The Pharma Innovation Journal 2019; 8(11): 68-78

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2019; 8(11): 68-78

www.thepharmajournal.com
Received: 04-09-2019
Accepted: 08-10-2019

Rukmani Dewangan
Assistant Professor, Department of Veterinary Surgery and Radiology, College of Veterinay Science and A.H. Anjora Durg, Chhattisgarh, India

SK Tiwari
Director Instructions, Department of Veterinary Surgery and Radiology, College of Veterinay Science and A.H. Anjora Durg, Chhattisgarh, India

Corresponding Author:
Rukmani Dewangan
Assistant Professor, Department of Veterinary Surgery and Radiology, College of Veterinay Science and A.H. Anjora Durg, Chhattisgarh, India

Physiology of pain and its management in veterinary patients

Rukmani Dewangan and SK Tiwari

Abstract
This article aims at reviewing the physiology of pain, important pain pathways, types of pain and its assessment alongwith different methods of pain management in veterinary patients. Pain is is unpleasant sensation that the brain interprets after a peripheral lesion of nociceptive intensity. It is both a sensory and emotional experience and patients past experiences, fears and anxieties can play an important role. Effective pain management is essential for facilitating uneventful recovery, decreases death, and enhances better quality of life alongwith solidification of relationship among veterinarian, owner and animals.

Keywords: Pain, Nociception, sensitization, gate control theory, pain management

Introduction
Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". The process by which pain is perceived is complex and incompletely understood. It is unpleasant experience that cannot be objectively measured. The term "nociception" (Latin – noci = harm or injury) is used only to describe the neural response to traumatic or noxious stimuli and nociceptors are free (naked) nerve endings that encode mechanical, chemical, thermal energy into electrical impulses.

Classification of pain
Several classifications have developed for categorizing pain including duration, severity, origin, etc. Each classification is useful; each has limitations; and the classifications overlap.

A. Based on origin/location

1. **Somatic pain:** Pain arising from body wall. If pain originates in the skin or superficial tissues is called superficial pain/cutaneous pain. Cutaneous nociceptors terminates just below the skin and due to the high concentration of nerve endings, produces a well-defined, localized pain of short duration. When pain originates in the muscles, bones, joints, ligaments or connective tissues it is called deep pain. In other words somatic pain refers to pain originating from the periphery. It is usually described as sharp, stabbing, and well-localized.
2. **Visceral pain:** Pain which originates from body's viscera. Visceral pain is usually more diffuse and unpleasant than somatic pain. It occurs as a result of visceral distention, ischemia, stretching of ligaments attaching viscera, or smooth muscle spasm. The pain is not well-localized, is dull, aching, and often radiates to other areas of the body.
3. **Referred pain:** Pain that occurs at the remote from the source of the disease or injury usually a visceral source. It is usually referred to superficial somatic structures innervated by the same segmental spinal nerve that supplies the affected viscera.
4. **Neuropathic pain:** It occurs as a result of injury or disease of the nervous system itself and arises as a disorder of processing of nociceptive activity or as a result of abnormal activity in nociceptive pathways. It disrupts the ability of sensory nerves to transmit correct information to the thalamus. Neuropathic pain is difficult to control.
5. **Phantom pain:** It occurs when an individual perceives pain from a part of the body that has been removed or amputated. Pain associated with a missing limb, kidney and tooth.
6. **Psychological pain:** It is pain experienced by a patient when there is no apparent pathology, although it usually follows a previous painful incident.

B. Based on duration and intensity

1. **Acute pain:** It occurs immediately after a stimulus is received and subsides once stimulus is removed. This type of pain responds well to the treatment.
2. **Chronic pain:** It persists longer than normal course of time (3-6 months) for injured tissue to be healed and can be more difficult to recognize. It is may or may not respond well to treatment but require a multimodal approach.

Pain theory

Several theoretical frameworks have been proposed to explain the physiological basis of pain, although none yet completely accounts for all aspects of pain perception.

1. Specificity Theory
2. Strong's Theory
3. Pattern theory
4. Central Summation Theory (Livingstone, 1943) [9].
5. The Fourth Theory of Pain (Hardy, Wolff, and Goodell, 1940s)
6. Sensory Interaction Theory (Noordenbos, 1959)
7. Gate Control Theory (Melzack and Wall, 1965): The beauty of theory is that it provides a physiological basis for the complex phenomenon of pain and the complex structure of the nervous system, which is comprised of the following two major divisions 1) Central nervous system (the spinal cord and the brain) 2) Peripheral nervous system (nerves outside of the brain and spinal cord, including branching nerves in the torso and extremities, as well as nerves in the lumbar spine region).
8. New theory (Melzack and Wall, 1999): In this theory, the neuromatrix theory stipulates that every human being has an innate network of neurons that they named the "body-self neuromatrix". Each person's matrix of neurons is unique and is affected by all facets of the person's physical, psychological and cognitive traits and also by their experience.
9. Biochemical Theory- Pain producing, pain mediating and pain chemoreceptors are located in the brain. Endogenous opiates inhibits pain by blocking Substance P. Periaquaductal gray area (PAG) releases enkaphalins and Nucleus raphe magnus (NRM) releases serotonin. The various chemical pain mediators and inhibitors are Bradykinin, Substance P, Histamine, Prostaglandin, Acetylcholine, Capsaicin and K^+ ions.

Physiology of pain

For effective pain management, it requires to understand the process of pain physiology. With this knowledge, recognition of pain is facilitated and the use of pharmacologic agents and various techniques can be optimized for better management of variety of pain syndromes. Four processes occur from the initial tissue trauma to the sensed pain responses which are a) Transduction b) Transmission c) Perception d) Modulation

a) Transduction: The conversion of pain stimuli from a noxious thermal, mechanical, or chemical stimulus into electrical energy. This electrical energy is known as transduction. This stimulus sends an impulse across a peripheral nerve fiber by sensory receptors called nociceptors. It means transfer of nociceptive signals from the site of injury into a neural impulse.

Most nociceptors are free nerve endings that sense heat, mechanical and chemical tissue damage. Several types are described: 1) mechanoreceptors, which respond to pinch and pinprick, 2) silent nociceptors, which respond only in the presence of inflammation, and 3) polymodal mechanoheat nociceptors.

b) Transmission: Transmission of these neural signals from the site of transduction (periphery) to the spinal cord and brain occurs in two phases (periphery to spinal cord and spinal cord to brain). Pain impulses are transmitted by two fiber systems. Aδ fibers (Myelinated) transmit fast, sharp and well localized sensation (first pain) and a duller slower onset and often poorly localized sensation (second pain) which is conducted by C fibers (Unmyelinated). Both fiber groups end in the dorsal horn of the spinal cord. Aδ fibers terminate predominantly on neurons in laminas I and V, whereas the dorsal root C fibers terminate in laminas I and II. The first order neurons (Aδ and C fibers) synapse with neurons in dorsal horn (Second order neurons). The synaptic junctions between these first order neurons and the dorsal horn cells in the spinal cord are sites of considerable plasticity. For this reason the dorsal horn has been called a gate, where pain impulses can be "gated" i.e., modified. The first order neurons, then cross the spinal cord (Decussate) and continue to travel along second order neurons (In the spinothalamic tract) to higher areas of the CNS. A number of excitatory neurotransmitters are responsible for signal transmission. The transmission of second order neurons terminates in the thalamus. Second-order neurons are either nociceptive-specific or wide dynamic range (WDR) neurons. Nociceptive-specific neurons serve only noxious stimuli and are arranged somatotopically in lamina I and have a discrete somatic receptive field; they are normally silent and respond only to high threshold noxious stimuli. WDR neurons receive both noxious and non-noxious afferent input from Aβ, Aδ and C fibres.

