
- Concentrations and doses should be adjusted in the perioperative period according to fluid therapy rates.

Box 4
The most important features of ketamine and its clinical use

- Ketamine is an NMDA antagonist used for the prevention and treatment of maladaptive pain.
- Dosage regimens usually consist of administering a loading dose (0.15–0.7 mg/kg), followed by variable infusion rates (2–10 μg/kg/min).
- Ketamine is often administered in the perioperative period by the intravenous route, and in combination with opioids, local anesthetic blocks, and nonsteroidal antiinflammatory drugs (ie, multimodal analgesia).

Ruel & Steagall, 2019

Pain Medicine

Section Editor: **Spencer S. Liu**

REVIEW ARTICLE

Topical and Peripheral Ketamine as an Analgesic

Jana Sawynok, PhD

www.anesthesia-analgesia.org July 2014 • Volume 119 • Number 1

Br J Psychiatry. 2016 Feb;208(2):108-13. doi: 10.1192/bjp.bp.115.165498.

Oral ketamine for the treatment of pain and treatment-resistant depression†.

Schoevers RA[1], Chaves TV[2], Balukova SM[2], aan het Rot M[2], Kortekaas R[2].

Randomized Controlled Trial

Int J Clin Pract. 2021 Dec;75(12):e15010. doi: 10.1111/ijcp.15010. Epub 2021 Nov 29.

The effect of low-dose ketamine on postoperative quality of recovery in patients undergoing breast cancer surgery: A randomised, placebo-controlled trial

Zijian Zhao [1 2], Qiqi Xu [2 3], Yao Chen [1], Chen Liu [1], Fangfang Zhang [1], Yuan Han [4], Junli Cao [1]

Affiliations + expand

PMID: 34807494 DOI: 10.1111/ijcp.15010

Pain Res Manag. 2021 Nov 17;2021:3290289. doi: 10.1155/2021/3290289. eCollection 2021.

Prevention of Acute Postoperative Pain in Breast Cancer: A Comparison between Opioids versus Ketamine in the Intraoperatory Analgesia

Mirian López [1], María Luz Padilla [1], Blas García [1], Javier Orozco [1], Ana María Rodilla [2]

Affiliations + expand

PMID: 34840635 PMCID: PMC8612786 DOI: 10.1155/2021/3290289

Free PMC article

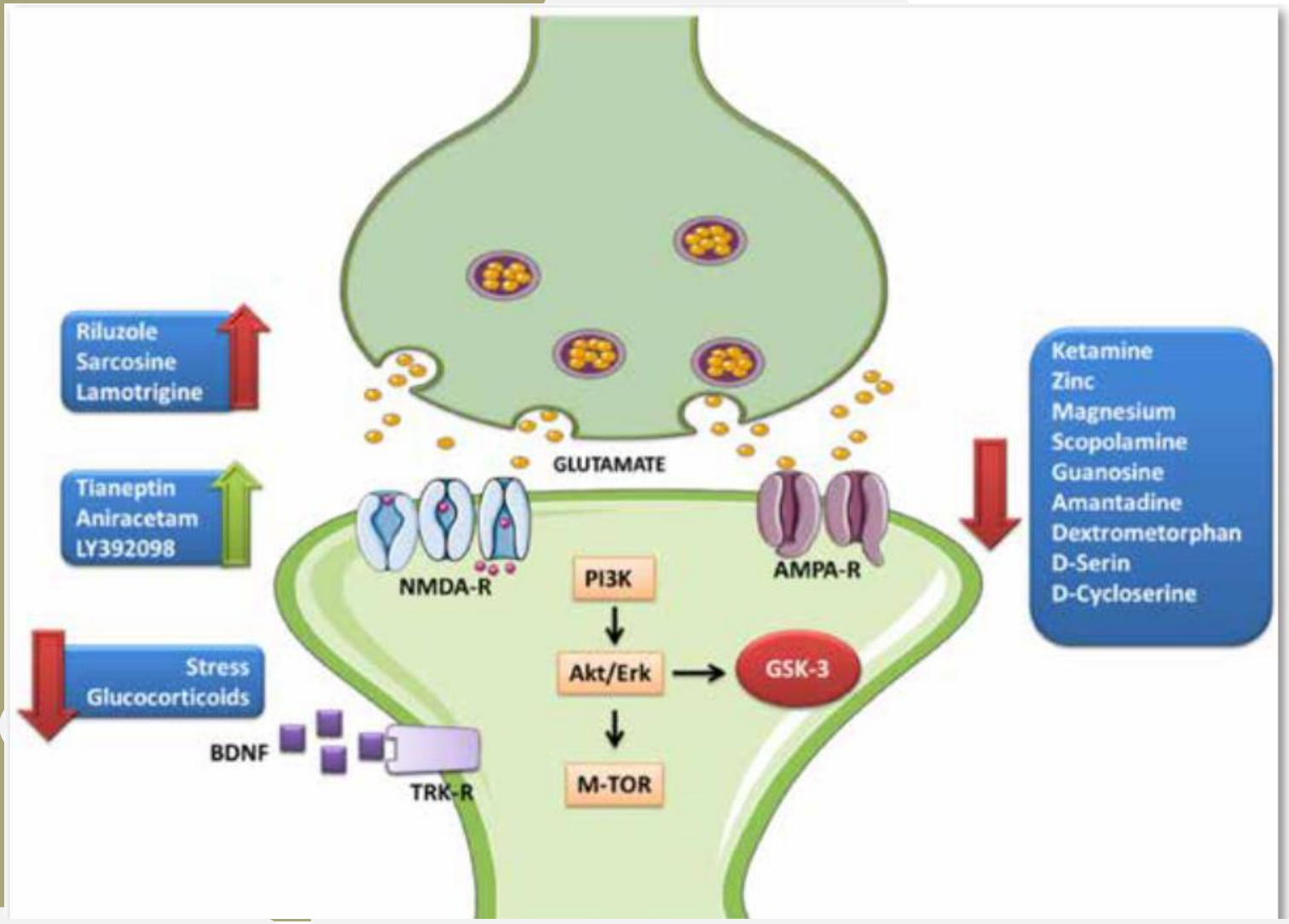
Pediatr Blood Cancer. 2022 Sep;69(9):e29693. doi: 10.1002/pbc.29693. Epub 2022 Apr 4.

Low-dose ketamine infusions reduce opioid use in pediatric and young adult oncology patients

Doralina L Anghelescu [1], Stephanie Ryan [1 2], Diana Wu [1], Kyle J Morgan [1], Tushar Patni [1], Yimei Li [1]

Affiliations + expand

PMID: 35373875 PMCID: PMC9329174 (available on 2023-09-01) DOI: 10.1002/pbc.29693


Riluzole
Sarcosine
Lamotrigine
Tianeptin
Aniracetam
LY392098
Stress
Glucocorticoids
Ketamine
Zinc
Magnesium
Scopolamine
Guanosine
Amantadine
Dextrometorphan
D-Serin
D-Cycloserine
GLUTAMATE
NMDA-R
AMPA-R
PI3K
Akt/Erk
GSK-3
M-TOR
BDNF
TRK-R

Amantadina

Comparative Study > J Neurosci. 2005 Mar 30;25(13):3312-22.
doi: 10.1523/JNEUROSCI.4262-04.2005.

Amantadine inhibits NMDA receptors by accelerating channel closure during channel block

Thomas A Blanpied [1], Richard J Clarke, Jon W Johnson

Affiliations + expand

PMID: 15800186 PMCID: PMC6724906 DOI: 10.1523/JNEUROSCI.4262-04.2005

Free PMC article

J Vet Intern Med 2008;22:53–59

Amantadine in a Multimodal Analgesic Regimen for Alleviation of Refractory Osteoarthritis Pain in Dogs

B.D.X. Lascelles, J.S. Gaynor, E.S. Smith, S.C. Roe, D.J. Marcellin-Little, G. Davidson, E. Boland, and J. Carr

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) do not always provide sufficient pain relief in dogs with osteoarthritis (OA).

Hypothesis: The use of amantadine in addition to NSAID therapy will provide improved pain relief when compared with the use of nonsteroidal analgesics alone in naturally occurring OA in dogs.

Animals: Thirty-one client-owned dogs with pelvic limb lameness despite the administration of an NSAID.

Methods: The study was randomized, blinded, and placebo controlled with parallel groups (days 21–42). On day 0, analgesic medications were discontinued. On day 7, all dogs received meloxicam for 5 weeks. On day 21, all dogs received amantadine (3–5 mg/kg once daily per os) or placebo for 21 days, in addition to receiving meloxicam. Assessments were performed before the study and on days 7, 21, and 42. Primary outcome measures were blinded owner assessments of activity using client-specific outcome measures (CSOM) on days 0, 7, 21, and 42. Data were analyzed by a mixed model approach.

Results: For CSOM activity, there was a significant time by treatment effect ($P = .009$). On the basis of the planned post hoc *t*-tests of postrandomization means, there was a significant difference between treatment groups on day 42 ($P = .030$), with the amantadine group being more active.

Conclusions and Clinical Importance: In dogs with osteoarthritic pain refractory to an NSAID, physical activity is improved by the addition of amantadine. Amantadine might be a useful adjunct therapy for the clinical management of canine osteoarthritic pain.

Key words: Dog; Nonsteroidal anti-inflammatory; Owner; Pain; Subjective assessment.

J. vet. Pharmacol. Therap. **38**, 305–308. doi: 10.1111/jvp.12190.

Pharmacokinetics of oral amantadine in greyhound dogs

C. NORKUS*
D. RANKIN*
M. WARNER† &
B. KUKANICH†

- $t_{1/2\beta}$: 4,96 (4,11 – 6,59) horas

J Vet Pharmacol Ther. 2011 Dec;34(6):599-604. doi: 10.1111/j.1365-2885.2011.01278.x. Epub 2011 Feb 16.

