

NEUROPATHIC PAIN IN CATS

Mechanisms and multimodal management

Clare Rusbridge

Nociception and pain perception

Pain is defined by the International Association for the Study of Pain (ISAP) as an 'unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'.¹ Pain and nociception are not the same. Nociception is the process by which the sensory nervous system encodes and transmits a painful stimulus to protect the body from injury. By contrast, pain perception is subjective,

Understanding the neural pathways and processes involved in nociception and pain perception is fundamental to understanding the most appropriate treatment modalities.



and influenced by biological, psychological and social factors.¹ Significantly, in a recent change to the ISAP definition of pain, the phrase 'or described in terms of such damage', which previously appeared at the end of the definition, was deleted because some humans as well as animals are unable to verbally articulate their pain. It also acknowledges that pain is expressed by many behaviours, and not just by a verbal description.¹ Chronic pain is considered both a clinical sign and a disease and, as such, is often referred to as maladaptive pain.

The anatomy of nociception and pain perception is illustrated in Figure 1. Table 1 details the pathophysiology of pain, with a specific focus on neuropathic pain, and describes possible drug targets. For ease of reference, some key terms are summarised in highlight boxes.

❖ Nociception

The detection of noxious stimuli by specialised peripheral receptors.

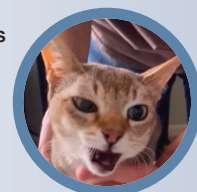
❖ Pain perception

The interpretation of these signals in the brain.



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Practical relevance:

Chronic pain is a significant welfare concern in cats, and neuropathic pain, which arises from aberrant processing of sensory signals within the nervous system, is a subcategory of this type of pain. To comprehend this condition and how multimodal pharmacotherapy plays a central role in alleviating discomfort, it is crucial to delve into the anatomy of nociception and pain perception. In addition, there is an intricate interplay between emotional health and chronic pain in cats, and understanding and addressing the emotional factors that contribute to pain perception, and vice versa, is essential for comprehensive care.

Clinical approach: Neuropathic pain is suspected if there is abnormal sensation in the area of the distribution of pain, together with a positive response to trial treatment with drugs effective for neuropathic pain. Ideally, this clinical suspicion would be supported by confirmation of a lesion at this neurolocalisation using diagnostic modalities such as MRI and neuroelectrophysiology.

Alternatively, there may be a history of known trauma at that site. A variety of therapies, including analgesic, anti-inflammatory and adjuvant drugs, and neuromodulation (eg, TENS or acupuncture), can be employed to address different facets of pain pathways.

Aim: This review article, aimed at primary care/general practitioners, focuses on the identification and management of neuropathic pain in cats. Three case vignettes are included and a structured treatment algorithm is presented to guide veterinarians in tailoring interventions.

Evidence base: The review draws on current literature, where available, along with the author's extensive experience and research.

Keywords: Maladaptive pain; chronic pain; pain matrix; therapy; gabapentin; pregabalin; topiramate; wind-up; central sensitisation; feline hyperaesthesia syndrome; feline orofacial pain; sciatica; mutilation; tail amputation; ketamine; NMDA receptor; amitriptyline; cannabinoid; CBD oil; palmitoylethanolamide; amantadine; tramadol

Table 1 Anatomy of nociception, pain perception and chronic (maladaptive) pain (continued on page 3)