c) Modulation: The process of altering pain transmission. It occurs at multiple (Peripheral, spinal, supraspinal) levels. This modulation can either inhibitory or facilitatory mechanism which modulate pain impulse transmission in the CNS and PNS. Neurotransmitters which are involved include (But aren't limited to) serotonin, GABA, glycine, somatostatin, norepinephrine, and endorphins. These substances bind to receptors on primary afferent and/or dorsal horn neurons and inhibit nociceptive transmission. This inhibition of the pain impulses is known as modulation.

d) Perception: It occurs once the transmitted signals reach higher centers in the CNS. From the spinothalamic tract, the neurons course through the pons and medulla, and terminate in the thalamus. The thalamus relays other nociceptive input to the limbic system. Both cortical and limbic system structures are involved for perception. These centers are responsible for the sensory and emotional processing of nociceptive information.

Nociceptors

Nociceptors are the specialized sensory receptors responsible for the detection of noxious (unpleasant) stimuli, transforming the stimuli into electrical signals, which are then conducted to the central nervous system. They are the free nerve endings of primary afferent Aδ and C fibres. Distributed throughout the body (skin, peritoneum, pleura, periosteum, viscera, muscles, blood vessels, joints, tendons, fascia, meninges) and they can

be stimulated by mechanical, thermal or chemical stimuli.

Primary afferent nerve fibres

In addition to the Aδ and C fibers that carry noxious sensory information, there are primary afferent Aβ fibers that carry non-noxious stimuli. Each of these fiber types possesses different characteristics that allow the transmission of particular types of sensory information.

Table 1: Showing characteristics of primary afferent nerve fibers

Parameters	Aβ fibers	Aδ fibers	C fibers
Diameter	Large	Small 2-5µm	Smallest < 2µm
Myelination	Highly	Thinly	Unmyelinated
Conduction velocity	Very fast > 40 m/s	Fast 5-15 m/s	Slow <2 m/s
Receptor activation thresholds	Low	High and low	High
Sensation on stimulation	Mechanical stimuli, Light touch, non-noxious	Cold, Rapid, fast, sharp, well localized pain, Mechanical stimuli	Heat, Cold, Slow, diffuse dull pain, Mechanical stimuli
Located in	Skin, joints	Skin and superficial tissues, deep somatic and visceral structures	Skin and superficial tissues, deep somatic and visceral structures

Dorsal horn neurons of the spinal cord

Cell bodies of both types of afferent nociceptive nerve fibers (Aδ and C fibres) are contained in the dorsal root ganglia and extend axons to synapse with dorsal horn neurons within the gray matter of the spinal cord. It is in the dorsal horn that initial integration and modulation of nociceptive input occur. Primary afferent axons may form direct or indirect connections with one of three functional populations of dorsal horn neurons: [1] Intemeurons, frequently divided into excitatory and inhibitory subtypes, which serve as relays and participate in local processing; [2] Propriospinal neurons, which extend over multiple spinal segments and are involved in segmental reflex activity and interactions among stimuli acting at separate loci; and [3] Projection neurons, which participate in rostral transmission by extending axons beyond the spinal cord to terminate in supraspinal centers such as the midbrain and the cortex. Projection neurons have been subclassified into three groups *viz*., Nociceptive- specific (NS) neurons, Wide dynamic range (WDR) neurons and complex neurons. All three components are interactive and are essential for the processing of nociceptive information, which facilitates the generation of an organized and appropriate pain response. In dorsal horn, the primary afferent fibers connect either directly or indirectly via neurones, interneurones and descending modulatory pathways with secondary afferent neurons, which convey the nociceptive information to higher centres in the CNS. These primary afferent terminals release a number of excitatory neurotransmitters including glutamate and substance P. Glycine and gamma-aminobutyric acid (GABA) are important neurotransmitters acting at inhibitory interneurones.

Ascending tracts in the spinal cord

Dorsal horn nociceptive input is conveyed to supraspinal centers by projection neurons extending through one of several ascending pathways. The function of the ascending pathways is simply the transmission of the nociceptive information. Nociceptive neurons have been identified in portions of the medulla, pons, mesencephalon (Midbrain), diencephalon (Thalamus and hypothalamus), and cerebral cortex. The brainstem structures (Medulla, pons, midbrain) contribute to nociceptive function through their contributions to the reticular system and the periaqueductal gray matter (PAG). Neuroanatomy of the ascending spinal pathways is complex and consist of following-

The spinothalamic tract (STT- spinal cord to thalamus) is the most prominent nociceptive pathway in the spinal cord; which is thought to be involved in transmission of pain, temperature and touch. A second ascending pathway is spinomesencephalic tract (SMT- spinal cord to mesencephalon) and is involved in pain modulation, sensory motor integration and motor reflex response to pain. Third ascending pathway is spinoreticular tract (SRT-spinal cord to reticular formation) which is involved in the emotional aspect of pain. Lesser contributions to nociceptive transmission is the spinocervical tract (SCT- spinal cord to cervical). More recently, a direct projection transmitting primarily nociceptive information from the dorsal horn to the hypothalamus has been discovered. This is the spinohypothalamic tract (SHT-spinal cord to hypothalamus) which provides an additional alternative route of activating the motivational component of pain and initiating neuroendocrine and allow autonomic adjustment for effective response to injury and intense pain.

Supraspinal centers

The numbers of supraspinal sites contribute to the control of ascending sensory signals by exerting inhibitory control of neurons in the spinal dorsal horn. Nociceptive neurons have been identified in portions of the medulla, pons, mesencephalon (Midbrain), diencephalon (Thalamus and hypothalamus), and cerebral cortex. The brainstem structures (Medulla, pons, midbrain) contribute to nociceptive function through their contributions to the reticular system and the periaqueductal gray matter (PAG). Reticular neurons can mediate motor, autonomic, or sensory function, and although there are circumscribed areas of specialized function within the formation. The reticular system is apparently critical to integration of the pain experience, as nociceptive input generates a profound effect on reticular neuronal activity. Ascending reticular neurons mediate the affective and motivational aspects of pain through their projections to the medial thalamus and limbic system. The PAG of the midbrain is a major locus of integration for homeostatic control. It is important in the descending modulation of nociceptive information and it also extends ascending projections to the thalamus and hypothalamus, thereby providing an indirect alternative pathway for nociceptive sensory activity to reach diencephalic structures. The thalamus serves as the relay point for sensory information en route to the cerebral cortex and is composed of numerous complex nuclei, several of which play key roles in nociception. Ascending pathways that mediate the sensory-discriminative aspects of pain terminate in the laterally located thalamic nuclei, and pathways contributing to the affective dimension of pain are destined for the medial

thalamic nuclei. The limbic system, also called the paleocortex, is derived from phylogenetically antiquated telencephalic structures as well as components of the diencephalon and mesencephalon. It consists of the amygdala, hippocampus, septa1 nuclei, preoptic region, hypothalamus, and certain thalamic components. Limbic structures mediate aversive drive and thus influence the motivational component of pain and determine purposeful behavior. Impulse transmission to the cerebral cortex is believed to play a vital role in integrating pain perception. The somatosensory cortex is important for localization of pain. The commonest areas activated include the the first and second somatosensory cortices (S1 and S2), the anterior insular cortex, and the anterior cingulate (a component of the limbic-associated cortex), and the thalamus, demonstrating that these areas are all important in pain perception. It seems clear that the cortex is able to modulate both the cognitive and aversive affective aspects of pain sensation and to mediate increasingly complex behavior patterns.

