COLLABORATIVE APPROACHES FOR IMPROVING YOUR PERI-OPERATIVE PAIN MANAGEMENT AND EXPANDING YOUR GERIATRIC CHRONIC PAIN CASE MANAGEMENT

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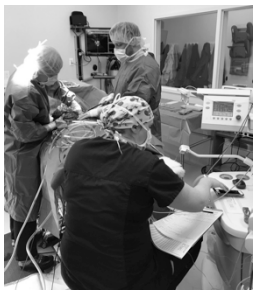
OBJECTIVES

- Different aspects of perioperative pain management
- Chronic pain management with focus on OA in geriatric pets
- Introducing Canadian OA treatment guidelines
- The role of cannabinoids in pain management

- Learning goals:
  - Add aspects of perioperative pain management that are outside the usual box
  - Understand different OA treatment options in senior pets including the palliative stage
  - Understand the role of endocannabinoid system in pain

PERIOPERATIVE PAIN MANAGEMENT



PERIOPERATIVE PAIN ASPECTS

- Pain has different components that may contribute to individual's sensation

- What can we do to improve the perioperative experience for our pets
  - Preoperative stress relief
  - Perioperative pain control
  - Postoperative stress and pain relief

PRE-OPERATIVE STRESS RELIEF

STRESS

- The link between stress/anxiety and pain

Depression and Anxiety in Pain

Adam KM Woo MB BS FRCA

Depression and Anxiety / Volume 26, Issue 10 / p. 888-901

Theoretical Review

Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art

Gordon J.G. Asmundson Ph.D., Joel Katz Ph.D.

First published: 18 August 2009

https://doi.org/10.1002/da.20600

Citations: 393

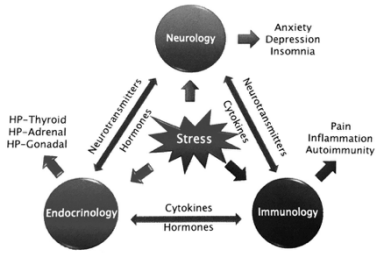
Condition Center Home > Research

Uncovering the Connection Between Anxiety and Pain

—Expression of the neuropeptide PACAP is increased in animal models of chronic pain and causes anxiety-like beh

Blocking the PACAP receptor could provide a therapeutic target for chronic pain and anxiety.

IMPACT OF STRESS



IMPACT OF STRESS

Stress

- Increased sympathetic tone
- Increased requirements of anesthesia
- Increased pain experience
- Worsen recovery
- Make things more difficult for next clinic visit
- Decreased wound healing

ANXIOUS PATIENTS

- Consider personality & history of patient before coming to clinic
  - Personality of pet
  - Breed
  - Age (senior-blind?)
  - History of clinic visits
  - Owner's personality

STRESS

- How do we reduce stress in our surgical patients?
  - Fear Free handling
    - Calm environment
    - Cozy kennels with blanket
    - 'Less is more' approach
      - Less people, less restraint, less rectal temperature taking
      - More sedation
  - Anxiolytic agents

ANXIOLYTIC AGENTS

- Trazadone
  - Anxiolytic due to serotonin reuptake inhibition
  - Alleviate stress & anxiety associated with travel, veterinary visits, hospitalization
  - 3-8mg/kg PO dogs or 50mg/cat PO
  - Onset 10- 20min without food, a little longer with food or pill pocket
  - 5mg/kg the night before the veterinary visit, 8-10mg/kg the morning of

Effects of trazodone on behavioral signs of stress in hospitalized dogs

Shana E. Gilbert-Gregory VMD
Jason W. Stull VMD, PhD
Mary Rose Rice BA
Meghan E. Herron DVM

OBJECTIVE
To determine the effects of trazodone treatment on behav stress in hospitalized dogs.

DESIGN
Prospective observational study.

Efficacy of a single dose of trazodone hydrochloride given to cats prior to veterinary visits to reduce signs of transport- and examination-related anxiety

Brenda J. Stevens DVM
Eva M. Frantz BS
Jillian M. Orlando DVM
Kristy Griffith PhD

OBJECTIVE
To evaluate the efficacy of a single dose of trazodone for reducing anxiety in cats during transport to a veterinary hospital and facilitating handling during veterinary examination.

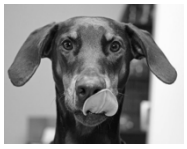
DESIGN

ANXIOLYTIC AGENTS

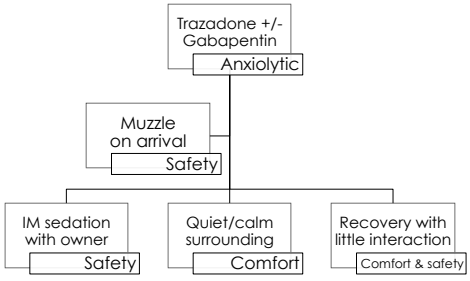
- Gabapentin
  - Mechanism as anxiolytic/sedative unclear
    - VGCC
      - Overall reduction in calcium currents and potentially impacting neurotransmitter release
      - Decreasing overall excitatory tone and modulating anxiety
    - GABA
      - Modulation of GABA biosynthesis and nonsynaptic GABA neurotransmission
        - Indirectly impact GABAergic tone
    - Serotonin
  - Dosing : 20-25mg/kg PO (cats), 10-20mg/kg PO (dogs)
    - May cause sedation, appears to reduce signs of stress, increases compliance (cats)

STRESS/FEAR CASE

- Doberman with fear/anxiety
- Does not like being away from owner
- Does NOT like restraint

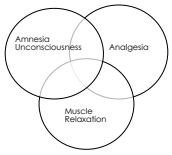


STRESS/FEAR CASE



DEXMEDETOMIDINE

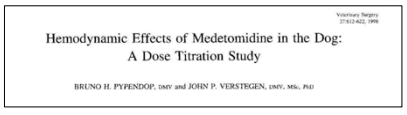
- Sedative
- Analgesic
- Muscle relaxant
- Reversible



- But significant CV effects
- But can offset inhalant induced hypotension

CV EFFECTS **NOT** DOSE DEPENDENT

- Cardiovascular effects do not change within clinically useful dose range
  - Predictability & reliability improved with higher dose
- Primary reasons for reducing dose, reduce cost & shorten duration of effects



Hemodynamic Effects of Medetomidine in the Dog: A Dose Titration Study

BRUNO H. PYPENDOP, DMV and JOHN P. VERSTEGEN, DMV, MSc, PhD

DEXMEDETOMEDINE

Clinical (CIM)	**Label**
• Dogs • 2-5 mcg/kg IV • 5-20 mcg/kg IM • Cats • 3-7 mcg/kg IV • 5-20 mcg/kg IM • 20-30 mcg/kg PO	• Dogs • 10-30 mcg/kg IV • 10-40 mcg/kg IM • Cats • 40 mcg/kg IM

Metabolic Scaling

PREDICTABILITY & EFFICACY

- Higher doses & combine with opioid better than alone
- IV better than IM
- Calm better than excited patient
- Semimembranosus better than lumbar

INJECTION IM OR IV

IV

Advantages:
- Faster onset
- Lower doses possible

Disadvantages:
- Requires restraint
- More profound effects
- Risk of small hematoma
- Pain on injection

