LIVISTO

PAIN RECOGNITION AND MANAGEMENT IN CATS

Guideline

Along with you

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LIVISTO supports animal welfare and pain control

Our objective is to minimize patient discomfort and improve quality of life.

This guideline will provide some practical information for veterinarians about pain mangement and treatment options.

The prevention of pain is key.

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Divinum est opus sedare dolorem
Divine is the work to subdue pain

Hippocrates

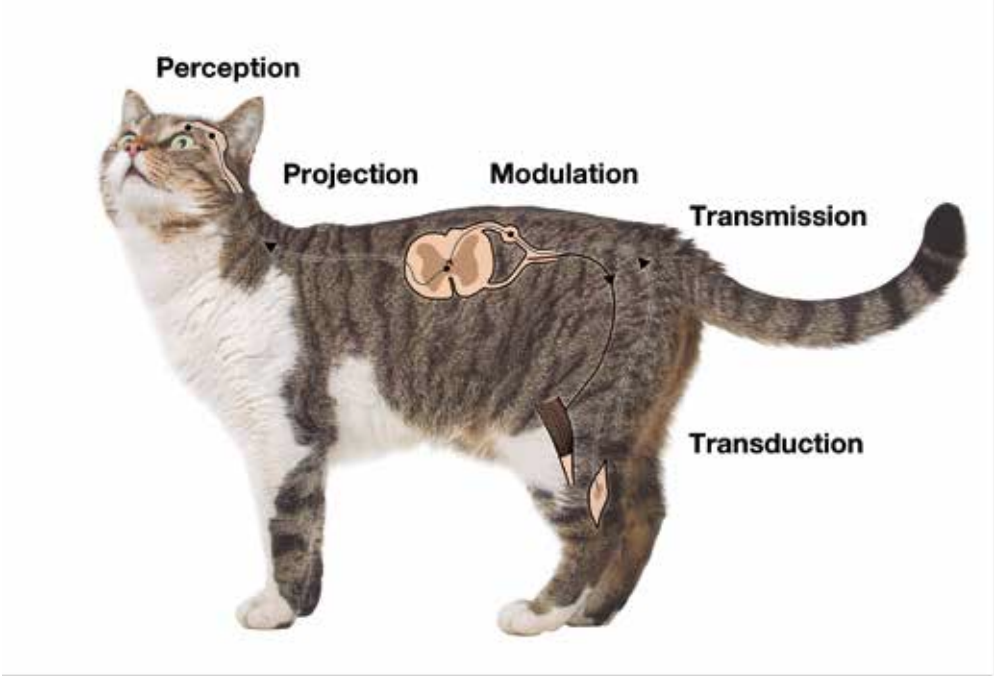
IDENTIFICATION AND MANAGEMENT OF PAIN IN THE FELINE SPECIES

Definition of pain

The term "pain" can appear easy to understand and easy to define. However, pain can have multifaceted presentations, and a debate about its definition is currently in progress. In this manual, we will give an overview of the different factors related to pain both internally and externally of the animal, and of the implications they have in terms of recognition and treatment.

The most commonly used definition of pain, considered applicable also to individuals not able to self-report, is that provided by IASP (International Association for the Study of Pain) in 1979, that defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. This definition clarifies that nociception is different from pain, the latter having two components:

- A sensorial component, corresponding to the neuronal processing of the noxious stimulus, starting from the activation of nociceptors and transformation of a noxious stimulus into an electric signal (transduction) until second-order neurons, located in the grey matter of spinal dorsal horn (transmission);
- An emotional component, corresponding to the perception of pain. Several brain structures, including the limbic system, are involved in this process, which results in suffering.



Many neurotransmitters are involved in pain transmission, some inhibitory (e.g serotonin, GABA and endorphins) and some excitatory (e.g. vasoactive intestinal peptide and cholecystokinin). In addition, each individual is equipped with an endogenous control system, incorporating descending signals working at different brain levels, that counter-act the ascending signals and thus modulate the final perception of pain (modulation).

The word unpleasant in the current definition of pain is simply an umbrella term to state that pain is a negatively valenced sensory experience. Williams and Craig (2016) propose the following definition to replace the current one: pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components. As discussed later, pain and stress are indeed linked.

Classifications of pain

Pain can be classified in various ways. For instance, based on duration, as in chronic and acute. For a complete classification, please see table 1. However, pain is often a multifactorial phenomenon. A more up-to-date classification (reported in table 2) takes into account the fact that the disease itself or the administered treatment can modify pain.

When classifying pain, its duration should not be underestimated: the longer the pain, the higher the impact on cat welfare, in turn reducing the cat's quality of life.

Table 1. Common classifications of pain based on different criteria (from Camps and Amat, 2012).

Classification criteria	Presentation	Characteristics	Examples
DURATION	Acute	< 2 weeks	Tooth pain
	Chronic	> 3 months	Cancer pain
PATHOGENY	Neuropathic	Caused by a lesion of the nervous system	Spinal lesion
	Nociceptive	Caused by stimulation of pain receptors	Sharp pain
	Inflammatory	Caused by tissue damage and inflammation	Post-surgery pain
LOCATION	Visceral	Activation of internal pelvic, abdominal or thoracic visceral nociceptors	Hepatic lesion
	Somatic	Activation of skin, bone and soft tissue nociceptors	Arthritis
COURSE	Intermittent	Episodes of pain followed by pain-free periods	
	Continuous	Always present	
INTENSITY	Mild	Daily routine can be carried out	Muscular lesion
	Moderate	It interferes with daily routine	Post-surgery recovery
	Severe	It interferes with rest	Spinal disc herniation

Figure 1. **Traumatic skin lesion in a cat that can produce neuropathic chronic pain.**

Courtesy of Veterinary Teaching Hospital, University of Pisa.

Figure 2. **Intestinal perforation; an example of minflammatory visceral pain.**

Courtesy of Veterinary Teaching Hospital, University of Pisa.

