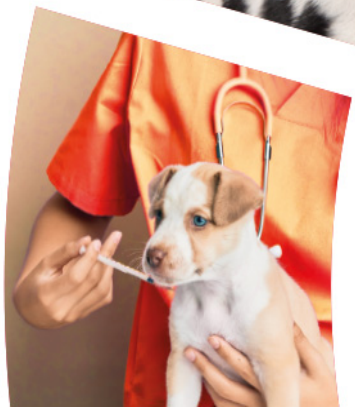
BSAVA 2023 congress

Join us at Manchester Central

23-25 March 2023

Together for companion animal health.



Early bird tickets available from mid-October

Register now

bsavaevents.com/bsavacongress2023

#BSAVA23

2022 WSAVA guidelines for the recognition, assessment and treatment of pain

AUTHORS:

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

[*]Department of Clinical Sciences, Faculty of Veterinary Medicine, Université de Montréal, 3200 rue Sicotte, Saint-Hyacinthe, Quebec, Canada
[†]Comparative Pain Research Laboratory and Surgery Section, North Carolina State University, 4700 Hillsborough Street, Raleigh, NC, USA
[‡]Highcroft Veterinary Referrals, 615 Wells Rd, Whitchurch, Bristol, BS149BE, UK
[§]Senior Medical Director, Lap of Love Veterinary Hospice, 17804 N US Highway 41, Lutz, FL 33549, USA
[¶]Department of Clinical Sciences, Faculty of Veterinary Medicine, Université de Montréal, 3200 rue Sicotte, Saint-Hyacinthe, Quebec, Canada
[‖]Mistral Vet, 4450 Thompson Pkwy, Fort Collins, CO 80534, USA
[**]Department of Veterinary Clinical Sciences and Centre for Companion Animal Health and Welfare, Jockey Club College of Veterinary Medicine and Life Sciences, City University of Hong Kong, Hong Kong, Hong Kong S.A.R.
[1]Corresponding author email: beatrizpmonteiro@gmail.com

Animal sentience refers to the capacity of animals to feel both positive and negative emotions including that of pain. As veterinary health professionals, we have a medical and ethical duty to mitigate suffering from pain to the best of our ability. In 2014, the first Global Pain Council World Small Animal Veterinary Association (WSAVA) Guidelines for the Recognition, Assessment and Treatment of Pain was published and remains to this day one of the most relevant and widespread documents of its kind. The 2022 WSAVA Global Pain Management Guidelines evolves from the first document with updated scientific information reflecting major advances in veterinary pain medicine in the last decade. This document is designed to provide the user with easy-to-implement, core fundamentals on the successful recognition and treatment of pain in the day-to-day small animal clinical practice setting. It provides basic and practical information with an extensive reference list to guide those who want to further their knowledge on pain management. The 2022 WSAVA Global Pain Management Guidelines should be easily implemented regardless of practice setting and/or location for the promotion and advance of pain management and animal welfare.

INTRODUCTION

The ability to experience pain is universally shared by all mammals and other vertebrates including fish, birds, reptiles and amphibians. Physiological and behavioural observations show that animals experience the sensory aspect of pain but also the unpleasantness, averseness and negative emotions attached to that experience. Animal sentience refers to the capacity of animals to feel both positive and negative emotions and is observed by animals seeking pleasure and avoiding suffering. Animal sentience is now legally recognised in numerous countries and jurisdictions.

As veterinary health professionals, we have a moral and ethical duty to mitigate suffering from pain to the best of our ability. Despite advances in the recognition and treatment of pain, there remains a gap between its occurrence and its successful management. This issue certainly benefits from the development, broad dissemination and adoption of pain assessment and management guidelines. The World Small Animal Veterinary Association (WSAVA) is the global voice of the small animal veterinary health care team with a long-standing and successful history of developing global guidelines on the recognition, diagnosis and/or treatment of common small animal ailments having a global relevance. The Global Pain Council (GPC) is one of WSAVA's committees charged with the task of developing pain management guidelines having universal relevance, considering regional differences in attitude, education and available analgesic modalities. Precisely, the GPC's mission is "*To raise global awareness and provide a call to action based upon the understanding that all animals are sentient and can therefore feel pain and suffer from it. The GPC strives to elevate the level of confidence and competence in recognising and managing pain in small animals*." In 2014, the first WSAVA Guidelines for the Recognition, Assessment and Treatment of Pain ("Global Pain Management Guidelines") was published and remains to this day one of the most relevant and widespread documents of its kind with an impressive number of citations and downloads. The 2022 WSAVA Global Pain Management Guidelines evolves from the first document with updated scientific information reflecting major advances in veterinary pain medicine in the last decade. It also complements the array of other WSAVA Guidelines available to aid in raising the standards of veterinary care worldwide (see https://wsava.org/global-guidelines/).

Use of this document

This document is designed to provide the user with easy-to-implement, core fundamentals on the successful recognition and treatment of pain in the day-to-day small animal clinical practice setting. It is not intended to be an exhaustive textbook on the subject; the goal is to provide basic and practical information with an extensive reference list to guide those who want to further their knowledge on pain management. Additional material is also available on the WSAVA website (https://wsava.org/committees/global-pain-council/).

There are no geographic limitations to the occurrence of pain, nor to the ability to recognise it. The only limiting factors are awareness, education, and a commitment to include pain assessment in every physical examination. As such, the 2022 WSAVA Global Pain Management Guidelines should be easily implemented regardless of practice setting and/or location. We acknowledge that there are regional differences in the availability of analgesics and the regulatory environment that governs their use. This represents a significant hurdle to the ideal management of pain in various regions of the world, irrespective of the ability to diagnose. In the treatment section of these guidelines, these issues are taken into account by the provision of "tiered" management protocols from comprehensive pain management modalities that represent the current "state of the art" followed by alternative protocols that may be considered where regulatory restrictions on analgesic products exist. It should also be recognised that in some situations, euthanasia may be the only moral or ethical (hence viable) treatment option available.

This document provides guidelines only and clinical decisions are made on an individual patient basis. The information provided herein is mostly evidence-based with references provided. When scientific evidence was not available for a certain topic, the information reflects a group consensus. Throughout these guidelines, various abbreviations and terms are used. Readers are encouraged to refer to the end of the document and the included appendix.

These guidelines are based on the following tenets:

- Pain is an illness that can be recognised and effectively managed in most cases
- Pain is the fourth vital sign and should be incorporated into the TPR (temperature, pulse, respiration) assessment of every patient
- Preventive and multi-modal analgesia should always be considered
- Perioperative pain can extend for several days and should be managed accordingly, including managing pain in the "home environment"
- Pain perception is influenced by numerous internal and external factors including the social and physical environment
- Treatment of pain should always include pharmacological and non-pharmacological therapies

SECTION 1

1.1 Understanding pain

Pain is a complex multi-dimensional experience involving sensory and emotional components. In other words, "*pain is not just about how it feels, but how it makes you feel*" and it is those unpleasant feelings that cause the suffering we associate with pain. The official definition of pain by the International Association for the Study of Pain (IASP) is: *"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" (IASP n.d.-a). It acknowledges that the "*inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain*." Pain is a uniquely individual experience which makes it difficult to appreciate how one feels (IASP n.d.-a). The conscious experience of pain is a subjective emotion that can be experienced even in the absence of obvious noxious stimulation, and which can be modified by fear, anxiety, memory and stress. In non-verbal patients, including animals, we use behavioural signs as the backbone for recognition and assessment of pain. Our knowledge of the expected severity and cause of pain guides clinical management.

Pain is often classified as either acute or chronic. Arbitrarily, pain of more than 3 months' duration has been considered chronic. However, there is nothing that suddenly changes after 3 months to create "chronic" pain. The mechanistic drivers of pain change on a continuum from acute nociceptive pain to pathological pain states. The extent of these changes is dependent on both the duration and the intensity and type of pain and affected by various other factors. The time pain has been present is considered a major contributor to the overall pain state, so the word "chronic" can still be used to communicate a pain state where the sensory pathways are pathologically altered. The terms "acute" and "adaptive" pain, and "chronic," "maladaptive" and "pathological" pain are used interchangeably in this document. Differences between these phenomena are described in Table 1.

"Inflammatory pain" is often included under "acute/adaptive pain," but obviously can be present in long-standing (chronic) pain conditions. Longer duration pain can result in changes in nociceptive transmission at multiple levels, collectively termed "algoplasticity." Such changes facilitate and amplify pain and can be drivers of pain separately from any peripheral input (*e.g.* phantom limb pain). These changes result in a progressive disconnection between the peripheral lesion and the pain being perceived, and as such, are often described as a "maladaptive" or "pathological" pain. Such pain has cumulative deleterious effects on multiple dimensions (physiological, sensory, affective, cognitive, behavioural and sociocultural) (McGuire 1992), including a significant negative impact upon the psychology of the sufferer. Long-standing (chronic/maladaptive/pathological) pain may be considered a disease state in and of itself (Woolf 2010). Approaches to management should reflect the different neurobiological profiles. In general, therapy of acute pain is aimed at treating the underlying cause and interrupting the nociceptive signals at different levels throughout the nervous system. Treatment approaches to long-standing pain are both focused on interrupting nociceptive input from the periphery, and on reversing pathological changes and the global negative effects pain has had on the body. Further, "dysfunctional pain" and "neuropathic pain" are considered forms of chronic/maladaptive/pathological pain, and in some publications "cancer pain" is called out as a separate pathological pain entity. "Mixed pain" is a term used to reflect the fact that clinical pain conditions, especially long-standing conditions, have components of the different pain types – *e.g.* inflammatory, dysfunctional and neuropathic pain all occur in established osteoarthritis (OA).

1.2 Physiology and pathophysiology of pain

Pain is a subjective emotion, which can be experienced even in the absence of obvious noxious stimulation, and which can be enhanced or abolished by a wide range of behavioural experiences including fear and memory (Fig 1). Adaptive "physiological" pain

Table 1. Differences between adaptive (acute) and maladaptive (chronic) pain

	Adaptive (acute)	Maladaptive (chronic)
Characteristics	• Associated with potential or actual tissue damage • Purpose: to rapidly alter the animal's behaviour to avoid or minimise damage and optimise the conditions in which healing can take place • Varies in severity and is proportional to the degree of tissue damage • Self-limiting: diminishes with healing and ceases when healing is complete	• Persists beyond the expected course of the acute disease • Not associated with healing • No clear endpoint • Associated with recurrent or long-standing disease conditions • Can exist without a cause • Serves little to no biological purpose
Examples	• Surgical procedures • Trauma (cut, wound, fracture) • Acute onset diseases (e.g. pancreatitis)	• Osteoarthritis • Cancer • Periodontal disease
Comments	• Often considered to serve a protective purpose However, in the context of controlled surgical or therapeutic interventions, this protective purpose is not needed • The mechanisms producing acute pain tend to reflect the normal physiological pain transmission system, and in general, acute pain is easier to manage than longer-standing (chronic) pain • Sometimes refer to as physiological pain and may involve inflammation	• Persistent postsurgical pain refers to acute surgical pain that becomes chronic • Patients with chronic pain can present with episodes of acute pain (*i.e.* "acute on chronic" or "breakthrough pain") • Sometimes referred to as pathological pain

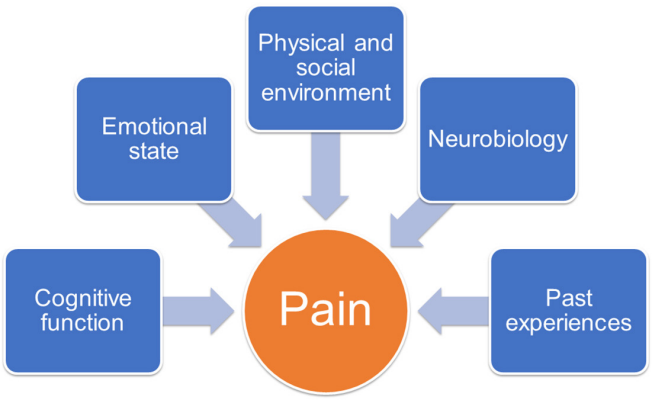


FIG 1. Pain is influenced by complex interactions between numerous internal and external factors. These influences can result in increased or decreased pain perception. Figure modified from Monteiro *et al*. (2020)

Table 2. Primary afferent fibres can be divided into three types based on their structure, diameters and conduction velocity

Fibre	Description	Diameter (μm)	Conduction velocity (m/second)
Aβ	• Large myelinated and rapidly conducting fibres involved in low threshold innocuous mechanical stimulation (*e.g.* touch)	More than 10	30 to 100
Aδ	• Thinly myelinated and slowly conducting fibres primarily involved in nociceptive signalling • Contribute to the rapid "stab" of the acute pain response and functions primarily as a warning, resulting in rapid withdrawal from the stimulus (*i.e.* fast pain)	2.0 to 6.0	12 to 30
C	• Unmyelinated and very slowly conducting fibres primarily involved in nociceptive signalling • Activated by intense mechanical, chemical and thermal stimuli contributing to the "slow burn" sensation of pain (*i.e.* slow pain) • A population of C-fibres called "silent" nociceptors may become active during inflammation or tissue damage and reflects one of the changes in peripheral sensitisation	0.4 to 1.2	0.5 to 2.0

Adapted from Monteiro & Simon 2022

announces the presence of a potentially harmful stimulus and thus has an essential protective function. In contrast, pathological or maladaptive pain represents malfunction of pain mechanisms and serves no physiological purpose, leading to chronic syndromes in which pain itself may become the primary disease. Perception of pain represents the final product of a complex neurological information-processing system, resulting from the interplay of facilitatory and inhibitory mechanisms throughout the periphery and central nervous systems (CNS).

The conscious experience of acute pain resulting from a noxious stimulus is mediated by a high-threshold nociceptive sensory system. The basic neuroanatomy of this system is reviewed elsewhere (Usunoff *et al.* 2006). Nociceptors are free nerve endings (primary afferent/sensory fibres) with their cell bodies located in the dorsal root and trigeminal ganglia. The primary afferent nerve fibres which carry information from these free nerve endings to their central location consist of two main types: C fibres and Aδ fibres (Table 2). Within these two broad categories are many sub-categories based on the precise receptors they express. Following tissue damage, changes in the properties of nociceptors occur such that Aβ fibres, normally not associated with nociception, may also transmit "pain information" (*i.e.* maladaptive pain). Continued noxious stimulation results in C fibre activation, the extent of which is dependent on the severity of injury.

Primary afferent fibres carrying sensory information from nociceptors synapse in the dorsal horn of the spinal cord onto second order neurons. From here, information (the "nociceptive message") is projected to various higher centres. Several spinal-brainstem-spinal pathways are activated simultaneously when a noxious stimulus occurs, providing widespread positive and negative feedback loops by which information relating to noxious stimulation can be amplified (pain facilitation) or diminished (pain inhibition). The cerebral cortex is the seat of conscious experience of pain (*i.e.* perception). It exerts top-down control (*e.g.* sending signals down to the spinal cord) modulating the sensation of pain. This is known as the descending noxious inhibitory control. In other words, the nociceptive input from the periphery to the spinal cord is modulated (amplified/facilitated or diminished/inhibited) locally but also by signals coming from the cerebral cortex before information is sent to the cerebral cortex and perceived as "pain." Pain is considered to consist of three key components: a *sensory-discriminatory* component (temporal, spatial, thermal/mechanical), an *affective* component (subjective and emotional, describing associated fear, tension, and autonomic responses) and an *evaluative* component, describing the magnitude of the quality (*e.g.* stabbing/ pounding;

Table 3. Types of pain

	Description	Relevant mechanisms
Inflammatory pain	• Acute postoperative pain until the wound has healed • Rapid onset. In general, its intensity and duration are related directly to the severity and duration of tissue damage • Results from the activity of inflammatory and immune cells, and the products of tissue damage	• Changes in the nociceptive system are generally reversible (*i.e.* normal sensitivity of the system is restored). However, if the noxious insult was severe, or if a focus of ongoing inflammation persists, then pain will persist • Longer duration and/or more intense noxious input to the pain sensing system progressively results in greater changes in the function of the pain transmission system. These changes involve not just the neurons, but the supporting cells (*e.g.* glia) and immune/inflammatory cells (Fig 3). This results in pathological, or maladaptive pain
Neuropathic pain	• Caused or initiated by a primary lesion, injury or dysfunction in the peripheral nervous system or CNS	• Related with a plethora of changes in the PNS, spinal cord, brainstem and brain as damaged nerves fire spontaneously and develop hyper-responsivity to both inflammatory and normally innocuous stimuli (Woolf 2010) • Endogenous systems that normally control pain are less functional • In humans, postamputation phantom limb pain and postherpetic neuropathy are examples of neuropathic pain which is the major cause of long-term postsurgical pain (Kehlet *et al*. 2006) • Not much described in the veterinary literature likely because the definition of neuropathic pain in humans relies heavily on descriptions of the quality of the pain (*e.g.* burning, stabbing, tingling)
Dysfunctional pain	• A state where the nervous system is grossly normal (*i.e.* there is no physical damage) but the functioning of the CNS is abnormal • Known as functional or dysfunctional pain	• Abnormal central processing results from repeated input to the CNS, causing nervous system plasticity [changes in neurons and in the way supporting elements (*e.g.* glia) communicate with neurons] with consequent amplification and facilitation of the processing of nociceptive information • As with neuropathic pain, descending inhibition may be defective

CNS Central nervous system, PNS Peripheral nervous system

mild/severe). Undoubtedly, an animal's pain experience has these three components; however, our tendency is to focus on pain intensity alone.

Clinical pain

Clinical pain results from an altered pain transmission system – either adaptive or pathological/maladaptive changes (Adrian *et al*. 2017). Effective treatment of pain relies on understanding these changes – the neurobiological drivers to pain. To help with this, adaptive pain has been sub-classified as nociceptive or inflammatory, and maladaptive pain as functional or neuropathic (Table 3, Figs 2 and 3) (Woolf 2010). Although useful, it must be remembered that most clinical pain conditions reflect a mixture of these types of pain – *e.g.* inflammatory and pathological types of pain occur simultaneously in OA.

The nociceptive sensory system is an inherently plastic system and when tissue injury or inflammation occurs, the sensitivity of an injured region is enhanced so that both noxious and, sometimes normally innocuous stimuli, are perceived as painful. The clinical hallmarks of sensitisation of the nociceptive system are hyperalgesia and allodynia. Hyperalgesia is an exaggerated and prolonged response to a noxious stimulus, while allodynia is a pain response to a low-intensity, normally innocuous stimulus such as light touch to the skin or gentle pressure. Hyperalgesia and allodynia are a consequence of peripheral and central sensitisation. *Peripheral sensitisation* is the result of changes in the environment bathing nociceptor terminals secondary to tissue injury or inflammation. Inflammatory mediators and neurotransmitters are released by damaged cells which either directly activate nociceptors or sensitise nerve terminals. This results in long-lasting changes in the functional properties of peripheral nociceptors. Sensitised and activated nerves also play a role in local inflammation through a phenomenon called neurogenic inflammation. Collectively, all these changes result in what is termed "peripheral sensitisation" (Fig 4).

Trauma and inflammation can also upregulate nociceptive transmission. Sustained noxious stimuli to the spinal cord and higher centres result in progressive changes in the pain mechanisms and endogenous analgesic systems and consequent facilitation and amplification of these signals. The term "*central sensitisation*" describes changes in the spinal cord, but also changes at supraspinal levels, such as decreased activity of descending inhibitory noxious controls including endogenous analgesic systems (Fig 5). Central sensitisation can occur as a result of surgery (Lascelles *et al*. 1998), but is most likely to occur in long-standing painful conditions where there is prolonged input of noxious signals into the CNS [*e.g.* dogs (Knazovicky *et al*. 2016) and cats (Monteiro *et al*. 2020) with OA/degenerative joint disease (DJD), or dogs with chronic neuropathic pain (Ruel *et al*. 2020)].

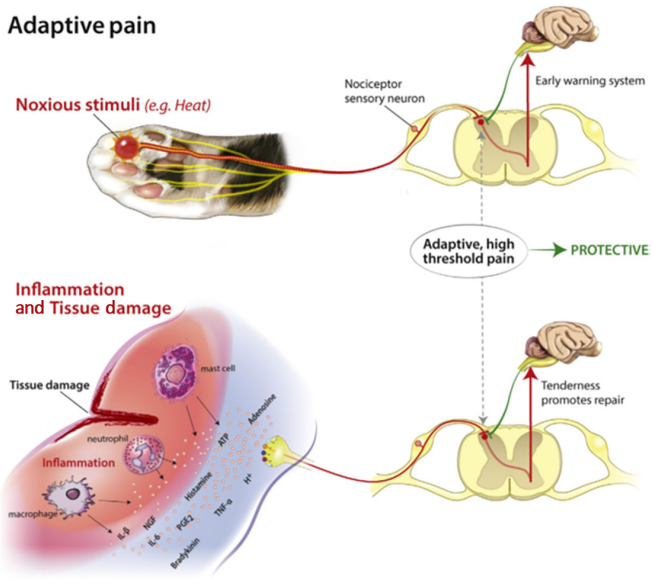


FIG 2. Schematic illustration of adaptive pain. In nociceptive pain, a noxious stimulus (red starburst) activates high-threshold primary afferent neurons (red/yellow lines). The nociceptive message is transmitted to second order neurons in the dorsal horn of the spinal cord and then to the brain *via* ascending tracts in the spinal cord (red arrow), where it is interpreted as a warning of actual or potential tissue damage. Descending inhibitory controls (green line) from higher brain modulate the nociceptive message in the spinal cord before conscious perception in the brain cortex. In inflammatory pain, local tissue damage results in release of inflammatory mediators which either sensitise sensory nerves, or directly stimulate them, resulting in a lowering of thresholds in sensory nerves and generation of nociceptive signals. Similarly, these signals are transmitted by afferent neurons (red line) through the spinal cord and then up to the brain (red arrow). Descending inhibitory controls (green line) may modulate the nociceptive message at the level of the spinal cord. The increased sensitivity in the periphery associated with inflammatory pain following tissue damage promotes protection of the area, allowing it to heal. Figure reproduced from Adrian *et al*. (2017)

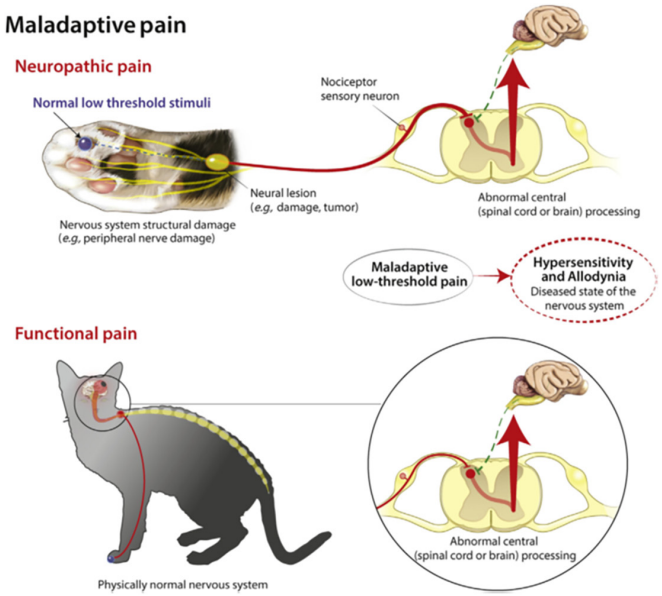


FIG 3. Schematic illustration of maladaptive pain. In neuropathic pain, physical damage to nervous system tissues (yellow circle) results in abnormal activation of sensory neurons which become activated in response to previously sub-threshold stimuli (blue circle). The subsequent pathway similar as in "adaptive" pain except that changes (nervous system plasticity) occur at the level of the dorsal root ganglion and dorsal horn of the spinal cord there resulting in amplification and facilitation of the nociceptive signals. Additionally, the descending inhibitory controls less effective (dashed green line), which again facilitates the signals being transmitted from the periphery to higher centres. Hyperalgesia and allodynia occur as a result of these changes. Spontaneous pain can occur due to abnormal activity in the nervous system (*e.g*. generated at the site of nervous system injury). In functional pain, the nervous system is grossly normal but its functioning is abnormal. This abnormal central processing results from repeated input to the system, causing nervous system plasticity [changes in neurons and changes in the way supporting elements (*e.g*. microglia) communicate with neurons] and thus amplification and facilitation of the nociceptive information. Under these conditions, a nociceptive stimulus (blue circle) activates a physically normal nociceptor (red line) but abnormal central processing in the spinal cord or brain (inset) results in the stimulus being interpreted as painful. As with neuropathic pain, descending inhibitory controls might be defective (dashed green line) and hyperalgesia, allodynia and spontaneous pain can occur. Figure reproduced from Adrian *et al*. (2017)

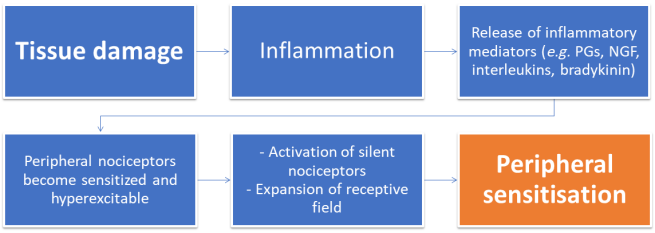


FIG 4. Peripheral sensitisation results in increased sensitivity around the lesion site. Affected patients may exhibit signs of hyperalgesia and allodynia. Adapted from Monteiro & Simon (2022). PGs Prostaglandins, NGF Nerve growth factor

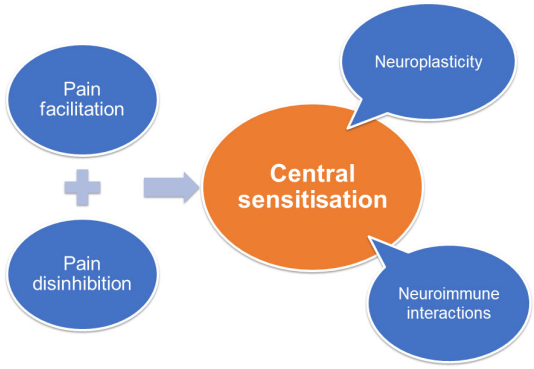


FIG 5. The constant noxious input (electrical signal) from the periphery to the spinal cord results in central sensitisation. Central sensitisation is the result from increased pain facilitation and decreased pain inhibition. Neuroplasticity and neuroimmune interactions also contribute to this phenomenon

1.3 Ethics and animal welfare

Ethics in pain management

Veterinary professionals have both an ethical and a medical duty to manage pain in animals (Steagall *et al.* 2021). The ethical duty relates to the fact that pain causes suffering, and "*prevention of and relief from suffering*" is frequently part of the Veterinarians' Oath. Indeed, Veterinary Medical Ethics refers to the need of these professionals to prevent, diagnose and treat pain (AVMA 2019). The medical duty relates to the fact that pain is a medical problem leading to unwanted physiological consequences such as activation of the sympathetic nervous system, immunosuppression, altered metabolism, impaired healing, increased morbidity and effects on disease progression, among others. Veterinarians should make decisions free of external influences based on ethical and medical responsibilities to the patient, and abstain from causing harm (Beauchamp 2016, Steagall *et al.* 2021). Ethics in pain management is the result of a complex interplay involving culture and societal norms, and the triad relationship between the animal, the veterinarian and the client. There is a financial cost to the use of analgesics. The WSAVA GPC is strongly opposed to giving the client an option to decline the use of analgesics.

Common ethical dilemmas in small animal pain management include onychectomy in cats and cosmetic surgery in dogs (*e.g.* ear cropping; tail docking). These procedures are rarely justified from a medical point of view and could result in persistent postoperative pain (Monteiro & Steagall 2019b). Another ethical conflict relates to painful and unnecessary or futile interventions. With the advance of veterinary medicine and referral to specialists in state-of-the-art facilities, clients' willingness to pay for veterinary care might result in the performance of invasive painful procedures or "over-treatment" that only prolong an animals' life without any benefit to its actual quality of life (QoL) leading to continuous suffering (Clutton 2017).

The Veterinary Ethics Tool (VET) aids decision-making in clinical treatment of companion animals based on responses to questions related to the caregiver, patient and clinician (Grimm *et al.* 2018). Finally, based on the ethical principal to end animal pain and suffering, euthanasia should always be considered in cases when pain cannot be effectively managed, and QoL is poor.

Pain management and animal welfare

Although various definitions exist, animal welfare can be thought of as *"a state of complete mental and physical health, where the animal is in harmony with its environment"* (Hughes 1976). It runs on a spectrum from good to poor and everything in between. Current animal welfare science focuses on ensuring animals have a good life. Five domains are proposed to influence animal welfare (nutrition, environment, health, behaviour and mental state), and increased importance is assigned to promoting positive mental (affective) states (Mellor *et al.* 2020). Pain is always unpleasant and can negatively influence these five domains (*e.g.* reduced appetite and social

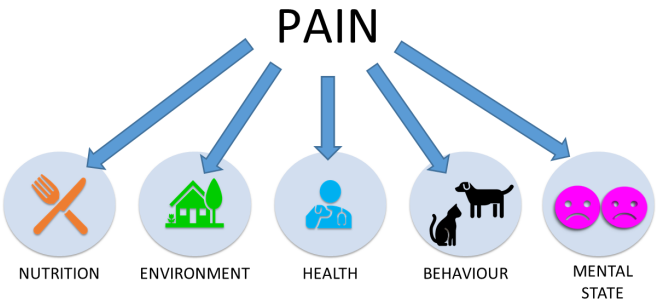


FIG 6. The Five Domains model of animal welfare. Each of the first four domains (nutrition, environment, health and behaviour) can impact on the fifth domain (mental state) both positively or negatively. Pain negatively affects the first four domains and is an unpleasant emotion by nature. Figure modified from Mellor *et al*. (2020)

interaction) (Fig 6). As animal sentience becomes widely accepted and legally recognised, reduction of suffering and pain becomes a moral and legal imperative (Beauchamp 2016). See the WSAVA Animal Welfare Guidelines for a thorough review on this topic (Ryan *et al*. 2019).

Pain causes negative emotions (*e.g*. stress, fear, anxiety and frustration), and emotions (both negative and positive) affect pain perception. Pain alleviation, and therefore welfare, can be improved by giving animals positive experiences (pleasure, comfort, contentment, curiosity, playfulness and positive social interactions) (Lawrence *et al*. 2019). Indeed, positive psychology intervention in humans is used in the treatment of maladaptive pain (Finan & Garland 2015, Hanssen *et al*. 2017). The possibility exists, although unproven, that, for example, enriching the indoor environment of cats and providing novel positive experiences to dogs may help in alleviation of pain.

It should be noted that the terminology regarding animal welfare, QoL and health-related QoL (HRQoL) is not uniformly defined in the literature although they all relate to observer assessment of an animal's subjective and personal experience in a given moment or throughout its life. In this document, animal welfare refers to the current state that an animal finds itself in considering its physical and mental states and its relationship with the physical and social environments. QoL refers to all aspects of an animal's life that make that life better or worse for that animal (Belshaw & Yeates 2018). Health-related QoL refers to the implications of specific health problems on QoL.

1.4 Recognition and assessment of acute pain in cats

Acute pain is the result of a traumatic, surgical, medical or infectious event that begins abruptly and has an expected duration related to its severity. Acute pain can usually be alleviated by the correct choice of analgesic drugs, most commonly opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and local anaesthetic techniques. When surgery is elective, analgesics are given before the procedure (preventive analgesia). After trauma, treatment should be initiated as soon as possible. Pain should be assessed using validated pain scales/scoring systems/tools.

Cats that have been injured or undergone surgery should be monitored closely, and pain must be treated promptly to prevent it from escalating. Treatment must be continued until the acute inflammatory response abates. The degree of trauma dictates the intensity and duration of the inflammatory response. The analgesic plan (choice of drugs and non-pharmacologic interventions and duration of treatment) should be individualised.

Neuroendocrine assays measuring beta-endorphin, catecholamine and cortisol concentrations in plasma have been correlated with acute pain in cats; however, these are also influenced by other factors such as anxiety, stress, fear and drugs (Cambridge *et al*. 2000). Objective measurements such as blood pressure, heart rate and respiratory rate are influenced by stress and should not be solely relied on as indicators of pain (Quimby *et al*. 2011). It is now accepted that *observations made by an observer that take behaviour, body posture and facial expressions into account are most likely to capture the complex experience of an animal's pain*. Multi-dimensional composite pain scales for assessing postoperative pain in cats are available including the UNESP-Botucatu multi-dimensional feline pain assessment scale – short form (UFEPS-SF) (Belli *et al*. 2021, Luna *et al*. 2022) (see https://animalpain.org/en/home-en/), and the Glasgow composite measure pain scale-Feline (CMPS-Feline) (Reid *et al*. 2017) (Table 4). These tools require interaction with the patient, which is not always possible (*e.g*. feral and unsocialised cats); however many components of these scales can be used to assess these populations. Facial expressions of pain appear to be exhibited in all mammals including cats, making species-specific grimace scales valuable (Evangelista *et al*. 2021). The Feline Grimace Scale© has been developed for cats and correlates well with multi-dimensional composite scales; it is a valid, reliable, valuable tool for rapid assessment for different types of pain and when interaction with a cat is not possible (Evangelista *et al*. 2019, 2020, Watanabe *et al*. 2020a) (see https://www.felinegrimacescale.com/) (Fig 7). Comprehensive reviews of the currently available tools and their clinical application are available including the 2022 International Society of Feline Medicine consensus guidelines on the management of acute pain in cats (Steagall & Monteiro 2019, Steagall 2020, Steagall *et al*. 2022).

Table 4. Tools used for assessing acute pain in cats

Tool	Type	Condition	Comments	References
Feline Grimace Scale (FGS)†	Facial expressions	Any surgical or medical pain including cats with oral disease and those undergoing dental extractions	Has been extensively studied and validated. Reliable when used by veterinarians, veterinary students, veterinary technicians/nurses and cat caregivers. Consists of five items that are scored from 0 to 2. The maximum score is 10. Cut-off for rescue analgesia: ≥4/10‡ Available at: http://www.felinegrimacescale.com Phone application available for iOs and Android in English, French and Spanish	(Evangelista *et al*. 2019, 2020, Watanabe *et al*. 2020a, Evangelista & Steagall 2021)
Unesp-Botucatu Feline Pain Scale (UFEPS-SF)†	Behaviour and facial expression	Any surgical or medical pain	Has been extensively studied and validated in eight languages in addition to English (Chinese, English, French, German, Italian, Japanese, Portuguese and Spanish) The most recent version (Short-Form) includes four items, each scored from 0 to 3. The maximum score is 12. Cut-off score for rescue analgesia: ≥4/12‡ Available at: http://www.animalpain.org	(Belli *et al*. 2021, Luna *et al*. 2022, Brondani *et al*. 2013)
Glasgow composite measure pain scale-Feline (CMPS-Feline)	Behaviour and facial expressions	Any surgical or medical pain	Moderately validated. Available in English and Spanish. Contains seven items; each having a different range of possible scores. The maximum score is 20. Cut-off score for rescue analgesia: ≥5/20‡ Available at: http://www.newmetrica.com/acute-pain-measurement/	(Reid *et al*. 2017, Holden *et al*. 2014)

†Recommended for use in practice due to higher degree of scientific evidence
‡The score at which rescue analgesia should be administered

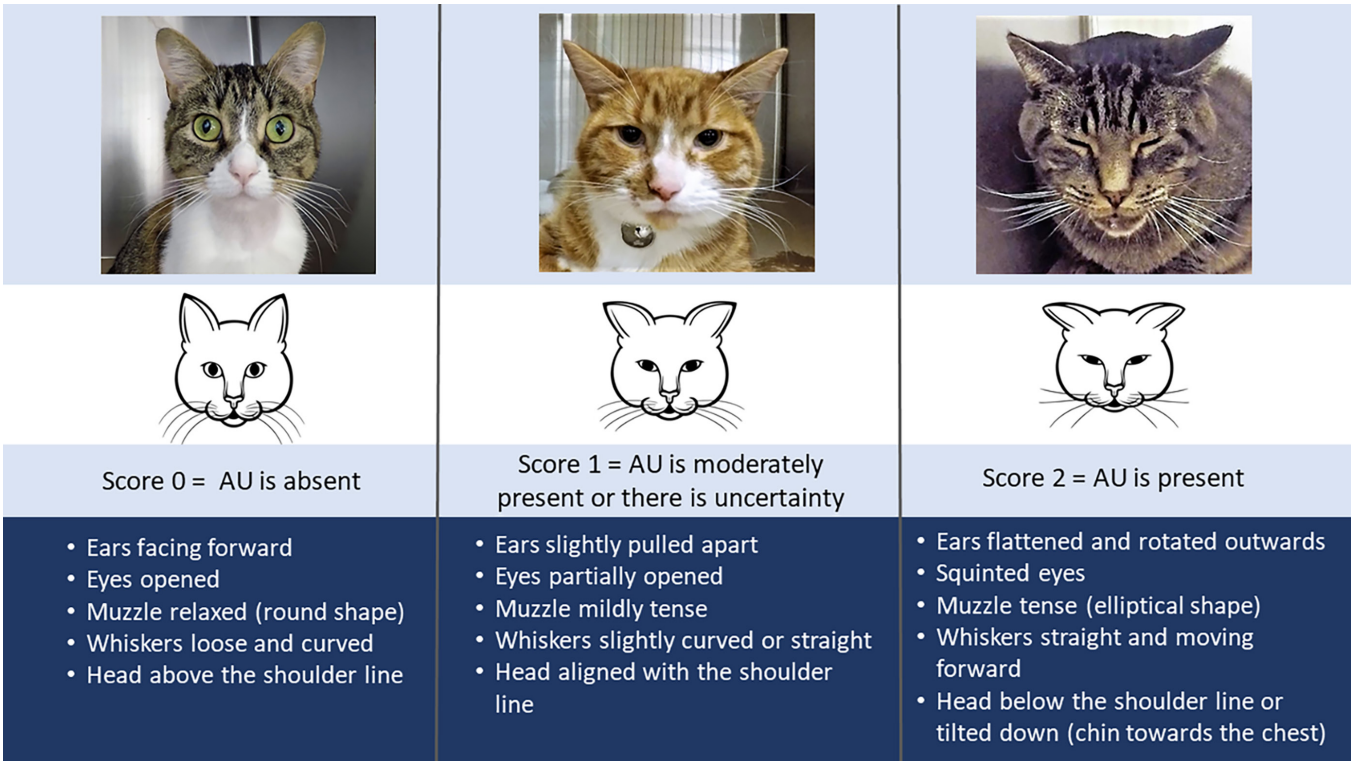


FIG 7. The Feline Grimace Scale© (FGS) is a tool for acute pain assessment of cats based on changes in facial expressions. Five action units (AU) (ear position, orbital tightening, muzzle tension, whiskers change and head position) are individually scored from 0 to 2. The total FGS score is the sum of the scores of all action units. The maximum possible score is 10. For example, the cat on the left scored 0 for each AU with a total FGS score of 0; the cat on the right scored 2 for each AU with a total FGS score of 10. Cats scoring ≥4/10 are likely to be painful and requiring the administration of rescue analgesia (*i.e.* cut-off score for rescue analgesia). A phone application of the FGS is freely available for Android and iOS in English, French and Spanish for real-time pain assessment. Figure courtesy of Paulo Steagall

Practical acute pain assessment and recognition

Take into consideration the type, anatomical location and duration of surgery or trauma, the environment, individual variation, clinical condition, age and health status (Box 1). A good knowledge of the cat's normal behaviour is helpful as changes in behaviour from baseline and presence of new behaviours (a previously friendly cat becoming aggressive, hiding or trying to escape) may provide helpful clues. Some cats may not display clear overt behaviour indicative of pain, especially in the presence of humans, other animals or in stressful situations.

Facial expressions and body postures

Comfortable cats should display normal facial expressions, postures and activity after successful analgesic therapy (Figs 8 and 9). Changes in facial expressions and postures can be altered in cats experiencing pain (Table 5, Fig 10).

Box 1 Step-by-step practical assessment and recognition of acute pain in cats and dogs

1. Observe the animal from a distance in its cage/bed/kennel (observe posture, facial expressions, attention to the wound, interest in surroundings, listen to the type of, or absence of vocalisation; Table 5). If the animal is clearly sleeping in a comfortable, relaxed position, do not disturbed it.
2. Approach the animal calmly and open the cage/kennel while observing the animal's response.
3. Interact with the animal by calling its name using a gentle voice, and petting and/or playing while observing the animal's response. If the animal shows no interest in interacting, do not force it and give it space.
4. If possible, while already touching the animal, slide your hand closer to the painful area. First, attempt to touch it, then apply gently pressure. Stop approaching, touching or pressing as soon as the animal shows a behavioural response (*e.g.* lip licking, swallowing, turning the head towards your hand, flinching, guarding, growling, snapping, attempting to bite, crying).
5. Use a pain scale to score the animal's level of pain based on your observations.

FIG 8. Examples of normal body postures and facial expressions in pain-free cats. Figures courtesy of Sheilah Robertson

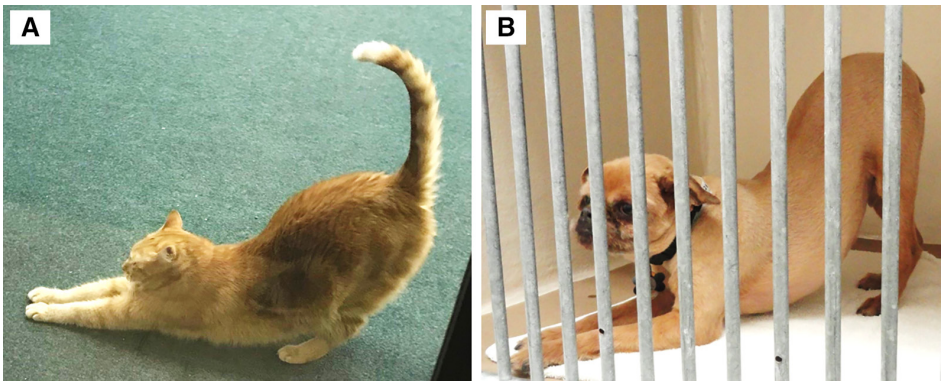


FIG 9. Pain-related behaviours are species-specific. (A) Normal behaviour of a cat stretching after resting. Observing stretching in a cat after abdominal surgery indicates that the cat is comfortable and non-painful. Cats with abdominal pain are normally in a hunched-up position (Fig 10). (B) Abnormal behaviour of a dog with postoperative abdominal pain ("praying position"). It should be noted that dogs also stretch after resting like cats. However, in this case, the dog is not stretching, but adopting a position to alleviate abdominal pain. This posture may also be seen in dogs with oesophageal pain. Figures courtesy of Sheilah Robertson

Table 5. Behavioural changes associated with acute pain in cats and dogs

Cats	Dogs
• Changes in facial expressions (Fig 7) • Change in body posture or body position (Fig 10) • Decreased activity and/or playfulness • Decreased interest in the environment • Decreased willingness to interact • Decreased appetite • Abnormal gait or shifting of weight • Sitting or lying in abnormal positions (may reflect discomfort and protection of an injured area) • Quietness, hiding • Hissing, growling or fear-related aggressiveness • Attention towards a specific area of the body (usually involving surgical wounds) • Guarding behaviour • Cessation of grooming (or increased grooming in one specific location) • Tail flicking • Hunched position and/or a tense abdomen† • Difficulties grasping food and increased head shaking during feeding‡ • Depression and immobility; appears tense and distant from the environment§	• Change in body posture or body position (Fig 14) • Decreased activity and/or playfulness • Decreased interest in the environment • Decreased willingness to interact • Decreased appetite • Abnormal gait or shifting of weight • Sitting or lying in abnormal positions (may reflect discomfort and protection of an injured area) • Change in demeanour • Vocalisation (whining, crying) • Reluctance to move • Attention towards a specific area of the body (usually involving surgical wounds) • Altered reaction to touch or gentle palpation of a painful area • Adopting positions to alleviate abdominal pain, such as adopting a "praying position" (Fig 14) or extending limbs and torso while in lateral or dorsal recumbency† • Depression and immobility; appears tense and distant from the environment§

†Seen with abdominal pain due to surgery or disease
‡Seen in painful cats after multiple dental extractions
§Seen with severe pain

FIG 10. Examples of cats showing signs of acute pain with changes in body posture and facial expressions. Individuals unaware of pain-related behaviours in cats might erroneously think these cats are resting ("feigned sleep"). All cats in these images received rescue analgesia. (A) A painful cat after orthopaedic surgery with Feline Grimace Scale© (FGS) score of 8/10. (B) A cat in severe pain after sternotomy. This cat was depressed, reluctant to move and not attentive to the surroundings. The body posture was tense and the FGS scores were 8/10. (C) A cat with abdominal pain uninterested in her surroundings. (D) A cat with postoperative pain following ovariohysterectomy. The cat was depressed, reluctant to move, uninterested in the surroundings. She was in a hunched-up position, had squinted eyes and lowered head. Figures (A) and (C) courtesy of Sheilah Robertson. Figures (B) and (D) reproduced from Steagall *et al*. (2022)

Dysphoria *versus* pain

Thrashing, restlessness and continuous activity can be signs of severe pain in cats. However, these can also be related to dysphoria. The latter is usually restricted to the early postoperative period (20 to 30 minutes) and associated with poor anaesthetic recoveries

after inhalant anaesthesia, ketamine administration and/or after high doses of opioids. To differentiate between them, analgesics can be administered. A decrease in the observed clinical signs suggests the patient was painful. Worsening of the clinical signs suggests the patient was dysphoric and reversal of the pharmacological agent or sedatives should be administered. If opioid antagonists (*e.g.* naloxone) are administered, analgesic effects might also be reversed and the patient must be closely monitored for signs of pain (Steagall & Monteiro 2019).

Timing of assessments

Ideally a cat should be assessed before surgery using one of the aforementioned validated tools, to establish a baseline (Fig 11); a cat's demeanour can influence pain assessments, so it is important to monitor changes, rather than actual numerical scores (Buisman *et al.* 2017). The presence of sedation and some anaesthetic drugs may interfere with assessment in the early postoperative period (Buisman *et al.* 2016); therefore, waiting for the cat to be in a sternal position and oriented in its surroundings is likely a good time to start. Studies have detected postoperative pain as early as 30 minutes until about 6 to 8 hours after ovariohysterectomy. Cats should not be awakened to check their pain status; rest and sleep are good signs of comfort, but one should ensure the cat is resting or sleeping in a normal posture (relaxed, curled up) (Fig 12). In some cases, cats will remain very still because they are afraid or too painful to move, and some cats "feign sleep" when painful or stressed (Fig 10).

1.5 Recognition and assessment of acute pain in dogs

Acute pain occurs commonly as a result of trauma, surgery, medical problems, infections or inflammatory disease. The severity of pain can range from mild to severe. The duration of pain can vary from a few hours to several days. The effective management of pain relies on the ability and training of the veterinary care staff to recognise and assess pain in a reliable manner. When the dog is discharged from the hospital, caregivers should be given guidance on signs of pain and how to treat it. Analgesics should be prescribed appropriately.

Objective measurements including heart rate, arterial blood pressure and plasma cortisol and catecholamine levels have been associated with acute pain in dogs (Hansen *et al.* 1997). However, they are unreliable because stress, fear, anxiety and anaesthetic drugs affect physiological parameters. Thus, pain assessment is primarily subjective and based on behavioural signs (Fig 13, Table 5).

