FACULTY OF VETERINARY MEDICINE
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V E R A | I C O N

12 MEI 2023

CHRONISCHE PIJN:
WAT WE WETEN & NIET WETEN
FARMACOLOGISCHE OPTIES.

Tim Bosmans, Vakgroep Kleine Huisdieren, UGent

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CONCEPTEN EFFECTIEVE CHRONISCHE PIJNBESTRIJDING

3 belangrijke concepten van aanpak:

1. screening & preventief
2. georganiseerde & proactief
3. multimodaal

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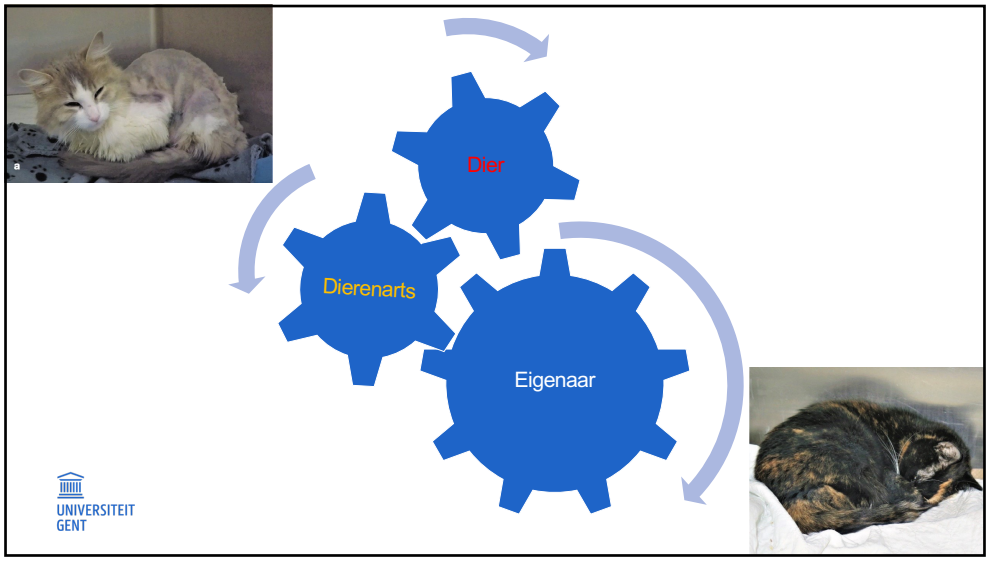

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CONCEPTEN EFFECTIEVE CHRONISCHE PIJNBESTRIJDING

1. preventieve aanpak van chronische pijn
   - moeilijker dan bij acute pijn
   - preventieve aanpak van chronische pijn
     - herkenning zo vroeg mogelijk in het begin van de aandoening
     - bijvoorbeeld screening van evolutie van OA met de COAST

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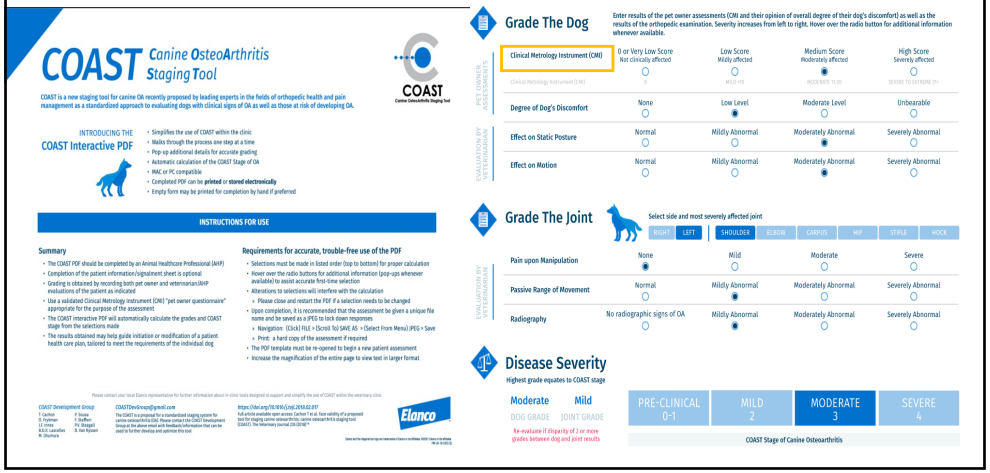
COAST TOOL



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CONCEPTEN EFFECTIEVE CHRONISCHE PIJNBESTRIJDING

2. georganiseerde & proactieve aanpak

- herkennen & scoren van pijn
- herhaaldelijke controle van pijnlevel tijdens behandeling
- informeren & betrekken vd eigenaar in het herkennen van pijn & pijnbehandeling
  - 'clinical metrology instruments'
- preventie van "breakthrough pain"

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CONCEPTEN EFFECTIEVE CHRONISCHE PIJNBESTRIJDING

Clinical metrology instruments, CMI's voor chronische pijn monitoring bij de hond:

Liverpool Osteoarthritis in Dogs (LOAD)[d]	Chronic, osteoarthritis	Owner	Simple	Monitoring	Valid
Canine Brief Pain Inventory (CBPI)[e]	Chronic, osteoarthritis	Owner	Simple	Monitoring	Valid
Helsinki chronic pain index[f]	Chronic, osteoarthritis	Owner	Simple	Monitoring	Limited validation
Sleep and nighttime restlessness evaluation (SNoRE)[g]	Chronic, osteoarthritis	Owner	Simple	Monitoring	Moderately validated
Client-specific outcome measures (CSOM)[h]	Chronic, osteoarthritis	Owner	Moderate	Monitoring	Moderately validated
Health related quality of life (HRQoL)[i]	Chronic	Owner	Simple	Monitoring	Valid, not specific to pain

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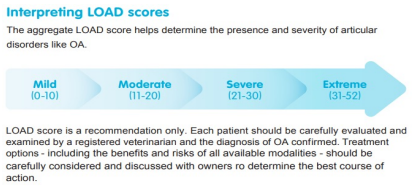
VOORBEELD CMI VOOR HONDEN - LOAD

- LOAD is gevalideerd voor het beoordelen van de impact van chronische OA pijn op het dagelijks leven van de hond (Walton et al. 2013)
- 23 vragen onderverdeeld in 3 groepen:
  - medische achtergrond
  - levensstijl
  - mobiliteit
- Interactieve pdf op de website van Elanco: Printable_LOAD_Form.pdf (kc-usercontent.com)



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VOORBEELD CMI VOOR HONDEN - LOAD

- 23 vragen onderverdeeld in 3 groepen:
  - 3 vragen toetsen de medische achtergrond van het dier
  - 7 vragen toetsen de levensstijl van het dier
  - 13 vragen over 3 verschillende factoren van de pijnervaring:
    - de activiteit van het dier
    - de stijfheid/mankheid
    - het meteorologische effect op deze eerste twee factoren

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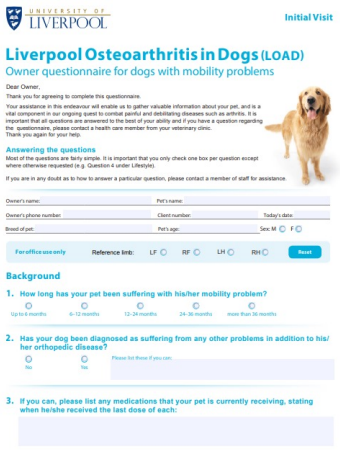
LOAD PAGE 1 & 2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Initial Visit

Liverpool Osteoarthritis in Dogs (LOAD)

Owner questionnaire for dogs with mobility problems

Dear Owner,

Thank you for agreeing to complete this questionnaire.

Your assistance in this endeavour will enable us to gather valuable information about your pet, and is a vital component in our ongoing quest to combat painful and debilitating diseases such as arthritis. It is important that all questions are answered to the best of your ability and if you have a question regarding the questionnaire, please contact a health care member from your veterinary clinic.

Thank you again for your help.

Answering the questions

Most of the questions are fairly simple. It is important that you only check one box per question except where otherwise requested (e.g. Question 4 under Lifestyle).

If you are in any doubt as to how to answer a particular question, please contact a member of staff for assistance.

Owner's name: Pet's name:

Owner's phone number: Client number: Today's date:

Breed of pet: Pet's age: Sex: M F

For office use only Reference limb: LF RF LH RH Reset

Background

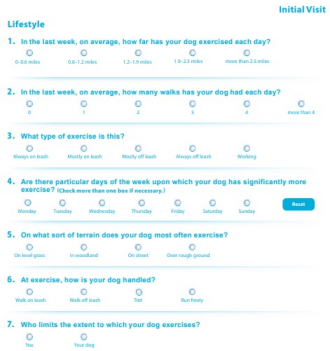
1. How long has your pet been suffering with his/her mobility problem?

Up to 6 months 6–12 months 12–24 months 24–36 months more than 36 months

2. Has your dog been diagnosed as suffering from any other problems in addition to his/her orthopedic disease?

No Yes Please list these if you can:

3. If you can, please list any medications that your pet is currently receiving, stating when he/she received the last dose of each:


Initial Visit

Lifestyle

1. In the last week, on average, how far has your dog exercised each day?

0–0.6 miles 0.6–1.2 miles 1.2–1.9 miles 1.9–2.5 miles more than 2.5 miles

2. In the last week, on average, how many walks has your dog had each day?

0 1 2 3 4 more than 4

3. What type of exercise is this?

Always on leash Mostly on leash Mostly off leash Always off leash Working

4. Are there particular days of the week upon which your dog has significantly more exercise? (Check more than one box if necessary.)