IM

Advantages:
- Less restraint needed

Disadvantages:
- Slower onset
- May require higher doses or redosing IV

FRACTIOUS/STRESS CASE

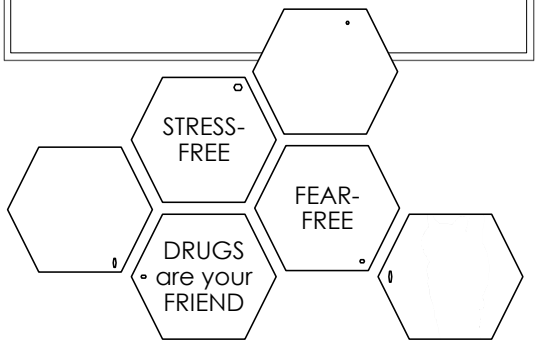
- Cats have a threshold
  - One try for IV (or IM)
  - Less stressful is IM injection
- Gabapentin
  - 25mg/kg PO

SEDATION PROTOCOL CATS

- "Fractious"/ misunderstood cats
  - Dexmedetomidine IM/PO
    - 10-15mcg/kg IM, 15-20mcg/kg PO
  - Opioid IM/PO
  - Alfaxalone IM
    - 1-2mg/kg IM
  - Acepromazine IM
    - 0.05mg/kg IM

COMMENTS ABOUT INJECTIONS

- **Dexmedetomidine IM**
  - NOT lumbar due to reduced absorption
  - Hindleg muscle preferred
- **Midazolam IV**
  - Inhibition effects
    - Noise and light sensitivity
    - Excitability
  - Better sedation at higher doses administered IM
- **Hydromorphone IV**
  - May sting administered IV
    - Response 30 sec delay in dogs
  - Less vomiting due to faster onset in conj with dexmed given IV
- **Methadone IM**
  - Reduced absorption
  - Large volume
- **Buprenorphine IM**
  - Slow uptake IM (45min)
  - Significantly faster IV/TM



METHADONE
WHY ALL THE FUSS?


Veterinary Anaesthesia and Analgesia

Formerly the Journal of Veterinary Anaesthesia

Veterinary Anaesthesia and Analgesia, 2010, **37**, 48–56 doi:10.1111/j.1467-2995.2009.00476.x

RESEARCH PAPER

Clinical pharmacology of methadone in dogs

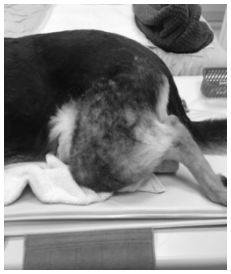
Carina Ingvast-Larsson*, Anja Holgersson*, Ulf Bondesson†, Anne-Sofie Lagerstedt‡ & Kerstin Olsson§

METHADONE VS HYDROMORPHONE

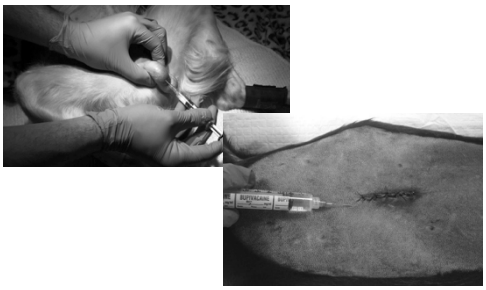
- **Veterinary labelled mu agonist opioid**
- Similar efficacy & duration of action
- Lower potential for side effects
  - Nausea/vomiting
  - Panting?
  - Dysphoria & hyperthermia (cats)?
- NMDA receptor antagonist activity – significance?
- Dose 0.2-0.5 mg/kg
  - IM/SQ bioavailability?
  - Larger volume (10mg/ml)
  - Less reactivity when administered IV
  - Cost – methadone > hydromorphone > morphine

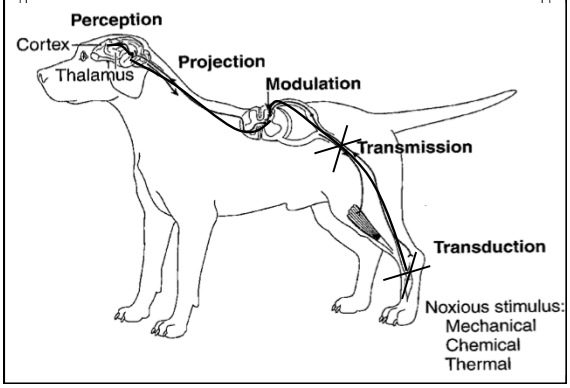
INTRAOPERATIVE PAIN

- Pre-emptive analgesia
- Local blocks
- NSAIDs



USE OF ROUTINE LOCAL BLOCKS… BESIDES DENTAL BLOCKS





CASE FOR MAROPITANT (CERENIA) USE IN THE PERIANESTHETIC PERIOD

MAROPITANT

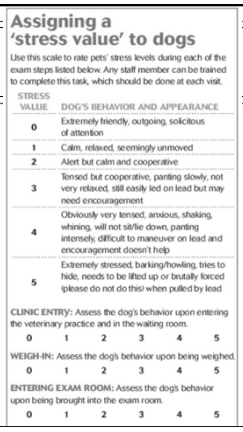
- Requires administration 1h prior to prevent vomiting
- No evidence it reduces:
  - Gastroesophageal reflux (GER)
  - Incidence of aspiration pneumonia or
  - Peri-anesthetic morbidity…. &
- Analgesic efficacy, largely insignificant when used with opioid/NSAID & locoregional techniques
- Expensive

MAROPITANT

- Indications
  - Those patients where vomiting may be detrimental (i.e. head trauma, brachycephalics)
- Routine use?
  - Better overall anesthetic quality?
  - Less vomiting (unpleasant)?
  - Animals tend to eat better post-operatively, less nausea
  - "Doesn't hurt"?

IMPROVING THE RECOVERY EXPERIENCE

STRESS VALUE SCALE (OVERALL, 2013)



Assigning a 'stress value' to dogs

Use this scale to rate pets' stress levels during each of the exam steps listed below. Any staff member can be trained to complete this task, which should be done at each visit.

STRESS VALUE	DOG'S BEHAVIOR AND APPEARANCE
0	Extremely friendly, outgoing, solicitous of attention
1	Calm, relaxed, seemingly unmoved
2	Alert but calm and cooperative
3	Tensed but cooperative, panting slowly, not very relaxed, still easily led on lead but may need encouragement
4	Obviously very tensed, anxious, shaking, whining, will not sit/lie down, panting intensely, difficult to maneuver on lead and encouragement doesn't help
5	Extremely stressed, barking/howling, tries to hide, needs to be lifted up or brutally forced (please do not do this) when pulled by lead

CLINIC ENTRY: Assess the dog's behavior upon entering the veterinary practice and in the waiting room.
0 1 2 3 4 5

WEIGH-IN: Assess the dog's behavior upon being weighed.
0 1 2 3 4 5

ENTERING EXAM ROOM: Assess the dog's behavior upon being brought into the exam room.
0 1 2 3 4 5