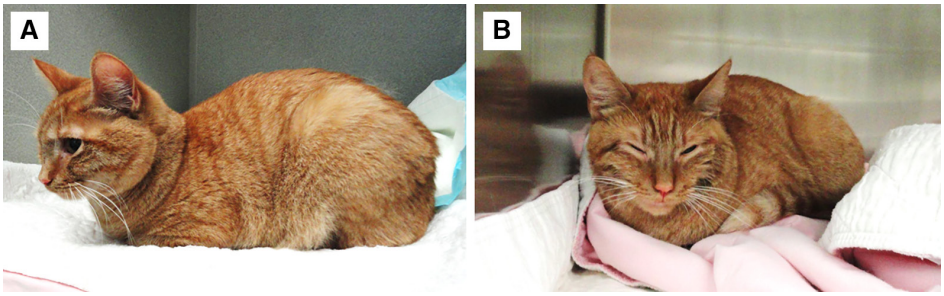


FIG 11. Pain assessment should be performed before surgery for comparison with postoperative behaviours. (A) A cat before a dental procedure with FGS scores of 2/10. (B) The same cat after dental extractions (1-hour postextubation) with FGS scores of 9/10. Figures courtesy of Sheilah Robertson

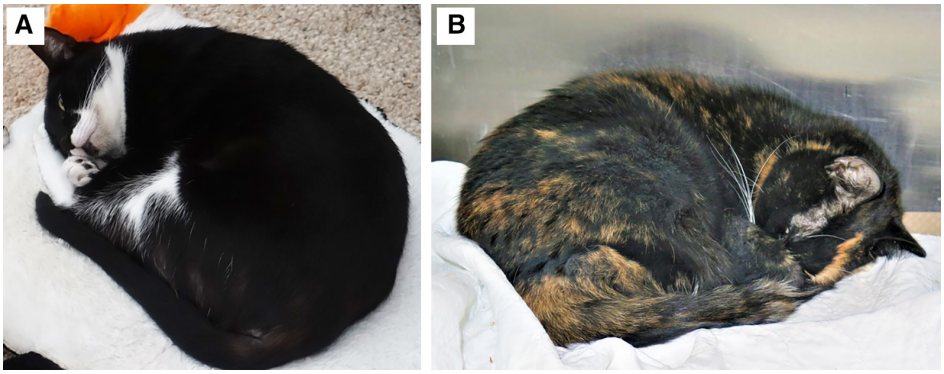


FIG 12. Examples of cats sleeping in a normal curled-up position. Painful cats do not sleep in this conformable position. Rather, "feign sleep" might be seen (see Figs 10 and 11). Figure (A) courtesy of Sheilah Robertson. Figure (B) reproduced from Steagall & Monteiro (2019)

FIG 13. Examples of normal body postures in pain-free dogs. Figures courtesy of Paulo Steagall

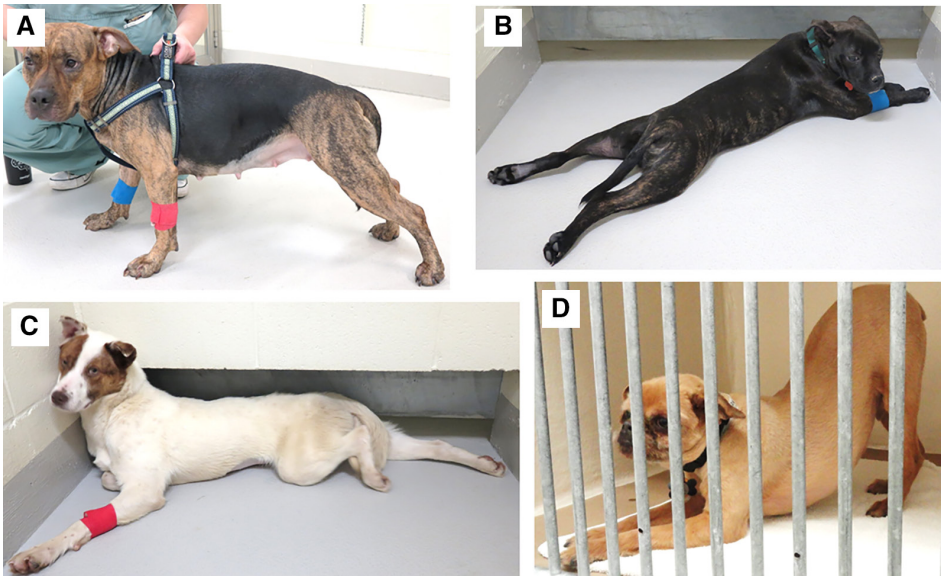


FIG 14. Dogs displaying postures of abdominal pain following abdominal surgery. (A) This dog was standing with her hind limbs extended caudally and was constantly stretching the hind limbs. Although she was friendly and stoic, a flinch was observed with gentle palpation around the incision. Scores from the Glasgow Composite Measure Pain Scale-Short Form were 9/24 indicating the need of rescue analgesia. (B) This dog was restless and alternating between the "praying position" and being in external recumbency with the hind limbs extended caudally. (C) This dog would lay in sternal recumbency and flex and extend her hind limbs due to abdominal discomfort. (D) This dog was adopting a "praying position" to alleviate abdominal pain. Figures (A), (B) and (C) courtesy of Paulo Steagall. Figure (D) courtesy of Sheilah Robertson

Practical acute pain assessment and recognition

Behavioural expression of pain is species-specific (Fig 9) and influenced by age, breed, demeanour, type and duration of pain, clinical condition and the presence of additional stressors such as anxiety or fear. Debilitating disease can dramatically reduce the range of behavioural indicators of pain that the animal would normally show (*e.g.* dogs may not vocalise and may be reluctant to move to prevent worsening pain). Therefore, when assessing a dog for pain a range of factors should be considered, including the type, anatomical location and duration of surgery, the medical problem, or extent of injury. It is helpful to know the dog's normal behaviour as changes in behaviours are important means of pain assessment (Figs 9 and 14). For example, a happy dog before surgery that no longer wants to play many hours after surgery (when normal behaviours should have returned) might be in pain. Changes in facial expression due to pain have not yet been documented in dogs, but likely exist.

Pain assessment protocol

Acute pain recognition is based on routine assessment of the dog for signs of pain. These signs are better identified through observation and interaction with the patient along with knowledge of the disease/surgical status and history of the animal (Box 1). A consistent, specific protocol and approach is recommended for pain assessment, particularly using pain scoring systems. Dysphoria should be considered where panting, nausea, vomiting or vocalisation occurs following opioid administration (Chapter 1.4).

Where a dog is judged to be in pain, treatment should be given immediately to provide relief. Dogs should be assessed continuously to ensure that treatment has been effective, and thereafter on a 2 to 4 hourly basis depending on the duration of action of analgesics. Pain can be assessed as early as 30 minutes after patient extubation. Frequency of pain assessment will depend on the type and severity of pain as well as duration of action of analgesic drugs being administered.

Pain scoring tools

These should possess the key properties of validity, reliability and sensitivity to change. Pain is an abstract construct so there is no gold standard for measurement, and as the goal is to measure the affective component of pain (*i.e.* how it makes the dog feel), this can be a real challenge. The WSAVA-GPC recommends the use of composite pain scales with reported validation (Table 6). Examples include the Glasgow Composite Measure Pain Scale and its short form (CMPS-SF) (Holton *et al.* 2001, Reid *et al.* 2007) and the French Association for Animal Anaesthesia and Analgesia pain scoring system, the 4A-Vet (Rialland *et al.* 2012) which are easy to use and include interactive components and behavioural categories. The CMPS-SF is a clinical decision-making tool used in conjunction with clinical judgement. Concurrent sedation is a confounding factor as deeply sedated dogs tend to score highly irrespective of whether they are painful or not. The effect of sedation on CMPS-SF scores should be considered when assessing patients and deciding on the requirement for additional analgesia.

1.6 Recognition and assessment of chronic pain in cats

As cats live longer there has been an increase in the prevalence of painful chronic conditions and comorbidities considered to impact negatively on their QoL [see the 2021 AAFP Feline Senior Care Guidelines (Ray *et al.* 2021)]. Such pathological or maladaptive pain is commonly associated with a variety of chronic diseases (*e.g.* DJD/OA, stomatitis, certain cancers and intervertebral disk disease). It may also be present in the absence of ongoing clinical disease, persisting beyond the expected course of an acute disease process – such as neuropathic pain following onychectomy, limb or tail amputation.

Pain recognition is the keystone of effective pain measurement and management. The behavioural changes associated with chronic pain may develop gradually and may be subtle, making them most easily detected by someone familiar with the animal (usually the caregiver). Cats, which are both predators and prey, are adept at masking pain through minimising the behavioural manifestations of pain. In addition, they are not normally taken on walks and expected to perform activities with their human caretakers – all of

Table 6. Tools used for assessing acute pain in dogs

Tool	Type	Condition	Comments	References
Glasgow composite measure pain scale-Short-Form (CMPS-SF)†	Behaviour	Any surgical or medical pain	Moderately validated. Available in English, French, Spanish, German, Italian, Norwegian and Swedish. Contains six items; each having a different range of possible scores. The maximum score is 24 (or 20 when mobility cannot be assessed). Cut-off score for rescue analgesia: ≥6/24 (or ≥5/20 when mobility cannot be assessed)‡ Available at: http://www.newmetrica.com/acute-pain-measurement/	(Holton *et al.* 2001, Reid *et al.* 2007, Murrell *et al.* 2008)
French Association for Animal Anaesthesia and Analgesia pain scoring system (4A-Vet)	Behaviour	Orthopaedic surgery	Preliminary validation has been reported. Contains six items scored from 0 to 3. The maximum score is 18. No cut-off score is available Available in the original article (open access): https://doi.org/10.1371/journal.pone.0049480	(Rialland *et al.* 2012)
University of Melbourne Pain Scale	Behaviour and physiologic data	Ovariohysterectomy	Preliminary validation has been performed. Includes multiple descriptors in six categories including physiologic data and behavioural responses. The maximum score is 27 No cut-off is available Available in the original article	(Firth & Haldane 1999)

†Recommended for use in practice due to higher degree of scientific evidence
‡The score at which analgesia should be administered

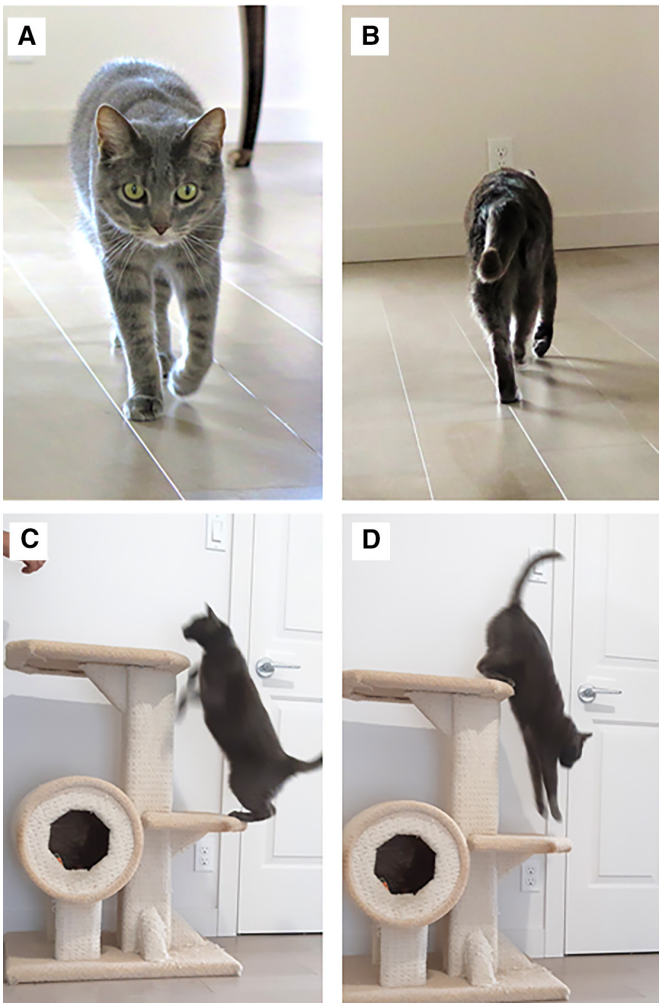


FIG 15. Home-made videos can be extremely helpful to evaluate how animals are performing routine activities in the home environment without the stress-related effects of being in a clinic or hospital environment. Ideally, cats should be observed while performing routine activities such as walking, jumping, using stairs, using the litter box, etc. Figures (A) and (B) reproduced from Monteiro & Steagall (2019). Figures (C) and (D) courtesy of Beatriz Monteiro

which add to the difficulty in identifying the behavioural changes associated with maladaptive pain. Overall, the recognition of long-standing maladaptive pain is based on a combination of caregiver assessment (with appropriate caregiver education), veterinarian observation and veterinarian examination. Home-made videos can be helpful in identifying pain-related behaviours (Fig 15). In the future, technology (such as cameras and wearables) may assist diagnosis.

Practical chronic pain assessment and recognition

The mainstay of assessment of chronic maladaptive pain is evaluation by the caregiver, and this information is captured using Client Reported Outcome Measures or Clinical Metrology Instruments (CMIs) (Lascelles *et al.* 2019, Monteiro & Steagall 2019b). A study has highlighted the importance of caregiver education in the identification of chronic pain (Enomoto *et al.* 2020). *Caregiver education is important because long-standing pain conditions produce gradual behavioural changes that may not be overtly noticed by caregivers or may be ascribed to ageing.*

Many of the tools for measuring chronic pain in humans measure its impact on the patient's QoL, which includes physical and psychological aspects. Studies assessing QoL or HRQoL in cats in relation to various chronic diseases are available (Reid *et al.* 2018a, Monteiro 2020) and have been systematically reviewed (Doit *et al.* 2021) although none are pain-specific.

Most work has been performed around the recognition of DJD-associated pain in cats (Box 2). Recently, a checklist [Feline Musculoskeletal Pain Screening Checklist (MiPSC)] has been produced to assist with the identification of cats with DJD pain based on a valid scientific approach (Enomoto *et al.* 2020) (Table 7). Such a checklist helps identify cats that may have DJD-associated pain and can be used as an important caregiver education tool. Client Reported Outcome Measures or CMIs have been designed to standardise the collection of caregiver reports and facilitate measurement (and identification) of chronic DJD-associated pain. Examples include

Box 2 Differences of chronic joint disease between cats and dogs

- The term "DJD" (degenerative joint disease) encompasses degeneration of all types of joints (synovial appendicular joints, fibrocartilagenous joints and intervertebral joints). Osteoarthritis (OA) refers to a chronic, low-grade inflammatory, overall degenerative process of synovial joints that is not driven by infection or immune-mediated disease.
- Cats presenting for treatment of musculoskeletal pain clearly have a combination of OA-pain and pain from non-synovial joints (Gruen *et al.* 2016, 2021a, Adrian *et al.* 2021). Additionally, it is not known if synovial joint degeneration in cats is caused by immune dysfunction, different to OA in dogs. For these reasons, the term "DJD" when referring to cats being treated for musculoskeletal joint pain is preferred.
- OA in dogs occurs primarily as a consequence of developmental orthopaedic disease (*e.g.* hip and elbow dysplasia, patella luxation, osteochondrosis dissecans or predisposition to cruciate ligament rupture). Developmental diseases result in increased or abnormal mechanical loading in the joint and drives chronic low-grade inflammation and degradation of joint tissues, and pain (OA-pain). For these reasons, OA (and OA-pain) develop early in life. Osteoarthritis should be considered a "young dog disease" despite being generally diagnosed at its later stages when the signs of OA-pain are obvious or require urgent attention.
- Although the mechanisms resulting in DJD in cats are not fully understood, they are generally not related to developmental disease. In cats, as OA in humans, DJD can be considered an age-related disease and is more prevalent as cats age. However, clinical data indicate that young cats can be affected by DJD and DJD-associated pain. Therefore, cats and dogs of any age should be investigated for the presence of DJD or OA, and associated pain, respectively.

the Feline Musculoskeletal Pain Index (FMPI), Client Specific Outcome Measure (CSOM), Montreal Instrument for Cat Arthritis Testing (MI-CAT) and the Feline Physical Function Formula (FPFF) (Lascelles *et al.* 2007, Klinck *et al.* 2015, Klinck *et al.* 2018, Stadig *et al.* 2019, Enomoto *et al.* 2022) [see Table 7 and the GPC website (https://wsava.org/committees/global-pain-council/)]. These instruments have been primarily designed to score the impact of DJD-pain on the cat, and monitor the effectiveness of treatments. When administered at intervals over time, they provide consistent data measuring the severity of chronic DJD-associated pain. However, they can also be used to assist with the initial diagnosis. Each of the above instruments vary in what they measure, but across these instruments similar behaviours considered to be important to evaluate in chronic pain conditions are being assessed (Table 8). Veterinary technicians and nurses are valuable in presenting pain scales to caregivers and guiding them on how to complete these whether at the time of consultation or using telemedicine. Based on current literature, clinicians are suggested to use the Feline MiPSC for screening of patients at risk and the FMPI or CSOM for monitoring signs of pain and response to treatment.

The use of physical activity monitors (Fig 16) to assist in the detection and monitoring of musculoskeletal pain is an active area of research, but there is still much to understand about how musculoskeletal pain affects activity, and how best to analyse such data (Guillot *et al.* 2013, Gruen *et al.* 2017, Yamazaki *et al.* 2020). Current studies are investigating assessment tools for other types of chronic maladaptive pain in the cat including stomatitis (Stathopoulou *et al.* 2018).

Quantitative Sensory Testing (QST) evaluates the transmission of information related to thermal, mechanical, and chemical stimuli from the periphery to the somatosensory cortex. It uses calibrated devices to induce a noxious stimulus against the skin of the animal until a behavioural reaction is observed (Fig 17). The end point is objectively recorded (*e.g.* value in Newtons, grams, °C, seconds). Quantification of sensory sensitivity allows researchers to compare animals with and without disease, as well as the effects of treatment. The use of QST shows that cats with OA present with hyperalgesia, allodynia and facilitated temporal summation of pain when compared with healthy cats, reflecting peripheral and central sensitisation mechanisms (Monteiro *et al.* 2020), similar to what is reported in people and dogs (Hunt *et al.* 2019).

1.7 Recognition and assessment of chronic pain in dogs

Chronic pain is of long duration and is commonly associated with chronic diseases. It may also be present in the absence of ongoing clinical disease (*e.g.* persistent postsurgical pain). As dogs live longer there has been an increased prevalence of painful chronic conditions such as OA, spinal cord disease, treatable forms of cancer and medical sources of pain (bladder, kidney, gastrointestinal). However, young dogs with developmental orthopaedic disease are at particular risk of being affected with chronic pain from the early stages of life (Box 2). The disease of OA (secondary to developmental disease) can be present in young dogs, and OA-associated pain is not uncommon in this population. Thus, *all dogs of all ages could be affected by chronic pain*. Early identification of pain means earlier intervention including lifestyle changes that could reduce the progression of this painful disease. Treatment options for chronic pain are complex, and response to treatment is subject to much individual variation.

Practical chronic pain assessment and recognition

Pain recognition is key to effective pain management. The behavioural changes associated with chronic pain may develop gradually and may be subtle, so that they can only be detected by someone familiar with the animal (usually the caregiver) (Table 8). Numerous pain scoring instruments are available to evaluate chronic pain or HRQoL in dogs; however only a few have been validated (Belshaw

Table 7. Tools used for screening and assessing chronic pain in cats (Clinical Metrology Instruments, CMI) and assessing health-related quality of life (HRQoL)†

Tool	Type	Condition	Comments	Main reference
Feline Musculoskeletal Pain Screening checklist (Feline MiPSC)†	Screening	DJD/OA	A simple checklist of six items asking if a specific activity can be performed normally or not. Thus, caregivers respond "yes" or "no" to each item. If any of the items is scored as "no" (*i.e.* the activity is not normal), this should prompt further evaluation Available at: https://cvm.ncsu.edu/research/labs/clinical-sciences/comparative-pain-research/clinical-metrology-instruments/ See also: https://www.zoetispetcare.com/checklist/osteoarthritis-checklist-cat	(Enomoto *et al*. 2020)
Feline musculoskeletal pain index (FMPI)†	CMI	DJD/OA	The most widely studied of the "off the shelf" CMIs (has been evaluated for construct validity, internal consistency, reliability, and discriminant ability) An updated version, the FMPI-Short Form, contains nine items/activities that are assessed on a Likert scale from "normal" to "not at all." Items are related to mobility and ability to perform daily activities Available at: https://cvm.ncsu.edu/research/labs/clinical-sciences/comparative-pain-research/clinical-metrology-instruments/	(Benito *et al*. 2013a,b, Stadig *et al*. 2019, Enomoto *et al*. 2022)
Client Specific Outcome Measure (CSOM)†	CMI	DJD/OA	Has been widely used but is not an "off the shelf" questionnaire. Rather, it is constructed for each individual case in which a number of activities that are particular to each cat and home environment. These activities are decided upon with the caregivers and monitored over time Available at: https://cvm.ncsu.edu/research/labs/clinical-sciences/comparative-pain-research/clinical-metrology-instruments/	(Lascelles *et al*. 2007, Stadig *et al*. 2019)
Montreal Instrument for Cat Arthritis Testing for use by owners (MICAT(C))	CMI	DJD/OA	Preliminary validation has been performed. Includes items pertaining to agility, social, play and exploratory behaviours, self-maintenance, and physical conditioning Available as a supplementary file with the original article	(Klinck *et al*. 2015, 2018)
Feline Physical Function Formula (FPFF)	CMI	DJD/OA	Preliminary validation has been performed. Includes evaluation of four domains (general activity, mobility, temperament and grooming) Not available for download. The items are described in the article	(Stadig *et al*. 2019)
Cat Health and Wellbeing (CHEW)	HRQOL	Any	Preliminary validation has been performed. Contains 33 items divided into eight domains (mobility, emotion, energy, engagement, eyes, coat, appetite, fitness) Available as supplementary material with the original article	(Freeman *et al*. 2016)
Feline QOL measure	HRQOL	Any	Preliminary validation has been performed. Contains 16 items divided into two domains (healthy behaviours and clinical signs) Not available for download. The items are described in the article	(Tatlock *et al*. 2017)
VetMetrica HRQOL for cats	HRQOL	Any	Preliminary validation has been performed. Contains 20 items divided into three domains (vitality, comfort and emotional wellbeing) Available as a web-based instrument *via* paid subscription (https://www.newmetrica.com/vetmetrica-hrql/). The 20 items of the questionnaire are listed in the original article	(Scott *et al*. 2021)

CMI Clinical metrology instrument, COP Cyclophosphamide, vincristine and prednisolone, DJD Degenerative joint disease, OA Osteoarthritis
†All instruments are meant to be completed by caregivers
†Recommended for use in practice due to higher degree of scientific evidence

et al. 2015, Belshaw & Yeates 2018, Reid *et al*. 2018a, Lascelles *et al*. 2019) (Table 9). Based on current evidence, the Canine Brief Pain Inventory (CBPI) and the Liverpool Osteoarthritis in Dogs (LOAD) are recommended for use in practice.

Similar to cats (Chapter 1.6) other tools such as QST and activity monitors are used in dogs. The use of QST may provide a window into chronic pain assessment (Knazovicky *et al*. 2016) and dogs with OA were shown to have increased widespread sensory sensitivity to external stimuli when compared to normal dogs (Knazovicky *et al*. 2016). Once valid, cage side QST testing paradigms may be a useful addition to clinical practice.

1.8 Oligoanalgesia and inappropriate polypharmacy

Oligoanalgesia

Oligoanalgesia is the failure to recognise and provide analgesia in patients with acute pain (Wilson & Pendleton 1989) (Box 3). An in-depth discussion on how the issue can influence patient outcomes and physiological consequences has been published elsewhere

Table 8. Behaviours included in the evaluation of chronic pain in cats and dogs

Cats	Dogs
• General mobility (*e.g.* ease of movement, fluidity of movement) • Ability to perform activities of daily living (*e.g.* playing, hunting, jumping, using a litterbox) • Eating, drinking • Grooming (*e.g.* scratching) • Resting, observing, relaxing (how well these activities can be enjoyed by the cat) • Social activities involving • Social activities involving people and other pets • Temperament	• Vitality and mobility (*e.g.* if the dog is energetic, happy, active/lethargic, contented, playful and how the dog is able to lay down, stand up, sit, jump or tolerate exercise) • Mood and demeanour (*e.g.* if the dog is alert, anxious, withdrawn, sad, dull, confident, playful and sociable) • Levels of distress [*e.g.* vocalisation (moaning, groaning), and response to other dogs and humans] • Indicators of pain (*e.g.* comfort levels, stiffness, lameness, orthopaedic exam) • Imprint of pain on the somatic structures (*e.g.* myofascial exam, muscle strain patterns)

FIG 16. A cat wearing an accelerometer-based activity monitor attached to its collar. Figure reproduced from Monteiro (2020)

FIG 17. Example of quantitative sensory testing in a cat using a von Frey which is gently pressed against the metacarpal pad of the cat until a behaviour response (*e.g.* paw withdrawal) is observed. The maximum amount of force used to elicit this response is known as the nociceptive threshold. Figure reproduced from Monteiro (2020)

(Simon *et al.* 2017). Failure to address acute perioperative pain can lead to peripheral and central sensitisation and maladaptive pain (*e.g.* persistent postsurgical pain) (Kalso *et al.* 2001, Johansen *et al.* 2012).

Oligoanalgesia is observed in human emergency departments after routine procedures not considered to be painful in patients unable to verbalise pain or those that do not receive immediate care due to inappropriate pain assessment (Todd *et al.* 2007, Rose *et al.* 2013, Carter *et al.* 2016). Some of or all these factors could lead to oligoanalgesia in veterinary medicine. Indeed, studies have revealed that, historically, many dogs and cats did not receive analgesics despite their painful status and conditions (Hansen & Hardie 1993, Dohoo & Dohoo 1996a,b, Wiese *et al.* 2005), and that pain is highly prevalent in the emergency setting (Wiese *et al.* 2005, Moran & Hofmeister 2013). Recent data show that perioperative use of analgesics has increased (Farnworth *et al.* 2014, Rae *et al.* 2021). For example, more than 90% of veterinarians in the UK administered some sort of perioperative analgesics for

Table 9. Tools used for screening and assessing chronic pain in dogs (clinical metrology instruments, CMI) and assessing health-related quality of life (HRQoL)†

Tool	Type	Condition	Comments	References
Canine Osteoarthritis Staging Tool (COAST)	Screening	OA	Preliminary validation has been performed Consists of three separate steps for grading the dog, grading the joint and staging OA Help veterinarians to identify OA earlier and monitor progression over time Available at: https://www.galliprantvet.com/us/en/coast-tools	(Cachon *et al*. 2018)
Canine Brief Pain Inventory (CBPI)†	CMI	OA and bone cancer	Validated instrument. Consists of 11 items for evaluation of pain severity and pain interference with function, and overall impression of quality of life. Items are scored on a Likert scale Available at: https://www.vet.upenn.edu/research/clinical-trials-vcic/our-services/pennchart/cbpi-tool	(Brown *et al*. 2008, 2009)
Liverpool Osteoarthritis in Dogs (LOAD)†	CMI	OA	Validated instrument. Contains 13 items for evaluation of general mobility and mobility at exercise. Items are scored on a Likert scale Available at: https://www.galliprantvet.com/us/en/coast-tools	(Walton *et al*. 2013)
Helsinki Chronic Pain Index (HCPI)	CMI	OA	Preliminary validation has been performed. Consists of 11 items scored on a Likert scale	(Hielm-Bjorkman *et al*. 2009)
Sleep and nighttime restlessness evaluation (SNoRE)	Sleep and nighttime restlessness	OA	Preliminary validation has been reported. Originally six items, currently a five-item version (2.0) is recommended, with questions focused on sleep scored on a Likert scale Available at: https://cvm.ncsu.edu/research/labs/clinical-sciences/comparative-pain-research/labs-comparative-pain-research-clinical-metrology-instruments-snore-evaluation/	(Knazovicky *et al*. 2015, Gruen *et al*. 2019)
Health-related quality of life (HRQoL)	HRQoL	Chronic disease	Validated instrument. The most recent version has 22 items divided into four domains of quality of life in dogs (Energetic and Enthusiastic, Happy and Content, Active and Comfortable and Calm and Relaxed) Available as a web-based instrument *via* paid subscription (https://www.newmetrica.com/vetmetrica-hrql/)	(Reid *et al*. 2013, 2018b)
Health-related quality of life (HRQoL)	HRQoL	OA	A conceptual framework for assessment of HRQoL was developed to inform a potential tool. Focused on four domains (physical appearance, capability, behaviour and mood) Tool not yet available	(Roberts *et al*. 2021)

CMI Clinical metrology instrument, DJD Degenerative joint disease, OA Osteoarthritis
†All instruments are meant to be completed by caregivers. This is not an exhaustive list of available tools but the ones with more studies available
†Recommended for use in practice due to higher degree of scientific evidence

Box 3 Reasons for oligoanalgesia. Based on Simon *et al*. (2017)

- Notes or instructions in the patient record that may lead to subjective interpretation such as, "analgesics as needed (PRN)," instead of instructions to use an objective pain scoring system (Hansen & Hardie 1993).
- Lack of pain assessment which may lead to inadequate pain control and the administration of analgesics.
- Lack of training in pain assessment of individuals involved in first-line treatment such as veterinary nurses, students and emergency veterinarians (Barletta *et al*. 2016).
- Fear and misconceptions of analgesic-induced adverse effects.
- Lack of analgesic availability (Berterame *et al*. 2016).
- Lack of compliance of the technical staff to administer analgesics (Armitage *et al*. 2005).
- Species: cats have historically received less analgesics when compared with dogs, even following the same surgical procedures (Hansen & Hardie 1993, Dohoo & Dohoo 1996a,b, Steagall *et al*. 2022).
- Other factors: lack of validated pain scoring instrument in the past; analgesic costs; potential for human drug abuse with specific analgesics; lack of clinical experience or confidence with pain assessment tool or a drug, and lack of familiarity with prescription procedures (Wiese *et al*. 2005, Moran & Hofmeister 2013, Lorena *et al*. 2014, Hunt *et al*. 2015).

routine procedures while the postincisional use of analgesics for neutering by Canadian veterinarians has also increased (Hewson *et al*. 2006a,b, Hunt *et al*. 2015). On the other hand, some studies indicated that postoperative analgesics are still not commonly provided after neutering in some countries (Lorena *et al*. 2014, Perret-Gentil *et al*. 2014).

Education and training in pain management (Mich *et al.* 2010, Lim *et al.* 2014, Lorena *et al.* 2014, Doodnaught *et al.* 2017) including discussion of alternative methods of pain control when analgesics are not available (Diep *et al.* 2020) and the use of validated pain scoring tools are needed to address the issue of oligoanalgesia.

Polypharmacy

Although the provision of adequate analgesia is imperative to ensure the welfare of dogs and cats with acute or chronic pain it is important to distinguish appropriate multi-modal analgesia from inappropriate polypharmacy. Polypharmacy is the use of a large number of medications in combination without good rationale and can lead to complex drug interactions and an increased risk of adverse effects. For example, combining drugs with similar effects on the serotonergic system can increase the risk of serotonergic syndrome (Chapter 2.7). Similarly, giving a NSAID in combination with a corticosteroid will increase the likelihood of adverse effects such as gastrointestinal ulceration or perforation. Although multi-modal analgesia is recognised to improve analgesia provision, injudicious use of polypharmacy can be expensive, both in the clinic and when applied in the home environment. Compliance and adherence to having to give multiple medications at different time points can also be difficult. A study investigating caregiver perceptions of chronic pain in dogs identified that having to give lots of medications had a significant caregiver burden in terms of cost and also the practicalities of ensuring that dogs received medications on time (Davis *et al.* 2019). Administering medications three times daily is often not practical for caregivers leading to poor compliance. A higher medication burden with polypharmacy leads to a greater deterioration in the human–animal relationship. For example, over half of caregivers reported that medicating their cat had changed their relationship with them (Taylor *et al.* 2022).

1.9 Neuropathic pain

Neuropathic pain is pain that arises as a direct consequence of a lesion or disease of the somatosensory system (Jensen *et al.* 2011) (Table 3). It is a maladaptive phenomenon that involves sensory aberrant ectopic spontaneous activity, neuroplasticity, peripheral and central sensitisation, impaired endogenous inhibitory modulation and glia activation, among others (Gilron *et al.* 2015). In veterinary medicine, neuropathic pain is an under-diagnosed, poorly understood and novel syndrome; review articles are available on the topic (Grubb 2010, Moore 2016, Epstein 2020). At the time of writing, there was no validated instrument for the diagnosis of neuropathic pain itself. The disease is usually presumed after detailed physical and neurological examinations, and when possible, advanced imaging of the affected area, such as magnetic resonance imaging (MRI). Neuropathic pain should be suspected when a patient is refractory to conventional analgesic therapy and has shown clinical signs of allodynia and/or hyperalgesia; however, hypoalgesia may also be present depending on the lesion and disease (Ruel *et al.* 2020). QST (Chapter 1.6) in dogs with thoracolumbar disc herniation (Gorney *et al.* 2016) and dogs with neuropathic pain conditions showed increased pain facilitation and/or decreased pain inhibition when compared with healthy individuals (Ruel *et al.* 2020); QST could provide useful clinical information when incorporated into physical/neurological examination in the future.

Several forms of neuropathy have been described in veterinary species including spinal cord disease, chronic musculoskeletal conditions, peripheral neuropathy, persistent postsurgical pain (Figs 18 and 19). For example, OA may lead to widespread central sensitisation and the occurrence of neuropathic pain (Knazovicky *et al.* 2016). Feline diabetic neuropathy is a syndrome developed secondary to diabetes that causes plantigrade stance and neuropathic pain (Mizisin *et al.* 1998, Estrella *et al.* 2008). Chiari-like malformation of Cavalier King Charles and Chihuahua dogs, among other small breeds, and syringomyelia are a significant source of neuropathic pain, and associated with fearful behaviour and decreased QoL (Rutherford *et al.* 2012). Genetic factors play a role in these condi-

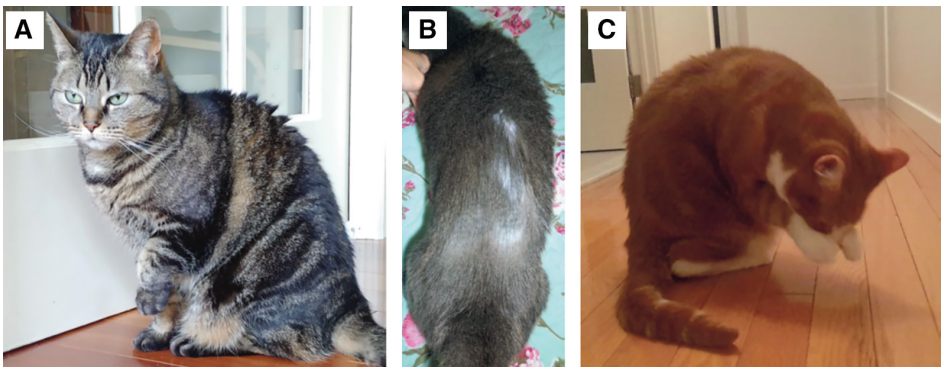


FIG 18. Examples of cats with neuropathic pain. (A) A cat with persistent postsurgical pain following onychectomy. This cat would frequently keep the left paw lifted while sitting to avoid bearing weight on it and would resent being touched on this same paw several years after surgery. (B) A cat with suspected feline hyperesthesia syndrome. This cat would suddenly start plucking his hair around the thoracolumbar area and would react to touching of this same area showing signs of allodynia. (C) A cat with feline orofacial pain syndrome. This cat would frantically rub his face with the front paws and would vocalise for "no apparent reason." Figures reproduced from Monteiro & Steagall (2019)

FIG 19. Example of a dog with neuropathic pain. This 13-year-old female dog had end-stage osteoarthritis of multiple joints. She had marked asymmetry of muscle mass and weight distribution of her hind limbs. She presented with severe mobility impairment and excessive licking of the hind paws. Figure courtesy of Beatriz Monteiro

tions whereby malformation of the skull and craniocervical junction result in overcrowding of brain parenchyma with consequent pain and disturbances in the cerebrospinal fluid circulation (Ancot *et al.* 2018, Knowler *et al.* 2018). Feline hyperesthesia syndrome (FHS) and orofacial pain syndrome (FOPS) are pain disorders with behavioural signs highly suspicious of neuropathic pain (Fig 18). Clinical features of a case series with seven cats with FHS showed skin rippling over the dorsal lumbar area, episodes of jumping and running, excessive vocalisation, tail chasing/mutilation (Batle *et al.* 2019). The prevalence of FOPS is high in Burmese cats compared with other breeds. Feline orofacial pain syndrome has similar pathophysiology to trigeminal neuralgia in people; it has acute unilateral episodes and a suspected hereditary component that could be related to stress (Rusbridge *et al.* 2010). Clinical signs can be triggered by mouth movement or occur spontaneously and include pawing at the mouth, exaggerated licking and chewing movements, tongue mutilation, spontaneous vocalisation with escape behaviour and decreased appetite.

Treatment of neuropathic pain is challenging. In the veterinary literature, gabapentinoids (gabapentin or pregabalin) have been used as the first line of treatment of neuropathic pain with significant improvements in QoL (Plessas *et al.* 2015, Batle *et al.* 2019, Sanchis-Mora *et al.* 2019, Ruel *et al.* 2020, Schmierer *et al.* 2020, Thoefner *et al.* 2020). Non-steroidal anti-inflammatory drugs have been used in combination with gabapentinoids when an inflammatory condition is also suspected. Antagonists of N-methyl-D-aspartate (NMDA) receptors (*i.e.* amantadine) have been also used for the treatment of OA in dogs (Lascelles *et al.* 2008) and cats (Shipley *et al.* 2021). Several physical medicine modalities including heat and cold therapy, acupuncture and trigger point needling, stretching, massage and exercise can be used although they need further research in veterinary species (Shah *et al.* 2015). Studies are warranted including different treatment options in a wide array of neuropathic painful conditions and investigations of potential placebo effect. See Chapter 3.12 for further information.

1.10 Orofacial and dental pain

According to the IASP, orofacial pain is a frequent form of pain perceived in the face and/or oral cavity (IASP n.d.-b). It may be caused by diseases or disorders of regional structures, dysfunction of the nervous system, or through referral from distant sources (Fig 20). Orofacial pain involves musculoligamentous, dentoalveolar and/or neurovascular mechanisms. Dental pain is a type of orofacial pain caused by dental diseases or pain referred to the teeth. Specific differences exist between the mechanisms of dental nociception and other body tissues. The underlying nociceptive process in orofacial conditions is less well understood than other somatic signalling mechanisms. For example, the tooth pulp is densely innervated and surrounded by mineralised dentin and enamel. The latter is avascular, non-innervated and non-porous offering a protective layer to the tooth. However, in this low-compliant environment and during inflammation, minimal swelling of the pulp will lead to severe pain especially when the enamel is compromised.

Orofacial pain is a common problem in veterinary medicine due to the high prevalence of oral disorders (*e.g.* periodontal disease, fractured teeth, stomatitis, malocclusions and neoplasia) leading to acute and chronic pain potentially affecting the QoL of animals and the caregiver-pet bond. The WSAVA Dental Standardization Committee has published an extensive document on the subject that includes information on anaesthesia and pain management in dentistry (Niemiec *et al.* 2020). Additional dental care guidelines by the American Animal Hospital Association are also available (Bellows *et al.* 2019).

Periodontal disease is a common condition in canine and feline practice and its treatment often involves general anaesthesia and dental extractions. For example, feline chronic gingivostomatitis is characterised by bilateral, multi-focal or diffuse, friable, proliferative ulcerative lesions around the tongue base and palatoglossal fold with intense oral discomfort. It leads to anorexia, dysphagia, sialor-

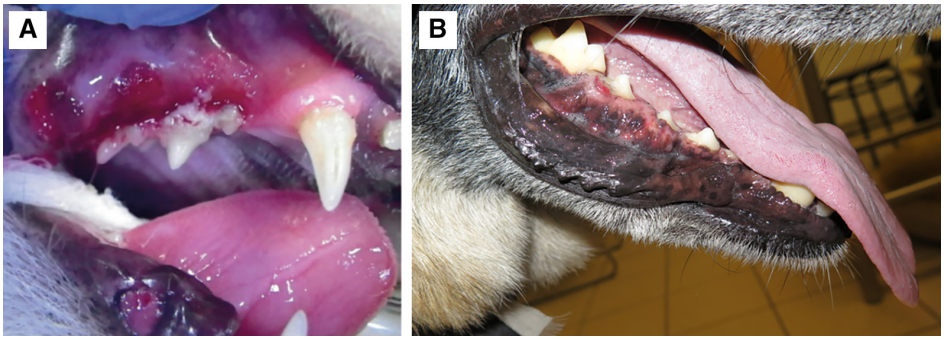


FIG 20. Examples of conditions causing orofacial pain and dental pain. (A) A female cat with severe periodontal disease. This cat would start pawing at the mouth while eating. She was anaesthetised to undergo dental treatment including dental extractions. The caregivers reported that after treatment these signs disappeared, and she became more friendly. (B) A dog with an osteosarcoma of the right mandible. The dog was no longer interested in catching a ball when the caregiver threw it, an activity that was previously enjoyed. Figure (A) reproduced from Monteiro & Steagall (2019). Figure (B) courtesy of Beatriz Monteiro

rhea, halitosis and weight loss. It can also produce oral haemorrhage and it often requires full-mouth extractions (Winer *et al.* 2016). Other common causes of dental pain include trauma, infection of the dental pulp (pulpitis) or pulp disease, neoplasia, occlusal trauma, abscesses, cracked tooth syndrome, fractures and invasive surgical oral procedures (*e.g.* maxillectomies, mandibulectomies, etc.). Despite being common, oral/dental pain is still under-recognised, undertreated and neglected in small animal practice. However, it is receiving attention as a high-priority welfare issue (Summers *et al.* 2019). In a survey of electronic canine health records in the UK, dental disorders were ranked as one of three diseases with a high-welfare impact based on their high prevalence, long duration and severity.

To date, most studies on the subject involve local anaesthetic blocks and their anaesthetic-sparing effect, but in terms of analgesia and oral pain-induced behaviours, not much has been investigated. Pain after dental extractions is inflammatory in nature and impacts nutrition and feeding behaviour in cats (Watanabe *et al.* 2019, Watanabe *et al.* 2020b). These patients require long-term opioid therapy (up to 72 hours in some individuals) for pain control in addition to the use of a multi-modal protocol during surgery involving opioids, local anaesthetics and NSAIDs. Cats demonstrate unique pain-induced behaviours and are less playful and active; a link to a video of pain-induced behaviours in cats following dental extractions is available with the original publication (Watanabe *et al.* 2020b). Similar studies have not yet been performed in dogs. It is also suspected that veterinary species with painful oral conditions experience a negative impact on their QoL and sleeping patterns as occurs in humans (Ferreira *et al.* 2017). Oral conditions are perceived by veterinarians as an important cause of chronic pain in dogs (Bell *et al.* 2014); the same is probably true for cats. Indeed, dogs and cats can be affected by neuropathic orofacial pain (see FOPS in Chapter 1.9) or malignant and non-malignant tumours of the oral cavity causing chronic pain (See Chapter 3.14).

The IASP stated that the multi-dimensional nature of orofacial pain requires an interdisciplinary approach to its management leading to the creation of a Special Interest Group (IASP n.d.-c). Instruments for pain assessment that are species-specific have not been published for veterinary dentistry. However, the Feline Grimace Scale© has shown good to excellent inter-reliability among observers in cats after dental extractions (Watanabe *et al.* 2020a). A prototype composite instrument could also be useful for pain assessment in dogs and cats with oral and maxillofacial conditions after additional validation (Della Rocca *et al.* 2019). The approach to dental pain is multi-modal. Most diagnostic (*e.g.* radiographs) procedures in animals require general anaesthesia and invasive and painful procedures such as tooth extractions must be performed under general anaesthesia. The administration of long-term NSAID therapy is often required after multiple dental extractions even when opioids and local anaesthetic techniques are used perioperatively (Bienhoff *et al.* 2012). In the pharmacological treatment of chronic pain, NSAIDs as well as centrally acting analgesics such as gabapentin, amitriptyline and tramadol (cats only) are considered. Examples for dental protocols are provided in Chapters 2.5 and 3.7.

1.11 Cancer

Pain can affect cancer patients during all stages of the disease. Clinical presentation can vary widely depending on the location and nature of the tumour. Generally, tumours involving the oral cavity, bone, genitourinary system, eyes, nose, nerve roots and gastrointestinal tract cause considerable pain (Lascelles 2013), but other cancers such as lymphoma have the potential to cause pain (Higginson *et al.* 2013). Pain is more severe with cancers affecting non-compliant tissues such as bone or when there is a component of neuropathic pain (Bennett *et al.* 2012). Regardless, as cancer advances, pain is more likely to be present and severe.

In human patients with cancer, pain is one of the most feared and debilitating symptoms affecting from 43 to 63% of patients at all disease stages and up to 90% of patients with advanced-staged disease (van den Beuken-van Everdingen *et al.* 2007). Although the true prevalence of cancer pain in small animals remains unknown, one might presume it to be high considering that dogs and cats are living longer, and that cancer is a major cause of morbidity and mortality in this population. Cancer pain is underrecognised and

undertreated in people, and the same is likely true for animals. A survey involving veterinarians from the UK revealed that 87% agree that cancer pain is underdiagnosed and 66% disagree that cancer pain is easy to treat (Bell *et al.* 2014).

Pain in cancer patients can have features of acute or chronic pain, or both, and is multi-dimensional in nature (Table 10). It can be somatic or visceral and it generally involves inflammatory and neuropathic components.

Bone cancer

Bone cancer can be primary in nature, such as osteosarcoma in dogs (Fig 21) or the bone can be infiltrated by other cancers (*e.g.* oral squamous cell carcinoma in cats). Osteosarcoma is an aggressive and invasive malignant bone tumour causing osteolytic and prolifera-

Table 10. Cancer pain is multi-factorial and related to the disease itself, but also to procedures related to cancer diagnosis and therapy itself, and concomitant conditions

Factor contributing to cancer pain	Comments
Direct consequence of tumour	Most tumours are space-occupying lesions that cause tissue necrosis, infiltration of soft tissues or bone, and affect peripheral nerves. Inflammatory pain results from tissue injury and inflammation. Neuropathic pain results from the involvement or compression of peripheral nerves or other nervous tissues
Neuroimmune interactions	Cancer pain is also a consequence of biochemical interactions between the tumour and its host environment. Complex communications between cancer cells, the immune system and the peripheral and central nervous systems play a fundamental role in potentiating the growth and spread of tumours and in the generation and maintenance of cancer pain
Diagnostic procedures	Biopsies, needle aspirates, endoscopy and positioning for imaging can cause temporary pain and discomfort
Anticancer therapies	Venipunctures, surgery, chemotherapy and radiation therapy have the potential to cause mild to severe pain including acute pain, persistent postsurgical pain (*e.g.* amputation, thoracotomy), chemotherapy-induced neuropathy and radiation-induced mucositis and pain
Metastatic disease	Cancers can invade healthy tissues such as in bone metastasis
Concomitant painful conditions	Patients with cancer frequently have other sources of chronic pain including osteoarthritis and periodontal disease

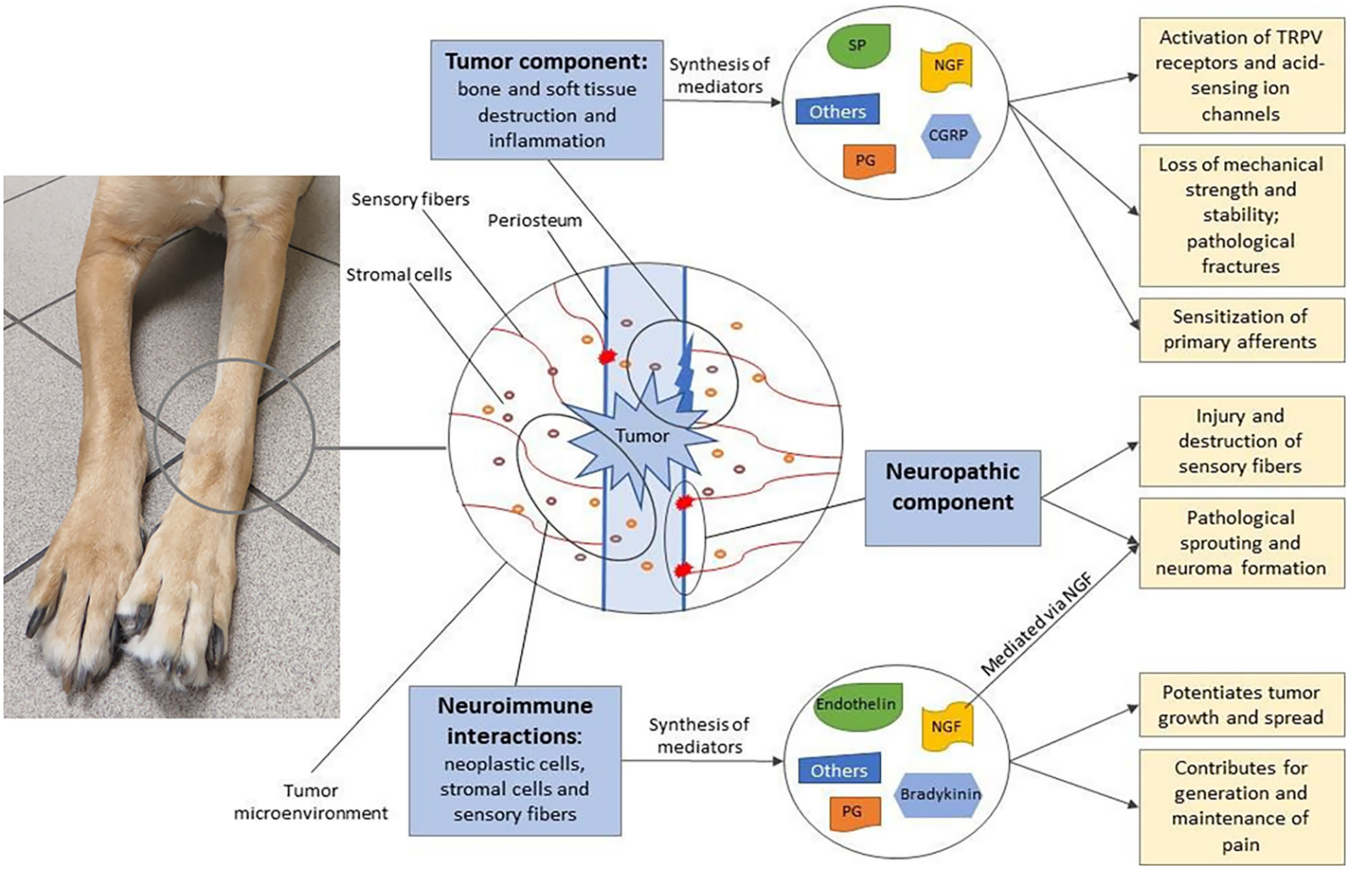


FIG 21. A dog with osteosarcoma of the distal left radius and illustration of the components contributing to peripheral and central sensitisation in patients with bone cancer. SP Substance P, NGF Nerve growth factor, CGRP Calcitonin-gene-related peptide, PG Prostaglandins, TRPV Transient receptor potential vanilloid. Figure modified from Monteiro (2019)

tive changes with a predilection for large and giant breed dogs (Simpson *et al*. 2017). These cancers cause severe pain and patients are usually diagnosed at an advanced stage of the disease. A study in dogs with osteosarcoma revealed that they have generalised increased pain sensitivity when compared with healthy dogs, meaning that they hurt more everywhere in the body. They have allodynia at the tumour site and hyperalgesia around the tumour and in other locations, and a dysfunction of inhibitory noxious mechanisms. They have low QoL scores, decreased mobility and increased sleep disturbance (Monteiro *et al*. 2018).