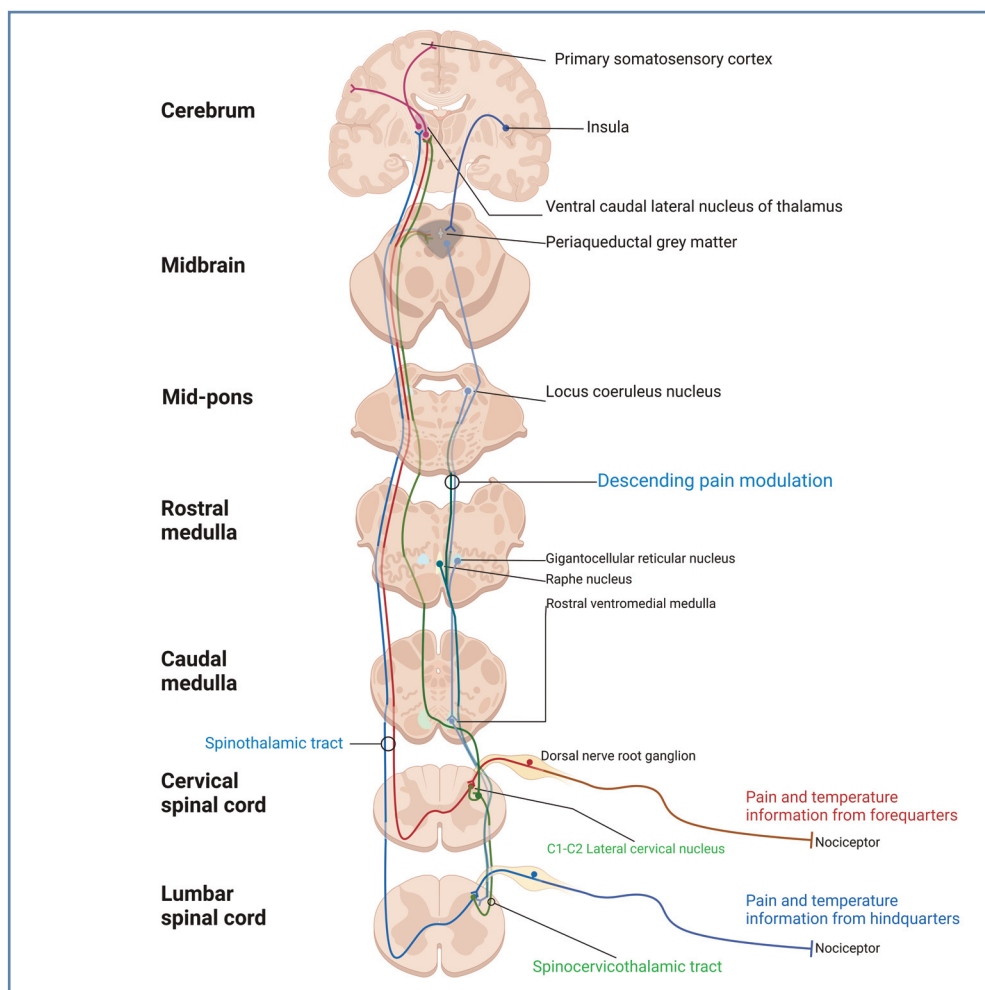
Anatomical site	Description and possible drug targets
Peripheral nociceptors	Nociceptors (pain receptors) are unmyelinated nerve endings that are numerous in the superficial layers of the skin, periosteum, arterial walls, joint capsules, muscles, tendons and meninges, and are also present, although in less density, in other tissues such as the internal organs. Sensory neurons are pseudounipolar; the cell body is within the dorsal root ganglion which lies just outside the intervertebral foramen (spinal nerves) or medial to the tympanic bullae (trigeminal nerve)
Nociceptor afferents	Two types of fibres transmit nociceptive information, A-delta (δ) and C fibres. The thinly myelinated Aδ fibres respond to injurious mechanical or noxious thermal information. Aδ fibres have a faster (6–30 m/s) conduction velocity than C fibres and transmit the first sharp pains after injury. They are the afferent arm of the withdrawal reflex and, as such, are important in limiting injury while nociceptive information is transmitted and processed by the forebrain.² This ‘first pain’ stimulus can be precisely localised because the nociceptors are clustered in small spots within an area. A more sustained insult activates the more broadly distributed and slower conducting unmyelinated C fibres, resulting in a deeper, more diffuse sensation (ie, a longer lasting, duller and less precisely localised ache) after the initial injury.³ This ‘second pain’ is involved in learning avoidance and other adaptive behaviours to limit further injury. Nociceptors associated with C fibres are polymodal, responding to thermal, mechanical and chemical stimuli. There are also specialised ‘itch’ C fibres which react to pruritogenic chemicals like histamine
Dorsal root ganglion	The dorsal root ganglion contains the cell bodies of the primary sensory neurons, including those for nociception. It transfers but also modulates sensory information to the spinal cord. Changes in dorsal root ganglion gene expression and upregulation of many processes are pivotal in the development of peripheral neuropathic pain. ⁴ Neuron cell bodies of the dorsal root ganglion are surrounded by satellite glial cells that also participate in signal processing and transmission. Activation of glia after peripheral nerve injury results in the release of a cascade of inflammatory mediators (neuroinflammation) that lead to peripheral and central sensitisation and neuropathic pain ⁴
Afferent fibre neurotransmitters and spinal cord dorsal horn receptors	All nociceptor afferents release the fast excitatory neurotransmitter glutamate. Glutamate binds to AMPA receptors, which are found on the surface of superficial dorsal horn neurons. Activation of AMPA receptors leads to an influx of sodium ions, neuronal depolarisation and pain signal transmission. When a certain threshold is reached, a magnesium block is removed from the NMDA receptor ion channel. Activation of the NMDA receptor requires both binding of glutamate and removal of the magnesium block. When the NMDA ion channel is open, calcium ions flow into the neuron and trigger a series of intracellular events that result in a progressive increase in the frequency and intensity of neuronal firing in response to repetitive low-frequency stimulation. Repeated activation of NMDA receptors and associated intracellular signalling leads to an increase in excitability of dorsal horn neurons, which become more easily triggered by incoming pain signals (‘wind-up’ – see ‘Spinal cord/medullary dorsal horn’ below). Some C fibres also release neuropeptides such as substance P, calcitonin gene-related peptide, galanin and somatostatin. Substance P is a regulatory peptide and inflammatory molecule produced by C fibre nociceptors terminating in the superficial dorsal horn. It binds to the NK1 receptor