Monday Tuesday Wednesday Thursday Friday Saturday Sunday Reset

5. On what sort of terrain does your dog most often exercise?

On level grass In woodland On street Over rough ground

6. At exercise, how is your dog handled?

Walk on leash Walk off leash Trot Run freely

7. Who limits the extent to which your dog exercises?

You Your dog

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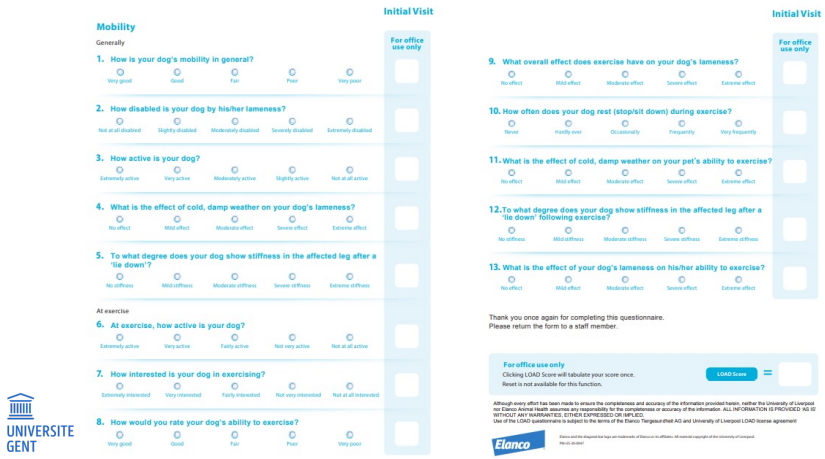
LOAD PAGE 3 & 4



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VOORBEELD CMI - CANINE BRIEF PAIN INVENTORY

- Pain Severity Score (PSS):
  - 4 vragen over pijnintensiteit
    - score 0 (geen pijn) – score 10 (extreme pijn)
    - gemiddelde geeft de PSS score
- Pain Interference Score (PIS):
  - 6 vragen over pijninterferentie met typische functie
    - score 0 (geen interferentie) – score 10 (complete interferentie)
    - Gemiddelde geeft de PIS score
- Overall quality of life score
  - descriptief: slecht tot excellent
- Evaluatie (Brown et al. 2013):
  - efficiënte behandeling:
    - afname van PSS ≥ 1 + PIS ≥ 2 tov baseline score + verbeterde of stabiele QoL-score

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CONCEPTEN EFFECTIEVE CHRONISCHE PIJNBESTRIJDING

Clinical metrology instruments, CMI's voor chronische pijn monitoring bij de kat:

Musculoskeletal Pain Screening Checklist (MiPSC)[e]	Chronic, osteoarthritis	Owner	Simple	Screening	Valid
Feline Musculoskeletal Pain Index (FMPI)[f]	Chronic, osteoarthritis	Owner	Simple	Monitoring	Valid
Montreal Instrument for Cat Arthritis Testing—Caretaker (MICAT-C)[g]	Chronic, osteoarthritis	Owner	Simple	Monitoring	Moderately validated
Client-specific outcome measures[h]	Chronic, osteoarthritis	Owner	Moderate	Monitoring	Moderately validated
Health-related quality of life (HRQoL)[i]	Chronic	Owner	Simple	Monitoring	Moderately valid (not specific to pain)

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VOORBEELD CMI - FELINE MUSCULOSKELETAL PAIN INDEX

Refinement of the Feline Musculoskeletal Pain Index (FMPI) and development of the short-form FMPI

Masataka Enomoto, B Duncan X Lascelles, James B Robertson, more... Show all authors

First Published May 18, 2021 | Research Article | Find in PubMed | Check for updates

https://doi.org/10.1177/1098612X211011984

Article information | Altmetric 1

Results

The data from 180 cats from four studies were included. The original FMPI had a reasonable reliability, but low/no responsiveness. The elimination process of FMPI items refined the responsiveness of the instrument while maintaining its reliability. When the responsiveness was compared between the original FMPI (17 items) and the FMPI-sf (nine items), the treatment effect between groups was always greater when the FMPI-sf was used.

Conclusions and relevance

The proposed FMPI-sf may be able to better distinguish between placebo and analgesic effects in cats with DJD.

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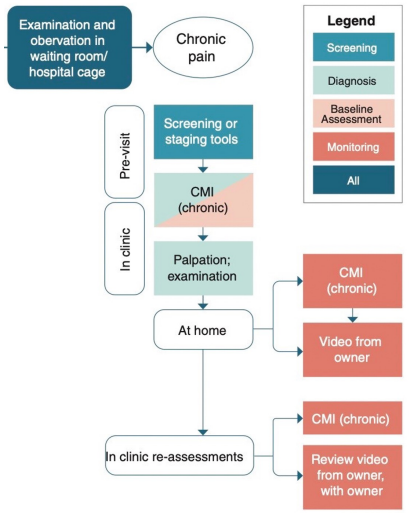
Flow Diagram voor het screenen, scoren en herkennen van chronische pijn, AAHA guidelines 2022



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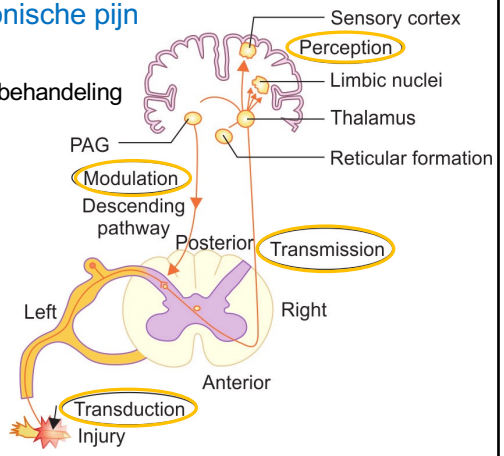
CONCEPTEN EFFECTIEVE CHRONISCHE PIJNBESTRIJDING

3. multimodale aanpak van chronische pijn

- verschillende aanknopingspunten voor pijnbehandeling
- ideaal op alle punten werken
- pijnsysteem is plastisch:
  vermijd perifere & centrale sensitizatie

samenvattend:
preventief & proactief
multimodaal



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CONCEPTEN EFFECTIEVE CHRONISCHE PIJNBESTRIJDING

- klassieke analgetica:
  - NSAID's + piprants
  - opioiden
  - alfa$_2$-agonisten
  - lokale anesthetica
  - ketamine

- bijkomende behandelingen:
  - analgetica:
    - paracetamol
    - amantadine
    - gabapentine & pregabaline
    - NMDA-receptor antagonisten
    - monoclonale antistoffen tegen NGF
    - …
  - niet-medicamenteuze methoden:
    - fysiotherapie & beweging
    - gewichtscontrole
    - acupunctuur
    - nutritionele ondersteuning
    - palliatieve radiatietherapie
    - chirurgie
    - Laser
    - …

- OA disease modulating agents:
  - gewrichtsinfiltraties:
    - cortico's
    - mesenchymale stamcellen
    - hyaluronzuur
    - platelet-rich plasma

etiologie en casus afhankelijk

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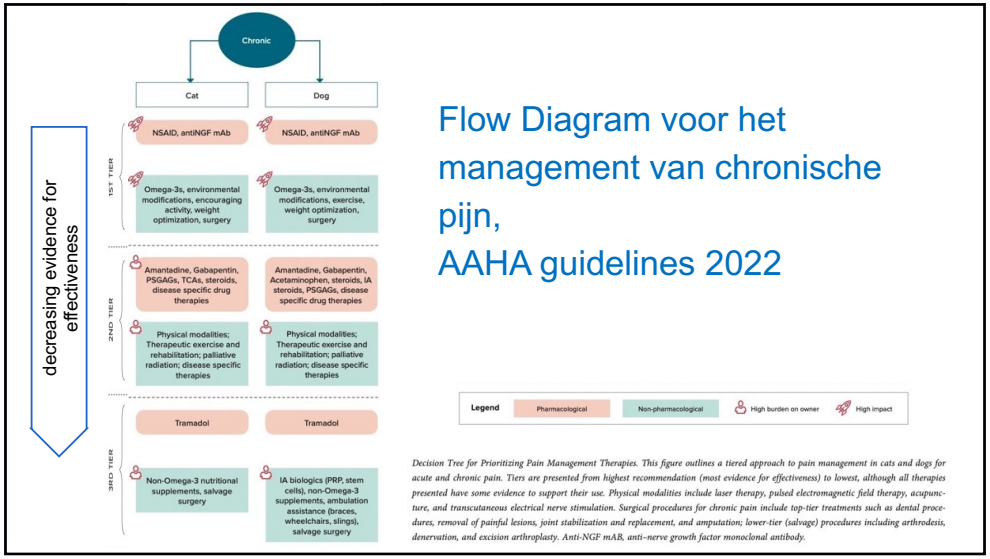

Flow Diagram voor het management van chronische pijn,
AAHA guidelines 2022

Decision Tree for Prioritizing Pain Management Therapies. This figure outlines a tiered approach to pain management in cats and dogs for acute and chronic pain. Tiers are presented from highest recommendation (most evidence for effectiveness) to lowest, although all therapies presented have some evidence to support their use. Physical modalities include laser therapy, pulsed electromagnetic field therapy, acupuncture, and transcutaneous electrical nerve stimulation. Surgical procedures for chronic pain include top-tier treatments such as dental procedures, removal of painful lesions, joint stabilization and replacement, and amputation; lower-tier (salvage) procedures including arthrodesis, denervation, and excision arthroplasty. Anti-NGF mAB, anti-nerve growth factor monoclonal antibody.