Visceral cancer

Visceral cancers (abdominal and thoracic) produce pain, but it may be difficult to locate the origin. It can result from the distension and contraction of hollow organs, stretching of the capsules of solid organs or mucosal surfaces, ischemia caused by tumour invasion or compression of visceral blood supply, or from compression or invasion of neural structures supplying the viscera or other structures such as ligaments, vessels or mesentery (Wordliczek & Zajaczkowska 2013).

1.12 Interplay of nutrition and pain

Diet, obesity and OA pain are inextricably linked in dogs and cats (Frye *et al*. 2016, Maniaki *et al*. 2021). Reductions in pain associated with weight loss have been documented in dogs (German *et al*. 2012). Information on body and muscle condition scoring is available at https://wsava.org/global-guidelines/global-nutrition-guidelines/.

Explanations for the strong relationship between obesity and OA pain include increased mechanical loading from excessive weight and metabolic changes due to adipose tissue-derived pro-inflammatory mediators (Tvarijonaviciute *et al*. 2012, Van de Velde *et al*. 2013, Barić Rafaj *et al*. 2017). Obesity is an inflammatory condition per se, and fat is an active "organ" that releases relevant amounts of cytokines.

Obesity is also known to affect the gut microbiome which in turn has been shown to affect both pain and disease status (Schott *et al*. 2018). Enteric microorganisms communicate with the nervous system (neuro-endocrine-immune axis) and influence pain regulation (Guo *et al*. 2019). Chronic pain states are marked by neuroinflammation which contributes to chronic pain and in turn drives further neuroinflammation (Nijs *et al*. 2020). Diet may also contribute to neuroinflammation through gut-brain interactions and alteration of the microbiome. Thus, in addition to obesity itself altering pain sensation, changes in diet have been implicated as a way to modulate pain sensation. However, the specifics of dietary interventions to modify pain in humans are unclear. Some studies show that low fibre, energy dense diets are associated with oxidative stress, cell necrosis and tissue damage throughout the body *via* pro-inflammatory central immune signalling and glial activation (Brain *et al*. 2021). Others show a benefit of ketogenic diets that are high in energy density and protein for producing pain relief and reduced inflammation (Field *et al*. 2021, Ruskin *et al*. 2021). Some enteric microorganism species may produce tryptophan, increasing serotonin analgesia, while others may produce NMDA receptor agonists, contributing to central sensitisation (Nijs *et al*. 2020). Although specific data for harnessing microbiota for pain control is lacking, prebiotic use in veterinary medicine is expanding and several studies show benefit for various gastro-intestinal and metabolic conditions (Grzeskowiak *et al*. 2015).

There is a link between obesity, inflammation, glucose levels and pain (Elma *et al*. 2020). A number of dietary supplements that decrease enteric (and systemic) inflammation may play a role, but the results are mixed (see Chapter 2.12). Nutritional management and pharmacological blockers of nutrition-based neuroinflammation may have a future in the management of chronic pain. At this time, the evidence points to obesity control as the most proven method for pain control (Impellizeri *et al*. 2000, Smith *et al*. 2006).

Acute pain may also affect food intake and feeding behaviours. Dry and soft food intake was significantly lower in cats that were painful after multiple dental extractions when compared with cats after dental cleaning or minimal dental extractions (Watanabe *et al*. 2019). Additionally, "difficulty grasping dry food" during feeding and "head shaking" postfeeding were commonly observed in cats after multiple dental extractions for up to 6 days after surgery (Watanabe *et al*. 2020b).

1.13 Perceived level of pain associated with various conditions

The designation of conditions into categories (Table 11) is intended to serve only as a guide. Pain may vary according to the patient and the condition, and its severity. Each patient should be assessed individually. It is also important to remember that the patient's "pain history" or "pain memory" impacts the pain that can be expected in the current condition being treated – a history of previous or ongoing pain in a patient can be expected to magnify the pain associated with any new condition or surgery (*i.e*. acute on chronic pain).

1.14 Common pain misconceptions

Opioids cause respiratory depression in awake dogs and cats

False. This misconception has arisen from the fact that humans are extremely sensitive to the respiratory depressant effects of opioids. Opioids rarely cause serious adverse effects in the perianaesthetic period when appropriate doses are used (Wagner *et al*. 2003). However, in sick animals, opioid drugs should be titrated to achieve analgesia, which will minimise the risk of respiratory com-

Table 11. Examples of medical and surgical conditions and their expected perceived level of pain

Severe to excruciating	Aortic saddle thrombosis
	Articular or pathological fractures
	Bone cancer
	Burn injury
	Central nervous system infarction/tumours
	Ear canal ablation
	Fracture repair where extensive soft tissue injury exists
	Hypertrophic osteodystrophy
	Inflammation (extensive, *e.g.* peritonitis, fasciitis)
	Limb amputation
	Meningitis
	Necrotizing pancreatitis or cholecystitis
	Neuropathic pain (nerve entrapment/inflammation, intervertebral disc herniation, etc.)
	Spinal surgery
	Thrombosis/ischemia
Moderate to severe (varies with degree of illness or injury)	Capsular pain due to organomegaly
	Corneal abrasion/ulceration
	Corrective orthopaedic surgery (osteotomies; cruciate surgery; open arthrotomies)
	Dystocia
	Early or resolving stages of soft tissue injuries/inflammation/disease
	Extensive resection and reconstruction for mass removal
	Frostbite
	Glaucoma
	Hollow organ distension
	Immune mediated arthritis
	Intervertebral disc disease
	Mastectomy
	Mastitis
	Mesenteric, gastric, testicular or other torsions
	Mucositis (including radiation therapy associated mucositis)
	Oral cancer
	Panosteitis
	Peritonitis/Pleuritis
	Stomatitis
	Trauma (*i.e.* orthopaedic, extensive soft tissue, head)
	Ureteral urethral/biliary obstruction
	Uveitis
Moderate	Cystitis
	Dental disease
	Arthroscopy and laparoscopy
	Osteoarthritis (it can be severe if neuropathic pain is involved; end-life stages)
	Ovariohysterectomy
	Soft tissue injuries (*i.e.* less severe than above)
	Urethral obstruction
Mild to moderate	Abscesses and their management
	Castration
	Chest drains
	Dental disease
	Cystitis
	Otitis
	Superficial lacerations

Conditions are ordered alphabetically and not in order of severity. Individual variability may be present and pain should be evaluated and assessed on a case-by-case basis

promise. Close observation and monitoring (*e.g.* respiratory rate and depth, pulse oximetry) are recommended in animals that are obtunded, have intracranial pathology (*e.g.* following head trauma), and in brachycephalic breeds, especially with the brachycephalic obstructive airway syndrome.

Obtunded animals are at risk of aspiration pneumonia

True. The cause of aspiration pneumonia (AP) in dogs and cats is multi-factorial and can occur in the perioperative period. In a retrospective study 18% of cats diagnosed with AP had been anaesthetised (Levy *et al.* 2019). In a large multi-centre retrospective study of dogs that were sedated or anaesthetised the incidence of AP was 0.17% (Ovbey *et al.* 2014). In that study, a regurgitation event or the use of hydromorphone were significantly associated with developing AP. Patients with laryngeal paralysis, oesophageal dysfunction and brachycephalic syndrome, or those undergoing specific surgical procedures (*e.g.* laparotomy, upper airway surgery, neurosurgery, thoracotomy and endoscopy) are at greater risk of developing AP (Ovbey *et al.* 2014, Darcy *et al.* 2018). Although no study causally links the level of consciousness (*e.g.* obtunded *versus* fully awake), to the development of AP, it seems intuitive that obtunded animals are less likely to possess rapid and effective laryngeal reflexes to protect their airway.

High doses of intraoperative opioids can cause problems

Can be true. Intraoperative opioids are beneficial as they decrease anaesthetic requirements and provide analgesia. Respiratory depression may occur due to the combined effects with anaesthetic drugs but is easily treated by manual or mechanical ventilation. Problems may occur during anaesthetic recovery; in one study almost 25% of dogs receiving a continuous rate infusion of fentanyl intraoperatively for orthopaedic procedures presented postanaesthetic dysphoria (Becker *et al*. 2013).

Opioids, especially at high doses, when given as the sole analgesic during a procedure, may potentiate pain wind-up through activation of the glia (*i.e*. opioid-induced hyperalgesia). This has not been confirmed in veterinary medicine but it may result in increasing dose escalation, inadequate analgesia, and in some cases, hyperalgesia (Colvin *et al*. 2019).

Non-steroidal anti-inflammatory drugs (NSAIDs) are toxic in dogs and cats

False. Inflammation is a common component of acute and chronic pain, therefore NSAIDs are a key component of treatment. NSAIDs are widely used to alleviate short and long-term pain in numerous animals globally. The analgesic benefits outweigh the potential risks. The pros and cons of NSAID use in animals with impaired liver function and advanced renal disease must be carefully considered. The most commonly reported adverse events in dogs are vomiting, diarrhoea and anorexia (Monteiro-Steagall *et al*. 2013). Individual patients should be screened for potential risk factors before administration and should be monitored during treatment. Many NSAIDs licensed for use in humans have a narrow safety margin in animals and should be used with caution, or not used in animals at all. Where species-specific approved drugs are available, they should be used preferentially.

If I alleviate pain, the animal will move, be more active and disrupt its suture line/fracture repair

False. Allowing animals to experience pain to control movement following surgery is unethical. Where activity needs to be controlled, other means should be adopted (*e.g*. cage confinement, controlled leash walking). In dogs, postoperative confinement was facilitated by the administration of trazodone (Gruen *et al*. 2014). Controlled weight bearing exercise is essential for postoperative orthopaedic repair to ensure appropriate bone healing and to maintain muscle mass to support the limb. Non-weight bearing results in impaired bone healing, muscle atrophy and contracture. Without analgesic administration, movement and physical therapy may be too painful. If the pain associated with abdominal or thoracic incisions is not alleviated, normal ventilation may be impaired.

Paediatrics do not feel pain

False. There is strong evidence to support the premise that human neonates experience pain and may in fact be more sensitive to pain if left untreated. This can result in long-term suffering (Anand 2001). Functional MRI studies in newborn babies infer that some features of pain are similar to those of adults (Ranger & Brunau 2015). Based on the similarities of neuroanatomy between mammals it must be assumed that neonatal dogs and cats can experience pain although it may differ from the adult experience.

Analgesic drugs mask signs of patient deterioration or prevent appropriate diagnosis or follow-ups

False. If a patient is in pain, analgesics are warranted for ethical reasons and to decrease pain-related adverse physiologic effects such as tachycardia, tachypnoea, low tidal volumes and ileus. Analgesics should be administered as soon as possible after a physical examination. In some patients, examination may not be possible until their pain has been relieved. Systemically administered analgesics (*e.g*. opioids) will provide relief but are unlikely to fully eliminate pain resulting from acute trauma or in emergency surgical cases (*e.g*. severe visceral pain due to gastric dilatation and volvulus). Short-acting opioids can be used and titrated to effect to allow patient assessment, appropriate pain relief with minimal sedation (*e.g*. neurological examination).

Anaesthetic drugs are analgesics and therefore prevent pain

False

Drugs such as inhalant (*e.g*. isoflurane, sevoflurane) and injectable anaesthetics (*e.g*. propofol, alfaxalone) block pain perception and have been referred to as analgesics in some textbooks. However, they are not anti-nociceptive medicines and classic analgesics. Therefore, nociception (transduction, transmission and modulation) still occurs during general anaesthesia if noxious stimuli occur and antinociceptive drugs are not administered. Upon awakening, the patient will experience pain (a conscious emotion with neuroendocrine changes).

Pain management is solely focused on the use of drugs

False. The approach to acute and chronic pain should be integrative, this means combining pharmacological and non-pharmacological therapies. Examples of non-drug therapies include but are not limited to acupuncture, medical massage, diet, nutri-

tional additives or supplements, physical rehabilitation, and nursing and supportive care. Ice or cold therapy (Chapter 2.10) is an effective and inexpensive modality (Wright *et al*. 2020). Just as using combinations of analgesic drugs is termed multi-modal, the use of pharmacological and non-pharmacological techniques is also multi-modal and likely to provide additional benefits to the patient.

Exercise is contraindicated in patients with joint pain

False. Controlled exercise reduces pain experience for various types of acute pain, and some types of chronic pain (Naugle *et al*. 2012). Studies demonstrate that exercise activates various endogenous analgesic neuro-modulatory systems, such as opioids, nitric oxide, serotonin, catecholamine and endocannabinoid (Santos & Galdino 2018). Exercise also benefits cartilage structure and function; muscle, fascia, tendon and ligament mobility; bone and intervertebral disk structure and function. Inactivity heightens pain sensation from various soft-tissue sources (Langevin *et al*. 2018). Controlled exercise, isometric and balance exercises, range of motion and strengthening exercises, swimming and exercising in an underwater treadmill can be beneficial.

Sedated animals are unlikely to be experiencing pain

False. Sedation only masks the behavioural signs of pain and our ability to recognise and assess pain. Sedation with non-analgesic drugs will result in patients with the outward appearance of being comfortable, however if they were assessed (*e.g*. palpation of their surgical site), they are likely to be painful. Sedation may be desirable but should be achieved with a combination of analgesics and sedatives or tranquillisers or an analgesic with sedative properties (*e.g*. dexmedetomidine, butorphanol), and the patient must undergo regular pain assessment.

All mobility impairment is a consequence of pain

False. OA/DJD-related pain are common causes of mobility impairment in dogs and cats. However, there are other causes including degenerative myelopathy, geriatric laryngeal paralysis polyneuropathy, diabetic neuropathy in cats, ataxia secondary to vestibular disease, and overgrown toenails. Failing eyesight or blindness may impair an animal's exploratory behaviour. Differentiation of pain *versus* other forms of weakness or mobility is vital for assessment of QoL.

Supplements and herbs are natural therefore always safe to use

False. Many caregivers and veterinarians support the use of herbs and supplements as adjunct treatments for pain. It is important to be well educated on these products including their side effects and interactions with pharmacological agents. Simply being natural does not suggest safety, as the textbooks on toxic plants reveal. For example, serotonin syndrome, a spectrum of clinical signs caused by elevated serotonin levels, is likely the most common adverse event reported with supplements such as St. John's Wort (*Hypericum perforatum)*. Serotonin syndrome can result from an overdose or because the patient is already receiving other drugs (*e.g*. clomipramine, fluoxetine, trazodone) that alter serotonin levels (Mohammad-Zadeh *et al*. 2008, Almgren & Lee 2013). Phytomedicines such as *Boswellia* and cannabinoids can modify liver enzymes and the rate of metabolism of other drugs.

The American Society of Anesthesiologists (2015) suggest withdrawal of many herbs and supplements before anaesthesia and surgery; this includes garlic, ginkgo, ginseng and Vitamin E which may increase bleeding, and kava and valerian that may prolong the effects of some anaesthetic drugs.

SECTION 2

2.1 General approaches to the treatment of pain

Pain is a complex disease. It is an unpleasant experience involving sensory and emotional components and is unique to each individual. Pain is best managed early and with a robust protocol. It is harder to treat pain once it is well established. Clearly this is not always possible but when it is, prevention should be the focus of the analgesic plan. In the treatment of pain, the aim is to abolish it or, at the very least, to reduce it to a minimum.

The terms "preemptive analgesia" and "preventive analgesia" can be confusing. *Preemptive* analgesia refers to the administration of analgesic drugs *before* tissue damage/insult (*i.e.* preoperatively). *Preventive analgesia* is a more appropriate clinical approach as it refers to the administration of analgesics pre-, intra- and postoperatively. It considers factors in all perioperative moments that can contribute to peripheral and central sensitisation and involves any perioperative analgesic techniques/drugs for pain relief (Dahl & Kehlet 2011). Drugs frequently used for preventive analgesia include NSAIDs, local anaesthetics, opioids, alpha$_2$-adrenocetor agonists, NMDA antagonists (*e.g.* ketamine) and gabapentin. Cold therapy is the most accessible non-pharmacological option used postoperatively (Wright *et al.* 2020). These therapies reduce the severity of perioperative pain and might contribute to a reduction in the prevalence of persistent postsurgical pain.

Multi-modal analgesia consists of the use of *pharmacological* and *non-pharmacological therapies* (an integrative approach). The concomitant administration of drugs and treatments that act at different sites of the nociceptive pathway provide optimal analgesia. Because they target different pain mechanisms, lower doses of each drug can be administered, minimising the occurrence of adverse effects. The choice of drug(s) used to treat pain will depend on the underlying cause of pain, its severity and duration. Knowledge of the drug pharmacology in each species and in patients of different age and physical status is required. For example, pharmacokinetic profiles of drugs are likely to be different among adults, paediatrics (puppies and kittens <12 weeks of age), seniors (dogs and cats that have reached >75% life expectancy) and patients with comorbidities, which may alter dosage regimens. Pharmacokinetic data should not be extrapolated from one species to another, particularly between dogs and cats.

Non-pharmacological therapies should be added to the pain management protocol whenever practicable. Positive emotions play a significant role in decreasing pain. All measures to reduce stress, fear and anxiety, and to provide positive mental and physical stimulation are encouraged. In the perioperative period, these include providing warm, clean and comfortable bedding in a quiet environment, gentle stroking and positively interacting with the animal, providing hiding spaces and elevated surfaces for cats, taking dogs for frequent walks if possible, etc. In chronic pain, these include increasing physical activity by stimulating play behaviour, promoting positive interactions to reinforce the human-pet bond, and providing environmental enrichment.

Acute pain

Acute pain is initiated by a traumatic, surgical, or infectious event. *Perioperative pain* is a classic example of acute pain. It can be divided into four key time-points: preoperative; intraoperative; immediate postoperative ("in hospital"); and later postoperative periods ("at home," "healing phase"). The analgesic plan influences the degree of postoperative pain. Perioperative pain management should incorporate drugs from several different classes applying the concepts of preventive and multi-modal analgesia. Pain relief can also be provided by non-drug therapies including cold therapy, acupuncture, passive range-of-motion exercises, massage, therapeutic exercise, hydrotherapy, ultrasound and electrical stimulation (Tick *et al.* 2018). Nursing care including careful considerations of the physical environment, wound care, bladder emptying and human–animal interactions are important for improved hospital experiences (Chapter 2.13).

The degree of perioperative pain can be influenced by the surgical technique (Xu & Brennan 2010) and location. Gentle tissue handling and techniques that minimise trauma (*e.g.* small incisions; minimally invasive surgery such as arthroscopy and laparoscopy) should be employed whenever possible (Culp *et al.* 2009). When inflammation or chronic pain are present before surgery (*e.g.* pyometra, cancer or OA), the degree of pain during and after surgery may be greater warranting more frequent or higher dosing of analgesics over a longer period. This is often described as "acute on chronic" pain. Pain scales can be used to optimise analgesic regimens.

Chronic pain

Chronic or maladaptive pain can be associated with a primary condition, or it can exist by itself. In humans, chronic pain is often accompanied by fear, anxiety, depression and anger, which can exacerbate pain and its negative impact on the patient's QoL. Although it can affect patients of any age, geriatric animals are more frequently affected. Behaviour changes related with chronic pain are insidious in onset and subtle and are often underdiagnosed or mistaken for "just getting old" (Monteiro & Steagall 2019b). Veterinarians treating animals with chronic disease (*e.g.* long-term otitis, chronic wounds, inflammatory bowel disease OA) should always consider the potential for accompanying chronic pain. The approach to treatment depends on the underlying cause of pain, its duration and how well it has been managed previously. Chronic pain may present with acute exacerbations of previously well-controlled pain ("acute on chronic" pain). A multi-modal approach is likely to be most effective, and caregiver education is essential, especially in terms of treatment expectations and prognosis. The mainstays of treatment of chronic pain are NSAIDs; however, evidence is increas-

ing for other therapies such as monoclonal antibodies. Adjunct therapies should also be considered and increased attention should be given to therapies that may decrease *widespread sensitisation*.

In chronic pain, pet caregivers are highly involved and are engaged as part of the health care team. For example, they are the ones observing the animal in the home environment, completing caregiver assessed CMIs and recording videos to share with the veterinary team. They are also the ones monitoring treatment efficacy, administering analgesics and applying changes to the animal's environment (*i.e.* environmental modifications; Fig 22) and lifestyle (*e.g.* weight control and physical activity).

2.2 Opioids

What they are

An opiate is a drug naturally derived from the flowering opium poppy plant. The term opioid is a broader term that includes opiates and refers to any substance, natural or synthetic, that binds to opioid receptors. For many years, opioids have been the cornerstone of acute pain management in veterinary medicine. They vary in their receptor specificity, potency and efficacy, resulting in different clinical effects. Opioids are usually divided in four groups: full agonists [morphine, methadone, fentanyl and its derivatives, pethidine (meperidine), etc.], agonist–antagonists (butorphanol and nalbuphine), partial agonists (buprenorphine) and antagonists (naloxone, nalmefene and naltrexone). The latter group is devoid of agonist activity. Opioids have high efficacy and are remarkably safe in animals, in part due to their reversibility (Simon & Steagall 2017). Most opioids are controlled or scheduled substances and in some countries are not accessible to veterinarians. They are considered core essential medicines, according to the WSAVA List of Essential Medicines for Cats and Dogs (Steagall *et al.* 2020a). Individual variability in response after opioid administration may be observed due to differences in pharmacokinetic–pharmacodynamic effects, gender, age, genotype, the type and number of opioid receptors and their distribution within the CNS, and brain transport mechanisms. For example, the metabolite of tramadol (*O*-desmethyl-tramadol; M1 metabolite) has opioid activity but the ability to metabolise tramadol to this metabolite is species-specific. The administration of tramadol in dogs, unlike cats and humans, does not result in significant plasma concentrations of this metabolite (Perez Jimenez *et al.* 2016) (see Chapter 2.7).

How they work

Opioids bind to opioid receptors [μ (mu), κ (kappa), δ (delta), nociceptin and their subtypes] in the central and peripheral nervous systems inhibiting release of excitatory neurotransmitters from afferent fibres in the spinal cord, thereby inhibiting synaptic transmission of nociceptive stimuli. Postsynaptically, enhanced potassium (K^+) efflux causes neuronal hyperpolarisation of spinal cord projection neurons and inhibits ascending nociceptive pathways. Opioids do not interfere with motor function or proprioception (Simon & Steagall 2017).

Indications

Opioids produce analgesia, euphoria, mydriasis (cats) or miosis (dogs), sedation, or excitement (dysphoria), and several other physiological effects depending on the species. They are used for the treatment of moderate to severe pain. Their analgesic effects depend on the opioid drug, dose, route of administration, delivery system and species to which the drug is given (Hofmeister & Egger 2004).

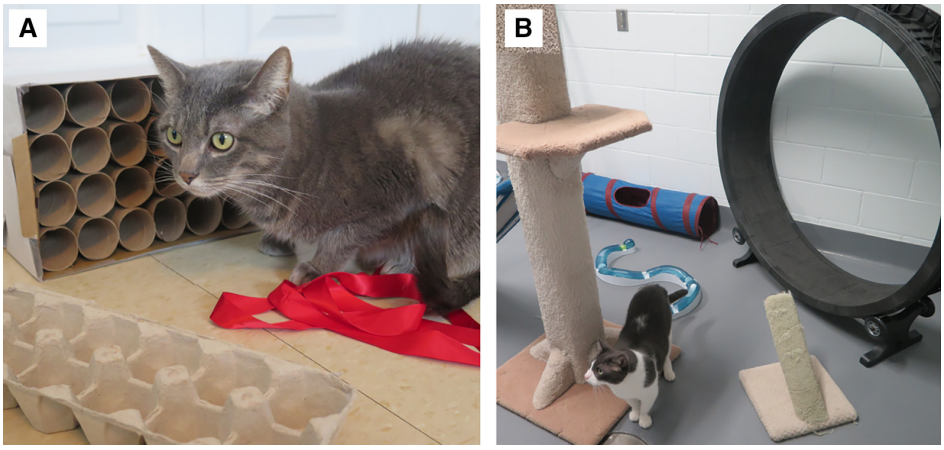


FIG 22. Strategies for environmental modifications. (A) Examples of home-made tools to stimulate the cat physically and mentally. Tapes from gift-wrapping, shopping bags and random boxes can all be used, and numerous ideas are available online. Note that strings and threads should not be used due to the risk of inadvertent ingestion resulting in linear foreign body. In this image, a shoe box and toilet paper rolls were used to create a "feeding puzzle." Dry kibble is distributed across the toilet paper rolls and the cat needs to search and reach for the food. Alternately, food can be place in egg boxes. Strategies that increase the time of food consumption contribute to satiety and weight control. (B) Examples of commercially available cat condos, tunnel, scratching post, food puzzle and running wheel. Figure (A) courtesy of Beatriz Monteiro. Figure (B) reproduced from Monteiro (2020)

Opioids are widely used in the perioperative setting as part of multi-modal and preventive analgesia as well as for their anaesthetic sparing effects (*i.e.* reduced requirements for inhalant anaesthetics) (Table 12). They are also widely administered in the emergency and critical care setting (*i.e.* pancreatitis, burns, trauma, meningitis). Epidural administration of morphine is used to provide postoperative analgesia in the clinical setting. Opioids rarely cause excitement ("morphine-mania") in cats if appropriate doses and dosing intervals are used. Sedation normally occurs in dogs and most commonly in geriatric, paediatric and critically ill patients. Intravenous (iv) and intramuscular (im) administration is preferred (Steagall *et al.* 2006); however, buprenorphine and methadone may be given by the oral transmucosal route to produce antinociception in cats. Oral opioids have an extremely low bioavailability in dogs and cats and should not be used for analgesia.

Research has shown that kittens and adult cats may respond differently to opioid administration. Magnitude of antinociception was consistently larger in cats at 12 months when compared with 6 months of age. In that study, hydromorphone provided a shorter duration and smaller magnitude of antinociception in the same cats at 6 months when compared with 9 and 12 months. These results suggest that 6-month-old kittens may require more frequent dosing of opioids than adults (Simon *et al.* 2019).

Adverse effects

Adverse effects can include nausea and vomiting, dysphoria, panting (dogs), bradycardia, histamine release [morphine and pethidine (meperidine) especially when given by rapid iv injection], urinary incontinence/retention (after the administration of epidural morphine) and respiratory depression. However, adverse effects are usually associated with high doses. Less commonly, inappetence, restlessness, constipation, and hypothermia or hyperthermia (most commonly after hydromorphone in cats) can be observed. Any of these adverse effects are readily reversed with careful titration of naloxone or butorphanol (Table 12). However, analgesia may also be reversed.

Table 12. Suggested recommendations for the use of opioid analgesic drugs and the opioid antagonist naloxone in cats and dogs†

Opioid analgesic	Dogs – doses and frequency	Cats – doses and frequency	Route of administration	Comments
Morphine	0.3 to 0.5 mg/kg every 2 to 4 hours	0.2 to 0.3 mg/kg every 4 to 6 hours	im	Slow iv administration is possible after drug dilution. However, histamine release can occur
Pethidine (meperidine)	3 to 5 mg/kg every 1 to 2 hours	3 to 5 mg/kg every 1 to 2 hours	im	Do not administer iv due to histamine release
Methadone	0.3 to 0.5 mg/kg every 3 to 4 hours	0.2 to 0.3 mg/kg every 4 hours	im, iv, OTM‡	Has NMDA receptor antagonist properties. OTM administration produces antinociception in cats
Hydromorphone	0.05 to 0.1 mg/kg every 4 to 6 hours	0.025 to 0.05 mg/kg every 4 to 6 hours	im, iv	May cause hyperthermia in cats
Fentanyl	Bolus 2 to 5 µg/kg +CRI 3 to 6 µg/kg/hour	Bolus 1 to 3 µg/kg +CRI 2 to 3 µg/kg/hour	iv	Doses may be increased for inhalant anaesthetic-sparing effect or for maximum analgesia
Remifentanil	6 to 12 µg/kg/hour	4 to 6 µg/kg/hour	iv	Doses may be increased for inhalant anaesthetic-sparing effect or for maximum analgesia. It does not require a bolus. Remifentanil has half of the potency of fentanyl
Butorphanol	0.2 to 0.4 mg/kg every 1 to 2 hours	0.2 to 0.4 mg/kg every 1 to 2 hours	im, iv	Limited analgesic efficacy, only suitable for the management of mild pain
Nalbuphine	0.3 to 0.5 mg/kg every 2 to 4 hours	0.2 to 0.4 mg/kg every 2 to 4 hours	im, iv	Limited analgesic efficacy, only suitable for the management of mild pain. Few studies in veterinary medicine
Buprenorphine	0.01 to 0.02 mg/kg every 4 to 8 hours	0.02 to 0.04 mg/kg every 4 to 8 hours	im, iv, OTM‡	A high-concentration formulation of buprenorphine is available (1.8 mg/mL) (currently only USA) – this formulation is administered at 0.24 mg/kg every 24 hours for up to 3 days for control of postoperative pain in cats A buprenorphine transdermal solution was recently approved for use in the USA – a single transdermal solution is applied to the skin at the base of the neck and provides up to 4 days of control of postoperative pain in cats. Dose volume is 0.4 mL (8 mg) for 1.2 to 3 kg bodyweight or 1 mL (20 mg) for >3 to 7.5 kg bodyweight in cats
Naloxone (antagonist)	0.04 mg/kg every 0.5 to 1 hour	0.04 mg/kg every 0.5 to 1 hour	im, iv	Dilute and titrate slowly to effect when reversing opioid-induced adverse effects in painful patients. Mix 0.25 mL of naloxone (0.4 mg/mL) with 5 to 10 mL saline. Slowly administer 1 mL/minute of the dilution until the adverse effects have subsided to avoid antagonism of opioid analgesia

im Intramuscular, iv Intravenous, OTM Oral transmucosal
†Doses can be increased or decreased on a case-by-case basis based on individual response and other drugs being concomitantly administered. Routine pain assessment and changes in pain scores guide decisions around analgesic therapy
‡OTM route of administration used in cats only

Contraindications

The veterinarian must balance the pros and cons of opioid administration as some unwanted or undesirable effects may be clinically irrelevant when pain management is a priority.

Drug interactions

Opioids are commonly combined with benzodiazepines, alpha$_2$-adrenoceptor agonists or acepromazine (neuroleptanalgesia) for premedication. Opioids may have a synergistic effect when combined with NSAIDs (Steagall *et al*. 2009) and local anaesthetics as part of multi-modal analgesia. Mixing of different groups of opioids (*i.e*. butorphanol and buprenorphine, butorphanol and hydromorphone) results in unpredictable effects and is not recommended.

Special considerations

Opioid tolerance is reported in humans and laboratory animals but is rarely a problem with short-term use in veterinary medicine. There are reports of opioid-induced hyperalgesia in humans and rats; however, this has not yet been documented in small animal practice.

Opioid-free or opioid-sparing anaesthesia

Unfortunately, the international veterinary community does not always have access to opioid analgesics leading to unnecessary animal suffering and compassion fatigue among veterinary personnel. Alternatives to opioids include techniques using multi-modal analgesia including local anaesthetics, NSAIDs and other adjuvant analgesics. They are often referred to as opioid-sparing or opioid-free anaesthesia. The anaesthetic and analgesic effects of an opioid-free injectable protocol (im) including ketamine (5 mg/kg), midazolam (0.25 mg/kg) and dexmedetomidine (40 µg/kg) were studied in cats undergoing ovariohysterectomy. Cats were also given bupivacaine intraperitoneally (2 mg/kg) and meloxicam (0.2 mg/kg) after surgery. The protocol provided adequate anaesthesia for surgery; however, postoperative analgesia was not optimal for most cats and the prevalence of rescue analgesia was higher in adult cats when compared to kittens (Diep *et al*. 2020). A subsequent study of similar design in adult cats compared an opioid-free with an opioid-sparing protocol (*i.e*. preoperative administration of buprenorphine). It showed that a single dose of buprenorphine eliminated the need for rescue analgesia postoperatively (0/14 and 5/14 cats required rescue analgesia in the opioid-sparing and opioid-free groups, respectively) (Rufiange *et al*. 2022). Another subsequent study in kittens compared a similar opioid-free protocol with or without multi-modal analgesia. Kittens in the multi-modal group were administered meloxicam preoperatively and intraperitoneal bupivacaine intraoperatively. Prevalence of rescue analgesia was higher in the control group (n=15/15) than the multi-modal group (n=1/14) (Malo *et a*l. 2022). Reviews on the use of opioids in dogs and cats including clinical guidance, and misconceptions and controversies related to opioid analgesia are recommended as further reading (Steagall *et al*. 2014, Bortolami & Love 2015, Simon & Steagall 2017, Kongara 2018).

2.3 Non-steroidal anti-inflammatory drugs (NSAIDs)

What they are

NSAIDs exert antipyretic, anti-inflammatory and analgesic effects (Table 13). They are commonly administered orally although some injectable formulations exist. NSAIDs are primarily metabolised in the liver and excreted *via* the biliary route (faecal) and in urine.

How they work

NSAIDs act within the arachidonic acid cascade. They either block the activity of cyclooxygenase (COX) enzymes and the consequent production of prostaglandins, or, as in the case of piprants (see later), block the interaction of prostaglandins with their receptors (Fig 23). COX-1 produces a range of prostaglandins involved in physiological processes including vascular homeostasis, gastroprotection, renal blood flow and blood clotting. COX-2 is also related with some physiological functions, but it is primarily released after tissue injury to produce inflammatory prostaglandins (Monteiro & Steagall 2019a). By inhibiting COX activity, NSAIDs provide analgesia (inhibition of inflammation and pain) but may also result in adverse effects (inhibition of physiological functions). Individual NSAIDs inhibit COX-1 and COX-2 to different degrees.

Indications

COX-inhibiting NSAIDs are effective analgesics in the perioperative period, as well as in other acute and chronic pain states such as OA, cancer and other inflammatory conditions (Table 13). They are given as a sole analgesic or in combination with adjuvant drugs

Table 13. Non-steroidal anti-inflammatory drugs (NSAIDs): canine and feline dosing recommendations†

Drug	Indication	Species, Dose‡, Route	Frequency
Carprofen	Surgical pain	Dogs: 4 or 4.4 mg/kg SC, iv, PO	Every 24 hours for up to 4 days
		Dogs: 2 or 2.2 mg/kg SC, iv, PO	Every 12 hours for up to 4 days
		Cats: 2 to 4 mg/kg SC, iv	One dose only; do not follow-up with any additional dosing
	Chronic pain	Dogs: 4 or 4.4 mg/kg PO	Every 24 hours; use lowest effective dose
		Dogs: 2 or 2.2 mg/kg PO	Every 12 hours; use lowest effective dose
Cimicoxib	Surgical pain	Dogs: 2 mg/kg PO	Every 24 hours for 4 to 8 days
	Chronic pain	Dogs: 2 mg/kg PO	Every 24 hours; use lowest effective dose
Deracoxib	Surgical pain	Dogs: 3 to 4 mg/kg PO	Every 24 hours for up to 7 days
	Chronic pain	Dogs: 1 to 2 mg/kg PO	Every 24 hours; use lowest effective dose
Enflicoxib	Osteoarthritis pain	Dogs: loading dose of 8 mg/kg followed by 4 mg/kg PO	Once weekly
Firocoxib	Surgical pain	Dogs: 5 mg/kg PO	Every 24 hours for up to 3 days
	Chronic pain	Dogs: 5 mg/kg PO	Every 24 hours; use lowest effective dose
Flunixin meglumine	Pyrexia	Dogs and Cats: 0.25 mg/kg SC	Once
	Surgical and ophthalmic procedures	Dogs and Cats: 0.25 to 1.0 mg/kg SC	Every 12 to 24 hours for 1 or 2 treatments
Grapiprant	Osteoarthritis pain	Dogs: 2 mg/kg PO	Every 24 hours
Ketoprofen	Surgical and chronic pain	Dogs: 2.0 mg/kg, iv, SC, im	Once postoperative
		Dogs: 1.0 mg/kg PO	Every 24 hours for up to 4 days
		Cats: same as for dogs	
Mavacoxib	Chronic pain	Dogs: 2 mg/kg PO	One dose on day 0 and another on day 14. Then once per month for up to 5 additional treatments
Meloxicam	Surgical pain/acute musculoskeletal pain	Dogs: 0.2 mg/kg iv, SC	Once
		Dogs: 0.1 mg/kg PO	Every 24 hours
		Cats: 0.2 to 0.3 mg/kg SC	One dose only
		Cats: 0.05 mg/kg PO	Every 24 hours for up to 5 days
	Chronic pain	Dogs: 0.2 mg/kg PO	Once on day 1
		Dogs: 0.1 mg/kg PO	Every 24 hours after day 1; use the lowest effective dose
		Cats: 0.1 mg/kg PO	Once on day 1
		Cats: 0.05 mg/kg PO	Every 24 hours after day 1; use the lowest effective dose
Metamizole (dipyrone)	Acute pain	Dogs and Cats: 25 mg/kg iv	Every 8 to 12 hours
Paracetamol (acetaminophen)	Surgical/acute or chronic pain	Dogs ONLY: 10 to 15 mg/kg PO	Every 8 to 12 hours. *Do not use in cats*
		Dogs ONLY: 10 mg/kg iv over 15 min	Every 8 to 12 hours. *Do not use in cats*
Piroxicam	Inflammation of the lower urinary tract	Dogs: 0.3 mg/kg PO	Every 24 hours for two treatments, then every 48 hours
Robenacoxib	Surgical pain/acute musculoskeletal pain	Dogs: 2 mg/kg SC	Every 24 hours for up to 3 days
		Dogs: 1 to 2 mg/kg PO	Every 24 hours
		Cats: 2 mg/kg SC	Every 24 hours for up to 3 days
		Cats: 1 to 2 mg/kg PO	Every 24 hours
	Chronic pain	Dogs: 1 mg/kg PO	Every 24 hours; use lowest effective dose
		Cats: 1 mg/kg PO	Every 24 hours; use the lowest effective dose
Tolfenamic acid	Acute and chronic pain	Dogs: 4 mg/kg SC, im, PO	Every 24 hours for 3 to 5 days. Repeat once per week
		Cats: same as for dogs	

iv Intravenous, SC Subcutaneous, im Intramuscular, OTM Oral transmucosal, PO Orally
†See text for details on the contraindications for use. For veterinary licensed products, the label will provide the best information as to product use relevant to the country where it is licensed. Veterinarians should use a product with market authorisation for the species, whenever this is available
‡Dose based on lean bodyweight

depending on the severity of pain (Monteiro & Steagall 2019a). When used for chronic pain conditions (*e.g.* OA), they are often titrated to the lowest effective dose, but this should be combined with careful patient reassessment (Wernham *et al.* 2011). Clinical effectiveness might differ among individuals; when there is an unsatisfactory patient response, switching NSAIDs may be warranted, with an appropriate wash-out period (see Chapter 1.14).

Contraindications

NSAID-related adverse effects are most commonly related to the gastrointestinal tract (anorexia, vomiting, diarrhoea, decreased appetite). Other less frequent adverse effects include decreased platelet aggregation and renal and hepatic toxicity. Gastrointestinal effects are usually self-limiting although ulceration and perforation can occur with inappropriate administration (Lascelles *et al.* 2005). Non-clinically relevant decreases in platelet aggregation after NSAIDs have been reported (Lemke *et al.* 2002). This should not be a concern

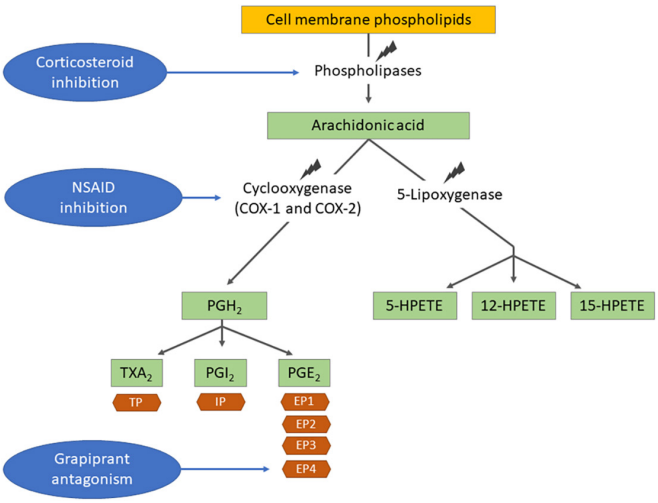


FIG 23. A simplified version of the arachidonic acid cascade with focus on cyclooxygenase (COX)-dependent prostaglandin production. Corticosteroids act by inhibiting the action of phospholipase enzymes early in the cascade. NSAIDs act by inhibiting COX-1 and COX-2 enzymes with consequent inhibition of prostaglandin biosynthesis. Grapiprant is an antagonist of the EP4 receptor. EP1 to EP4 Prostaglandin E2 receptor, HPETE Hydroperoxyeicosatetraenate, IP Prostacyclin receptor, PGE2 Prostaglandin E2, PGH2 Prostaglandin H2, PGI2 Prostacyclin, TP Thromboxane receptor, TXA2 Thromboxane. Figure reproduced from Monteiro & Steagall (2020)

in healthy animals; however, caution is advised when using COX-1 selective drugs or aspirin. Aspirin may inhibit COX throughout the lifespan of platelets; thus, it should be avoided preoperatively and only administered at the end of surgery when haemostasis is confirmed. Hepatotoxicity is rarely reported and in most cases is thought to be an idiosyncratic reaction (MacPhail *et al.* 1998). Periodic monitoring with telemedicine or physical exam ±blood chemistry profile on a case-by-case basis is recommended with long-term use. NSAIDs are contraindicated in patients with uncontrolled gastrointestinal, hepatic disease, coagulation disorders, hypovolemia, dehydration or hypotension. Feline patients with concomitant chronic pain and stable chronic kidney disease [International Renal Interest Society (IRIS) stages I to III] can be treated with meloxicam or robenacoxib provided that they are closely monitored (Monteiro *et al.* 2019). Overall, NSAIDs appear to be associated with a low incidence of adverse effects, and most clinical studies fail to show a difference in adverse effects compared to placebo (Monteiro-Steagall *et al.* 2013); however, most studies have not been properly designed to detect significant differences between placebo and treated dogs in terms of adverse effects. When adverse effects occur, they can be catastrophic for an individual patient, and alternative analgesia must be provided. In mild cases, clinicians are advised to immediately stop administration of NSAIDs and provide supportive treatment including fluid therapy and gastroprotectants. Serious cases might require surgical intervention and critical care (Lascelles *et al.* 2005). Adverse effects should be reported to the drug company or regional regulatory body (*e.g.* Food and Drug Administration Center for Veterinary Medicine in the USA or Veterinary Medicines Directorate in the UK).

Drug interactions

NSAIDs should not be given with or in close temporal association with corticosteroids or other NSAIDs including aspirin. They should be administered with caution in conjunction with angiotensin converting enzyme-inhibitors, diuretics, warfarin, phenobarbital or chemotherapeutics.

Switching from one NSAID to another

There may be variations among animals being administered different NSAIDs with respect to tolerance of adverse effects and clinical response. For both reasons (lack of analgesic response or adverse effects) switching between NSAIDs, or switching between COX-inhibiting and non-COX-inhibiting NSAIDs is appropriate. When considering a switch from one NSAID to another for reasons of lack of efficacy, a washout period (*i.e.* the patient receives no NSAID drugs) should be considered. Although the most conservative approach is to use a washout period of a few days, there is no scientific evidence that this is required, or any scientific evidence to inform what duration is appropriate. If switching between NSAIDs is being considered due to the gastrointestinal adverse effects, rapid switching to a drug that inhibits COX-2 could delay healing and worsen the lesions. In this scenario, a washout period of 7 days may be required. In dogs but not in cats, paracetamol (acetaminophen) might be used during washout. Switching between NSAIDs in the perioperative period is not recommended (*i.e.* if a patient is already on an NSAID, continue to administer the same one). Finally, in the authors' experience, a washout is not required when switching between grapiprant and NSAIDs although there are no studies evaluating the safety of this practice.

Other anti-inflammatory drugs

Grapiprant is considered an NSAID – a non-COX-inhibiting NSAID. Grapiprant belongs to the piprant class of drugs (PGE2 receptor antagonists), which act further down the arachidonic acid cascade, blocking the interaction of PGE2 with its receptors (Fig 23). Specifically, grapiprant is an EP4 receptor antagonist licensed in some countries for the management of pain and inflammation associated with canine OA. The drug was shown to be safe and effective in a randomised, placebo-controlled clinical trial involving dogs with OA (Rausch-Derra *et al*. 2016).

Paracetamol (acetaminophen) is an NSAID that is thought to act on a sub-form of COX-1 present in the CNS. It has analgesic and antipyretic effects but little anti-inflammatory activity (Pacheco *et al*. 2020). In the perioperative period, both oral and iv paracetamol have been found to be non-inferior to licensed NSAIDs in dogs undergoing soft tissue or orthopaedic surgery (Hernández-Avalos *et al*. 2020). Controversially, postoperative pain scores were not different when paracetamol or saline were administered iv in dogs following ovariohysterectomy (Leung *et al*. 2021). Paracetamol alone or in combination with codeine is anecdotally used for chronic pain in dogs as part of a multi-modal approach; yet little evidence is available to support its use for acute or chronic pain management in dogs (Budsberg *et al*. 2020). *In cats, paracetamol (acetaminophen) is strictly contraindicated* due to increased risk of developing methemoglobinemia.

Metamizole (dipyrone) is also a weak anti-inflammatory with analgesic, antipyretic and spasmolytic properties produced predominantly *via* inhibition of a sub-form of COX-1 in the CNS. Metamizole (dipyrone) is licensed for perioperative use in dogs in several countries and can be used in combination with NSAIDs (Zanuzzo *et al*. 2015). There is some evidence of efficacy in dogs and cats (Imagawa *et al*. 2011, Teixeira *et al*. 2020, Pereira *et al*. 2021). In cats undergoing ovariohysterectomy, metamizole (dipyrone) (25 mg/kg q24 or 12.5 mg/kg q12h) provided similar analgesic effects to meloxicam (0.1 mg kg q24h) (Pereira *et al*. 2021).

Glucocorticosteroids are analgesic in inflammatory conditions by virtue of their strong anti-inflammatory effects. They are, however, commonly associated with adverse effects and should not be thought of as analgesics. When the pain condition is not driven by inflammation, glucocorticoids are not an effective analgesic choice.