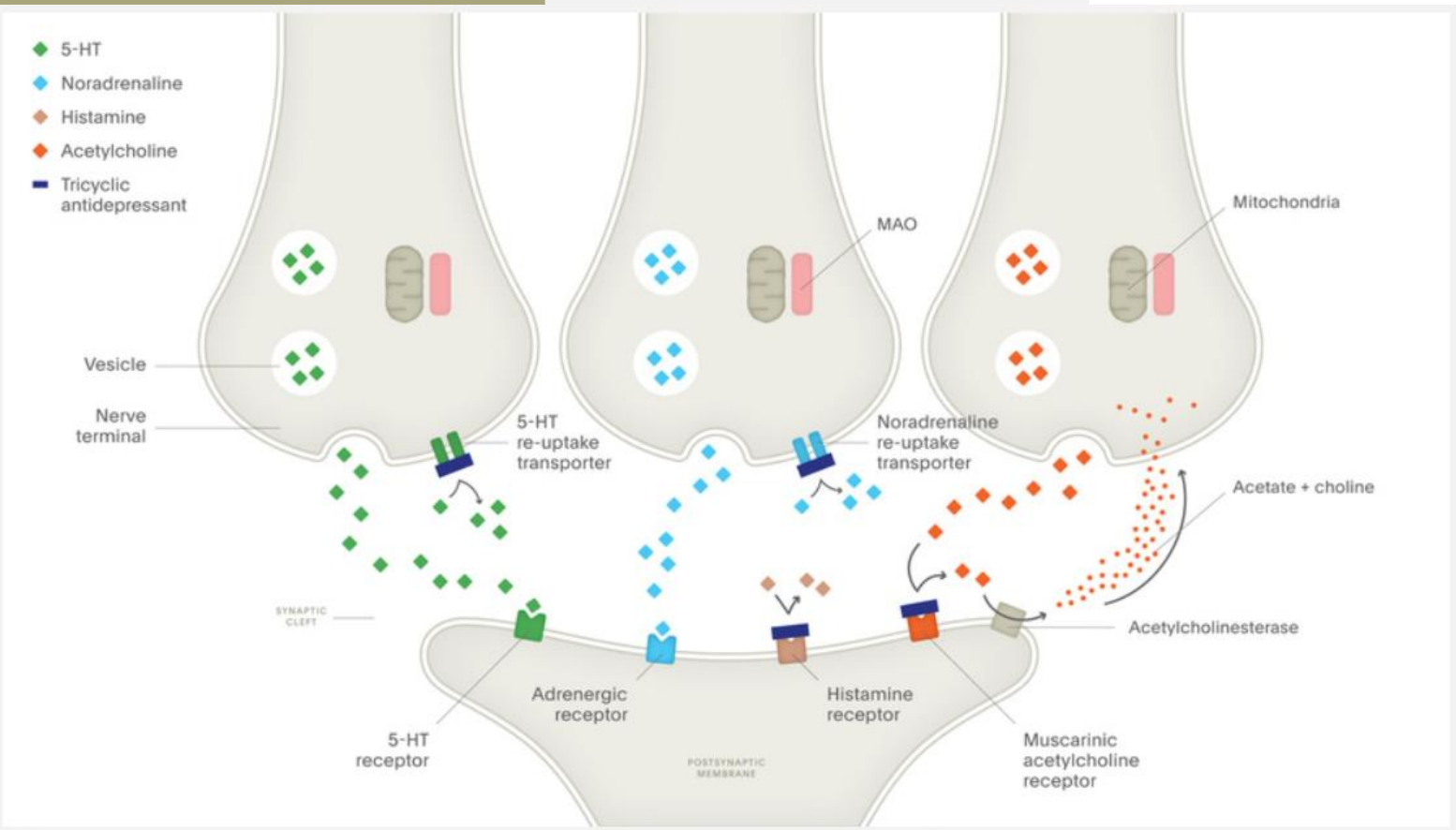
Pharmacokinetics of amantadine in cats.

Siao KT[1], Pypendop BH, Stanley SD, Ilkiw JE.

- $t_{1/2\beta}$: 324 ± 41 (277–381) min

Droga	Indicación	Especie, Dosis, Vía	Frecuencia	Comentarios
Amantadina	Dolor crónico	Perros y Gatos: 2-5 mg/kg PO	Cada 12-24h	Eficaz en perros con OA refractaria al tratamiento. Administrar con AINE u otros analgésicos. Se han informado dosis de hasta 14 mg/kg en combinación con meloxicam en un perro con dolor neuropático (Madden et al., 2014)

Directrices WSAVA, Monteiro et al., 2022.



Amitriptilina

Antidepresivos tricíclicos

- Primera línea en el tratamiento de dolor neuropático
- Inhibe recaptación de serotonina y norepinefrina

- Antagonista NMDA

- Bloquea canales de Na

Antidepressivos triciclicos

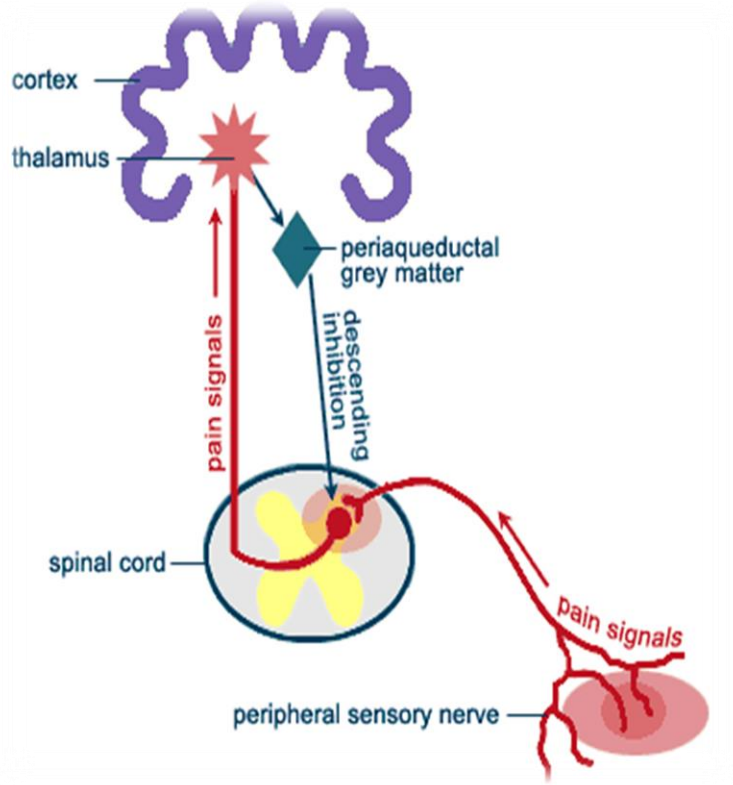
- Efectos antiinflamatórios
- Efeitos adversos?
  - Electrofisiologia cardíaca
  - Visão turbia
  - Sedación

Amitriptilina

Antidepressants for neuropathic pain.

Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005454.

Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005454.



AUTHORS' CONCLUSIONS: Antidepressants are effective for a variety of neuropathic pains.

The best evidence available is for amitriptyline.

Pharmacokinetics of intravenous and oral amitriptyline and its active metabolite nortriptyline in Greyhound dogs

Veterinary Anaesthesia and Analgesia, 2015

Christopher Norkus*, David Rankin* & Butch KuKanich†

- $t_{1/2\beta}$: 4,33 horas
- Biodisponibilidad: 60%

J Vet Pharmacol Ther. 2015 May 18. doi: 10.1111/jvp.12237. [Epub ahead of print]

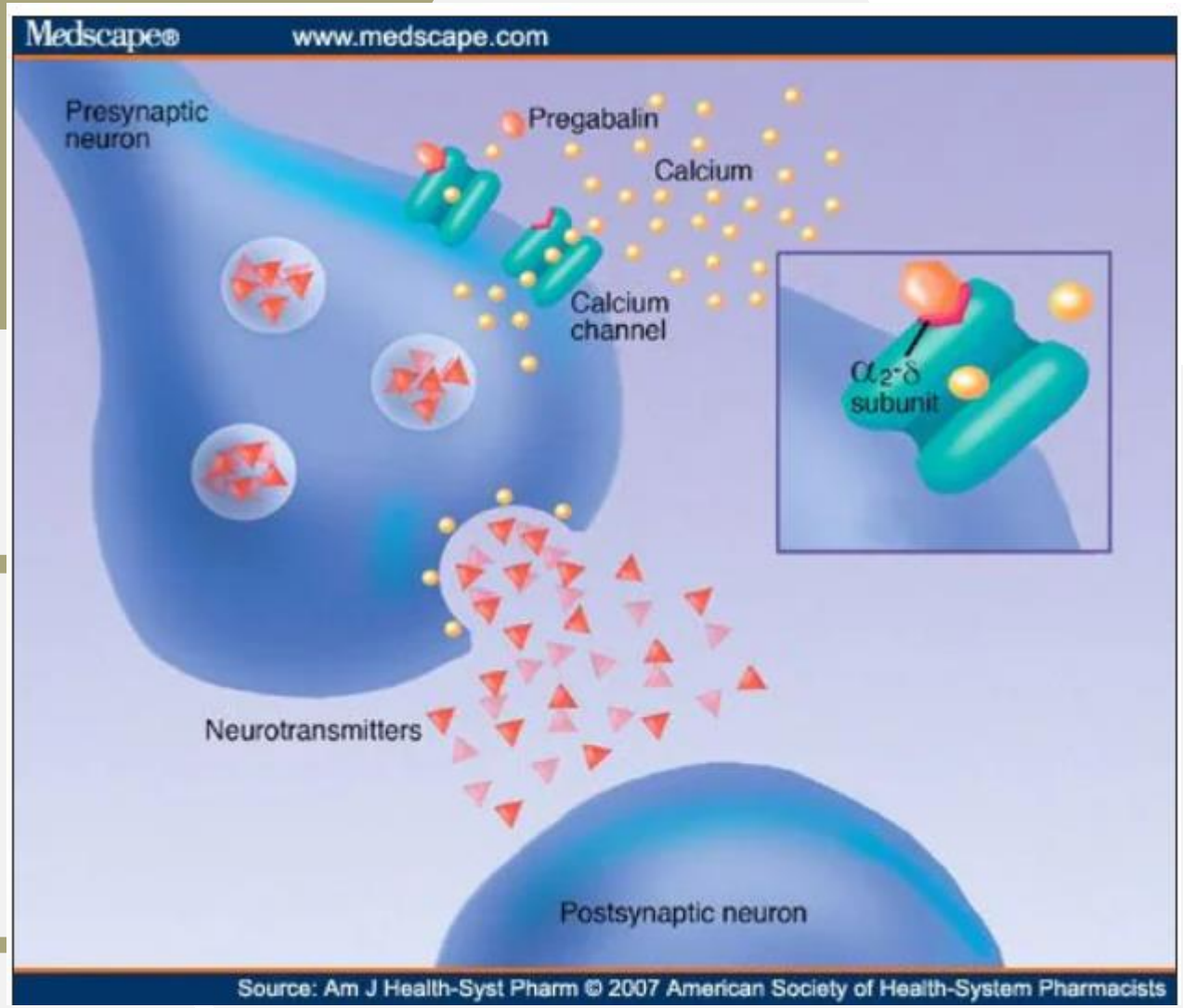
Evaluation of the pharmacokinetics of oral amitriptyline and its active metabolite nortriptyline in fed and fasted Greyhound dogs.

Norkus C[1], Rankin D[1], KuKanich B[2].

- Biodisponibilidad:
  - Perros en ayuno 69 a 91% sin ayuno

Amitriptilina	Dolor crónico	Perros: 1-4 mg/kg	Cada 12-24h	No administrar concomitantemente con otros fármacos serotoninérgicos.
		Gatos: 2.5-12.5 mg total	Cada 12-24h	Sabor desagradable; puede no ser una opción si la administración se vuelve estresante o forzada. No administrar concomitantemente con otros fármacos serotoninérgicos.

Directrices WSAVA, Monteiro et al., 2022.