Table 2. **New classification of pain (modified from Camps and Amat, 2012).**

Type of pain	Definition	Implications	Classification
ADAPTIVE PAIN	Pain that appears as a result of the normal response of a damaged tissue	It has a protective function	• Inflammatory • Nociceptive
NON-ADAPTIVE PAIN	Pain caused by physical changes in the central nervous system due to a missing or ineffective treatment of the adaptive pain	It does not have a protective function and it is often more difficult to be treated. In order to restore central transmission, specific drugs such as NMDA receptor antagonists may be required	• Neuropathic • Functional • Central

The importance of pain prevention and treatment

Relief from pain and suffering should be part of standard veterinary practice, not only for ethical reasons related to animal welfare, but also to ensure proper medical and surgical procedures.

Pain can have detrimental effects on the health of the cat, by reducing cat welfare and altering the cat's physiological functions, e.g. reducing food intake and/or immunological competence etc. However, some studies suggest that in veterinary medicine the use of analgesic drugs is lower than it should be (Camps and Amat, 2012). In particular in cats, pain management is frequently overlooked and they are prescribed less analgesic drugs when compared with dogs. This is due to challenges in feline pain recognition and assessment, lack of specific training in the assessors and limited availability of pain assessment scoring tools in this species (Evangelista *et al.*, 2019).

The lack of adequate prevention and treatment of pain can have a long-lasting, negative impact on cat welfare. In fact, when an individual experiences pain, sensitization can be established. Sensitization is a phenomenon of increased pain sensitivity occurring when an individual in pain receives new stimuli. It can result from two different processes:

- Hyperalgesia: the individual shows a response higher than normal to a painful stimulus;
- Allodynia: the individual shows a pain response to stimuli that normally do not cause pain.

Sensitization can be established at both the peripheral and the central level. Peripheral sensitization is due to the strict link between inflammation and pain: a damaged tissue attracts inflammatory cells, which release the mediators of inflammation responsible for sensitization. Central sensitization is due to an overstimulation of central neurons, leading to changes in the properties of neurons in the central nervous system: therefore, the pain is no longer coupled, as acute nociceptive pain is, to the presence, intensity, or duration of noxious peripheral stimuli. Central sensitization can therefore lead to hyperalgesia in areas far from the original painful ones, and it can persist even after the elimination of the initial cause of pain. It is therefore very important to prevent pain before surgical procedures, in order to avoid the establishment of a central sensitization (Camps and Amat, 2012), since it is that which is responsible for many of the temporal, spatial, and threshold changes in pain sensibility in acute and chronic clinical pain settings.

Another negative impact of untreated pain is that on the relationship between the cat and humans. When experiencing pain, especially during interaction (daily, at home, or during physical examination), cats often develop avoidance and even aggressive behaviours that cause the relationship with the owner and the veterinarian to deteriorate. Owners may bypass veterinary care to avoid distressing their animals, and may also choose to replace their vet with a more attentive one (Mariti *et al.*, 2016).

- **If untreated, acute pain can become chronic**
- **Chronic pain sensitizes animals to other stimuli**
- **A prolonged, painful experience is detrimental to the overall healing process as well as to the general well-being of the cat**

Finally, veterinarians must be aware that activation of the neuroendocrine system (increases in cortisol and catecholamine levels) in response to pain and stress can be a confounding factor in the outcome of the clinical examination and of laboratory analyses: the less the cat is in pain and stress, the more reliable the visit outcome.

Misconceptions and false myths on pain to debunk

Pain is beneficial and has to be allowed to occur

The most common reason for that belief is that pain is a great immobilizer, thus some veterinarians recommend to maintain some pain to make the animal stay still after surgery. This is often a misconception, as animals that are scared, highly stressed or even aroused move despite feeling pain (exactly as humans do, due to the action of neurotransmitters such as endorphins and noradrenaline).

Although some pain-related behaviours are adaptive and have a protective function, a missing or ineffective treatment can lead to a non-adaptive pain.

Indeed, the advantages of eliminating pain exceed the disadvantages of eliminating its protective biological effects, by reducing recovery and healing time, as well as risk of infection (Camps and Amat, 2012).

Pain is part of the healing process

Behavioural changes associated with pain are usually adaptive: e.g. lameness is a way to reduce load on a damaged limb. However, showing lameness does not mean that the limb is healing, and maintaining lameness without treatments does not guarantee healing. Actually, the prolonged lack of use of a body part can have long-term consequences.

Cats don't feel pain the way humans or other animals do

In fact, animals feel and anticipate pain by similar mechanisms as people and other mammals, as has been widely demonstrated by physiological and pharmacological research.

Since animals have adaptive mechanisms which may mask signs of pain, an absence of painful behaviours does not necessarily mean an absence of pain. To address pain in pets adequately, veterinarians and owners should begin with the assumption that procedures and medical conditions that are painful in humans would cause similar pain in cats (Landsberg *et al.*, 2013).

What is painful/not painful for a cat, is painful/not painful for another cat

The level of tolerance to pain stimuli varies with individuals. This discrepancy can be widened further when cases in which sensitization has occurred are taken into consideration.

It must also be noted that pain expression can vary across species and, within the same species, among individuals.

Pain is easy to be identified

As reported before, the experience and expression of pain are highly variable and individual. Factors such as age, genetics, previous experience etc. are known to affect its expression.

In addition cats, unlike dogs, do not always demonstrate pain overtly, making its recognition more difficult. Cats are predators but, at the same time, they are prey. The latter aspect is probably responsible for some of their characteristics, such as a wide range of stress- and fear- inducing stimuli, and for some feline behavioural strategies, including a lower level of expression of certain behaviours. For instance, cats may show behavioural signs of pain to a lower intensity compared with other species. However, a lower intensity of expression does not imply a lower perception of pain.

Pain-related response decreases over time

Usually the opposite can be observed. The avoidance/aggressive response, for example, is likely to be reinforced by continued examination, making the behaviour more likely to appear, and in turn possibly also extend into different contexts and at a higher intensity. Such an increase is more likely to occur when the pain is intense and/or long-lasting, and so can be prevented by avoiding unnecessary manipulations and administering adequate drugs for pain prevention and treatment.