2.4 Alpha$_2$-adrenoceptor agonists

What they are

Alpha$_2$-adrenoceptor agonists are drugs that produce sedation and hypnosis, analgesia and muscle relaxation (Table 14). This class of drug varies in their receptor specificity and potency. Alpha$_2$-adrenoceptor agonists have the benefit of reversibility when an antagonist (atipamezole or yohimbine) is given; however, analgesia is also reversed. Sedative effects vary from 30 to 90 minutes depending on the drug, route of administration and dose used. These drugs are metabolised by the liver and excreted by the kidneys (Murrell & Hellebrekers 2005).

How they work

These drugs bind to different alpha$_2$-adrenoceptor subtype receptors in the dorsal horn of the spinal cord (spinal analgesia), and cerebral cortex and locus coeruleus (sedation and supraspinal analgesia). Noradrenaline (norepinephrine) is the endogenous ligand for these receptors and is present on noradrenergic and non-noradrenergic neurons. These drugs inhibit the release of excitatory neurotransmitters through complex mechanisms causing membrane hyperpolarisation in a similar way to opioid analgesic drugs. Alpha$_2$-adrenoceptor agonists also bind to their receptors in the vascular endothelium causing peripheral vasoconstriction with increases in systemic and pulmonary vascular resistance while decreasing cardiac output in a dose-dependent manner.

Indications

Alpha$_2$-adrenoceptor agonists are widely used for sedation for non-invasive procedures and as part of neuroleptanalgesia and balanced anaesthesia protocols. They are considered analgesic adjuvants in a variety of clinical settings as they can supplement analgesia while reducing the stress response. Small doses (1 to 2 µg/kg iv dexmedetomidine) may be administered during recovery from anaesthesia,

Table 14. Pharmacological characteristics of different alpha$_2$-adrenoceptor agonists and antagonists

Drug	Components	Agonist or antagonist	Alpha 1: Alpha 2 selectivity	Duration of action (analgesia)†	Duration of action (sedation)†
Medetomidine	Dexmedetomidine and Levomedetomidine	Agonist	1:1620	1 hour	2 to 4 hours
Dexmedetomidine	Dexmedetomidine	Agonist	1:1620	1 hour	2 to 4 hours
Xylazine	Xylazine	Agonist	1: 160	15 to 30 minutes	1 to 2 hours
Romifidine	Romifidine	Agonist	1:340	Not determined	1 to 2 hours
Atipamezole	Atipamezole	Antagonist	1: 8500	N/A	N/A
Yohimbine	Yohimbine	Antagonist	Less selective for the alpha$_2$ receptor than atipamezole	N/A	N/A

†Duration of analgesic and sedative effects are dose-dependent

particularly in cases of emergence delirium and dysphoria. Their use is generally reserved for healthy animals that can tolerate significant haemodynamic changes and/or with feral and unsocialised animals (Pypendop & Verstegen 1998).

Concurrent use of alpha$_2$-adrenoceptor agonists and opioids may improve analgesia due to a synergistic effect with consequent decrease in opioid requirements (Pascoe *et al*. 2006).

Continuous rate infusion

Administration of dexmedetomidine or medetomidine by continuous rate infusion (CRI) is becoming popular to provide sedation or continuous analgesia in the perioperative period in dogs and cats. Using the drugs by CRI overcomes the limitation of the relatively short duration of analgesia provided by a single dose of dexmedetomidine or medetomidine. Using a CRI intra-operatively allows a significant minimum alveolar concentration (MAC) sparing effect of inhalant anaesthetics while providing a very stable plane of depth of anaesthesia. Postoperatively, sedation is produced but animals may respond to external stimuli. This can be useful when frequent reassessment of the patient is needed or for patient walks and toileting. However, this can be problematic when unexpected sudden arousal occurs (*e.g*. loud noise or noxious stimulus) resulting disorientation leading to defensive behaviour (*e.g*. biting). Doses that have been investigated are typically of dexmedetomidine 1 μg/kg/hour preceded by a loading dose of 1 to 2 μg/kg (Lin *et al*. 2008, Valtolina *et al*. 2009).

Dexmedetomidine oromucosal gel

Dexmedetomidine formulated in an oromucosal gel (0.1 mg/mL) is marketed for the management of noise aversion in dogs and is administered between the cheek and gum. The suggested dose of dexmedetomidine is too low to cause sedation but has been shown to reduce anxiety, presumably *via* an effect that reduces activity in the locus coeruleus, an important modulator of vigilance, sympathetic tone and attention (Korpivaara *et al*. 2017). Whether dexmedetomidine oromucosal gel has a role to reduce anxiety in other situations such as before, or during a veterinary visit is currently unexplored.

Detomidine oromucosal gel

Detomidine formulated in a gel (7.6 mg/mL) is indicated for sedation and chemical restraint in horses and is intended to be placed beneath the tongue. In dogs, detomidine gel at doses of 0.35 to 2.0 mg/m^2 placed in the buccal pouch have been studied to facilitate handling and to perform minimally invasive procedures of short duration in healthy dogs (Hopfensperger *et al*. 2013, Messenger *et al*. 2016, Kasten *et al*. 2018). Time to peak sedation is approximately 45 minutes with a duration of approximately 30 minutes; cardiopulmonary effects are similar to those induced by other alpha$_2$-adrenoceptor agonists and both these, and sedation are reversible with atipamezole (Hopfensperger *et al*. 2013, Kasten *et al*. 2018). In healthy cats, doses of 4 mg/m^2 provided variable sedation and emesis occurred in every case, suggesting this is a less desirable technique in this species (Smith *et al*. 2020).

Adverse effects

Most common adverse effects include hyper and/or hypotension, bradycardia, hypothermia, decreases in sympathetic tone and gastrointestinal motility, increases in urinary output, transient hypoinsulinaemia and hyperglycaemia. Other less common adverse effects such as emesis, salivation and bradyarrhythmias may be observed (Granholm *et al*. 2006, 2007).

Precautions

Use with caution in animals with cardiopulmonary disease with or without arrhythmias or conduction disturbances, significant systemic disease, pre-existing hypo/hypertension, diabetes mellitus and liver/renal failure. Cats with hypertrophic cardiomyopathy and left ventricular outflow obstruction (LVOT) may be an exception: medetomidine has been shown to reduce LVOT and reduce heart rate, improving ventricular filling (Lamont *et al*. 2002). Caution should be exercised when using in patients with trauma. The use of anticholinergics in combination with alpha$_2$-adrenoceptor agonists is contraindicated, unless both bradycardia and hypotension are present together.

Peripherally acting alpha$_2$-adrenoreceptor antagonist (Vatinoxan/ MK-467)

Vatinoxan is a peripherally acting alpha$_2$-adrenoceptor antagonist used in combination with alpha$_2$-adrenoceptor agonists. It prevents the peripherally mediated vasoconstriction and therefore reduces the reflex bradycardia seen after alpha$_2$-adrenoceptor agonists (Kallio-Kujala *et al*. 2018) and has been shown to improve cardiac output in dogs compared to administration of an alpha$_2$-adrenoceptor agonist alone (Honkavaara *et al*. 2011). Studies have been published investigating sedative, analgesic, neuroendocrine and cardiovascular effects of alpha$_2$-adrenoceptor agonists combined with vatinoxan in dogs and cats. Vatinoxan leaves sedative and analgesic effects largely unchanged while cardiovascular and neuroendocrine effects are blunted. In March 2022, the United States Food and

Drug Administration approved the combination of medetomidine and vatinoxan hydrochloride injection for use as a sedative and analgesic in dogs during minor procedures.

Special considerations

Some animals appear unaffected by the administration of alpha$_2$-adrenoceptor agonist drugs and do not sedate well following administration. This is often associated with a pre-existing state of high arousal.

2.5 Local anaesthetics

What they are and how they work

Local anaesthetics inhibit membrane depolarization, nerve excitation and conduction by blocking primarily inward sodium (Na^+) currents through voltage-gated Na^+ channels. These drugs are inexpensive, not scheduled, readily available worldwide and are core medicines of the WSAVA List of Essential Medicines in Cats and Dogs (Steagall *et al.* 2020a). Therefore, there is the potential for widespread applicability of local anaesthetics for the management of pain in cats and dogs.

The most widely used local anaesthetic drugs in small animals are lidocaine, mepivacaine, bupivacaine and ropivacaine. All these agents are classed as aminoamides. Local anaesthetics are weak bases and therefore equilibrate within the body according to their pKa. The pKa of a drug is the pH at which 50% of the drug is in the ionised form and 50% of the drug is in the non-ionised form. This is important for local anaesthetics because it is the non-ionised form of the drug that can cross the neuronal cell membrane to access the voltage gated Na^+ channel, whereas it is the ionised form of the drug that binds to the Na^+ channel receptor to block Na^+ ion entry into the neuron. Therefore, local anaesthetics with a low pKa nearer physiological pH such as lidocaine will have a more rapid onset of action because a greater proportion of the drug will be non-ionised at physiological pH. The other physicochemical properties that determine the characteristics of local anaesthetic drugs are molecular weight, lipid solubility and protein binding (Box 4, Table 15).

Systemic toxicity of local anaesthetics

Systemic toxicity of local anaesthetics is most likely to occur through accidental overdose and is therefore more likely in smaller patients such as cats and small dogs.

Factors affecting systemic toxicity include

- The site of injection: Vascular injection sites lead to a more rapid absorption of the drug into the systemic circulation and therefore higher plasma concentrations of the drug with a greater risk of toxicity. Inadvertent iv or intra-arterial injection is also a significant risk factor for toxicity especially for bupivacaine.

Box 4 Description of characteristics affecting local anaesthetics

- Molecular weight is inversely related to the ability of the local anaesthetic to diffuse through tissue.
- Lipid solubility will determine the potency of the local anaesthetic and duration of action. Local anaesthetic drugs with a low lipid solubility have a lower potency and a shorter duration of action because they do not penetrate the nerve membrane as well as drugs with a high lipid solubility. Drugs with high lipid solubility also tend to have a slower onset of action because the drug becomes trapped in the myelin surrounding the neuronal cell membrane.
- Protein binding determines the duration of action of local anaesthetic drugs. Drugs that are highly protein bound bind more firmly to the receptor site within the Na^+ channel and therefore have a more prolonged duration of action.

Table 15. Physicochemical properties of different local anaesthetic drugs

Local anaesthetic	pKa/onset time (minutes)	Protein binding/duration of action (hours)	Potency	Maximum recommended dose (mg/kg)†
Lidocaine	7.8/5 to 10	Moderate/1 to 1.5	Moderate	Canine: 5 Feline: 5
Bupivacaine	8.1/20 to 30	Long/3 to 10	Potent	Canine: 2 Feline: 2
Ropivacaine	8.1/20 to 30	Long/3 to 6	Potent	Canine: 2 Feline: 2
Mepivacaine	7.7/5 to 10	Moderate/1.5 to 2	Moderate	Canine: 5 Feline: 3

†Local anaesthetics should be administered slowly using best practices such as avoiding accidental intravascular injection during loco-regional anaesthetic blocks. Administration should be stopped immediately if signs of toxicosis are observed

- Drug used: For example, bupivacaine is particularly cardiotoxic due to its slow dissociation from voltage gated Na^+ channel receptors in the heart.

Cardiovascular effects of local anaesthetics

Due to a combination of slowing of conduction in the myocardium, myocardial depression and peripheral vasodilation, hypotension, bradycardia and cardiac arrest can occur when systemic concentrations of local anaesthetics reach toxic levels.

CNS effects of local anaesthetics

Local anaesthetics are lipid soluble and have a low molecular weight and therefore readily cross the blood–brain-barrier. At higher concentrations, they cause convulsions followed by generalised CNS depression.

Management of local anaesthetic toxicity

Treatment of local anaesthetic drug toxicity is focused on supportive care and targeted treatment of adverse events (*e.g.* seizures). Benzodiazepines can be administered to manage seizures along with oxygen therapy and endotracheal intubation and ventilation if needed. Fluid support and inotropes may be needed to manage cardiotoxicity. Lipid solutions can directly counter local anaesthetic toxicity by creating a lipid compartment within the plasma that attracts lipophilic compounds such as local anaesthetics, thereby separating them from the aqueous phase of the plasma (Weinberg *et al.* 2003, O'Brien *et al.* 2010, Muller *et al.* 2015).

Small animal local anaesthetic/analgesic techniques

Local anaesthetic techniques are still often neglected as part of small animal anaesthetic and analgesic regimens. However, use of a local technique can often reduce the dose of other anaesthetic drugs required for maintenance of anaesthesia and contributes to a multi-modal analgesic technique. Use of specific nerve blocks to prevent the relay of nociceptive information from the site of injury to the spinal cord can also provide preemptive analgesia and prevent or reduce the development of central sensitisation.

Topical anaesthesia (transmucosal). The application of some local anaesthetic drugs to mucous membranes produces analgesia rapidly (within 5 minutes). Locations for the topical administration include the cornea for ocular examinations, the nasal passages (*e.g.* before placement of a nasal oxygen cannula and the larynx during intubation). The depth of analgesia produced in tissues is usually small (1 to 2 mm). The absorption of local anaesthetic through the skin (stratum corneum) is generally poor. An eutectic mixture of lidocaine and prilocaine can produce anaesthesia if applied to skin and covered with a non-permeable dressing for 30 to 40 minutes. This is useful to provide local analgesia before iv catheter placement or venipuncture in cats and dogs.

Infiltration anaesthesia. The infiltration of local anaesthetics is commonly performed in veterinary practice; it is safe, reliable and does not require extensive experience. Sterile needles should be used. For example, local anaesthetics can be infiltrated along abdominal and hemilaminectomy incisions (*i.e.* incisional anaesthesia). This technique may be applied before and/or after surgery. When performing a hemilaminectomy, presurgical peri-incisional infiltration yielded more benefit than infiltration at the time of wound closure (McFadzean *et al.* 2021).

Regional anaesthesia. Use of a nerve stimulator or ultrasound to locate peripheral nerves can significantly increase the accuracy of drug deposition and therefore effectiveness of the block. It can also allow a lower total volume of the local anaesthetic drug to be used, reducing motor adverse effects and the risk of toxicity due to absorption of local anaesthetic agents into the systemic circulation (*e.g.* brachial plexus block results in loss of sensation and motor function distal to the elbow). See Fig 24 for an example of regional anaesthesia.

Epidural anaesthesia. Lumbosacral epidural anaesthesia may be used to provide analgesia for all procedures caudal to the diaphragm (Figs 25 and 26). It is especially useful for orthopaedic procedures in the hindquarters. Sacrococcygeal epidural can be used for caudal urogenital surgery (Fig 26).

Dental nerve blocks. Maxillary and mandibular nerve blocks are extremely useful to provide analgesia for dental procedures or mandibular or maxillary surgery. The maxillary and mandibular nerves can be blocked as they exit from the infra-orbital and mental foramens, respectively, or they can be blocked more proximally to provide a wider area of analgesia.

Intraperitoneal disposition of local anaesthetics. The WSAVA-GPC recommends intraperitoneal and incisional anaesthesia for the management of pain, particularly as adjuvant techniques in dogs and cats undergoing abdominal surgery (Steagall *et al.* 2020b). See both techniques in the following link (https://www.youtube.com/watch?v=76dwKuirqt0).

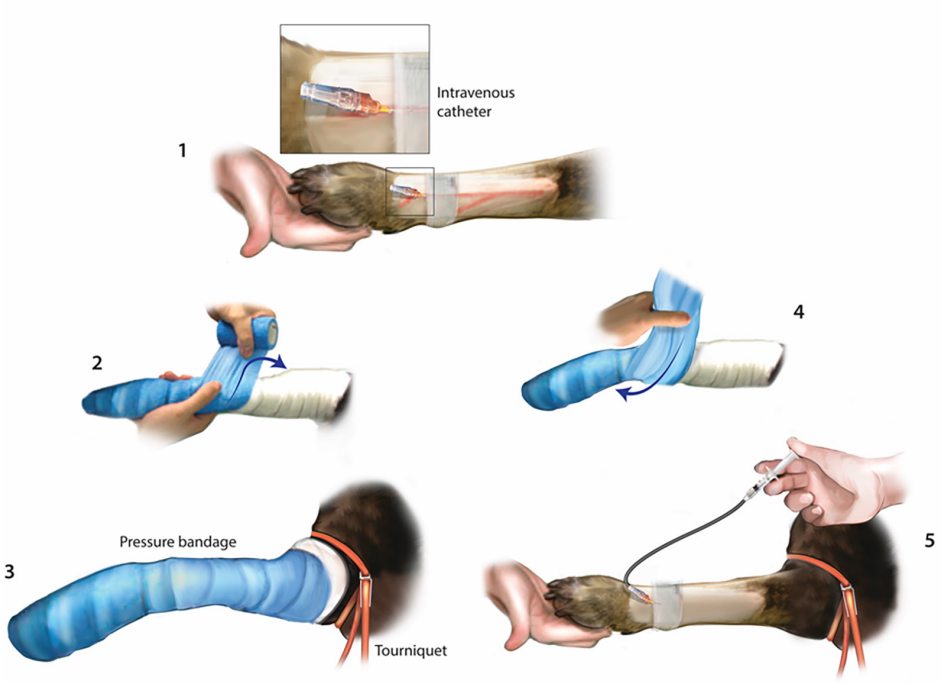


FIG 24. Intravenous regional anaesthesia (IVRA/Bier-block). (1) The limb to be blocked is shaved and the catheter puncture site aseptically prepared. An intravenous catheter is placed into the distal limb. The direction of the catheter could be both ways (proximal or distal direction). (2) Maintain the catheter in place. The circulating blood in the distal limb is reduced by applying a pressure bandage to it from distal towards proximal. (3) A tourniquet is placed just proximal to the elbow joint (or the stifle). (4) The bandage is subsequently removed with the tourniquet in place. (5) The local anaesthetic drug is injected iv using the previously placed catheter. The tourniquet can be left in place for up to 60 minutes. It should be released carefully as high concentrations of local anaesthetics will be also released into the circulation and could induce local anaesthetic toxicity. Illustration from Alice MacGregor Harvey

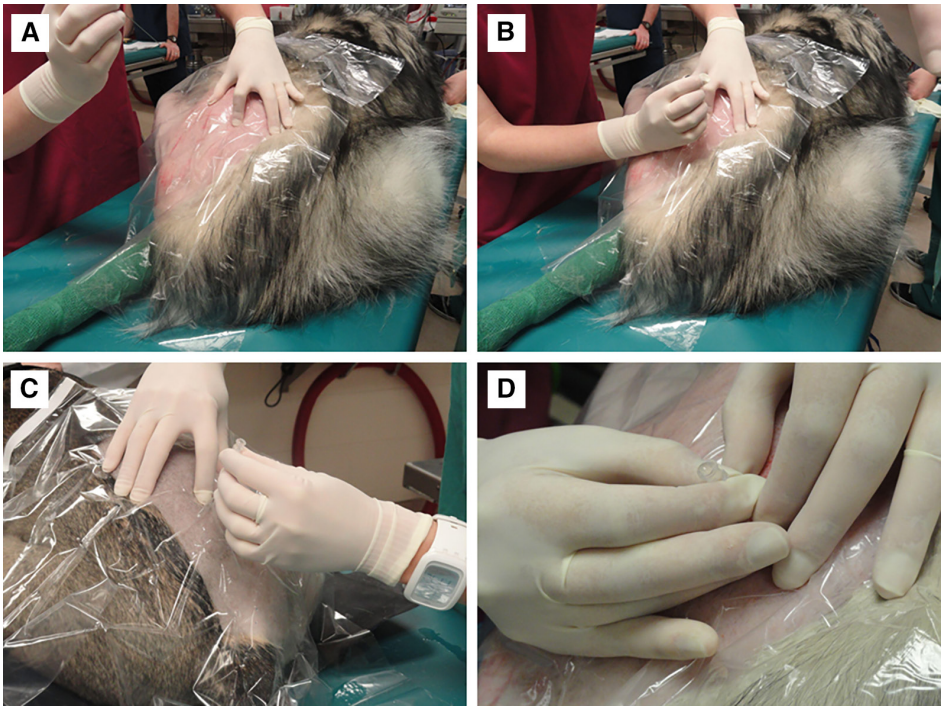


FIG 25. Lumbosacral epidural anaesthesia. The patient is positioned in sternal recumbency with the hind limbs pulled forward. Some clinicians prefer to position the patient in lateral recumbency. The lumbosacral junction is palpated with the index finger while the thumb and middle fingers are placed over the wings of the ilium. (A) A right-handed person uses the left hand to find the anatomical landmarks and (B) the right hand to insert the needle. (C) A left-handed person does the opposite. (D) The "hanging-drop" technique is a positive control mechanism by which a drop of 0.9%NaCl placed in the needle hub is "sucked" into the needle and epidural space by the vacuum prevailing this virtual space. Figures courtesy of Sheilah Robertson

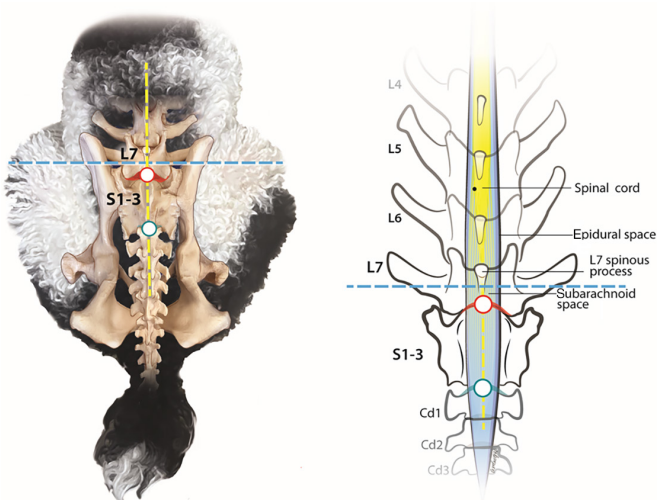


FIG 26. Locations for the administration of a lumbosacral (L7-S1) (red circle) or sacrococcygeal (blue circle) epidural anaesthesia and/or analgesia. Illustration from Alice MacGregor Harvey

Intravenous use of local anaesthetics

Lidocaine can be administered systemically by CRI to provide analgesia and reduce the concentration of inhalant agent required to maintain anaesthesia (MAC sparing effect). Systemically, the mechanisms of analgesia are considered to be multiple. The plasma concentration of lidocaine following systemic administration is too low to block sodium channels directly. Therefore, mechanisms to block the production of cytokines and inhibition of NMDA receptors are considered to be more important. Data in humans undergoing abdominal surgery are fairly convincing that perioperative lidocaine provides an analgesia sparing effect with a reduced consumption of postoperative opioids. However, data for other types of surgery are less certain (Sun *et al.* 2012).

A number of studies have investigated the antinociceptive effects of a perioperative lidocaine CRI in dogs undergoing surgery. Some studies show a positive benefit of a lidocaine CRI to reduce nociceptive responses during surgery (changes in blood pressure and heart rate) and postoperative pain while others show no benefit (Tsai *et al.* 2013, Gutierrez-Blanco *et al.* 2015). Dose rates that have been studied are 2 mg/kg loading dose followed by a CRI of 50 µg/kg/minute, although dose rates do vary between the different studies both in terms of loading dose and CRI rate. There is more convincing evidence for a MAC sparing effect of a lidocaine CRI in dogs which may be advantageous in animals that are hypotensive and require high concentrations of inhalant to maintain anaesthesia during surgery (Wilson *et al.* 2008, Moran-Muñoz *et al.* 2014). This effect should be remembered when anaesthetising an animal receiving a CRI of lidocaine and the inhalant agent concentration carefully adjusted to the required needs of the patient. The use of lidocaine CRIs to provide analgesia in cats is controversial due to the potential cardiovascular negative effects. An experimental study showed that lidocaine CRI also had a significant MAC sparing effect for isoflurane in cats but negative haemodynamic effects were observed (Pypendop & Ilkiw 2005). For this reason, lidocaine infusions should be used cautiously in cats due to the risk of haemodynamic depression. However, in some cases, lidocaine might contribute to multi-modal analgesia in cats under severe noxious stimulation and hyperdynamic states (high blood pressure and high heart rates).

Extended-release local anaesthetics (bupivacaine liposome injectable suspension) are discussed in Chapter 2.6.

2.6 Analgesic delivery techniques and tools

The method by which a drug is delivered can have a significant effect on its safety and efficacy. Drug delivery systems are used to minimise toxicity and improve efficacy of analgesics in pain management. Sustained- or extended-release dosage formulations are designed to release a drug slowly over a specific period (*i.e.* hours or days). Such systems may provide "hands-off" analgesia, minimise systemic side effects and drug accumulation, reduce fluctuations in plasma concentrations and avoid the need for infusion devices (Krugner-Higby *et al.* 2011).

Transdermal patches

Transdermal patches (TD) (fentanyl, lidocaine, and buprenorphine) are human-approved adhesive patches that are intended to deliver a controlled dose of drug over time through the skin using a reservoir or a matrix patch (Hofmeister & Egger 2004, Murrell *et al.* 2007, Weil *et al.* 2007). These reservoir patches have been used for small animal pain management with mixed results as uptake is dependent on skin thickness, temperature, vascularity, among other factors, and often failure of the adhesive to maintain

constant contact with the skin. The use of TD drugs does not preclude the need for use of local anaesthetics and other analgesic techniques.

In cats, the analgesic effects of fentanyl patches can be highly variable due to the individual variability in its uptake and pharmacokinetics (Egger *et al*. 2003). In dogs undergoing orthopaedic surgery, fentanyl TD provided adequate postoperative analgesia when administered with a NSAID (Hofmeister & Egger 2004). Fentanyl patches have a long onset period and must be in place from 12 hours (cats) to 24 hours (dogs) before analgesia is required. Matrix-based fentanyl patches are less susceptible to diversion as the drug is integrated into the patch.

In cats, a transdermal matrix buprenorphine patch did not increase thermal thresholds despite detectable plasma concentrations of the drug (Murrell *et al*. 2007). Thermal thresholds did increase in dogs using a buprenorphine patch (Pieper *et al*. 2011). Further trials are required to determine clinical application in dogs and cats.

Extended-release formulations

An extended release bupivacaine liposome injectable suspension is approved in the USA for use as a peripheral nerve block. It provides up to 72 hours of regional postoperative pain control after a single perineural administration in cats undergoing distal limb procedures and after infiltration in dogs undergoing cranial cruciate ligament surgery (Lascelles *et al*. 2016, Gordon-Evans *et al*. 2020, Reader *et al*. 2020). This commercial formulation of bupivacaine liposome has not been studied in cats younger than 5 months of age or in other locoregional techniques. An advantage to this technique is "guaranteed" compliance with analgesia for up to 3 days because it is placed by the surgeon and is not dependent on caregivers medicating their dog or cat.

Intravenous infusions

Constant rate infusions involve the continuous administration of a set dose regimen through an electronic delivery device to maintain constant plasma levels. Variable rate infusions are more appropriate as doses can be titrated to effect according to analgesic needs and the occurrence of adverse effects. Target-controlled infusions are based on complex algorithms where infusion rates are administered by a delivery device to obtain a specific plasma (effect site) concentration to produce a desired effect.

Infusion devices are normally volumetric infusion pumps with different delivery systems (peristaltic, piston, shuttle). They can deliver high volumes with low accuracy (±10%). Syringe pumps are suitable for administering more concentrated analgesic formulations with greater accuracy (±5%). A calculator feature allows the user to enter bodyweight, drug concentration and the infusion rate (Amoore & Adamson 2003). However, errors are still possible with these drug delivery tools when incorrect concentrations or dosage regimens are entered.

Wound infusion catheters

Wound infusion catheters are flexible indwelling catheters that are embedded near, or in, surgical sites that are used to deliver intermittent infusions of local anaesthetics for postoperative pain management (Abelson *et al*. 2009). Continuous infusions have been associated with unequal distribution (Hansen *et al*. 2013), and the technique is best used as part of a multi-modal analgesia approach.

Epidural catheters

Epidural catheters can be used for repeated epidural drug delivery. Catheterization is accomplished with the use of commercial kits (19-, 20- and 24-gauge sizes). These catheters are usually inserted through the lumbo-sacral intervertebral space and allow intermittent or continuous administration of analgesic drugs for prolonged postoperative periods. Dislodgement or coiling, and contamination of the catheter are the most common complications with this technique (Valverde 2008).

Nerve locators

Electrical nerve locators are convenient, safe, and affordable devices used to locate nerves. Their clinical use helps with needle placement and may shorten onset time, prolong duration of action, and reduce risk of nerve injury. They consist of a constant-current generator (low frequency and duration) that is connected to an insulated needle and a remote electrode that is attached to the skin. The needle is advanced towards target nerves and generates an electric field in the tissues surrounding nerves. The appropriate needle location is identified when a specific motor response is obtained during electrical stimulation. The volume of local anaesthetic to be injected varies depending on the technique. As the solution is injected, the nerve is mechanically displaced and motor response is lost (Campoy *et al*. 2012). Examples of the technique can be seen in the sciatic and femoral nerve blocks at the following link (https://wsava.org/committees/global-pain-council/).

Ultrasound-guided techniques

Ultrasonography may be used for performing some peripheral nerve blocks. Similar to the use of electrical nerve stimulators, ultrasound-guided locoregional techniques aim to reduce the dose of local anaesthetic that is required to provide an effective nerve block

while reducing the likelihood of local anaesthetic toxicity and increasing the rate of success. The technique may allow visualisation of nerves, vessels, and surrounding structures during the administration of peripheral nerve blocks. This should minimise complications including nerve damage, hematoma, and bleeding. However, it requires training and expensive/specific equipment. Review articles have been published on the subject (Portela *et al.* 2018a,b).

2.7 Adjunctive drugs

Adjuvant drugs are not considered "stand-alone" analgesics but can be incorporated into a pain management protocol in conjunction with opioids, NSAIDs and local anaesthetics, or as a substitute when there is a contra-indication to one of the above classes of analgesics (Ruel & Steagall 2019) (Table 16).

Ketamine

Mode of action: NMDA receptor activation is one of the primary contributors to the initiation and maintenance of central sensitisation. By reversibly antagonising NMDA receptors, ketamine modulates central sensitisation and exerts antihyperalgesic

Table 16. Adjuvant drugs in pain management: canine and feline dosing recommendations†

Drug	Indication	Species, dose, route	Frequency	Comments
Amantadine	Chronic pain	Dogs and cats: 2 to 5 mg/kg PO	Every 12 to 24 hours	Efficacy in dogs with OA refractory to treatment. Administer with NSAIDs or other analgesics. Doses up to 14 mg/kg have been reported in combination with meloxicam in a dog with neuropathic pain (Madden *et al.* 2014)
Amitriptyline	Chronic pain	Dogs: 1 to 4 mg/kg	Every 12 to 24 hours	Do not administer concomitantly with other serotoninergic drugs
		Cats: 2.5 to 12.5 mg total	Every 12 to 24 hours	Unpalatable; may not be an option if administration becomes stressful or forceful. Do not administer concomitantly with other serotoninergic drugs
Gabapentin	Perioperative pain	Dogs: 10 mg/kg PO	At 2 hours before surgery	Administer in combination with opioids
		Cats: 50 mg total PO	At 12 hours and 1 to 2 hours before surgery	Administer in combination with opioids
	Chronic pain	Dogs and Cats: 5 to 10 mg/kg PO	Every 8 to 12 hours	Initiate at 3 to 5 mg/kg and gradually increase to targeted dose. Increase or decrease dose depending on therapeutic response. Higher doses have been anecdotally reported. Reduced doses are recommended in cats with chronic kidney disease. May cause sedation and ataxia
	Transport- and veterinary visit-related stress	Cats: studies have reported dose ranges of 50 to 200 mg total PO	At 90 minutes before transporting the cat to the veterinarian	In this situation, gabapentin is used to decrease stress and anxiety related to transporting and physical examination; however, if surgery is scheduled, it might also contribute to postoperative analgesia
Pregabalin	Chronic pain	Dogs: 2 to 5 m/kg PO	Every 8 to 12 hours	Initiate at lower doses and/or interval of administration and gradually increase to target dose Doses of 13 to 19 mg/kg every 12 hours were reported in dogs with syringomyelia-related neuropathic pain (Thoefner *et al.* 2020) Can be administered once 1 hour before intervertebral disc surgery followed by administration every 8 hours for 5 days after surgery
		Cats: 1 to 4 mg/kg PO	Every 12 hours	May cause sedation and ataxia
	Transport-related stress	Cats: 5 to 10 mg/kg PO	At 90 minutes before transporting the cat	In this situation, pregabalin is used to decrease stress and anxiety related to transporting
Ketamine	Perioperative pain	Dogs: 0.2 to 0.5 mg/kg iv (bolus) then 2 to 10 µg/kg/minute (CRI)	Bolus (loading dose before surgery) then CRI for up to 72 hours	Higher infusion rates are used during surgery and then tapered down following surgery
		Cats: 0.2 to 0.5 mg/kg iv (bolus) then 2 to 10 µg/kg/minute (CRI)	Bolus (loading dose before surgery) then CRI for up to 72 hours	Higher infusion rates are used during surgery and then tapered down following surgery; some cats might show signs of anaesthesia at higher doses
Tramadol	Perioperative pain	Cats: 2 to 4 mg/kg PO, iv or im	Used for premedication in combination with sedatives	Do not administer concomitantly with other serotoninergic drugs
	Chronic pain	Cats: 2 to 4 mg/kg PO	Every 8 to 12 hours	Unpalatable; may not be an option if administration becomes stressful or forceful. Do not administer concomitantly with other serotoninergic drugs

iv Intravenous, SC Subcutaneous, im Intramuscular, PO Orally
†See text for details on the indications and contraindications for use

effects. Ketamine may also have immunomodulatory effects and directly suppress proinflammatory cytokine production (Beilin *et al*. 2003).

Indications: To prevent and treat central sensitisation as part of a multi-modal perioperative pain management plan in major, invasive surgery and in trauma patients. It can also be administered in patients with chronic pain presenting with severe signs of hyperalgesia and allodynia. Postoperative analgesia and improved appetite have been shown in dogs undergoing surgery (Wagner *et al*. 2002, Sarrau *et al*. 2007); however, data for its analgesic effects are lacking in cats. In trauma patients, treatment should begin as soon as possible after triage.

Amantadine

Mode of action: Inhibition of NMDA receptor activity similar to ketamine but it is devoid of hallucinogenic effects.

Indications: Long-standing pain syndromes involving a neuropathic component. For example, in dogs with OA-related pain that is not well managed on an NSAID alone (Lascelles *et al*. 2008). Cats with OA had improved client reported pain scores, however they showed decreased activity when treated with amantadine alone (Shipley *et al*. 2021). Amantadine is excreted by the kidneys; therefore, care should be taken in animals with decreased renal function.

Gabapentinoids (gabapentin and pregabalin)

Mode of action: Similar for both drugs and not yet fully elucidated; it may modulate pain by altering calcium channels and suppressing glutamate and substance P release in the dorsal horn of the spinal cord. Pregabalin binds more potently to calcium channels than gabapentin.

Indications: Chronic pain with a known or potential neuropathic component (*e.g*. OA, cancer, diabetic neuropathy, pelvic trauma, amputation, intervertebral disc disease) in both cats and dogs (Chapter 3.12). Also used to reduce anxiety during transport and hospital visits, and as an adjuvant in acute pain. In dogs with naturally occurring neuropathic pain, Canine Brief Pain Inventory scores were significantly lower in gabapentin alone and gabapentin-meloxicam when compared with baseline, but not placebo (Ruel & Steagall 2019, Ruel *et al*. 2020). Both drugs can be associated with ataxia and sedation, which can complicate management and affect QoL (Platt *et al*. 2006, Bleuer-Elsner *et al*. 2021). Dose reduction of gabapentin should be considered in cats with chronic kidney disease as drug excretion may be impaired (Quimby *et al*. 2022). In people, gabapentin is administered before surgery to provide postoperative analgesia and to reduce anxiety. A few studies show similar effects in dogs and cats undergoing surgery and in cats during transport and clinic visits (Crociolli *et al*. 2015, van Haaften *et al*. 2017, Steagall *et al*. 2018). One study also showed decreased transport-related stress and anxiety with the administration of pregabalin (Lamminen *et al*. 2021). In dogs undergoing forelimb amputation, adding preoperative gabapentin to an already robust protocol that included intra- and postoperative fentanyl infusion and other analgesics failed to provide significant benefits in the first three postoperative days (Wagner *et al*. 2010).

Amitriptyline

Mode of action: Tricyclic antidepressants (TCAs) block catecholamine reuptake, thereby enhancing the inhibitory system of pain. Amitriptyline also has NMDA receptor antagonist properties.

Indications: Chronic pain with a known or potential neuropathic component. TCAs can also be used in combination with environmental enrichment for treatment of cats with inflammatory bowel disease and feline lower urinary tract disease (FLUTD) (Chew *et al*. 1998). However, there is large individual variability in response to treatment and many cats with idiopathic FLUTD will not show improvements after treatment over a 7-day course (10 mg/cat every 24 hours) (Kraijer *et al*. 2003). On the other hand, long-term treatment of cats with refractory FLUTD for 12 months eliminated caregiver-observed signs of lower urinary tract disease with reduced haematuria and proteinuria. Sedation, increased bodyweight and decreased coat quality were observed (Chew *et al*. 1998). The addition of amitriptyline may prove successful in managing some cases with refractory chronic pain, but there is limited evidence available.

Other antidepressants

Although TCAs are the most used antidepressants for the management of neuropathic pain in humans, other antidepressants such as selective serotonin and norepinephrine reuptake inhibitors (*e.g*. duloxetine) and selective serotonin reuptake inhibitors (*e.g*. fluoxetine) have been studied with strong evidence of efficacy for the former and lack of efficacy for the latter. In veterinary medicine, these drugs have been evaluated in the context of problem-behaviours and limited data is available for their efficacy in pain management.

Note that the concomitant administration of adjunctive analgesics with serotonin actions (*e.g*. tramadol, amitriptyline, imipramine, duloxetine) can result in a condition called "Serotonin Syndrome." Thus, caution should be taken when managing painful patients that are being treated for anxiety and receiving drugs like selective serotonin reuptake inhibitors, TCAs or monoamine oxidase inhibitors (*e.g*. selegiline). Serotonin syndrome is characterised by neuromuscular hyperactivity, fever, tachycardia, tachypnoea and agitation (Mohammad-Zadeh *et al*. 2008, Indrawirawan & McAlees 2014).

Tramadol

Mode of action: Tramadol is a centrally acting analgesic with a dual mechanism of action (weak μ opioid agonist and inhibition of serotonin and norepinephrine reuptake), among other mechanisms.

Indications: For the treatment of acute (injectable formulation) or chronic (oral formulation) pain in cats in combination with other analgesics (Evangelista *et al*. 2014, Monteiro *et al*. 2017, Guedes *et al*. 2018).

Differences between dogs and cats: The most important metabolite of tramadol, *O*-desmethyl tramadol (M1), is related with the μ opioid agonist effects. This metabolite is produced at much faster rates with reported longer half-life and slower clearance in cats when compared with dogs (Perez Jimenez *et al*. 2016). Dogs are unable to produce significant concentrations of O-desmethyl tramadol and analgesic effects were not observed in dogs with OA (Budsberg *et al*. 2018) or postoperative pain (Donati *et al*. 2021). There is good evidence for the use of tramadol in cats (although the bitter taste may preclude oral administration in some cases). The level of evidence for using tramadol in dogs is low. Thus, tramadol should only be used as an adjuvant analgesic in dogs when there is limited availability of drugs (*i.e*. although opioid effects are not expected in dogs, a potential analgesic effect from the inhibition of serotonin and norepinephrine reuptake might exist).

2.8 Non-analgesic drugs in the management of the painful patient

Glucocorticosteroids (GCs)

There is little evidence that supports the administration of these drugs in the clinical setting for analgesia; however, their use can result in pain relief through their anti-inflammatory properties. These drugs are better indicated in the management of allergic and autoimmune disorders (*e.g*. immune mediated anaemia) and specific inflammatory conditions (*e.g*. inflammatory bowel disease, meningitis). It is the combination of the effects of GCs on reducing the production of prostaglandins, and their role in the resolution of these conditions that confers pain relief. The combination of GCs with NSAIDs is contraindicated due to the increased incidence of adverse effects (Boston *et al*. 2003).

Inhalant anaesthetics

These are used for general anaesthesia in animals. Depth of anaesthesia can be predictably, and rapidly adjusted, and cardiorespiratory depression is dose-dependent. Agents in this class include halothane, isoflurane and sevoflurane but *none have antinociceptive properties*. Inhalant anaesthetics will simply block perception of pain during general anaesthesia; patients will wake up painful if analgesic drugs have not been used.

Maropitant

Maropitant is a neurokinin-1 receptor (NK-1) antagonist used to treat and prevent emesis by blocking NK-1 receptors in the chemoreceptor trigger zone in the CNS. The NK-1 receptor and its ligand, substance P, are present in spinal cord sensory afferents involved in nociception. Studies in mice and rabbits have demonstrated that NK-1 receptor antagonists consistently induce analgesia to visceral noxious stimulation but this information should not be extrapolated to small animals as clinical analgesia does not seem to be relevant. Maropitant may decrease inhalant anaesthetic requirements after iv administration in dogs and cats (Boscan *et al*. 2011, Niyom *et al*. 2013). At this point, *there is no clear evidence that maropitant should be relied upon as an analgesic in the clinical setting* (Kinobe & Miyake 2020). Maropitant decreases vomiting, but does not eliminate nausea, and may contribute to reduced gastrointestinal motility (Koh *et al*. 2014, Mikawa *et al*. 2015). Overall, the drug may be used as part of the anaesthetic plan to improve the patient's hospital experience and reduce motion sickness with transportation.

Ondansetron

Ondansetron is a serotonin type 3 ($5\text{-}HT_3$) receptor antagonist and is an efficacious antiemetic and antinausea drug (Santos *et al*. 2011, Foth *et al*. 2021). Although maropitant and ondansetron have no proven analgesic actions, they are still important components in overall patient management to prevent the adverse effects of vomiting, and thus, to promote patient comfort.

Acepromazine (ACP)

Acepromazine is one the most widely used tranquillisers in veterinary medicine; it has no analgesic properties. The administration of ACP decreases injectable and inhalant anaesthetic requirements. At high doses or in hypovolemic animals it can cause clinically significant hypotension. Acepromazine is widely used in the perioperative period (neuroleptanalgesia) and may cause hypothermia secondary to peripheral vasodilation and central effects on the hypothalamus.

2.9 Physical rehabilitation

Physical rehabilitation involves the clinical evaluation and treatment of musculoskeletal and neurological impairments in intra-articular, capsular, ligamentous, muscular, myofascial, and central and peripheral neural tissues. Posture, gait, function, strength, muscle flexibility, passive range of motion and joint mobility are evaluated to develop a treatment plan (Millis & Levine 2014) (see an example of a myofascial exam https://www.youtube.com/watch?v=69YWXX_zUL8). Physical modalities, manual therapy and therapeutic exercise may be used to treat pain (Fig 27). Treatment frequency, intensity and duration are decided upon the target tissue's healing ability and the chronicity of the injury.

Therapeutic exercise

Exercise improves blood and lymph flow, increases soft tissue support to skeletal and spinal structures, increases tendon and ligament pliability, and improves cartilage health. The patient's caretakers can be educated to perform therapeutic exercises in the home environment. Simple exercise such as static weight bearing can be used in the acute phase of injury, with gradual increases in intensity as healing progresses and strength improves. In humans, strengthening and aerobic exercise provide pain relief with analgesic effects as large as, or larger than, those seen with NSAIDS (Polaski *et al*. 2019).

Physical modalities

Physical modalities can be used to diminish pain, promote soft tissue healing, improve muscle extensibility and facilitate muscle strengthening.

Thermotherapy (heat). Application of heat to tissues increases distensibility and blood flow to facilitate healing. Heat may be pronociceptive early in disease states. In the chronic state, once inflammation has subsided; muscle and fascia restrictions predominate and heat can have analgesic effects (McCarberg & O'Connor 2004).

Cryotherapy. See Chapter 2.10.

Photobiomodulation (low-level laser/light). Application of photons using red/near infrared light results in reduced inflammation and analgesia. Different classes exist and the dose is based on wavelength, radiant power, irradiance, fluence and treatment area. Photobiomodulation showed analgesic efficacy in dogs with elbow or hip joint pain (10 to 20 J/cm^2) (Looney *et al*. 2018, Alves *et al*. 2022).

Electrical stimulation. Transcutaneous electrical nerve stimulation (TENS) provides analgesia for about half of human patients with moderate pain (Rushton 2002). The treatment is titrated for each patient based on frequency (pulses per second), intensity (pulse amplitude) and pulse duration (periods when the electrical current is deliver).

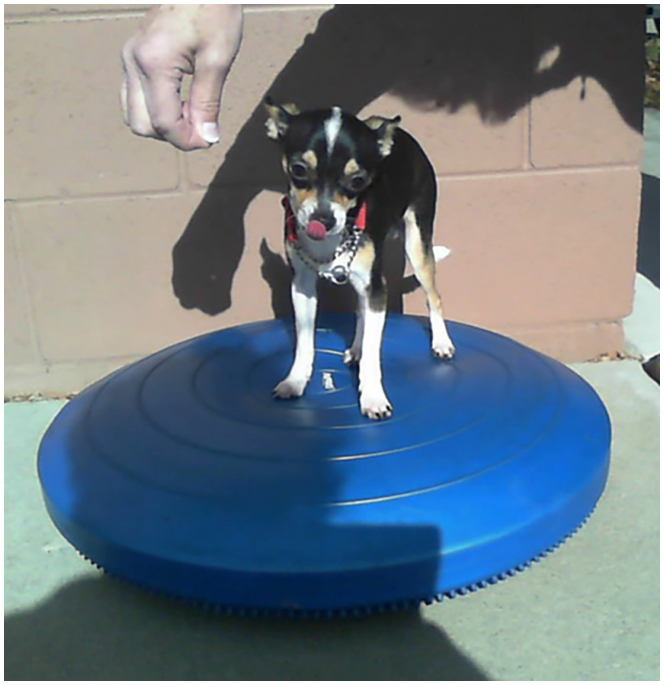


FIG 27. Example of a dog undergoing physical therapy exercise using a balance disc. Figure courtesy of Bonnie Wright

Pulsed electromagnetic therapy. Application of non-thermal, non-invasive electromagnetic therapy decreased knee OA pain in people and improved functional outcomes in dogs after hemilaminectomy (Nelson *et al*. 2013, Alvarez *et al*. 2019).

Shock wave therapy. Deformation of tissues using high-intensity sound waves leads to neovascularization, reversal of chronic inflammation, stimulation of collagen production, treatment of tendon and ligament injuries, and provision of short- and long-term analgesia (Chamberlain & Colborne 2016). Studies have found improved limb use after stifle surgery in dogs and long-term benefits in humans with low back pain (Barnes *et al*. 2019, Walewicz *et al*. 2019).

Trigger point pressure. Trigger points are located within a taut band of muscle fibres (painful, hard nodular structure). They can be stimulated using therapeutic lasers, electrotherapies, or physical or manual therapies such as the injection of local anaesthetics or acupuncture (dry needle) (Wall 2014). Although data is limited in veterinary medicine, the use of acupuncture is preferred.

Massage. See Chapter 2.15.

2.10 Cold therapy

What it is

Cold therapy is a non-pharmacological analgesic tool medically useful, scientifically sound, globally available and not limited by regulation (Wright *et al*. 2020). It involves topical application of ice or frozen substrate *via* paper cups, buckets and bags, or use of cold compression devices and circulation sleeves (Fig 28). It should be applied adequately and for an adequate period to the target tissues.

How it works

Applying cold to skin decreases the temperature of underlying tissues up to a depth of 2 to 4 cm. This results in decreased activation of tissue nociceptors and slower conduction velocity along peripheral axons (cold-induced neuropraxia) (Malanga *et al*. 2015). Specific peripheral cold-sensitive ion channels contribute to decreasing nociceptive signalling and activating inhibitory interneurons (Liu *et al*. 2013). Cold therapy also decreases oedema *via* sympathetically mediated vasoconstriction and reduces muscle spasm (Lee *et al*. 2002). Muscle spasm may be present in patients with acute and chronic pain and is a major cause of discomfort (Malanga *et al*. 2015).

Indications and consideration

Cold therapy is recommended on any surgical incision as a component of the analgesic protocol. Application of cold for 15 to 20 minutes every 6 to 8 hours can be performed immediately after surgery and for several days after; the technique can be taught to caregivers and continued after discharge (Wright *et al*. 2020).

