Pain Assessment and Management in Companion Animals Veterinary Update

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The International Association for the Study of Pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Loeser and Treede, 2008). A significant change in attitude towards animal pain has occurred over the past 15 years, highlighted by the adoption of this definition by animal and human pain experts when describing pain in animals.

All animals, from reptiles to birds, to mammals, possess the neuro-anatomic and neuro-pharmacologic components necessary for the transduction, transmission and perception of noxious stimuli. Like humans, animals experience pain as a complex physiological, sensory and emotional phenomenon, even if they cannot verbally express the emotional component that is unique to every individual.

The process by which pain is perceived is complex and incompletely understood. It is an unpleasant experience that cannot be objectively measured. Accompanying the unpleasant experience, are measurable physiological responses that are mediated primarily by the autonomic nervous system.

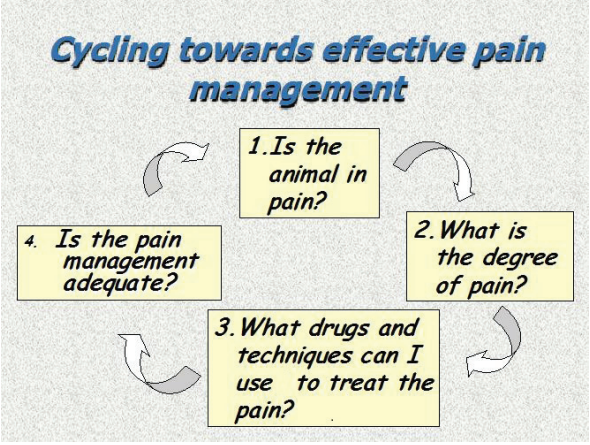
Many of these responses are not unique to pain, and merely reflect a physiological stress response. Therefore, the parameters we use to identify and define pain often limit our understanding of its complexity and our ability to treat it effectively.

Changes in behaviour, posture and even facial expression provide valuable clues about an animal's pain experience (Langford et al., 2010, Jirkof et al., 2013, Brown et al., 2013). As veterinarians we need to learn to interpret these clues in the species we deal with for the long-term benefit of our animal patients.

Effective pain management is a complex decision making process. The veterinary practitioner wanting to alleviate pain in an animal faces four key challenges (Figure 1):

i. Deciding if the animal is in pain
ii. Assessing the degree of pain
iii. Deciding on what drugs and techniques are most appropriate to treat the pain
iv. Evaluating the effectiveness of any analgesics that are administered

Figure 1 The pain management cycle



1. Identifying an animal in pain

Veterinarians rely primarily on the observation and interpretation of abnormal behaviour as an indicator of pain in animal patients. However, significant behavioural differences exist between species (Table 1) and individual animals, and a veterinarian may not be familiar with an animal's 'normal' behaviour. Veterinarians will also have preconceived ideas about how an animal should behave when in pain, and about what an animal's pain tolerance threshold should be. This can all limit the ability to detect pain in some patients.

Perhaps then, the most humane approach is to assume that if something is painful for humans it probably is painful for animals too.

Table 1: Pain behaviours in cats and dogs

	Cats	Dogs
Acute Pain[1]	Quiet/immobile	Vocalisation (whimpering)
	Seeking safe hiding place	Disinterest/withdrawn
	Minimal vocalisation	Aggression
	Disinterest/withdrawn	Comfort seeking
	Hyperventilation	Reluctance to move
	Excessive licking & chewing of injury sight	Rapid shallow breathing (panting)
	Sternal recumbency (hunched posture and abdominal tension)	Guarding injury sight/apprehensive
	Anorexia	Restlessness
Chronic Pain[2]		
	Reduced activity	Lameness/gait abnormalities
	Disinterest in environment	Muscle atrophy
	Anorexia and weight loss	Reduced appetite
	Poor grooming	Depression & lethargy
	Lameness/gait abnormalities	Weight loss

2. Assessing an animal in pain

Defining the "pain potential" of common procedures (Table 2) is one way to ensure treatment of pain is addressed even if the observable behaviours are subtle and difficult to identify.