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LADDER CHRONISCHE PIJNBEHANDELING

VOORBEELD, WANT AFHANKELIJK VAN DE AANDOENING, STAGERING & INDIVIDUELE PATIËNT

•STAP 3: ZEER ERGE PIJN
•NSAID + adjuvant(s) + gabapentine

•STAP 2: VERERGERENDE PIJN
•NSAID + adjuvant(s) + paracetamol (hond)/amantadine

•STAP 1: MILDE PIJN
•NSAID + adjuvant

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OA BEHANDELING: COAST STAGE 1

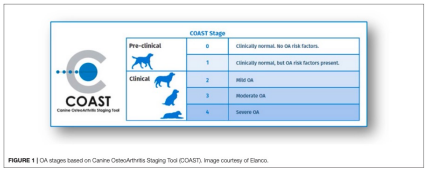

FIGURE 1 | OA stages based on Canine OsteoArthritis Staging Tool (COAST). Image courtesy of Elanco.

Proposed Canadian Consensus Guidelines on Osteoarthritis Treatment Based on OA-COAST Stages 1–4

Conny Mosley[1,2], Tara Edwards[3], Laura Romano[4], Geoffrey Truchetti[5], Laurie Dunbar[6], Teresa Schiller[7], Tom Gibson[8], Charles Bruce[9] and Eric Troncy[10]*

Frontiers in Veterinary Science,volume 9, april 2022

STAGE 1

Core treatment recommendations	
Client education	Risk factors identification, disease prevention, assessment plan
Weight optimization and nutrition	Adequate DHA/EPA supplementation, joint focused diets
Regular exercise	Well-balanced training and injury prevention
Physical rehabilitation	Injury prevention strategies, risk factor identification, muscle strength support

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OA BEHANDELING: COAST STAGE 2

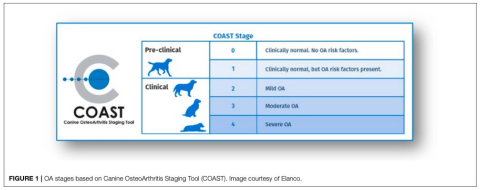

FIGURE 1 | OA stages based on Canine OsteoArthritis Staging Tool (COAST). Image courtesy of Elanco.

STAGE 2

Core treatment recommendations

Client education	Disease and progression, assessment and treatment plan
Weight optimization and nutrition	Adequate DHA/EPA supplementation, joint focused diets
Regular exercise	Well-balanced training and suitable daily exercise
Physical rehabilitation	Injury prevention, risk factor identification, muscle strength support
Pain management	NSAIDs, flare up reduction

Secondary treatment considerations

Chondroprotective joint health support	Additional supplements for joint support

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OA BEHANDELING: COAST STAGE 3

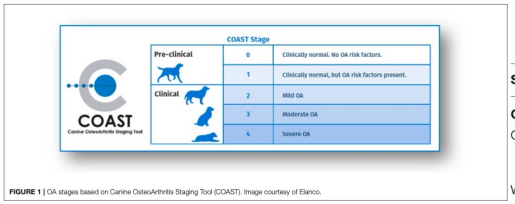

FIGURE 1 | OA stages based on Canine OsteoArthritis Staging Tool (COAST). Image courtesy of Elanco.

Potential modalities to support OA treatment plan

- Acupuncture
- Photobiomodulation
- Pulsed ElectroMagnetic Field therapy (PEMF)
- Extracorporeal Shock Wave therapy (ESWT)
- Joint injections
- Steroid epidural

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STAGE 3

Core treatment recommendations

Client education	Disease progression, regular assessment and adequate treatment plan, QoL, pain management
Weight optimization and nutrition	Adequate DHA/EPA supplementation, joint health focused diets
Regular exercise	Suitable daily exercise, case specific exercises
Physical rehabilitation	Tailored rehabilitation program for muscle strength and joint support
Lifestyle adjustments	Changes for mobility support and injury prevention
Pain management	NSAIDs with individualized multimodal pain management plan

Secondary treatment considerations

Pharmaceutical medications	Pregabalin/Gabapentin, Anti-NGFmAb
Nutraceutical supplements	Cannabinoids, chondroprotective joint health support (DMOAD)
Modalities	Tailored supportive modalities
Interventional modalities	Joint injections, steroid epidural

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OA BEHANDELING: COAST STAGE 4

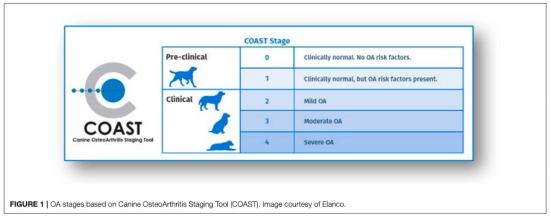

FIGURE 1 | OA stages based on Canine OsteoArthritis Staging Tool (COAST). Image courtesy of Elanco.

Potential modalities to support OA treatment plan

Acupuncture
Photobiomodulation
Pulsed ElectroMagnetic Field therapy (PEMF)
Extracorporeal Shock Wave therapy (ESWT)
Joint injections
Steroid epidural

STAGE 4

Core treatment recommendations	
Client education	QoL discussion and pain management, regular assessment, owner support
Weight optimization and nutrition	Adequate DHA/EPA supplementation, joint health focused diets
Regular exercise	Suitable daily exercise, case specific exercises
Physical rehabilitation	Tailored rehabilitation program for muscle strength and joint support, mental stimulation and QoL support
Lifestyle adjustments	Mobility and QoL support, injury prevention
Pain Management	NSAIDs, anti NGF mAb, individualized multimodal pain management plan
Secondary treatment considerations	
Pharmaceutical medications	Pregabalin/Gabapentin, Amantadine
Nutraceutical supplements	Cannabinoids, chondroprotective joint health support (DMOAD)
Modalities	Tailored supportive modalities
Interventional modalities	Joint injections, steroid epidural

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NIET-STEROÏDALE ONTSTEKINGSREMMERS

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NSAIDS

- inhibitie van COX-enzymen
- grijpen aan op de TRANSDUCTIE in de pijnpathway:
  - belangrijk, want STAP 1 in de pijnpathway!!
  - remmen de vorming van prostaglandines
    - PGE_2
  - verminderen nociceptie & primaire hyperalgesie
    - preventie EP4 receptor activatie & upregulatie

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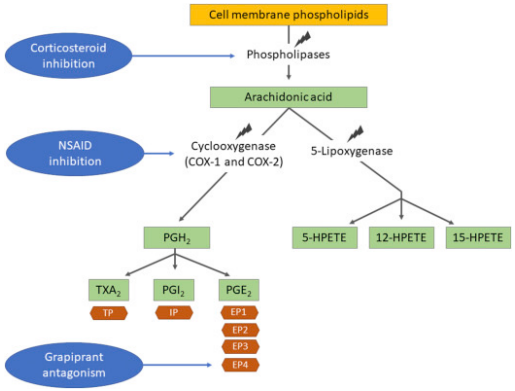
NSAIDS

- werking NSAIDs:
- klassieke NSAIDs
  - verminderen vorming van prostanoïden
- piprants (grapiprant)
  - verminderen activatie EP4 receptor



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Monteiro & Steagall 2020 Antiinflammatory Drugs. Vet Clin Small Anim 49 (2019) 993–1011.

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NSAIDS

- NSAIDs zijn vaak de hoeksteen van de behandeling igv een belangrijke ontstekingscomponent, mits er geen tegenindicaties zijn voor hun gebruik.
- Nummer 1 optie in de behandeling van OA
- langdurige, efficiënte onderdrukking van de ontstekingsreactie & sensitizatie van nociceptoren
- het gebruik van een 'individueel geschikt' NSAID is aangewezen
  - efficiëntie is patiëntafhankelijk
  - nevenwerkingen zijn patiëntafhankelijk
  - behandelingsduur is patiëntafhankelijk

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Mosley C, Edwards T, Romano L, Truchetti G, Dunbar L, Schiller T, Gibson T, Bruce C, Troncy E. Proposed Canadian Consensus Guidelines on Osteoarthritis Treatment Based on OA-COAST Stages 1-4. Front Vet Sci. 2022 Apr 26;9:830098.

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BEHANDELING – NSAIDS

- behandelingsduur voor OA bij de hond:
  - minimaal 4 weken aan geregistreerde dosis
    - efficiënte ontstekingsremming op cellulair niveau!
    - ook indien er reeds klinische verbetering is op W1
  - opvolging na 1 week: tolerantie NSAID
  - reëvaluatie effect na 4 weken
  - lange termijn behandeling kan nodig zijn
    - bloedonderzoek (CBC/biochemie) elke 3-6 maanden

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Mosley C, Edwards T, Romano L, Truchetti G, Dunbar L, Schiller T, Gibson T, Bruce C, Troncy E. Proposed Canadian Consensus Guidelines on Osteoarthritis Treatment Based on OA-COAST Stages 1-4. Front Vet Sci. 2022 Apr 26;9:830098.

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BEHANDELING - NSAIDS

- langdurige toediening vereist soms het zoeken naar de laagst effectieve dosis en het langste doseringsinterval
  - maar dosisreductie minder efficiënt dan continue toediening (meer patiënten vallen uit)
    - alleen eerste dosisreductie v 15% was efficiënt bij 87% vd honden (Wernham et al., 2011)
  - dosisreductie met behoud van efficiëntie is individu afh
    - niet <60% van de initiële dosis
- therapietrouw blijft echter belangrijk (eigenaar motivatie!)

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Wernham, B. G. J., Trumpatori, B., Hash, J., Lipsett, J., Davidson, G., Wackerow, P., et al. (2011). Dose Reduction of Meloxicam in Dogs with Osteoarthritis-Associated Pain and Impaired Mobility. J Vet Intern Med, 25(6), 1298–1305.

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NSAIDS

NSAIDs voor behandeling van chronische pijn bij de hond.

Bij de kat is enkel meloxicam geregistreerd voor langdurige toediening!