In cases of chronic pain with an inflammatory component or muscle spasm, cold therapy might also be valuable. As with any drug or medical procedure, it has dose-related, time-related and disease-related effects that vary on a patient basis. Therefore, it should be used after careful consideration of its potential value to each individual.

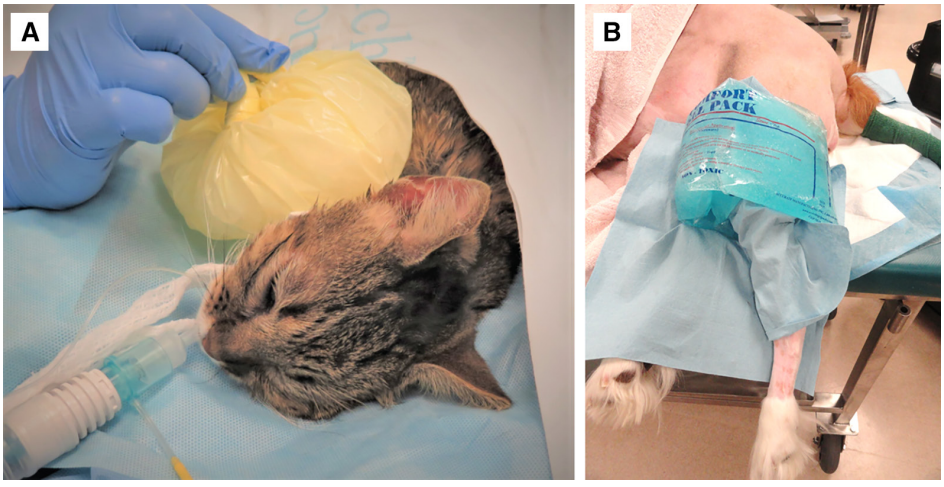


FIG 28. Example of cold therapy. Ice packs are never in direct contact with the skin. There should be a layer (e.g. paper or cloth) between the ice pack and skin. (A) A cat immediately after total ear canal ablation. Sterile gauze pads were used to protect the skin. (B) A dog immediately after stifle surgery. Surgical drapes were used to protect the skin. Figure (A) reproduced from Steagall *et al*. (2022). Figure (B) courtesy of Sheilah Robertson

Cautions include avoiding nerve damage by prolonged use, or applying it over regions without sensation or with poor blood flow (*e.g.* distal extremities). An appropriate barrier (*e.g.* towel) should be placed between the cold material and the skin. Non-sterile surfaces contacting fresh surgical incisions should be avoided. Ice should not be applied for more than 20 minutes within a period of 1 to 2 hours. Most patients accept the cold sensation after a brief period of discomfort that should not last more than 2 minutes (Francisco *et al.* 2018). Patients may initially react negatively to cold therapy but usually quickly demonstrate acceptance as the tissue becomes desensitised. Nevertheless, cold allodynia can occur in chronic pain syndromes and therapy should be stopped in patients that appear disproportionally irritated by the cold stimulus or continue to attempt to avoid the treatment.

2.11 Cannabinoids

Endocannabinoid system

In all vertebrates, the endocannabinoid system works alongside other neuro-modulatory systems such as the serotonergic, dopaminergic, noradrenergic and opioidergic systems. These systems interact in an effort to maintain homeostasis (McPartland *et al.* 2014). Several forms of physical medicine such as exercise, acupuncture and diet also contribute to changes in the endocannabinoid system (Howlett & Abood 2017, Toczek & Malinowska 2018).

Cannabinoid receptors (CB) are neuro-modulatory, G-protein coupled receptors found on cell membranes and nerve presynaptic terminals. There are two recognised CB: CB1 (primarily on the nervous system) and CB2 (widely distributed and immune cell related). There are three types of cannabinoids: endocannabinoids (produced by the body), phytocannabinoids (produced from plants) and synthetic cannabinoids. These molecules modify nociceptive signals peripherally and centrally. Via their glial effects, they are anti-hyperalgesic and may reduce neuro-degenerative conditions (such as degenerative myelopathy) (Fine & Rosenfeld 2013, Fernandez-Trapero *et al.* 2017). A variety of endogenous and exogenous ligands are recognised to bind to or modify CB receptors.

Exogenous cannabinoids

Phytocannabinoids are derived mainly from *Cannabis sativa* and are often more diverse than synthetic compounds. Cannabinol (CBD) and delta-9-tetrahydrocannabinol (THC) are two of the most studied phytocannabinoid molecules; yet there are more than 180 compounds. Regulatory body approved pharmaceuticals are derived from biological sources and reduced to one or two molecules. Plant derived cannabinoids contain terpenes and flavonoids which also have biological effects. The large variety of compounds contributes to the complexity and variable effects of different phytocannabinoids, and a lack of standardisation in commercially available products for regulation and research.

CBD is commonly used in veterinary medicine for analgesic and immune modulating effects at CB2 receptors. The psychotropic and sedating effects are minimal, while the medicinal effects are relatively predictable (Gamble *et al.* 2018). THC is a strong agonist of CB1 receptors although it also binds to CB2. It is related with psychoactive effects, anxiety, tachycardia, and peripheral vasodilation and thus THC is difficult to titrate for medical use in veterinary species. However, small amounts of THC can significantly increase efficacy when used in combination with CBD (Vaughn *et al.* 2020).

Marijuana and cannabinoids

Marijuana and hemp are both plants of the genus *Cannabis sativa*. The distinction is the amount of THC present (hemp has <0.3% of THC by dry weight) (Deabold *et al.* 2019). Plants are incredibly diverse due to hybridization; thus, individual species are not important for medical consideration (Solymosi & Kofalvi 2017). The variable effects of common plant varieties are based on the proportion of active cannabinoids, terpenes and flavonoids (Piomelli & Russo 2016). A certificate of analysis provides this information for a given product (Wakshlag *et al.* 2020).

Clinical approach to cannabinoids

It is currently impossible to recommend a universal approach to veterinarians regarding cannabinoids. The laws vary widely from regions where they there is little legal risk, to those where it is a criminal offence to prescribe or sell. These compounds are being widely used and are often sourced without veterinary oversight, but veterinary professionals should serve in a protective, advice-giving role, at least regarding harm reduction. Continuing education training exists to improve the knowledge on this topic.

Intoxications are widely reported in dogs, especially with THC. Clinical signs vary in severity and include CNS depression, anxiety, sensory hypersensitivity, urinary leakage, tachycardia, and death. Cannabinoids are also potent inhibitors of cytochrome P450 enzymes (especially CBD). Caution should be used in combining with other drugs, and monitoring should be done to evaluate changes in liver enzymes and function. Doses should be decreased when cannabinoids are used in combination with other drugs that work through calcium channels (such as gabapentin) to avoid excessive sedation. Likewise, the vasodilatory effects of THC can alter underlying disease states, such as kidney and cardiac conditions (Ho *et al.* 2019).

The endocannabinoid system is a homeostatic system, and individuals can have extremely different "baseline" activity resulting in unpredictability with treatment. It is suggested to start phytocannabinoids at low doses and titrate over a period of weeks. In dogs with OA, doses of 2 mg/kg CBD oil twice daily orally are generally used and some degree of efficacy has been reported; elevations in liver enzymes were seen in some dogs (Gamble *et al.* 2018, Brioschi *et al.* 2020, Vaughn *et al.* 2020). Data on efficacy are not available for cats, but their pharmacokinetics appear quite different from dogs (Deabold *et al.* 2019). The endocannabinoid system may be immature in neonates, along with immature liver function, so cannabinoids should be avoided in pregnancy, nursing animals, and animals under 8 weeks of age.

2.12 Diet and supplements

Diet

Therapeutic diets should be considered in pain management (Vandeweerd *et al.* 2012). For example, increased levels of activity were seen in cats with OA after being fed a diet high in eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) content and supplemented with green-lipped mussel extract and glucosamine/chondroitin sulphate for 9 weeks (Lascelles *et al.* 2010a). Similarly, dogs with OA that were fed a diet enriched with fish oil omega-3 fatty acids for 90 days showed improvement in objective assessment of weight bearing (gait analysis) (Roush *et al.* 2010). The interplay between nutrition and pain management, and how commercial diets could contribute to multi-modal analgesia in a multi-disciplinary approach in small animals is yet to be explored.

Supplements

Supplements are products derived from food sources that are purported to provide extra health benefits beyond nutrition. It should be noted that dietary supplements do not require proof of safety, efficacy or quality control to be marketed. However, supplements have a long history of use, there is increasing information regarding efficacy of specific supplements, and they may be an alternative when access to pharmaceuticals is limited.

Box 5 provides a non-exhaustive list of basic compounds. Several commercial diets include one or more of these supplements. Randomised, prospective clinical trials are required to investigate the role of supplements in pain management, particularly in chronic conditions.

2.13 Nursing and supportive care

Quality nursing care (TLC, tender loving care) should be applied as an adjunct to other therapies for managing pain, anxiety and stress (Fig 29). It is important to create an environment where the animal is emotionally and physically comfortable. This can be approached through environmental and handling modifications as well as specific treatments for pain and comfort.

Environmental modifications can include management of auditory, visual and olfactory input. Negative auditory input can be limited by keeping dogs and cats separated, keeping quiet pets away from boisterous ones, housing patients away from busy treatment rooms, provision

Box 5 Examples of supplements

- Poly-unsaturated Fatty Acids (PUFA)
- Glucosamine/ chondroitin
- Hyaluronic Acid (HA)
- Avocado-Soybean Unsaponifiables
- Green-lipped mussels (GLM) (*Perna canaliculus*)
- Undenatured type II collagen (UC-II)
- Boswellia Serrata
- Ashwaganda (*Withania somnifera*)
- Curcumin (Turmeric)
- *Arnica montana* or *Solidago chilensis* (Brazilian Arnica)
- Devil's Claw (*Harpagophytum procumbens*)
- White willow bark (*Salix alba*)
- Quercetin, resveratrol and other polyphenols
- Acetyl l-carnitine
- Milk-derived products
- Cetyl myristoleate
- *N*-acetyl cysteine
- *N*-palmitoyl-ethanolamine (PEA)
- Fertilised egg-shell membrane (fortetropin)

of calming music or white-noise (Hampton *et al.* 2020, Lindig *et al.* 2020), and speaking calmly. Visual modifications can include lower lighting during rest and especially at night, places to hide and perch in the kennel or cage. Some data support that certain light wavelengths provide relaxation or analgesia (Tamarova *et al.* 2009). Olfactory modifications include the housing adaptations mentioned above, and exposure to pheromone or herbal agents that have relaxing qualities (*e.g.* feline and canine pheromones, and lavender in certain species such as rabbits) (Pageat & Gaultier 2003, Amaya *et al.* 2020, Van Vertloo *et al.* 2021). Finally, the cage environment should ideally provide comfort, space and opportunities for movement and possibility to retreat or hide. For example, cats use three-dimensional spaces, and providing them with a cardboard box offers both a "safe place" to hide and opportunity to use vertical spaces (Fig 29).

Handling modifications can include identifying anxious patients and treating anxiety before transportation and/or during hospitalisation with anxiety reducing drugs (*e.g.* gabapentin or trazodone) (Gilbert-Gregory *et al.* 2016) (Table 16). Pain assessment is imperative along with provision of comforting touch and positive interactions to patients that seek it, while providing space to those that seek isolation. Stress and anxiety and sleep disruption can intensify pain across species (Lefman & Prittie 2019).

Other nursing care techniques for calming and analgesia

Massage

Gentle pressure, compression and rocking can soothe some patients both physically and psychologically if they are accustomed to close human contact (Chapter 2.15).

Application of warmth or cold. Cold therapy during acute injury can reduce swelling and provide analgesia (Chapter 2.10). Heat can be comforting in the absence of inflammatory pain.

Patient handling. When handling and moving an animal, avoid painful areas (surgical/trauma sites, osteoarthritic joints, etc.), even when the animal is anaesthetized or sedated to avoid inflicting a painful stimulus. Long bone injuries should always be immobilised with a cast or splint before moving the patient. Restraint can be accomplished without force (*e.g.* using towels to wrap the patient), using a calm voice and gentle movements. Scruffing should be avoided at all costs in cats. Feline-friendly handling guidelines are available elsewhere (Rodan *et al.* 2011).

FIG 29. Examples of nursing care to provide comfort to hospitalised patients. (A) A kitten being monitored during anaesthetic recovery immediately following ovariohysterectomy. Nursing care ensures this patient is normothermic and comfortable before being returned to her cage. (B) A cardboard box in a cat's cage provides a safe place to hide and opportunities to perch. These contribute to the welfare of hospitalised cats. (C) An anxious dog after receiving trazodone to reduce anxiety postoperatively. (D) A dog recovering over a warm water circulating blanket after surgery. Nursing care ensures the dog is in a clean and quiet place feeling warm and comfortable. Figures (A), (C) and (D) courtesy of Paulo Steagall. Figure (B) reproduced from Steagall *et al.* (2022)

Bedding and positioning. The creation of a soft, cushioned surface for the animal to rest on will help prevent additional pain. Laying for prolonged periods on a hard or cold surface is extremely uncomfortable and predisposes to anxiety, heightening the sensation of pain and the potential for decubital ulcers. Rolled blankets or pillows can facilitate the patient being able to choose the most comfortable body position. Furthermore, the patient can be assisted with positioning that encourages elevation of injured limbs to reduce oedema or facilitates air flow around wounds.

Changing positions. Repositioning a patient every 4 hours prevents muscle stiffness, decubital ulcers, pulmonary atelectasis, promotes circulation and gives an opportunity for pain assessment and analgesic adjustment if required.

Movement and gentle exercise. When done with care, movement and gentle exercise can reduce pain, tissue stickiness and improve patient comfort (Polaski *et al*. 2019). Mobility aids such as ergonomic harnesses, carts and exercise equipment can facilitate movement and activities. Assisted walks can improve attitude, reduce stress and allow for independent elimination in toilet-trained patients.

Laser therapy and TENS. These modalities can be a part of nursing care for pain relief (Chapter 2.13).

2.14 Acupuncture

What it is

Acupuncture is the placement and manipulation of fine needles at defined locations in the body rich in neurovascular or myofascial structures (neuroanatomic points) to stimulate an endogenous response to promote analgesia, healing, and immune modulation. The use of needles implicates tissue mechano-transduction and neuromodulation as mechanisms behind the biochemical effects of acupuncture (Wright 2019). The term acupuncture is defined by the use of needles but neuroanatomic points are not exclusive to acupuncture. These specific points can be stimulated using other related modalities, such as acupressure, laser, electrical therapies and aquapuncture (the injection of liquid such as saline of Vitamin B12 at acupuncture sites) (Fig 30). Although these related modalities may also have efficacy, the reliance on tissue mechano-transduction has not been established for them (Langevin & Wayne 2018).

How it works

Neuroanatomical approach

Neuroanatomic points are anatomically rich and characterised by myelinated and unmyelinated nerves, low-threshold mechanoreceptors, fibroblasts and the collagen matrix, mast cells and microcirculatory complexes (Zhang *et al*. 2012). With needle placement,

FIG 30. Examples of dogs and cats undergoing acupuncture treatment for different painful conditions. (A) and (C) Electroacupuncture. (B) and (D) Acupuncture. Figures (A), (B) and (D) courtesy of Bonnie Wright. Figure (C) courtesy of Sheilah Robertson

nerve stimulation occurs directly and also secondary to mechanical forces applied to the fascia and cellular milieu in the region surrounding the point. For example, fibroblasts are stretched by needle traction on the collagen network. Fibroblast cellular function is modified through mechano-transduction over a period of 36 hours increasesing fluid flux through lymphatic channels. The direct effect of needles on the nerve and fibroblast alter peripheral nociceptive input, spinal neurotransmitter modulation, sympathetic/parasympathetic balance and immune function (Wright 2019).

In contrast to the documented physiological processes, Traditional Chinese Veterinary Medicine approaches acupuncture based on descriptions of moving chi (invisible energy). Both approaches involve the placement and manipulation of needles at specific points to produce beneficial clinical effects (Kaptchuk *et al.* 2010).

Indications

In human medicine, acupuncture as a treatment for various forms of acute and chronic pain has risen in esteem. In the USA, the National Institutes of Health's National Center for Complementary and Integrative Health (NIH n.d.) maintains a website of acupuncture related scientific data and funds research. Although the evidence is limited in veterinary medicine, studies generally indicate analgesic effects of acupuncture for the management of acute and chronic pain in dogs and cats (*i.e.* ovariohysterectomy, OA, hemilaminectomy and other neurological and musculoskeletal diseases) (Teixeira *et al.* 2016, Ribeiro *et al.* 2017, Silva *et al.* 2017, Nascimento *et al.* 2019, Baker-Meuten *et al.* 2020, Machin *et al.* 2020).

Adverse effects

Risks of acupuncture are extremely low when performed by an appropriately trained clinician. Reported adverse incidents are rare and include unintentional puncture of vital structures (especially the lungs), infection (linked to not using sterile, single-use needles), and introduction of foreign material. Sterile, single use needles are essential.

Intentional implantation of foreign material (such as gold beads or pieces of metal) is not recommended. In dogs, gold beads cause long-term inflammatory changes and in humans, life-threatening consequences of migrated needles have been reported (Lie *et al.* 2011).

Acupuncture equipment is inexpensive and readily available, but requires training. Acupuncture has been shown to reduce opioid requirements and is increasingly being suggested as an alternative to opioid based treatments in chronic pain (Tick *et al.* 2018). Acupuncture is a valuable adjunct, when used properly, to pharmaceutical approaches, and is meant to be used in a multi-modal regimen rather than as a stand-alone therapy.

2.15 Soft tissue mobilisation and massage

The concept of soft tissue mobilisation requires an understanding of the presence of fascia and connective tissue linking the somatic and visceral body structures. With its diverse components, the fascial system builds a three-dimensional continuum of soft, collagen-containing, loose and dense fibrous connective tissue that permeates the body and enables all body systems to operate in an integrated manner (Zügel *et al.* 2018).

Traditional methods of fascia mobilisation include massage, stretching and chiropractic techniques. When fascial tissue is manipulated, growth factors and a variety of proteins and neurotransmitters are released leading to changes in pain processing, metabolic processes, blood flow and healing capacity, and reducing peripheral and central sensitisation, and inflammation (Weerapong *et al.* 2005, Langevin 2014, Berrueta *et al.* 2016).

Exercise as a form of tissue mobilisation is associated with improved analgesia and function in chronic pain as well as positive influence on the immune system and reduced ageing-related immunosenescence (Naugle *et al.* 2012, Sluka *et al.* 2018) (Chapter 2.9). Acupuncture research over the last 30 years has shown that fascial mobilisation is an important contributor to the biochemical effects of acupuncture (Langevin 2014) (Chapter 2.14). Newer machine-based techniques that work through mobilisation of tissue include focused and radial shock wave therapies used for tendon injuries, pain relief and bone healing (Dedes *et al.* 2018).

Fascial mobilisation ranges from simple techniques that can be provided by nursing staff such as soft tissue massage and touch, to complex modalities requiring significant training such as shock wave therapy and acupuncture. Many of these techniques can be adopted as a component of pain control. Recommendations for tissue mobilisation can be as simple as recommending regular and gentle exercise as part of the pain management plan, especially for chronic and ongoing pain.

2.16 Salvage surgical procedures

In some cases, a surgical approach to the alleviation of pain is recommended. These procedures are often referred to as salvage procedures, although they can be employed as a first line treatment. For example, the pain associated with limb osteosarcoma can be difficult to control with analgesic therapies, and amputation provides a rapid means of alleviating pain. Salvage surgical procedures can be complex and should be performed by experienced surgeons. Many of the patients undergoing these procedures will have been

in pain for a considerable period of time, and comprehensive analgesic techniques should be employed to prevent acute pain on top of a sensitised state resulting in persistent postsurgical pain, as clearly seen in humans.

Limb amputation

Indications: limb trauma/severe avulsion or failed reparative surgery (*e.g.* failed fracture repair), appendicular osteosarcoma, other painful limb neoplasia, other chronically painful limb conditions.

With appropriate perioperative analgesic provision, in most cases recovery time is rapid, and animals adapt well to walking on three limbs. Function is best in animals that have no musculoskeletal disease in the other limbs and are not overweight or obese.

Total joint replacement

Indications: to relieve pain in a diseased joint (DJD/OA, subluxation, luxation and intra-articular fracture).

These procedures (total hip replacement, total elbow replacement, total knee replacement, custom joint replacement) are technically advanced and require specialised equipment. If performed correctly, they can eliminate joint pain (Lascelles *et al*. 2010b).

Excision arthroplasty

Indications: to relieve pain in a diseased joint (DJD, subluxation, luxation and intra-articular fracture).

Most often performed in the hip joint (femoral head and neck excision), this procedure is less technically demanding than total joint replacement. However, data indicate that functional outcomes are not optimal (Off & Matis 2010, Montasell *et al*. 2018). Excision arthroplasty should not be thought of as an "easy fix" – effective perioperative analgesic techniques and aggressive physical rehabilitation are required to optimise outcome.

Arthrodesis

Indications: to relieve pain in a diseased joint. Arthrodesis techniques aim to permanently eliminate movement of a joint and the pain associated with this; however, the procedure usually results in mechanical (functional) lameness.

Denervation

Indications: to relieve pain when medical therapies have failed, as an alternative to arthrodesis.

Sensory denervation aims to provide pain relief by disturbing the neural pathways that transmit nociceptive message from the joint to the brain. Denervation techniques have been described for the canine hip (coxofemoral joint) and elbow and are performed when other treatments such as medical, surgical and adjunctive therapies have failed (Zamprogno *et al*. 2011). Motor function can usually be well maintained when these procedures are correctly performed. There are no long-term follow-up data available, and conflicting data on whether denervation of a joint results in accelerated joint degeneration.

The procedures outlined above constitute major surgery with the potential to cause significant pain (acute and persistent) if adequate perioperative analgesia is not provided for a sufficient duration of time. A multi-modal approach is recommended with an emphasis on local analgesia, particularly given that most patients undergoing these procedures will be suffering chronic pathological pain before surgery. They should only be performed by surgeons with appropriate experience with the procedures and postoperative patient care (Lister *et al*. 2009).

2.17 Monoclonal antibodies for pain control

Monoclonal antibodies (mAbs) have proven to be extremely effective in a variety of diseases in humans and are now being introduced in veterinary medicine. Monoclonal antibodies are monovalent antibodies which specifically bind to target molecules including cytokines, receptors or cells (Liu 2014). The binding results in blocking the activity of the target. There are multiple mechanisms by which mAbs produce their effect. These include blockade of ligand-receptor interaction or signalling pathways; altering cell populations (by engaging effector functions including the complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity; and antibody dependent phagocytosis or apoptosis) (Khan & Sadroddiny 2015). Therapeutic antibodies need to be species-specific, to reduce the prevalence of developing an immune reaction against the drug (anti-drug antibodies).

Targeting nerve growth factor (NGF) has emerged as a potentially useful therapeutic avenue for pain control in OA, and possibly other conditions. Nerve growth factor was originally identified as a critical factor for the development and maintenance of sensory and sympathetic neurons in the developing nervous system. However, it is now clear that NGF has an important role in pro-nociception (Enomoto *et al*. 2019). Nerve growth factor sensitises nerves, altering the way they function, activating immune/inflammatory cells, further sensitising neurons due to the products released by these cells; it also contributes to neuronal sprouting in pain conditions

(Barker *et al*. 2020). In human clinical studies, several anti-NGF mAbs have been evaluated and been shown to reduce pain and improve function in patients with OA (Wise *et al*. 2021). However, no anti-NGF mAbs are currently approved in humans, partly due to concerns about adverse effects, especially cases of more rapidly progressing OA (Wise *et al*. 2021).

In the last few years, studies have been reported that demonstrate the significant analgesic effect of single doses of anti-NGF mAbs for OA pain control in dogs and cats. The efficacy of a caninized anti-NGF mAb (ranevetmab), a fully canine anti-NGF mAb (bedinvetmab) and felinized anti-NGF mAb (frunevetmab) have been described (Webster *et al*. 2014, Lascelles *et al*. 2015, Gruen *et al*. 2016, 2021a,b, Corral *et al*. 2021). Recently, the first anti-NGF mAbs (frunevetmab and bedinvetmab) have been approved for use in veterinary medicine for the alleviation of OA pain in dogs and cats in many countries. Published data indicate they are effective across a range of OA-pain severity in both species, and are appropriate as a first line treatment. In both species, single subcutaneous injections of the mAb provide at least 1 month of pain alleviation in patients with OA. No studies are currently available looking at other pain conditions. Anti-NGF mAbs do not appear to be associated with organ-related adverse effects, but mild skin reactions (*e.g*. alopecia) have been reported in cats. The full safety profile will only be known once these products have been used extensively in practice.

Notwithstanding the need for additional information on safety, as well as the need for larger efficacy studies, the development of anti-NGF monoclonal antibodies, which are species-specific and may provide several weeks of efficacious pain control following a single injection in dogs and cats addresses an unmet need in clinical practice.

2.18 Adjunctive musculoskeletal treatments

Regenerative medicine

Regenerative medicine is focused on strategies to grow, repair or replace injured or diseased cells, organs or tissues (Voga *et al*. 2020). Mesenchymal stem cells (MSC) are used in regenerative medicine. They are unspecialized adult cells with immunomodulatory and anti-inflammatory effects that have the ability to migrate to sites of tissue injury, known as "homing capacity." These cells can be isolated from various tissues such as bone marrow or adipose tissue sourced from the patient itself (autologous), or from a donor of the same species (allogeneic) or different species (xenogeneic) and can be administered by the iv, intra-articular or other routes. Thorough reviews on this topic are available elsewhere (Voga *et al*. 2020, Brondeel *et al*. 2021). In dogs with OA, MSC therapy is promising and current studies generally show decreased lameness, joint pain and range of motion (Harman *et al*. 2016, Brondeel *et al*. 2021). In cats with OA, MSC therapy resulted in complete remission or substantial clinical improvement in some cats with severe refractory gingivostomatitis (Arzi *et al*. 2016). Further evidence will elucidate the true role of MSC in chronic pain management in animals including the best therapeutic approach (*e.g*. intra-articular *versus* iv administration; auto- *versus* allo- *versus* xenotransplantation, etc.).

Therapies administered by intra-articular injections

Hyaluronic acid (HA) is a natural component of joint fluid and cartilage that can be injected into osteoarthritic joints or given orally (Chapter 2.12) and promotes lubrication. Platelet rich plasma (PRP) contains growth factors and proteins with anti-inflammatory properties. It involves the collection and processing of the patients' blood with subsequent injection into affected joints. Both HA and PRP improve joint pain and mobility in people. Evidence is still limited in veterinary medicine but seems to indicate positive effects on pain and function when intra-articular HA or PRP are used alone or in combination with MSC in dogs with OA (Nganvongpanit *et al*. 2013, Carapeba *et al*. 2016, Venator *et al*. 2020, Brondeel *et al*. 2021, Okamoto-Okubo *et al*. 2021).

Tin (^{117m}Sn) colloid is a conversion electron therapeutic veterinary device used for radiosynoviorthesis. The latter is the intra-articular injection of a radioisotope with the goal of reducing synovial inflammation. This product was recently licensed in the USA to treat canine elbow OA and may provide analgesia for up to 1 year. A licence to use radioactive medical therapies is required. Early studies show that the product appears safe and provides long-term analgesia in canine elbow OA (Lattimer *et al*. 2019, Aulakh *et al*. 2021, Donecker *et al*. 2021a,b).

Transient receptor potential vanilloid 1 (TRPV1) agonists are predominantly expressed in nociceptive sensory neurons and are promising targets for chronic pain management. Resiniferatoxin and capsaicin are potent TRPV1 agonists currently under investigation, but not yet commercially available, that show promising results in dogs with OA (Iadarola *et al*. 2018, Campbell *et al*. 2021).

Therapies administered by intramuscular or subcutaneous injections

Polysulfated glycosaminoglycan inhibits catabolic enzymes that are overexpressed in osteoarthritic joints and contribute to cartilage loss. It is labelled for im use in dogs but studies also report SC administration in dogs (Varcoe *et al*. 2021) and administration in cats (Adrian *et al*. 2018). The few available studies indicate efficacy in dogs with OA (de Haan *et al*. 1994, Fujiki *et al*. 2007).

Pentosan polysulfate is a semi-synthetic glycosaminoglycan that inhibits and modulates proinflammatory mediators. It is labelled for SC use in dogs and is anecdotally also used in cats. Evidence for clinical efficacy in dogs is limited (Budsberg *et al*. 2007).

SECTION 3

Examples of protocols and approaches to pain management in different conditions are provided in this section. Drug dosage regimen recommendations can be found across Tables 12, 13, 15, 16 and 17. Guidance on the anaesthetic management of dogs and cats can be found in review articles (Warne *et al.* 2018, Grubb *et al.* 2020) or at the following link:

https://www.fecava.org/policies-actions/fecava-basic-practices-in-anesthesia-and-analgesia/

3.1 Castration and ovariohysterectomy/ovariectomy: cats

Castration and ovariohysterectomy/ovariectomy in cats are associated with pain of varying severity and is influenced by the degree of surgical trauma. For this reason, surgery should be performed with careful tissue handling and adherence to good surgical principles. General anaesthesia and preventive/multi-modal analgesia techniques are strongly recommended. There are many options available for perioperative management (Tables 18 and 19). Postoperative treatment with analgesics may be required for up to 3 days after surgery especially after ovariohysterectomy/ovariectomy, or if laparotomy is required in males (*e.g.* a cryptorchid) to remove a testicle. The same NSAID should be used pre- and postoperatively.

In some cats, the im administration of the combination of an opioid, an alpha$_2$-adrenoceptor agonist and ketamine will provide sufficient analgesia and anaesthesia for the surgical procedure (*i.e.* work as premedication, induction and maintenance of anaesthesia). These mixtures are often referred to as "kitty magic" although there are many different versions. There should be a plan for extending the anaesthesia time in the event the cat becomes responsive or complications arise. Due to the short procedure time, many cats are not intubated, however equipment should also be available for endotracheal intubation. Venous access is recommended for all cases.

Analgesia may be supplemented after most surgical techniques by application of non-pharmacological therapies such as cold therapy, laser therapy, acupuncture and nursing care.

Table 17. Suggested doses for commonly used sedative and anaesthetic drugs in dogs and cats

Drug	Dogs	Cats	Comments
Acepromazine†	0.01 to 0.03 mg/kg iv	0.01 to 0.03 mg/kg im	
Ketamine‡	3 to 5 mg/kg iv	5 to 10 mg/kg im 3 to 5 mg/kg iv	Higher doses are selected for cats that are more difficult to handle
Propofol‡	3 to 5 mg/kg iv	3 to 10 mg/kg iv	Given to effect
Alfaxalone‡	1 to 2 mg/kg iv	3 to 5 mg/kg iv	Given to effect
Diazepam	0.25 mg/kg iv	0.25 mg/kg iv	Best given iv since im administration is painful
Midazolam	0.25 mg/kg iv	0.25 mg/kg iv	
Pentobarbital§	2 to 5 mg/kg iv	2 to 5 mg/kg iv	
Thiopental‡§	2 to 8 mg/kg iv	2 to 8 mg/kg iv	
Tiletamine/zolazepam	3 to 10 mg/kg iv or im	3 to 4 mg/kg iv or im	

†Higher doses of acepromazine can be used but will usually prolong effect without increasing magnitude of action
‡Doses are usually given to effect according to the patient needs, coexisting disease, health condition and use of other sedative and anaesthetic drugs
§Drug accumulation may be expected with prolonged and agitated anaesthetic recoveries

Table 18. Suggested protocols for castration in cats

		Protocol with controlled drugs	Protocol without controlled drugs	Protocol with limited availability of analgesic drugs
Preoperative		Opioid ± acepromazine or alpha$_2$-adrenoceptor agonist ± ketamine	NSAID + alpha$_2$-adrenoceptor agonist	Same as protocol without controlled drugs
Induction of anaesthesia	iv†	Choose one of the following: • Propofol • Ketamine + diazepam or midazolam • Alfaxalone	Choose one of the following: • Propofol • Alfaxalone	Any available injectable agent
	im	Alpha$_2$-adrenoceptor agonist + ketamine or tiletamine/zolazepam	Alpha$_2$-adrenoceptor agonist + tiletamine/zolazepam	
Maintenance of anaesthesia‡		Choose one of the following: • Inhalation anaesthesia • Ketamine • Propofol • Alfaxalone	Choose one of the following: • Inhalation anaesthesia • Propofol • Alfaxalone	Any available injectable or inhalant agent
Local anaesthetic techniques		Intratesticular block	Same as protocol with controlled drugs	Same as protocol with controlled drugs
Postoperative analgesia		NSAID	Same as protocol with controlled drugs	Same as protocol with controlled drugs

iv Intravenous, im Intramuscular, NSAID Non-steroidal anti-inflammatory drug
†Note that premedication reduces iv anaesthetic requirements; thus, induction doses should be titrated to effect
‡Injectable drugs are administered iv to effect (1/3 or 1/2 of initial dose)

Table 19. Suggested protocol for ovariohysterectomy/ovariectomy in cats

		Protocol with controlled drugs	Protocol without controlled drugs	Protocol with limited availability of analgesic drugs
Preoperative		Opioid ±acepromazine or alpha2-adrenoceptor agonist ±ketamine	NSAID + alpha2-adrenoceptor agonist	Same as protocol without controlled drugs
Induction of anaesthesia	iv†	Choose one of the following: • Propofol • Ketamine + diazepam or midazolam • Alfaxalone	Choose one of the following: • Propofol • Alfaxalone	Any available injectable agent
	im	Opioid + alpha2-adrenoceptor agonist + ketamine or tiletamine/zolazepam	Alpha2-adrenoceptor agonist + tiletamine/zolazepam	
Maintenance of anaesthesia†		Choose one of the following: • Inhalation anaesthesia • Ketamine • Propofol • Alfaxalone	Choose one of the following: • Inhalation anaesthesia • Propofol • Alfaxalone	Any available injectable or inhalant agent
Local anaesthetic techniques		Incisional ±intraperitoneal block	Same as protocol with controlled drugs	Same as protocol with controlled drugs
Postoperative analgesia		NSAID	Same as protocol with controlled drugs	Same as protocol with controlled drugs

iv intravenous, im intramuscular, NSAID non-steroidal anti-inflammatory drug
†Note that premedication reduces iv anaesthetic requirements; thus, induction doses should be titrated to effect
‡Injectable drugs are administered iv to effect (1/3 or 1/2 of initial dose)

3.2 Castration and ovariohysterectomy/ovariectomy: dogs

Castration and ovariohysterectomy/ovariectomy in dogs are associated with pain of varying severity and is influenced by the degree of surgical trauma. For this reason, surgery should be performed with careful tissue handling and adherence to good surgical principles. General anaesthesia and preventive/multi-modal analgesia techniques are strongly recommended. There are many options available for perioperative management (Tables 20 and 21). Postoperative treatment with analgesics may be required for up to 3 days after surgery especially after ovariohysterectomy/ovariectomy, or if laparotomy is required in males (*e.g.* a cryptorchid) to remove a testicle. The same NSAID should be used pre- and postoperatively.

In some dogs, the im administration of the combination of an opioid, an alpha$_2$-adrenoceptor agonist and ketamine will provide sufficient analgesia and anaesthesia for the surgical procedure (*i.e.* work as premedication, induction and maintenance of anaesthesia). These mixtures are often referred to as "doggy magic" although there are many different versions. There should be a plan for extending the anaesthesia time in the event the dog becomes responsive or complications arise. Due to the short procedure time, many dogs are not intubated, however equipment should also be available for endotracheal intubation. Venous access is recommended for all cases.

Analgesia may be supplemented after most surgical techniques by application of non-pharmacological therapies such as cold therapy, laser therapy, acupuncture and nursing care.

3.3 Orthopaedic surgery

Orthopaedic surgery has the potential to result in moderate to severe postoperative pain. Surgery should be performed under general anaesthesia combined with aggressive perioperative analgesia (Table 22, Boxes 6 and 7). Preventive and multi-modal analgesic techniques should be employed for all procedures. The balance between pre-, intra- and postoperative analgesia will depend on the severity of the preoperative condition and the location and magnitude of surgical trauma, and patient status. Frequent pain assessment should be performed and when pain is not successfully controlled, alternative or additional analgesics or analgesic techniques should be employed to improve patient comfort. NSAIDs provide excellent perioperative analgesia and should be used, unless contraindicated (approved drugs should be preferred). The same NSAID should be used pre- and postoperatively; switching between NSAIDs in the immediate perioperative period should be avoided. Nerve transection (*e.g.* during limb amputation) or manipulation, may lead to severe pain and development of neuropathic pain and persistent postoperative pain. Gabapentin may be used perioperatively due to a potential benefit in preventing persistent postoperative pain.

The choice of opioid, alpha$_2$-adrenoceptor agonist or NSAID used will vary based on availability, personal preferences and contraindications. Locoregional anaesthetic techniques (*e.g.* intra-articular, incisional and locoregional nerve blocks, wound infusion catheters) (Fig 31) or combinations thereof before and/or after surgery are recommended in all cases. Such techniques should be considered mandatory when opioids and other controlled analgesic drugs are not available. Longer acting local anaesthetic agents such as bupivacaine or ropivacaine are recommended due to their prolonged duration of action. Where available, long-acting formulations of local anaesthetics (*e.g.* bupivacaine liposomal injectable suspension which may provide analgesia for up to 72 hours) are recommended for incisional anaesthesia for cranial cruciate ligament surgery in dogs. The provision of effective analgesia after the patient is discharged from the hospital is critical.

Table 20. Suggested protocol for castration in dogs

		Protocol with controlled drugs	Protocol without controlled drugs	Protocol with limited availability of analgesic drugs
Preoperative		Opioid ±acepromazine or benzodiazepines (midazolam or diazepam)±alpha2-adrenoceptor agonist	NSAID + alpha2-adrenoceptor agonist	Same as protocol without controlled drugs
Induction of anaesthesia	iv†	Choose one of the following: • Propofol • Ketamine + diazepam or midazolam • Alfaxalone	Choose one of the following: • Propofol • Alfaxalone	Any available injectable agent
	im	Opioid + alpha2-adrenoceptor agonist + ketamine or tiletamine/zolazepam	Alpha2-adrenoceptor agonist + tiletamine/zolazepam	
Maintenance of anaesthesia†		Choose one of the following: • Inhalation anaesthesia • Ketamine • Propofol • Alfaxalone	Choose one of the following: • Inhalation anaesthesia or • Propofol • Alfaxalone	Any available injectable or inhalant agent
Local anaesthetic techniques		Intratesticular ±incisional block	Same as protocol with controlled drugs	Same as protocol with controlled drugs
Postoperative analgesia		NSAID	Same as protocol with controlled drugs	Same as protocol with controlled drugs

iv Intravenous, im Intramuscular, NSAID Non-steroidal anti-inflammatory drug
†Note that premedication reduces iv anaesthetic requirements; thus, induction doses should be titrated to effect
‡Injectable drugs are administered iv to effect (1/ 3 or 1/2 of initial dose)

Table 21. Suggested protocol for ovariohysterectomy/ovariectomy in dogs

		Protocol with controlled drugs	Protocol without controlled drugs	Protocol with limited availability of analgesic drugs
Preoperative		Opioid ±acepromazine ±alpha2-adrenoceptor agonist or benzodiazepines (midazolam or diazepam)	NSAID + metamizole (dipyrone)+alpha2-adrenoceptor agonist	Same as protocol without controlled drugs
Induction of anaesthesia	iv†	Choose one of the following: • Propofol • Ketamine + diazepam or midazolam • Alfaxalone	Choose one of the following: • Propofol • Alfaxalone	Any available injectable agent
	im	Opioid + alpha2-adrenoceptor agonist + ketamine or tiletamine/zolazepam	Alpha2-adrenoceptor agonist + tiletamine/zolazepam	
Maintenance of anaesthesia†		Choose one of the following: • Inhalation anaesthesia or • Ketamine • Propofol • Alfaxalone	Choose one of the following: • Inhalation anaesthesia or • Propofol • Alfaxalone	Any available injectable or inhalant agent
Local anaesthetic techniques		Incisional ±intraperitoneal block	Same as protocol with controlled drugs	Same as protocol with controlled drugs
Postoperative analgesia		NSAID	NSAID ±metamizole (dipyrone)	Same as protocol without controlled drugs

iv Intravenous, im Intramuscular, NSAID Non-steroidal anti-inflammatory drug
†Note that premedication reduces iv anaesthetic requirements; thus, induction doses should be titrated to effect
‡Injectable drugs are administered iv to effect (1/3 or 1/2 of initial dose)

3.4 Soft tissue surgery

Soft tissue surgery may cause mild, moderate or severe postoperative pain. Preventive and multi-modal analgesic techniques should be used and local anaesthetic techniques included whenever possible. The balance between pre-, intra- and postoperative analgesia will depend on the severity of preoperative pain and the location and magnitude of surgical trauma (Tables 23 and 24, Box 8). Where postoperative pain is not successfully controlled with NSAIDs, alternative or additional analgesics or analgesic techniques should be employed such as the regular administration of opioids. Major soft tissue surgery may lead to chronic pain which may have a neuropathic component. The choice of opioid, alpha$_2$-adrenoceptor agonist or NSAID will vary based on availability and contraindications.

Loco-regional anaesthetic techniques such as incisional and specific nerve blocks, wound infusion catheters (Fig 31) or combinations thereof before and/or after surgery are highly recommended in all cases. Such techniques become mandatory when opioids and other controlled analgesic drugs are not available.

Table 22. Suggested protocol for orthopaedic surgery

	Protocol with controlled drugs	Protocol without controlled drugs§	Protocol with limited availability of analgesic drugs§
Preoperative	Opioid + NSAID ±alpha2-adrenoceptor agonist ±ketamine (cats only)	NSAID ±alpha2-adrenoceptor agonist ±metamizole (dipyrone) or paracetamol (acetaminophen) – *not in cats* ±gabapentin¶	Same as protocol without controlled drugs
Induction of anaesthesia	See Tables 18 to 21	See Tables 18 to 21	See Tables 18 to 21
Maintenance of anaesthesia	See Tables 18 to 21	See Tables 18 to 21	See Tables 18 to 21
Local anaesthetic techniques†	Choose one of the following: • Locoregional blocks (*e.g.* RUMM, sciatic-femoral nerve, incisional) • Neuraxial nerve blocks (*e.g.* epidural)	Same as protocol with controlled drugs	Same as protocol with controlled drugs
Intraoperative analgesics	Boluses and/or infusions of the following alone or in combination:† • Opioids • Alpha2-adrenoceptor agonists • Ketamine • Lidocaine (use cautiously in cats; see Chapter 2.5)	Boluses and/or infusions of the following alone or in combination: †¶ • Alpha2-adrenoceptor agonists • Lidocaine (use cautiously in cats; see Chapter 2.5) Acupuncture may also be used	Same as protocol without controlled drugs
Immediate postoperative (24 hours)	Drug options: • NSAID (unless if already administered preoperatively) • Continued intraoperative infusions or boluses with gradual reduction in doses • Adjuvant analgesics • Locoregional anaesthetic blocks or wound infusion catheters Non-drug options: • Cold therapy • Appropriate bandaging • Careful positioning, comfortable bedding, elimination support • Gentle massage of compensatory regions (back, non-operated limbs) • Acupuncture • Tender, Loving, Care	Same as protocol with controlled drugs	Same as protocol with controlled drugs
Later postoperative days	Drug options: • Opioid with titration to effect and gradual discontinuation • Local anaesthetics *via* wound catheter may be employed until hospital discharge • Continue NSAIDs for days to weeks unless contraindicated • Metamizole (dipyrone) • Paracetamol (acetaminophen) – *not in cats* • Adjuvant analgesics (*e.g.* lidocaine patches, gabapentin, amantadine) Non-drug options: • First 3 days: cold therapy for a minimum of 3 days • After 3 days: alternate cold and heat therapy before stretching and gentle weight-bearing (with cold therapy following these therapies) • Physical rehabilitation • Acupuncture	Drug options:¶ • Local anaesthetics *via* wound catheter may be employed until hospital discharge • Continue NSAIDs for days to weeks unless contraindicated • Metamizole (dipyrone) • Paracetamol (acetaminophen) – *not in cats* • Adjuvant analgesics (*e.g.* lidocaine patches, gabapentin, amantadine) Non-drug options: • First 3 days: cold therapy for a minimum of 3 days • After 3 days: alternate cold and heat therapy before stretching and gentle weight-bearing (with cold therapy following these therapies) • Physical rehabilitation • Acupuncture	Same as protocol without controlled drugs

iv Intravenous, NSAID Non-steroidal anti-inflammatory drug, RUMM Radial, ulnar, musculocutaneous and median nerve block
†Continuous intra-articular injections of local anaesthetics are contraindicated as this can result in cartilage damage; the risk of ascending contamination leading to infection is high
†These drugs may not be required if an effective local anaesthetic block has been performed but may provide additional analgesia and further reduction of inhalant anaesthetic requirements
§The use of local anaesthetic techniques, NSAIDs, iv boluses or infusions and non-drug therapies become critical when opioids are not available
¶Injectable tramadol (cats only) may be administered in place of the opioid

3.5 Loco-regional techniques

This chapter describes a few simple techniques. Readers are referred to review articles containing detailed descriptions of a variety of loco-regional anaesthetic techniques (Grubb & Lobprise 2020a,b) as well as the WSAVA Global Dental Guidelines for detailed descriptions of dental nerve blocks (Niemiec *et al.* 2020). Additionally, a number of instructional videos are available at the WSAVA

Box 6 Example of a protocol for dogs undergoing femoral fracture repair

Preoperative: NSAID (24-hour dose; ideally one approved for dogs), methadone 0.3 mg/kg im, acepromazine 0.02 to 0.03 mg/kg im
Induction of anaesthesia: propofol to effect iv.

Maintenance of anaesthesia: inhalation anaesthesia with lumbosacral epidural administration of bupivacaine 0.5% with morphine (preservative free) 0.1 to 0.2 mg/kg (1 mL/4 kg up to 6 mL before surgery).

Immediate postoperative (for 24 hours): methadone 0.3 mg/kg im (every 4 to 6 hours depending on pain scoring and need for rescue analgesia), icing, range of motion and other non-drug techniques.

Later postoperative days: NSAID (same drug as preoperative, starting 24 hours after preoperative dose) every 24 hours and gabapentin 5 to 10 mg/kg PO every 8 to 12 hours for up to 14 days after surgery. Continue with non-drug techniques and re-evaluate the need for analgesics at follow-up appointments.

Box 7 Example of a protocol for cats undergoing femoral fracture repair

Preoperative: NSAID (24-hour dose; ideally one approved for cats), methadone 0.3 mg/kg im, medetomidine 0.01 mg/kg im.
Induction of anaesthesia: propofol to effect iv.

Maintenance of anaesthesia: inhalation anaesthesia with lumbosacral epidural administration of 0.5% bupivacaine with morphine (preservative free) 0.1 to 0.2 mg/kg (1 mL/4 kg up to 6 mL before surgery).

Immediate postoperative (for 24 hours): methadone 0.2 to 0.3 mg/kg iv (every 4 to 6 hours depending on pain scoring and need for rescue analgesia), icing, range of motion and other non-drug therapies.

Later postoperative days: Buprenorphine 0.02 mg/kg OTM (or iv if catheter available), every 6 to 8 hours for up to 3 days after surgery (where available, the high concentration formulation of buprenorphine (1.8 mg/mL) or the buprenorphine transdermal formulation can be used instead; Table 12). NSAID (same drug as preoperative, starting 24 hours after preoperative dose), every 24 hours after surgery. Please see labels for approved-NSAIDs for use in cats. Continue with non-drug techniques and re-evaluate the need for analgesics at follow-up appointments.