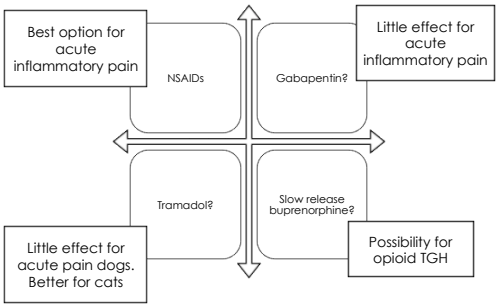
404 STRESS VALUE SCALE

Stress Value	Patient Behaviour & Appearance
0	Extremely friendly and outgoing; attention seeking. Calm, relaxed, amiable
1	Alert but calm and cooperative
2	Tensed but cooperative, not very relaxed Dogs may pant slowly and need encouragement to walk on leash
3	Obviously very tensed, shaking, anxious Cats will hide at back of kennel, dogs will not sit/lie down Dogs may whine, pant intensely and are difficult to walk on lead even when with encouragement
4	Extremely stressed Barking, howling, hissing Dogs needs to be lifted, will not walk

SMALL THINGS MAKE A BIG DIFFERENCE

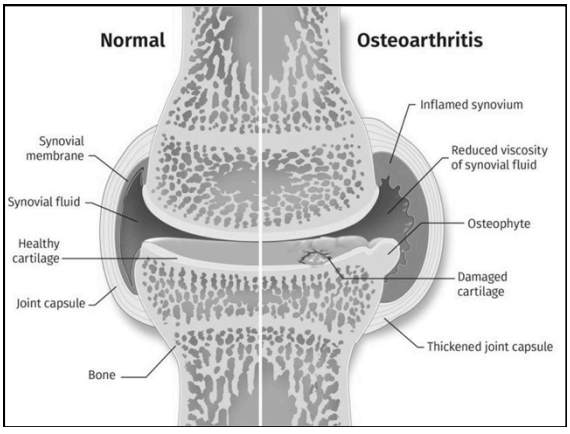
- Bladder expression post procedure; especially after epidurals
  - Placement of urinary catheters if required
- Fans provided for thick-coated or brachycephalic patients
  - Rule out hyperthermia for panting
- Comfortable bedding and padding
- Feliway
- Pain infusion catheters
- Yoga mats in kennel and outside kennel for easier walking when mobility issues
- Laser wounds
- Reduce anxiety
- **LOW STRESS handling**

TGH ANALGESIA



OSTEOARTHRITIS

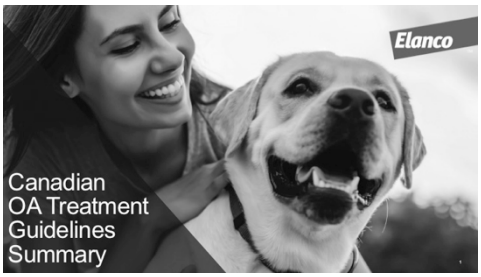
- Which drugs work?



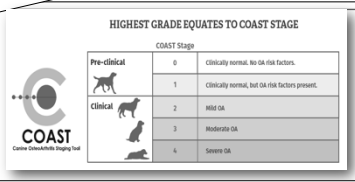
OA TREATMENT OPTIONS

- Chronicity and complexity of OA require extensive education of pet owner
- Treatment plans can be complex, involving multiple re-assessments over a pet's life dependent on disease progression
- Multitude of potential OA treatments, but no clear differentiation or priority based on OA stage is available

CANADIAN OSTEOARTHRITIS TREATMENT GUIDELINES



Canine OsteoArthritis Staging Tool (COAST)



- An established diagnostic tool providing clear guidance on how to decide on a dog's current OA stage based on owner input, orthopedic exam and radiographic findings.
- This tool helps veterinarians recognize and treat canine OA from its earliest stages

Cachon T, et al ; COAST Development Group. Face validity of a proposed tool for staging canine osteoarthritis: Canine OsteoArthritis Staging Tool (COAST). Vet.J.2018 May;235:1-8

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COAST STAGE 1

- Case

Stage 1 refers to a patient that is currently normal (preclinical) but has risk factors for developing OA.

Risk Factors:
- Genetic predisposition
- Participation in activity prone to injury
- Joint injury
- Surgery
- Excess body weight
- Age

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COAST STAGE 2

- Case

Stage 2 represents the early clinical stage of OA that results in mild clinical signs.

Clinical Signs:
- Can be inconsistent and subtle and can occur with or after activities.
- May affect gait, subtle changes/shifting in body weight distribution, and abnormal limb loading.

Examination:
- Range of motion (ROM) may be minimally reduced, but crepitus is unlikely at this stage.
- Mild osteophytosis and other early signs of OA may be visible on diagnostic images.

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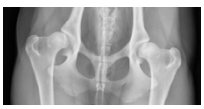
NINA

- Young Golden Retriever
- 3 years old, FS
- Smaller than usual for her breed
- Kind of sluggish & appears to be lazy
- Gains weight easily, food "motivated"
- "Salmon-style walk"
- Not a fan of steep stairs



COAST STAGE 4

Stage 4 is a clinical stage of OA with significant clinical signs and a higher level of dysfunction and pain.

Clinical Signs:
- Obvious, constantly present, and significantly affecting the dog's QoL. Severely abnormal limb loading and shifting of weight distribution, reluctance & restlessness when standing; significant lameness, reluctance to move, marked difficulties in rising and laying down.

Examination:
- Limited ROM with crepitus, joint thickening, anatomical misalignment and extreme muscle atrophy.
- Diagnostic imaging will show advanced osteophytes and signs of bone remodeling.

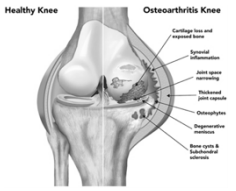
BEAU

- 12 year old GSD
- Hind-end weakness
  - Muscle atrophy
- LS-pain
- Knee DJD (L)
  - Had TPLO procedure 6 years ago
- Seems to be restless at night
- Always panting

BEAU

- 12 year old GSD
- Hind-end weakness
  - Muscle atrophy
- LS-pain
- Knee DJD (L)
  - Had TPLO 6 years ago
- Restless at night
- Always panting

- ❑ **Chronic inflammatory pain**
- ❑ **Additional neurogenic/ neuropathic component**



BEAU - PROBLEM LIST

- Knee osteoarthritis
  - PAIN, mobility issues
- Hind-end weakness
  - Tired, muscle atrophy, lack of strength, immobility
- LS pain
  - PAIN, mobility issues
- Panting & restlessness at night
- Drinking more

REHABILITATION & PHYSICAL THERAPY

- Simultaneously:
  - Manages pain
  - Restores and maintains optimal function
  - Regains mobility and muscle strength

REHABILITATION & PHYSICAL THERAPY

- Specific exercises
- Manual therapies
  - Stretches
  - Massages
- Laser
- PEMF
- Swimming/aqua treadmill
- Thermal therapy
- Ultrasound therapy
- Acupuncture

Most modalities require training

SPECIFIC EXERCISES

PHYSICAL SUPPORT

- For owner
- For patient

SUPPORT

The HELP 'EM UP HARNESS

PHYSICAL SUPPORT

PAIN MANAGEMENT OPTIONS BEAU

- NSAIDs
  - Inflammatory nature of OA
- Gabapentin or pregabalin
  - Aspect of neurogenic component
  - Chronicity
  - Back pain (LS)

GABAPENTINOIDS

Gabapentin	Pregabalin

• MOA
  • Blocks $VGCa^{2+}$ channels
  • Some serotonin effects
  • Increase in GABA
• PK:
  • TID necessary
• Side effects
  • Drunken sailor walk
	• Same MOA
	• Superior PK
	  • ↑ Bioavailability
	  • ↑ Duration
	  • ↓ Side effects