Table 2: "Pain Potential" of common procedures

Mild	Mild to Moderate	Moderate to severe	Severe
Anal gland expression	Minor incision	Major laparotomy	Thoracotomy
SC/IM injections	Vascular catheterisation	Minor orthopaedic	Major orthopaedic
Venipuncture	Biopsy	Neutering/c-section	Trauma/burns
	Lumpectomy	Tooth extraction	Acute abdomen/ pancreatitis

Pain assessment utilising a *Pain Scale*, is another strategy that can be used in the clinical setting. Numerous pain score systems have been developed and adapted for veterinary use in an attempt to improve pain management in animals. Only some of these have been validated (Brown et al., 2008; Firth and Haldane, 1999; Holton et al., 2001; Lascelles et al., 2007; Murrell et al., 2008).

[1] **Cats are generally more quiet and withdrawn compared to dogs in acute pain states**
[2] **Listed in order of significance**

Pain scoring is a useful technique that improves the consistency with which different members of staff in a practice are able to detect pain in animal patients. To ensure staff compliance, a pain-scoring tool needs to be simple and easy to perform, and it needs to make sense (Coleman and Slingsby, 2007).

However, not all pain states are simple in nature and easy to characterise.

Pain starts with stimulation of specialised nerve endings (nociceptors) and subsequent transmission of signals along afferent peripheral sensory nerves to the dorsal horn of the spinal cord. These sensory nerves comprise two main types: myelinated A delta fibres that are fast conducting and localised; and non-myelinated C fibres that are slow conducting and more diffuse.

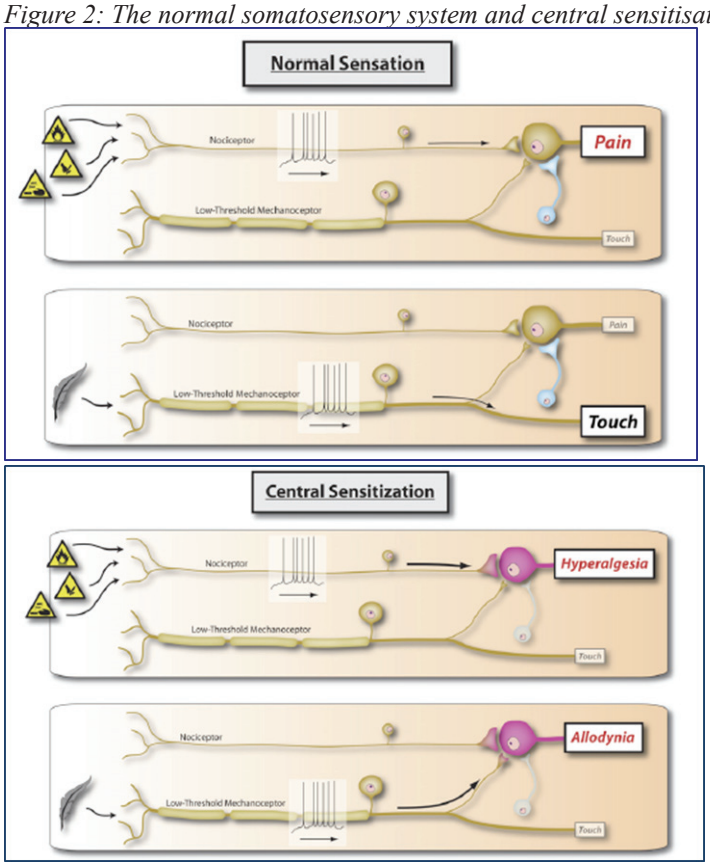
The cell bodies of these afferent neurons reside in the dorsal root ganglia (DRG). From the spinal cord this signal is then transmitted via a number of pathways to the higher brain centres for processing into what is then perceived as pain.

Pain perception is thought to occur at the level of the thalamus and the localisation of the pain somewhere in the sensory cortex. But the nervous system has an added complexity. The pain pathway is not a simple 'hard-wired' neuronal circuit, as was once thought. All along this "pain pathway" are opportunities for intrinsic and extrinsic factors to influence the nature, amplitude and perceived location and duration of the original sensory signal.
Research has altered our understanding of pain and we now view pain as a complex neurophysiological process that can be modulated, amplified and interrupted. This nervous system plasticity makes diagnosis and treatment of complex pain states a challenge for veterinarians (Woolf, 2011).