Gabapentinoides

Gabapentin as an adjuvant for postoperative pain management in dogs undergoing mastectomy

J. Vet. Med. Sci. 77(8): 1011–1015, 2015

Giulianne Carla CROCIOLLI[1)], Renata Navarro CASSU[1)]*, Rafael Cabral BARBERO[1)], Thalita Leone A ROCHA[1)], Denis Robson GOMES[1)] and Gabriel Montoro NICÁCIO[1)]

10 mg/kg gabapentina

2hs antes y a cada 12 hs por 3 días

Gabapentin as an adjuvant for postoperative pain management in dogs undergoing mastectomy

J. Vet. Med. Sci. 77(8): 1011–1015, 2015

Giulianne Carla CROCIOLLI[1)], Renata Navarro CASSU[1)]*, Rafael Cabral BARBERO[1)], Thalita Leone A ROCHA[1)], Denis Robson GOMES[1)] and Gabriel Montoro NICÁCIO[1)]

Groups	Postoperative time (hr)								
	0.5	1	2	4	8	12	18	24	32
Gabapentin /Dogs									
No. 1	0	0	0	0	0	0	0	0	0
No. 2	0	0	0	0	0	1	0	0	0
No. 3	0	0	0	0	0	0	0	0	0
No. 4	0	0	0	0	0	0	0	1	0
No. 5	0	0	0	0	0	0	0	0	0
No. 6	0	0	0	0	0	0	0	0	0
No. 7	0	0	0	1	0	0	1	0	0
No. 8	0	1	0	0	0	0	1	0	0
No. 9	0	0	1	0	0	0	0	1	0
No. 10	0	0	1				0	0	0
Total n° of morphine doses									

9 rescates

Gabapentin as an adjuvant for postoperative pain management in dogs undergoing mastectomy

J. Vet. Med. Sci. 77(8): 1011–1015, 2015

Giulianne Carla CROCIOLLI[1)], Renata Navarro CASSU[1)]*, Rafael Cabral BARBERO[1)], Thalita Leone A ROCHA[1)], Denis Robson GOMES[1)] and Gabriel Montoro NICÁCIO[1)]

Groups	Postoperative time (hr)								
	0.5	1	2	4	8	12	18	24	32
Placebo/Dogs									
No. 1	0	0	1	0	0	0	0	0	0
No. 2	0	0	0	0	1	0	0	1	0
No. 3	0	0	0	0	0	0	0	0	0
No. 4	0	0	0	0	0	0	0	0	0
No. 5	0	0	0	0	1	1	0	0	0
No. 6	0	1	0	0	1	1	0	0	0
No. 7	0	0	0	0	1	0	0	1	0
No. 8	0	0	0	0	1	0	0	0	0
No. 9	0	0	1	0	0	0	1	0	0
No. 10	0	1						0	0
Total n° of morphine doses									

16 rescates*

J Feline Med Surg. 2018 Aug;20(8):741-748. doi: 10.1177/1098612X17730173. Epub 2017 Sep 18.

Analgesic effects of gabapentin and buprenorphine in cats undergoing ovariohysterectomy using two pain-scoring systems: a randomized clinical trial

Paulo V Steagall [1,2], Javier Benito [1], Beatriz P Monteiro [2,3], Graeme M Doodnaught [1,2], Guy Beauchamp [4], Marina C Evangelista [1,2]

Affiliations + expand

PMID: 28920534 DOI: 10.1177/1098612X17730173

Postoperative analgesia produced by gabapentin (using 50 mg, PO, at 12 and 1 hour before surgery) and buprenorphine was similar to combining meloxicam with buprenorphine in cats undergoing ovariohysterectomy.[31]

Box 2
The most important features of gabapentin for acute pain management in companion animals

- Gabapentin should be administered every 6 to 8 hours orally to sustain plasma concentrations of the drug. Studies using 12-hour intervals of administration showed that gabapentin had poor response.[9,12]
- The plasma concentrations of gabapentin associated with acute pain relief are unknown in companion animals. Based on the human literature and a study in cats,[11] single or double preoperative doses of 15 to 30 mg/kg orally are recommended for postoperative pain relief to reduce opioid consumption. These doses are similar to those used to facilitate transportation and veterinary examination and reduce fear responses in cage-trap cats.[13,14]
- The following doses for chronic pain or persistent postsurgical pain have been suggested:
  - Dogs: 10 mg/kg every 8 hours orally[25]
  - Cats: 8 mg/kg every 6 hours orally.[5]
- Adverse effects may include sedation and dizziness in humans and are usually self-limited. In companion animals, sedation and ataxia can occur. Loose stools have been reported; however, the association with the administration of gabapentin was not clearly established.[7] Gabapentin seems safe for companion animals.

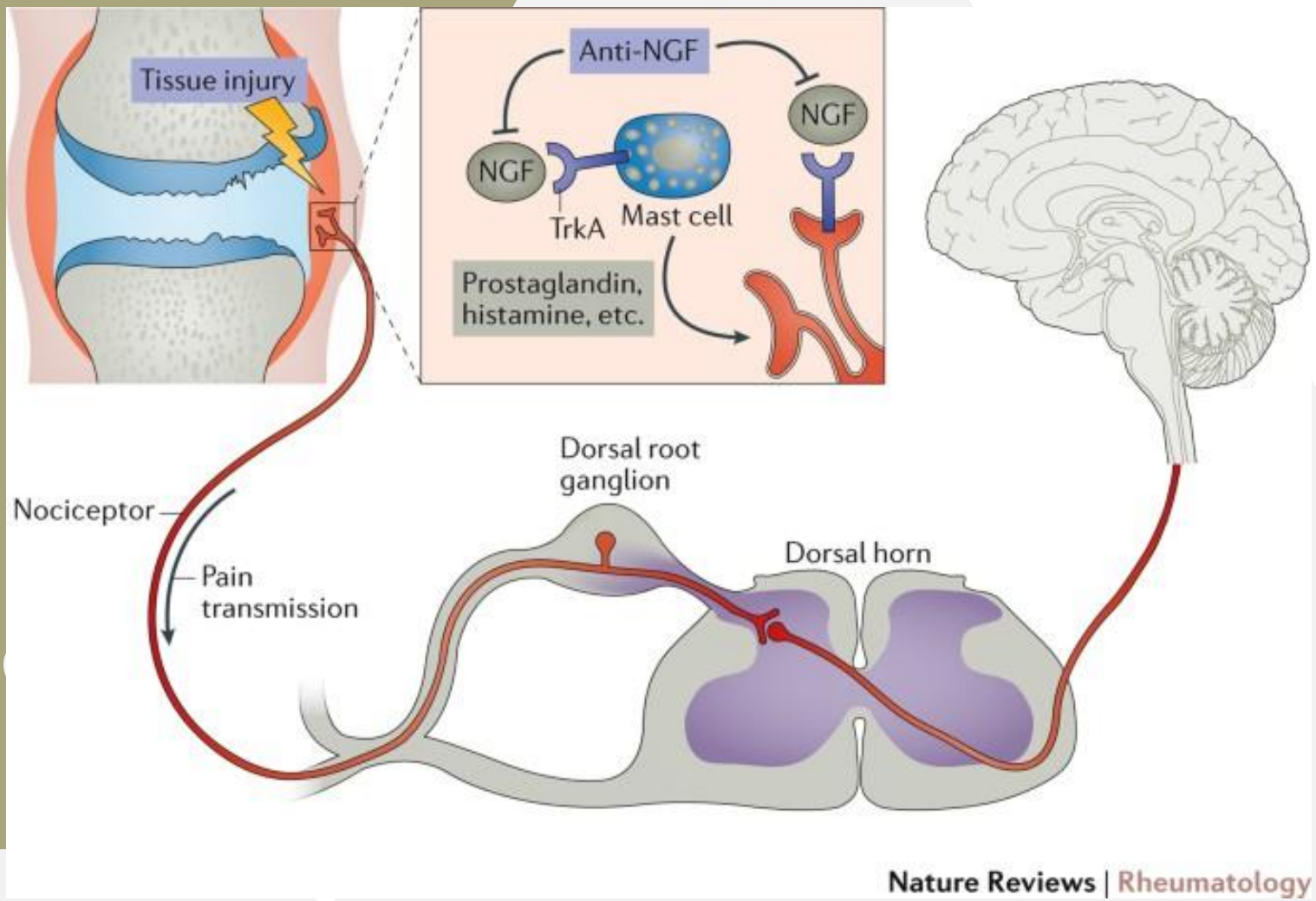
Ruel & Steagall, 2019

Gabapentina	Dolor preoperatorio	Perros: 10 mg/kg PO	2h antes de la cirugía	Administrar en combinación con opioides.
		Gatos: 50 mg total PO	12h y 1-2h antes de la cirugía	Administrar en combinación con opioides.
	Dolor crónico	Perros y gatos: 5-10 mg/kg PO	Cada 8-12h	Iniciar con 3-5 mg/kg y aumentar gradualmente hasta la dosis deseada. Aumentar o disminuir la dosis dependiendo de la respuesta terapéutica. Se han informado dosis más altas de manera anecdótica. Se recomiendan dosis reducidas en gatos con enfermedad renal crónica. Puede causar sedación y ataxia.
	Estrés relacionado con transporte y visitas veterinarias	Gatos: los estudios han informado rangos de dosis de 50-200 mg PO total	90 minutos antes de transportar al gato al veterinario	En esta situación, la gabapentina se usa para disminuir el estrés y la ansiedad relacionados con el transporte y el examen físico; sin embargo, si se programa la cirugía, también podría contribuir a la analgesia posoperatoria.
Pregabalina	Dolor crónico	Perros: 2-5 m/kg PO	Cada 8-12h	Iniciar con dosis y/o intervalos de administración más bajos y aumentar gradualmente hasta la dosis objetivo. Se informaron dosis de 13 a 19 mg/kg cada 12 horas en perros con dolor neuropático relacionado con la siringomielia (Thoefner et al., 2020). Puede administrarse una vez 1 hora antes de la cirugía de disco intervertebral seguido de una administración cada 8 horas durante 5 días después de la cirugía.
		Perros: 1-4 mg/kg PO	Cada 12h	Puede causar sedación y ataxia.
	Estrés relacionado con transporte	Gatos: 5-10 mg/kg PO	90 minutos antes de transportar al gato	En esta situación, la pregabalina se usa para disminuir el estrés y la ansiedad relacionados con el transporte.

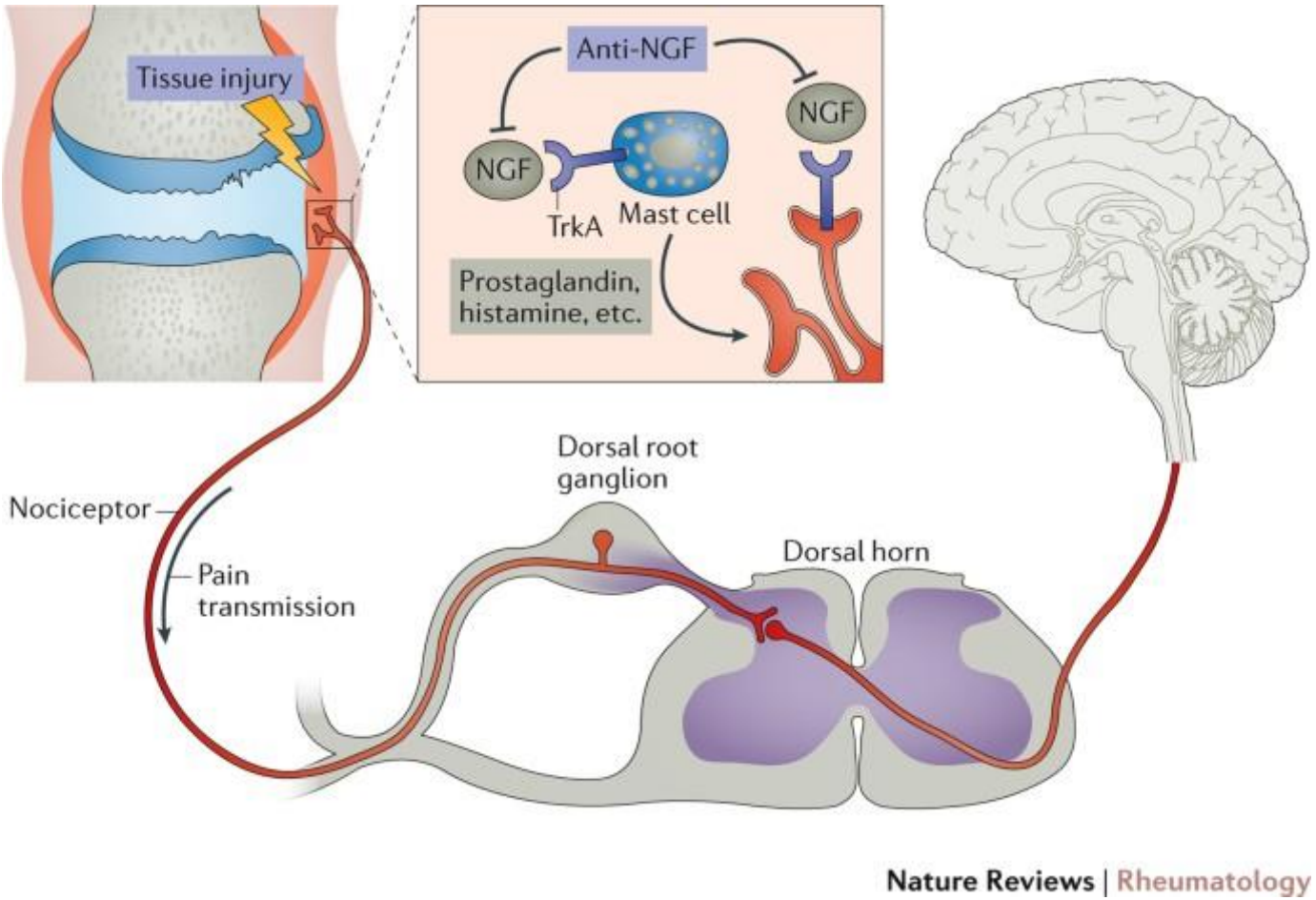
Directrices WSAVA, Monteiro et al., 2022.