Response to pain is proportional to its perception

As reported before, cats tend to display subtle signs of pain (and stress, Mariti *et al.*, 2017), i.e. the response can appear mild or even be missed although pain is there; not complaining does not mean not hurting. By treating inapparent pain, its presence may be confirmed by the subsequent display of behaviours more normal or indicative of well-being.

In other cases, the high intensity and/or the long duration of the pain, through sensitization and learning, can lead to very intense responses by the animal. In these cases, veterinarians and owners might believe that the cat is overreacting. For these reasons, both the absence of complaint and dramatic behavioural displays can lead to under-treatment.

Purring means the cat is fine

Although purring is usually associated in cats with positive emotions, such as kittens sucking milk or adult cats being stroked and kneading, it is not uncommon to hear cats purring even when severely injured or during hospitalization. In that context purring should not be confused with a well-being indicator, as in fact it is pain-related purring.

PAIN, BEHAVIOUR, STRESS, AND WELFARE

Pain is a multidimensional phenomenon that includes perceptual, emotional and learning-related components.

There is a strong link between behaviour and pain: pain assessment, response to pain medications, and the overall well-being of the cat largely depends on the measurement and evaluation of the cat's behaviour. Pain can alter motivation and emotional states, which results in a wide range of potential changes in behaviour. In general, cats which are in pain favour defensive and avoidance-related strategies to reduce further loss and/or injury.

On one hand, any change in mobility or behaviour should be regarded as a possible indication of pain; on the other hand, it could also be an indication of stress (e.g. due to hospitalization or a visit to the clinic), surgical complications, drug side-effects, or progression of an underlying illness.

In fact pain and stress in cats may not be independent. For instance, some behavioural complaints are the results of stress and/or pain, or may cause more stress and/or pain. If the behavioural problem has a pain and stress component, it follows that its resolution requires that both components are treated. An example of how pain, behaviour and stress are interconnected is represented by serotonin levels. Serotonin is an inhibitory neurotransmitter for pain. In case of chronic stress (even when caused by chronic pain), serotonin levels decrease. This reduction, together with the decreasing inhibitory effect on pain, can affect the behaviour of the animal, including resulting in the display of undesired behaviours (Camps and Amat, 2012).

Behavioural measures are often the primary determinant in pain assessment but, as reported before, the experience and expression of pain are highly variable and individual. For instance, studies consistently show that, in cats, changes in lifestyle (including activity and mobility) and in behaviour (including grooming and temperament) are the most sensitive method of diagnosing arthritic pain; however, studies also show that less than half of cats with arthritis show lameness or gait alterations (Landsberg *et al.*, 2013).

Health problems and pain can have both suppressive and intensifying effects on behaviours (Fatjò and Bowen, 2009):

- Suppressive effects are characterised by a decrease in certain behaviours, such as activity, alertness, social interaction, feeding and play;
- Intensifying effects are characterised by an increase in the expression of behaviours that were previously expressed at a lower level, and the appearance of new behaviours that were previously absent. For example, aggression, elimination problems, and self-mutilation.

In fact, pain is often responsible for behavioural problems, which do not always disappear even after the original pain has subsided. For instance, once intraspecific aggression (to avoid interaction-related pain) or house soiling (to avoid locations where the animal has previously experienced pain) has been established, it can persist due to learning or to the impact it has had in everyday life. It must also be emphasised that avoidance and defensive strategies that are connected with pain are particularly resistant to extinction, due to the learning process and the brain structures involved.

Pain is often exhibited with non-specific signs. The owner, being familiar with the behaviour of

that individual cat, is important in recognizing if a certain behaviour is common or had a sudden onset, making pain a possible cause for it. When feeling pain, cats routinely show decreased activity, decreased grooming and increased reactivity (e.g. vocalizing, tensing, increased heart and respiratory rate, mydriasis) when approached or manipulated. Other common signs of pain in cats include guarding/protecting body parts, withdrawal from social and physical interactions, growling, hissing and anorexia. Pain scales (see annexes) suggest that these behaviours may move from intermittent to more continuous behaviours as pain worsens, and aggression may be part of the normal progression until the cat is quite ill, at which point aggression may diminish (Overall, 2013).

Pain-related aggression is probably underestimated, for both its prevalence and relevance. Usually, when caused by pain, the aggression exhibited is greater than that required to indicate concern and to effect cessation of the offending stimulus, and usually is related to manipulation. As aggression often has a learned component, aggression can precede the actual treatment/manipulation, with the animal guarding or protecting the body part while growling and hissing, even before he is actually touched or reached for.

Avoidance-related behaviours are maintained and reinforced, and they help the individual to escape from negative experiences that are perceived as threatening. But learning can lead to other negative consequences. On one hand, if the animal has already experienced pain when manipulated, the animal can show overt aggression without warning signals (Camps *et al.*, 2012). On the other hand, behavioural and physiological signs of fear, including avoidance and aggression, may become sequelae (Overall, 2013). An association can be made by the pet with the physical and social environment of the place where the pet experiences pain, typically the veterinary clinic.

Veterinarians should endeavour to avoid and/or control pain and anxiety deriving from routine procedures, as well as tuning their own behaviour according to the cat's state. Veterinarians should also advise owners with the aim of decreasing the risk of aggression and welfare impairment (Mariti *et al.*, 2016).

- **Pain, behaviour, stress, and welfare are closely related.**
- **Behaviour is often the primary determinant in pain assessment and monitoring.**
- **Pain, stress and restraint can lead to aggression towards the vet and the owner.**

PREVENTION OF PAIN

Where pain is concerned, prevention is better than cure. In fact, preventing the onset of pain has many advantages, i.e. not provoking all the negative consequences of having experienced pain: no impact on the cat's welfare, no display of avoidance/aggression, no possibility of establishing a learned response, no possibility of establishing sensitization nor of the pain becoming chronic, etc. Preventing pain means protecting the welfare of the feline patient; that is the duty of veterinarians.

Table 3 gives some protocols used for the prevention of pain in cats.

Table 3. Examples of analgesic protocols for the prevention of pain in cats.