Adaptive pain is initiated by tissue injury and is a normal response driven in part by the inflammatory process; the amplitude of the pain response is aligned with the degree of tissue damage. However, if this pain is not managed effectively it can lead to a more complex, maladaptive pain state (Woolf, 2004).

Maladaptive pain is difficult to quantify and to treat. Pain originating from cancer, metabolic diseases (such as diabetes), nerve injury and chronic disease states such as arthritis, can give rise to maladaptive pain. This type of pain results in hypersensitivity that manifests as hyperalgesia, allodynia and spontaneous pain, and translates to behaviour that is difficult to assess or has yet to be clearly defined in animals (Bennett, 2012; Mogil, 2012).

Figure 2: The normal somatosensory system and central sensitisation[3]



[3] **Source: Woolf, C. J. 2011. Central sensitization: implications for the diagnosis and treatment of pain. Pain, 152, S2-15.**

Peripheral and central pain sensitisation is a feature of maladaptive pain (Figure 2). This sensitisation is mediated by a number of pro inflammatory cytokines that are released after cell injury. These include prostaglandins, bradykinin, and tumour necrosis factor (TNF alpha).

Central pain sensitisation occurs at the level of the spinal cord or somatosensory cortex, and is mediated by numerous inflammatory neuropeptides such as calcitonin gene related peptide (CGRP), substance P, glutamate and vasoactive intestinal peptide (VIP). In addition, endogenous opioids and cannabinoids can act to inhibit the pain signal. These are all potential therapeutic targets for managing pain.

3. Treating an animal in pain

There are numerous analgesic drugs and techniques available to the veterinary practitioner today, and a number of pain management guidelines have been published (Hellyer et al., 2007, KuKanich, 2013). However, there is no single drug or technique that will treat all pain effectively. Knowing that the pain pathway does not follow a direct route from the site of stimulation to the site of perception, but rather that it is malleable and undergoes modulation and modification along the way, alerts the clinician to the need for a multi modal approach to pain management (Table 3).

i. NSAIDs

Traditionally NSAIDs were used to manage chronic musculoskeletal pain but have since gained popularity for the treatment of acute and post-surgical pain. NSAID analgesia is mediated through both peripheral (anti-inflammatory/anti-peripheral sensitisation) and central (anti-central sensitisation) mechanisms.

NSAIDs complement the analgesic effects of opioids; they are generally long acting and have good bioavailability via the oral route. Although very effective against pain associated with inflammation and tissue damage, they are not without their side effects and care should be taken with their use (see the Boardtalk insert from May 2013 by Georgina Child).

Administering NSAIDs to susceptible animals can result in gastrointestinal (diarrhoea, nausea, vomiting, and gastric ulceration), renal and haemostatic side effects. Most adverse effects are reversible (if detected early) once administration of the drug is stopped.

Particular care is required when administering to cats. Cats have slow clearance and dose-dependent elimination of NSAIDs due to deficiencies in glucuronidation enzymes. Generally, NSAIDs should only be used in animals with normal renal function and haemostasis, and no history of GIT disease or concurrent use of corticosteroids or other NSAIDs.

Surgical patients receiving NSAIDs in the peri-operative period should always receive intravenous fluids.