Spinal cord/medullary dorsal horn	The medullary and spinal cord dorsal horn is arranged in six laminae. The superficial dorsal horn (lamina 1 [marginal zone] and lamina 2 [substantia gelatinosa]) is the main target for pain and itch afferents, whereas the deeper laminae mainly receive light touch, proprioception and vibration afferents. The dorsal horn has complex neurocircuitry and most of the neuronal population are short interneurons that are either inhibitory (GABA and glycine neurotransmission) or excitatory (glutamate neurotransmission). The remaining neuronal constituents of the dorsal horn are the glutaminergic projection axons with targets in the brainstem and thalamus, and descending noradrenergic and serotonergic inhibitory projections from the locus coeruleus and rostral ventromedial medulla and raphe nucleus. Pivotal to the development of central sensitisation and neuropathic pain is wind-up, an intensification of pain due to a long-lasting increase in excitability of spinal cord neurons following repetitive stimulation of C fibres. Dorsal horn NMDA receptors (recruited following loss of a magnesium block), NK1 receptors and excitatory interneurons play key roles in wind-up.^{5,6} Wind-up is a phenomenon that occurs specifically in the spinal cord dorsal horn neurons. By contributing to the development of central sensitisation – a broader process that involves changes in the processing of pain signals throughout the CNS (spinal cord, brainstem and higher brain centres) – it results in increased sensitivity to pain. Pain can persist even after the initial injury or inflammation has resolved
Central projection	Dorsal horn projection neurons travel via the spinocervicothalamic (via the lateral cervical nucleus) and spinothalamic tract to the ventral caudal lateral thalamus (most contralateral) and then on to the brain’s pain-processing centres – leading to conscious and unconscious pain perceptions, and the emotions and actions that these evoke.⁷ The spinocervicothalamic pathway is dominant in carnivores, whereas the decussating spinothalamic tract is dominant in primates. Nociceptive information also ascends via the spinomesencephalic (to midbrain including periaqueductal grey matter), spinoreticular (to brainstem nuclei), spinohypothalamic (to hypothalamus), spinopontoamygdalar and other spinal tracts⁸
Thalamus	The thalamus (via GABA neurotransmission) is a key relay station for transmitting and modulating nociceptive information to the cerebral cortex. There is also two-way communication with the periaqueductal grey matter. ⁹ Thalamic neuropathic pain syndromes are rare and, in cats, have only been reported in association with diencephalic tumours ¹⁰
Corticolimbic system (pain matrix)	The ‘pain matrix’ is a theoretical concept used to understand the neural mechanisms of pain in health and disease.¹¹ Anatomically, the pain matrix is an extensive cortical network that includes the amygdala, hippocampus, and somatosensory, insular, cingulate, prefrontal, frontal and parietal areas. Functionally, it describes three domains of pain processing in the CNS:^{2,11,12} ❖ <i>Sensory discriminative dimension</i> – dealing with the localisation and severity of pain (first pain) ❖ <i>Affective–motivational dimension</i> – dealing with the emotional response to pain and the motivation to stop it. Based on the cat’s instinctive repertoire and previous experience, specific behaviours are employed to prevent ongoing or repeat injury (second pain) ❖ <i>Cognitive dimension</i> – the modulation and evaluation of pain by cognitive circuits. If pain persists with one nocifensive behaviour (protective or defensive response), then behaviour is modified. Alternatively, if the goal outweighs the pain, then the cat may elect to endure the pain to prioritise that need (eg, continuing to eat despite periodontal disease)