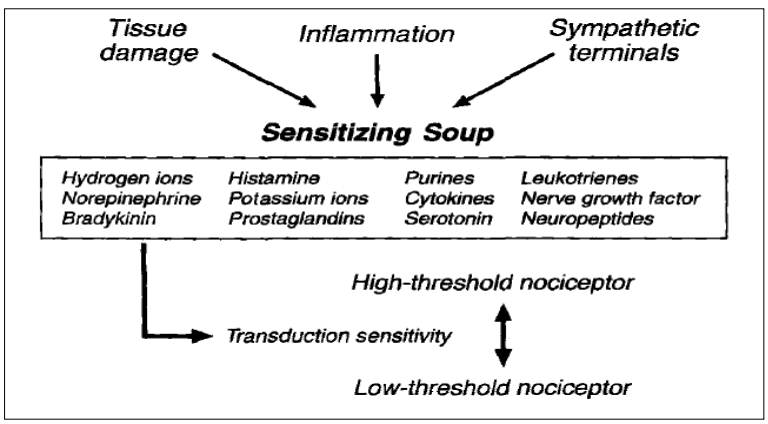
Descending modulatory pathway

The descending modulatory system has been described as having four tiers: (1) the cortical and thalamic structures, (2) the periaqueductal gray (PAG) of the midbrain, (3) the rostral medulla and pons of the brainstem, and (4) the medullary and spinal cord dorsal horn. The periaqueductal gray (PAG) in the midbrain and the rostal ventromedial medulla (RVM) are two important areas of the brain involved in descending inhibitory modulation. Both these areas contain dense concentration of opioid receptors and endogenous opioids which is a substrate for opioid antinociception and contribute to the endogenous opioid analgesia system. Dense concentrations of GABA, lycine, serotonin, norepinephrine and been identified in dorsal horn neurons, and all produce inhibitory effects on nociceptive transmission. The spinal opioid system fine tunes descending control mechanisms by acting presynaptically (by blocking release of substance P) as well as postsynaptically. Discriminative and affective aspects of pain are transmitted in related but distinct ascending pathways, with modifications made by both segmental and descending modulatory systems.

Peripheral and central sensitization

Peripheral sensitization

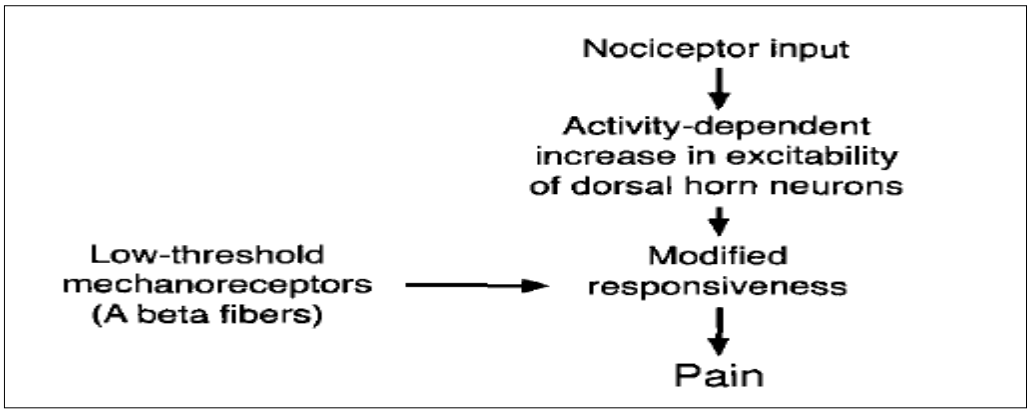
Peripheral sensitization is caused by the increased sensitivity of the nociceptors resulting from extensive trauma and inflammation. Peripheral tissue trauma results in the release of substances called mediators from damaged cells and also attracts inflammatory cells, which also releases mediators. Theses mediators mostly arise from the damage done to cells in the immediate location of the injury. Damaged cells release potassium ions and release of variety of chemical mediators. Bradykinin, one of the chemical produced by proteolytic enzymes at the site of injury and by cellular damage, is a powerful pain mediating peptide that directly excites Aδ and C- polymodal receptors. Bradykinin also induces increased capillary permeability with a resultant plasma extravasation, and stimulates cytokine production indirectly activating the phospholipase A_2- cyclooxygenase cascade that results in the formation of prostaglandins. Prostaglandins do not directly stimulate nociceptor, instead they sensitize peripheral sensory neurons to other stimuli. The lipoxygenase pathway produces leukotrienes that promote sensitization of local primary afferents. Release of substance P causes release of histamine from nearby mast cells furthering the activation of the free nerve endings. Neurotrophic factors (NGF's), which are released during tissue damage or by inflammatory cells, sensitize the transducers to subsequent stimuli. Nociceptive input will activate the sympathetic nervous system, resulting in the release of norepinephrine, which in turn accelerates sensitization of the nociceptors. In the end, the free nerve endings of the nociceptive afferents will be "bathed" in an environment of inflammatory mediators, the so-called "Sensitizing soup". This "soup" consists of the vasoactive amines, ions, neuropeptides and prostaglandins, leukotrienes. These inflammatory mediators help to sensitize the primary peripheral afferent receptors causing subsequent painful stimuli to be enhanced. The increase in sensitivity is exhibited by lowering of the threshold for stimulation of nociceptors and activation of nociceptors that were previously not responsive to the stimuli. This sensitization and stimulation by tissue damage is known as peripheral sensitization. In the initial stages of inflammation, this will result in a decrease in pain threshold, a subsequent exaggerated response to noxious stimuli, and often spontaneous pain at the site of injury. This phenomenon is defined as primary hyperalgesia, whereas secondary hyperalgesia refers to changes in the area surrounding the site of tissue injury. The latter changes cannot be explained by peripheral sensitization, because no change in nociceptor transduction was found outside the area of primary hyperalgesia. Peripheral sensitization will also lead to a reduction in the intensity of the stimulus necessary to initiate pain, so stimuli that would normally not cause pain begin to do so (Allodynia). Peripheral sensitization may lead to increased transmission to the second order neurons.