TRAMADOL

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

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. (*J Am Vet Med Assoc* 2018;252:427–432)

AMANTADINE

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

BEAU-TOP TREATMENT LIST

- Control pain
- Improve his muscle strength
- Assure a restful sleep to regain strength and motivation
- Evaluate co-existing diseases

NUTRACEUTICALS

- Chondroprotective properties
  - Disease Modifying OA Drugs (DMOAD)
- Anti-inflammatory properties
- Muscle support
- Immune support

NUTRACEUTICAL SUPPLEMENTS

- Omega 3 FAs
- Glucosamine/Chondroitin
- Green lipped mussel extract
- Eggshell membranes extract
- Elk Antler Velvet Extract
- Boswellia
- Epiitalis
- Fortetropin

ORIGINAL ARTICLE WILEY

Effects of a nutritional supplement in dogs affected by osteoarthritis

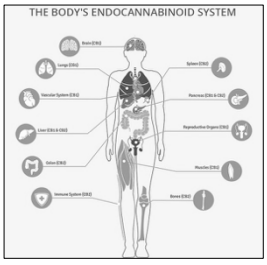
Nadia Musco[1] | Giuseppe Vassalotti[2] | Vincenzo Mastellone[1] | Laura Cortese[1] | Giorgia della Rocca[3] | Maria Luce Molinari[4] | Serena Calabrò[5] | Raffaella Tudisco[1] | Monica Isabella Cutrignelli[1] | Pietro Lombardi[1]

CANNABINOIDS ROLE IN PAIN MANAGEMENT

BREAK

ENDOCANNABINOID SYSTEM

- ECS plays key roles in control of various systems:
  - Nervous
  - Metabolic
  - Digestive
  - Reproductive
  - Immune function

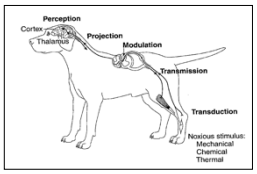


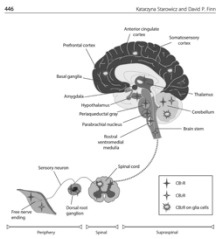
ECS RESEARCH FOCUS

- Energy metabolism
  - Appetite regulation
  - Obesity & associated metabolic abnormalities
  - Cachexia & Anorexia
- CNS disorders
  - Neurotoxicity & neurotrauma
  - Stroke
  - MS & spinal cord injury
  - Movement disorders
    - Parkinson's dx, Huntington's dx
  - Alzheimer's dx
  - Epilepsy
  - Mental disorders
    - Anxiety, depression, drug addiction
  - Insomnia
- Cardiovascular & respiratory disorders
  - Hypertension
  - Circulatory shock
  - Myocardial reperfusion injury
  - Atherosclerosis
  - Asthma
- GI and liver disorders
  - IBD & Crohn's
  - Acute & chronic liver dx
- Cancer
- Musculoskeletal disorders
  - Osteoporosis
  - Osteoarthritis
- Pain and Inflammation

MOA

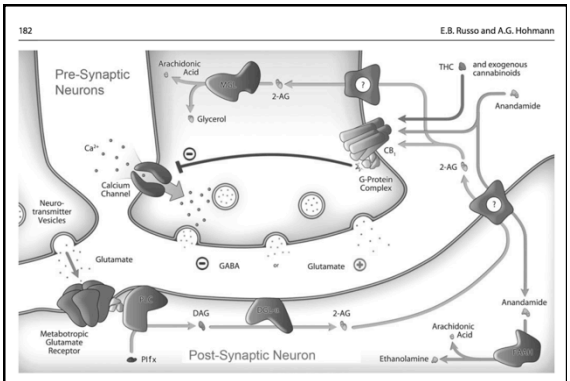
- Understanding the MOA for adequate knowledge in cannabinoid medicine





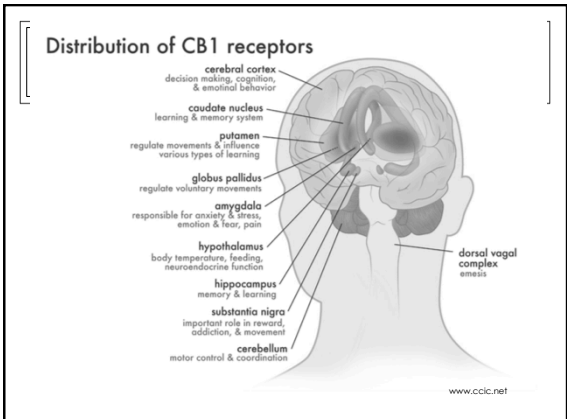
ENDOCANNABINOID SYSTEM

- Consisting of:
  - Cannabinoid receptor 1 (CB_1R)
  - Cannabinoid receptor 2 (CB_2R)
  - Endogenous cannabinoid ligands (endocannabinoids, eCB)
    - Anandamide, (AEA)
    - 2-AG
  - Metabolizing enzymes
    - Fatty acid amide hydrolase (FAAH): hydrolyzes AEA
    - Monoacylglycerol lipase (MGL): hydrolyzes 2-AG



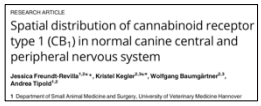
CB_1 RECEPTOR

- Locations for CB_1R:
  - Pre-and postsynaptic neurons in CNS
  - Nucleus of solitary tract (anti-emetic effects)
  - Motor cortex & motor neurons of spinal cord
  - Eye
  - Sympathetic ganglia (enteric nervous system)
  - Immune system (bone marrow, thymus, spleen, tonsils)
  - Peripheral sites:
    - Heart, lungs, adrenal glands, kidneys, liver, prostate, testes, ovaries, mast cells

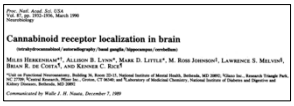


DOG'S SENSITIVITY TO THC

- Not really "more" CB1 receptors
- Different distribution
  - Higher concentration in cerebellum, brain stem and medulla oblongata
    - May be causing "static ataxia"


RESEARCH ARTICLE

Spatial distribution of cannabinoid receptor type 1 (CB_1) in normal canine central and peripheral nervous system


Cannabinoid receptor localization in brain

EXAMPLE CB_1R

- Epilepsy
  - Seizure threshold is mediated by the ECS in particular via CB_1R and plasticity of CB_1R
  - Animal studies demonstrated both acute increases in endocannabinoid production and a long-term up-regulation of CB_1 production as apparent compensatory effects counteracting glutamate excitotoxicity

CB_2 RECEPTOR

- Thought to be a peripheral immuno-modulatory receptor
  - Due to presence on immune related cells & tissues
  - Lack of detection in 'healthy brain'
- **Highly inducible**:
  - CB_2R expression ⇧ 100fold after tissue injury/ inflammation
  - Significant presence in brain
    - Role in neurodegenerative Dx
- Regulating immune system & inflammatory conditions
- Important effects on pain (neuropathic & inflammatory)

CB_2 RECEPTOR

- Location:
  - Central CB_2R on glial & endothelial cells, neuron
    - Agonists supress microglial activation and reduce neuropathic pain syndrome
  - In DRG & dorsal horn of spinal cord
    - Upregulated during neuropathic & inflammatory pain
  - High expression in tissue of immune cells (spleen, thymus)
    - Specific immune cells
  - Peripheral
    - Keratinocytes
    - CB_2 R activation inhibits:
      - Cytokine & chemokine release
      - Substance P induced mast cell degranulation & plasma extravasation