Drug	Dosage form	Dose	Licence duration
Carprofen	20, 50, 100 and 120 mg chewable tablets; 20, 50 and 100 mg tablets	4 mg/kg for seven days, then reduce to 2 mg/kg	No upper limit for duration, although regular veterinary supervision is advised
Meloxicam	1.5 mg/ml oral liquid; 1 and 2.5 mg chewable tablets; oral transmucosal spray	0.2 mg/kg loading dose followed 24 hours later with 0.1 mg/kg once a day. Adjust to lowest effective dose	No upper time limit, although regular veterinary assessment is advised
Cimicoxib	8, 30 and 80 mg chewable tablets	2 mg/kg once a day	Six months for osteoarthritis; beyond this, regular monitoring is required
Ketoprofen	5 and 20 mg tablets	0.25 mg/kg once a day	Up to 30 days, then the patient must be re-examined
Robenacoxib	5, 10, 20 and 40 mg flavoured tablets	1 to 2 mg/kg orally once a day initially and then at the lowest effective dose	No upper time limit at the lowest effective dose
Firocoxib	57 and 227 mg chewable tablets	5 mg/kg orally once a day for osteoarthritis	If used for more than 90 days, the patient requires monitoring
Mavacoxib	6, 20, 30, 75 or 95 mg chewable tablets	2 mg/kg orally, repeated after 14 days and then once monthly. This is not a daily NSAID	Do not exceed seven consecutive doses in a treatment cycle
Enflicoxib	15, 30, 45, 70, 100 mg chewable tablets	1st dose: 8 mg/kg orally with food 2nd & further doses: 4 mg/kg orally every 7 days This is not a daily NSAID	

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BEHANDELING NSAIDS – ENFLICOXIB

Multicenter Study > Vet Rec. 2022 Sep;191(6):e949. doi: 10.1002/vetr.949. Epub 2021 Sep 29.

Efficacy and safety of enflicoxib for treatment of canine osteoarthritis: A 6-week randomised, controlled, blind, multicentre clinical trial

Marta Salichs [1], Llorenç Badiella [2], Patxi Sarasola [3], Josep Homedes [1]

Abstract

Background: Enflicoxib is a new COX-2 selective NSAID intended for the treatment of pain and inflammation associated with canine osteoarthritis.

Methods: A prospective, multisite, blinded, randomised, controlled, parallel-group field study was performed to determine the efficacy and safety of enflicoxib in canine osteoarthritis. A total of 242 dogs were randomised to receive enflicoxib at 4 or 2 mg/kg, mavacoxib at 2 mg/kg or placebo, orally. Enflicoxib and placebo were administered once weekly from day 0 to day 35. Mavacoxib was administered on D0 and day 14. Veterinarians assessed efficacy with a numerical rating scale and owners used the Canine Brief Pain Inventory.

Results: After 6 weeks, enflicoxib at 4 mg/kg showed the highest percentage of responders as assessed by the veterinarians (68%) and the owners (84%), followed by mavacoxib (62and 83%, respectively), and enflicoxib at 2 mg/kg (57 and 80%, respectively). All treatments reached statistical significance versus placebo, which obtained success rates of 37% and 53%, respectively. No differences in the incidence of adverse reactions were detected among the different groups.

Conclusions: Enflicoxib administered weekly for 6 weeks, at 4 mg/kg PO with an initial loading dose of 8 mg/kg, is efficacious and safe for the treatment of canine osteoarthritis.

Randomized Controlled Trial > PLoS One. 2022 Sep 20;17(9):e0274800. doi: 10.1371/journal.pone.0274800. eCollection 2022.

Enflicoxib for canine osteoarthritis: A randomized, blind, multicentre, non-inferiority clinical trial compared to mavacoxib

Marta Salichs [1], Llorenç Badiella [2], Patxi Sarasola [3], Josep Homedes [1]

Results: The overall CSS expressed as area under the curve demonstrated non-inferiority of enflicoxib compared to mavacoxib, and both showed superiority over placebo. At the end of the study, average CSS, and the percentage of CSS responders for enflicoxib (3.64 and 74%) and mavacoxib (4.49 and 68%), was superior to placebo (7.15 and 29%). A faster onset of action was observed for enflicoxib as superiority over placebo was evidenced from the first efficacy assessment (day 7) onwards for both parameters, whereas mavacoxib was only significantly different from day 14 onwards. According to the owner assessment, the percentage of CBPI responders was 90%, 79%, and 43% for dogs treated with enflicoxib, mavacoxib and placebo, respectively, and superiority over placebo was demonstrated for both active treatments. In all secondary parameters, non-inferiority of enflicoxib versus mavacoxib was confirmed. The dog's quality of life improved in all groups, but only enflicoxib showed superiority versus placebo. When assessing severely affected dogs only, results were similar, thus confirming the efficacy of enflicoxib in all stages of canine OA. There were no differences between groups in the frequency of adverse events, which were most frequently mild affecting the gastrointestinal tract and recovered without treatment.

Conclusions: Enflicoxib is efficacious and safe for the treatment of pain and inflammation in any stage of canine osteoarthritis with a faster onset of action compared to mavacoxib.

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NSAIDS NEVENEFFECTEN

- alle NSAIDs (ook piprants) kunnen nevenwerkingen veroorzaken
- bij inefficiëntie of neveneffecten overschakelen naar ander NSAID
  - respecteer een wash-out periode
    - 4-5 eliminatie halftijden = 5-7 dagen
    - langer bij mavacoxib & enflicoxib
  - toediening gastroprotectiva??? risico op bacteriële dysbiose & daarom baten/risio analyse
  - QOL belangrijker dan eventuele aanvaardbare neveneffecten

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Pye C, Bruniges N, Peffers M, Comerford E. Advances in the pharmaceutical treatment options for canine osteoarthritis. J Small Anim Pract. 2022 Oct;63(10):721-738. doi: 10.1111/jsap.13495. Epub 2022 Mar 14. 32

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NSAIDS NEVENEFFECTEN

- Incidentie:
  - geen robuste data beschikbaar over de lange termijn veiligheid van NSAID toediening bij honden.
  - de echte incidentie van neveneffecten is dus onbekend.
  - gebrek aan melding van neveneffecten door de eigenaar
  - sommige neveneffecten worden getolereerd

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Hunt, J. R., Dean, R. S., Davis, G. N. D., & Murrell, J. C. (2015). An analysis of the relative frequencies of reported adverse events associated with NSAID administration in dogs and cats in the United Kingdom. *Veterinary Journal*, *206*(2), 183–190. https://doi.org/10.1016/j.tvjl.2015.07.025

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NSAIDS NEVENEFFECTEN

- GI-irritatie braken, (bloederige)diarree, ulceratie
- anorexie
- lethargie
- nierinsufficiëntie (komt zelden voor)
- verlengde bloedingstijden door verminderde bloedplaatjesaggregatie (komt zelden voor)

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Lawson, A. (2019). Monitoring side effects of long-term NSAID use in dogs with chronic osteoarthritis. *In Practice*, *41*(4), 148–154. https://doi.org/10.1136/inp.l1506

Hunt, J. R., Dean, R. S., Davis, G. N. D., & Murrell, J. C. (2015). An analysis of the relative frequencies of reported adverse events associated with NSAID administration in dogs and cats in the United Kingdom.

Innes JF, Clayton J, Lascelles BDX. Review of the safety and efficacy of long- term NSAID use in the treatment of canine osteoarthritis. *Vet Record.* (2010) 166:226–30.

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NSAIDS NEVENEFFECTEN

- leverfalen (komt zelden voor)
  - extensieve hepatische klaring
  - idiosyncratisch hepatotoxicosis (onafhankelijk van de dosis) 1/1000 tot 1/10.000
    - beschreven bij carprofen
    - verhoging van leverenzymen & bilirubine
  - intrinsiek (dosis afhankelijk)

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NSAIDS SCREENING BIJ LANGE TERMIJN GEBRUIK

- baseline serumbiochemie nier- & leverwaarden bepalen alvorens een langdurige NSAID therapie te starten = SCREENING.
- vervolgens:
  - op regelmatige basis hercontroles (iedere 3-6 m)
  - eigenaars motiveren om neveneffecten op te volgen

Mosley C, Edwards T, Romano L, Truchetti G, Dunbar L, Schiller T, Gibson T, Bruce C, Troncy E. Proposed Canadian Consensus Guidelines on Osteoarthritis Treatment Based on OA-COAST Stages 1-4. Front Vet Sci. 2022 Apr 26;9:830098.

Chalifoux, N. V., Kaiman, G., Drobatz, K. J., & Thawley, V. J. (2020). Evaluation of renal and hepatic blood value screening before non-steroidal anti-inflammatory drug administration in dogs. *Journal of Small Animal Practice*, 1–7. https://doi.org/10.1111/jsap.13230

Kukanich, B., Bidgood, T., & Knesl, O. (2012). Clinical pharmacology of nonsteroidal anti-inflammatory drugs in dogs. *Veterinary Anaesthesia and Analgesia*, *39*(1), 69–90. https://doi.org/10.1111/j.1467-2995.2011.00675.x

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NSAIDS SCREENING

- bevindingen studie bij de hond:
  - een leeftijdsgrens van 8 jaar is een potentiële predictor voor milde afwijkingen in lever- en nierwaarden, die een invloed kunnen hebben op het voorschrijven van NSAIDs
  - vooral afwijkende leverwaarden weerhielden d'artsen ervan om NSAIDs voor te schrijven

Chalifoux, N. V., Kaiman, G., Drobatz, K. J., & Thawley, V. J. (2021). Evaluation of renal and hepatic blood value screening before non-steroidal anti-inflammatory drug administration in dogs. *Journal of Small Animal Practice 62*, 12-18.

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!CONTRAINDICATIES VOOR NSAIDS!

- geschiedenis van GI aandoeningen
- NSAID intolerantie (ander type NSAID is wel een optie)
- ongecontroleerde nier- of leveraandoeningen
- anemie
- coagulopathie
- hypovolemie of dehydratatie
- hypotensie

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!CONTRAINDICATIES VOOR NSAIDS!