Central sensitization

The IASP defines central sensitization as "an enhanced responsiveness of nociceptive neurons in the central nervous system to their normal afferent input". Increased afferent

traffic into the dorsal horn due to peripheral sensitization can cause subsequent changes in the dorsal horn neurons excitability. This occurs when repetitive thermal or mechanical stimulation of peripheral nociceptors, which modifies their receptive field properties. Generally central sensitization represents a modification in sensory processing within the central nervous system, such that innocuous sensations elicited by low-threshold primary sensory neurons can become painful. Nociceptor input not only has that capcacity to produce pain directly, but in producing hyperexcitability in the spinal cord, can produce pain indirectly by changing the response to inputs that do not normally produce pain.



The first stage is related to the duration of the slow synaptic action potentials generated by Aδ and C fibers that have an impact on dorsal horn neurons. These synaptic potentials may last up to 20 seconds, and this results in a summation of potentials during low-frequency repeated nociceptor inputs, creating a progressively increasing and long-lasting depolarization in dorsal horn neurons. Just a few seconds of C-fiber input can generate several minutes of postsynaptic depolarization. This so-called "windup" of spinal neurons is mediated by N-methy1-D-aspartate (NMDA) receptors, which bind glutamate, and tachykinin receptors, which bind substance P and neurokinin A. The activation of NMDA receptors results in an influx of calcium into postsynaptic neurons, followed by persistent changes in the excitability of the neuron and activation of protein kin'] ase C. The whole of NMDA receptor activation (i.e. making it more available for activation by glutamate through the removal of the magnesium block) which structurally modifies the NMDA channel to increase its sensitivity to glutamate and the increased excitability of projection neurons is called "*wind-up*", which is supposed to be the physiological trigger for central sensitization. This is fundamentally different from peripheral sensitization because central sensitization enables low intensity stimuli to produce pain sensations. Windup thus contributes to the overall state of increased membrane excitability in dorsal horn neurons commonly referred to as central sensitization. This phenomenon of central sensitization to is sometimes referred as wind up, although the two terms are not synonomous. Windup can result in an increased responsiveness and zone of secondary hyperalgesia (increased sensitivity in neighboring areas). Central sensitization is manifested at the cellular level as a change in receptive field properties with a reduction in threshold, an increase in responsiveness and spatial extent, and the recruitment of novel inputs. Specifically, Aβ fibers, which are large myelinated primary sensory neurons associated with highly specialized low-threshold peripheral mechanoreceptors, are recruited. Under normal circumstances, they are the peripheral sensory fibers responsible for generating innocuous sensations. Activation of Aβ afferents typically elicits unitary sensations of pressure, flutter, or vibration depending on the rate of adaptation of the fiber, but it never elicits pain even when high-frequency stimuli are applied. Once the dorsal horn has been sensitized by nociceptive input, however, activation of Aβ fiber mechanoreceptors by previously nonpainful tactile stimuli actually contributes to the pain response. The secondary hyperalgesia and mechanical allodynia manifested clinically can be explained in terms of a misinterpretation of normal inputs that are not part of the physiologic pain system and would never normally generate pain but arise as a direct consequence of central sensitization. Thus, the pathophysiology of post injury pain hypersensitivity involves dynamic changes occurring in the periphery, which enable low-intensity stimuli to produce pain by activating sensitized Aδ and C fibers, while input in low-threshold Aβ sensory fibers generates pain as a result of altered central processing in the dorsal horn of the spinal cord. The central sensitization has profound effects on pain transmission. The changes in the receptors's properties greatly increase the intensity and duration of the painful stimulus. Pain perception is enhanced. The increased response to pain is known as hyperalgesia. Once central sensitization or hyperalgesia is propagated, it is very difficult to stop.

Behavioral responses to pain and injury

Unlike most human patients, animals lack the ability to verbalize their pain state. Behavioral responses to pain differ between species, breeds, and individuals. Instinctively, many animals do not display signs of pain as to do so would make them potential prey. This *absolutely* does not mean they don't hurt; it just makes our ability to recognize and treat pain a challenge. It is therefore, mandatory for behavioral assessment of pain that veterinarian must be familiar with normal behavior of the species, breeds and individuals. If any change from normal behavioral pattern and appearance of the animal, then that animal can be in pain. There may be change in pattern of vocalization, body posture, locomotor activity, feeding pattern and facial expression.

Cattle: May grunt or bellow; reluctance to move; inappetence or decreased appetite; decreased milk production; teeth grinding; painful facial expression; hunched appearance.

Goats, llamas, sheep: may grunt or bleat; teeth grinding;

reluctance to move; inappetence or decreased appetite; painful facial expression; hunched appearance; recumbency; loss of social behavior.

Swine: decreased appetite; recumbency; aggression; vocalization; loss of social behavior.

Dog: may groan, whine, whimper, growl, scream, cry, facial expression may be fixed stare, glazed appearance, ears pulled back, hunched or laterally recumbent position, licking, chewing and rubbing wounds and surgical sites, limping, loss of weight bearing, decreased appetite, restless or restricted movement, trembling (shivering), increased aggressiveness or timidity (fearfulness), increased urination, failure of house training, urinary retention, loss of shine in hair coat, particularly in chronically painful dogs and response to palpation are biting, vocalizing, withdrawing, orienting, escape. NOTE-tail wagging does not mean pain is not present.

Cats: may groan, growl, hiss, scream, cry, facial expression may be furrowed brow, squinted eyes, ears pulled back, sterna or laterally recumbent position, licking, chewing and rubbing wounds and surgical sites, limping, loss of weight bearing, restricted movement, stereotypes (meaningless encircling movement), decreased appetite, attempt to hide, aggressiveness, fail to use litter box, lack of grooming, particularly in chronically painful cats and response to palpation are biting, scratching, vocalizing, withdrawing, orienting, escape NOTE- purring does not mean pain is not present.

Horses: may grunt, moan, quiet, dull eyes, teeth grinding, ears pulled back, body posture may be standing with head down, standing on 3 legs, recumbent, licking, chewing and rubbing wounds and surgical sites, limping, loss of weight bearing, restless or restricted movement, trembling (Shivering), uncooperative, aggressive hiding, decreased appetite, increased urination, urinary retention, fecal retention and response to palpation are aggressive, kicking, biting, fighting, escape.

Systemic responses to pain and injury

The nervous system is the principal target of nociceptive information and provides the vehicle by which an organism can react to such input. Pain induces segmental and suprasegmental reflex responses that result in increased sympathetic tone, vasoconstriction, increased systemic vascular resistance, increased cardiac output through increases in stroke volume and heart rate, increased myocardial work through increases in metabolic rate and oxygen consumption, decreased gastrointestinal and urinary tone, and increased skeletal muscle tone. Endocrine responses include increased secretion of corticotropin, cortisol, antidiuretic hormone, growth hormone, cyclic adenosine monophosphate, catecholamines, renin, angiotensin II, aldosterone, glucagon, and interleukin 1, with concomitant decreases in insulin and testosterone secretion. Metabolically, this translates into a catabolic state characterized by hyperglycemia, increased protein catabolism and lipolysis, renal retention of water and sodium with increased potassium excretion, and decreased glomerular filtration rate. Nociceptive stimulation of brainstem centers causes increased respiratory drive, although segmental hypoventilation may occur as a result of splinting or bronchospasm. At the diencephalic and cortical levels, intense anxiety and fear greatly enhance the reflex sympathetic responses outlined previously and contribute to increased blood viscosity, prolonged clotting time, fibrinolysis, and platelet aggregation. These effects constitute the classic "stress response," the magnitude and duration of which parallel the degree of tissue damage, which often persists for days or more. The stress response is an evolutionary adaptation designed to optimize survival in the immediate postinjury period; however, its persistence in a clinical setting can be deleterious and have an impact on patient morbidity. In many patients with severe posttraumatic or postsurgical pain, the ensuing neuroendocrine responses are sufficient to initiate and maintain a state of shock. Therefore, attenuation of the stress response is an important component of any pain management strategy. Indeed, the presence or absence of stress related physiologic changes forms the foundation of most pain assessment schemes currently used in animal patients.