CB_2R EXAMPLE


Cellular and Molecular Life Sciences

REVIEW

The CB_2 receptor and its role as a regulator of inflammation

- Rheumatoid arthritis (RA)
  - Characterized by chronic inflammation of synovium, cartilage destruction & bone loss
    - Influx of innate (neutrophils, macrophages) & adaptive (lymphocytes) immune cells in synovial cavity with cytokine production
    - Osteoclasts become exaggeratedly activated & cause bone resorption
  - Endocannabinoids present in synovial fluids of RA patients
  - CB_1 + CB_2 mRNA and proteins found in synovial tissues
    - CB_2 activation inhibits production of pro-inflammatory cytokines & promotes osteoblast differentiation
  - CB_2 activation in RA joints could improve multiple aspects of Dx. including inflammation & bone loss
    - Promising target for treatment of RA

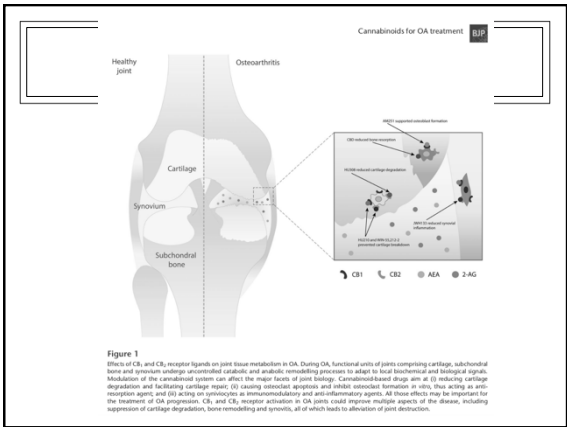
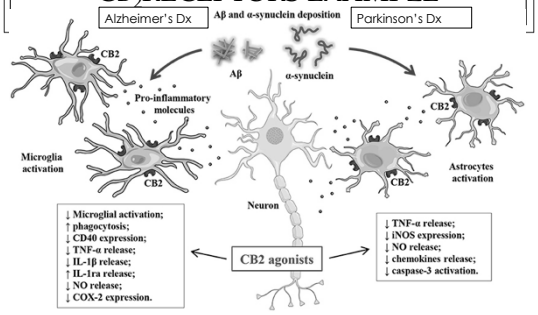


Figure 1

Effects of CB_1 and CB_2 receptor ligands on joint tissue metabolism in OA. During OA, functional units of joints comprising cartilage, subchondral bone and synovium undergo uncontrolled catabolic and anabolic remodelling processes to adapt to local biochemical and biological signals. Modulation of the cannabinoid system can affect the major facets of joint biology. Cannabinoid-based drugs aim at (i) reducing cartilage degradation and facilitating cartilage repair; (ii) causing osteoclast apoptosis and inhibit osteoclast formation *in vitro*, thus acting as anti-resorption agent; and (iii) acting on synoviocytes as immunomodulatory and anti-inflammatory agents. All those effects may be important for the treatment of OA progression. CB_1 and CB_2 receptor activation in OA joints could improve multiple aspects of the disease, including suppression of cartilage degradation, bone remodelling and synovitis, all of which leads to alleviation of joint destruction.

CB_2RECEPTORS EXAMPLE

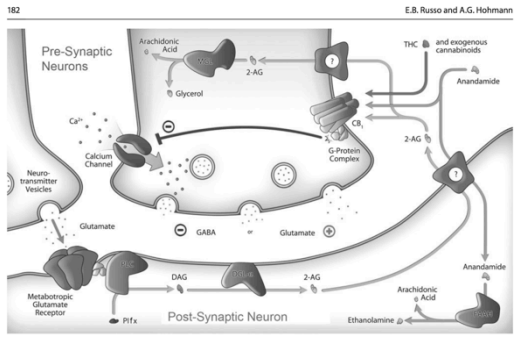


Cannabinoid Receptor 2 Signaling in Neurodegenerative Disorders: From Pathogenesis to a Promising Therapeutic Target. Front. Neurosci., 02 February 2017

ENDOCANNABINOIDS

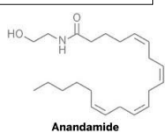
- Endogenous lipid-based retrograde neurotransmitters
- Precursors are present in lipid membranes
- Upon demand endocannabinoids are liberated via enzymatic process & released into extracellular space
- 6 endocannabinoids identified
  - Two most studied being anandamide and 2-AG
  - N-Palmitoylethanolamine (PEA)

ON DEMAND PRODUCTION



ENDOCANNABINOIDS

- **Anandamide (AEA)**
  - **Arachidonoyl ethanolamide**



- High affinity, CB_1R-selective partial agonist
- Low efficacy agonist at CB_2R
- Affinity for other non-CBR:
  - TRPV1, GPR55, PPARs
    - "Endovanilloid activity"
  - Inhibition of VGCC and 5-HT3A receptors
- Break down to arachidonic acid + ethanolamine by FAAH

ENDOCANNABINOIDS

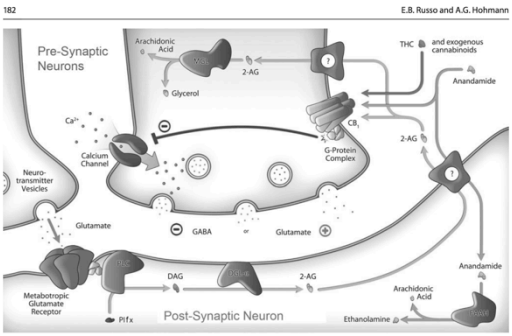
- **2-AG**
  - **2-arachidonoyl glycerol**

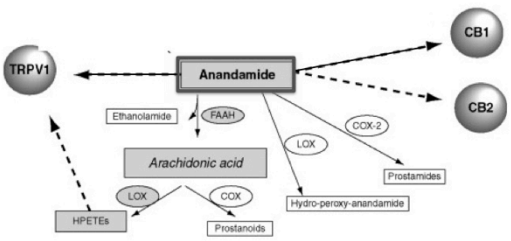
- Moderate affinity, CB_1R/CB_2R full agonist
  - Transforms into 2 enantiomers that appear to be full agonists
  - Higher affinity for CB_2R
- Potentiate $GABA_A$ receptor & activity of PPAR receptors
  - Decreasing neuronal excitability and inflammatory response

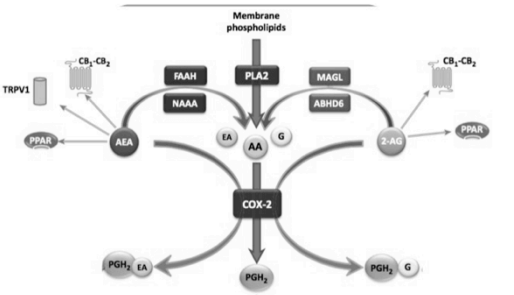
- Break down to arachidonic acid + glycerol by MGL
  - Serves as a major source of arachidonic acid in prostaglandin synthesis in certain organs