- heel erg belangrijk om dierenartsen/eigenaars in te lichten over:
  - welke neveneffecten te verwachten
  - onmiddellijk stoppen met toediening van een NSAID wanneer neveneffecten zich voordoen
  - screening bij lange termijn toediening van NSAIDS
  - follow-up van de patiënt in chronische pijnconsultaties

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PARACETAMOL

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BEHANDELING - PARACETAMOL

- complex niet volledig gekend werkingsmechanisme:
  - COX inhibitie perifeer & centraal (COX-3)
  - serotonergische pathway – stimuleert descenderende pijnbanen
  - endocannabinoid systeem

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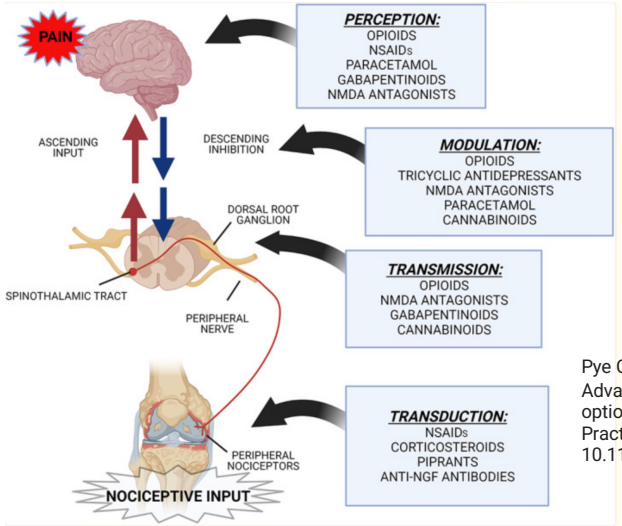

Pye C, Bruniges N, Peffers M, Comerford E. Advances in the pharmaceutical treatment options for canine osteoarthritis. J Small Anim Pract. 2022 Oct;63(10):721-738. doi: 10.1111/jsap.13495. Epub 2022 Mar 14.

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BEHANDELING- PARACETAMOL

- dosering ALLEEN HOND!!:
  - 10-25 mg/kg TID, indien langer dan 5 dagen
  - nauwe therapeutische breedte
- off label gebruik voor bijkomende analgesie samen met een NSAID
  - bij kanker pijn
  - 'breakthrough OA pain'
- off label: tolerantieproblemen NSAIDs (Pettit & German, 2015)

- humaan niet aangeraden als single-treatment voor OA, wegens gebrek aan effect
  - 'evidence gap' in DGK, maar gedocumenteerde case efficiëntie
  - geen gecontroleerde studies voor chronische pijn & multimodale aanpak van bijvoorbeeld OA

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Towheed TE, Judd MJ, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev.* (2003) 2:CD004257. doi: 10.1002/14651858.CD004257

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BEHANDELING - PARACETAMOL

- **Clinical evaluation of postoperative analgesia, cardiorespiratory parameters and changes in liver and renal function tests of paracetamol compared to meloxicam and carprofen in dogs undergoing ovariohysterectomy. Hernández-Avalos et al. 2020.**
  PLoS One 2020 Feb 14;15(2):e0223697 doi: 10.1371/journal.pone.0223697.

Paracetamol was as effective as meloxicam and carprofen for post-surgical analgesia in bitches subjected to elective ovariohysterectomy. The present study demonstrates that paracetamol may be considered a tool for the effective treatment of acute perioperative pain in dogs.

- **Comparing paracetamol/codeine and meloxicam for postoperative analgesia in dogs: a non-inferiority trial. Pacheco et al. 2020.**
  Vet Rec. 2020 Oct 17;187(8):e61. doi: 10.1136/vr.105487. Epub 2020 Jan 3. PMID: 31900324.

Paracetamol/codeine is a useful perioperative analgesic that within the context of the perioperative analgesia regimen studied (methadone premedication, buprenorphine for the first 24 hours after surgery) shows non-inferiority to the NSAID meloxicam.

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BEDINVETMAB
LIBRELA

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BEHANDELING – LIBRELA (BEDINVETMAB)

- Librela (bedinvetmab)
  - Canine monoclonale antistof tegen NGF
  - behandeling van OA pijn bij de hond
  - NGF activeert de TrkA receptor, belangrijk voor pijn bij OA
    - perifere sensitisatie: meer NGF, threshold reductie nociceptoren & ontstekingsmediatoren release
    - centrale sensitisatie: verandert dorsale hoorn gene expression & versterkt glutamaat transmissie

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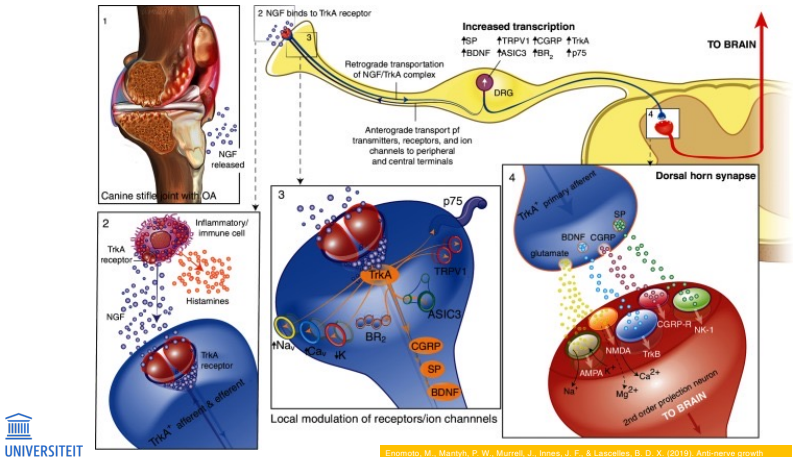
BEHANDELING – LIBRELA (BEDINVETMAB)



Enomoto, M., Mantyh, P. W., Murrell, J., Innes, J. F., & Lascelles, B. D. X. (2019). Anti-nerve growth factor monoclonal antibodies for the control of pain in dogs and cats. *Veterinary Record, 184*(1), 1–14. https://doi.org/10.1136/vr.104590

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BEHANDELING – LIBRELA (BEDINVETMAB)

- Librela (bedinvetmab)
  - 0.5-1 mg/kg SC per maand
  - 3 maanden veldstudie:
    - succes na dosis 1 (CBPI): 43.5% Lib vs. 16.9% Plac
  - steady state concentratie na 2 doses
  - neveneffect: milde reacties op de injectieplaats

	LIBRELA toe te dienen sterkte (mg)				
Lichaamsgewicht (kg) van de hond	5	10	15	20	30
5,0-10,0	1 flacon				
10,1-20,0		1 flacon			
20,1-30,0			1 flacon		
30,1-40,0				1 flacon	
40,1-60,0					1 flacon
60,1-80,0				2 flacons	
80,1-100,0				1 flacon	1 flacon
100,1-120,0					2 flacons

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BEHANDELING – LIBRELA (BEDINVETMAB)

- D28, 43.5% Lib vs. 16.9% Plac (p = 0.0017)
- D56 (50.8%) and 84 (48.2%) vs. < 25% Plac op alle tijdstippen
- bewijs van effectiviteit en veiligheid van bedinvetmab voor een maandelijkse toediening gedurende 9 maanden bij honden met OA

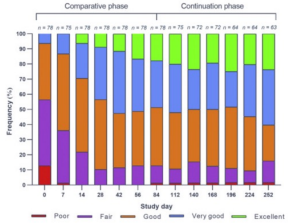

Figure 4 Percentage of dogs with osteoarthritis administered bedinvetmab (bedinvetmab group, n = 89) by subcutaneous monthly injection for 9 months, enrolled in the comparative and continuation phases of the study, and were classified by the owners as having a 'poor', 'fair', 'good', 'very good' or 'excellent' overall impression of quality of life (QoL) on the CBPI assessment. A protocol deviation resulted in exclusion of 11 dogs enrolled in the continuation phase from all efficacy assessments at all time points. Data excluded from the efficacy analysis due to protocol deviations (visits out of the allowed window, different owner completing the assessments) or administration of prohibited treatments explains the cases excluded from the efficacy analysis. Data are presented as percentage of dogs (%) for each QoL category. CBPI, canine brief pain inventory; n, number of dogs.

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BEHANDELING – LIBRELA (BEDINVETMAB)

- Librela (bedinvetmab)
  - combinatie met een NSAID?
    - getest met carprofen in gezonde honden! gedurende enkel 2 weken (Krautmann et al. 2021)
    - bij de mens: snel progressieve OA na combi (Hefti, 2020)
    - bij de hond: lange termijn gecombineerde toediening kan nog niet aangeraden worden, geen studies
  - positief effect op de 3 componenten van de CBPI:
    - ernst van de pijn
    - interferentie pijn met typische activiteiten
    - quality of life
  - focust ook op het verhinderen van 'breakthrough pain'
  - wordt ook ingezet bij de refractaire OA patiënten (COAST stage 4)

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FRUNEVETMAB SOLENSIA

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BEHANDELING – SOLENSIA (FRUNEVETMAB)

- Solensia (Frunevetmab)
  - Feline monoclonale antistof tegen NGF
  - behandeling van OA pijn bij de kat

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BEHANDELING – SOLENSIA (FRUNEVETMAB)

- Solensia (Frunevetmab)
  - 1-2.8 mg/kg SC per maand
  - steady state concentratie na 2 doses

Lichaamsgewicht (kg) van de kat	**SOLENSIA (7 mg/ml) toe te dienen volume**
2,5 – 7,0	**1 flacon**
7,1 – 14,0	**2 flacons**

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BEHANDELING – SOLENSIA (FRUNEVETMAB)