Pain assessment

Assessment of pain in animals is the most important step for successful management of pain. Animals cannot describe their pain as human patients can. Assessing pain in our patients is subjective and often difficult. Knowledge of an animal's individual behavior, species behavior, observational skills and attitudes towards pain will influence how an observer judges an animal's pain. Numerous pain score systems have been developed and adapted for veterinary use in an attempt to improve pain management in animals. Pain scoring is a useful technique to detect pain in animals. Only some of these have been validated.

A. Pain models

Pain models use behavior to assess pain by observing reflexes/responses to a painful stimulus i.e. hot plate test-somatic pain; colonic balloon - visceral pain; injection of irritating substances- inflammatory pain. These tests allow measurement of pain thresholds as well as response to some analgesics, but do not help clinicians to assess pain.

B. Pain scales

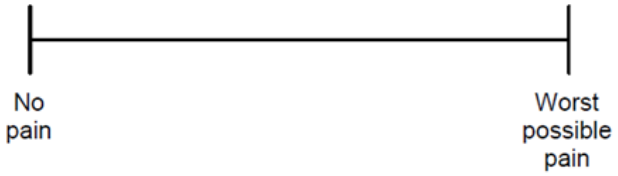
There is no "gold standard" with which to assess pain. Numerous studies have been preformed to develop pain scoring methods or pain scales. These pain scales can be helpful to ensure pain is assessed in every patient. Pain scales do have limitations and a good physical exam and thorough patient assessment is always required. Pain scales should be used as a guide. If a certain behavior suggests pain although an animal's overall pain score does not, analgesics should still be given.

Types of pain scales

1. **Simple descriptive scale (SDS):** It is most basic method and easy to use but it is not very sensitive and may over or underestimate pain. This is a semi objective scoring system that consists of four or five categories. Each category is given a number, which becomes the animal's pain score. a) No pain -1 b) Mild pain-2 c) Moderate pain -3 d) Severe pain-4
2. **Numerical Rating Scale (NRS):** This can be assessed by assigning the numerical values for different degrees of behavioral and physiological alterations due to pain. In this scores assigned to descriptive categories are given a whole number. Categories are weighted. This prompts the

observer to evaluate areas that might otherwise go unnoticed. Although the NRS involves a more thorough patient evaluation, it provides little improvement over the SDS a) Comfort 0 - asleep or calm b) 1 -awake, interested in surroundings c) 2- mild agitation, uninterested in surroundings d) 3- moderate agitation, restless or uncomfortable

3. **Visual analog scale (VAS):** It is utilized in human being very widely. This is simple scale consisting of a straight 100 mm horizontal line with descriptions of pain intensity at either end. The person performing the pain assessment draws a vertical line across the scale that best represents the animal's degree of pain. Although simple to use its usefulness is highly dependent on the observers experience because it does not use defined categories.



4. **Behavioral and physiological response scales**: In this detailed pain scales have been developed which appear to be much less affected by observer. It consists of three scoring systems which appear to be the most useful and there is currently limited validation in actual animal studies.
   a. University of Melbourne Pain Scale – It is based on specific behavioral and physiological responses. It appears to have increased accuracy over previous scoring systems. It is useful in recording the pain in animals. This scale includes 6 categories (heart rate, respiration rate, rectal temperature, vocalization, body posture and response to palpation) and are assigned with numeric values for each category. Then the scores are added to know the final degree of pain.
   b. Glasgow Composite Pain Tool- It is based on specific behavioral signs believed to represent pain in the dog (only validated scoring system)
   c. Colorado State Acute Pain Scale- Feline

Newer approaches have been developed in recent years for assessment of pain which includes “Power spectral analysis of electroencephalogram” which is a quantified analysis of the electroencephalogram when animal is exposed to noxious stimuli.

Methods of pain management

1. **Preemptive analgesia:** Giving analgesic drugs before or very soon after causing pain has become preferred practice in both human and veterinary medicine. The goals of preemptive analgesia are to reduce dosage requirements of anaesthetic and additional analgesic agents; to prevent peripheral and central sensitization and thus prevent hyperalgesia and long-lasting pain; to minimize pain in the recovery period; and to speed recovery time. Blockade of nerve impulse transmission by local anaesthetic agents has been shown to be the most effective form of preemptive analgesia. Many of the drugs mentioned in this discussion are also used as preanesthetic medications in an effort to provide preemptive analgesia.
2. **Multimodal pain management:** Giving combination of more than one analgesic drug with different mechanisms of action is more effective than attempting to control pain using single agents. Analgesics that interrupt the pain pathway at different receptors/neurotransmitters drug combinations also allows for reduced dosages of each agent; this may decrease the likelihood of adverse drug effects. It is suitable to control persisting pain, which is difficult to manage with the use of a single drug. It is also known as balanced analgesia.
3. **Perioperative pain management:** Pain management within the perioperative period involves three stages such as preoperatively if in pain (preemptively), intraoperative during surgery and postoperative after surgery. This will help to minimize pain and stress of the animals. Adequate rest and minimal exposure to external stimuli can also be beneficial.

Analgesic drugs used for pain management

Analgesics are those drugs whose primary effect is to suppress pain or induce analgesia.

A) Medicinal/pharmacological management of pain

There are numerous analgesic drugs are available to the veterinary practitioner today but no single drug will treat all pain effectively. Pain is needed to be controlled during all perioperative period i.e preoperative, intraoperative and postoperative after surgery. The choice of analgesic drugs depends upon the severity and type of pain and condition of the animal. Pharmacologically analgesia can be achieved by variety of drugs including opioids, NSAIDs, alpha$_2$ agonists, ketamine and local anaesthetics. The veterinarian also selects the route of delivery, which may be intravenous, intramuscular, subcutaneous, epidural, local infiltration, oral route, transdermal patch.