Normal temperament	Dexmedetomidine 3-5 mcg/kg
	Methadone 0.2-0.5 mg/kg
Nervous temperament	Dexmedetomidine 7-10 mcg/kg
	Methadone 0.3-0.5 mg/kg
	Ketamine 1-2 mg/kg
Geriatric normal temperament	Dexmedetomidine 3 mcg/kg
	Methadone 0.2 mg/kg
Geriatric nervous temperament	Dexmedetomidine 3-5mcg/kg
	Methadone 0.2-0.3 mg/kg
	Alfaxalone 1 mg/kg
Heart disease	Methadone 0.2 mg/kg
	Alfaxalone 1 mg/kg
	Midazolam 0.2-0.5mg/kg
Diagnostic or painless procedures	Butorphanol 0.2-0.3 mg/kg
	Dexmedetomidine 3-5 mcg/kg

TREATMENT OF PAIN

The advantages of eliminating pain exceed the disadvantages of eliminating its protective biological effects, by reducing recovery and healing time, as well as the risk of infection. Treating, as well as preventing pain means protecting the welfare of the feline patient; that is the duty of veterinarians.

The first step is recognition of pain. This allows the veterinarian to achieve a correct diagnosis and prescribe adequate analgesic treatment. The second step is the actual treatment. In order to obtain better results, more measures can be combined: for instance, the administration of analgesic products is more effective if associated with non-pharmacological measures.

Tools to assess and monitor pain in cats

Pain management is an integrated medical and surgical aspect in veterinary medicine, making it necessary to use objective parameters to quantify the severity of the pain experienced.

For veterinary practitioners there are three areas of pain management on which to focus: 1) assessment in the hospital; 2) owner monitoring and assessment after hospitalization or surgery; 3) owner measures to identify the onset and progress of pain, especially chronic disease states such as degenerative joint disease (Landsberg *et al.*, 2013).

Behavioural measures are often the primary determinant in pain assessment. However, changes in behaviour may be subtle and easily missed, therefore veterinarians must act as patients' advocate, educating staff and owners about pain monitoring. Pain can also be responsible for sympathetic stimulation that causes physiological changes in heart rate, cortisol and catecholamines levels, blood pressure, etc. As for behaviour, such changes can also be due to fear, stress, or pharmacological treatments.

Scales for the assessment of pain in cats are provided in annex 1, 2 and 3.

Two validated behaviour-based pain assessment instruments have been published, the UNESP-Botucatu multidimensional composite pain scale (annex 1, Brondani *et al.*, 2013) and the Glasgow composite measure pain scale-feline (rCMPS-F, annex 2, Calvo *et al.*, 2014).

Recently, the Feline Grimace Scale (FGS, annex 3, Evangelista *et al.*, 2019) has been demonstrated to be an effective, simplified method of assessing cat facial expressions specifically related to pain. Five action units (ear position, orbital tightening, muzzle tension, whiskers position and head position) were identified. The FGS scores were higher in painful than in control cats and the assessment showed validity (a very strong correlation with rCMPS-F, good intra and inter-rater reliability and internal consistency). However, at the moment the impact of training experience is unknown, and results are probably affected by morphological characteristics of the cats, in particular for brachycephalic cats.

Although the use of scales can be affected by the training of the observer, other methods such as visual analogue scales, numerical rating scales or picture-guided evaluations can also be used,

even by non-experienced people. Veterinarians should involve cat owners as much as possible in the process of early and accurate detection of pain. Cat owners can use tools provided by the veterinarian at the beginning, as well as ongoing, to evaluate the effectiveness of the treatment. Owners can also use the same tools on a regular basis, e.g. yearly, to help the early detection of the onset of pain. In addition, cat owners can be asked to compile a diary, noting any change in behaviour and when it occurs (e.g. if it can be related to withdrawal of pain medications).

Pharmacological treatment of pain in cats

Analgesic drugs should be used every time the animal is in pain or in cases when a painful procedure is planned.

The concept of multimodal approach to pain treatment is well-established and its application leads to both an increase in analgesic effectiveness and a reduction of side effects (Epstein *et al.*, 2015). The multimodal approach is based on the idea that the pain signal can be blocked at several levels.

Pre-emptive analgesia (the giving of analgesic drugs before the nociceptive insult) is crucial to reduce the sensitisation phenomenon, thus reducing the perioperative analgesic requirement.

Depending on the drugs and on the technique used, the pain signal can be completely stopped, reduced or re-modelled. In order to use the right drugs and to have the most efficacious treatment, it is fundamental to evaluate the kind of pain stimulus and its source. When planning an analgesic protocol for a surgical procedure, it is useful to think about the pain which will be stimulated in order to use the most appropriate drugs and procedure (see tables 4 and 5).

Table 4. Indications for analgesic use based on type of pain. LA: local anaesthetic; NSAIDs: non-steroidal anti-inflammatory drugs.

Classification criteria	Presentation	Drugs
DURATION	Acute	LA, opioids, NSAIDs, alfa-2-agonists
	Chronic	LA, NSAIDs, ketamine, gabapentin, alfa-2-agonists
PATHWAY	Neuropathic	Gabapentin
	Nociceptive	LA, opioids, NSAIDs, alfa-2-agonists
	Inflammatory	NSAIDs, alfa-2-agonist
LOCATION	Visceral	LA, opioids, alfa-2-agonists
	Somatic	LA, ketamine, NSAIDs

Table 5. Indications for analgesic drugs and techniques on the basis of pain intensity. LRA: loco-regional anaesthesia, NSAIDs, non-steroidal anti-inflammatory drugs.

Pain intensity	Technique, analgesic drugs and dosage
MILD	LRA, Butorphanol 0.2-0.4 mg/kg q4-6 h; tramadol 1-2 mg/kg q12 h, alfa-2-agonists, NSAIDs (if not contraindicated)
MODERATE	LRA, Buprenorphine 10-20 mg/kg IM/IV q6-8 h, NSAIDs (if not contraindicated)
SEVERE	LRA, methadone 0.2-05 mg/kg IM/IV, q4-6h; fentanyl IV infusion 2-10 mcg/kg/h, ketamine IV infusion 0.5 mg/kg/h; dexmedetomidine IV infusion 0.5-1 mcg/kg/h; gabapentin 10 mg/kg PO q12h.