- Solensia (Frunevetmab)
  - 1-2.8 mg/kg SC per maand
  - 3 maanden veldstudie:

	Group	N	% success[b]	95% confidence interval	*P*-value
Day 28	Frunevetmab	178	66.7	59.64, 73.09	.02*
	Placebo	93	52.06	41.84, 62.11	
Day 56	Frunevetmab	176	75.91	69.06, 81.65	.03*
	Placebo	91	64.65	53.99, 74.02	
Day 84	Frunevetmab	167	76.47	69.57, 82.21	.08
	Placebo	89	68.09	57.60, 77.01	

TABLE 2 Summary of treatment success[a] for CSOM at days 28, 56, and 84

How to cite this article: Gruen ME, Myers JAE, Tena J-KS, Becskei C, Cleaver DM, Lascelles BDX. Frunevetmab, a felinized anti-nerve growth factor monoclonal antibody, for the treatment of pain from osteoarthritis in cats. *J Vet Intern Med*. 2021;35(6):2752-2762. doi:10.1111/jvim.16291

  - significant meer dermatologische neveneffecten in de frunevetmab groep (alopecia, pruritis, eczema, dermatitis,…)

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TRAMADOL

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BEHANDELING – TRAMADOL

- Tramadol

  - synthetisch codeine analoog
  - 1/10de potentie van morfine
  - zwakke μ-receptor agonist (40%)
    - (+)-enantiomeer van tramadol en M1 metaboliet
  - inhibitie van norepinephrine reuptake (20%)
    - (-)-enantiomeer van tramadol
  - inhibitie van serotonine reuptake (20%)
    - (+)-enantiomeer van tramadol
  - stimuleert descenderende inhibitorische pijn pathways

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BEHANDELING – TRAMADOL

- Tramadol
  - opioid analgetisch effect is afhankelijk van de vorming van de M1-metaboliet
  - CYP450 enzyme is verantwoordelijk hiervoor
  - interspecies, intraspecies & interindividuele variatie in analgetische potentie wordt veroorzaakt door verschillen in metabolisatie
  - mens: CYP2D6: ‘poor metabolizers’ resulteert in minder goede analgesie

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BEHANDELING – TRAMADOL

- Tramadol
  - M1 synthese bij de hond is lager dan de concentraties die geassocieerd worden met analgesie bij de mens
  - M1 synthese bij de kat is vergelijkbaar met concentraties die geassocieerd worden met analgesie bij de mens
  - orale toediening van tramadol bij de hond voor een periode langer dan 1 week kan resulteren in een reductie van de plasma concentratie te wijten aan een ongekend mechanisme

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BEHANDELING – TRAMADOL

- Tramadol
  - dosis hond: 2-5 mg/kg bid tot qid, variabele efficiëntie!
  - dosis kat: 2-4 mg/kg bid (mindere metabolisatie, lagere klaring) (off-label)

    Am J Vet Res. 2009 Dec;70(12):1465-70. doi: 10.2460/ajvr.70.12.1465.

    Effects of tramadol hydrochloride on the thermal threshold in cats.

    Pypendop BH[1], Siao KT, Ilkiw JE.
  - aandacht: serotonine syndroom! wanneer samen gebruikt wordt met SSRI's, MAOI's, tricyclische antidepressiva!

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BEHANDELING – TRAMADOL

- Tramadol
  - neveneffecten (vooral bij de kat):
    - sedatie
    - dysphorie
    - braken/diarree bij de hond
  - niet combineren met MAO-inhibitoren/SSRI's
- Tapentadol
  - toekomst: efficiëntie is onafhankelijk van metabolieten
  - nog geen aanbevolen dosering beschikbaar

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BEHANDELING – TRAMADOL

J Am Vet Med Assoc. 2018 Feb 15;252(4):427-432. doi: 10.2460/javma.252.4.427.

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

Budsberg SC, Torres BT, Kleine SA, Sandberg GS, Berjeski AK.

Abstract

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. RESULTS 35 dogs completed the study. No significant changes from baseline in VI and PVF were identified for placebo and tramadol treatments; however, these values increased significantly with carprofen treatment. Changes from baseline in VI and PVF values were significantly greater with carprofen versus placebo or tramadol treatment. A significant improvement from baseline in CBPI scores was identified with carprofen treatment but not placebo or tramadol treatment. 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.

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BEHANDELING - TRAMADOL

Vet Anaesth Analg. 2017 Mar;44(2):309-316. doi: 10.1016/j.vaa.2016.02.003. Epub 2017 Jan 7.

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

Schütter AF[1], Tünsmeyer J[2], Kästner SBR[2].

Author information

Abstract

OBJECTIVE: The aim of the study was to evaluate the influence of tramadol on acute nociception in dogs.

STUDY DESIGN: Experimental, blinded, randomized, crossover study.

ANIMALS: Six healthy laboratory Beagle dogs.

METHODS: Dogs received three treatments intravenously (IV): isotonic saline placebo (P), tramadol 1 mg kg^{-1} (T1) and tramadol 4 mg kg^{-1} (T4). Thermal thresholds were determined by ramped contact heat stimulation (0.6 °C $second^{-1}$) at the lateral thoracic wall. Mechanical thresholds (MT) were measured using a probe containing three blunted pins which were constantly advanced over the radial bone, using a rate of force increase of 0.8 N $second^{-1}$. Stimulation end points were defined responses (e.g. skin twitch, head turn, repositioning, vocalization) or pre-set cut-out values (55 °C, 20 N). Thresholds were determined before treatment and at predetermined time points up to 24 hours after treatment. At each measurement point, blood was collected for determination of O-desmethyltramadol concentrations. The degree of sedation and behavioural side effects were recorded. Data were analysed by one-way anova and two-way anova for repeated measurements.

RESULTS: Thermal nociception was not influenced by drug treatment. Mechanical nociception was significantly increased between P and T1 at 120 and 240 minutes, and between P and T4 at 30, 60, 240 and 420 minutes. T1 and T4 did not differ. O-desmethyltramadol (M1) maximum plasma concentrations (C_{max}) were 4.2±0.8 ng mL^{-1} and 14.3±2.8 ng mL^{-1} for T1 and T4, respectively. Times to reach maximum plasma concentrations (T_{max}) were 27.6±6.3 minutes for T1 and 32.1±7.8 minutes for T4. No sedation occurred. There were signs of nausea and mild to moderate salivation in both groups.

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.

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BEHANDELING - TRAMADOL

Am J Vet Res. 2015 Sep;76(9):763-70. doi: 10.2460/ajvr.76.9.763.

Pharmacokinetics of hydrocodone and tramadol administered for control of postoperative pain in dogs following tibial plateau leveling osteotomy.

Benitez ME, Roush JK, KuKanich B, McMurphy R

Abstract

OBJECTIVE: To evaluate the pharmacokinetics of hydrocodone (delivered in combination with acetaminophen) and tramadol in dogs undergoing tibial plateau leveling osteotomy (TPLO).

ANIMALS: 50 client-owned dogs.

PROCEDURES: Dogs were randomly assigned to receive tramadol hydrochloride (5 to 7 mg/kg, PO, q 8 h; tramadol group) or hydrocodone bitartrate-acetaminophen (0.5 to 0.6 mg of hydrocodone/kg, PO, q 8 h; hydrocodone group) following TPLO with standard anesthetic and surgical protocols. Blood samples were collected for pharmacokinetic analysis of study drugs and their metabolites over an 8-hour period beginning after the second dose of the study medication.

RESULTS: The terminal half-life, maximum serum concentration, and time to maximum serum concentration for tramadol following naïve pooled modeling were 1.56 hours, 155.6 ng/mL, and 3.90 hours, respectively. Serum concentrations of the tramadol metabolite O-desmethyltramadol (M1) were low. For hydrocodone, maximum serum concentration determined by naïve pooled modeling was 7.90 ng/mL, and time to maximum serum concentration was 3.47 hours. The terminal half-life for hydrocodone was 15.85 hours, but was likely influenced by delayed drug absorption in some dogs and may not have been a robust estimate. Serum concentrations of hydromorphone were low.

CONCLUSIONS AND CLINICAL RELEVANCE: The pharmacokinetics of tramadol and metabolites were similar to those in previous studies. Serum tramadol concentrations varied widely, and concentrations of the active M1 metabolite were low. Metabolism of hydrocodone to hydromorphone in dogs was poor. Further study is warranted to assess variables that affect metabolism and efficacy of these drugs in dogs.

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BEHANDELING - TRAMADOL

Efficacy of tramadol for postoperative pain management in dogs: systematic review and meta-analysis. Donati et al. 2021.
VAA; February 09, 2021DOI:https://doi.org/10.1016/j.vaa.2021.01.003

Overall 26 RCTs involving 848 dogs were included. Tramadol administration probably results in a lower need for rescue analgesia *versus* no treatment or placebo [moderate CoE; relative risk (RR): 0.47; 95% confidence interval (CI): 0.26–0.85; I^2 = 0%], and may result in a lower need for rescue analgesia *versus* buprenorphine (low CoE; RR: 0.50; 95% CI: 0.20–1.24), codeine (low CoE; RR: 0.75; 95% CI: 0.16–3.41) and nalbuphine (low CoE; RR: 0.05; 95% CI: 0.00–0.72). However, tramadol administration may result in an increased requirement for rescue analgesia *versus* methadone (low CoE; RR: 3.45; 95% CI: 0.66–18.08; I^2 = 43%) and COX inhibitors (low CoE; RR: 2.27; 95% CI: 0.68–7.60; I^2 = 45%). Compared with multimodal therapy, tramadol administration may make minimal to no difference in the requirement for rescue analgesia (low CoE; RR: 1.12; 95% CI: 0.48–2.60; I^2 = 0%). Adverse events were inconsistently reported and the CoE was very low. The overall CoE 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.