Table: Table showing common analgesic drugs with their mechanism of action

Analgesic drugs	Examples	Mechanism of action
Opioids	Morphine, meperidine, methadone, oxymorphone, pentazocine, butorphanol, nalbuphine, buprenorphine	Damping of peripheral and central afferent nociceptive processes
NSAIDs	Aspirin, acetaminophen, Phenylbutazone, flunixin, caprofen, meloxicam, ketoprofen, etodolac	Inhibition of sensitizing mediators peripherally and centrally
Alpha$_2$ agonists	Xylazine, detomidine, medetomideine, romifidine, dexmedetomidine	Activation of central descending inhibitory pathways
Dissociatives	Ketamine	NMDA(N-methyl –D- aspartate) antagonist (produces antihyperalgesic action)
Local anaesthetics	Procaine. Lidocaine, mepivacaine, tetracaine, bupivacaine	Blocks nerve impulse transmission and nociceptor excitation

1. Opioids

Opioids are the most effective analgesics for the treatment of pain but they are also very effective sedatives. The side effects associated with opioids include respiratory depression, bradycardia, decreased gastrointestinal motility, nausea, vomiting and constipation. Opioids are classified according to their receptor selectivity (mu (μ), kappa (κ), delta (δ). Generally, mu (μ) receptor selective opioids are the most effective analgesics. The effect of opioid agonists can be reversed by the administration of an antagonist (naloxone). Pure mu (μ) opioid agonists commonly available are morphine, hydromorphone, oxymorphone and fentanyl. Butorphanol is kappa (κ) opioid agonist with mu opioid antagonist activity. In general, the kappa agonists provide less intense analgesia but cause fewer side effects but cannot be reversed. The analgesic action of opioids is mediated via three mechanisms:

1. 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
2. Opioids block transmission of noxious stimuli and increase the amount of descending inhibition by acting on higher brain centres
3. Opioids block transmission of noxious stimuli by acting peripherally on opioid receptors generate 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. Fentanyl patches have become quite popular for treating pain in variety species. The ability to provide fairly steady state analgesia for days and while at home is advantageous. In cats, positive behavior changes while the patch is being used. The patches come in several doses each recommended accordingly for different patient sizes. They need to be applied at least 12 hours before the expected start of the operation to be effective in dogs (much faster onset in horses). After placement, therapeutic levels are reached in cats in 6 hrs and 12 hrs in dogs. Patches are designed to last for 3 days but differences can occur with differences in uptake, warm skin facilitates uptake whereas cold skin decreases uptake. Patches should not be cut. Transmucosal buprenorphine where buprenorphine is a partial mu (μ) opioid agonist and has a ceiling effect that after a certain dose with increased dosing will not result in more analgesia effect. Buprenorphine can be administered transmucosally (not orally) at 0.02 mg/kg (20 μg/kg). Research has shown that transmucosal administration is as effective and IV administration in cats. 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. It has mild mu opioid action but its metabolite (M1) has 200 X the opioid binding affinity of the parent drug. 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. Additionally, tramadol analgesic properties are due to the inhibition of re-uptake of serotonin and noradrenaline. Tramadol is well absorbed orally. It should be used with caution for patients taking serotonin uptake inhibitors (Selegiline hydrochloride or fluoxetine). Elevated serotonine levels can lead to "Serotonine Syndrome" which can be expressed as drowsiness, restlessness, altered mentation, muscle twitching, high body temperature. High doses may cause anorexia.

2. Nonsteroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are drugs that have anti-inflammatory, antipyretic and analgesic properties. NSAIDs include any drug with antiinflammatory properties that is not a steroid. NSAIDs specifically are drugs that inhibit formation of prostaglandins (PG) and thromboxanes (TX) from arachidonic acid. NSAIDs inhibit either or both the cyclooxygenase (COX-1 and COX-2) enzyme of arachidonic acid metabolism resulting in a number of anti-inflammatory, antipyretic and analgesic effects. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain relief from mild-to- moderate pain. Useful perioperative NSAIDs analgesics used in veterinary includes ketoprofen, meloxicam, firocoxib, etodolac, and tepoxalin, and much of the toxicity is claimed to have been lessened due to their selective COX (particularly COX2) or LOX inhibitory action. Tepoxalin (and ketoprofen) also inhibit 5 - LOX and thus reduce leukotriene (LT) production, which results in anti-inflammatory and ant bronchospasm effects. The main limitation of all NSAID's revolves around the potential for adverse effects, since many of the drugs (ketoprofen, flunixin meglumine, etc.) do not selectively inhibit COX-2 which is inducible prostaglandin. Newer NSAIDs like meloxicam, carprofen, etc. selectively block COX-2 thus avoids the undesirable side effects. They produce analgesia by reducing the sensitization of nociceptors. NSAIDs cannot be given for longer periods because they it leads to gastric erosion/ulceration and nephrotoxicity. NSAIDs are contraindicated in hypovolemic or hypotensive patients. When compared with opioids for post-operative analgesia, the NSAIDs have the advantage of not decreasing consciousness or causing respiratory depression. Meloxicam selectively block COX - 2 and used for cattle, pigs, dogs, cats, horses. The analgesic dose is often less than the anti-inflammatory dose (as for other NSAIDs), so higher doses are commonly administered peri-operatively. Carprofen (Rimadyl) is a commonly used NSAID in veterinary that is approved for dogs and appears very effective at doses of 4mg/kg. Ketoprofen is mostly used for horses, cattle, pigs, dogs, cats. Ketoprofen is reportedly as potent as flunixin in masking the signs of colic. It is only licensed for post - operative use as it has been reported to cause clotting problems.

3. NMDA antagonists

Ketamine is currently the drug used in veterinary and is a phencyclidine congener. Mechanism of action of ketamine is a non-competitive antagonist of calcium ion pores at NMDA receptors. N-methyi-D-aspartate (NMDA) is a member of the glutamate family of excitatory amino acids mediating pain transmission and increasing the likelihood of central sensitization in the CNS and exerts an anti-hyperalgesic effect. Drugs antagonizing NMDA are capable of providing analgesia and preventing central sensitization. Ketamine binds

to a phencyclidine receptor inside the NMDA receptors. Once bound, it decreases the calcium channel's opening time and frequency thus reducing Ca+ ion. Hence it is unlikely to be truly analgesic in nature, rather it appears to be protective against hyperalgesia and central hypersensitization in the postoperative setting. Amantadine causes inhibition of NMDA responses and may cause NMDA receptors to remain closed. Amantadine may be beneficial in patients with long-standing pain syndromes with a neuropathic component.

4. Corticosteroids

These are used to decrease inflammation and to prevent or treat immune-mediated responses. Corticosteroids are primarily used to manage chronic pain. Mechanism of action is it enters the nucleus of cells, bind to chromatin, and alter RNA synthesis. End results include suppression of inflammatory responses; blockade of phospholipase A- leading to inhibition of prostaglandin cascade; suppression of WBC function and retardation of wound healing; suppression of delayed allergic reactions. There are many adverse effects of corticosteroids can be serious viz., inhibition of wound healing, iatrogenic hyperadrenocorticism, muscle wasting, polyuria, polydipsia, increased appetite, alopecia, gastric ulceration, immunosuppression, hepatopathy, and abdominomegaly and often limit their usefulness in pain management.