Outras opciones

- PRP vs Triamcinolona (6 a 8 mg/articulação) + acido hialuronico (0,5 a 2 mL/art)
- Células Tronco
- Ozonoterapia
- Injecoes intraarticulares de agentes radioativos radiosinoviortesis (RSO)
- Fisioterapia
- Acupuntura
- Estímulos positivos



Anticuerpos anti-Nerve Growth Factor (NGF)



- El factor de crecimiento nervioso se expresa en sitios lesionados
- promueve hiperalgesia, aumentando la liberación de neurotransmisores algogénicos, y alterando el fenotipo de neuronas a través de factores neurotróficos
- Felinos se cuenta con el Frunevetmab (1-2,8mg/kg), el cual mejora cuadros de dolor crónico osteoarticular luego de una única dosis por períodos de hasta seis semanas.

Glucosaminoglicanos Polisulfatados

How Adequan® Canine (polysulfated glycosaminoglycan) can help extend a dog's mobility over a lifetime.

practice with it

Make mobility a "vital sign" at every visit.

- Look for clinical signs of osteoarthritis (OA)
- Ask the owner about any changes that may indicate onset of a joint problem

start treatment early

At early diagnosis of OA, prescribe Adequan® Canine at the approved dose:

- 2 mg/lb body weight (0.02 mL/lb or 1 mL/50 lb), intramuscularly twice weekly for up to 4 weeks
- Maximum of 8 injections

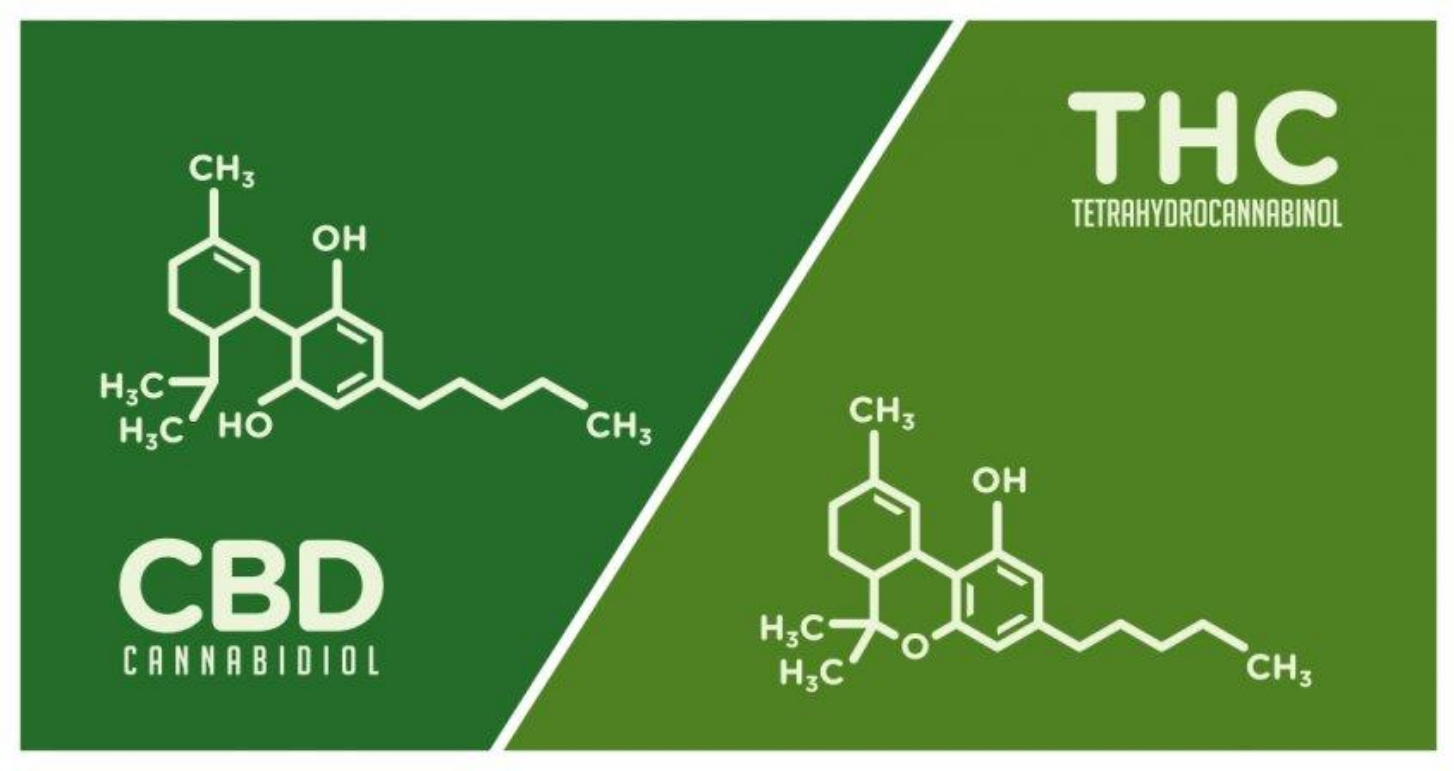
be proactive with it

- Continue monitoring the patient's joint health and mobility
- Educate clients on early signs with OA problems

repeat treatment

Repeat the dosing series as needed upon recurrence of clinical signs to help keep joints working and dogs enjoying their everyday life of adventure with mobility

The specific mechanism of action of Adequan® in canine joints is not known.



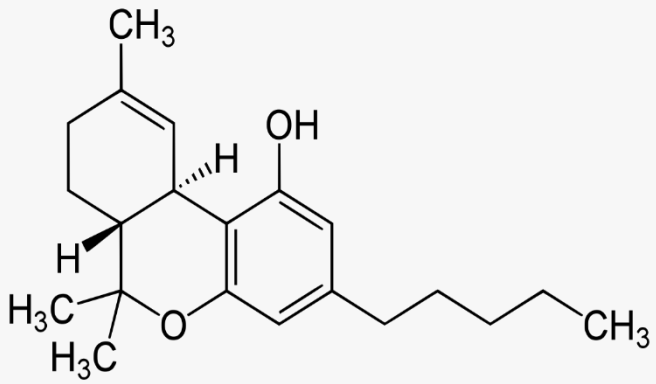
Cannabis

Más de 538 compuestos químicos

Compuestos fenólicos

Acidos fenólicos y Flavonoides

Fitocannabinoides



Terpenos

Aroma y sabor

CANNA FARMS

1.855.882.0988 · info@cannafarms.ca · @cannafarmsltd

TERPENES

Terpenes are the **essential oils** found in cannabis, and are responsible for the different smells and tastes of each cannabis strain. Terpenes may also **modulate the effects of cannabinoids** such as THC and CBD (Russo, 2011). To help our clients with interpreting terpene concentrations and choosing an appropriate strain of dried cannabis, we have developed a simple way to visualize the levels of major terpenes.

The different colours in the chart below correspond to the relative levels of terpenes in a strain of dried cannabis.

LIMONENE
major component of
oranges, citrus fruits*

CAROPHYLLENE
major component of
black pepper*

PINENE
major component of
pine trees*

LINALOOL
major component of
lavendar*

TERPINEOL
major component of
lilac, spring flowers*

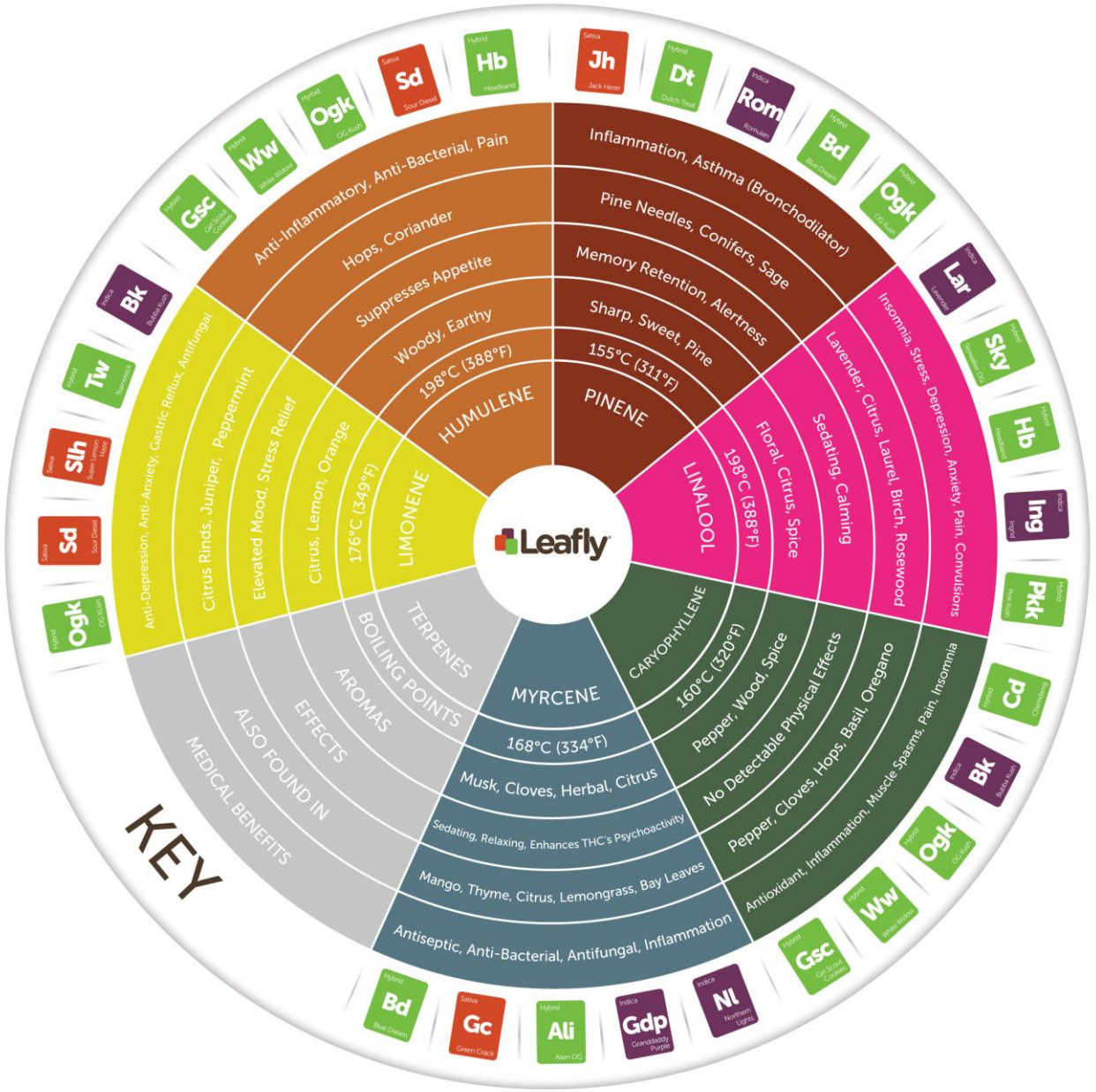
TERPINOLENE
major component of
wood*

MYRCENE
major component of
hops*

*For more information about terpenes and the entourage effect, please see:

Russo, Ethan B. *"Taming THC: Potential Cannabis Synergy and Phytocannabinoid-Terpenoid Entourage Effects."* British Journal of Pharmacology 163.7 (2011): 1344–1364.