Table 3: Dosage Chart: Analgesic drugs for acute and chronic pain management in cats and dogs

Drug	Classification	Duration	Administration/Dosage
Morphine	Opioid (pure agonist)	2-4 hrs	SC, IM, 0.1-1.0 mg/kg IV infusion 0.1-0.2 mg/kg/hr Intra-articular, epidural 0.1 mg/kg
Methadone	Opioid (pure agonist)	4-6 hrs	SC, IM, IV 0.1-0.5 mg/kg IV infusion 0.1-0.2 mg/kg/hr
Pethidine	Opioid (pure agonist)	1-2 hrs	SC, IM 1-4 mg/kg Epidural infusion 1-2mg/kg/hr
Butorphanol	Opioid (agonist/ antagonist)	1-2 hrs	SC, IM, IV 0.1-0.4 mg/kg
Buprenorphine	Opioid (partial agonist)	6-8 hrs	IM, IV 0.005-0.02 mg/kg Slow onset of action (30 mins) Transmucosal (cats only)

Fentanyl	Opioid (pure agonist)	20 mins (accumulates)	SC, IM, IV 1-10 µg/kg Administer very slowly for IV IV infusion 1-2 µg/kg/min
Naloxone	Opioid (pure antagonist)	1 hr	SC, IM, IV 0.04 mg/kg Administer to effect
Tramadol	Mu agonist Mono-amine reuptake inhibitor		PO 3-10 mg/kg q6-8 (dogs) PO 2-4 mg/kg q12 (cats)
Ketamine	NMDA antagonists	mins dose dependent	0.2-1 mg/kg 2-10 µg/kg/min
Lignocaine[4]	Na channel blocker	1-2 hrs	Infiltration 4 mg/kg (cats) and 8 mg/kg (dogs) IV infusion10-50 µg/kg/min (dog)
Bupivicaine	Na channel blocker	4-6 hrs	Infiltration 2 mg/kg (maximum)
Medetomodine	Mono-amine reuptake inhibitor	mins dose dependent	IM, IV 1-3 µg/kg IV infusion 0.5-3 µg/kg/min
Gabapentin	Blocks Ca^{2+} channel in dorsal horn	n/a	PO 2-10 mg/kg q6 –12 PO 2-10 mg/kg q12
Amantadine	NMDA antagonists	n/a	PO 3-5 mg/kg q12 or 24

ii. Local anaesthetics

Local anaesthetics are effective analgesics as well as useful adjuncts to general anaesthesia. Use of local anaesthetics in combination with general anaesthesia can greatly reduce anaesthetic requirements and therefore anaesthetic risk.

Their use can also facilitate pain management in the recovery period. Nerve blocks applied effectively prior to surgery (pre-emptive) will prevent the transmission of nociceptive information to the spinal cord and potentially reduce the development of central sensitisation.

Local anaesthetics act by blocking neural transmission peripherally and in the spinal cord; they act on sodium channels, reversibly blocking the conduction of action potentials thereby stabilising membranes.

The most commonly used local anaesthetics are the amide-linked local anaesthetics such as lignocaine, bupivacaine and mepivacaine. They differ in their potency, speed of onset and duration of action. Blood flow and tissue pH will also influence duration of action. To prolong duration of action, some local anaesthetic preparations contain a vasoconstrictor (usually adrenaline), allowing the drug to remain at the effector site for longer. These preparations should not be used for epidural injection, injection around an incision site, or for intravenous analgesia.

Nerve fibres vary in their susceptibility to local anaesthetic blockade. In the case of myelinated nerve fibres, the larger the nerve fibre the more difficult it is to block. Unmyelinated fibres are more susceptible to blockade because only a small length of nerve fibre membrane requires blockade to prevent transmission of action potentials.

Sensory nerve fibres comprise small, fast conducting, myelinated A delta fibres (responsible for localised pain e.g. pin prick) and slower conducting, unmyelinated C fibres (responsible for burning/throbbing pain).

Motor nerve fibres (A beta) are large and myelinated, making them more resistant to blockade. This means that pain is usually the first sensation to be blocked; nociceptor fibres are the most sensitive. Motor blockade follows and requires higher doses. Therefore, where it is undesirable, motor blockade (paralysis) can be minimised by using low effective doses of local anaesthetic.

[4] **Use < 25 µg/kg/min IV in cats, and do not administered for prolonged periods (> 4 hrs)**

There are side effects associated with the use of local anaesthetics and these are seen when doses higher than those required for induction of peripheral sensory blockade are used, or where there is inadvertent injection into a vein or artery. Because of the wide distribution of sodium channels throughout the body, local anaesthetics can potentially affect all excitable membranes including those located in the heart, brain and neuromuscular junction. Animals overdosed with a local anaesthetic will show signs such as restlessness and convulsions, and eventually depression, coma and death.