For footnotes, see page 3

Table 1 Anatomy of nociception, pain perception and chronic (maladaptive) pain (continued from page 2)

Anatomical site	Description and possible drug targets
Descending control of pain	The brain modulates, as well as receives, information about pain and can inhibit or potentiate impulses. A circuit consisting of the periaqueductal grey matter in the rostral brainstem (multiple neurotransmitters including glutamate, GABA, opioids [particularly enkephalin], substance P, neurotensin and endocannabinoids), the locus coeruleus (noradrenergic), the raphe nucleus, the rostral ventromedial medulla and the nucleus reticularis gigantocellularis (serotonergic) contributes to descending inhibitory pathways synapsing on inhibitory interneurons in the superficial dorsal horn. ^{3,8,13,14} These brainstem circuits receive input from the corticolimbic system and the central stress response (hypothalamic–pituitary–adrenal axis), which may suppress or amplify and prolong pain. Inhibition of pain is important for survival; for example, allowing a severely injured animal to escape from a predator. It is also the proposed mechanism for placebo-induced analgesia. By contrast, chronic stress or fear–anxiety can potentiate pain. The basal nuclei and cerebellum are also involved in pain modulation ¹³
Dorsal horn interneuron inhibition of pain	In the dorsal horn, 30–40% of interneurons are inhibitory. Imbalance between the excitatory and inhibitory side of the nervous system (disinhibition) is an important mechanism in the pathogenesis of neuropathic pain. The inhibitory interneurons are activated by descending noradrenergic and serotonergic inhibitory projections from the brainstem
A-beta (β) nerve fibre afferents	Fast-conducting myelinated A- β nerve fibres convey information about non-noxious stimuli (pressure and touch) to laminae III and IV of the dorsal horn. These mechanoreceptive fibres are pertinent to neuropathic pain through two distinct mechanisms: ❖ <i>Allodynia</i> – where innocuous or non-painful stimuli become painful or induce discomfort. It is suggested that a functional cross-excitation between A-β and C fibres develops, such that activation of one set of neurons influences or excites another set of neurons¹⁵ ❖ <i>'Gate control theory of pain'</i> – proposed by Melzack and Wall in 1965,¹⁶ this suggests that there is a 'gate' in the spinal cord that can either facilitate or inhibit the transmission of pain signals to the brain. It is hypothesised that when A-β nerve fibres transmit signals related to non-noxious stimuli, they can inhibit the transmission of pain signals by slower, unmyelinated C fibres. For example, activities such as rubbing or applying pressure to an injured area may alleviate pain. This is the mechanism by which massage and TENS are thought to decrease pain, as they selectively stimulate A-β nerve fibres

AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CNS = central nervous system; GABA = gamma-aminobutyric acid; NK1 = neurokinin-1; NMDA = *N*-methyl-D-aspartate; TENS = transcutaneous electrical nerve stimulation

**Figure 1** Anatomy of nociception and pain perception in the cat. Created with BioRender.com**❖ Nocifensive behaviour**

If pain persists with one nocifensive behaviour (protective or defensive response), then behaviour is modified. Alternatively, if the goal outweighs the pain, then the cat may elect to endure the pain to prioritise that need (eg, eating with periodontal disease).