METABOLIZING ENZYMES

- **FAAH** (Fatty acid amide hydrolase)
  - Postsynaptic enzyme: controls anandamide levels near site of synthesis
    - Broadly distributed in CNS
- **MGL** (Monoacylglycerol lipase)
  - Presynaptic enzyme: terminates 2-AG signaling following CB_1R activation
    - Distributed in CNS areas close to CB_1R location
- Options for therapeutic targets:
  - Inhibition of endocannabinoid deactivation will increase levels of endocannabinoids at site with ongoing synthesis and release







ECS

- ECS parallels and interacts at many points with other major endogenous pain control systems
  - Endorphin/enkephalin
  - Vanilloid/transient receptor potential
  - Inflammatory (eicosanoid) pathways
  - Serotonergic & dopaminergic

ENDOCANNABINOIDOME (ECBOME)

- 'Expanded endocannabinoid system'
- ECS is much more complex than anticipated
- Endocannabinoids and enzymes play important roles in other physiological systems with complex buffer systems for physiology to prevent pathophysiology
- If degradation of endocannabinoids are blocked, it will interfere with other receptors and pathways

ECS AND ECBOME

ECS	eCBome
• Endogenous pathway encompassing: • CB_1R+ CB_2R • Endocannabinoids • Metabolizing enzymes	• Extends the ECS system to include other receptors: • TRPVs and TRPAs • PPAR α • GPR55, GPR18, GPR119 • 5-HTs • GlyR • And others

ECS AND GUT-BRAIN AXIS

- The ECS is important regulator of intestinal function and brain-gut axis due to its homeostatic system
  - ECS regulates visceral sensation, pain, motility, inflammation
  - Inhibition of neuronal activity in pathways involved in GI regulation

Gastroenterology 2016;151:252–266

REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Ernst J. Kuipers and Vincent W. Yang, Section Editors

The Role of the Endocannabinoid System in the Brain–Gut Axis

Keith A. Sharkey[1] and John W. Wiley[2]

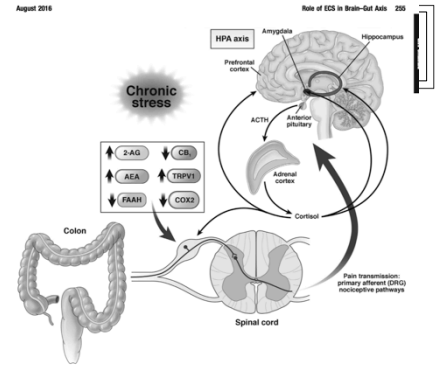


Figure 2. Effects of chronic stress on peripheral endocannabinoid pathways in visceral primary afferent neurons. Under conditions of chronic stress, levels of 2-AG and anandamide (AEA) increase, and endocannabinoid degradation enzymes COX-2 and FAAH are decreased in nociceptive dorsal root ganglia (DRG) neurons that innervate the colon and pelvis. Along with this, levels of CB1 are reduced and there is an increase in TRPV1 expression and phosphorylation in nociceptive primary afferent neurons. These effects are mediated by corticosteroids from the HPA pathway.

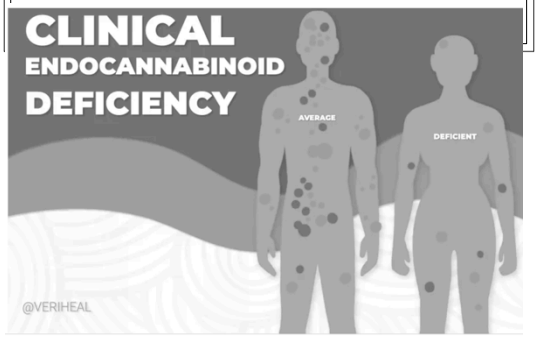
ENDOCANNABINOID DEFICIENCY SYNDROME

- Migraines
  - Decreased levels of endocannabinoids
- Diseases linked
  - Fibromyalgia, IBD, chronic pain

REVIEW Open Access

Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes

Ethan B. Russo*



ENDOCANNABINOID TONE

- Describes the overall state of your ECS
- ECS suggested to be tonically active in control of pain and mediating stress controlled analgesia
- Reflection of how receptors, endocannabinoids and enzymes act & react
  - Balanced ECS maintains homeostasis
  - Imbalanced or deficient system related to problems
    - Decreased pain threshold, mood, sleep

PHARMACOGENETICS

- Individual responses to treatment
  - Responders/non-responders
    - Individual genetic predispositions lead to various body responses to cannabinoid treatment
  - Deficiencies in ECS, basal endocannabinoid tone
    - Migraines/fibromyalgia
  - Receptor expression, up- and downregulations of CBRs
    - Chronic use – higher doses THC in particular
    - Break for therapy might be necessary to reinstate CB_1 density and responsiveness
    - Clinical significance in pet population?

PHARMACOGENETICS

- Patient's response may depend on gene polymorphism involved in action, metabolism, biotransformation & transport
- Gene expression variances
  - CB_1R is encoded by cannabinoid receptor type 1 gene (CBN1) on chromosomes
    - Variances show higher incidence of substance dependence, negative effects
  - CBN2 variances may contribute to etiology of certain diseases
- Cannabinoids metabolism genes
  - Cytochrome (CYP) activity
  - Glucuronidation ability
- Endocannabinoids biosynthesis & bioactivation gene
  - FAAH, MAGL, COX

PHYTOCANNABINOIDS

Cannabichromenes

- Cannabichromene (CBC)
- Cannabichromenic acid (CBCA)
- Cannabichromevarin (CBCV)
- Cannabichromevarinic acid (CBCVA)

Cannabicyclols

- Cannabicyclol (CBL)
- Cannabicyclolic acid (CBLA)
- Cannabicyclovarin (CBLV)

Cannabidiols

- Cannabidiol (CBD)
- Cannabidiol monomethylether (CBDM)
- Cannabidiolic acid (CBDA)
- Cannabidiorcol (CBD-C1)
- Cannabidivarin (CBDV)
- Cannabidivarinic acid (CBDVA)

Cannabielsoins

- Cannabielsoic acid B (CBEA-B)
- Cannabielsoin (CBE)
- Cannabielsoin acid A (CBEA-A)

Cannabigerols

- Cannabigerol (CBG)
- Cannabigerol monomethylether (CBGM)
- Cannabigerolic acid (CBGA)
- Cannabigerolic acid monomethylether (CBGAM)
- Cannabigerovarin (CBGV)
- Cannabigerovarinic acid (CBGVA)

Cannabinols and cannabinodiols

- Cannabinodiol (CBND)
- Cannabinodivarin (CBVD)
- Cannabinol (CBN)
- Cannabinol methylether (CBNM)
- Cannabinol-C2 (CBN-C2)
- Cannabinol-C4 (CBN-C4)
- Cannabinolic acid (CBNA)
- Cannabiorcool (CBN-C1)
- Cannabivarin (CBV)

Cannabitriols

- 10-Ethoxy-9-hydroxy-delta-6a-tetrahydrocannabinol
- 8,9-Dihydroxy-delta-6a-tetrahydrocannabinol
- Cannabitriol (CBT)
- Cannabitriolvarin (CBTV)

Delta-8-tetrahydrocannabinols

- Delta-8-tetrahydrocannabinol (Δ^8-THC)
- Delta-8-tetrahydrocannabinolic acid (Δ^8-THCA)