Local anaesthetics can also result in decreased BP via their negative inotropic effects as well as a direct vasodilatory action on arterioles. Bupivacaine has severe cardiotoxic effects and care needs to be taken not to exceed maximum therapeutic doses and to avoid intravascular administration.

Cats are considered to be more susceptible to toxicity from use of local anaesthetics. However, in both cats and dogs, toxicity is easily avoided if recommended maximal doses are adhered to (4 mg/kg for lignocaine and 2 mg/kg for bupivacaine) and injection is always preceded by aspiration to ensure the needle is not inside a blood vessel.

Pain associated with injection of lignocaine can be reduced by combining 9 parts 1% or 2% lignocaine (1.8 ml) with 1 part sodium bicarbonate (0.2 ml) to make up a buffered lignocaine solution. Buffered lignocaine remains effective for up to 7 days after preparation, so can be made up in advance and refrigerated for storage.

iii. Opioids

There are numerous opioids available in Australia and all have similar properties, differing primarily with respect to potency, time of onset, duration of action and degree of side effects. No single opioid is ideal in all situations, so in order to optimise the analgesic benefits and minimise the undesirable side effects, a good working knowledge of the commonly used opioids is required.

When an opioid is administered to an animal, three key processes determine the outcome of the opioid/receptor interaction:

a. Selectivity: Opioids can act at mu, kappa, delta, or any combination of the three receptor types.
b. Efficacy: Drugs can be *pure agonists* (inducing a maximal response once bound to the receptor); *partial agonists* (inducing a sub maximal response once bound to the receptor regardless of the dose administered); or *antagonists* (inducing no response once bound to the receptor). Some drugs are agonists at one receptor type and antagonists or partial agonists at another receptor type.
c. Affinity: Opioids with a high affinity for the receptor (e.g. buprenorphine) have a long duration of action that is unrelated to the plasma half-life of the drug.

This means when deciding on the suitability of any given opioid in the clinical setting, the following questions need to be considered:

i. Which type of receptor does this opioid act on?
ii. What is the intrinsic activity of the opioid once it binds to the receptor?
iii. How strongly does the opioid bind to the receptor?

Opioids are not just very good analgesics they are also very effective sedatives.

All opioids produce a degree of dose related respiratory depression. This respiratory depression is more marked in patients that have other centrally acting drugs on board. Opioids have minimal cardiovascular side effects but cause a dose dependent decrease in heart rate. Opioids can also cause nausea, vomiting and constipation.

Opioids are classified according to their receptor selectivity. Generally, mu receptor selective opioids are the most effective analgesics. The effect of opioid agonists can be reversed by the administration of an antagonist (naloxone). Partial agonists such as butorphanol and buprenorphine are less efficacious analgesics, cause fewer side effects but cannot be reversed.

The analgesic action of opioids is mediated via three mechanisms:

i. Opioids block transmission of noxious stimuli by acting on pre and post-synaptic receptors of primary afferent sensory nerves at the level of the spinal cord
ii. Opioids block transmission of noxious stimuli and increase the amount of descending inhibition by acting on higher brain centres
iii. Opioids block transmission of noxious stimuli by acting peripherally on opioid receptors generated in inflammatory conditions. Opioid receptors have been identified on nerve endings and inflammatory cells.

Opioids can be used to treat mild, moderate and severe pain states. Duration of action ranges from a few minutes to several hours, depending on which drug is selected. In addition to traditional routes of administration (SC, IM and IV), opioids can be effectively administration via the transdermal (fentanyl), transmucosal (buprenorphine), oral (morphine and butorphanol), intra-articular (morphine), epidural (morphine, pethidine) and intrathecal routes.

Methadone, pethidine and butorphanol are currently the only opioids registered for use in cats, dogs and horses in Australia.

iv. Tramadol

Tramadol is a synthetic opioid like drug that has been used in human medicine since 1977 and is starting to be widely used in veterinary medicine. Its effects are attributable to both a direct opioid effect and the inhibition of re-uptake of serotonin and noradrenaline.