**❖ Central sensitisation**

This phenomenon entails significant alterations in the processing of pain signals across the entire central nervous system, including the spinal cord, brainstem and higher brain centres. The heightened sensitivity to pain can persist even after the initial injury or inflammation has resolved.



Chronic (maladaptive) pain

Chronic pain is pain that persists or recurs and is associated with significant emotional distress or functional disability. In humans, chronic pain is defined as pain that persists for longer than 3 months, but it has been suggested that this definition should be adapted to incorporate a shorter duration for companion animals to reflect their shorter lifespan.¹⁷ Chronic pain may be associated with a chronic health condition such as degenerative joint disease or cancer.¹⁸ See box 'Chronic pain syndromes (with examples) in the cat' for a description of chronic pain categories.

Regardless of the aetiology, chronic pain will result in neuroplastic changes in the nervous system, leading to amplified pain signals, altered pain perception and changes in emotional processing. Therefore, management of chronic pain has some similarity with, and relevance for, management of neuropathic pain.

Neuropathic pain

Neuropathic pain is a subcategory of chronic pain that is a consequence of damage to or dysfunction of the nervous system.²¹ It is characterised by spontaneous pain, heightened sensitivity to touch and what humans describe as abnormal sensations, such as tingling, burning or electric shocks (Table 2).

There are three fundamental phenomena intrinsic to the development of neuropathic pain – central sensitisation, central disinhibition and phenotypic change.²²

Central sensitisation

Central sensitisation is the amplification of pain signal processing as it travels to the brain, leading to increased pain sensitivity (disproportionate pain in relation to the injury or stimulus), allodynia and hyperalgesia (Table 2).

The spinal cord and the medullary dorsal horn neurons play a crucial role in pain perception through a mechanism known as 'wind-up' (Table 1). This involves substance P (neurokinin-1 receptors) as well as glutamate (NMDA receptors).²³ These alterations include ectopic generation of action potentials, facilitation and disinhibition of synaptic transmission, loss of synaptic connectivity and formation of new synaptic circuits, and neuroimmune interactions.

Although neural lesions are necessary, they are not sufficient in themselves to generate neuropathic pain; genetic polymorphisms, sex and age all influence the risk of developing persistent pain.²¹

Chronic pain syndromes (with examples) in the cat

Chronic musculoskeletal pain

- ❖ Osteoarthritis
- ❖ Degenerative joint disease

Chronic visceral pain

- ❖ Cystitis
- ❖ Inflammatory bowel disease
- ❖ Pancreatitis

Chronic peripheral neuropathic pain

- ❖ Tail mutilation (post-traumatic or idiopathic)
- ❖ Traumatic/ischaemic nerve injury
- ❖ Painful polyneuropathies
- ❖ Painful radiculopathy (eg, nerve root impingement in lumbosacral disease)
- ❖ FOPS
- ❖ FHS (unproven aetiology)

Chronic central neuropathic pain

- ❖ Spinal cord injury
- ❖ Brain injury (lesion or disease of the somatosensory cortex, connected brain regions or associated pathways in the brain)

Chronic cancer-related pain

- ❖ Osteosarcoma and other bone tumours
- ❖ Tumours causing spinal cord or nerve root compression
- ❖ Abdominal masses causing visceral pain
- ❖ Renal tumours (expansion of renal capsule)
- ❖ Oral squamous cell carcinoma
- ❖ Inflammatory mammary carcinoma
- ❖ Injection-site sarcoma
- ❖ Pain as a consequence of treatment (surgery, chemotherapy, radiotherapy)