Delta-9-tetrahydrocannabinols

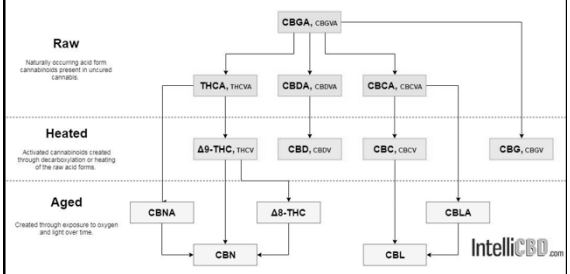
- Delta-9-tetrahydrocannabinol (THC)
- Delta-9-tetrahydrocannabinol-C4 (THC-C4)
- Delta-9-tetrahydrocannabinolic acid A (THCA-A)
- Delta-9-tetrahydrocannabinolic acid B (THCA-B)
- Delta-9-tetrahydrocannabinolic acid-C4 (THCA-C4)
- Delta-9-tetrahydrocannabiorcol (THC-C1)
- Delta-9-tetrahydrocannabiorcolic acid (THCA-C1)
- Delta-9-tetrahydrocannabivarin (THCV)
- Delta-9-tetrahydrocannabivarinic acid (THCVA)

Miscellaneous cannabinoids

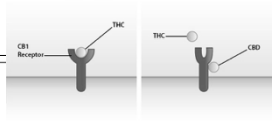
The following are other cannabinoids not classified in a class, class they fit into.

- 10-Oxo-delta-6a-tetrahydrocannabinol (OTHC)
- Cannabichromanon (CBCF)
- Cannabifuran (CBF)
- Cannabiglendol
- Cannabiripsol (CBR)
- Canniberitran (CBT)
- Dehydrocannabifuran (DCBF)
- Delta-9-cis-tetrahydrocannabinol (cis-THC)
- Tryhydroxy-delta-9-tetrahydrocannabinol (triOH-THC)

RELATIONSHIP OF CANNABINOIDS



CBD



- Low affinity for CBR
- Inhibits FAAH
- Inhibits anandamide reuptake
- Inhibits hepatic metabolism of THC
- Negative allosteric modulator at CB_1R in presence of THC
- TRPV1 agonist

Acts as endocannabinoid modulator

- GPR55 antagonist
- Inhibits TNF- α
- Activates the $5\text{-}HT_{1A}$ receptor
- Inhibits voltage gated Ca^{2+} channels
- Inhibits glutamate neurotoxicity
- Inhibiting adenosine transporter

THC

- CB_1R & CB_2R agonist/partial agonist
- Inhibits prostaglandin E_2 synthesis
- Stimulates lipoxygenase
- Inhibition of glutamine release
  - Reduces NMDA response
- Serotonergic system:
  - Increases cerebral serotonin production
  - Decreasing synaptosomal re-uptake
  - Decrease 5-HT release from platelets
- Dopaminergic blocking actions
- Stimulation of β -endorphin release
- Neuroprotective antioxidant

THCA AND CBDA

- Raw acid forms
- THCA
  - Does not cross BBB
  - Inhibits TRP activity
  - Inhibits COX_{1+2}
  - Reduce levels of TNF-α
  - Potent $PPAR_{\gamma}$ agonist
  - Not stable
- CBDA
  - Selective COX_2 inhibitor
  - Potent 5-HT_{1A}
  - Reduces anticipatory nausea

CBG - CANNABIGEROL

- Lacks psychotropic effects
- Strong analgesic, anti-erythema, lipooxygenase agent
  - Weak bindings to CB_1R + CB_2R
  - Potent GABA re-uptake inhibitor (>THC, CBD)
    - Muscle relaxant
  - Inhibits anandamide reuptake
  - TRPA1 + TRPV1 agonist, TRPV8 antagonization
  - Blocks lipoxygenase
  - Phospholipase A2 modulator
    - Reduces PGE-2 release in synovial cells
  - Stimulates α2-adrenoceptor activation
  - 5-HT_{1A} antagonist
  - Inhibits keratinocytes proliferation

CBN - CANNABINOL

- Byproduct of THC
  - Commonly an artifact after prolonged storage at higher temp
  - Maintains ¼ of potency of THC
- Weak CB_1R partial agonist
- Various activity on TRP channels
- Inhibition of synaptosomal uptake of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) and GABA
- Antiinflammatory
  - Inhibition of COX, LOX
- Considered for topical application
  - Inhibiting keratinocyte proliferation
  - TRPV2 (high threshold thermosensor) agonist – for burn treatment
- Stimulates recruitment of mesenchymal stem cell in marrow
  - Promoting bone formation

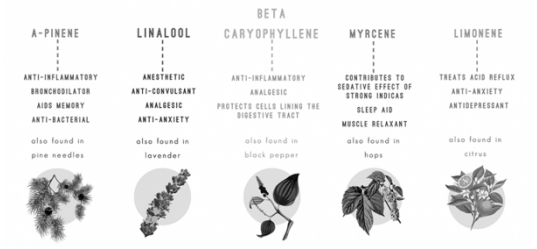
CBDV – CANNABIDIVARIN

- Propyl analogue of CBD
- Devoid of psychoactive effects, but crosses BBB
- Agonist for TRP- channels
- Inhibits diacylglycerol lipase-α
- Inhibits endocannabinoid degradation & cellular uptake of anandamide
- With CBD most researched cannabinoid for anti-seizure effects (especially focal seizures)

THCV – TETRAHYDROCANNABIVARIN

- Propyl analogue of THC
- Encountered in low concentration in dried plant
- Dose dependent MOA:
  - Agonist (high dose) and antagonist (low dose) at CB_1R
    - Weight loss, decreases body fat & serum leptin conc., increases energy-metabolism
    - Anticonvulsant properties in cerebellum and pyrifom cortex (mice)
  - Potent CB_2R partial agonist: CB_2R based reduction of hyperalgesia and inflammation
- Research focus: epilepsy, obesity, diabetis

TERPENES



TERPENES

- β -Caryophyllene*
  - Anti-inflammatory action via inhibiting the main inflammatory mediators and enzymes
    - IL-1 β , IL-6, TNF- α , NF- κ B, iNOS,COX1+2
    - Gastrocytoprotective properties despite PGE_2 inhibition
  - Potent CB_2R agonist
    - Synergism with THC
    - Reduces immunoinflammatory process

β -Caryophyllene: A Sesquiterpene with Countless Biological Properties. Francomano F et.al.:. Applied Sciences. 2019; 9(24):5420

TERPENES

- Myrcene
  - TRPV1 activity
  - Reduces inflammation via PGE-2
  - Inhibits NO production by IL-1 β
  - Sedative/analgesic effects via α -2 adrenoceptor
    - Reversable with yohimbine & naloxone
  - Muscle relaxant effects
  - Also present in hops

TERPENES

- α -Pinene
  - Inhibits PGE-1
  - Bronchodilatory effects at low doses
- Linalool
  - Acts as local anesthetic
  - Anti-glutamatergic activity
  - Anxiolytic properties
  - Anticonvulsant effects

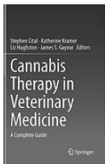
ENTOURAGE EFFECTS

"The whole is greater than the sum of its parts"
Aristotle

- Cannabis is inherently polypharmaceutical with synergy arising from interactions between its multiple components
- More effective than one component by itself
- Room for therapeutic research combining different components for specific disease, deficiencies and species