Loco-regional anaesthesia (LRA)

This is the most effective analgesic technique; the local anaesthetic (LA) enters the sensitive fibres and completely blocks the nociceptive stimulus towards the brain. In this way, the nociceptive stimulus does not produce the typical modification of the central nervous system. The inflammatory response to the surgical insult is not blocked, and for this reason the combination with NSAIDs would be indicated to have an adequate control of the pain pathways.

The LA, in order to produce a solid block of the sensitive fibres, needs to enter the nerve in an appropriate concentration; the precision of the regional technique used (blind, nerve-stimulated, ultrasound-guided), the volume and the concentration of the LA, as well as the experience of the clinician, can affect the level of analgesia produced.

Combination with an opioid reduces the sympathetic stimulation which can derive from a partial LRA.

When deciding on the LA to use, it is important to consider the duration of the surgical procedure and the total maximum dose that can be employed (table 6).

LRA should always be used whenever possible, because of the excellent perioperative analgesia it can produce.

Table 6. Concentration, dosage and duration of the most common local anaesthetic drugs.

Drug	Concentration	Maximum safe dose	Duration of effect
LIDOCAINE	2%	5 mg/kg	2-3 hours
ROPIVACAINE	0.25-0.5%	3 mg/kg	6-10 hours
BUPIVACAINE	0.25-0.5%	2 mg/kg	6-8 hours

Opioids

These are considered "the analgesics" by definition. They are essential in acute pain management, and their use in pre-emptive analgesia is of great importance for the reduction of postoperative pain.

Opioids have a synergistic effect when combined with alpha-2-agonists, and produce a sparing effect on the perioperative anaesthetic requirement. They affect the modulation and the perception of the nociceptive stimulus at central nervous system level.

Opioids are classified on the basis of their receptor interaction: mu pure agonists, partial agonists and agonists-antagonists. Mu pure agonists such as morphine, methadone and fentanyl are generally used for moderate-severely painful procedures; while buprenorphine, a partial agonist, is used for moderate pain. Butorphanol is a mu antagonist

Figure 3. Mydriasis in a cat who received methadone as analgesia.

Courtesy of Veterinary Teaching Hospital, University of Pisa.

opioid with a good sedative effect but it has very low analgesic capacity; it mainly produces visceral analgesia and is indicated for treatment of mild pain.

In cats opioids can produce euphoria, with an increase in activity, and mydriasis (figure 3); for this reason, it is important to keep animals in a quiet environment with dim lighting. It is also reported that opioids can provoke hyperthermia in cats (Posner *et al.*, 2010).

NSAIDs

Non-steroidal anti-inflammatory drugs are a central component of pain management since an inflammatory component is frequently present in painful conditions. NSAIDs interfere in the pain pathway both at central and peripheral levels. Feline approved NSAIDs have demonstrated satisfactory safety profiles; meloxicam and robenacoxib have been approved for long-term use in cats in many countries.

The main side-effects related to the NSAIDs use are gastrointestinal and renal. A scrupulous evaluation of the patient is mandatory to reduce the possibility of side effects. Haemato-biochemical examination, dose optimisation, use of gastroprotectants, evaluation of the volemic and hydration status, and avoiding combination with furosemide and potential nephrotoxic agents, are important to ensure the correct use of these drugs.

OTHER DRUGS

Alpha-2-agonists

This is a group of sedatives frequently used in veterinary medicine. The most frequently employed in pets are medetomidine and its right enantiomer, dexmedetomidine. Alpha-2-agonists produce analgesia by acting in the nociceptive pathway at a peripheral and central level.

These drugs are not able to produce an adequate level of analgesia by themselves, but within a multimodal management plan they offer several advantages. Alpha-2-agonists maintain blood pressure through a certain degree of vasoconstriction, reduce the heart rate and cardiac oxygen consumption, and stimulate diuresis. They can be used as a bolus in premedication or as a continuous infusion for intraoperative and postoperative pain management.

Ketamine

This is an anaesthetic drug that can produce somatic analgesia because of its interaction with NMDA receptors. More specifically, the antagonist effect on NMDA can reduce the wind up that is responsible for the sensitisation phenomenon. The analgesic effect of ketamine has not yet been studied in a feline surgical model, but the International Veterinary Academy of Pain Management has considered the use of ketamine useful as part of a multimodal approach in patients with the risk of maladaptive pain states (Eipstein *et al.* 2015). It was shown to be a useful adjuvant when given as an infusion in a case report of traumatic injuries (Goich *et al.*, 2019).

Tramadol

Compared with dogs, tramadol has a higher efficacy in cats as it produces the M1 metabolite. It can be used for pain control at home in those animals in which the NSAIDs are not sufficient or cannot be used.

Gabapentin

The analgesic effects of this molecule are related to calcium channel down regulation. It is well tolerated with very few side effects. In cats a dosage of about 100 mg/cat is also used to produce sedation and/or to reduce anxiety before a clinical visit or before a journey. There is a lack of studies of this use in the veterinary literature to confirm this anecdotal evidence.

Non-pharmacological aids for the treatment of pain in cats

The combination of analgesic products with non-pharmacological measures results in more effective pain relief and improved time to recovery, therefore further protecting the welfare of the cat.

Many different non-pharmacological measures can be taken, including changes in management and/or the cat's environment, supplementation, other veterinary care etc. Depending on the type of pain, some measures are more appropriate than others. For instance, in case of a skin lesion, reducing the healing time and the risk of infection is a beneficial aid.