Cannabinoides



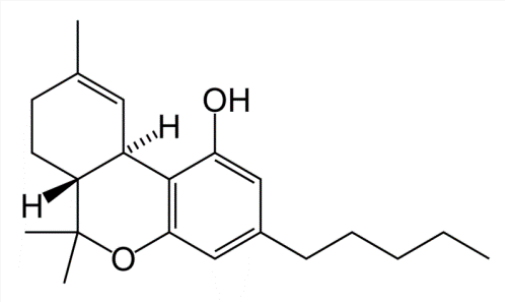
References

http://steephill.com/resources/cannabinoid-and-terpenoid-reference-guide/
http://sclabs.com/learn/terpenes.html

Fitocannabinoides

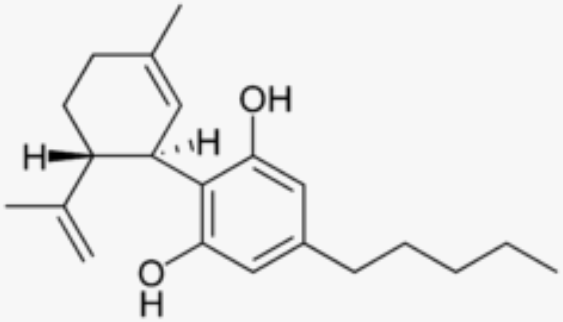
- Producidos por tricomas glandulares de las flores de *Cannabis*
- Altamente liposolubles