CoE=Certainty of Evidence

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BEHANDELING - TRAMADOL

Efficacy of tramadol for postoperative pain management in dogs: systematic review and meta-analysis. (Donati et al. 2021)

VAA; February 09, 2021DOI:https://doi.org/10.1016/j.vaa.2021.01.003

- meta-analyse: 26 randomized controlled trials, 848 honden.
- De overall coefficient of evidence voor postoperatieve analgesie was laag tot zeer laag:
  - waarschijnlijk minder nood aan rescue analgesia tov geen behandeling
  - misschien minder nood aan rescue analgesie dan buprenorphine
  - misschien inferieur aan methadone en NSAIDs

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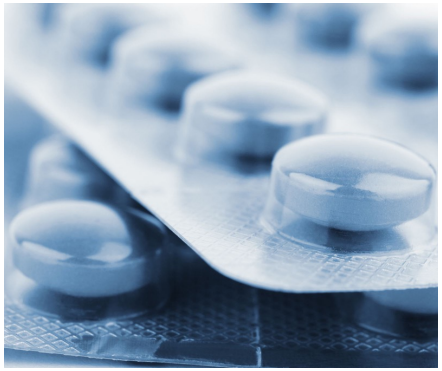
BEHANDELING - TRAMADOL

- plaats voor tramadol in pijnbehandeling
  - korte termijn post-operatieve acute pijnbehandeling
    - ter vervanging van opiaten (‘at home’ treatment)
  - multimodale & ‘breakthrough pain’ behandeling
    - osteoarthritis in combinatie met andere analgetica
  - Monteiro et al. 2019: + verminderde dosis ketoprofen voor 28d
  - Miles et al. 2020: + NSAID voor 28d
  - effect is patiëntafhankelijk



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NMDA - ANTAGONISTEN

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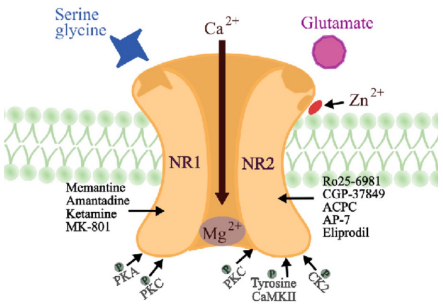
BEHANDELING - NMDA-ANTAGONISTEN

- werkingsmechanisme:
  - dopamine agonist & glutamaat antagonist
  - effect:
    - NMDA-receptor blokkade op het niveau van de dorsale hoorn (ruggemerg)
    - verhindert activatie v NMDA receptor na sterke of langdurige C-vezels input (= > glutamaat vrijstelling)
    - versnelt NMDA receptor sluiting na activatie van de receptor



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BEHANDELING – NMDA-ANTAGONISTEN

- Amantadine (Amantan®)
  - anti-viraal geneesmidel/behandeling van Parkinson
  - orale NMDA-receptor antagonist
  - dosisreductie van & synergistisch effect met opioiden
  - combinaties met NSAID/paracetamol (hond)/ gabapentine
  - effect pas na 3 weken
  - dosis hond: 3-5 mg/kg SID tot BID
  - dosis kat: 1-4 mg/kg SID
  - neveneffecten:
    - diarree (stop toediening & herintroduceer later)
  - EMA aanbeveling om amantadine te beperken tot humaan gebruik

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Norkus C, Rankin D, Warner M, KuKanich B. Pharmacokinetics of oral amantadine in greyhound dogs. *J Vet Pharmacol Ther.* (2015) 38:305–8. doi: 10.1111/jvp.12190

Lascelles, B. D. X., Gaynor, J. S., Smith, E. S. et al. (2008). Amantadine in a Multimodal Analgesic Regimen for Alleviation of Refractory Osteoarthritis Pain in Dogs. *Journal of Veterinary Internal Medicine*, *22*(1), 53–59.

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BEHANDELING – NMDA ANTAGONISTEN

J Vet Intern Med. 2008 Jan-Feb;22(1):53-9. doi: 10.1111/j.1939-1676.2007.0014.x.

Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs.

Lascelles BD[1], Gaynor JS, Smith ES, Roe SC, Marcellin-Little DJ, Davidson G, Boland E, Carr J.

Author information

Abstract

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.

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BEHANDELING – NMDA ANTAGONISTEN

Original Article

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SAGE

Owner evaluation of quality of life and mobility in osteoarthritic cats treated with amantadine or placebo

Hilary Shipley[1,2], Kristi Flynn[1], Laura Tucker[1,3], Erin Wendt-Hornickle[1], Caroline Baldo[1], Daniel Almeida[1], Sandra Allweiler[1,4] and Alonso Guedes[1]

Abstract

Objectives The aim of the study was to determine if amantadine improves owner-identified mobility impairment and quality of life associated with osteoarthritis in cats.

Methods Using a blinded, placebo-controlled, randomized, crossover design, 13 healthy client-owned cats with clinical and radiographic evidence of osteoarthritis and owner-identified mobility impairment were studied. Cats received 5 mg/kg amantadine or placebo q24h PO for 3 weeks each with no washout period in between. Locomotor activity was continuously assessed with a collar-mounted activity monitor system, and owners chose and rated two mobility-impaired activities using a client-specific outcome measures (CSOM) questionnaire on a weekly basis. Locomotor activity on the third treatment week was analyzed with two-tailed paired *t*-tests. The CSOM scores were analyzed using a mixed-effect model and the Bonferroni post-hoc test. Owner-perceived changes in quality of life were compared between treatments using the χ^2 test. Statistical significance was set at $P < 0.05$.

Results Mean ± SD activity counts during the third week of each treatment were significantly lower with amantadine (240,537 ± 53,880) compared with placebo (326,032 ± 91,759). CSOM scores assigned by the owners were significantly better with amantadine on the second (3 ± 1) and third (3 ± 1) weeks compared with placebo (5 ± 2 and 5 ± 1, respectively). A significantly greater proportion of owners reported improvement in quality of life with amantadine compared with placebo.

Conclusions and relevance Amantadine significantly decreased activity, but improved owner-identified impaired mobility and owner-perceived quality of life in cats with osteoarthritis. Amantadine appears to be an option for the symptomatic treatment of osteoarthritis in cats.

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BEHANDELING - MEMANTINE

- Memantine
  - orale NMDA-receptor antagonist
  - dosis hond: 0.3-0.5 mg/kg SID, verhogen tot max 1 mg/kg BID
  - dosis afgeleid uit behandeling van honden met OCD
  - anecdotisch gebruik
  - orale oplossing, 10 & 20 mg tabletten
  - combinatie met NSAID/paracetamol (hond)/gabapentine

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Schneider BM, Dodman NH, Maranda L. (2009) Use of memantine in treatment of canine compulsive disorders. *J Vet Behav Clin Appl Res* 4(3):118–26.

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GABAPENTINOIDS: GABAPENTINE & PREGABALINE

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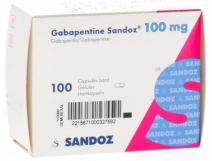
BEHANDELING - GABAPENTINOIDS

- Gabapentine
  - anti-epileptisch geneesmiddel, GABA-analoog
  - anticonvulsief, anxiolytisch
  - analgetisch effect (?)



  - blokkeert presynaptische Ca-kanalen in de dorsale hoorn
    - reduceert presynaptische glutamaat (excitatoire neurotransmitter) vrijstelling
    - vermindert postsynaptische excitatie van glutamaat receptoren
  - blokkeert centrale sensitizatie
  - activeert descenderend pijnsysteem

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BEHANDELING - GABAPENTINOIDS

- Gabapentine
  - overall body of evidence is laag, niet solo gebruiken
  - combinatie met NSAID (bij centrale sensitizatie & neurogene pijn)
    - ontstekingsremmende & neurogene component
  - dosis = geëxtrapoleerd van de mens (Kukanich & Cohen 2011)
  - gesuggereerde start dosis:
    - Ca: 10-20 mg/kg tid
    - Fe: 5-10 mg/kg tid

Randomized Controlled Trial > Vet Rec. 2015 Sep 19;177(11):288.
doi: 10.1136/vr.103234. Epub 2015 Aug 12.

Comparison of gabapentin versus topiramate on clinically affected dogs with Chiari-like malformation and syringomyelia

I N Plessas [1], H A Volk [1], C Rusbridge [2], A E Vanhaesebrouck [3], N D Jeffery [4]

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BEHANDELING -GABAPENTINOIDS

- Gabapentine
  - titreer op effect (dosis range: 2.5-50 mg/kg)
  - lange termijn behandeling kan noodzakelijk zijn (weken tot maanden)
  - sedatie & ataxie zijn dosis afhankelijk
  - normale nierfunctie is noodzakelijk (klaring)
    - dosis halveren bij verminderde nierfunctie

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BEHANDELING - GABAPENTINOIDS

› PLoS One. 2020 Nov 30;15(11):e0237121. doi: 10.1371/journal.pone.0237121. eCollection 2020.

Pain burden, sensory profile and inflammatory cytokines of dogs with naturally-occurring neuropathic pain treated with gabapentin alone or with meloxicam

Hélène L M Ruel [1], Ryota Watanabe [1], Marina C Evangelista [1], Guy Beauchamp [2], Jean-Philippe Auger [3], Mariela Segura [3], Paulo V Steagall [1]

with baseline, but not placebo. The CBPI scores were not significantly different between placebo and baseline. The concentration of cytokines was not different between groups or treatments. Dogs with NeuP have deficient inhibitory pain mechanisms. Pain burden was reduced after gabapentin and/or gabapentin-meloxicam when compared with baseline using CBPI and CMPS-SF scores. However, these scores were not superior than placebo, nor placebo was superior to baseline evaluations. A caregiver placebo effect may have biased the results.