The metabolites of tramadol have a higher affinity for mu receptors than the parent drug, and are largely responsible for the analgesic affects at the mu receptor attributed to the administration of tramadol. This may account for the variability in therapeutic response between species and individual animals. For example, cats produce more of the active metabolite than dogs, and so the analgesic effect in cats is likely to be mediated primarily through mu receptor activity, where as in the dog there is very little opioid mediated analgesia after tramadol administration.

Tramadol still requires further investigation in both cats and dogs to determine its efficacy and optimise its therapeutic use. This drug is not registered for use in non-human species so remember that it is off-label use when dispensing!

v. Ketamine

Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist and produces a state of dissociative anaesthesia at high doses. Through NMDA antagonism it interferes with the development of central sensitisation within the central nervous system. Ketamine has been used in human medicine for the treatment of acute irretractable pain such as severe burns and trauma, neuropathic pain and chronic pain. The analgesic effects of ketamine outlast the anaesthetic effects – most likely through the modification of sensitisation.

The pharmacokinetics of ketamine is well reported in the veterinary literature and ketamine is a popular injectable induction agent and sedative (in combination with alpha 2 agonists, benzodiazepines and opioids). It is also well absorbed across oral mucous membranes.

The analgesic effects of ketamine occur at doses lower than those required to achieve sedation or anaesthesia. Thus it can be used effectively for analgesia while avoiding concurrent excitatory central nervous system side effects. Ketamine demonstrates profound analgesic properties, when administered in combination with other analgesics. Ketamine is best used as an infusion in combination with an opioid or lignocaine.

vi. Alpha 2 agonists

Alpha 2 adrenoreceptor agonists are recognised to be potent sedative, hypnotic and analgesic agents; properties that make them useful adjuncts for anaesthesia in small animal practice. Alpha 2 agonist drugs like medetomidine, detomidine and romifidine have gained popularity as they are reliable and predictable sedative agents that can be reversed, but concerns about the cardiovascular side effects of alpha 2- agonists still limits their clinical use in Australian veterinary practice.

However, the analgesic properties of alpha 2 agonists can be harnessed at 'microdoses' resulting in very mild sedation and minimal cardiovascular effects. Care should still be taken in hypovolaemic, hypotensive and diabetic patients.

These drugs can also be administered as an infusion for longer-term pain control in an intensive care setting.

The new generation alpha 2 agonist is dexmedetomidine. It is one of the enantomers of medetomidine and has fewer cardiovascular effects but comparable analgesic and sedative effects. Dexmedetomidine is approximately twice as potent as medetomidine.

vii. Gabapentin

Gabapentin is an anti-epileptic drug that has been used in humans for the treatment of neuropathic pain. Its mechanism of action is not entirely understood, and there is little data in the veterinary literature regarding its pharmacokinetics or its analgesic efficacy in cats and dogs.

However, it is being used off label by veterinarian practitioners in patients with chronic and neuropathic pain that does not respond to conventional therapies and there is anecdotal evidence of its efficacy in these patients.

viii. Amantadine

Amantadine is an anti-viral drug that has been used in human medicine for the treatment of Parkinson's disease. It is also an NMDA antagonist and has proven useful in the management of chronic pain in humans and more recently cats and dogs (off label).

The pharmacokinetics has been more fully described in the cat than the dog, but both efficacy and safety data are not well reported in either species.

Amantadine is not thought to provide effective analgesia when used as a sole therapy, but may enhance the analgesic effects of NSAIDs and opioids, and may be a useful adjunct in managing chronic and neuropathic pain where NMDA mediated central sensitisation may be a feature. Its efficacy in combination with meloxicam in dogs with osteoarthritis has been reported (Lascelles et al., 2008).

4. Evaluating the effectiveness of the treatment

On going reassessment of patients utilising a systematic approach such as a pain scale, for hospitalised animals or a client-specific outcome measures (CSOM) instrument, for at-home patients, allows the veterinarian to modify pain management therapy to ensure pain control is maintained and side effects are minimised.

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