Briefly report below are the most commonly recommended non-pharmacological aids to analgesia in cats (Epstein *et al.*, 2015):

- Environmental modifications: every attempt to reduce fear, anxiety and stress should be made, as these conditions predispose animals to hyperalgesia. This measure should be carried out in the veterinary setting as well as at home, by providing the cat with a quiet and comfortable environment: using bedding, blankets or clothing with familiar scents; separating cats, at least visually, from dogs and other cats etc. (Figure 4).
- Nutritional management: the primary aim is to allow the cat to regain or maintain a lean body condition score and avoid the negative consequences of being or becoming overweight. Nutritional management can also include supplementation. For instance, omega-3 fatty acids were effective at reducing signs associated with feline degenerative joint disease. Also HC-complex (hyaluronic acid and chondroitin) is helpful in improving joint functionality.
- Physical rehabilitation: although less commonly used than in dogs, the use of rehabilitation for cats is increasing. Its foundation is to restore musculoskeletal strength and function, endurance and proprioception, and to reduce pain. Together with exercise and manual therapy (including joint mobilizations, massage and myofascial release), some additional aids can be used. For the reduction of pain, magnetotherapy and laser therapy are more commonly used, the latter also being helpful for pain from conditions other than musculoskeletal pain, e.g. stomatitis (Squarzoni *et al.*, 2017) (Figures 5 and 6).
- Acupuncture: there is a solid and still growing body of evidence suggesting that acupuncture, as a part of multimodal pain management plans, offers a compelling and safe method for pain management.

Figure 4. A cat which is very depressed and painful. The environment has been adjusted in order to reduce stress and pain, by providing the cat with his own carrier and a blanket with familiar scent, as well as putting the cat in a quiet environment out of sight of other animals. During therapy, the presence of the owner was also allowed.

Courtesy of Veterinary Teaching Hospital, University of Pisa.

Figure 5. Joint mobilization exercises in a kitten with a traumatic lesion of the brachial plexus and elbow fracture.
Courtesy of Fisioterapia Veterinaria Lucca, Italy.

Figure 6. Magnetotherapy for lumbar pain in a 12-year old cat.
Courtesy of Fisioterapia Veterinaria Lucca, Italy.

- Thermal modification: in acute injury, including surgical areas, cold compression has a demonstrable benefit in reducing pain and inflammation, and promotes early return to function. In the case of chronic injury, heat can improve comfort and function through a variety of mechanisms.
- Gentle handling: this advice, which is of course always valid, is particularly important in case of an animal in pain. Veterinarians should familiarize themselves with recognized feline-friendly handling techniques (Rodan *et al.*, 2011) and educate staff and owners accordingly.

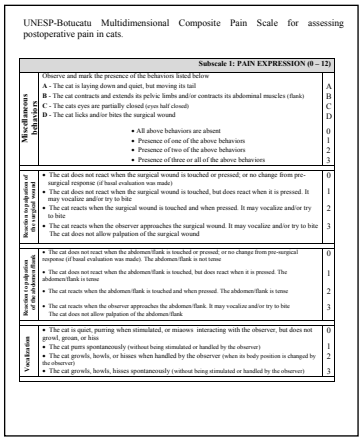
A general component of the advice to be given to owners of any animal is: avoid punishment. Whatever the cause of an undesired behaviour (e.g. house soiling) and whatever the condition of the animal (feeling pain or not), punishment must be avoided, due to its negative consequences on the welfare of the cat, on the cat-human relationship and sometimes even on the behaviour of the cat. Physical punishment is particularly unacceptable as it can cause or worsen the pain experienced by the cat.

ANNEXES

Annex 1

UNESP-Botucatu Multidimensional Composite Pain Scale for assessing postoperative pain in cats.

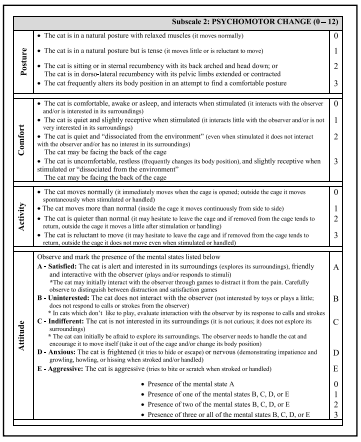
http://www.animalpain.com.br/assets/upload/escala-en-us.pdf



UNESP-Botucatu Multidimensional Composite Pain Scale for assessing postoperative pain in cats.

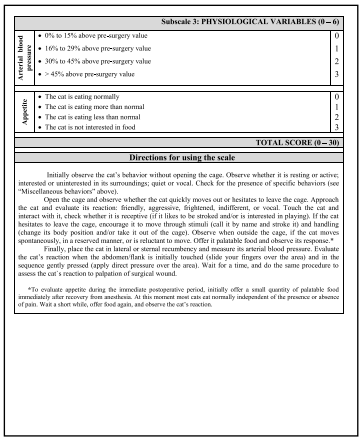
Subscale 1: PAIN EXPRESSION (0 – 12)

Miscellaneous behaviors	Observe and mark the presence of the behaviors listed below A - The cat is laying down and quiet, but moving its tail B - The cat contracts and extends its pelvic limbs and/or contracts its abdominal muscles (flank) C - The cats eyes are partially closed (eyes half closed) D - The cat licks and/or bites the surgical wound	A B C D
	• All above behaviors are absent	0
	• Presence of one of the above behaviors	1
	• Presence of two of the above behaviors	2
	• Presence of three or all of the above behaviors	3
Reactive to palpation of surgical wound	• The cat does not react when the surgical wound is touched or pressed; or no change from pre-surgical response (if basal evaluation was made)	0
	• The cat does not react when the surgical wound is touched, but does react when it is pressed. It may vocalize and/or try to bite	1
	• The cat reacts when the surgical wound is touched and when pressed. It may vocalize and/or try to bite	2
	• The cat reacts when the observer approaches the surgical wound. It may vocalize and/or try to bite The cat does not allow palpation of the surgical wound	3
Reactive to palpation of abdominal flank	• The cat does not react when the abdomen/flank is touched or pressed; or no change from pre-surgical response (if basal evaluation was made). The abdomen/flank is not tense	0
	• The cat does not react when the abdomen/flank is touched, but does react when it is pressed. The abdomen/flank is tense	1
	• The cat reacts when the abdomen/flank is touched and when pressed. The abdomen/flank is tense	2
	• The cat reacts when the observer approaches the abdomen/flank. It may vocalize and/or try to bite The cat does not allow palpation of the abdomen/flank	3
Vocalization	• The cat is quiet, purring when stimulated, or miaows interacting with the observer, but does not growl, groan, or hiss	0
	• The cat purrs spontaneously (without being stimulated or handled by the observer)	1
	• The cat growls, howls, or hisses when handled by the observer (when its body position is changed by the observer)	2
	• The cat growls, howls, hisses spontaneously (without being stimulated or handled by the observer)	3