CONSIDERATIONS FOR VETERINARY MEDICINE

- How to apply that information to cases you see
  - Different diseases may require different products
  - Different product availability and related PK
  - Available research variable
    - Species and product specific
  - Clinically observed individual differences



EFFECTIVENESS FOR PAIN

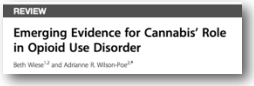
- Chronic pain:
  - Multiple human, laboratory animal studies, cell models show evidence and promising results for effectiveness of cannabinoids for chronic pain
    - Inflammatory pain
    - Neuropathic pain
    - Cancer pain
- Acute Pain:
  - Human clinical trails show discrepancies on effectiveness in acute pain models
    - Varying methodology, product & dosing protocols preventing conclusions
  - Animal models (tail flick, thermothreshold, carrageenan injections) show significant anti-nociceptive effects
    - Both CBRs involved in peripheral inhibition of sensitization

DRUG INTERACTIONS - PAIN

- In general, cannabinoids are considered safe
  - Dose related side effects
  - Age related side effects
  - Co-existing disease and drug related side effects
- Limited research on drug interaction
  - Multimodal pain management
- Several drugs may be enhanced when taken with CBD
  - Temporary Cytochrome P450 (CYP) deactivation/inhibition
  - -> delayed metabolism and prolonged activity
  - Pharmacological understanding limited
    - Dose dependency may have influence

DRUG INTERACTIONS WITH CANNABINOIDS

- Opioids:
  - Overlapping pathway with ECS
  - Opiate sparing effects, tolerance & withdrawal
- Gabapentin:
  - CYP450 related
  - Inhibition of VDCCs
    - Sedative effects of gabapentin may increase when CBD added
- NSAIDS:
  - Overlapping pathways
  - CYP450
  - Acetaminophen


REVIEW

Emerging Evidence for Cannabis' Role in Opioid Use Disorder

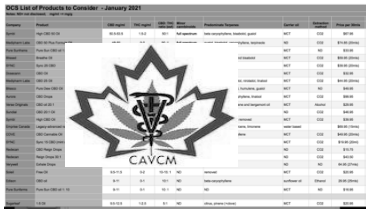
Beth Wiese[1,2] and Adrianne R. Wilson-Poe[3*]

CANNABINOIDS FOR BEAU

- Consider his disease state
  - Weak, painful
- Consider the multimodal regimen
  - Drug interactions
  - Synergism of medications
- Consider owner's position on topic
  - Interested, but cautious

https://gem.cbc.ca/media/marketplace/s49e04

AVAILABLE LEGAL PRODUCTS


DCS List of Products to Consider - January 2021

CAVCM

CANNABINOID PRODUCT FOR BEAU

- Medipharm 50
  - 50 (CBD) : 1-2 (THC)
    - Higher conc to reduce volume of oil
  - Legal "full spectrum" product with terpenes that include β caryophyllene
- Bloodwork
- Dosing :
  - Start at 0.2mg/kg BID and slowly increase to 0.5mg/kg BID
  - Evaluation and journal / video

BEAU

- Modalities part of rehab
- Massages
- Laser
- Acupuncture
- PEMF
- Steroid epidural

QUALITY OF LIFE

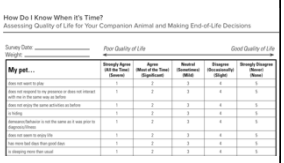
How Do I Know When it's Time?

Assessing Quality of Life for Your Companion Animal and Making End-of-Life Decisions

Deciding to euthanize your companion animal may be one of the most difficult decisions you ever make. Often, well-loved pets are euthanized to minimize unnecessary suffering. The quality of animals' lives is defined by their overall physical and mental well-being, not just one aspect of their lives. The chart on the opposite side of this fact sheet attempts to consider all aspects of your pet's life. It is important to remember that all pets are different. What may be considered a poor quality of life for one may be different for another.

Higher numbers on this chart equal a better quality of life. This chart may help you to better visualize the general well-being of your pet. In some cases, even one item on the left-hand side of the chart (for example: pain) may indicate a poor quality of life, even if many of the other items are still positive. Some items or symptoms on the list may be expected side effects of the treatments that your pet is undergoing. It is important to discuss these symptoms and side effects with your veterinarian.

Questions to ask yourself: **"How do I know when it's time?"**



How Do I Know When It's Time?

Assessing Quality of Life for Your Companion Animal and Making End-of-Life Decisions

Survey Date _____ *Poor Quality of Life* ← → *Good Quality of Life*

Weight _____

My pet…	Strongly Agree (All the Time) (Severe)	Agree (Most of the Time) (Significant)	Neutral (Sometimes) (Mild)	Disagree (Occasionally) (Slight)	Strongly Disagree (Never) (None)
does not want to play	1	2	3	4	5
does not respond to my presence or does not interact with me in the same way as before	1	2	3	4	5
does not enjoy the same activities as before	1	2	3	4	5
is hiding	1	2	3	4	5
Appearance/behavior is not the same as it was prior to diagnosis/illness	1	2	3	4	5
does not seem to enjoy life	1	2	3	4	5
has more bad days than good days	1	2	3	4	5
is sleeping more than usual	1	2	3	4	5

QUALITY OF LIFE

Lap of Love Pet

Quality-of-Life Scale

When evaluating the quality of life of your pet, personalized patient and family information is important when reaching an educated, informed, and supported choice that fits not only your pet's medical condition, but also your wishes and expectations. In short, quality of life applies not only to the pet, it also applies to you!

SCORE EACH SUBSECTION ON A SCALE OF 0-2:

0 = agree with statement (describes my pet)
1 = some changes seen
2 = disagree with statement (does not describe my pet)

RESULTS:

0-4: Your concerns are minimal at this time. You have either accepted the inevitable loss of your pet and understand what lies ahead, or have not yet given it much thought. If you have not considered these things, now is the time to begin evaluating your own concerns and limitations.

5-9: Your concerns are mounting. Begin your search for information by educating yourself on your pet's condition; it's the best way to ensure you are prepared for the emotional changes ahead.

10-16: Although you may not place much value on your own quality of life, your concerns about the changes in your pet are valid. Now is the time to prepare yourself and to build a support system around you. Veterinary guidance will help you prepare for the medical changes in your pet while counselors and other health professionals can begin helping you with anticipatory grief.

DISCUSS THE FOLLOWING BELOW, AND THE ENTIRE QUALITY-OF-LIFE SCALE, WITH YOUR VETERINARIAN:

Below are some open-ended questions that assist gauge your family's time, emotional, and (when appropriate, financial) budgets:

1. Have you ever been through the loss of a pet before? If so, what was your experience (good or bad, and why)?
2. What do you hope the life expectancy of your pet will be? What do you think it will be?
3. What is the ideal situation you wish for your pet's end of life experience? (at home, pass away in her sleep, etc.)

Suggestions on using this quality-of-life scale:

1. Complete the scale at different times of the day, note circadian fluctuations in well-being. (We find most pets tend to do worse at night and better during the day.)
2. Request multiple members of the family complete the scale; compare observations.
3. Take periodic photos of your pet to help you remember their physical appearance.

OA PAIN MANAGEMENT

- Time consuming & complex disease
- Treatment is individualized with continuing fine-tuning & adjusting with evidence based knowledge
- Objective and subjective assessment of progress
- Set realistic expectations with QoL goals
- Empower owner to be part of the treatment

Elanco