5. Alpha$_2$ adrenergic agonists

Alpha$_2$ agonist drugs like medetomidine, detomidine and romifidine are powerful analgesic agents which used especially for the treatment of abdominal organ pain. These drugs may be useful for providing sedation and allowing the patient to rest. It produces profound sedation and profound analgesia by binding to pre-synaptic alpha$_2$ receptors at the locus ceruleus in brain, the dorsal horn of spinal cord and at sympathetic nerve endings. Binding of these presynaptic receptors causes a decrease in norepinephrine release which results in decreased pain conduction, decreased in arousal and increased parasympathetic tone (vagal). Alpha$_2$ receptors also bind postsynaptically to alpha receptors in the peripheral vasculature causing intense vasoconstriction. The vasoconstriction can lead to a reflex bradycardia and reduction in cardiac output. Almost all drugs in this category at any dose will decrease cardiac output. Alpha$_2$ agonists should be used with caution in patients with cardiovascular instability or hypovolemic. 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. Micro-doses (0.5-2 µg/kg dexmedetomidine) of these drugs are quite effect for analgesia with less sedation. Micro-dose constant rate infusions (CRI) can provide rescue analgesia for hours to days. Also alpha$_2$ agonists given epidurally or intrathecally can provide analgesia with a decreased incidence of untoward side effects.

6. Local anaesthetics

Local anesthetics exert their action by binding to a hydrophilic site within Na+ channels, thereby blocking it and disallowing the Na+ influx. Thus blocking depolarization of neurons and thereby stopping the propagation of action potential and the effect can be complete anaesthesia to a site rather than mere analgesia. Lidocaine and bupivacaine are the most commonly used injected local anaesthetics. The effects of bupivacaine (4-8 hrs) are of longer duration than those of lidocaine (1.5-3 hrs) so it is preferred for postoperative analgesia. Local nerve blocks provide superb analgesia and can be useful at all three stages of perioperative period. Major disadvantage of local anaesthetics are blockade of motor functions. Local anaesthetics can be used as intercostal nerve blocks are particularly useful after thoracotomy, epidural analgesia may be used after abdominal, pelvic or pelvic limb surgery, local infiltration at site of operation and different nerve blocks. Prilocaine in conjunction with lidocaine is available as a topical cream (EMLA®). EMLA cream is quite effective but needs to be applied for 30 minutes before effective. It can be used on radiation burns and terminal soft tissue pain. Lidocaine patches (Lidoderm®) have been used transdermally but do not completely desensitize the area it covers. The patches appear to be effective for musculoskeletal, inflammatory and neurologic pain. These patches can be cut. Almost no systemic levels were detected in dogs, so unlikely to see any toxicity. The surgical placement of "soaker catheters" which are small fenestrated catheters that are left in a surgical site are becoming more popular. By leaving the catheter at the sight of the wound or injury, local anaesthetics can be administered at a consistent time frame with less discomfort to the patient.

7. Gabapentin

Gabapentin is an anti-epileptic drug that has been used in humans for the treatment of neuropathic pain. Gabapentin was designed as a structural analog of GABA, an inhibitory neurotransmitter, however the analgesic effects appears to be mediated via voltage-dependent calcium ion channels (VDCC). Many of these channels in the dorsal root ganglia and spinal cord are upregulated after peripheral nerve injury. It results in decreased glutamate release and thus a decrease in NMDA receptor activation. Gabapentin activates the descending inhibitory pathway by inducing norepinephrine release which subsequently induces analgesia due to spinal alpha$_2$ adrenoceptor stimulation. It is found particularly effective in cases of spinal injury.

8. Nutriceuticals

Nutriceuticals are non-drug that play a major role in strengthening normal body tissues, aid in repairing damaged tissues and assist in improving efficient body metabolism. Adding nutriceuticals to the daily diet has noticeably improved the quality of life of many dogs. Most commonly used nutriceuticals are EFAs (Essential fatty acids such as Omega-3 and Omege-6 fatty acid), glucosamine, chondroitin sulfate, methylsulfonylmethane, hyaluronic acid, building blocks for cartilage and synovial fluid and flax seed oil. They have been proven to be helpful in decreasing pain and discomfort from arthritis and degenerative processes. Many believe that using nutriceuticals life long will assist in delaying the degenerative effects and the discomfort of aging. Nutriceuticals are employed to deal with low grade pain and discomfort and can take six to eight weeks for their beneficial effects to be noticed.

B) Non-medicinal management of pain

1. Cryotherapy: Application of ice slows down of the nerve conduction of small diameter myelinated fibers (Aδ and C). Also it causes peripheral vasoconstriction (and subsequent reduced blood flow) and slows down of local

inflammation. Application of cryotherapy is indicated for acute attacks of arthritis or to relieve pain and prevent inflammation. The simplest way to apply cryotherapy is to massage with ice (5 to 10 minutes) for 3 to 6 times a day.

2. Thermotherapy: Heat causes peripheral vasodilatation and stimulates numerous thermosensitive receptors that increase gate-control mechanisms causing local analgesia. Hot water bottles or hot-packs are simple methods for applying superficial heat. Tissue can be heated up to approximately 1 cm in depth and they are recommended particularly for distal joints. Superficial heat should be applied for 15 to 20 minutes, one to three times a day.
3. Actinotherapy: Actinotherapy involves treatment of disease using rays of light especially ultra-violet or actinic rays. These rays can heat up deep seated tissues producing warmth and analgesia. It is mainly applied in joints affected with arthritis. The duration of exposure should be 15 minutes to one hour.
4. Ultrasound Therapy: Ultrasonic therapy is treatment of diseases using sound waves which have frequencies higher than what the human ear can hear. Ultrasound waves can penetrate biological tissue up to 5 cm in depth. During application the temperature rise varies depending on the treated site by +1 °C to +4 °C. High-frequency ultrasound is characterized by low-depth penetration (0.5-1 cm) but a powerful calorific effect which can be used only on distal joints of limbs. Low-frequency ultrasound (0.8-1 MHz) penetrates tissue more deeply (0.5-5 cm) which can be used to treat hip and shoulder joints and to reduce muscular spasm. In general, it should be applied for 5 to 10 minutes for two to three times a week.
5. Transcutaneous Electrical Neuro-Stimulation (TENS): TENS (Transcutaneous Electrical Nerve Stimulation) is commonly employed by physiotherapists and doctors and is used locally, near to the painful site (i.e. segmentally). Two modalities of TENS currents are used on arthritic animals namely gate-control TENS and endorphinic TENS. Gate-control TENS works by causing peripheral hyperstimulation of large caliber sensitive fibers (Aâ) at high-frequency (80 or 100 Hz) thus inhibiting the transmission of nociceptive influxes conveyed by small-caliber fibers (Aä and C) in the dorsal horn of the spinal cord. This type of current generates rapid but short analgesia and is indicated mainly for acute pain. The endorphinic TENS works by causing stimulation of small-caliber fibers (Aä and C) at very low frequency (2 to 8 Hz) which favours the release of endorphins. Endorphinic TENS is indicated for subacute and chronic pain. To be effective, a TENS current should be applied for a minimum of 20 to 30 minutes. It is mostly used to treat chronic back pain, and so its application may be limited in animals as such conditions may be difficult to diagnose.
6. Extra-corporeal shock wave therapy (ESWT): Based on lithotripsy techniques, ESWT has been used effectively since the 1990's to treat diverse rheumato-orthopaedic disorders in man (epicondylitis) and horses (desmitis of the suspensor ligament of the fetlock). It was observed that ESWT is effective in reducing pain rapidly and sustainably (pain relieved for several weeks or months) and in improving mobility and quality of life of arthritic dogs.
7. Acupuncture: The analgesic action of acupuncture results from gate-control mechanisms when focal acupoints are treated and from stimulating the release of endogenous opioids when distal spots are treated to procure long term analgesia. Acupuncture can be used to treat acute as well as subacute and chronic attacks of arthritis. In the event of acute inflammatory attack, one session every two to three days is necessary until clinical signs resolve whereas for chronic pain, several sessions are required.
8. Low Level Laser Therapy (LLLT): The localized and systemic increase in â endorphins after LLLT irradiation has been clinically reported in multiple studies with subsequent pain reductions. Laser irradiation suppresses the excitation of these fibers in the afferent sensory pathway. LLLT restores nerve cell action potential back to its normal value. It also helps to reduce levels of bradykinin which elicit pain by stimulating nociceptive afferents in the skin and viscera.