Subscale 2: PSYCHOMOTOR CHANGE (0 – 12)

Posture	• The cat is in a natural posture with relaxed muscles (it moves normally)	0
	• The cat is in a natural posture but is tense (it moves little or is reluctant to move)	1
	• The cat is sitting or in sternal recumbency with its back arched and head down; or The cat is in dorso-lateral recumbency with its pelvic limbs extended or contracted	2
	• The cat frequently alters its body position in an attempt to find a comfortable posture	3
Comfort	• The cat is comfortable, awake or asleep, and interacts when stimulated (it interacts with the observer and/or is interested in its surroundings)	0
	• The cat is quiet and slightly receptive when stimulated (it interacts little with the observer and/or is not very interested in its surroundings)	1
	• The cat is quiet and "dissociated from the environment" (even when stimulated it does not interact with the observer and/or has no interest in its surroundings) The cat may be facing the back of the cage	2
	• The cat is uncomfortable, restless (frequently changes its body position), and slightly receptive when stimulated or "dissociated from the environment" The cat may be facing the back of the cage	3
Activity	• The cat moves normally (it immediately moves when the cage is opened; outside the cage it moves spontaneously when stimulated or handled)	0
	• The cat moves more than normal (inside the cage it moves continuously from side to side)	1
	• The cat is quieter than normal (it may hesitate to leave the cage and if removed from the cage tends to return, outside the cage it moves a little after stimulation or handling)	2
	• The cat is reluctant to move (it may hesitate to leave the cage and if removed from the cage tends to return, outside the cage it does not move even when stimulated or handled)	3
Attitude	Observe and mark the presence of the mental states listed below **A - Satisfied:** The cat is alert and interested in its surroundings (explores its surroundings), friendly and interactive with the observer (plays and/or responds to stimuli) *The cat may initially interact with the observer through games to distract it from the pain. Carefully observe to distinguish between distraction and satisfaction games **B - Uninterested:** The cat does not interact with the observer (not interested by toys or plays a little; does not respond to calls or strokes from the observer) * In cats which don't like to play, evaluate interaction with the observer by its response to calls and strokes **C - Indifferent:** The cat is not interested in its surroundings (it is not curious; it does not explore its surroundings) * The cat can initially be afraid to explore its surroundings. The observer needs to handle the cat and encourage it to move itself (take it out of the cage and/or change its body position) **D - Anxious:** The cat is frightened (it tries to hide or escape) or nervous (demonstrating impatience and growling, howling, or hissing when stroked and/or handled) **E - Aggressive:** The cat is aggressive (tries to bite or scratch when stroked or handled)	A B C D E
	• Presence of the mental state A	0
	• Presence of one of the mental states B, C, D, or E	1
	• Presence of two of the mental states B, C, D, or E	2
	• Presence of three or all of the mental states B, C, D, or E	3



Subscale 3: PHYSIOLOGICAL VARIABLES (0 – 6)

Arterial blood pressure	• 0% to 15% above pre-surgery value	0
	• 16% to 29% above pre-surgery value	1
	• 30% to 45% above pre-surgery value	2
	• > 45% above pre-surgery value	3
Appetite	• The cat is eating normally	0
	• The cat is eating more than normal	1
	• The cat is eating less than normal	2
	• The cat is not interested in food	3

TOTAL SCORE (0 – 30)

Directions for using the scale

Initially observe the cat's behavior without opening the cage. Observe whether it is resting or active; interested or uninterested in its surroundings; quiet or vocal. Check for the presence of specific behaviors (see "Miscellaneous behaviors" above).

Open the cage and observe whether the cat quickly moves out or hesitates to leave the cage. Approach the cat and evaluate its reaction: friendly, aggressive, frightened, indifferent, or vocal. Touch the cat and interact with it, check whether it is receptive (if it likes to be stroked and/or is interested in playing). If the cat hesitates to leave the cage, encourage it to move through stimuli (call it by name and stroke it) and handling (change its body position and/or take it out of the cage). Observe when outside the cage, if the cat moves spontaneously, in a reserved manner, or is reluctant to move. Offer it palatable food and observe its response.*

Finally, place the cat in lateral or sternal recumbency and measure its arterial blood pressure. Evaluate the cat's reaction when the abdomen/flank is initially touched (slide your fingers over the area) and in the sequence gently pressed (apply direct pressure over the area). Wait for a time, and do the same procedure to assess the cat's reaction to palpation of surgical wound.

*To evaluate appetite during the immediate postoperative period, initially offer a small quantity of palatable food immediately after recovery from anesthesia. At this moment most cats eat normally independent of the presence or absence of pain. Wait a short while, offer food again, and observe the cat's reaction.

Annex 2

Glasgow Composite Measure Pain Scale: CMPS - Feline

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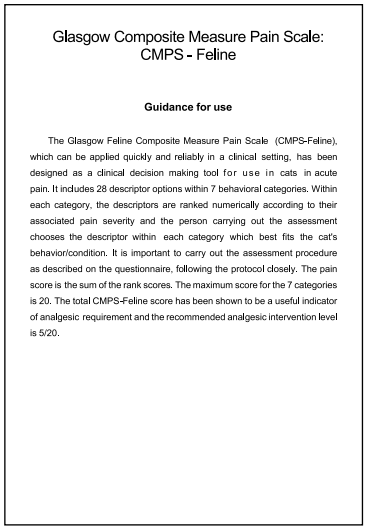
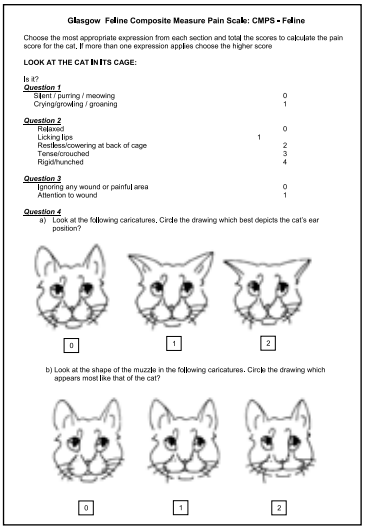


Glasgow Composite Measure Pain Scale: CMPS - Feline

Guidance for use

The Glasgow Feline Composite Measure Pain Scale (CMPS-Feline), which can be applied quickly and reliably in a clinical setting, has been designed as a clinical decision making tool for use in cats in acute pain. It includes 28 descriptor options within 7 behavioral categories. Within each category, the descriptors are ranked numerically according to their associated pain severity and the person carrying out the assessment chooses the descriptor within each category which best fits the cat's behavior/condition. It is important to carry out the assessment procedure as described on the questionnaire, following the protocol closely. The pain score is the sum of the rank scores. The maximum score for the 7 categories is 20. The total CMPS-Feline score has been shown to be a useful indicator of analgesic requirement and the recommended analgesic intervention level is 5/20.