Δ9-THC

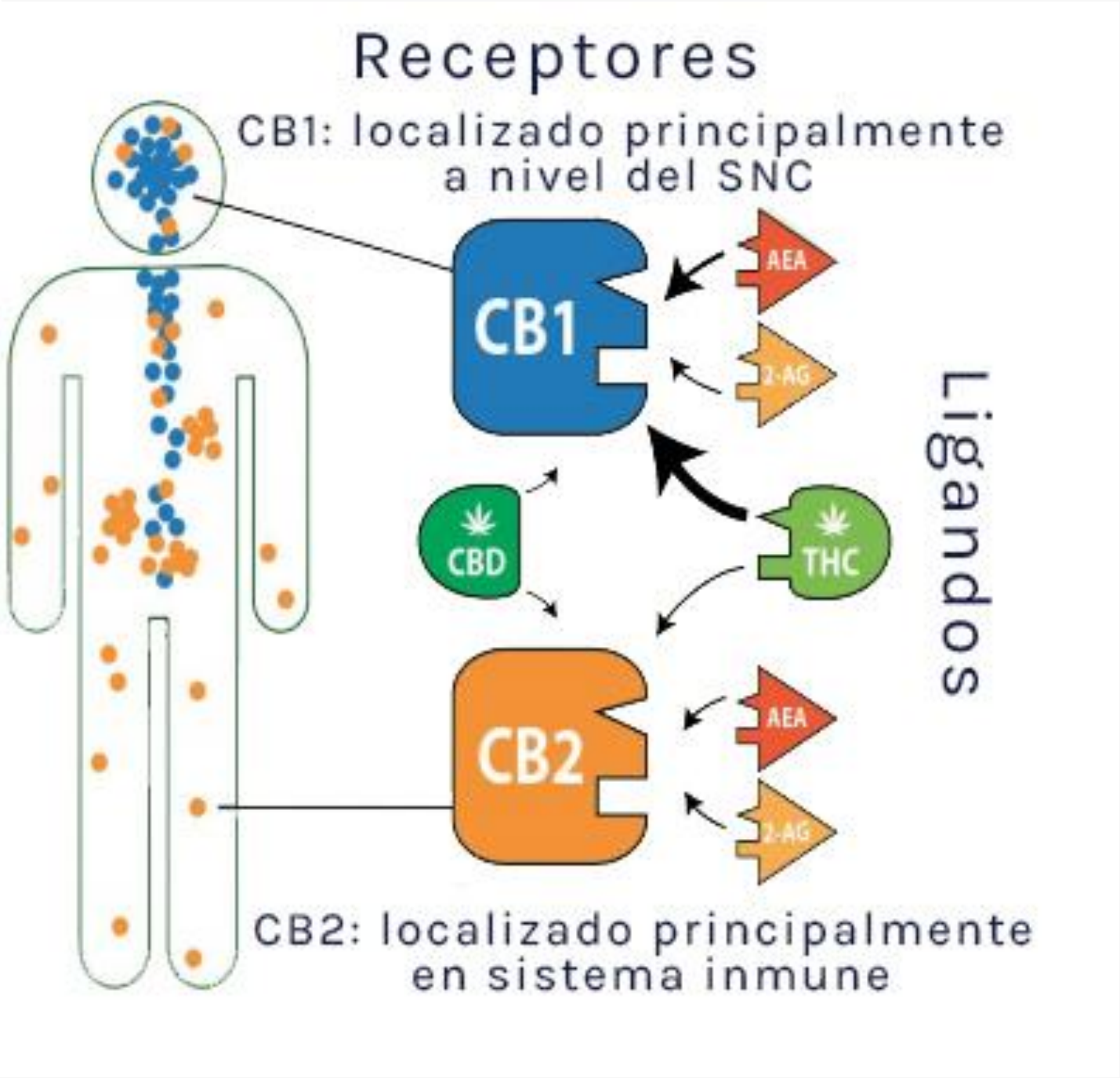


Psicoactivo

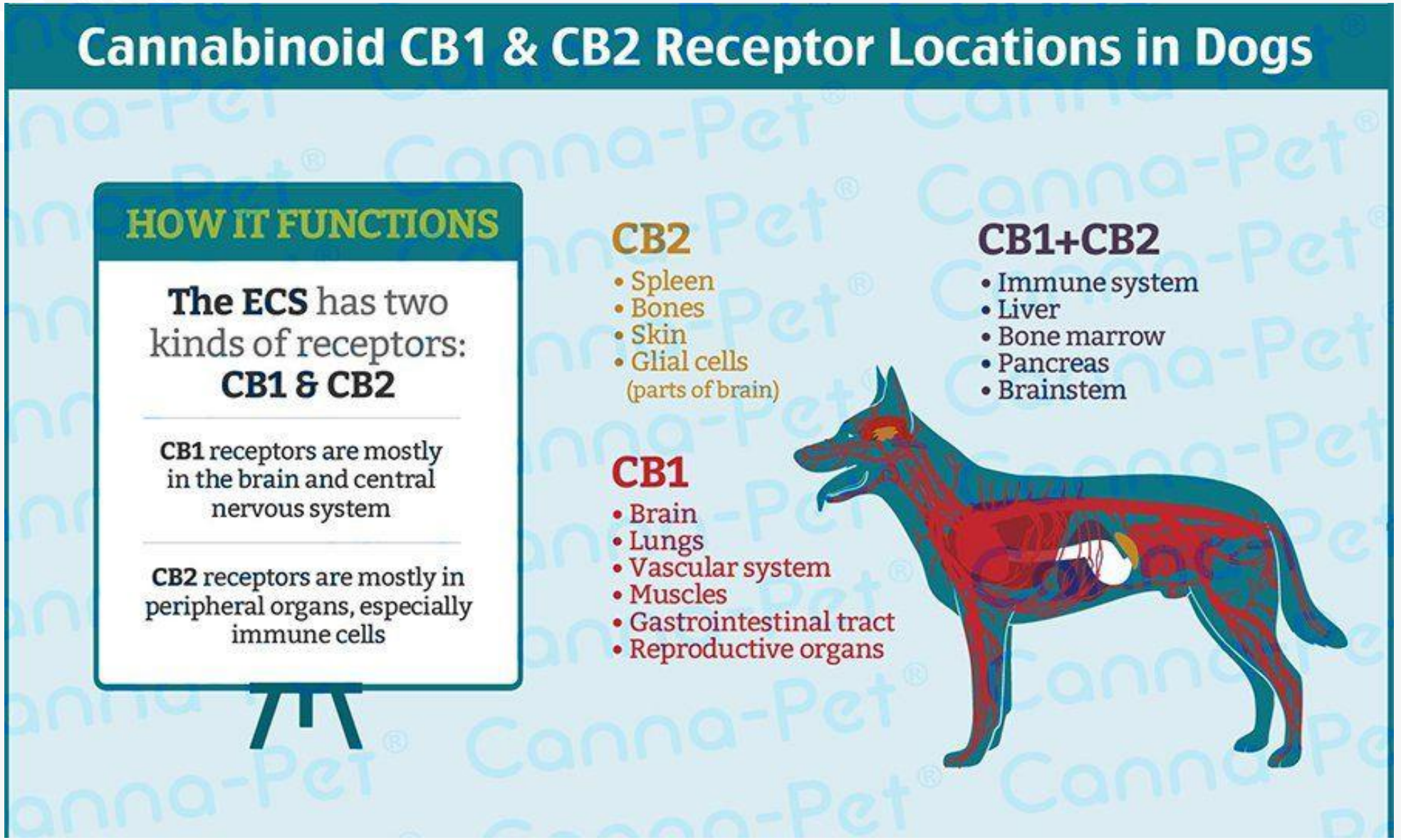
CBD



Sistema Endocannabinoide

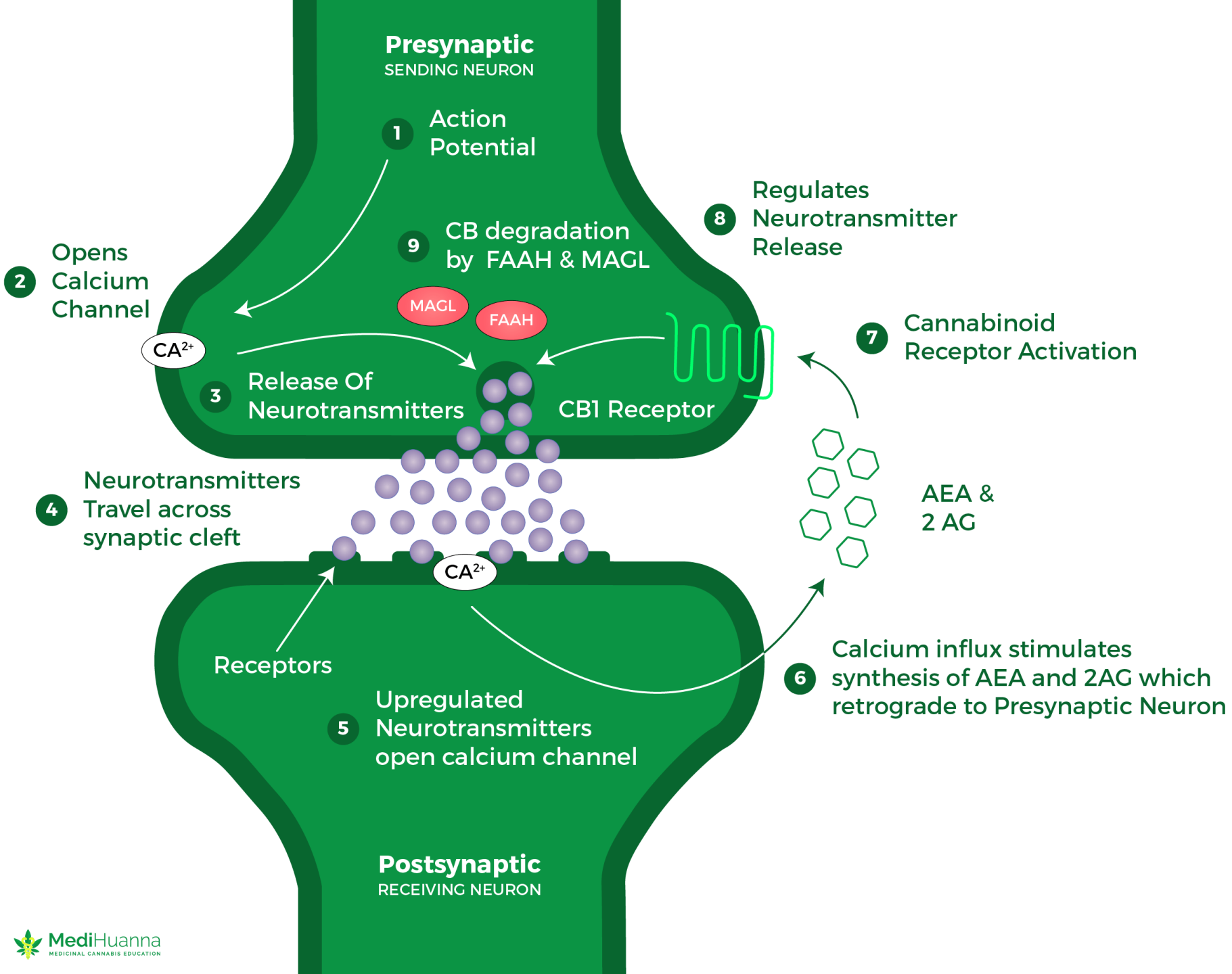


Fuente: https://canna-pet.com/



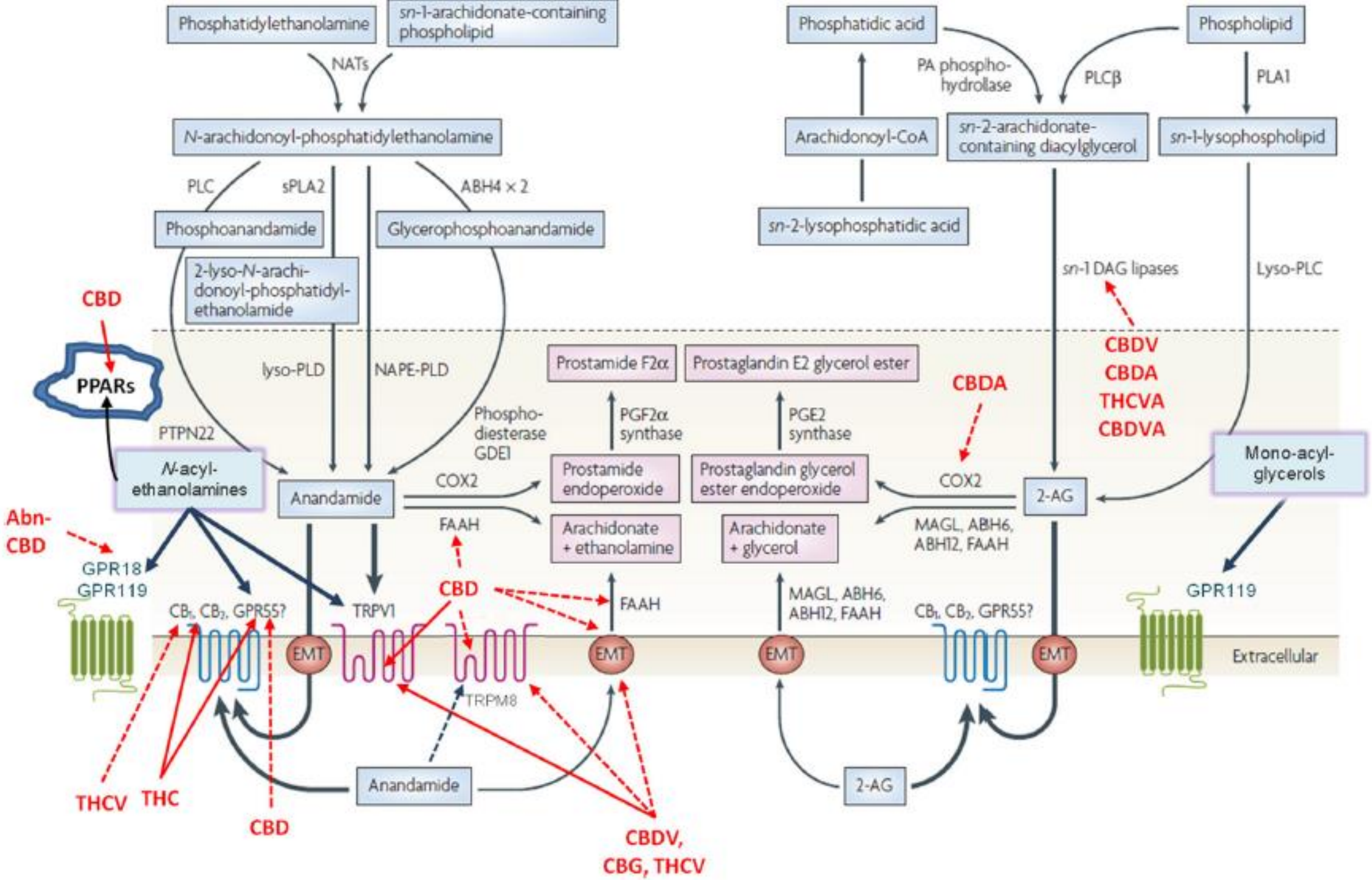
Fuente: https://canna-pet.com/

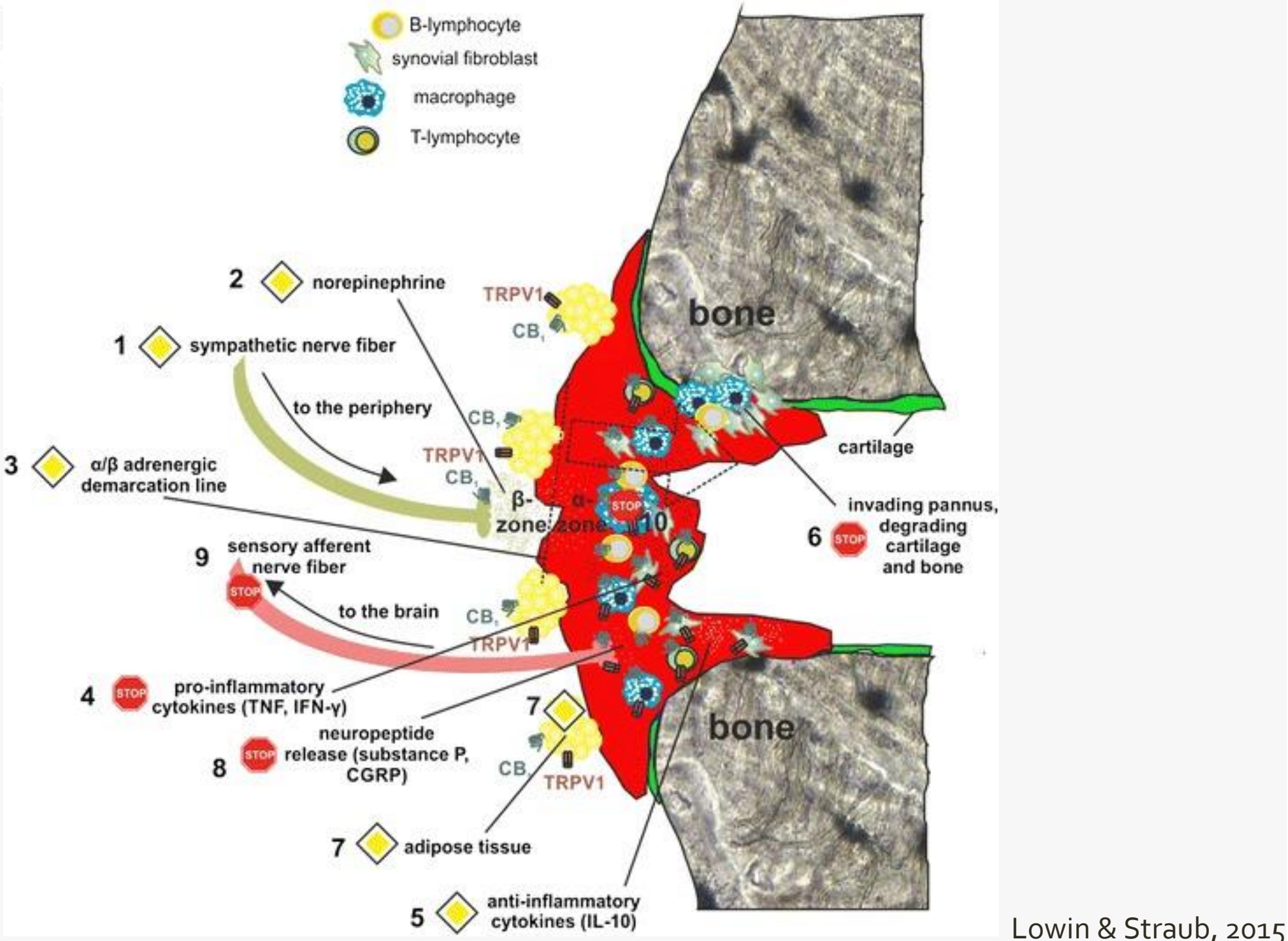
Sistema Endocannabinoide



MediHuanna
MEDICINAL CANNABIS EDUCATION

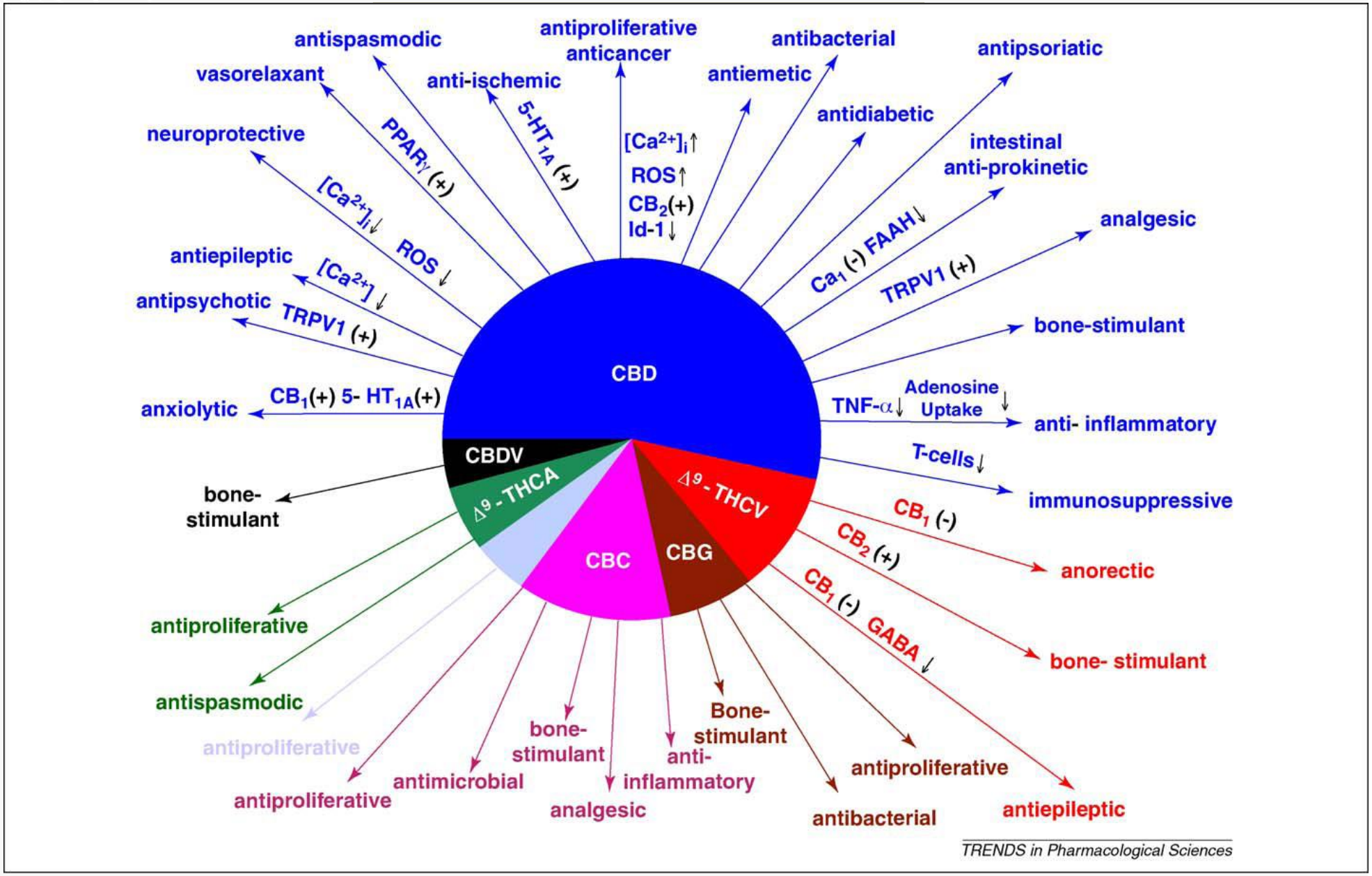
Sistema Endocannabinoide





Lowin & Straub, 2015

Uso Medicinal *Cannabis*



PK

Canadian Journal of Veterinary Research
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Journal Web site
How to Submit

Can J Vet Res. 2018 Jul; 82(3): 178–183.

PMCID: PMC6038832
PMID: 30026641

Language: English | French

Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs

Lisa R. Bartner, Stephanie McGrath,✉ Sangeeta Rao, Linda K. Hyatt, and Luke A. Wittenburg

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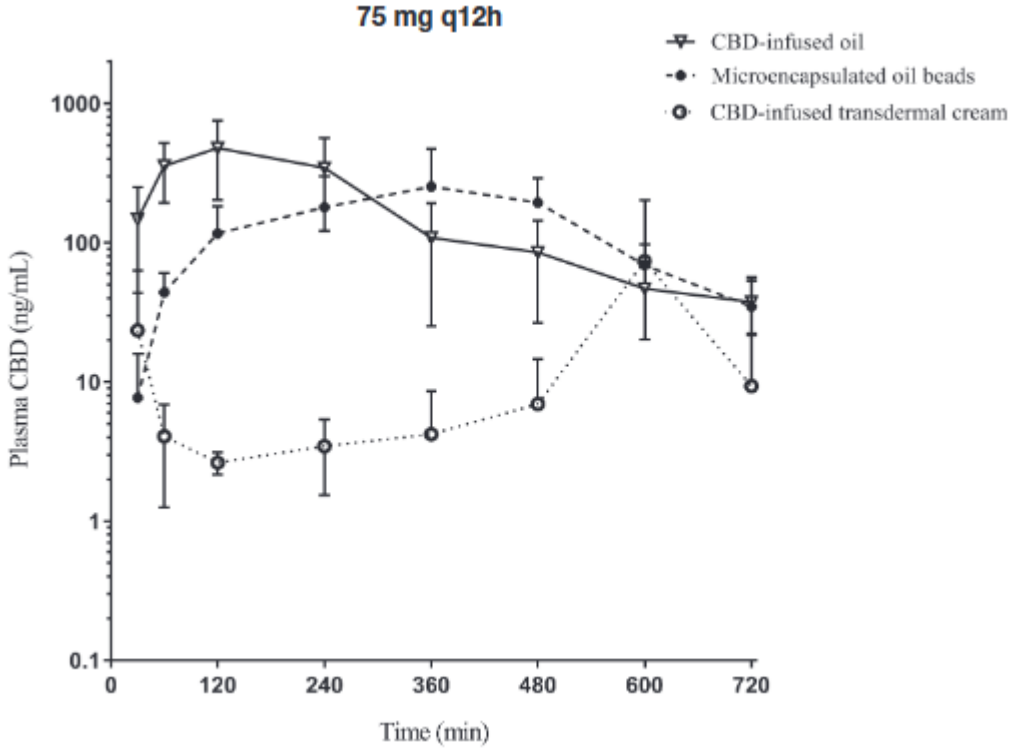

Investigaciones en Veterinaria

Research in Veterinary Science 123 (2019) 26–28

Contents lists available at ScienceDirect

Research in Veterinary Science

journal homepage: www.elsevier.com/locate/rvsc

Pharmacokinetics of Bedrocan®, a cannabis oil extract, in fasting and fed dogs: An explorative study