FIG 31. Wound infusion catheters. (A) Example of a sterile catheter that can be placed in dogs after (B and C) thoracic limb amputation and (D) pelvic limb amputation for infusion of local anaesthetics. Figures courtesy of Sheilah Robertson

Table 23. Suggested protocol for minor soft tissue surgery

	Protocol with controlled drugs	Protocol without controlled drugs†	Protocol with limited availability of analgesic drugs†
Pre- and intraoperative	Opioid + NSAID ±alpha$_2$-adrenoceptor agonist ±ketamine	NSAID ±alpha$_2$-adrenoceptor agonist + metamizole (dipyrone) or paracetamol (acetaminophen) – *not in cats* ±gabapentin†	Same as protocol without controlled drugs
Induction of anaesthesia	See Tables 18 to 21	See Tables 18 to 21	See Tables 18 to 21
Maintenance of anaesthesia	See Tables 18 to 21	See Tables 18 to 21	See Tables 18 to 21
Local anaesthetic techniques	Choose one of the following: • Locoregional blocks (*e.g.* incisional) • Neuraxial nerve blocks (*e.g.* epidural)	Same as protocol with controlled drugs	Same as protocol with controlled drugs
Immediate postoperative (24 hours)	Drug options: • NSAID (unless if already administered preoperatively) • Opioids Non-drug options: • Cold therapy • Appropriate bandaging • Careful positioning, comfortable bedding, elimination support • Acupuncture • Tender, loving, care	Drug options:† • NSAID (unless if already administered preoperatively) + metamizole (dipyrone) or paracetamol (acetaminophen) – *not in cats* Non-drug options: • Cold therapy • Appropriate bandaging • Careful positioning, comfortable bedding, elimination support • Acupuncture • Tender, loving, care	Same as protocol without controlled drugs
Later postoperative days	Drug options: • Continue NSAIDs for days to weeks unless contraindicated • Metamizole (dipyrone) • Paracetamol (acetaminophen) – *not in cats* Non-drug options: • First 3 days: cold therapy for a minimum of 3 days • Acupuncture	Same as protocol with controlled drugs	Same as protocol with controlled drugs

iv Intravenous, NSAID Non-steroidal anti-inflammatory drug
†The use of local anaesthetic techniques, NSAIDs, iv boluses or infusions and non-drug therapies become critical when opioids are not available
†Injectable tramadol (cats only) may be administered in place of the opioid

GPC website (https://wsava.org/Committees/global-pain-council/). Different local anaesthetic block techniques require various levels of training.

For all loco-regional anaesthetic techniques, with the exception of dental nerve blocks, it is imperative to maintain sterile injection techniques (clipping and sterile preparation of the injection site) (Box 9). The techniques should be performed on patients that are anaesthetized or deeply sedated, the latter requiring inclusion of an analgesic because these procedures are painful to perform. After needle placement and before injection of local anaesthetic, the syringe should be gently aspirated. If blood can be withdrawn, injections are not made and the needle is repositioned. While many landmarks and nerves themselves can be palpated transcutaneously, use of a nerve stimulator or ultrasound-guided techniques can reduce the risk of incomplete blocks and damage to nervous, vascular and other structures.

Incisional anaesthesia

Any wound (trauma related; surgical) or tissue can be infiltrated with local anaesthetics. For example, in a celiotomy before ovariohysterectomy, all layers (muscle, subcutaneous, subcutis) can be infiltrated along the full extent of both sides of the wound (incisional anaesthesia). Bupivacaine (2 mg/kg) or lidocaine (5 mg/kg) can be used in cats and dogs. The injectate volume can be increased using sterile solution. This allows for sufficient volume to inject the local anaesthetic solution as needed (but without increasing the dose). The WSAVA-GPC has published a short review on the subject (Steagall *et al.* 2020b).

The infiltration is performed using a moving needle technique whereby the needle is introduced into the tissues, and, following aspiration to ensure the needle is not in a blood vessel, the needle is gradually withdrawn while injecting local anaesthetic (https://www.youtube.com/watch?v=43Km46WJ2zI) .

Intratesticular

The intratesticular block is performed in dogs and cats under general anaesthesia and can provide postoperative analgesia, reduce inhalant requirements, and blunt sympathetic responses to surgery. Lidocaine or bupivacaine (0.2 to 0.3 mL/side in cats; 0.5 to 1 mL/side

Table 24. Suggested protocol for major soft tissue surgery

	Protocol with controlled drugs	Protocol without controlled drugs†	Protocol with limited availability of analgesic drugs†
Preoperative	Opioid + NSAID ±alpha$_2$-adrenoceptor agonist ±ketamine	NSAID ±alpha$_2$-adrenoceptor agonist + metamizole (dipyrone) or paracetamol (acetaminophen) – *not in cats* ±gabapentin†	Same as protocol without controlled drugs
Induction of anaesthesia	See Tables 18 to 21	See Tables 18 to 21	See Tables 18 to 21
Maintenance of anaesthesia	See Tables 18 to 21	See Tables 18 to 21	See Tables 18 to 21
Local anaesthetic techniques	Choose one of the following: • Locoregional blocks (*e.g.* intercostal) • Neuraxial nerve blocks (*e.g.* epidural)	Same as protocol with controlled drugs	Same as protocol with controlled drugs
Intraoperative	Boluses and/or infusions of the following alone or in combination:§ • Opioids • Alpha2-adrenoceptor agonists • Ketamine • Lidocaine (use cautiously in cats; see Chapter 2.5)	Boluses and/or infusions of the following alone or in combination:†§ • Alpha2-adrenoceptor agonists • Lidocaine (use cautiously in cats; see Chapter 2.5)	Same as protocol without controlled drugs
Immediate postoperative (24 hours)	Drug options: • NSAID (unless if already administered preoperatively) • Continued intraoperative infusions or boluses with gradual reduction in doses • Adjuvant analgesics (*e.g.* lidocaine patches, gabapentin, amantadine) • Locoregional anaesthetic blocks or wound infusion catheters Non-drug options: • Cold therapy • Appropriate bandaging • Careful positioning, comfortable bedding, elimination support • Acupuncture • Tender, Loving, Care	Drug options:† • NSAID (unless if already administered preoperatively) + metamizole (dipyrone) or paracetamol (acetaminophen) – *not in cats* • Continued intraoperative infusions or boluses with gradual reduction in doses • Adjuvant analgesics (*e.g.* lidocaine patches, gabapentin, amantadine) • Locoregional anaesthetic blocks or wound infusion catheters Non-drug options: • Cold therapy • Appropriate bandaging • Careful positioning, comfortable bedding, elimination support • Acupuncture • Tender, Loving, Care	Same as protocol without controlled drugs
Later postoperative days	Drug options: • Opioid with titration to effect and gradual discontinuation • Local anaesthetics *via* wound catheter may be employed until hospital discharge • Continue NSAIDs for days to weeks unless contraindicated • Metamizole (dipyrone) • Paracetamol (acetaminophen) – *not in cats* • Adjuvant analgesics (*e.g.* lidocaine patches, gabapentin, amantadine) Non-drug options: • First 3 days: cold therapy for a minimum of 3 days • After 3 days: alternate cold and heat therapy • Physical rehabilitation • Acupuncture	Drug options:† • Local anaesthetics *via* wound catheter may be employed until hospital discharge • Continue NSAIDs for days to weeks unless contraindicated • Metamizole (dipyrone) • Paracetamol (acetaminophen) – *not in cats* • Adjuvant analgesics (*e.g.* lidocaine patches, gabapentin, amantadine) Non-drug options: • First 3 days: cold therapy for a minimum of 3 days • After 3 days: alternate cold and heat therapy • Physical rehabilitation • Acupuncture	Same as protocol without controlled drugs

iv intravenous, NSAID non-steroidal anti-inflammatory drug
†The use of local anaesthetic techniques, NSAIDs, iv boluses or infusions and non-drug therapies become critical when opioids are not available
‡Injectable tramadol (cats only) may be administered in place of the opioid
§These drugs may not be required if an effective local anaesthetic block has been performed but may provide additional analgesia and further reduction of inhalant anaesthetic requirements

in dogs) is injected into the testis parenchyma which will be absorbed by lymphatic vessels and desensitise the spermatic cord (Fig 32). An incisional block can be performed to desensitise the skin (https://www.youtube.com/watch?v=VHfqoUPse-c).

Ring block

A "ring block" can be performed at the distal areas of the limb or tail using lidocaine or bupivacaine, for example. Local anaesthetic solutions with adrenaline (epinephrine) should never be used for these blocks. The technique involves the subcutaneous infiltration around the limb to desensitise superficial sensory nerves and branches distal to where the block was performed (Figs 33 and 34).

Box 8 Example of a protocol for a cat undergoing a surgical removal of injection site sarcoma (major soft tissue surgery)

Preoperative: NSAID (24 hours dose; one approved in cats), methadone 0.3 mg/kg im, ketamine 5 mg/kg and midazolam 0.25 mg/kg im.
Induction of anaesthesia: Propofol to effect iv.
Maintenance of anaesthesia: Inhalation anaesthesia with constant rate infusions of fentanyl 5 to 10 µg/kg/hour following a loading dose of 5 µg/kg iv, and ketamine at 2 to 10 µg/kg/minute following a loading dose of 0.5 mg/kg iv. Infiltration anaesthesia with local anaesthetics, consider placement of a wound infusion catheter.
Immediate postoperative (24 hours): Constant rate infusions of fentanyl 1 to 3 µg/kg/hour and ketamine 2 to 10 µg/kg/minute. Cold therapy ±acupuncture. Wound therapy catheter with administration of bupivacaine 0.5% (up to 2 mg/kg every 8 hours).
Later postoperative days: Buprenorphine 0.02 mg/kg OTM (or iv if catheter available), every 6 to 8 hours for up to 3 days after surgery (where available, the high concentration formulation of buprenorphine (1.8 mg/mL) or the buprenorphine transdermal formulation can be used instead; Table 12). NSAID (same drug as preoperative, starting 24 hours after preoperative dose), every 24 hours after surgery. Please see labels for approved-NSAIDs for use in cats. Continue with non-drug techniques and re-evaluate the need for analgesics at follow-up appointments.

Box 9 Key steps for the safe and effective application of local anaesthetic blocks

- It is imperative that sterile techniques are used. Except for dental blocks the area of injection should be clipped and prepped.
- Calculate the safe maximum dose and do not exceed this dose. If more volume is needed for wider distribution of the drug, then dilute the local anaesthetic with sodium chloride.
- Use appropriately sized needles and syringes. This will minimise tissue trauma during injection, while using a suitably sized syringe will allow accurate dosing.
- Avoid inadvertent intravascular injection by drawing back on the syringe and checking that no blood is aspirated before injection.

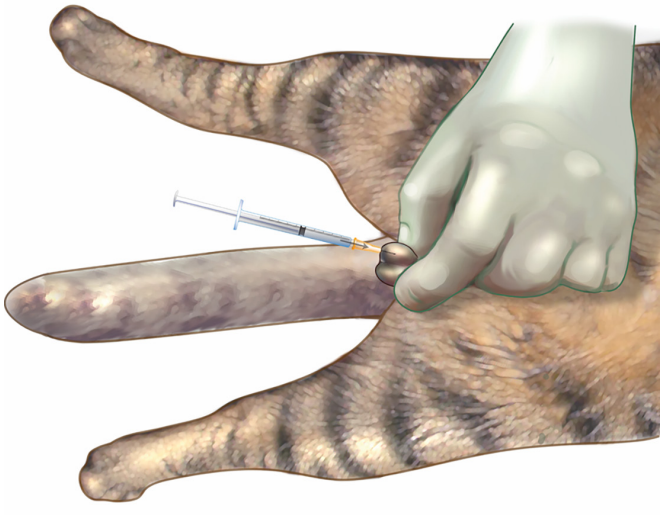


FIG 32. Intratesticular block. The needle is inserted in the centre of the testis and lidocaine is injected. Approximately, 0.1 to 0.25 mL of local anaesthetic is injected per testicle depending on the size of the cat (*i.e.* kittens *versus* adults). The testis will become firm after injection. Illustration from Alice MacGregor Harvey

Intraperitoneal block

Intraperitoneal analgesia is a useful adjunct to other analgesics following abdominal surgery and for pain associated with abdominal conditions, particularly when opioids are not available (Steagall *et al.* 2020b). The technique should be performed under general anaesthesia to avoid laceration or puncture of abdominal organs and peritonitis using bupivacaine (2 mg/kg in cats or dogs). The intraperitoneal analgesia technique provides early postoperative analgesia, but does not blunt sympathetic responses or anaesthetises viscera during surgery.

The drug can be diluted in equal parts with saline to increase the volume of intraperitoneal injection. It can be instilled directly into the intraperitoneal space of dogs or cats before ovariohysterectomy or before abdominal closure following abdominal exploratory surgery. Aseptic technique is required (https://www.youtube.com/watch?v=eLa1UxWboh0).

3.6 Ophthalmic procedures

Procedures of the eye, eyelid and surrounding tissues can be associated with mild to severe pain. Unfortunately, little is known about ocular pain in small animals. Studies are required about pain-induced behaviours and analgesic requirements in these patients with medical or surgical ophthalmic pain.

The conjunctiva and the cornea can be desensitised by topical application of local anaesthetic drops (proxymetacaine, tetracaine, proparacaine). The number of applications should be limited since repetitive application particularly with tetracaine may cause epithelial or stromal keratitis (Giuliano 2008). Topical local anaesthetics have a duration of effect of approximately 15 minutes and can be useful for ophthalmic examinations or quick removal of foreign bodies. Application of artificial tears is essential.

Retro- or peribulbar anaesthesia can be performed to produce local anaesthesia of the eye (nerves opticus, oculomotorius, trochlear, ophthalmicus and maxillaris, and nerve abducens) in combination with opioids and NSAIDs (Shilo-Benjamini 2019, Grubb & Lobprise 2020b). Several techniques are described in detail elsewhere (Shilo-Benjamini 2019). An inferior-temporal retrobulbar

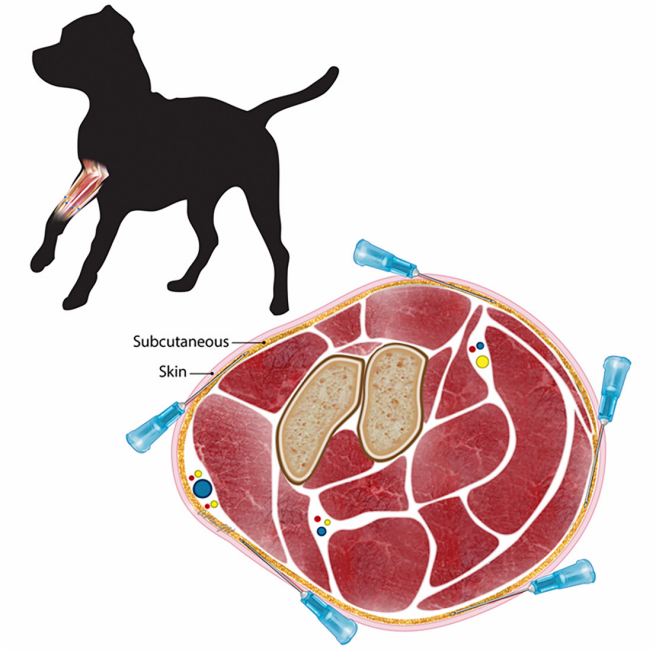


FIG 33. Illustration of a ring block on the thoracic limb of a dog. The subcutaneous tissues around the limb are infiltrated with a local anaesthetic drug. The needle is inserted parallel to the skin into the subcutaneous tissues. After negative blood aspiration, the local anaesthetic is injected at the same time as the needle is slowly withdrawn. This is procedure is repeated until the local anaesthetic has been injected around the complete circumference of the limb. The technique is similar to performing an incisional line block. Illustration from Alice MacGregor Harvey

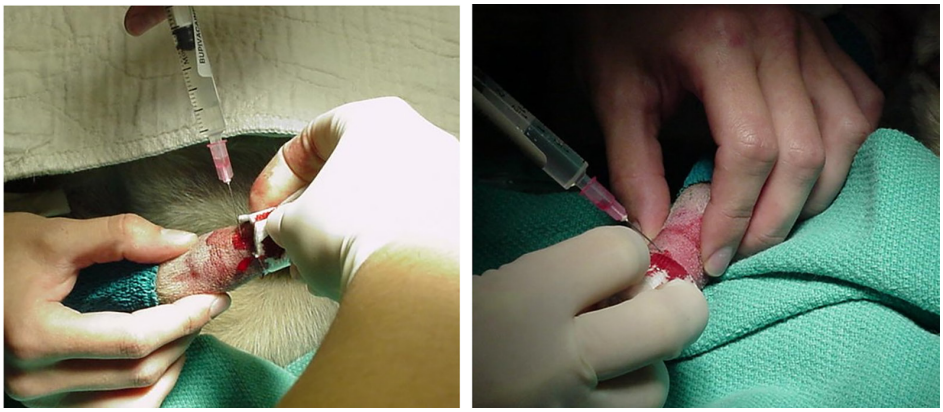


FIG 34. Example of a ring block being performed for tail amputation in a dog. Figures courtesy of Sheilah Robertson

block with bupivacaine 0.5% (at 2 mL for dogs weighing up to 15 kg and 3 mL for dogs >15 kg; or approximately 1 mL/10 kg) has shown to provide early postoperative analgesia after enucleation in dogs (Myrna *et al.* 2010). In a retrospective study, dogs undergoing enucleation had a much greater risk for postoperative recovery complications when a block was not performed. The risk of haemorrhage during surgery did not seem to change whether a retrobulbar block was performed or not (Bartholomew *et al.* 2020). Therefore, the technique does not increase the risk of complications in dogs undergoing enucleation.

Lidocaine (2 mg/kg bolus followed by CRI at 25 to 50 µg/kg/minute) may provide intraoperative analgesia similar to that provided by morphine in dogs undergoing ocular surgery. However, caution should be used when combining CRI lidocaine with a local anaesthetic block to avoid toxicity. Lidocaine infusions should be used cautiously in cats due to the risk of haemodynamic compromise (see Chapter 2.5).

The use of systemic NSAIDs (starting 24 hours before surgery) in ophthalmologic procedures is indicated, as they produce analgesia and decrease the risk of uveitis and aqueous humour-prostaglandin production which leads to posterior chamber flare.

Intra- and postoperative administration of opioids and/or alpha$_2$-adrenoceptor agonists may improve the analgesic effects of local anaesthetics and NSAIDs. Morphine produces miosis in dogs and mydriasis in cats. Opioids (*e.g.* methadone and buprenorphine), that do not cause vomiting and associated increases in intraocular pressure (IOP), are preferred.

The use of ketamine (0.5 to 1 mg/kg) has been associated with increased intraocular pressure due to increases in extraocular muscle tone. While there are clear species differences, and conflicting results, it should be used with caution in patients where increased IOP may result in expulsion of ocular contents (*e.g.* corneal trauma or glaucoma) or any other manoeuvre that could potentially increase IOP (*e.g.* neck leashes). If ketamine is used, other drugs (*e.g.* benzodiazepines, alpha$_2$-adrenoceptor agonists) may be administered concomitantly to mitigate potential ketamine-induced increases in IOP. It is unlikely that subanaesthetic doses of ketamine (2 to 10 µg/kg/minute) used for analgesia produce changes in IOP.

Cool packs can be used to reduce swelling after surgery. For postoperative analgesia, NSAIDs can be given (systemic and/or topical). Gabapentin (dogs and cats) and paracetamol (acetaminophen) (dogs only) may be considered for postoperative analgesia in the home environment. However, there is little evidence to support these treatments. Tramadol did not provide analgesia in dogs after enucleation and should not be used in these individuals (Delgado *et al.* 2014). Patients should receive artificial tears for 1 to 3 days postoperatively as general anaesthesia and opioids decrease tear production.

3.7 Dental protocols

Oral disease often involves pain and inflammation. An analgesic plan should be in place during the perioperative period and for several days after hospital discharge (Table 25). See tables in Chapters 2.2, 2.3, 2.4 and 2.5 for specific drug doses for each species. The choice of perioperative opioid (*e.g.* hydromorphone, methadone, morphine, butorphanol or buprenorphine) will be based on the severity of pain. When extractions are required, local anaesthetic techniques (see Chapter 2.5 and the WSAVA Global Dental Guidelines) including the infraorbital, inferior alveolar, mandibular, maxillary, palatine, and mental nerve blocks should be used depending on the affected area(s).

3.8 Emergency and critical care

Injured or ill animals require analgesia for painful conditions as well as diagnostic and emergency procedures. Due to their safety, opioids are the mainstay of immediate analgesia in the intensive care unit (ICU), and most also provide some degree of sedation, which may facilitate restraint for procedures and diagnostics (Chapter 2.2). Intravenous access should be achieved as soon as possible so that volume deficits can be corrected, and additional analgesics and sedatives can be titrated to effect (Dyson 2008, Hansen 2008, Tainter 2012).

In general, short-acting opioids are preferred, and titrated to an effective dose by starting with 10 to 20% of the recommended dose, and incrementally increasing until establishing a positive response (*i.e.* pain relief) while avoiding adverse effects. A CRI can be started afterwards and adjusted as the patient is stabilised and frequently assessed.

NMDA antagonists such as ketamine may prevent or treat central sensitisation particularly in cases of invasive and severe pain involving a neuropathic component. Ketamine infusions (5 to 10 µg/kg/minute following a bolus of 0.2 to 0.3 mg/kg iv) can be started concurrently or after opioid therapy. The drug must be administered as an infusion as boluses are short-acting and more likely to induce behavioural changes. In dogs and cats, lidocaine may also be given iv (loading dose and infusion), but lidocaine infusions should be used cautiously in cats due to the risk of haemodynamic compromise (see Chapter 2.5). The CRI rates should be adjusted based upon pain assessment, patient tolerance, and response; for example, rates can be increased for break-through pain, and decreased if the patient becomes heavily sedated and difficult to arouse.

Non-steroidal anti-inflammatory medications can be valuable in emergency and critical care situations, but should be withheld until volume, cardiovascular and renal status are stabilised, and with diseases that do not involve the gastro-intestinal system. When not contra-indicated, the anti-inflammatory effects of NSAIDs can be valuable for decreasing secondary inflammatory cascades (Monteiro-Steagall *et al.* 2013). Likewise, low-dose alpha$_2$-adrenoceptor agonists (dexmedetomidine, medetomidine) can be part of multi-modal analgesia and provide sedation and muscle relaxation (Chapter 2.4).

Managing stress, fear and anxiety are also an important consideration in critically ill, hospitalised cases and can be addressed with medications (*e.g.* trazodone, acepromazine or gabapentin), nursing care and low-stress handling techniques (Lefman & Prittie 2019).

Table 25. Suggested protocol for dental surgical procedures (*e.g.* extractions)

	Protocol with controlled drugs	Protocol without controlled drugs†	Protocol with limited availability of analgesic drugs†
Preoperative	Opioid ±acepromazine or alpha2-adrenoceptor agonist or benzodiazepines (midazolam or diazepam) ±NSAID	Acepromazine or alpha2-adrenoceptor agonist or benzodiazepines (midazolam or diazepam) ±NSAID‡	Same as protocol without controlled drugs or xylazine
Induction of anaesthesia	See Tables 18 to 21	Same as protocol with controlled drugs	Same as protocol with controlled drugs
Maintenance of anaesthesia	Inhalation anaesthesia with isoflurane or sevoflurane	Same as protocol with controlled drugs	iv to effect: pentobarbital, thiopental, propofol or alfaxalone iv or im: tiletamine/zolazepam
Local anaesthetic techniques	Dental blocks as appropriate (Chapter 2.5)	Same as protocol with controlled drugs	Same as protocol with controlled drugs
Immediate postoperative (24 hours) and later postoperative days	Drug options: • NSAID (unless contraindicated and 24 hours apart if preoperative dose is administered) and continued for several days • Opioids Non-drug options: • Soft food • Tender, Loving, Care	Drug options:† • NSAID (unless contraindicated and 24 hours apart if preoperative dose is administered) and continued for several days • Metamizole (dipyrone) • Paracetamol (acetaminophen) – *not in cats* Non-drug options: • Soft food Tender, Loving, Care	Same as protocol without controlled drugs

iv Intravenous, NSAID Non-steroidal anti-inflammatory drug, RUMM Radial, ulnar, musculocutaneous and median nerve block
†The use of local anaesthetic techniques, NSAIDs, iv boluses or infusions and non-drug therapies become critical when opioids are not available
‡Injectable tramadol (cats only) may be administered in place of the opioid

Resources

A CRI calculator is available at the International Veterinary Academy of Pain Management website: https://ivapm.org/professionals/cri-calculator/

3.9 Medical pain

The term "medical pain" encompasses conditions not primarily associated with surgery or trauma. Abdominal, pelvic and thoracic visceral pain occurs in conditions associated with distension and/or inflammation of hollow organs, ischaemia, pulmonary thrombosis, acute enlargement of solid organs resulting in stretching of the capsule and inflammation of any organ (*e.g.* pancreatitis, acute kidney injury, pneumonia/pleuritis). Visceral pain tends to be diffuse in nature and difficult to localise. The goal of therapy is to treat the underlying medical problem, but analgesics are often required before a definitive diagnosis and during treatment (Table 26).

Adjunctive therapies can be used with all levels of pain where indicated:

- Antiemetic and anti-nausea drugs are indicated where vomiting and nausea are present.
- Acupuncture can be useful for pain, gastrointestinal and urinary cases in particular. Acupuncture may also be used if vomiting is present (Wright 2019).
- Medical massage, cold therapy and warm compress are recommended where indicated.
- Environmental enhancement to reduce stress and anxiety. In cats, pheromone therapy may be helpful (Kronen *et al.* 2006)

3.10 Paediatric pain

Studies in human neonates show that when anaesthesia or analgesia are withheld (*e.g.* during circumcision), altered pain sensitivity increases with subsequent painful experiences (*e.g.* vaccination), when compared to those receiving analgesia (Taddio *et al.* 1997). There is also an increased vulnerability to stress disorders and anxiety in adulthood. This suggests that infants retain a "memory" of a painful experience with subsequent altered response to a painful stimulus. These phenomena also occur in animals (Anand *et al.* 1999). What has been learned about pain, and its management in human neonates can be applied to animals (Lee 2002).

Recently, the American Association of Feline Practitioner/American Animal Hospital Association Life Stage Guidelines have simplified the terminology for different life stages. The subdivisions of age are now described as: kitten (birth up to 1 year of age), young adult (1 to 6 years), mature adult (6 to 10 years) and senior (10 years and older) (Quimby *et al.* 2021). Dog breeds may vary in longevity but similar life stages could be applied. However, it is still acceptable to consider kittens or puppies of up to 12 weeks as paediatric patients.

Table 26. Treatment options for severe, moderate and mild medical-related pain

Pain severity	Treatment options
Severe pain	• μ agonist opioids can be titrated to effect (Chapter 2.2); opioids that cause vomiting (*e.g.* morphine or hydromorphone) are best avoided. Opioid infusions are recommended • NSAIDs (Chapter 2.3) when patients are haemodynamically stable with no contraindications; these can be combined with opioid therapy • Locoregional anaesthetic techniques (Chapter 3.5) • Ketamine (Chapter 2.7) and/or lidocaine CRI (Chapter 2.5). Lidocaine infusions should be used cautiously in cats due to the risk of haemodynamic compromise • Intrapleural and intraperitoneal (Steagall *et al*. 2020b) blocks for somatic and visceral pain, respectively
Moderate pain	• μ agonist opioid as described for severe pain. Frequent im or SC injections are painful and stressful and should be avoided when possible, therefore a catheter is recommended for iv injections • NSAID when patients are haemodynamically stable with no contraindications; these can be combined with opioid therapy • Ketamine (Chapter 2.7) and/or lidocaine CRI (Chapter 2.5). Lidocaine infusions should be used cautiously in cats due to the risk of haemodynamic compromise • Buprenorphine can be used, especially as part of multi-modal analgesia and when pain is controlled (Chapter 2.2)

Mild to moderate pain (non-hospitalised or hospitalised patients)	• NSAID of choice (if no contraindications) ±buprenorphine (OTM is suitable for home settings)
	• Gabapentin 10 mg/kg PO every 8 hours for dogs, or every 12 hours for cats may be of benefit, although there is little published evidence to support its use in acute pain. Gabapentinoids are better administered for naturally occurring medical, chronic pain with a neuropathic component. Sedation may be observed. Doses should be adjusted in patients with renal disease
	• Mouth wash solutions for alleviating oral mucositis pain (Chapter 3.14). Gently rinse or flush oral cavity using a syringe containing one of the following:
	  • Lidocaine 2% viscous solution mixed in a 1:1:1 ratio with magnesium/aluminium hydroxide and diphenhydramine: maximum dose 0.4 mL/kg every 8 hours (De Lorimier & Fan 2005, Shanan *et al*. 2017)
	  • Green Tea flushes can be used in the mouth or on wounds (Liao *et al*. 2021)

There tends to be apprehension in administering analgesic drugs to young animals due to the often cited "decreased ability for drug metabolism and elevated risk of overdose." While this may be a potential concern, there are few published studies in puppies or kittens to guide the clinician and dosing remains a challenge (Ku & Smith 2015). Reduced clearance of many drugs occurs in young animals when compared with older individuals largely because of:

- Their greater body water content leading to a higher volume of distribution
- A larger fraction of body mass that consists of highly perfused tissues
- Incomplete maturation of the hepatic-enzymes systems
- Decreased glomerular filtration rate and renal excretion

The hepatorenal system continues to develop during early life stages; this may result in reduced metabolism and excretion, which may require alterations in dosing and dosing intervals. Drugs that act in the CNS (*e.g.* opioids, sedatives, tranquilisers, anaesthetic agents), may reach a higher concentration in the neonatal brain due to differences in the blood brain barrier and immaturity of efflux transport systems (Ku & Smith 2015).

Opioids

Lower doses of fentanyl and morphine are required for analgesia in the neonatal puppy (0 to 2 weeks) when compared to 5-week-old puppies (Luks *et al*. 1998). Puppies and kittens are also more sensitive to the sedative and respiratory depressant effects of morphine than adults. Fentanyl may be a more suitable opioid in paediatrics; however, as it is short-acting continuous iv access and titration are required (Luks *et al*. 1998). Buprenorphine may be an alternative and associated with minimal respiratory depression. The duration and magnitude of thermal antinociception after hydromorphone administration in cats was shorter and lower, respectively, in cats aged 6 months compared to 9 and 12 months of age, respectively (Simon *et al*. 2019). In each case, the clinical response to treatment should guide dosing. Opioids can be reversed with titration of naloxone should there be clinical evidence of overdosing (*e.g.* respiratory depression and marked somnolence).

Non-steroidal anti-inflammatory drugs

NSAIDs rarely have market authorisation in small animals less than 12 to 16 weeks of age, however meloxicam has approval in some countries for use in dogs and cats ≥6 weeks of age. This does not mean they cannot be used in young populations; rather, it reflects the lack of preclinical trials in all age groups. Non-steroidal anti-inflammatory agents are used in dogs and cats undergoing neutering at a young age. Prepubertal kittens (n=380, aged 8 to 12 weeks) undergoing ovariohysterectomy or castration received carprofen or meloxicam before surgery with no reported adverse effects (Porters *et al*. 2015). The clinician should ensure the patient is an appropriate candidate for NSAID use, *e.g.* they are not hypovolemic or hypotensive (Chapter 2.3).

Local anaesthetics

Topical local anaesthetics

Topical anaesthetics include a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine, and liposome encapsulated formulations of 4% lidocaine, which can be used to desensitise the skin. This technique is suitable for venipuncture, iv catheter placement and other minor superficial procedures. The skin over the area is clipped, cleansed and the anaesthetic cream is used to cover the area, then an occlusive dressing (*e.g.* a thin film of plastic) is placed and secured using a multi-purpose cohesive bandage. Onset of action is variable but occurs between 15 to 20 minutes. In cats, no adverse effects were reported with either product and transdermal uptake of 4% liposome-encapsulated lidocaine cream (dosed at 15 mg/kg) resulted in plasma concentrations well below toxic levels for this species (Fransson *et al.* 2002, Gibbon *et al.* 2003).

Injectable local anaesthetic. Local anaesthetic techniques should be used whenever possible. Neonatal organ maturation and body composition should be taken in consideration when choosing appropriate doses. Repeated injections or continuous infusions (*e.g.* iv lidocaine) may lead to accumulation and should be avoided or used with caution. If repeated, successive doses or CRI rates should be reduced compared to adults, and the patient watched carefully for signs of toxicity (Chapters 2.5 and 3.5).

In the conscious patient, injection associated pain can be ameliorated by using small gauge needles (27 to 30 G), injecting slowly, buffering with sodium bicarbonate, and warming the solution to body temperature (Chapters 2.5 and 3.5).

Alpha$_2$-adrenoceptor agonist drugs

Cardiac output is heart rate dependent in neonates and due to the bradycardia associated with alpha$_2$-adrenoceptor agonists, these drugs are not recommended. However, many paediatric neutering anaesthetic protocols include a combination of an alpha$_2$-adrenoceptor agonist (*e.g.* medetomidine or dexmedetomidine), ketamine and an opioid used as a total injectable technique, with success. There are several published reports of these techniques in kittens under 12 weeks of age (Joyce & Yates 2011, Porters *et al.* 2015).

Nonpharmacologic techniques

Good nursing care and low stress handling are important in all patients. In neonates, separation from littermates and the dam can be stressful and should be avoided whenever possible. In human neonates, non-pharmacologic techniques are used alongside analgesic drugs to alleviate pain despite varying degrees of evidence to support them (Riddell *et al.* 2015), and an integrative approach is encouraged with puppies and kittens. Techniques to consider include suckling, swaddling, body contact with the dam (or a human) and warmth (Gray *et al.* 2012, Riddell *et al.* 2015).

3.11 Dermatological conditions

Dermatologic diseases cause inflammation resulting in mild to severe pain (*e.g.* necrotizing fasciitis). Pruritis or itch is a common sensation in dogs and cats and bears many similarities to pain. Pruritis is defined as an unpleasant sensory perception which causes an intense desire to scratch, causing a detrimental impact on QoL (Grundmann & Stander 2011). The sensations of pain and itch are both transmitted by unmyelinated slowly conducting C-fibres but there are many differences in the physiological mechanisms of pain and itch. Itch is a sensation felt in response to dermal chemonociceptors and polymodal nociceptor free nerve endings located in the dermal-epidermal junction and these free nerve endings are implicated as a primary cause of pruritis (Institute of Medicine Committee on Advancing Pain Research, Care, & Education 2011). The C-fibre pathway important in the sensation of itch includes mechanically insensitive C-fibres that are responsive to histamine. The triggering of these fibres leads to the release of neurotransmitter and neuropeptides such as acetylcholine, catecholamines, substance P, somatostatin and neurotensin that all contribute to pruritis (Burkhart & Burkhart 2003). A major problem with chronic pruritis is the fact that scratching the site brings immediate psychological and physical relief of the sensation, but continued scratching will cause further inflammation and possible peripheral and central sensitisation to itch which further exacerbates the pruritis; infection is another possible complication.

Caregiver completed QoL questionnaires have been developed for dogs and cats with pruritic skin disease and pruritis has been shown to decrease QoL of animals and their caregivers in clinical studies (Noli *et al.* 2011a,b, 2019). This illustrates the importance of effectively managing pruritis in cats and dogs, although for treatment to be effective establishing the underlying cause is important.

Specific drugs used to manage pruritis in cats and dogs

Four different classes of drug are used to manage pruritis in cats and dogs: steroids, Janus kinase inhibitors (*e.g.* oclacitinib); cyclosporins (*e.g.* cyclosporine); mAbs (*e.g.* lokivetmab). The indications for these different drugs depend on the underlying cause of the pruritis, species (licensing considerations) and adverse effects (Olivry *et al.* 2015, Saridomichelakis & Olivry 2016).

Specific analgesics for pruritus

Analgesics may be helpful for the management of pruritus alongside specific drugs to prevent the sensation of itch. This is because pruritus is usually associated with inflammation of the skin and is therefore painful. Opioids are not the first line treatment for the management of pain associated with itch because although rare, systemic opioids can cause pruritus due to histamine release. Non-steroidal anti-inflammatory drugs can be highly effective at treating pain associated with inflammation but cannot be given in association with steroids. Neuropathic pain-like syndromes associated with itch have been described in dogs (*e.g.* itch associated with syringomyelia or acral mutilation syndrome) (Chapters 1.9 and 3.12) and may be responsive to drugs such as gabapentin or pregabalin although robust research into treatment for these conditions is lacking.

Ear disease

Ear disease (otitis externa) is a common dermatological disease, particularly in dogs and may be managed medically or surgically depending on the underlying cause and response to medical therapy. Dogs with marked ear disease can be excruciatingly painful so that treatment with analgesics alongside specific treatment for the ear disease is warranted. NSAIDs are the first line treatment for pain associated with ear disease in dogs and cats, but only if steroids have not been prescribed. If steroids have been prescribed, then analgesic treatment becomes more challenging, although paracetamol (acetaminophen) may safely be given in combination with steroids in dogs, but not in cats. In the perioperative period after surgery (*e.g.* Total Ear Canal Ablation or Ventral Bulla Osteotomy), pain can be managed with a full μ agonist opioid (bolus or infusions) (Chapter 2.2) in combination with ketamine infusions, for example.

In the home environment there is no good evidence to guide the clinician in the selection of an oral analgesic if NSAIDs are contraindicated. Gabapentin is indicated if there is likely to be a neuropathic component to the pain, such as occurs with chronic otitis externa. In dogs but not in cats, paracetamol (acetaminophen) (with or without codeine) may be prescribed alongside NSAIDs or corticosteroids for the management of pain in the home environment.

3.12 Neuropathic pain protocols

Neuropathic pain is classically difficult to treat and recommendations are based on the human literature and an increasing body of evidence from veterinary medicine (Rusbridge *et al.* 2010). Gabapentinoids (gabapentin or pregabalin) have been used as the first line of treatment with significant improvements in QoL (Plessas *et al.* 2015, Batle *et al.* 2019). These treatments have been used in both medical and surgical treatment of neuropathic pain (Sanchis-Mora *et al.* 2019, Schmierer *et al.* 2020, Thoefner *et al.* 2020). Non-steroidal anti-inflammatory drugs have been used in combination with gabapentinoids when an inflammatory condition is also suspected. Antagonists of NMDA receptors (*i.e.* amantadine) have also been used for the treatment of OA in dogs that were refractory to NSAID treatment alone suggesting a potential component of neuropathic pain in these cases (Lascelles *et al.* 2008). The role of anti-NGF mAbs in neuropathic pain has not been investigated, but a benefit might exist. Opioids may exacerbate chronic neuropathic pain *via* neuroinflammation and glial amplification. Several physical modalities are directed at addressing neuropathic pain of myofascial origin. This includes use of heat and cold therapy, acupuncture and trigger point needling, stretching, massage and exercise. All these modalities need further research in veterinary medicine (Shah *et al.* 2015). Further studies are warranted including different treatment options in a wide array of neuropathic painful conditions and investigations of potential placebo effect.

Patients with chronic neuropathic pain

In patients with neuropathic pain conditions such as intervertebral disc disease, chronic postoperative pain following amputation or thoracotomy, Chiari-like malformation, syringomyelia, diabetic neuropathy, orofacial pain syndrome, FHS, among others, multimodal analgesia is likely to provide the greatest benefit. An approach based on trial-and-error might be needed to define the best treatment for a patient. Non-pharmacologic techniques should be included in the treatment of neuropathic pain states. Pharmacological treatments in dogs and cats can be started with the combination of a NSAID with one or more of the following adjuvant analgesics (see Tables 13 and 16 for doses): gabapentin, pregabalin, amantadine and amitriptyline. The final treatment combination and how long treatment is continued will be based on patient response and adverse effects. Dosage regimens of analgesics can sometimes be slowly tapered down while monitoring to ensure signs of pain do not re-emerge.

Patients with acute on chronic neuropathic pain

In dogs and cats presenting with severe clinical signs of hyperalgesia and allodynia, hospitalisation might be required for the application of neuro-modifying techniques (*e.g.* local anaesthetic blocks) and/or administration of iv analgesics such as lidocaine (1 mg/kg bolus with 30 μg/kg/minute CRI) (lidocaine infusions should be used cautiously in cats due to the risk of haemodynamic compro-

mise; Chapter 2.5) or ketamine (bolus of 0.5 to 1 mg/kg followed by a CRI of 2 to 10 μg/kg/minute) in combination with systemic opioids until clinical signs have improved.

Patients undergoing invasive surgery with the potential to develop neuropathic pain

See Chapter 3.3.

3.13 Musculoskeletal pain

The management of OA and DJD associated pain has advanced and grown in complexity in the past two decades. There are many recommendations for treatment of the pain and dysfunction associated with this disease, although not all options are equally efficacious (Aragon *et al*. 2007, Sanderson *et al*. 2009, Vandeweerd *et al*. 2012, Monteiro 2020). Options include surgical intervention, systemic analgesic therapy (NSAIDs, anti-NGF mAbs, paracetamol (acetaminophen) [*not in cats*], corticosteroids, adjunctive drugs), local pharmacologic therapy (transcutaneous; intra-articular), home-based exercises, clinic-based therapeutic exercises, weight optimization, nutritional supplementation, massage, acupuncture, laser therapy, heat/cold therapy, neuromuscular electrical stimulation, transcutaneous electrical stimulation and joint mobilisation. However, it should be remembered that DJD/OA in any patient is not a single "type" of problem – indeed, it is now becoming recognised that DJD presents differently in the growing, *versus* middle-aged, *versus* older cat or dog (Box 2). DJD presenting at different "life-stages" requires different approaches to optimise care.

Regardless of the stage of disease or the treatments selected, the veterinarian should aim to maximise the benefit and minimise the risks associated with managing this disease. The mainstays of treatment involve methods to alleviate pain, and currently the approved (and therefore proven) analgesic options are the COX-inhibiting and non-COX-inhibiting (grapiprant) NSAIDs and the anti-NGF mAbs.

In cats and dogs, the broad categories of treatments for OA pain can be summarised as:

Non-surgery, non-drug treatment

Exercise; weight optimization; diet modulation (type; amount); therapeutic exercise and physical modalities; environmental modification; nutritional supplements; acupuncture.

Systemic and local administration of drugs

Drugs with market authorisation for the treatment of OA (COX-inhibiting and non-COX-inhibiting NSAIDs; Anti-NGF mAbs); other analgesic options include paracetamol (acetaminophen) (not in cats), corticosteroids (treating the underlying immune-mediated disease resulting in polyarthritis, or local intraarticular treatment); adjunctive analgesics (*e.g*. tramadol in cats, amantadine, gabapentin, tricyclic antidepressants); postulated disease modifying drugs (*e.g*. polysulfated glycosaminoglycan).

Surgery

Joint replacement; excision arthroplasty; arthrodesis; joint denervation.

The efficacy across these treatment options varies tremendously, and unfortunately there is little information available to guide clinicians on the comparative efficacy, or relative efficacy, of these treatment options. However, reviews in human medicine do provide information on relative efficacy (Zhang *et al*. 2010, Katz *et al*. 2021).

Evidence-based medicine in OA management

Overall, the greatest weight of evidence for efficacy is for COX-inhibiting and non-COX-inhibiting (piprant) NSAIDs, anti-NGF mAbs, weight management, dietary optimization (omega-3 fatty acid content) and exercise (Aragon *et al*. 2007, Sanderson *et al*. 2009, Enomoto *et al*. 2019, Monteiro 2020). This is not to say that other treatment options are not efficacious, or should not be used, but clinicians should prioritise the treatments that are associated with most efficacy.

3.14 Cancer-related pain

Pain in cancer patients can be associated with the cancer itself, diagnostic procedures, or treatments, or it can be unrelated to cancer. Pain from cancer itself has varying degrees of severity that is dependent on duration, location, and type of cancer. It may be associated with inflammation, tissue infiltration, mechanical factors (*e.g*. organ distension), nerve infiltration or compression and potentially factors released by the tumour. Most patients with cancer suffer pain at some point in the course of the disease. In people, some cancers such as lymphomas and leukaemia are associated with a low prevalence of pain. The prevalence and severity of pain associated with various cancer types in animals is not well documented.

One of the best documented types of cancer pain is that associated with primary or metastatic bone tumours. Pain results from direct invasion of the bone, microfractures, increased pressure of endosteum, distortion of the periosteum or perilesional inflam-

mation. Another important mechanism is the release of chemical mediators such as amines, peptides, fatty acids, potassium, and prostaglandins (Mantyh 2014). Cancer pain, and bone pain in particular, are often associated with neuropathic-like clinical signs. Dogs with bone cancer can be affected by widespread somatosensory sensitivity and clinical pain is generally refractory to palliative treatment with orally administered analgesics (Monteiro *et al*. 2018).

Cancer treatments including specific chemotherapy agents [chemotherapy-induced peripheral neuropathy (CIPN)] (Argyriou *et al*. 2014) and therapeutic radiation [radiation-associated pain (RAP)] (Trotti *et al*. 2003) can be associated with significant pain at the time of treatment, but also for prolonged periods afterwards (Table 26). Mechanisms of CIPN and RAP are poorly understood and undergoing investigation (Nolan *et al*. 2017, 2020b, Ma *et al*. 2018).

The presence of pain itself (unrelated to cancer) may promote the progression of cancer (Page *et al*. 2001), and emerging evidence indicates that pretreatment cancer pain levels may be negatively related to survival (Nolan *et al*. 2020a). Additionally, evidence indicates that some cancers may coapt (*i.e*. to bring together) sensory nerves and pain signalling mechanisms to facilitate its progression (Gasparini *et al*. 2019, Venkatesh *et al*. 2019).

While a detailed understanding of cancer pain mechanisms will eventually lead to specific recommendations, currently a multimodal drug approach to the control of chronic cancer pain is recommended and appropriate management of any non-cancer pain, such as procedure, perioperative pain or other chronic pain conditions such as OA, is recommended. In general, for chronic cancer pain, NSAIDs are recommended with the addition of opioids and adjunctive drugs (such as gabapentin) as needed. Other modalities that can prove beneficial are bisphosphonates, chemotherapy, and radiotherapy. Non-drug therapies should be used concurrently. Other forms of adjunctive therapy tend to improve QoL in cancer patients, although it is not known if they directly induce analgesia.

CLOSING REMARKS

Animals experience both positive and negative emotions including suffering from pain. Acute (adaptive) and chronic (maladaptive) pain are different phenomena and both can negatively affect the health and welfare of animals resulting in stress, fear, anxiety and frustration. An animal's social and physical environment can influence their pain perception.

As veterinary health professionals, we have a medical and ethical duty to mitigate suffering from pain to the best of our ability. This includes appropriately recognising and assessing pain in all animals based on the evaluation of behaviours and using validated pain scales. It also includes using pharmacological and non-pharmacological strategies for pain management. With regard to analgesic drugs, preventive and multi-modal therapy should be regarded as best practice. Regarding non-drug therapies, numerous strategies can be easily implemented to reduce pain and improve the experience of hospitalised patients with acute pain, and to improve the QoL and human-animal bond of those with chronic pain. It should also be recognised that in some situations, euthanasia may be the only viable option to end suffering from pain.

Considering that pain is the fourth vital sign and that it negatively impacts all domains of animal welfare, the veterinary health care team should join forces in an effort to optimise pain management in all patients to promote their health and wellbeing.

ACKNOWLEDGEMENTS

The WSAVA GPC currently receives financial support from Zoetis through sponsorship of the WSAVA. The sponsor did not participate or provide any input on the writing, content and publication of these guidelines.

Conflict of interest

All of the authors have provided/provide consultancy services to several pharmaceutical companies.