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BEHANDELING -GABAPENTINOIDS

- Pregabaline
  - overall body of evidence is laag
    - combinatie met NSAIDs
    - efficiënter bij de mens
  - hogere orale beschikbaarheid dan gabapentine & langere halfwaardetijd
  - dosis:
    - Ca: 3-5 mg/kg BID
    - Fe: 4 mg/kg??? SID of BID???

Ohtori S, Inoue G, Orita S, Takaso M, Eguchi Y, Ochiai N, et al. Efficacy of combination of meloxicam and pregabalin for pain in knee osteoarthritis. *Yonsei Med J.* (2013) 54:1253–8.

Salazar V, Dewey CW, Schwark W, Badgley BL, Gleed RD, Horne W, et al. Pharmacokinetics of single-dose oral pregabalin administration in normal dogs. *Vet Anaesth Analg.* (2009) 36:574–80.

› Front Vet Sci. 2018 Jul 20;5:136. doi: 10.3389/fvets.2018.00136. eCollection 2018.

Pharmacokinetics of Single-Dose Oral Pregabalin Administration in Normal Cats

Michaela A Esteban [1], Curtis W Dewey [1], Wayne S Schwark [2], Mark Rishniw [1], Dawn M Boothe [3]

› J Vet Pharmacol Ther. 2022 Jul;45(4):385-391. doi: 10.1111/jvp.13061. Epub 2022 Apr 25.

Pharmacokinetics of single and repeated oral doses of pregabalin oral solution formulation in cats

Terttu Lamminen [1], Anne Doedée [2], Minja Hyttilä-Hopponen [1], Janne Kaskinoro [1]

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BEHANDELING - GABAPENTINOIDS

› Vet J. 2019 Aug;250:55-62. doi: 10.1016/j.tvjl.2019.06.006. Epub 2019 Jul 5.

Pregabalin for the treatment of syringomyelia-associated neuropathic pain in dogs: A randomised, placebo-controlled, double-masked clinical trial

S Sanchis-Mora [1], Y M Chang [2], S M Abeyesinghe [3], A Fisher [4], N Upton [4], H A Volk [5], L Pelligand [6]

P=0.004). There was no pregabalin accumulation between first and last dose. This study demonstrates the efficacy of pregabalin for the treatment of NeP due to CM/SM on daily pain scores recorded by dog owners. Pregabalin significantly reduced mechanical hyperalgesia, cold hyperalgesia (0°C) and allodynia (15°C) compared to placebo. Pregabalin was non-cumulative and well tolerated with occasional mild sedation.

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BEHANDELING - GABAPENTINOIDS

› Vet Anaesth Analg. 2020 Mar;47(2):238-248. doi: 10.1016/j.vaa.2019.09.007. Epub 2019 Nov 18.

Pregabalin alleviates clinical signs of syringomyelia-related central neuropathic pain in Cavalier King Charles Spaniel dogs: a randomized controlled trial

Maria S Thoefner [1], Lene T Skovgaard [2], Fintan J McEvoy [3], Mette Berendt [3], Ole J Bjerrum [4]

Conclusions and clinical relevance: PGN is superior to placebo in the reduction of clinical signs of SM-related CNeP in dogs. At a dose range of 13-19 mg kg^{-1} orally twice daily, the encountered adverse events were acceptable to all but one owner.

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TRICYCLISCHE ANTIDEPRESSIVA

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BEHANDELING – TRICYCLISCHE ANTIDEPRESSIVA

Tricyclische antidepressiva gebruikt voor de behandeling van neuropathische pijn bij hond en kat.

Drug	Dog	Cat	Comments
Amitriptyline	1 to 2 mg/kg orally every 12 hours	0.5 to 1 mg/kg orally every 24 hours	
Imipramine	0.5 mg/kg orally every 12 to 24 hours	0.5 to 1 mg/kg orally every 12 to 24 hours	
Clomipramine	None	None	Not generally considered useful in pain management. The serotonin effect is greater than the adrenergic effect

Een dosis van 4 mg/kg amitriptyline werd beschreven niet te resulteren in voldoende amitriptyline & nortriptyline spiegels, waardoor het interessant is om bij onvoldoende effect de dosis te herevalueren (ECVAA Dipl. Matt Guerney, Zero Pain Philosophy). Norkus C, Rankin D, KuKanich B. Pharmacokinetics of intravenous and oral amitriptyline and its active metabolite nortriptyline in Greyhound dogs. Vet Anaesth Analg. 2015 Nov;42(6):580-9.

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BEHANDELING – TRICYCLISCHE ANTIDEPRESSIVA

- werkingsmechanisme:
  - inhibitie van de re-uptake van noradrenaline/serotonine & versterken van het descenderende pijnsysteem
  - verhogen de endogene opioid spiegels, wat kan leiden tot veranderingen in opioid receptor densiteit
  - antagonisme van voltage-gated Na-kanalen
  - antagonisme NMDA-receptor
  - combinatie met andere analgetica
  - effect na 2 dagen, staat los van het anti-depressief effect

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BEHANDELING – TRICYCLISCHE ANTIDEPRESSIVA

- neveneffecten:
  - tachycardie
  - gewichtstoename
  - sedatie
  - serotonine syndroom

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BEHANDELING – TRICYCLISCHE ANTIDEPRESSIVA

Aust Vet J. 2009 Jan-Feb;87(1):45-50. doi: 10.1111/j.1751-0813.2008.00379.x.

Clinical diagnosis and treatment of suspected neuropathic pain in three dogs.

Cashmore RG[1], Harcourt-Brown TR, Freeman PM, Jeffery ND, Granger N.

Author information

Abstract

Three dogs were referred to The Queen's Veterinary School Hospital at University of Cambridge for chronic behavioural or locomotor disorders associated with pain. All three had been unsuccessfully treated with conventional analgesics, including non-steroidal anti-inflammatory drugs, glucocorticoids and opiate agonists, prior to referral, with minimal or no response. They were investigated by neurological examination plus conventional ancillary diagnostic tests and therapeutic drug trials. Ruling out other causes of pain and applying previously well-described criteria, each case was diagnosed as consistent with neuropathic pain, a poorly recognised condition in domestic dogs. Treatment with the tricyclic antidepressant drug, amitriptyline, or the antiepileptic drug, gabapentin, resulted in either a dramatic improvement or full resolution of clinical signs in all cases.

Aust Vet J. 2006 Mar;84(3):83-6.

Neuropathic pain in a cat post-amputation.

O'Hagan BJ[1].

Author information

Abstract

Phantom limb pain is a form of neuropathic pain experienced by human patients who have had amputations. To date there are no reported cases of phantom limb pain in the veterinary literature. A cat presented with signs consistent with neuropathic or phantom limb pain 42 days after iatrogenic sciatic nerve injury and 38 days after subsequent hind limb amputation. Multimodal analgesic therapy resulted in resolution of signs of pain.

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CANNABINOÏDEN

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BEHANDELING - CANNABINOÏDEN

- Tetrahydrocannabinol (THC) max. 0.2%
  - psychotroop effect (hersenen)
  - CB1-receptor (centraal zenuwstelsel)

- Cannabidiol (CBD)
  - therapeutische effecten:
    - endogeen cannabinoïd systeem (ECS)
      - CB1 & CB2-receptor (perifeer zenuwstelsel & synovia)
      - enzymen (productie, transport & afbraak van endocannabinoïden)
    - ascenderende (opioid, TRPV,…) & descenderende (serotonine,…) pijnsystemen
  - PAINS
    - Pain (anti-hyperalgesie; neurogene pijn)
    - Anti-inflammatoir
    - Immunologisch
    - Nociceptief (anti-nociceptie)
    - Seizures

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BEHANDELING - CANNABINOÏDEN

- Cannabidiol CBD
  - niet geregistreerd als geneesmiddel
  - supplement & vrij verkrijgbaar:
    - geen exacte controle over samenstelling & verhouding CBD's
    - gebruik best een product met meerdere cannabinoïden(>60 # cannabinoïden)
    - titreren (laag beginnen tot effect)

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BEHANDELING - CANNABINOÏDEN

- Veilig?
  - geen lange termijn veiligheidsstudies
  - stijging ALP:
    - inductie CYP450 oxydatief metabolisme
  - geneesmiddelinteracties: CYP450 metabolisme
  - invloed op # orgaansystemen: opletten bij cardiologische aandoeningen
  - lange termijnbehandeling: regelmatige controles nodig, zeker leverfunctie

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frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 25 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]†*

HHS Public Access
Author manuscript
Pain. Author manuscript; available in PMC 2021 September 01.

Published in final edited form as:
Pain. 2020 September 01; 161(9): 2191–2202. doi:10.1097/j.pain.0000000000001896.

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

Chris D. Verrico[1,2,*], Shonda Wesson[3,*], Vanaja Konduri[4], Colby J. Hofferek[4], Jonathan Vazquez-Perez[4], Emek Blair[5], Kenneth Dunner Jr[6], Pedram Salimpour[7], William K. Decker[4,8,9,*,*], Matthew M. Halpert[4,*]

Scientific Report

The Use of Cannabidiol-Rich Hemp Oil Extract to Treat Canine Osteoarthritis-Related Pain: A Pilot Study

Lori Kogan, PhD, Peter Hellyer, DVM, Robin Downing, DVM, MS

•Gamble LJ, Boesch JM, Frye CW, et al. Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic dogs. *Front Vet Sci*. 2018;5:165. doi:10.3389/fvets.2018.00165
•Verrico CD, Wesson S, Konduri V, et al. A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain. *Pain*. 2020;161(9):2191-2202. doi:10.1097/j.pain.0000000000001896
•Kogan L, Hellyer P, Downing R. The use of cannabidiol-rich hemp oil extract to treat canine osteoarthritis-related pain: a pilot study. *J Am Holistic Vet Med Assoc*. 2020;58:35-43.

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