Beata Łebkowska-Wieruszewska[a], Fabio Stefanelli[b], Silvio Chericoni[b], Helen Owen[c], Amnart Poapolathep[d], Andrzej Lisowski[e], Mario Giorgi[f,*]

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[b] Department of Patologia, Chirurgica, Medica, Molecolare e dell'Area Critica, Università di Pisa, Italy
[c] School of Veterinary Science, The University of Queensland, Gatton Campus, Gatton, Queensland 4343, Australia
[d] Department of Pharmacology, Faculty of Veterinary Medicine, Kasetsart University, Bangkok, Thailand
[e] Department of Animal Biology and Animal Breeding, University of Life Sciences, Lublin, Poland
[f] Department of Veterinary Sciences, University of Pisa, Via Livornese (lato monte), San Piero a Grado, 56122 Pisa, Italy

Investigaciones en Veterinaria

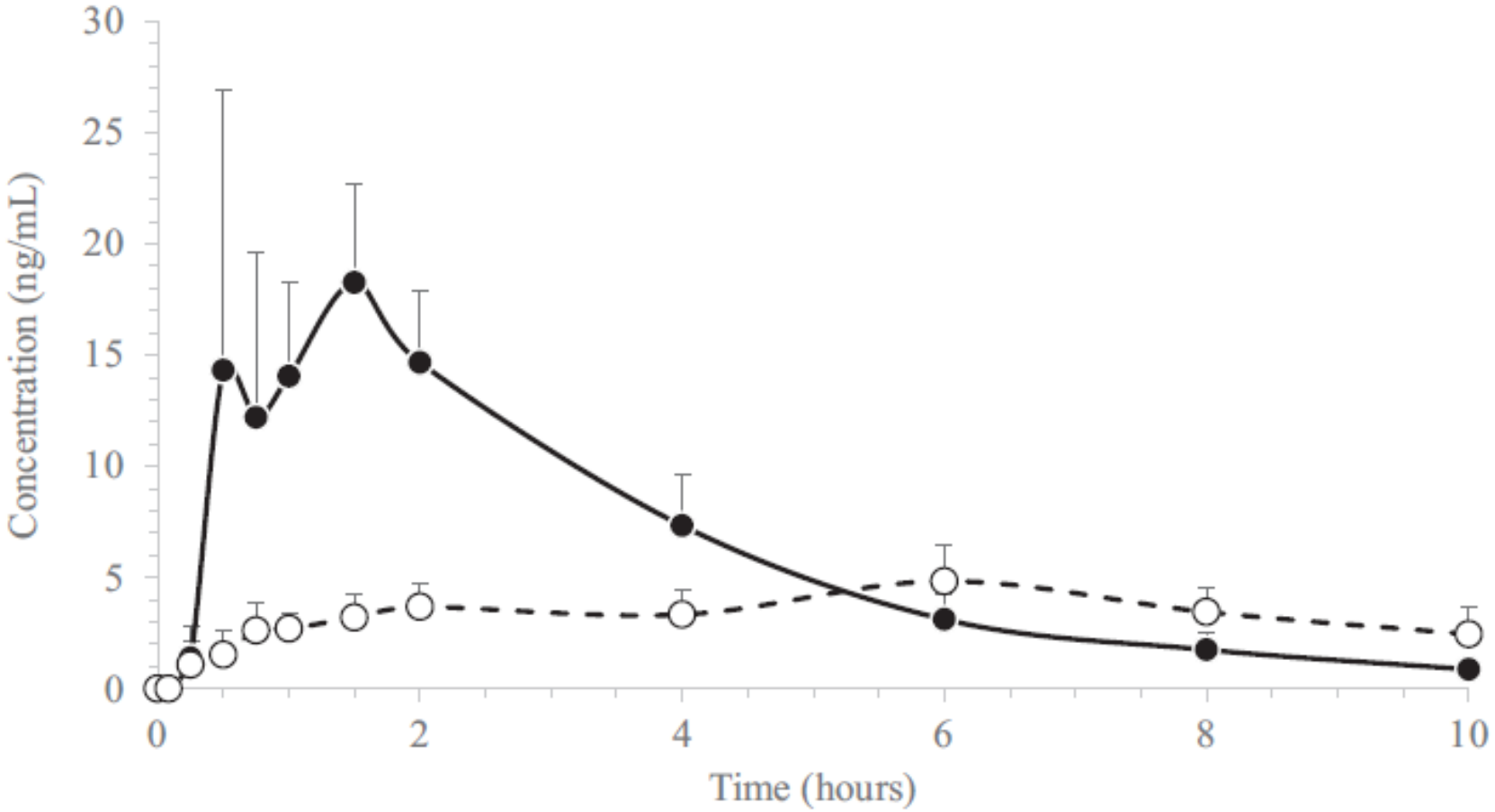

Fig. 1. THC average blood concentration vs time after oral administration of Bedrocan (1.5 mg/kg THC) in fasting (—●—) and fed (—○—) dogs.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 23 July 2018
doi: 10.3389/fvets.2018.00165

Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol 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

TABLE 3 | Canine Brief Pain Inventory (Pain and Activity questions) and Hudson Scale mean and standard deviation; lameness, weight-bearing and pain scores median and ranges at each time for cannabidiol (CBD) and placebo oils.