Abbreviations

AP	Aspiration penumonia
CB	Cannabinoid receptors
CBD	Cannabinol
CBPI	Canine Brief Pain Inventory
CIPN	Chemotherapy induced peripheral neuropathy
CMIs	Clinical Metrology Instruments
CMPS-SF	Glasgow Composite Measure Pain Scale and its short form
CNS	Central Nervous System
COX	Cyclooxygenase
CRI	Continuous Rate Infusion

CSOM	Client Specific Outcome Measure
DJD	Degenerative Joint Disease
FHS	Feline hyperesthesia syndrome
FLUTD	Feline lower urinary tract disease
FMPI:	Feline Musculoskeletal Pain Index
FOPS	Feline orofacial pain syndrome
FPFF	The Feline Physical Function Formula
GCs	Glucocorticosteroids
HA	Hyaluronic acid
HRQoL	Health related quality of life
IASP	International Association for the Study of Pain
IOP	Intraocular pressure
IRIS	International Renal Interest Society
iv	Intravenous
LOAD:	Liverpool Osteoarthritis in Dogs
mAbs	Monoclonal antibodies
MAC	Minimum alveolar concentration
MI-CAT	Montreal Cat Assessment Tool
MiPSC	Feline Musculoskeletal Pain Screening Checklist
MSC	Mesenchymal Stem Cells
NGF	Nerve growth factor
NK-1	Neurokinin-1 receptor
NMDA	N-methyl-D-aspartate
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PRP	Platelet rich plasma
QoL	Quality of Life
QST	Quantitative Sensory Testing
RAP	Radiation associated pain
TCAs	Tricyclic antidepressants
TD	Transdermal patches
TENS	Transcutaneous Electrical Stimulation
THC	Delta-9-tetrahydrocannabinol
TRPV1	Transient receptor potential vanilloid 1
WSAVA-GPC	World Small Animal Veterinary Association-Global Pain Council

References

Abelson, A. L., McCobb, E. C., Shaw, S., *et al*. (2009) Use of wound soaker catheters for the administration of local anesthetic for post-operative analgesia: 56 cases. *Veterinary Anaesthesia and Analgesia* **36**, 597-602

Adrian, D., Papich, M., Baynes, R., *et al*. (2017) Chronic maladaptive pain in cats: a review of current and future drug treatment options. *The Veterinary Journal* **230**, 52-61

Adrian, D. E., Rishniw, M., Scherk, M., *et al*. (2018) Prescribing practices of veterinarians in the treatment of chronic musculoskeletal pain in cats. *Journal of Feline Medicine and Surgery* **21**, 495-506

Adrian, D., King, J. N., Parrish, R. S., *et al*. (2021) Robenacoxib shows efficacy for the treatment of chronic degenerative joint disease-associated pain in cats: a randomized and blinded pilot clinical trial. *Scientific Reports* **11**, 7721

Almgren, C. M. & Lee, J. A. (2013) Serotonin syndrome. Clinician's Brief, 11-16

Alvarez, L. X., McCue, J., Lam, N. K., *et al*. (2019) Effect of targeted pulsed electromagnetic field therapy on canine postoperative hemilaminectomy: a double-blind, randomized, placebo-controlled clinical trial. *Journal of the American Animal Hospital Association* **55**, 83-91

Alves, J. C., Santos, A., Jorge, P., *et al*. (2022) A randomized double-blinded controlled trial on the effects of photobiomodulation therapy in dogs with osteoarthritis. *American Journal of Veterinary Research* **83**, ajvr.22.03.0036

Amaya, V., Paterson, M. B. A., Descovich, K., *et al*. (2020) Effects of olfactory and auditory enrichment on heart rate variability in shelter dogs. *Animals (Basel)* **10**, 1385

American Society of Anesthesiologists. (2015) Herbal and dietary supplements and anesthesia. ASA

Amoore, J. & Adamson, L. (2003) Infusion devices: characteristics, limitations and risk management. *Nursing Standard* **17**, 45-52; quiz 54-45

Anand, K. J. S. (2001) Consensus statement for the prevention and management of pain in the newborn. *Archives of Pediatrics & Adolescent Medicine* **155**, 173-180

Anand, K. J., Coskun, V., Thrivikraman, K. V., *et al*. (1999) Long-term behavioral effects of repetitive pain in neonatal rat pups. *Physiology & Behavior* **66**, 627-637

Ancot, F., Lemay, P., Knowler, S. P., *et al*. (2018) A genome-wide association study identifies candidate loci associated to syringomyelia secondary to chiari-like malformation in cavalier king charles spaniels. *BMC Genetics* **19**, 16

Aragon, C. L., Hofmeister, E. H. & Budsberg, S. C. (2007) Systematic review of clinical trials of treatments for osteoarthritis in dogs. *Journal of the American Veterinary Medical Association* **230**, 514-521

Argyriou, A. A., Kyritsis, A. P., Makatsoris, T., *et al*. (2014) Chemotherapy-induced peripheral neuropathy in adults: a comprehensive update of the literature. *Cancer Management and Research* **6**, 135-147

Armitage, E. A., Wetmore, L. A., Chan, D. L., *et al*. (2005) Evaluation of compliance among nursing staff in administration of prescribed analgesic drugs to critically ill dogs and cats. *Journal of the American Veterinary Medical Association* **227**, 425-429

Arzi, B., Mills-Ko, E., Verstraete, F. J. M., *et al*. (2016) Therapeutic efficacy of fresh, autologous mesenchymal stem cells for severe refractory gingivostomatitis in cats. *Stem Cells Translational Medicine* **5**, 75-86

Aulakh, K. S., Lopez, M. J., Hudson, C., *et al*. (2021) Prospective clinical evaluation of intra-articular injection of tin-117m (117msn) radiosynoviorthesis agent for management of naturally occurring elbow osteoarthritis in dogs: a pilot study. *Veterinary Medicine: Research and Reports* **12**, 117-128

AVMA (2019) Principles of veterinary medical ethics of the AVMAjhs. *AVMA*
Baker-Meuten, A., Wendland, T., Shamir, S. K., *et al*. (2020) Evaluation of acupuncture for the treatment of pain associated with naturally-occurring osteoarthritis in dogs: a prospective, randomized, placebo-controlled, blinded clinical trial. *BMC Veterinary Research* **16**, 357
Barić Rafaj, R., Kuleš, J., Marinculić, A., *et al*. (2017) Plasma markers of inflammation and hemostatic and endothelial activity in naturally overweight and obese dogs. *BMC Veterinary Research* **13**, 13
Barletta, M., Young, C. N., Quandt, J. E., *et al*. (2016) Agreement between veterinary students and anesthesiologists regarding postoperative pain assessment in dogs. *Veterinary Anaesthesia and Analgesia* **43**, 91-98
Barker, P. A., Mantyh, P., Arendt-Nielsen, L., *et al*. (2020) Nerve growth factor signaling and its contribution to pain. *Journal of Pain Research* **13**, 1223-1241
Barnes, K., Faludi, A., Takawira, C., *et al*. (2019) Extracorporeal shock wave therapy improves short-term limb use after canine tibial plateau leveling osteotomy. *Veterinary Surgery* **48**, 1382-1390
Bartholomew, K. J., Smith, L. J., Bentley, E., *et al*. (2020) Retrospective analysis of complications associated with retrobulbar bupivacaine in dogs undergoing enucleation surgery. *Veterinary Anaesthesia and Analgesia* **47**, 588-594
Batle, P. A., Rusbridge, C., Nuttall, T., *et al*. (2019) Feline hyperaesthesia syndrome with self-trauma to the tail: retrospective study of seven cases and proposal for an integrated multidisciplinary diagnostic approach. *Journal of Feline Medicine and Surgery* **21**, 178-185
Beauchamp, T. L. (2016) Principlism in bioethics. In: Bioethical Decision Making and Argumentation. Eds P. Serna and J. A. Seoane. Springer, Cham, Germany. pp 1-16
Becker, W. M., Mama, K. R., Rao, S., *et al*. (2013) Prevalence of dysphoria after fentanyl in dogs undergoing stifle surgery. *Veterinary Surgery* **42**, 302-307
Beilin, B., Bessler, H., Mayburd, E., *et al*. (2003) Effects of preemptive analgesia on pain and cytokine production in the postoperative period. *Anesthesiology* **98**, 151-155
Bell, A., Helm, J. & Reid, J. (2014) Veterinarians' attitudes to chronic pain in dogs. *Veterinary Record* **175**, 428
Belli, M., de Oliveira, A. R., de Lima, M. T., *et al*. (2021) Clinical validation of the short and long UNESP-Botucatu scales for feline pain assessment. *PeerJ* **9**, e11225
Bellows, J., Berg, M. L., Dennis, S., *et al*. (2019) 2019 aaha dental care guidelines for dogs and cats. *Journal of the American Animal Hospital Association* **55**, 49-69
Belshaw, Z. & Yeates, J. (2018) Assessment of quality of life and chronic pain in dogs. *The Veterinary Journal* **239**, 59-64
Belshaw, Z., Asher, L., Harvey, N. D., *et al*. (2015) Quality of life assessment in domestic dogs: an evidence-based rapid review. *The Veterinary Journal* **206**, 203-212
Benito, J., Depuy, V., Hardie, E., *et al*. (2013a) Reliability and discriminatory testing of a client-based metrology instrument, feline musculoskeletal pain index (FMPI) for the evaluation of degenerative joint disease-associated pain in cats. *Veterinary Journal* **196**, 368-373
Benito, J., Hansen, B., Depuy, V., *et al*. (2013b) Feline musculoskeletal pain index: responsiveness and testing of criterion validity. *Journal of Veterinary Internal Medicine* **27**, 474-482
Bennett, M. I., Rayment, C., Hjermstad, M., *et al*. (2012) Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. *Pain* **153**, 359-365
Berrueta, L., Muskaj, I., Olenich, S., *et al*. (2016) Stretching impacts inflammation resolution in connective tissue. *Journal of Cellular Physiology* **231**, 1621-1627
Berterame, S., Erthal, J., Thomas, J., *et al*. (2016) Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet* **387**, 1644-1656
Bienhoff, S. E., Smith, E. S., Roycroft, L. M., *et al*. (2012) Efficacy and safety of deracoxib for control of postoperative pain and inflammation associated with soft tissue surgery in dogs. *Veterinary Surgery* **41**, 336-344
Bleuer-Elsner, S., Medam, T. & Masson, S. (2021) Effects of a single oral dose of gabapentin on storm phobia in dogs: a double-blind, placebo-controlled crossover trial. *Veterinary Record* **189**, e453
Bortolami, E. & Love, E. J. (2015) Practical use of opioids in cats: a state-of-the-art, evidence-based review. *Journal of Feline Medicine and Surgery* **17**, 283-311
Boscan, P., Monnet, E., Mama, K., *et al*. (2011) Effect of maropitant, a neurokinin 1 receptor antagonist, on anesthetic requirements during noxious visceral stimulation of the ovary in dogs. *American Journal of Veterinary Research* **72**, 1576-1579
Boston, S. E., Moens, N. M., Kruth, S. A., *et al*. (2003) Endoscopic evaluation of the gastroduodenal mucosa to determine the safety of short-term concurrent administration of meloxicam and dexamethasone in healthy dogs. *American Journal of Veterinary Research* **64**, 1369-1375
Brain, K., Burrows, T. L., Bruggink, L., *et al*. (2021) Diet and chronic non-cancer pain: the state of the art and future directions. *Journal of Clinical Medicine* **10**, 5203
Brioschi, F. A., Di Cesare, F., Gioeni, D., *et al*. (2020) Oral transmucosal cannabidiol oil formulation as part of a multimodal analgesic regimen: effects on pain relief and quality of life improvement in dogs affected by spontaneous osteoarthritis. *Animals (Basel)* **10**, 1505
Brondani, J. T., Mama, K. R., Luna, S. P., *et al*. (2013) Validation of the English version of the UNESP-Botucatu multidimensional composite pain scale for assessing postoperative pain in cats. *BMC Veterinary Research* **9**, 143
Brondeel, C., Pauwelyn, G., de Bakker, E., *et al*. (2021) Review: mesenchymal stem cell therapy in canine osteoarthritis research: "Experientia docet" (experience will teach us). *Frontiers in Veterinary Science* **8**, 668881
Brown, D. C., Boston, R. C., Coyne, J. C., *et al*. (2008) Ability of the canine brief pain inventory to detect response to treatment in dogs with osteoarthritis. *Journal of the American Veterinary Medical Association* **233**, 1278-1283
Brown, D. C., Boston, R., Coyne, J. C., *et al*. (2009) A novel approach to the use of animals in studies of pain: validation of the canine brief pain inventory in canine bone cancer. *Pain Medicine* **10**, 133-142
Budsberg, S. C., Bergh, M. S., Reynolds, L. R., *et al*. (2007) Evaluation of pentosan polysulfate sodium in the postoperative recovery from cranial cruciate injury in dogs: a randomized, placebo-controlled clinical trial. *Veterinary Surgery* **36**, 234-244
Budsberg, S. C., Torres, B. T., Kleine, S. A., *et al*. (2018) Lack of effectiveness of tramadol hydrochloride for the treatment of pain and joint dysfunction in dogs with chronic osteoarthritis. *Journal of the American Veterinary Medical Association* **252**, 427-432
Budsberg, S. C., Kleine, S. A., Norton, M. M., *et al*. (2020) Comparison of the effects on lameness of orally administered acetaminophen-codeine and carprofen in dogs with experimentally induced synovitis. *American Journal of Veterinary Research* **81**, 627-634
Buisman, M., Wagner, M. C., Hasiuk, M. M., *et al*. (2016) Effects of ketamine and alfaxalone on application of a feline pain assessment scale. *Journal of Feline Medicine and Surgery* **18**, 643-651
Buisman, M., Hasiuk, M. M. M., Gunn, M., *et al*. (2017) The influence of demeanor on scores from two validated feline pain assessment scales during the perioperative period. *Veterinary Anaesthesia and Analgesia* **44**, 646-655
Burkhart, C. G. & Burkhart, H. R. (2003) Contact irritant dermatitis and anti-pruritic agents: the need to address the itch. *Journal of Drugs in Dermatology* **2**, 143-146
Cachon, T., Frykman, O., Innes, J. F., *et al*. (2018) Face validity of a proposed tool for staging canine osteoarthritis: Canine OsteoArthritis Staging Tool (COAST). *Veterinary Journal* **235**, 1-8
Cambridge, A. J., Tobias, K. M., Newberry, R. C., *et al*. (2000) Subjective and objective measurements of postoperative pain in cats. *Journal of the American Veterinary Medical Association* **217**, 685-690
Campbell, J. N., Stevens, R., Hanson, P., *et al*. (2021) Injectable capsaicin for the management of pain due to osteoarthritis. *Molecules* **26**, 778
Campoy, L., Martin-Flores, M., Ludders, J. W., *et al*. (2012) Comparison of bupivacaine femoral and sciatic nerve block versus bupivacaine and morphine epidural for stifle surgery in dogs. *Veterinary Anaesthesia and Analgesia* **39**, 91-98
Carapeba, G. O. L., Cavaleti, P., Nicácio, G. M., *et al*. (2016) Intra-articular hyaluronic acid compared to traditional conservative treatment in dogs with osteoarthritis associated with hip dysplasia. *Evidence-based Complementary and Alternative Medicine* **2016**, 2076921-2076910
Carter, D., Sendziuk, P., Eliott, J. A., *et al*. (2016) Why is pain still under-treated in the emergency department? Two new hypotheses. *Bioethics* **30**, 195-202
Chamberlain, G. A. & Colborne, G. R. (2016) A review of the cellular and molecular effects of extracorporeal shockwave therapy. *Veterinary and Comparative Orthopaedics and Traumatology* **29**, 99-107
Chew, D. J., Buffington, C. A., Kendall, M. S., *et al*. (1998) Amitriptyline treatment for severe recurrent idiopathic cystitis in cats. *Journal of the American Veterinary Medical Association* **213**, 1282-1286
Clutton, R. E. (2017) Recognising the boundary between heroism and futility in veterinary intensive care. *Veterinary Anaesthesia and Analgesia* **44**, 199-202
Colvin, L. A., Bull, F. & Hales, T. G. (2019) Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia. *Lancet* **393**, 1558-1568
Corral, M. J., Moyaert, H., Fernandes, T., *et al*. (2021) A prospective, randomized, blinded, placebo-controlled multisite clinical study of bedinvetmab, a canine monoclonal antibody targeting nerve growth factor, in dogs with osteoarthritis. *Veterinary Anaesthesia and Analgesia* **48**, 943-955
Crociolli, G. C., Cassu, R. N., Barbero, R. C., *et al*. (2015) Gabapentin as an adjuvant for postoperative pain management in dogs undergoing mastectomy. *Journal of Veterinary Medical Science* **77**, 1011-1015
Culp, W. T., Mayhew, P. D. & Brown, D. C. (2009) The effect of laparoscopic versus open ovariectomy on postsurgical activity in small dogs. *Veterinary Surgery* **38**, 811-817

Dahl, J. B. & Kehlet, H. (2011) Preventive analgesia. *Current Opinion in Anaesthesiology* **24**, 331-338
Darcy, H. P., Humm, K. & Ter Haar, G. (2018) Retrospective analysis of incidence, clinical features, potential risk factors, and prognostic indicators for aspiration pneumonia in three brachycephalic dog breeds. *Journal of the American Veterinary Medical Association* **253**, 869-876
Davis, K. N., Hellyer, P. W., Carr, E. C. J., *et al*. (2019) Qualitative study of owner perceptions of chronic pain in their dogs. *Journal of the American Veterinary Medical Association* **254**, 88-92
de Haan, J. J., Goring, R. L. & Beale, B. S. (1994) Evaluation of polysulfated glycosaminoglycan for the treatment of hip dysplasia in dogs. *Veterinary Surgery* **23**, 177-181
De Lorimier, L. P. & Fan, T. M. (2005) Treating cancer pain in dogs and cats. dvm360. https://www.dvm360.com/view/treating-cancer-pain-dogs-and-cats. Accessed April 15, 2006
Deabold, K. A., Schwark, W. S., Wolf, L., *et al*. (2019) Single-dose pharmacokinetics and preliminary safety assessment with use of cbd-rich hemp nutraceutical in healthy dogs and cats. *Animals (Basel)* **9**, 832
Dedes, V., Stergioulas, A., Kipreos, G., *et al*. (2018) Effectiveness and safety of shockwave therapy in tendinopathies. *Materia Socio-medica* **30**, 131-146
Delgado, C., Bentley, E., Hetzel, S., *et al*. (2014) Comparison of carprofen and tramadol for postoperative analgesia in dogs undergoing enucleation. *Journal of the American Veterinary Medical Association* **245**, 1375-1381
Della Rocca, G., Di Salvo, A., Marenzoni, M. L., *et al*. (2019) Development, preliminary validation, and refinement of the composite oral and maxillofacial pain scale-canine/feline (cops-c/f). *Frontiers in Veterinary Science* **6**, 274
Diep, T. N., Monteiro, B. P., Evangelista, M. C., *et al*. (2020) Anesthetic and analgesic effects of an opioid-free, injectable protocol in cats undergoing ovariohysterectomy: a prospective, blinded, randomized clinical trial. *Canadian Veterinary Journal* **61**, 621-628
Dohoo, S. E. & Dohoo, I. R. (1996a) Factors influencing the postoperative use of analgesics in dogs and cats by Canadian veterinarians. *Canadian Veterinary Journal* **37**, 552-556
Dohoo, S. E. & Dohoo, I. R. (1996b) Postoperative use of analgesics in dogs and cats by Canadian veterinarians. *Canadian Veterinary Journal* **37**, 546-551
Doit, H., Dean, R. S., Duz, M., *et al*. (2021) A systematic review of the quality of life assessment tools for cats in the published literature. *The Veterinary Journal* **272**, 105658
Donati, P. A., Tarragona, L., Franco, J. V. A., *et al*. (2021) Efficacy of tramadol for postoperative pain management in dogs: systematic review and meta-analysis. *Veterinary Anaesthesia and Analgesia* **48**, 283-296
Donecker, J., Fabiani, M., Gaschen, L., *et al*. (2021a) Treatment response in dogs with naturally occurring grade 3 elbow osteoarthritis following intra-articular injection of 117msn (tin) colloid. *PLoS One* **16**, e0254613
Donecker, J., Lattimer, J. C., Gaschen, L., *et al*. (2021b) Safety and clinical response following a repeat intraarticular injection of tin-117m (117msn) colloid in dogs with elbow osteoarthritis. *Veterinary Medicine: Research and Reports* **12**, 325-335
Doodnaught, G. M., Benito, J., Monteiro, B. P., *et al*. (2017) Agreement among undergraduate and graduate veterinary students and veterinary anesthesiologists on pain assessment in cats and dogs: a preliminary study. *Canadian Veterinary Journal* **58**, 805-808
Dyson, D. H. (2008) Analgesia and chemical restraint for the emergent veterinary patient. *Veterinary Clinics of North America: Small Animal Practice* **38**, 1329-1352, vii
Egger, C. M., Glerum, L. E., Allen, S. W., *et al*. (2003) Plasma fentanyl concentrations in awake cats and cats undergoing anesthesia and ovariohysterectomy using transdermal administration. *Veterinary Anaesthesia and Analgesia* **30**, 229-236
Elma, Ö., Yilmaz, S. T., Deliens, T., *et al*. (2020) Do nutritional factors interact with chronic musculoskeletal pain? A systematic review. *Journal of Clinical Medicine* **9**, 7
Enomoto, M., Mantyh, P. W., Murrell, J., *et al*. (2019) Anti-nerve growth factor monoclonal antibodies for the control of pain in dogs and cats. *Veterinary Record* **184**, 23
Enomoto, M., Lascelles, B. D. X. & Gruen, M. E. (2020) Development of a checklist for the detection of degenerative joint disease-associated pain in cats. *Journal of Feline Medicine and Surgery* **22**, 1137-1147
Enomoto, M., Lascelles, B. D. X., Robertson, J. B., *et al*. (2022) Refinement of the feline musculoskeletal pain index (FMPI) and development of the short-form FMPI. *Journal of Feline Medicine and Surgery* **24**, 142-151
Epstein, M. E. (2020) Feline neuropathic pain. *Veterinary Clinics of North America: Small Animal Practice* **50**, 789-809
Estrella, J. S., Nelson, R. N., Sturges, B. K., *et al*. (2008) Endoneurial microvascular pathology in feline diabetic neuropathy. *Microvascular Research* **75**, 403-410
Evangelista, M. C. & Steagall, P. V. (2021) Agreement and reliability of the Feline Grimace Scale among cat caretakers, veterinarians, veterinary students and nurses. *Scientific Reports* **11**, 5262
Evangelista, M. C., Silva, R. A., Cardozo, L. B., *et al*. (2014) Comparison of preoperative tramadol and pethidine on postoperative pain in cats undergoing ovariohysterectomy. *BMC Veterinary Research* **10**, 252
Evangelista, M. C., Watanabe, R., Leung, V. S. Y., *et al*. (2019) Facial expressions of pain in cats: the development and validation of a feline grimace scale. *Scientific Reports* **9**, 19128
Evangelista, M. C., Benito, J., Monteiro, B. P., *et al*. (2020) Clinical applicability of the feline grimace scale: real-time versus image scoring and the influence of sedation and surgery. *PeerJ* **8**, e8967
Evangelista, M. C., Monteiro, B. P. & Steagall, P. V. (2021) Measurement properties of grimace scales for pain assessment in nonhuman mammals: a systematic review. *Pain* **163**, e697-e714
Farnworth, M., Adams, N., Keown, A., *et al*. (2014) Veterinary provision of analgesia for domestic cats (felis catus) undergoing gonadectomy: a comparison of samples from New Zealand, Australia and the United Kingdom. *New Zealand Veterinary Journal* **62**, 117-122
Fernandez-Trapero, M., Espejo-Porras, F., Rodriguez-Cueto, C., *et al*. (2017) Upregulation of cb2 receptors in reactive astrocytes in canine degenerative myelopathy, a disease model of amyotrophic lateral sclerosis. *Disease Models & Mechanisms* **10**, 551-558
Ferreira, M. C., Dias-Pereira, A. C., Branco-de-Almeida, L. S., *et al*. (2017) Impact of periodontal disease on quality of life: a systematic review. *Journal of Periodontal Research* **52**, 651-665
Field, R., Field, T., Pourkazemi, F., *et al*. (2021) Ketogenic diets and the nervous system: a scoping review of neurological outcomes from nutritional ketosis in animal studies. *Nutrition Research Reviews*, 1-14. [published online ahead of print]
Finan, P. H. & Garland, E. L. (2015) The role of positive affect in pain and its treatment. *Clinical Journal of Pain* **31**, 177-187
Fine, P. G. & Rosenfeld, M. J. (2013) The endocannabinoid system, cannabinoids, and pain. *Rambam Maimonides Medical Journal* **4**, e0022
Firth, A. M. & Haldane, S. L. (1999) Development of a scale to evaluate postoperative pain in dogs. *Journal of the American Veterinary Medical Association* **214**, 651-659
Foth, S., Meller, S., Kenward, H., *et al*. (2021) The use of ondansetron for the treatment of nausea in dogs with vestibular syndrome. *BMC Veterinary Research* **17**, 222
Francisco, A. A., De Oliveira, S., Steen, M., *et al*. (2018) Ice pack induced perineal analgesia after spontaneous vaginal birth: randomized controlled trial. *Women and Birth* **31**, e334-e340
Fransson, B. A., Peck, K. E., Smith, J. K., *et al*. (2002) Transdermal absorption of a liposome-encapsulated formulation of lidocaine following topical administration in cats. *American Journal of Veterinary Research* **63**, 1309-1312
Freeman, L. M., Rodenberg, C., Narayanan, A., *et al*. (2016) Development and initial validation of the Cat HEalth and Wellbeing (CHEW) Questionnaire: a generic health-related quality of life instrument for cats. *Journal of Feline Medicine and Surgery* **18**, 689-701
Frye, C. W., Shmalberg, J. W. & Wakshlag, J. J. (2016) Obesity, exercise and orthopedic disease. *Veterinary Clinics of North America: Small Animal Practice* **46**, 831-841
Fujiki, M., Shineha, J., Yamanokuchi, K., *et al*. (2007) Effects of treatment with polysulfated glycosaminoglycan on serum cartilage oligomeric matrix protein and c-reactive protein concentrations, serum matrix metalloproteinase-2 and -9 activities, and lameness in dogs with osteoarthritis. *American Journal of Veterinary Research* **68**, 827-833
Gamble, L. J., Boesch, J. M., Frye, C. W., *et al*. (2018) Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic dogs. *Frontiers in Veterinary Science* **5**, 165
Gasparini, G., Pellegatta, M., Crippa, S., *et al*. (2019) Nerves and pancreatic cancer: new insights into a dangerous relationship. *Cancers (Basel)* **11**, 893
German, A. J., Holden, S. L., Wiseman-Orr, M. L., *et al*. (2012) Quality of life is reduced in obese dogs but improves after successful weight loss. *The Veterinary Journal* **192**, 428-434
Gibbon, K. J., Cyborski, J. M., Guzinski, M. V., *et al*. (2003) Evaluation of adverse effects of emla (lidocaine/prilocaine) cream for the placement of jugular catheters in healthy cats. *Journal of Veterinary Pharmacology and Therapeutics* **26**, 439-441
Gilbert-Gregory, S. E., Stull, J. W., Rice, M. R., *et al*. (2016) Effects of trazodone on behavioral signs of stress in hospitalized dogs. *Journal of the American Veterinary Medical Association* **249**, 1281-1291
Gilron, I., Baron, R. & Jensen, T. (2015) Neuropathic pain: principles of diagnosis and treatment. *Mayo Clinic Proceedings* **90**, 532-545
Giuliano, E. A. (2008) Regional anesthesia as an adjunct for eyelid surgery in dogs. *Topics in Companion Animal Medicine* **23**, 51-56

Gordon-Evans, W. J., Suh, H. Y. & Guedes, A. G. (2020) Controlled, non-inferiority trial of bupivacaine liposome injectable suspension. *Journal of Feline Medicine and Surgery* **22**, 916-921
Gorney, A. M., Blau, S. R., Dohse, C. S., *et al*. (2016) Mechanical and thermal sensory testing in normal chondrodystrophoid dogs and dogs with spinal cord injury caused by thoracolumbar intervertebral disc herniations. *Journal of Veterinary Internal Medicine* **30**, 627-635
Granholm, M., McKusick, B. C., Westerholm, F. C., *et al*. (2006) Evaluation of the clinical efficacy and safety of dexmedetomidine or medetomidine in cats and their reversal with atipamezole. *Veterinary Anaesthesia and Analgesia* **33**, 214-223
Granholm, M., McKusick, B. C., Westerholm, F. C., *et al*. (2007) Evaluation of the clinical efficacy and safety of intramuscular and intravenous doses of dexmedetomidine and medetomidine in dogs and their reversal with atipamezole. *Veterinary Record* **160**, 891-897
Gray, L., Lang, C. W. & Porges, S. W. (2012) Warmth is analgesic in healthy newborns. *Pain* **153**, 960-966
Grimm, H., Bergadano, A., Musk, G. C., *et al*. (2018) Drawing the line in clinical treatment of companion animals: recommendations from an ethics working party. *Veterinary Record* **182**, 664
Grubb, T. (2010) Chronic neuropathic pain in veterinary patients. *Topics in Companion Animal Medicine* **25**, 45-52
Grubb, T. & Lobprise, H. (2020a) Local and regional anaesthesia in dogs and cats: descriptions of specific local and regional techniques (part 2). *Veterinary Medicine and Science* **6**, 218-234
Grubb, T. & Lobprise, H. (2020b) Local and regional anaesthesia in dogs and cats: overview of concepts and drugs (part 1). *Veterinary Medicine and Science* **6**, 209-217
Grubb, T., Sager, J., Gaynor, J. S., *et al*. (2020) 2020 aaha anesthesia and monitoring guidelines for dogs and cats. *Journal of the American Animal Hospital Association* **56**, 59-82
Gruen, M. E., Roe, S. C., Griffith, E., *et al*. (2014) Use of trazodone to facilitate postsurgical confinement in dogs. *Journal of the American Veterinary Medical Association* **245**, 296-301
Gruen, M. E., Thomson, A. E., Griffith, E. H., *et al*. (2016) A feline-specific anti-nerve growth factor antibody improves mobility in cats with degenerative joint disease-associated pain: a pilot proof of concept study. *Journal of Veterinary Internal Medicine* **30**, 1138-1148
Gruen, M. E., Alfaro-Cordoba, M., Thomson, A. E., *et al*. (2017) The use of functional data analysis to evaluate activity in a spontaneous model of degenerative joint disease associated pain in cats. *PLoS One* **12**, e0169576
Gruen, M. E., Samson, D. R. & Lascelles, B. D. X. (2019) Functional linear modeling of activity data shows analgesic-mediated improved sleep in dogs with spontaneous osteoarthritis pain. *Scientific Reports* **9**, 14192
Gruen, M. E., Myers, J. A. E. & Lascelles, B. D. X. (2021a) Efficacy and safety of an anti-nerve growth factor antibody (frunevetmab) for the treatment of degenerative joint disease-associated chronic pain in cats: a multisite pilot field study. *Frontiers in Veterinary Science* **8**, 610028
Gruen, M. E., Myers, J. A. E., Tena, J. S., *et al*. (2021b) Frunevetmab, a felinized anti-nerve growth factor monoclonal antibody, for the treatment of pain from osteoarthritis in cats. *Journal of Veterinary Internal Medicine* **35**, 2752-2762
Grundmann, S. & Stander, S. (2011) Chronic pruritus: clinics and treatment. *Annals of Dermatology* **23**, 1-11
Grzeskowiak, L., Endo, A., Beasley, S., *et al*. (2015) Microbiota and probiotics in canine and feline welfare. *Anaerobe* **34**, 14-23
Guedes, A. G. P., Meadows, J. M., Pypendop, B. H., *et al*. (2018) Evaluation of tramadol for treatment of osteoarthritis in geriatric cats. *Journal of the American Veterinary Medical Association* **252**, 565-571
Guillot, M., Moreau, M., Heit, M., *et al*. (2013) Characterization of osteoarthritis in cats and meloxicam efficacy using objective chronic pain evaluation tools. *The Veterinary Journal* **196**, 360-367
Guo, R., Chen, L. H., Xing, C., *et al*. (2019) Pain regulation by gut microbiota: molecular mechanisms and therapeutic potential. *British Journal of Anaesthesia* **123**, 637-654
Gutierrez-Blanco, E., Victoria-Mora, J. M., Ibancovichi-Camarillo, J. A., *et al*. (2015) Postoperative analgesic effects of either a constant rate infusion of fentanyl, lidocaine, ketamine, dexmedetomidine, or the combination lidocaine-ketamine-dexmedetomidine after ovariohysterectomy in dogs. *Veterinary Anaesthesia and Analgesia* **42**, 309-318
Hampton, A., Ford, A., Cox, R. E. 3rd, *et al*. (2020) Effects of music on behavior and physiological stress response of domestic cats in a veterinary clinic. *Journal of Feline Medicine and Surgery* **22**, 122-128
Hansen, B. (2008) Analgesia for the critically ill dog or cat: an update. *Veterinary Clinics of North America: Small Animal Practice* **38**, 1353-1363, vii
Hansen, B. & Hardie, E. (1993) Prescription and use of analgesics in dogs and cats in a veterinary teaching hospital: 258 cases (1983-1989). *Journal of the American Veterinary Medical Association* **202**, 1485-1494
Hansen, B. D., Hardie, E. M. & Carroll, G. S. (1997) Physiological measurements after ovariohysterectomy in dogs: What's normal? *Applied Animal Behaviour Science* **51**, 101-109
Hansen, B., Lascelles, B. D., Thomson, A., *et al*. (2013) Variability of performance of wound infusion catheters. *Veterinary Anaesthesia and Analgesia* **40**, 308-315
Hanssen, M. M., Peters, M. L., Boselie, J. J., *et al*. (2017) Can positive affect attenuate (persistent) pain? State of the art and clinical implications. *Current Rheumatology Reports* **19**, 80
Harman, R., Carlson, K., Gaynor, J., *et al*. (2016) A prospective, randomized, masked, and placebo-controlled efficacy study of intraarticular allogeneic adipose stem cells for the treatment of osteoarthritis in dogs. *Frontiers in Veterinary Science* **3**, 81
Hernández-Avalos, I., Valverde, A., Ibancovichi-Camarillo, J. A., *et al*. (2020) 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. *PLoS One* **15**, e0223697
Hewson, C. J., Dohoo, I. R. & Lemke, K. A. (2006a) Factors affecting the use of postincisional analgesics in dogs and cats by Canadian veterinarians in 2001. *Canadian Veterinary Journal* **47**, 453-459
Hewson, C. J., Dohoo, I. R. & Lemke, K. A. (2006b) Perioperative use of analgesics in dogs and cats by Canadian veterinarians in 2001. *Canadian Veterinary Journal* **47**, 352-359
Hielm-Bjorkman, A. K., Rita, H. & Tulamo, R. M. (2009) Psychometric testing of the Helsinki chronic pain index by completion of a questionnaire in Finnish by caretakers of dogs with chronic signs of pain caused by osteoarthritis. *American Journal of Veterinary Research* **70**, 727-734
Higginson, I. J., Murtagh, F. E. M. & Osborne, T. R. (2013) Epidemiology of pain in cancer. In: Cancer Pain. Eds M. Hanna and Z. Zlicz. Springer, London, UK. pp 5-24
Ho, C., Martinusen, D. & Lo, C. (2019) A review of cannabis in chronic kidney disease symptom management. *Canadian Journal of Kidney Health and Disease* **6**, 2054358119828391
Hofmeister, E. H. & Egger, C. M. (2004) Transdermal fentanyl patches in small animals. *Journal of the American Animal Hospital Association* **40**, 468-478
Holden, E., Calvo, G., Collins, M., *et al*. (2014) Evaluation of facial expression in acute pain in cats. *The Journal of Small Animal Practice* **55**, 615-621
Holton, L., Reid, J., Scott, E. M., *et al*. (2001) Development of a behaviour-based scale to measure acute pain in dogs. *Veterinary Record* **148**, 525-531
Honkavaara, J. M., Restitutti, F., Raekallio, M. R., *et al*. (2011) The effects of increasing doses of mk-467, a peripheral alpha(2)-adrenergic receptor antagonist, on the cardiopulmonary effects of intravenous dexmedetomidine in conscious dogs. *Journal of Veterinary Pharmacology and Therapeutics* **34**, 332-337
Hopfensperger, M., Messenger, K. M., Papich, M. G., *et al*. (2013) The use of oral transmucosal detomidine hydrochloride gel to facilitate handling in dogs. *Journal of Veterinary Behavior* **8**, 114-123
Howlett, A. C. & Abood, M. E. (2017) Cb1 and cb2 receptor pharmacology. *Advances in Pharmacology* **80**, 169-206
Hughes, B. O. (1976) Behaviour as an index of welfare. In: *Fifth European Poultry Conference*, Malta. pp 1005-1018
Hunt, J. R., Knowles, T. G., Lascelles, B. D., *et al*. (2015) Prescription of perioperative analgesics by UK small animal veterinary surgeons in 2013. *Veterinary Record* **176**, 493
Hunt, J., Knazovicky, D., Lascelles, B. D. X., *et al*. (2019) Quantitative sensory testing in dogs with painful disease: a window to pain mechanisms? *The Veterinary Journal* **243**, 33-41
Iadarola, M. J., Sapio, M. R., Raithel, S. J., *et al*. (2018) Long-term pain relief in canine osteoarthritis by a single intra-articular injection of resiniferatoxin, a potent trpv1 agonist. *Pain* **159**, 2105-2114
IASP. (n.d.-a) Terminology. IASP
IASP. (n.d.-b) Orofacial pain. IASP
IASP. (n.d.-c) Orofacial and head pain. IASP
Imagawa, V. H., Fantoni, D. T., Tatarunas, A. C., *et al*. (2011) The use of different doses of metamizol for post-operative analgesia in dogs. *Veterinary Anaesthesia and Analgesia* **38**, 385-393
Impellizeri, J. A., Tetrick, M. A. & Muir, P. (2000) Effect of weight reduction on clinical signs of lameness in dogs with hip osteoarthritis. *Journal of the American Veterinary Medical Association* **216**, 1089-1091

Indrawirawan, Y. & McAlees, T. (2014) Tramadol toxicity in a cat: Case report and literature review of serotonin syndrome. *Journal of Feline Medicine and Surgery* **16**, 572-578
Institute of Medicine Committee on Advancing Pain Research, Care, & Education (2011) The national academies collection: Reports funded by national institutes of health. In: Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. National Academies Press (US) Copyright © 2011, National Academy of Sciences, Washington, DC, USA
Jensen, T. S., Baron, R., Haanpaa, M., *et al*. (2011) A new definition of neuropathic pain. *Pain* **152**, 2204-2205
Johansen, A., Romundstad, L., Nielsen, C. S., *et al*. (2012) Persistent postsurgical pain in a general population: prevalence and predictors in the tromsø study. *Pain* **153**, 1390-1396
Joyce, A. & Yates, D. (2011) Help stop teenage pregnancy! Early-age neutering in cats. *Journal of Feline Medicine and Surgery* **13**, 3-10
Kallio-Kujala, I. J., Turunen, H. A., Raekallio, M. R., *et al*. (2018) Peripherally acting alpha-adrenoceptor antagonist mk-467 with intramuscular medetomidine and butorphanol in dogs: a prospective, randomised, clinical trial. *The Veterinary Journal* **240**, 22-26
Kalso, E., Mennander, S., Tasmuth, T., *et al*. (2001) Chronic post-sternotomy pain. *Acta Anaesthesiologica Scandinavica* **45**, 935-939
Kaptchuk, T. J., Chen, K. J. & Song, J. (2010) Recent clinical trials of acupuncture in the west: responses from the practitioners. *Chinese Journal of Integrative Medicine* **16**, 197-203
Kasten, J. I., Messenger, K. M. & Campbell, N. B. (2018) Sedative and cardiopulmonary effects of buccally administered detomidine gel and reversal with atipamezole in dogs. *American Journal of Veterinary Research* **79**, 1253-1260
Katz, J. N., Arant, K. R. & Loeser, R. F. (2021) Diagnosis and treatment of hip and knee osteoarthritis: a review. *Journal of the American Medical Association* **325**, 568-578
Kehlet, H., Jensen, T. S. & Woolf, C. J. (2006) Persistent postsurgical pain: risk factors and prevention. *Lancet* **367**, 1618-1625
Khan, A. H. & Sadroddiny, E. (2015) Licensed monoclonal antibodies and associated challenges. *Human Antibodies* **23**, 63-72
Kinobe, R. T. & Miyake, Y. (2020) Evaluating the anti-inflammatory and analgesic properties of maropitant: a systematic review and meta-analysis. *The Veterinary Journal* **259-260**, 105471
Klinck, M. P., Rialland, P., Guillot, M., *et al*. (2015) Preliminary validation and reliability testing of the Montreal instrument for cat arthritis testing, for use by veterinarians, in a colony of laboratory cats. *Animals (Basel)* **5**, 1252-1267
Klinck, M. P., Monteiro, B. P., Lussier, B., *et al*. (2018) Refinement of the Montreal instrument for cat arthritis testing, for use by veterinarians: detection of naturally occurring osteoarthritis in laboratory cats. *Journal of Feline Medicine and Surgery* **20**, 728-740
Knazovicky, D., Tomas, A., Motsinger-REIF, A., *et al*. (2015) Initial evaluation of nighttime restlessness in a naturally occurring canine model of osteoarthritis pain. *PeerJ* **3**, e772
Knazovicky, D., Helgeson, E. S., Case, B., *et al*. (2016) Widespread somatosensory sensitivity in naturally occurring canine model of osteoarthritis. *Pain* **157**, 1325-1332
Knowler, S. P., Galea, G. L. & Rusbridge, C. (2018) Morphogenesis of canine chiari malformation and secondary syringomyelia: disorders of cerebrospinal fluid circulation. *Frontiers in Veterinary Science* **5**, 171
Koh, R. B., Isaza, N., Xie, H., *et al*. (2014) Effects of maropitant, acepromazine, and electroacupuncture on vomiting associated with administration of morphine in dogs. *Journal of the American Veterinary Medical Association* **244**, 820-829
Kongara, K. (2018) Pharmacogenetics of opioid analgesics in dogs. *Journal of Veterinary Pharmacology and Therapeutics* **41**, 195-204
Korpivaara, M., Laapas, K., Huhtinen, M., *et al*. (2017) Dexmedetomidine oromucosal gel for noise-associated acute anxiety and fear in dogs-a randomised, double-blind, placebo-controlled clinical study. *Veterinary Record* **180**, 356
Kraijer, M., Fink-Gremmels, J. & Nickel, R. F. (2003) The short-term clinical efficacy of amitriptyline in the management of idiopathic feline lower urinary tract disease: a controlled clinical study. *Journal of Feline Medicine and Surgery* **5**, 191-196
Kronen, P. W., Ludders, J. W., Erb, H. N., *et al*. (2006) A synthetic fraction of feline facial pheromones calms but does not reduce struggling in cats before venous catheterization. *Veterinary Anaesthesia and Analgesia* **33**, 258-265
Krugner-Higby, L., Smith, L., Schmidt, B., *et al*. (2011) Experimental pharmacodynamics and analgesic efficacy of liposome-encapsulated hydromorphone in dogs. *Journal of the American Animal Hospital Association* **47**, 185-195
Ku, L. C. & Smith, P. B. (2015) Dosing in neonates: special considerations in physiology and trial design. *Pediatric Research* **77**, 2-9
Lamminen, T., Korpivaara, M., Suokko, M., *et al*. (2021) Efficacy of a single dose of pregabalin on signs of anxiety in cats during transportation-a pilot study. *Frontiers in Veterinary Science* **8**, 711816
Lamont, L. A., Bulmer, B. J., Sisson, D. D., *et al*. (2002) Doppler echocardiographic effects of medetomidine on dynamic left ventricular outflow tract obstruction in cats. *Journal of the American Veterinary Medical Association* **221**, 1276-1281
Langevin, H. M. (2014) Acupuncture, connective tissue, and peripheral sensory modulation. *Critical Reviews in Eukaryotic Gene Expression* **24**, 249-253
Langevin, H. M. & Wayne, P. M. (2018) What is the point? The problem with acupuncture research that no one wants to talk about. *Journal of Alternative and Complementary Medicine* **24**, 200-207
Langevin, H. M., Bishop, J., Maple, R., *et al*. (2018) Effect of stretching on thoracolumbar fascia injury and movement restriction in a porcine model. *American Journal of Physical Medicine & Rehabilitation* **97**, 187-191
Lascelles, B. D. X. (2013) Management of chronic cancer pain. In: Small animal clinical oncology. 5th edn. Eds S. J. Withrow, D. M. Vail and R. L. Page. Elsevier, St. Louis, MO, USA. pp 245-259
Lascelles, B. D., Cripps, P. J., Jones, A., *et al*. (1998) Efficacy and kinetics of carprofen, administered preoperatively or postoperatively, for the prevention of pain in dogs undergoing ovariohysterectomy. *Veterinary Surgery* **27**, 568-582
Lascelles, B. D., Blikslager, A. T., Fox, S. M., *et al*. (2005) Gastrointestinal tract perforation in dogs treated with a selective cyclooxygenase-2 inhibitor: 29 cases (2002-2003). *Journal of the American Veterinary Medical Association* **227**, 1112-1117
Lascelles, B. D., Hansen, B. D., Roe, S., *et al*. (2007) Evaluation of client-specific outcome measures and activity monitoring to measure pain relief in cats with osteoarthritis. *Journal of Veterinary Internal Medicine* **21**, 410-416
Lascelles, B. D., 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**, 53-59
Lascelles, B. D., DePuy, V., Thomson, A., *et al*. (2010a) Evaluation of a therapeutic diet for feline degenerative joint disease. *Journal of Veterinary Internal Medicine* **24**, 487-495
Lascelles, B. D., Freire, M., Roe, S. C., *et al*. (2010b) Evaluation of functional outcome after bfx total hip replacement using a pressure sensitive walkway. *Veterinary Surgery* **39**, 71-77
Lascelles, B. D., Knazovicky, D., Case, B., *et al*. (2015) A canine-specific anti-nerve growth factor antibody alleviates pain and improves mobility and function in dogs with degenerative joint disease-associated pain. *BMC Veterinary Research* **11**, 101
Lascelles, B. D., Rausch-Derra, L. C., Wofford, J. A., *et al*. (2016) Pilot, randomized, placebo-controlled clinical field study to evaluate the effectiveness of bupivacaine liposome injectable suspension for the provision of post-surgical analgesia in dogs undergoing stifle surgery. *BMC Veterinary Research* **12**, 168
Lascelles, B. D. X., Brown, D. C., Conzemius, M. G., *et al*. (2019) Measurement of chronic pain in companion animals: discussions from the pain in animals workshop (paw) 2017. *The Veterinary Journal* **250**, 71-78
Lattimer, J. C., Selting, K. A., Lunceford, J. M., *et al*. (2019) Intraarticular injection of a tin-117 m radiosynoviorthesis agent in normal canine elbows causes no adverse effects. *Veterinary Radiology & Ultrasound* **60**, 567-574
Lawrence, A. B., Vigors, B. & Sandøe, P. (2019) What is so positive about positive animal welfare?-a critical review of the literature. *Animals (Basel)* **9**, 783
Lee, B. H. (2002) Managing pain in human neonates–applications for animals. *Journal of the American Veterinary Medical Association* **221**, 233-237
Lee, S. U., Bang, M. S. & Han, T. R. (2002) Effect of cold air therapy in relieving spasticity: applied to spinalized rabbits. *Spinal Cord* **40**, 167-173
Lefman, S. H. & Prittie, J. E. (2019) Psychogenic stress in hospitalized veterinary patients: causation, implications, and therapies. *Journal of Veterinary Emergency and Critical Care (San Antonio, Tex.)* **29**, 107-120
Lemke, K. A., Runyon, C. L. & Horney, B. S. (2002) Effects of preoperative administration of ketoprofen on whole blood platelet aggregation, buccal mucosal bleeding time, and hematologic indices in dogs undergoing elective ovariohysterectomy. *Journal of the American Veterinary Medical Association* **220**, 1818-1822
Leung, J., Beths, T., Carter, J. E., *et al*. (2021) Intravenous acetaminophen does not provide adequate postoperative analgesia in dogs following ovariohysterectomy. *Animals (Basel)* **11**, 3609
Levy, N., Ballegeer, E. & Koenigshof, A. (2019) Clinical and radiographic findings in cats with aspiration pneumonia: retrospective evaluation of 28 cases. *Journal of Small Animal Practice* **60**, 356-360