Glasgow Feline Composite Measure Pain Scale: CMPS - Feline

Choose the most appropriate expression from each section and total the scores to calculate the pain score for the cat. If more than one expression applies choose the higher score

LOOK AT THE CAT IN ITS CAGE:

Is it?

Question 1

Silent / purring / meowing 0
Crying/growling / groaning 1

Question 2

Relaxed 0
Licking lips 1
Restless/cowering at back of cage 2
Tense/crouched 3
Rigid/hunched 4

Question 3

Ignoring any wound or painful area 0
Attention to wound 1

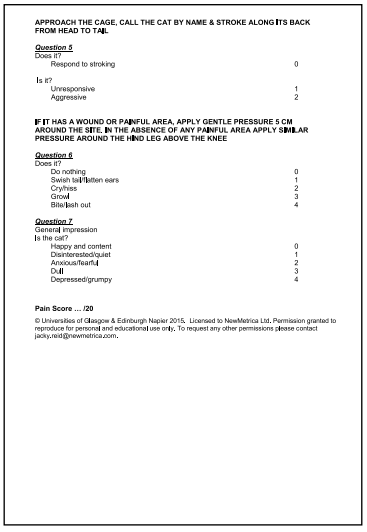
Question 4

a) Look at the following caricatures. Circle the drawing which best depicts the cat's ear position?

0 1 2

b) Look at the shape of the muzzle in the following caricatures. Circle the drawing which appears most like that of the cat?

0 1 2



APPROACH THE CAGE, CALL THE CAT BY NAME & STROKE ALONG ITS BACK FROM HEAD TO TAIL

Question 5

Does it?
Respond to stroking 0

Is it?
Unresponsive 1
Aggressive 2

IF IT HAS A WOUND OR PAINFUL AREA, APPLY GENTLE PRESSURE 5 CM AROUND THE SITE. IN THE ABSENCE OF ANY PAINFUL AREA APPLY SIMILAR PRESSURE AROUND THE HIND LEG ABOVE THE KNEE

Question 6

Does it?
Do nothing 0
Swish tail/flatten ears 1
Cry/hiss 2
Growl 3
Bite/lash out 4

Question 7

General impression
Is the cat?
Happy and content 0
Disinterested/quiet 1
Anxious/fearful 2
Dull 3
Depressed/grumpy 4

Pain Score … /20

Annex 3

Feline Grimace Scale

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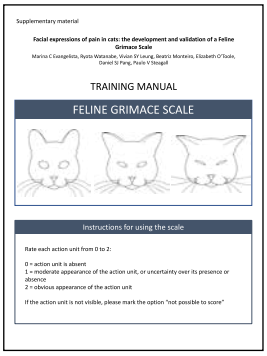


Supplementary material

Facial expressions of pain in cats: the development and validation of a Feline Grimace Scale

Marina C Evangelista, Ryota Watanabe, Vivian SY Leung, Beatriz Monteiro, Elizabeth O'Toole, Daniel SJ Pang, Paolo V Steagall

TRAINING MANUAL

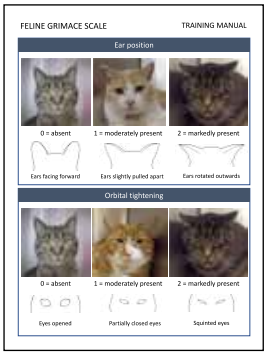
FELINE GRIMACE SCALE

Instructions for using the scale

Rate each action unit from 0 to 2:

0 = action unit is absent
1 = moderate appearance of the action unit, or uncertainty over its presence or absence
2 = obvious appearance of the action unit

If the action unit is not visible, please mark the option "not possible to score"



FELINE GRIMACE SCALE TRAINING MANUAL

Ear position

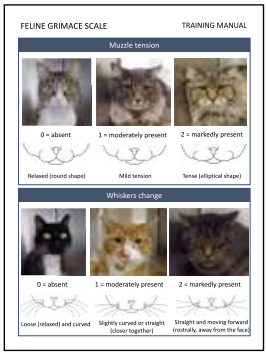
0 = absent 1 = moderately present 2 = markedly present

Ears facing forward Ears slightly pulled apart Ears rotated outwards

Orbital tightening

0 = absent 1 = moderately present 2 = markedly present

Eyes opened Partially closed eyes Squinted eyes



FELINE GRIMACE SCALE TRAINING MANUAL

Muzzle tension

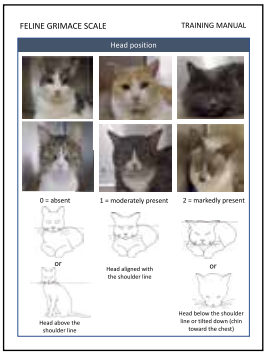
0 = absent 1 = moderately present 2 = markedly present

Relaxed (round shape) Mild tension Tense (elliptical shape)

Whiskers change

0 = absent 1 = moderately present 2 = markedly present

Loose (relaxed) and curved Slightly curved or straight (closer together) Straight and moving forward (rostrally, away from the face)



FELINE GRIMACE SCALE TRAINING MANUAL

Head position

0 = absent 1 = moderately present 2 = markedly present

or

Head above the shoulder line

Head aligned with the shoulder line

or

Head below the shoulder line or tilted down (chin toward the chest)

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