	CBD oil			Placebo oil		
	Week 0	**Week 2**	**Week 4**	**Week 0**	**Week 2**	**Week 4**
CBPI Pain (0–40)	21 ± 8	14 ± 6*	14 ± 8*	17 ± 7	19 ± 9	19 ± 9
CBPI activity interference (0–60)	35 ± 15	25 ± 15*	26 ± 14*	27 ± 15	29 ± 15	31 ± 16
Hudson (0–110)	54 ± 13	67 ± 15*	67 ± 10*	65 ± 14	64 ± 16	60 ± 19
Veterinary lameness§	3 (1–4)	3 (1–4)	3 (1–4)	3 (2–4)	3 (2–4)	3 (1–4)
Veterinary pain ∫	3 (3–4)	3 (2–4)*	3 (1–4)*	3 (2–4)**	3 (2–4)	3 (2–4)**
Veterinary weight-bearing =	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)

Investigaciones en Veterinaria

TABLE 4 | Serum chemistry values of dogs receiving CBD or placebo oils.

	Reference	CBD oil			Placebo oil		
		Week 0	Week 2	Week 4	Week 0	Week 2	Week 4
Sodium	145–153 mEq/L	149 ± 3	149 ± 2	149 ± 1	149 ± 1	149 ± 2	149 ± 2
Potassium	4.1–5.6 mEq/L	4.9 ± 0.3	4.9 ± 0.5	4.9 ± 0.3	4.8 ± 0.4	4.9 ± 0.4	4.9 ± 0.3
Chloride	105–116 mEq/L	110 ± 3	109 ± 3	109 ± 2	110 ± 2	110 ± 2	110 ± 2
SUN	10–32 mg/dL	20 ± 9	20 ± 7	20 ± 6	19 ± 6	21 ± 7	19 ± 6
Creatinine	0.6–1.4 mg/dL	1.0 ± 0.3	1.1 ± 0.3*	1.0 ± 0.3*	0.9 ± 0.3	1.0 ± 0.3*	1.0 ± 0.3*
Calcium	9.3–11.4 mg/dL	10.4 ± 0.5	10.4 ± 0.4	10.3 ± 0.4	10.4 ± 0.6	10.4 ± 0.4	10.4 ± 0.4
Phosphorus	2.9–5.2 mg/dL	3.8 ± 0.8	3.9 ± 0.8	3.9 ± 0.6	4.0 ± 0.7	3.9 ± 0.6	4.0 ± 0.5
Magnesium	1.4–2.2 mg/dL	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1
Glucose	63–118 mg/dL	92 ± 9	89 ± 9	92 ± 9	97 ± 10*	93 ± 8	97 ± 10*
ALT	20–98 U/L	93 ± 86	93 ± 88	114 ± 119	90 ± 89	222 ± 606	166 ± 284
AST	14–51 U/L	31 ± 8	33 ± 13	34 ± 16	30 ± 8	56 ± 99	45 ± 34
ALP	17–111 U/L	160 ± 212	238 ± 268	323 ± 407*	204 ± 287	186 ± 287	175 ± 248
GGT	0–6 U/L	4 ± 3	3 ± 2	3 ± 2	3 ± 2	4 ± 6	5 ± 4
Bilirubin	0.0–0.2 mg/dL	0.1 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.1
Total protein	5.3–7.0 g/dL	6.3 ± 0.4	6.4 ± 0.5	6.3 ± 0.4	6.3 ± 0.4	6.3 ± 0.4	6.3 ± 0.4
Albumin	3.1–4.2 g/dL	3.7 ± 0.2	3.7 ± 0.2	3.7 ± 0.2	3.7 ± 0.2	3.7 ± 0.2	3.7 ± 0.2
Globulin	1.9–3.6 g/dL	2.6 ± 0.3	2.6 ± 0.4	2.6 ± 0.4	2.6 ± 0.4	2.6 ± 0.4	2.6 ± 0.4
Cholesterol	138–332 mg/dL	291 ± 64	301 ± 62	302 ± 62	295 ± 71	300 ± 71	308 ± 83
CK	48–260 U/L	148 ± 81	147 ± 59	134 ± 61	139 ± 57	158 ± 80	168 ± 105

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], Jonathan Vazquez-Perez[d], Emek Blair[e], Kenneth Dunner Jr[f], Pedram Salimpour[g], William K. Decker[d,h,i], Matthew M. Halpert[d,*]

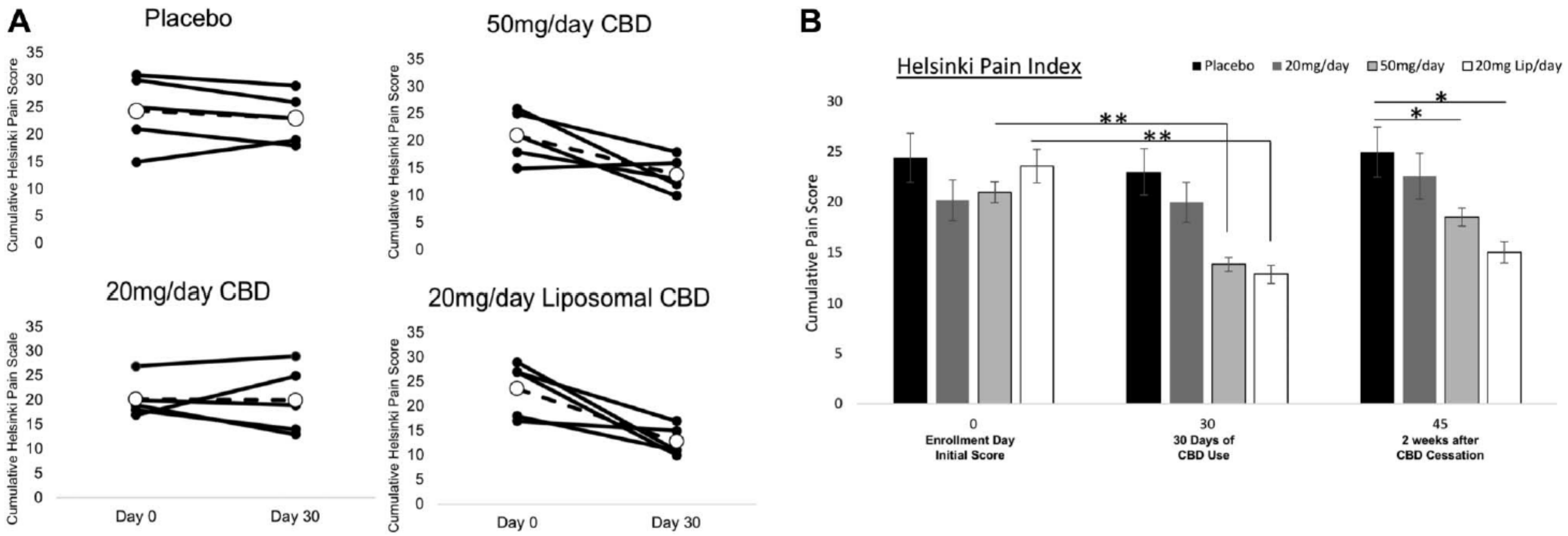

Figure 4. Daily administration of CBD for 30 days improves owner-perspective quality of life scores among large dogs with affirmative diagnosis of osteoarthritis. Twenty large domestic canines with affirmative diagnosis of osteoarthritis were enrolled in a double-blind, placebo-controlled randomized study. Animals were administered coconut oil placebo, 20-mg/day naked CBD, 50-mg/day naked CBD, or 20-mg/day liposomal CBD. Owners assessed their animals by means of the Helsinki Chronic Pain Index (HPCI) on days 0, 30, and 45. (A) Individual HPCI values were plotted for each study cohort on days 0 and 30. (B) Cohort HPCI values were plotted on days 0, 30, and 45. Error bars ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$ by Student's two-tailed *t* test. CBD, cannabidiol.

animals

MDPI

Article

Oral Transmucosal Cannabidiol Oil Formulation as Part of a Multimodal Analgesic Regimen: Effects on Pain Relief and Quality of Life Improvement in Dogs Affected by Spontaneous Osteoarthritis

Federica Alessandra Brioschi [1], Federica Di Cesare [2], Daniela Gioeni [1], Vanessa Rabbogliatti [3], Francesco Ferrari [3], Elisa Silvia D'Urso [4], Martina Amari [3] and Giuliano Ravasio [1,*]

Table 2. Breed, age, weight, gender and analgesic therapies administered to the dogs recruited in CBD (n = 9) and C (n = 12) groups. SID, once daily; BID, twice daily.

	Group	Breed	Age (months)	Weight (kg)	Gender	NSAIDs	Glucocorticoids	Gabapentin	Amitriptyline	CBD
1	CBD	Mongrel	156	23	Female	Firocoxib (5–1.25 mg kg^{-1} SID)	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	2 mg kg^{-1} BID
2	CBD	Épagneul Breton	144	18	Female	None	Prednisone (0.5–0.12 mg kg^{-1} BID)	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	2 mg kg^{-1} BID
3	CBD	English Bulldog	96	25	Male	Firocoxib (5–2.5 mg kg^{-1} SID)	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	2 mg kg^{-1} BID
4	CBD	Cane Corso	125	45	Female	Firocoxib (5–2.5 mg kg^{-1} SID)	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	2 mg kg^{-1} BID
5	CBD	Labrador Retriever	110	45	Male	Firocoxib (5–1.25 mg kg^{-1} SID)	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	2 mg kg^{-1} BID
6	CBD	Dogue de Bordeaux	84	60	Male	Firocoxib (5–1.25 mg kg^{-1} SID)	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	2 mg kg^{-1} BID
7	CBD	Border Collie	156	20	Male	None	Prednisone (0.5–0.12 mg kg^{-1} BID)	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	2 mg kg^{-1} BID
8	CBD	Boxer	108	33	Male	Firocoxib (5–1.25 mg kg^{-1} SID)	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	2 mg kg^{-1} BID
9	CBD	Boxer	108	40	Female	Firocoxib (5–1.25 mg kg^{-1} SID)	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	2 mg kg^{-1} BID
1	C	Australian Sheperd	156	24	Male	Firocoxib (5–1.25 mg kg^{-1} SID)	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None
2	C	Labrador Retriever	152	41	Male	Firocoxib (5–1.25 mg kg^{-1} SID	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None
3	C	Golden Retriever	173	29	Male	Firocoxib (5–2.5 mg kg^{-1} SID	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None
4	C	Cocker Spaniel	167	13	Female	Firocoxib (5–2.5 mg kg^{-1} SID	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None
5	C	Labrador Retriever	161	30	Female	Firocoxib (5–1.25 mg kg^{-1} SID	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None
6	C	German Sheperd	115	25	Female	Firocoxib (5–1.25 mg kg^{-1} SID)	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None
7	C	Labrador Retriever	153	34	Male	None	Prednisone (0.5–0.12 mg kg^{-1} BID)	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None
8	C	German Sheperd	108	25	Female	None	Prednisone (0.5–0.12 mg kg^{-1} BID)	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None
9	C	Mongrel	180	10	Male	Firocoxib (5–2.5 mg kg^{-1} SID	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None
10	C	Mongrel	127	22	Male	None	Prednisone (0.5–0.12 mg kg^{-1} BID)	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None
11	C	English Bulldog	108	27	Female	Firocoxib (5–2.5 mg kg^{-1} SID)	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None
12	C	Mongrel	182	18	Male	Firocoxib (5–1.25 mg kg^{-1} SID)	None	10–5 mg kg^{-1} BID	1 mg kg^{-1} SID	None

Gracias

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