Table: Table showing doses of common analgesic drugs used in domestic animals

Drug	Cat	Dog	Horse	Cattle
Morphine	0.2-0.5 mg/kg IV, IM, SC 0.1 mg/kg epidural 0.1-0.2 mg/kg/hr CRI	0.5-1 mg/kg IV, IM, SC 0.1 mg/kg epidural 0.1-0.3 mg/kg/hr CRI	0.05-0.1 mg/kg IV, IM, epidural	0.1-0.5 mg/kg IV, IM 0.1 mg/kg epidural
Oxymorphone	0.05-0.1 mg/kg IV, IM,SC	0.05-0.4 mg/kg IV, IM, SC	0.001-0.005 mg/kg IV	-
Meperidine	3-5 mg/kg IM, SC	3-5 mg/kg IM, SC	0.2-1 mg/kg IV	-
Fentanyl	1-3 mcg/kg IV 1-4 mcg/kg CRI Transdermal patch 2-5 mcg/kg/hr	2-5 mcg/kg IV 2-10 mcg/kg CRI Transdermal patch 2-4 mcg/kg/hr	1-10 mcg/kg IV ansdermal patch 0.5 -1 mcg/kg/hr	-
Buprenorphine	0.005-0.2 mg/kg IV,IM,SC Transmucosal 0.01-0.02 mg/kg	0.005-0.2 mg/kg IV,IM, SC	0.01-0.04 mg/kg IV	-
Butorphanol	0.1-0.4 mg/kg IV,IM,SC 0.1-0.2 mg/kg/hr CRI 0.5-1 mg/kg PO	0.1-0.4 mg/kg IV, IM, SC 0.1-0.5 mg/kg/hr 0.5-2 mg/kg PO	0.01-0.04 mg/kg IV	0.05-0.1 mg/kg IV
Tramadol	PO 2-4 mg/kg q12 hr	PO 3-10 mg/kg q6-8hr	-	-
Pentazocine	2-3 mg/kg IV, IM	2 mg/kg IM	0.33 mg/kg IV	-
Xylazine	0.1 -0.3 mg/kg IV 0.2 -0.5 mg/kg IM, SC	0.1-02 mg/kg IV 0.2-0.5 mg/kg IM, SC	0.5-1 mg/kg IV 0.03-0.05 mg/kg Epidural	0.05 mg/kg epidural
Dexmedetomidine	10-40 mcg/kg IM,SC	5-20 mcg/kg IM,SC 0.5-1 mcg/kg/hrCRI		
Medetomidine	0.005-0.02 mg/kg IV, IM, SC	0.01- 0.04 mg/kg IM	-	-
Detomidine	-	-	0.01-0.02 mg/kg IV 0.03-0.06 mg/kg epidural	0.06 mg/kg epidural

Romifidine	-	-	0.04-0.08 mg/kg IV 0.08 mg/kg epidural	
Flunixin meglumine	0.25 mg/kg IM, SC	0.25-1 mg/kg IV, IM, SC	0.2-1.1 mg/kg IV	1 mg/kg IV
Ketoprofen	2 mg/kg SC	2 mg/kg IV, IM, SC	1.1-2.2 mg/kg IV	2 mg/kg IV
Ketorolac	0.25 mg/kg IM	0.3 mg/kg IM,IV	-	-
Phenylbutazone	-	-	2-4 mg/kg IV	-
Carprofen	2 mg/kg SC	2-4 mg/kg IV,IM,SC	0.5-1.1 mg/kg IV	-
Meloxicam	0.1 mg/kg SC	0.1-0.2 mg/kgSC	-	-
Ketamine	2 mg/kg IV	0.25 to 0.5 mg/kg IV 10-20 mcg/kg/hr	10-20 mcg/kg/hr CRI	-
Bupivacaine	2 mg/kg local blocks	1.5-3.0 mg/kg local blocks/ epidural	1-2 mg/kg infiltration	1-2 mg/kg infiltration
Lignocaine	2-4 mg/kg local blocks	1-2 local blocks/epidural	1-2 mg/kg infiltration	4-5 ml (2%) epidural
Gabapentin	2-10 mg/kg q6-12 hr	2-10 mg/kg q 12 hr	-	-
Amantadine	3-5 mg/kg q12 or 24 hr	-	-	-

References

1. Bufalari A, Adami C, Angeli G, Short CE. Pain assessment in animals. Veterinary Research Communication. 2007; 31(1):55-58.
2. Carl Hug C. In: Pain Management (Clinical Anaesthesiology third edition) Lange/ McGraw-Hill, 2002, 309-344.
3. Gaynor JS, Muir WW. Handbook of Veterinary Pain Management, 2nd Ed. St. Louis MO, Mosby, Elsevier, 2009.
4. Hug CC. In: Pain management (Clinical Anaesthesiology, 3rd Ed.) Lange/McGraw-Hill, 2002, 309-344.
5. Johnson CB. Proceedings of AAWSS Summit on pain and pain management, 2007.
6. Lamont LA, Tranquilli WJ, Grimm KA. Physiology of pain. Veterinary Clinics of North America: Small Animal Practice. 2000; 30(4):703-728.
7. Landa L. Pain in domestic animals and how to assess it: A review. Veterinarni Medicina. 2012; 57(4):185-192.
8. Lee, Lyon. Perioperative pain management. Centre for Veterinary Health Sciences, VMED 7412, 2006, 1-13.
9. Perry G, Fine Ashburn M. In: Functional Neuroanatomy and Nociception (The Management of Pain) New York: Churchill Livingstone, 1998, 1-16.
10. Redddi D, Currans N, Stephens R. An introduction to pain pathways and mechanisms. From internet, 2012.
11. Sackman JE. Pain and its management. Vet. Clin. North. Am. Small An. Pra. 1997; 27(6):1487-1504.
12. Serpell M. Anatomy, physiology and pharmacology of pain. Surgery. 2006; 24(10):350-353.
13. Tranquilli WJ, Grimm KA, Lamont LA. Pain management for the Small Animal Practitioner, 2nd Ed. Jackson-Teton New Media, 2004.
14. Venugopal K, Swamy M. Physiology of pain. World Anaesthesia Tutorial of the Week. WWW. AnaesthesiaUK.com/ World Anaesthesia, 2006, 1-5.
15. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. 2011; 152:1-15.
16. Zaki S. Pain assessment and management in companion animals veterinary update. From internet. Boardtalk December- Insert, 2013, 1-7.