Liao, Y. C., HSU, L. F., Hsieh, L. Y., *et al*. (2021) Effectiveness of green tea mouthwash for improving oral health status in oral cancer patients: a single-blind randomized controlled trial. *International Journal of Nursing Studies* **121**, 103985
Lie, K. I., Jaeger, G., Nordstoga, K., *et al*. (2011) Inflammatory response to therapeutic gold bead implantation in canine hip joint osteoarthritis. *Veterinary Pathology* **48**, 1118-1124
Lim, M. Y., Chen, H. C. & Omar, M. A. (2014) Assessment of post-operative pain in cats: a case study on veterinary students of universiti putra Malaysia. *Journal of Veterinary Medical Education* **41**, 197-203
Lin, G. Y., Robben, J. H., Murrell, J. C., *et al*. (2008) Dexmedetomidine constant rate infusion for 24 hours during and after propofol or isoflurane anaesthesia in dogs. *Veterinary Anaesthesia and Analgesia* **35**, 141-153
Lindig, A. M., McGreevy, P. D. & Crean, A. J. (2020) Musical dogs: a review of the influence of auditory enrichment on canine health and behavior. *Animals (Basel)* **10**, 127
Lister, S. A., Roush, J. K., Renberg, W. C., *et al*. (2009) Ground reaction force analysis of unilateral coxofemoral denervation for the treatment of canine hip dysplasia. *Veterinary and Comparative Orthopaedics and Traumatology* **22**, 137-141
Liu, J. K. (2014) The history of monoclonal antibody development – progress, remaining challenges and future innovations. *Annals of Medicine and Surgery* **3**, 113-116
Liu, B., Fan, L., Balakrishna, S., *et al*. (2013) Trpm8 is the principal mediator of menthol-induced analgesia of acute and inflammatory pain. *Pain* **154**, 2169-2177
Looney, A. L., Huntingford, J. L., Blaeser, L. L., *et al*. (2018) A randomized blind placebo-controlled trial investigating the effects of photobiomodulation therapy (pbmt) on canine elbow osteoarthritis. *Canadian Veterinary Journal* **59**, 959-966
Lorena, S. E., Luna, S. P., Lascelles, B. D., *et al*. (2014) Current attitudes regarding the use of perioperative analgesics in dogs and cats by brazilian veterinarians. *Veterinary Anaesthesia and Analgesia* **41**, 82-89
Luks, A. M., Zwass, M. S., Brown, R. C., *et al*. (1998) Opioid-induced analgesia in neonatal dogs: Pharmacodynamic differences between morphine and fentanyl. *Journal of Pharmacology and Experimental Therapeutics* **284**, 136-141
Luna, S. P. L., Trindade, P. H. E., Monteiro, B. P., *et al*. (2022) Multilingual validation of the short form of the UNESP-Botucatu feline pain scale (ufeps-sf). *PeerJ* **10**, e13134
Ma, J., Kavelaars, A., Dougherty, P. M., *et al*. (2018) Beyond symptomatic relief for chemotherapy-induced peripheral neuropathy: targeting the source. *Cancer* **124**, 2289-2298
Machin, H., Taylor-Brown, F. & Adami, C. (2020) Use of acupuncture as adjuvant analgesic technique in dogs undergoing thoracolumbar hemilaminectomy. *The Veterinary Journal* **264**, 105536
MacPhail, C. M., Lappin, M. R., Meyer, D. J., *et al*. (1998) Hepatocellular toxicosis associated with administration of carprofen in 21 dogs. *Journal of the American Veterinary Medical Association* **212**, 1895-1901
Madden, M., Gurney, M. & Bright, S. (2014) Amantadine, an *N*-methyl-d-aspartate antagonist, for treatment of chronic neuropathic pain in a dog. *Veterinary Anaesthesia and Analgesia* **41**, 440-441
Malanga, G. A., Yan, N. & Stark, J. (2015) Mechanisms and efficacy of heat and cold therapies for musculoskeletal injury. *Postgraduate Medicine* **127**, 57-65
Malo, A., Ruel, H. L. M., Monteiro, B. P., *et al*. (2022) A Comparison of an Opioid-Free Injectable Anesthesia Protocol with or without Multimodal Analgesia in Kittens Undergoing Ovariohysterectomy. Association of Veterinary Anaesthetists Spring Meeting 2022. Nafplio, Greece. p94
Maniaki, E., Murrell, J., Langley-Hobbs, S. J., *et al*. (2021) Associations between early neutering, obesity, outdoor access, trauma and feline degenerative joint disease. *Journal of Feline Medicine and Surgery* **23**, 965-975
Mantyh, P. W. (2014) Bone cancer pain: from mechanism to therapy. *Current Opinion in Supportive and Palliative Care* **8**, 83-90
McCarberg, W. & O'Connor, A. (2004) A new look at heat treatment for pain disorders part 1. *American Pain Society Bulletin* **14**, 34-41
McFadzean, W. J. M., Macfarlane, P., Granger, N., *et al*. (2021) Influence of peri-incisional epaxial muscle infiltration with bupivacaine pre- or post-surgery on opioid administration in dogs undergoing thoraco-lumbar hemilaminectomy. *The Veterinary Journal* **270**, 105622
McGuire, D. B. (1992) Comprehensive and multidimensional assessment and measurement of pain. *Journal of Pain and Symptom Management* **7**, 312-319
McPartland, J. M., Guy, G. W. & Di Marzo, V. (2014) Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. *PLoS One* **9**, e89566
Mellor, D. J., Beausoleil, N. J., Littlewood, K. E., *et al*. (2020) The 2020 five domains model: including human-animal interactions in assessments of animal welfare. *Animals (Basel)* **10**, 1870
Messenger, K. M., Hopfensperger, M., Knych, H. K., *et al*. (2016) Pharmacokinetics of detomidine following intravenous or oral-transmucosal administration and sedative effects of the oral-transmucosal treatment in dogs. *American Journal of Veterinary Research* **77**, 413-420
Mich, P. M., Hellyer, P. W., Kogan, L., *et al*. (2010) Effects of a pilot training program on veterinary students' pain knowledge, attitude, and assessment skills. *Journal of Veterinary Medical Education* **37**, 358-368
Mikawa, S., Yamamoto, S., Islam, M. S., *et al*. (2015) Anti-emetic drug maropitant induces intestinal motility disorder but not anti-inflammatory action in mice. *Journal of Veterinary Medical Science* **77**, 1195-1199
Millis, D. L. & Levine, D. (2014) Assessing and measuring outcomes. In: Canine Rehabilitation & Physical Therapy. Eds D. L. Millis and D. Levine. Saunders, St. Louis, MO, USA. pp 220-240
Mizisin, A. P., Shelton, G. D., Wagner, S., *et al*. (1998) Myelin splitting, schwann cell injury and demyelination in feline diabetic neuropathy. *Acta Neuropathologica* **95**, 171-174
Mohammad-Zadeh, L. F., Moses, L. & Gwaltney-Brant, S. M. (2008) Serotonin: a review. *Journal of Veterinary Pharmacology and Therapeutics* **31**, 187-199
Montasell, X., Dupuis, J., Huneault, L., *et al*. (2018) Short- and long-term outcomes after shoulder excision arthroplasty in 7 small breed dogs. *Canadian Veterinary Journal* **59**, 277-283
Monteiro, B. (2019) Assessment of chronic pain in companion animals: development and concurrent validation of neurophysiological methods. In: Faculté de médecine vétérinaire. Université de Montréal, Montreal, Canada. p 270
Monteiro, B. P. (2020) Feline chronic pain and osteoarthritis. *Veterinary Clinics of North America: Small Animal Practice* **50**, 769-788
Monteiro, B. & Simon, B. (2022) Pain management. In: Clinical Medicine of the Dog and Cat. 4th edn. Eds M. Schaer, F. Gaschen and S. Walton. CRC Press, Boca Raton, FL, USA. pp 997-1018
Monteiro, B. & Steagall, P. V. (2019a) Antiinflammatory drugs. *Veterinary Clinics of North America: Small Animal Practice* **49**, 993-1011
Monteiro, B. P. & Steagall, P. V. (2019b) Chronic pain in cats: recent advances in clinical assessment. *Journal of Feline Medicine and Surgery* **21**, 601-614
Monteiro, B. P., Klinck, M. P., Moreau, M., *et al*. (2017) Analgesic efficacy of tramadol in cats with naturally occurring osteoarthritis. *PLoS One* **12**, e0175565
Monteiro, B. P., de Lorimier, L. P., Moreau, M., *et al*. (2018) Pain characterization and response to palliative care in dogs with naturally-occurring appendicular osteosarcoma: an open label clinical trial. *PLoS One* **13**, e0207200
Monteiro, B., Steagall, P. V. M., Lascelles, B. D. X., *et al*. (2019) Long-term use of non-steroidal anti-inflammatory drugs in cats with chronic kidney disease: from controversy to optimism. *Journal of Small Animal Practice* **60**, 459-462
Monteiro, B. P., Otis, C., Del Castillo, J. R. E., *et al*. (2020) Quantitative sensory testing in feline osteoarthritic pain – a systematic review and meta-analysis. *Osteoarthritis and Cartilage* **28**, 885-896
Monteiro-Steagall, B. P., Steagall, P. V. & Lascelles, B. D. (2013) Systematic review of nonsteroidal anti-inflammatory drug-induced adverse effects in dogs. *Journal of Veterinary Internal Medicine* **27**, 1011-1019
Moore, S. A. (2016) Managing neuropathic pain in dogs. *Frontiers in Veterinary Science* **3**, 12
Moran, C. E. & Hofmeister, E. H. (2013) Prevalence of pain in a university veterinary intensive care unit. *Journal of Veterinary Emergency and Critical Care (San Antonio, Tex.)* **23**, 29-36
Moran-Muñoz, R., Ibancovichi, J. A., Gutierrez-Blanco, E., *et al*. (2014) Effects of lidocaine, dexmedetomidine or their combination on the minimum alveolar concentration of sevoflurane in dogs. *Journal of Veterinary Medical Science* **76**, 847-853
Muller, S. H., Diaz, J. H. & Kaye, A. D. (2015) Clinical applications of intravenous lipid emulsion therapy. *Journal of Anesthesia* **29**, 920-926
Murrell, J. C. & Hellebrekers, L. J. (2005) Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog. *Veterinary Anaesthesia and Analgesia* **32**, 117-127
Murrell, J. C., Robertson, S. A., Taylor, P. M., *et al*. (2007) Use of a transdermal matrix patch of buprenorphine in cats: preliminary pharmacokinetic and pharmacodynamic data. *Veterinary Record* **160**, 578-583
Murrell, J. C., Psatha, E. P., Scott, E. M., *et al*. (2008) Application of a modified form of the Glasgow pain scale in a veterinary teaching centre in the Netherlands. *The Veterinary Record* **162**, 403-408
Myrna, K. E., Bentley, E. & Smith, L. J. (2010) Effectiveness of injection of local anesthetic into the retrobulbar space for postoperative analgesia following eye enucleation in dogs. *Journal of the American Veterinary Medical Association* **237**, 174-177

Nascimento, F. F., Marques, V. I., Crociolli, G. C., *et al*. (2019) Analgesic efficacy of laser acupuncture and electroacupuncture in cats undergoing ovariohysterectomy. *Journal of Veterinary Medical Science* **81**, 764-770
National Center for Complementary and Integrative Health. (n.d.) Acupuncture: in depth. NIH
Naugle, K. M., Fillingim, R. B. & Riley, J. L. 3rd (2012) A meta-analytic review of the hypoalgesic effects of exercise. *Journal of Pain* **13**, 1139-1150
Nelson, F. R., Zvirbulis, R. & Pilla, A. A. (2013) Non-invasive electromagnetic field therapy produces rapid and substantial pain reduction in early knee osteoarthritis: a randomized double-blind pilot study. *Rheumatology International* **33**, 2169-2173
Nganvongpanit, K., Boonsri, B., Sripratak, T., *et al*. (2013) Effects of one-time and two-time intra-articular injection of hyaluronic acid sodium salt after joint surgery in dogs. *Journal of Veterinary Science* **14**, 215-222
Niemiec, B., Gawor, J., Nemec, A., *et al*. (2020) World small animal veterinary association global dental guidelines. *Journal of Small Animal Practice* **61**, E36-E161
Nijs, J., Tumkaya Yilmaz, S., Elma, O., *et al*. (2020) Nutritional intervention in chronic pain: an innovative way of targeting central nervous system sensitization? *Expert Opinion on Therapeutic Targets* **24**, 793-803
Niyom, S., Boscan, P., Twedt, D. C., *et al*. (2013) Effect of maropitant, a neurokinin-1 receptor antagonist, on the minimum alveolar concentration of sevoflurane during stimulation of the ovarian ligament in cats. *Veterinary Anaesthesia and Analgesia* **40**, 425-431
Nolan, M. W., Long, C. T., Marcus, K. L., *et al*. (2017) Nocifensive behaviors in mice with radiation-induced oral mucositis. *Radiation Research* **187**, 397-403
Nolan, M. W., Green, N. A., DiVito, E. M., *et al*. (2020a) Impact of radiation dose and pre-treatment pain levels on survival in dogs undergoing radiotherapy with or without chemotherapy for presumed extremity osteosarcoma. *Veterinary and Comparative Oncology* **18**, 538-547
Nolan, M. W., Kelsey, K. L., Enomoto, M., *et al*. (2020b) Pet dogs with subclinical acute radiodermatitis experience widespread somatosensory sensitization. *Radiation Research* **193**, 241-248
Noli, C., Colombo, S., Cornegliani, L., *et al*. (2011a) Quality of life of dogs with skin disease and of their owners. Part 2: administration of a questionnaire in various skin diseases and correlation to efficacy of therapy. *Veterinary Dermatology* **22**, 344-351
Noli, C., Minafo, G. & Galzerano, M. (2011b) Quality of life of dogs with skin diseases and their owners. Part 1: development and validation of a questionnaire. *Veterinary Dermatology* **22**, 335-343
Noli, C., Matricoti, I. & Schievano, C. (2019) A double-blinded, randomized, methylprednisolone-controlled study on the efficacy of oclacitinib in the management of pruritus in cats with nonflea nonfood-induced hypersensitivity dermatitis. *Veterinary Dermatology* **30**, 110-e130
O'Brien, T. Q., Clark-Price, S. C., Evans, E. E., *et al*. (2010) Infusion of a lipid emulsion to treat lidocaine intoxication in a cat. *Journal of the American Veterinary Medical Association* **237**, 1455-1458
Off, W. & Matis, U. (2010) Excision arthroplasty of the hip joint in dogs and cats. Clinical, radiographic, and gait analysis findings from the department of surgery, veterinary faculty of the Ludwig-Maximilians-University of Munich, Germany. 1997. *Veterinary and Comparative Orthopaedics and Traumatology* **23**, 297-305
Okamoto-Okubo, C. E., Cassu, R. N., Joaquim, J. G. F., *et al*. (2021) Chronic pain and gait analysis in dogs with degenerative hip joint disease treated with repeated intra-articular injections of platelet-rich plasma or allogeneic adipose-derived stem cells. *The Journal of Veterinary Medical Science* **83**, 881-888
Olivry, T., DeBoer, D. J., Favrot, C., *et al*. (2015) Treatment of canine atopic dermatitis: 2015 updated guidelines from the International Committee on Allergic Diseases of Animals (ICADA). *BMC Veterinary Research* **11**, 210
Ovbey, D. H., Wilson, D. V., Bednarski, R. M., *et al*. (2014) Prevalence and risk factors for canine post-anesthetic aspiration pneumonia (1999-2009): a multicenter study. *Veterinary Anaesthesia and Analgesia* **41**, 127-136
Pacheco, M., Knowles, T. G., Hunt, J., *et al*. (2020) Comparing paracetamol/codeine and meloxicam for postoperative analgesia in dogs: a non-inferiority trial. *Veterinary Record* **187**, e61
Page, G. G., Blakely, W. P., Ben-Eliyahu, S., *et al*. (2001) Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. *Pain* **90**, 191-199
Pageat, P. & Gaultier, E. (2003) Current research in canine and feline pheromones. *Veterinary Clinics of North America: Small Animal Practice* **33**, 187-211
Pascoe, P. J., Raekallio, M., Kuusela, E., *et al*. (2006) Changes in the minimum alveolar concentration of isoflurane and some cardiopulmonary measurements during three continuous infusion rates of dexmedetomidine in dogs. *Veterinary Anaesthesia and Analgesia* **33**, 97-103
Pereira, M. A., Campos, K. D., Gonçalves, L. A., *et al*. (2021) Cyclooxygenases 1 and 2 inhibition and analgesic efficacy of dipyrone at different doses or meloxicam in cats after ovariohysterectomy. *Veterinary Anaesthesia and Analgesia* **48**, 7-16
Perez Jimenez, T. E., Mealey, K. L., Grubb, T. L., *et al*. (2016) Tramadol metabolism to *o*-desmethyl tramadol (m1) and *n*-desmethyl tramadol (m2) by dog liver microsomes: species comparison and identification of responsible canine cytochrome p-450s (cyps). *Drug Metabolism and Disposition* **44**, 1963-1972
Perret-Gentil, F., Doherr, M. G., Spadavecchia, C., *et al*. (2014) Attitudes of swiss veterinarians towards pain and analgesia in dogs and cats. *Schweizer Archiv für Tierheilkunde* **156**, 111-117
Pieper, K., Schuster, T., Levionnois, O., *et al*. (2011) Antinociceptive efficacy and plasma concentrations of transdermal buprenorphine in dogs. *The Veterinary Journal* **187**, 335-341
Piomelli, D. & Russo, E. B. (2016) The cannabis sativa versus cannabis indica debate: an interview with Ethan Russo, MD. *Cannabis and Cannabinoid Research* **1**, 44-46
Platt, S. R., Adams, V., Garosi, L. S., *et al*. (2006) Treatment with gabapentin of 11 dogs with refractory idiopathic epilepsy. *Veterinary Record* **159**, 881-884
Plessas, I. N., Volk, H. A., Rusbridge, C., *et al*. (2015) Comparison of gabapentin versus topiramate on clinically affected dogs with chiari-like malformation and syringomyelia. *Veterinary Record* **177**, 288
Polaski, A. M., Phelps, A. L., Kostek, M. C., *et al*. (2019) Exercise-induced hypoalgesia: a meta-analysis of exercise dosing for the treatment of chronic pain. *PLoS One* **14**, e0210418
Portela, D. A., Verdier, N. & Otero, P. E. (2018a) Regional anesthetic techniques for the pelvic limb and abdominal wall in small animals: a review of the literature and technique description. *The Veterinary Journal* **238**, 27-40
Portela, D. A., Verdier, N. & Otero, P. E. (2018b) Regional anesthetic techniques for the thoracic limb and thorax in small animals: a review of the literature and technique description. *The Veterinary Journal* **241**, 8-19
Porters, N., de Rooster, H., Moons, C. P., *et al*. (2015) Prepubertal gonadectomy in cats: different injectable anaesthetic combinations and comparison with gonadectomy at traditional age. *Journal of Feline Medicine and Surgery* **17**, 458-467
Pypendop, B. H. & Ilkiw, J. E. (2005) Assessment of the hemodynamic effects of lidocaine administered iv in isoflurane-anesthetized cats. *American Journal of Veterinary Research* **66**, 661-668
Pypendop, B. H. & Verstegen, J. P. (1998) Hemodynamic effects of medetomidine in the dog: a dose titration study. *Veterinary Surgery* **27**, 612-622
Quimby, J. M., Smith, M. L. & Lunn, K. F. (2011) Evaluation of the effects of hospital visit stress on physiologic parameters in the cat. *Journal of Feline Medicine and Surgery* **13**, 733-737
Quimby, J., Gowland, S., Carney, H. C., *et al*. (2021) 2021 aaha/aafp feline life stage guidelines. *Journal of Feline Medicine and Surgery* **23**, 211-233
Quimby, J. M., Lorbach, S. K., Saffire, A., *et al*. (2022) Serum concentrations of gabapentin in cats with chronic kidney disease. *Journal of Feline Medicine and Surgery* **1098612x221077017**
Rae, L., MacNab, N., Bidner, S., *et al*. (2021) Attitudes and practices of veterinarians in Australia to acute pain management in cats. *Journal of Feline Medicine and Surgery* **24**, 715-725
Ranger, M. & Brunau, R. E. (2015) How do babies feel pain? *eLife* **4**, e07552
Rausch-Derra, L., Huebner, M., Wofford, J., *et al*. (2016) A prospective, randomized, masked, placebo-controlled multisite clinical study of grapiprant, an ep4 prostaglandin receptor antagonist (pra), in dogs with osteoarthritis. *Journal of Veterinary Internal Medicine* **30**, 756-763
Ray, M., Carney, H. C., Boynton, B., *et al*. (2021) 2021 aafp feline senior care guidelines. *Journal of Feline Medicine and Surgery* **23**, 613-638
Reader, R. C., McCarthy, R. J., Schultz, K. L., *et al*. (2020) Comparison of liposomal bupivacaine and 0.5% bupivacaine hydrochloride for control of postoperative pain in dogs undergoing tibial plateau leveling osteotomy. *Journal of the American Veterinary Medical Association* **256**, 1011-1019
Reid, J., Nolan, A. M., Hughes, J. M. L., *et al*. (2007) Development of the short-form Glasgow composite measure pain scale (CMPS-SF) and derivation of an analgesic intervention score. *Animal Welfare* **16**, 97-104
Reid, J., Wiseman-ORR, M. L., Scott, E. M., *et al*. (2013) Development, validation and reliability of a web-based questionnaire to measure health-related quality of life in dogs. *The Journal of Small Animal Practice* **54**, 227-233
Reid, J., Scott, E. M., Calvo, G., *et al*. (2017) Definitive Glasgow acute pain scale for cats: validation and intervention level. *Veterinary Record* **180**, 449
Reid, J., Nolan, A. M. & Scott, E. M. (2018a) Measuring pain in dogs and cats using structured behavioural observation. *The Veterinary Journal* **236**, 72-79
Reid, J., Wiseman-Orr, L. & Scott, M. (2018b) Shortening of an existing generic online health-related quality of life instrument for dogs. *The Journal of Small Animal Practice* **59**, 334-342

Rialland, P., Authier, S., Guillot, M., *et al*. (2012) Validation of orthopedic postoperative pain assessment methods for dogs: a prospective, blinded, randomized, placebo-controlled study. *PLoS One* **7**, e49480
Ribeiro, M. R., de Carvalho, C. B., Pereira, R. H. Z., *et al*. (2017) Yamamoto new scalp acupuncture for postoperative pain management in cats undergoing ovariohysterectomy. *Veterinary Anaesthesia and Analgesia* **44**, 1236-1244
Riddell, R. R. P., Racine, N. M., Gennis, H. G., *et al*. (2015) Non-pharmacological management of infant and young child procedural pain. *Cochrane Database of Systematic Reviews* **10**, CD006275
Roberts, C., Armson, B., Bartram, D., *et al*. (2021) Construction of a conceptual framework for assessment of health-related quality of life in dogs with osteoarthritis. *Frontiers in Veterinary Science* **8**, 741864
Rodan, I., Sundahl, E., Carney, H., *et al*. (2011) Aafp and isfm feline-friendly handling guidelines. *Journal of Feline Medicine and Surgery* **13**, 364-375
Rose, L., Haslam, L., Dale, C., *et al*. (2013) Behavioral pain assessment tool for critically ill adults unable to self-report pain. *American Journal of Critical Care* **22**, 246-255
Roush, J. K., Cross, A. R., Renberg, W. C., *et al*. (2010) Evaluation of the effects of dietary supplementation with fish oil omega-3 fatty acids on weight bearing in dogs with osteoarthritis. *Journal of the American Veterinary Medical Association* **236**, 67-73
Ruel, H. L. M. & Steagall, P. V. (2019) Adjuvant analgesics in acute pain management. *Veterinary Clinics of North America: Small Animal Practice* **49**, 1127-1141
Ruel, H. L. M., Watanabe, R., Evangelista, M. C., *et al*. (2020) Pain burden, sensory profile and inflammatory cytokines of dogs with naturally-occurring neuropathic pain treated with gabapentin alone or with meloxicam. *PLoS One* **15**, e0237121
Rufiange M., Monteiro, B., Watanabe, R., *et al*. (2022) Does opioid-free anesthesia provide adequate analgesia within a multimodal protocol in cats undergoing ovariohysterectomy? Association of Veterinary Anaesthestists Spring Meeting 2022. Nafplio, Greece. p93
Rusbridge, C., Heath, S., Gunn-Moore, D. A., *et al*. (2010) Feline orofacial pain syndrome (fops): a retrospective study of 113 cases. *Journal of Feline Medicine and Surgery* **12**, 498-508
Rushton, D. N. (2002) Electrical stimulation in the treatment of pain. *Disability and Rehabilitation* **24**, 407-415
Ruskin, D. N., Sturdevant, I. C., Wyss, L. S., *et al*. (2021) Ketogenic diet effects on inflammatory allodynia and ongoing pain in rodents. *Scientific Reports* **11**, 725
Rutherford, L., Wessmann, A., Rusbridge, C., *et al*. (2012) Questionnaire-based behaviour analysis of cavalier king charles spaniels with neuropathic pain due to chiari-like malformation and syringomyelia. *The Veterinary Journal* **194**, 294-298
Ryan, S., Bacon, H., Endenburg, N., *et al*. (2019) WSAVA animal welfare guidelines. *Journal of Small Animal Practice* **60**, E1-e46
Sanchis-Mora, S., Chang, Y. M., Abeyesinghe, S. M., *et al*. (2019) Pregabalin for the treatment of syringomyelia-associated neuropathic pain in dogs: a randomised, placebo-controlled, double-masked clinical trial. *The Veterinary Journal* **250**, 55-62
Sanderson, R. O., Beata, C., Flipo, R. M., *et al*. (2009) Systematic review of the management of canine osteoarthritis. *Veterinary Record* **164**, 418-424
Santos, R. D. S. & Galdino, G. (2018) Endogenous systems involved in exercise-induced analgesia. *Journal of Physiology and Pharmacology* **69**, 3-13
Santos, L. C., Ludders, J. W., Erb, H. N., *et al*. (2011) A randomized, blinded, controlled trial of the antiemetic effect of ondansetron on dexmedetomidine-induced emesis in cats. *Veterinary Anaesthesia and Analgesia* **38**, 320-327
Saridomichelakis, M. N. & Olivry, T. (2016) An update on the treatment of canine atopic dermatitis. *The Veterinary Journal* **207**, 29-37
Sarrau, S., Jourdan, J., Dupuis-Soyris, F., *et al*. (2007) Effects of postoperative ketamine infusion on pain control and feeding behaviour in bitches undergoing mastectomy. *Journal of Small Animal Practice* **48**, 670-676
Schmierer, P. A., Tunsmeyer, J., Tipold, A., *et al*. (2020) Randomized controlled trial of pregabalin for analgesia after surgical treatment of intervertebral disc disease in dogs. *Veterinary Surgery* **49**, 905-913
Schott, E. M., Farnsworth, C. W., Grier, A., *et al*. (2018) Targeting the gut microbiome to treat the osteoarthritis of obesity. *JCI Insight* **3**, e95997
Scott, E. M., Davies, V., Nolan, A. M., *et al*. (2021) Validity and responsiveness of the generic health-related quality of life instrument (VetMetrica™) in cats with osteoarthritis. Comparison of vet and owner impressions of quality of life impact. *Frontiers in Veterinary Science* **8**, 733812
Shah, J. P., Thaker, N., Heimur, J., *et al*. (2015) Myofascial trigger points then and now: a historical and scientific perspective. *PM & R: The Journal of Injury, Function, and Rehabilitation* **7**, 746-761
Shanan, A., Pierce, J. & Shearer, T. (2017) Hospice and Palliative Care for Companion Animals: Principles and Practice. John Wiley & Sons, Hoboken, NJ, USA
Shilo-Benjamini, Y. (2019) A review of ophthalmic local and regional anesthesia in dogs and cats. *Veterinary Anaesthesia and Analgesia* **46**, 14-27
Shipley, H., Flynn, K., Tucker, L., *et al*. (2021) Owner evaluation of quality of life and mobility in osteoarthritic cats treated with amantadine or placebo. *Journal of Feline Medicine and Surgery* **23**, 568-574
Silva, N., Luna, S. P. L., Joaquim, J. G. F., *et al*. (2017) Effect of acupuncture on pain and quality of life in canine neurological and musculoskeletal diseases. *Canadian Veterinary Journal* **58**, 941-951
Simon, B. T. & Steagall, P. V. (2017) The present and future of opioid analgesics in small animal practice. *Journal of Veterinary Pharmacology and Therapeutics* **40**, 315-326
Simon, B. T., Scallan, E. M., Carroll, G., *et al*. (2017) The lack of analgesic use (oligoanalgesia) in small animal practice. *Journal of Small Animal Practice* **58**, 543-554
Simon, B. T., Scallan, E. M., Monteiro, B. P., *et al*. (2019) The effects of aging on hydromorphone-induced thermal antinociception in healthy female cats. *Pain Reports* **4**, e722
Simpson, S., Dunning, M. D., de Brot, S., *et al*. (2017) Comparative review of human and canine osteosarcoma: morphology, epidemiology, prognosis, treatment and genetics. *Acta Veterinaria Scandinavica* **59**, 71
Sluka, K. A., Frey-Law, L. & Hoeger Bement, M. (2018) Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation. *Pain* **159**(Suppl 1), S91-S97
Smith, G. K., Paster, E. R., Powers, M. Y., *et al*. (2006) Lifelong diet restriction and radiographic evidence of osteoarthritis of the hip joint in dogs. *Journal of the American Veterinary Medical Association* **229**, 690-693
Smith, P., Tolbert, M. K., Gould, E., *et al*. (2020) Pharmacokinetics, sedation and hemodynamic changes following the administration of oral transmucosal detomidine gel in cats. *Journal of Feline Medicine and Surgery* **22**, 1184-1190
Solymosi, K. & Kofalvi, A. (2017) Cannabis: a treasure trove or pandora's box? *Mini-Reviews in Medicinal Chemistry* **17**, 1223-1291
Stadig, S., Lascelles, B. D. X., Nyman, G., *et al*. (2019) Evaluation and comparison of pain questionnaires for clinical screening of osteoarthritis in cats. *Veterinary Record* **185**, 757
Stathopoulou, T. R., Kouki, M., Pypendop, B. H., *et al*. (2018) Evaluation of analgesic effect and absorption of buprenorphine after buccal administration in cats with oral disease. *Journal of Feline Medicine and Surgery* **20**, 704-710
Steagall, P. V. (2020) Analgesia: what makes cats different/challenging and what is critical for cats? *Veterinary Clinics of North America: Small Animal Practice* **50**, 749-767
Steagall, P. V. & Monteiro, B. P. (2019) Acute pain in cats: recent advances in clinical assessment. *Journal of Feline Medicine and Surgery* **21**, 25-34
Steagall, P. V., Carnicelli, P., Taylor, P. M., *et al*. (2006) Effects of subcutaneous methadone, morphine, buprenorphine or saline on thermal and pressure thresholds in cats. *Journal of Veterinary Pharmacology and Therapeutics* **29**, 531-537
Steagall, P. V., Taylor, P. M., Rodrigues, L. C., *et al*. (2009) Analgesia for cats after ovariohysterectomy with either buprenorphine or carprofen alone or in combination. *Veterinary Record* **164**, 359-363
Steagall, P. V., Monteiro-Steagall, B. P. & Taylor, P. M. (2014) A review of the studies using buprenorphine in cats. *Journal of Veterinary Internal Medicine* **28**, 762-770
Steagall, P. V., Benito, J., Monteiro, B. P., *et al*. (2018) Analgesic effects of gabapentin and buprenorphine in cats undergoing ovariohysterectomy using two pain-scoring systems: a randomized clinical trial. *Journal of Feline Medicine and Surgery* **20**, 741-748
Steagall, P. V., Pelligand, L., Page, S. W., *et al*. (2020a) The world small animal veterinary association (wsava): list of essential medicines for cats and dogs. *Journal of Small Animal Practice* **61**, E162-e176
Steagall, P. V. M., Benito, J., Monteiro, B., *et al*. (2020b) Intraperitoneal and incisional analgesia in small animals: simple, cost-effective techniques. *Journal of Small Animal Practice* **61**, 19-23
Steagall, P. V., Bustamante, H., Johnson, C. B., *et al*. (2021) Pain management in farm animals: focus on cattle, sheep and pigs. *Animals (Basel)* **11**, 1483
Steagall, P. V., Robertson, S., Simon, B., *et al*. (2022) 2022 isfm consensus guidelines on the management of acute pain in cats. *Journal of Feline Medicine and Surgery* **24**, 4-30
Summers, J. F., O'Neill, D. G., Church, D., *et al*. (2019) Health-related welfare prioritisation of canine disorders using electronic health records in primary care practice in the UK. *BMC Veterinary Research* **15**, 163
Sun, Y., Li, T., Wang, N., *et al*. (2012) Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. *Diseases of the Colon & Rectum* **55**, 1183-1194

Taddio, A., Katz, J., Ilersich, A. L., *et al*. (1997) Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet* **349**, 599-603
Tainter, C. R. (2012) An evidence-based approach to traumatic pain management in the emergency department. *Emergency Medicine Practice* **14**, 1-26
Tamarova, Z. A., Limansky, Y. & Gulyar, S. A. (2009) Antinociceptive effects of color polarized light in animal with formalin test. *Fiziologicheskiĭ Zhurnal* **55**, 81-93
Tatlock, S., Gober, M., Williamson, N., *et al*. (2017) Development and preliminary psychometric evaluation of an owner-completed measure of feline quality of life. *Veterinary Journal* **228**, 22-32
Taylor, S., Caney, S., Bessant, C., *et al*. (2022) Online survey of owners' experiences of medicating their cats at home. *Journal of Feline Medicine and Surgery* 1098612x221083752
Teixeira, L. R., Luna, S. P., Matsubara, L. M., *et al*. (2016) Owner assessment of chronic pain intensity and results of gait analysis of dogs with hip dysplasia treated with acupuncture. *Journal of the American Veterinary Medical Association* **249**, 1031-1039
Teixeira, L. G., Martins, L. R., Schimites, P. I., *et al*. (2020) Evaluation of postoperative pain and toxicological aspects of the use of dipyrone and tramadol in cats. *Journal of Feline Medicine and Surgery* **22**, 467-475
Thoefner, M. S., Skovgaard, L. T., McEvoy, F. J., *et al*. (2020) Pregabalin alleviates clinical signs of syringomyelia-related central neuropathic pain in Cavalier King Charles spaniel dogs: a randomized controlled trial. *Veterinary Anaesthesia and Analgesia* **47**, 238-248
Tick, H., Nielsen, A., Pelletier, K. R., *et al*. (2018) Evidence-based nonpharmacologic strategies for comprehensive pain care: the consortium pain task force white paper. *Explore (New York, N.Y.)* **14**, 177-211
Toczek, M. & Malinowska, B. (2018) Enhanced endocannabinoid tone as a potential target of pharmacotherapy. *Life Sciences* **204**, 20-45
Todd, K. H., Ducharme, J., Choiniere, M., *et al*. (2007) Pain in the emergency department: results of the pain and emergency medicine initiative (pemi) multicenter study. *Journal of Pain* **8**, 460-466
Trotti, A., Bellm, L. A., Epstein, J. B., *et al*. (2003) Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiotherapy and Oncology* **66**, 253-262
Tsai, T. Y., Chang, S. K., Chou, P. Y., *et al*. (2013) Comparison of postoperative effects between lidocaine infusion, meloxicam, and their combination in dogs undergoing ovariohysterectomy. *Veterinary Anaesthesia and Analgesia* **40**, 615-622
Tvarijonaviciute, A., Ceron, J. J., Holden, S. L., *et al*. (2012) Effects of weight loss in obese cats on biochemical analytes related to inflammation and glucose homeostasis. *Domestic Animal Endocrinology* **42**, 129-141
Usunoff, K. G., Popratiloff, A., Schmitt, O., *et al*. (2006) Functional neuroanatomy of pain. *Advances in Anatomy, Embryology and Cell Biology* **184**, 1-115
Valtolina, C., Robben, J. H., Uilenreef, J., *et al*. (2009) Clinical evaluation of the efficacy and safety of a constant rate infusion of dexmedetomidine for postoperative pain management in dogs. *Veterinary Anaesthesia and Analgesia* **36**, 369-383
Valverde, A. (2008) Epidural analgesia and anesthesia in dogs and cats. *Veterinary Clinics of North America: Small Animal Practice* **38**, 1205-1230, v
Van de Velde, H., Janssens, G. P., de Rooster, H., *et al*. (2013) The cat as a model for human obesity: insights into depot-specific inflammation associated with feline obesity. *British Journal of Nutrition* **110**, 1326-1335
van den Beuken-van Everdingen, M. H., de Rijke, J. M., Kessels, A. G., *et al*. (2007) Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Annals of Oncology* **18**, 1437-1449
van Haaften, K. A., Forsythe, L. R. E., Stelow, E. A., *et al*. (2017) Effects of a single preappointment dose of gabapentin on signs of stress in cats during transportation and veterinary examination. *Journal of the American Veterinary Medical Association* **251**, 1175-1181
Van Vertloo, L. R., Carnevale, J. M., Parsons, R. L., *et al*. (2021) Effects of waiting room and feline facial pheromone experience on blood pressure in cats. *Frontiers in Veterinary Science* **8**, 640751
Vandeweerd, J. M., Coisnon, C., Clegg, P., *et al*. (2012) Systematic review of efficacy of nutraceuticals to alleviate clinical signs of osteoarthritis. *Journal of Veterinary Internal Medicine* **26**, 448-456
Varcoe, G., Tomlinson, J. & Manfredi, J. (2021) Owner perceptions of long-term systemic use of subcutaneous administration of polysulfated glycosaminoglycan. *Journal of the American Animal Hospital Association* **57**, 205-211
Vaughn, D., Kulpa, J. & Paulionis, L. (2020) Preliminary investigation of the safety of escalating cannabinoid doses in healthy dogs. *Frontiers in Veterinary Science* **7**, 51
Venator, K. P., Frye, C. W., Gamble, L.-J., *et al*. (2020) Assessment of a single intra-articular stifle injection of pure platelet rich plasma on symmetry indices in dogs with unilateral or bilateral stifle osteoarthritis from long-term medically managed cranial cruciate ligament disease. *Veterinary medicine (Auckland, N.Z.)* **11**, 31-38
Venkatesh, H. S., Morishita, W., Geraghty, A. C., *et al*. (2019) Electrical and synaptic integration of glioma into neural circuits. *Nature* **573**, 539-545
Voga, M., Adamic, N., Vengust, M., *et al*. (2020) Stem cells in veterinary medicine-current state and treatment options. *Frontiers in Veterinary Science* **7**, 278
Wagner, A. E., Walton, J. A., Hellyer, P. W., *et al*. (2002) Use of low doses of ketamine administered by constant rate infusion as an adjunct for postoperative analgesia in dogs. *Journal of the American Veterinary Medical Association* **221**, 72-75
Wagner, A. E., Wright, B. D. & Hellyer, P. W. (2003) Myths and misconceptions in small animal anesthesia. *Journal of the American Veterinary Medical Association* **223**, 1426-1432
Wagner, A. E., Mich, P. M., Uhrig, S. R., *et al*. (2010) Clinical evaluation of perioperative administration of gabapentin as an adjunct for postoperative analgesia in dogs undergoing amputation of a forelimb. *Journal of the American Veterinary Medical Association* **236**, 751-756
Wakshlag, J. J., Cital, S., Eaton, S. J., *et al*. (2020) Cannabinoid, terpene, and heavy metal analysis of 29 over-the-counter commercial veterinary hemp supplements. *Veterinary medicine (Auckland, N.Z.)* **11**, 45-55
Walewicz, K., Taradaj, J., Rajfur, K., *et al*. (2019) The effectiveness of radial extracorporeal shock wave therapy in patients with chronic low back pain: a prospective, randomized, single-blinded pilot study. *Clinical Interventions in Aging* **14**, 1859-1869
Wall, R. (2014) Introduction to myofascial trigger points in dogs. *Topics in Companion Animal Medicine* **29**, 43-48
Walton, M. B., Cowderoy, E., Lascelles, D., *et al*. (2013) Evaluation of construct and criterion validity for the 'Liverpool Osteoarthritis in Dogs' (LOAD) clinical metrology instrument and comparison to two other instruments. *PLoS One* **8**, e58125
Warne, L. N., Bauquier, S. H., Pengelly, J., *et al*. (2018) Standards of care anaesthesia guidelines for dogs and cats. *Australian Veterinary Journal* **96**, 413-427
Watanabe, R., Doodnaught, G., Proulx, C., *et al*. (2019) A multidisciplinary study of pain in cats undergoing dental extractions: a prospective, blinded, clinical trial. *PLoS One* **14**, e0213195
Watanabe, R., Doodnaught, G. M., Evangelista, M. C., *et al*. (2020a) Inter-rater reliability of the Feline Grimace Scale in cats undergoing dental extractions. *Frontiers in Veterinary Science* **7**, 302
Watanabe, R., Frank, D. & Steagall, P. V. (2020b) Pain behaviors before and after treatment of oral disease in cats using video assessment: a prospective, blinded, randomized clinical trial. *BMC Veterinary Research* **16**, 100
Webster, R. P., Anderson, G. I. & Gearing, D. P. (2014) Canine brief pain inventory scores for dogs with osteoarthritis before and after administration of a monoclonal antibody against nerve growth factor. *American Journal of Veterinary Research* **75**, 532-535
Weerapong, P., Hume, P. A. & Kolt, G. S. (2005) The mechanisms of massage and effects on performance, muscle recovery and injury prevention. *Sports Medicine* **35**, 235-256
Weil, A. B., Ko, J. & Inoue, T. (2007) The use of lidocaine patches. *Compendium on Continuing Education for the Practicing Veterinarian* **29**, 208-210, 212, 214-206
Weinberg, G., Ripper, R., Feinstein, D. L., *et al*. (2003) Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. *Regional Anesthesia & Pain Medicine* **28**, 198-202
Wernham, B. G., Trumpatori, B., Hash, J., *et al*. (2011) Dose reduction of meloxicam in dogs with osteoarthritis-associated pain and impaired mobility. *Journal of Veterinary Internal Medicine* **25**, 1298-1305
Wiese, A. J., Muir, W. W. 3rd & Wittum, T. E. (2005) Characteristics of pain and response to analgesic treatment in dogs and cats examined at a veterinary teaching hospital emergency service. *Journal of the American Veterinary Medical Association* **226**, 2004-2009
Wilson, J. E. & Pendleton, J. M. (1989) Oligoanalgesia in the emergency department. *American Journal of Emergency Medicine* **7**, 620-623
Wilson, J., Doherty, T. J., Egger, C. M., *et al*. (2008) Effects of intravenous lidocaine, ketamine, and the combination on the minimum alveolar concentration of sevoflurane in dogs. *Veterinary Anaesthesia and Analgesia* **35**, 289-296
Winer, J. N., Arzi, B. & Verstraete, F. J. (2016) Therapeutic management of feline chronic gingivostomatitis: a systematic review of the literature. *Frontiers in Veterinary Science* **3**, 54
Wise, B. L., Seidel, M. F. & Lane, N. E. (2021) The evolution of nerve growth factor inhibition in clinical medicine. *Nature Reviews Rheumatology* **17**, 34-46
Woolf, C. J. (2010) What is this thing called pain? *The Journal of Clinical Investigation* **120**, 3742-3744
Wordliczek, J. & Zajaczkowska, R. (2013) Mechanisms in cancer pain. In: Cancer Pain. Eds M. Hanna and Z. B. Zylicz. Springer-Verlag, London, UK. pp 47-70
Wright, B. D. (2019) Acupuncture for the treatment of animal pain. *Veterinary Clinics of North America: Small Animal Practice* **49**, 1029-1039

Wright, B., Kronen, P. W., Lascelles, D., *et al*. (2020) Ice therapy: cool, current and complicated. *Journal of Small Animal Practice* **61**, 267-271
Xu, J. & Brennan, T. J. (2010) Guarding pain and spontaneous activity of nociceptors after skin versus skin plus deep tissue incision. *Anesthesiology* **112**, 153-164
Yamazaki, A., Edamura, K., Tanegashima, K., *et al*. (2020) Utility of a novel activity monitor assessing physical activities and sleep quality in cats. *PLoS One* **15**, e0236795
Zamprogno, H., Hash, J., Hulse, D. A., *et al*. (2011) Elbow denervation in dogs: development of an in vivo surgical procedure and pilot testing. *The Veterinary Journal* **190**, 220-224
Zanuzzo, F. S., Teixeira-Neto, F. J., Teixeira, L. R., *et al*. (2015) Analgesic and antihyperalgesic effects of dipyrone, meloxicam or a dipyrone-meloxicam combination in bitches undergoing ovariohysterectomy. *The Veterinary Journal* **205**, 33-37
Zhang, W., Nuki, G., Moskowitz, R. W., *et al*. (2010) Oarsi recommendations for the management of hip and knee osteoarthritis: part iii: changes in evidence following systematic cumulative update of research published through january 2009. *Osteoarthritis and Cartilage* **18**, 476-499
Zhang, Z. J., Wang, X. M. & McAlonan, G. M. (2012) Neural acupuncture unit: a new concept for interpreting effects and mechanisms of acupuncture. *Evidence-based Complementary and Alternative Medicine* **2012**, 429412
Zügel, M., Maganaris, C. N., Wilke, J., *et al*. (2018) Fascial tissue research in sports medicine: from molecules to tissue adaptation, injury and diagnostics: consensus statement. *British Journal of Sports Medicine* **52**, 1497

APPENDIX A

A.1 Definitions

Based on the following documents:

- Proceedings of the 2017 Pain in Animals Workshop, November 29-30, 2017. National Institutes of Health, Bethesda, Maryland
- IASP Pain Terms and Definition (https://www.iasp-pain.org/resources/terminology/)
- Werner, M. U., & Kongsgaard, U. E. (2014). I. Defining persistent post-surgical pain: is an update required? Br J Anaesth 113(1), 1-4. (https://doi.org/10.1093/bja/aeu012)

Activity monitor: A device that measures activity. *Note: there is no standard measure of activity or "activity count."*

Acute pain (also adaptive pain or physiological pain): Pain that is obviously coupled with tissue injury, generally short-lived and can be considered protective in nature. Often defined as lasting less than 1 month, or less than 3 months.

Acute on chronic pain: Brief and transitory flare-up of pain from a chronic condition. Also known as breakthrough pain.

Allodynia: Pain due to a stimulus that does not normally provoke pain (*e.g.* pain due to touch or gentle pressure).

Central sensitisation: Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.

Chronic pain (also maladaptive pain or pathological pain): Chronic pain has been defined as pain that lasts beyond the normal healing time, thus lacking the acute warning function of physiological nociception.

Clinical metrology instrument (CMI): A clinical metrology instrument (CMI) is a sequence of items which are ascribed a score based on the subjective experiences or observations of the person completing it. These scores are then usually processed in some way to quantify the level of disease.

Diffuse noxious inhibitory control (DNIC): Diffuse noxious inhibitory control describes a type of descending inhibitory control system in animals that *is triggered by a noxious stimulus distant to the primary test stimulus*. The term Conditioned Pain Modulation (CPM) describes activation of this system, wherein the test stimulus is used to assess the level of sensitivity while the "conditioning" stimulus refers to the noxious stimulus used to activate DNIC.

Drug: A drug is defined as:

- A substance recognised by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process *versus* biological process.)

Dysphoria: State of agitation and restlessness usually associated with the administration of high doses of opioids.

Health-related quality of life (HRQL): The subjective evaluation of circumstances that include an altered health state and related interventions.

Hyperalgesia: Increased pain from a stimulus that normally provokes pain.

Hyperesthesia: Increased sensitivity to stimulation, excluding the special senses. Note: *Hyperesthesia* includes both allodynia and hyperalgesia.

Hypoalgesia: Diminished pain in response to a normally painful stimulus.

Multi-modal analgesia: The administration of two or more analgesic drugs with different mechanisms of action usually resulting in synergistic effects and reduced dosage requirements. Multi-modal analgesia can also include the use of non-pharmacological analgesic therapies such as cold therapy, acupuncture, etc.

Neuropathic pain: Pain caused by a lesion or disease of the somatosensory nervous system.

The presence of symptoms or signs (*e.g.* touch-evoked pain) alone does not justify the use of the term *neuropathic*.

Neuroplasticity: Refers to the ability of the nervous system to reorganise its structure and function. Also known as neural or brain plasticity.

Nociception: The neural process of encoding noxious stimuli.

Nociceptive pain: Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.

Noxious stimulation: A stimulus that is damaging or threatens damage to normal tissues.

Perioperative pain: Pain related to the period of time surrounding surgical procedures including the pre-, intra-, and postoperative periods.

Peripheral sensitisation: Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields.

Persistent postsurgical pain: Pain that arises or increases in intensity after a surgical procedur, that has at least 3 to 6 months' duration, and for which other causes cannot be found. Also known as persistent postoperative pain, chronic postoperative pain or post-procedural pain.

Placebo: A sham or non-active treatment that is administered during a trial.

Placebo effect: This effect represents a beneficial response to an inert treatment that exists for reasons unrelated to the actual treatment given, but depends on the context in which the treatment is provided and the patient's experience and expectations. Strictly, the "placebo effect" is the effect of administering the placebo over and above any effect of no intervention at all.

Plasticity: See neuroplasticity.

Preventive analgesia: Refers to all types of perioperative techniques and efforts (drug and non-drug) to decrease postoperative pain. Note: Preemptive analgesia refers only to the administration of analgesics before surgery.

Quality of life (Qol): A general term used in a variety of disciplines in which it is accepted that QOL is, like pain, a multi-dimensional construct that is subjectively experienced by and is uniquely personal to the individual. It is a subjective and dynamic evaluation of its circumstances by the individual which results in an affective (emotional) response.

Quantitative sensory testing (QST): Quantitative sensory testing involves the application of a stimulus at a peripheral site, and measurement of the time to reach an endpoint or elicit a reaction. In humans, various endpoints can be measured (first detection, noxious, maximum tolerated), but in veterinary medicine, the response is generally defined as a reaction such as withdrawal, or vocalisation, or some other sign of central appreciation of the stimulus. Threshold refers to the point at which the response occurred, and is measured in units of the stimulus (for ramped stimuli) or time (for fixed stimuli).

Sensitisation: Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.