Chronic postsurgical or post-traumatic pain

- ❖ Oral pain (tooth root fractures/dental disease)
- ❖ Chronic post-traumatic musculoskeletal pain
- ❖ Post-thoracotomy pain
- ❖ Limb/tail amputation
- ❖ Surgery with inadequate intra/postoperative pain control

Modified from the International Classification of Diseases (ICD-11) adopted by the World Health Organization.^{19,20} Note that there can be crossover between categories; for example, chronic post-traumatic pain is often peripheral neuropathic in nature and spinal cord tumours can have a central neuropathic component. FOPS = feline orofacial pain syndrome; FHS = feline hyperaesthesia syndrome

Central disinhibition

Central disinhibition refers to an imbalance between the excitatory and inhibitory side of the nervous system, such that there is reduced inhibition to the spinal cord dorsal horn.

Phenotypic change

In response to ongoing pain signals, injury or inflammation, neurons and glial cells may undergo phenotypic changes. These changes can include increased expression of pain-related receptors, altered neurotransmitter release and enhanced synaptic plasticity. Mechanoreceptive A- β fibres in the deeper laminae of the dorsal horn (Table 1) become activated and produce substance P so that input from them is perceived as pain (tactile allodynia).^{8,24}



Overlapping neurobiological mechanisms mean there is a high comorbidity of negative affective disorders with chronic pain.

Interplay between chronic pain and emotional health

The corticolimbic system (Figure 2) integrates emotion with cognition and produces a behavioural output that must be flexible, dependent on the environmental and social circumstances.^{25,26}

The corticolimbic circuitry of the prefrontal cortex, amygdala and hippocampus is connected to the hypothalamic–pituitary–adrenal axis. Environmental and social factors leading to stress and fear–anxiety affect decision-making, emotion regulation and memory.²⁶ The corticolimbic system is also the modulator for acute pain, a mediator for chronic pain and critical for the chronification of pain.²⁷ Owing to the anatomical overlap in the corticolimbic circuitry for pain, emotion regulation, decision-making and memory, there is influence of these brain functions on each other. Consequently, there is a high comorbidity of negative affective disorders

Table 2 Common terms associated with pain

Term	Characteristics
Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. Pain is a perception, rather than a quantifiable entity, and is subjective. Consequently, it is challenging to apply some of the pain terms listed below to non-verbal animals	
Nociceptive pain	Pain that arises from activation of nociceptors during actual or threatened damage to non-neural tissue and transmitted by normal functioning nerves to the central nervous system. The pain is localised to the area of damage, and removal of the insult results in resolution of pain. The term is used to describe pain with a normal functioning nervous system
Nociplastic pain	Pain that arises from altered nociception, despite no clear evidence of (i) actual or threatened tissue damage causing the activation of peripheral nociceptors, or (ii) disease or a lesion affecting the somatosensory system. It is possible to have a combination of nociceptive and nociplastic pain
Neuropathic pain	Pain due to abnormal somatosensory processing in the peripheral or central nervous system. In humans, the description requires demonstrating a lesion or disease of the somatosensory system (eg, history of peripheral nerve trauma). The presence of signs (eg, touch-evoked pain) alone does not justify use of the term neuropathic pain. It is a clinical description that may accompany another diagnosis, and not a diagnosis in isolation (eg, sciatic nerve damage with neuropathic pain)
Neuralgia	Pain in the distribution of one or more nerves
Allodynia	Pain from a stimulus that does not normally provoke pain. The mechanism of the stimulus is not implicated (eg, light touch, pressure, warmth, cold, movement) but the term does imply a change in a quality of sensation (eg, light touch perceived as burning). This distinguishes allodynia from hyperalgesia or hyperaesthesia. Allodynia affects a defined area and, for diagnostic purposes, the individual's normal response to the stimulus is tested elsewhere in the body
Hyperalgesia	Meaning 'pain in the area stimulated'. Hyperalgesia describes increased pain from a stimulus that normally provokes pain. It can include nociceptive as well as neuropathic pain
Hyperpathia	In humans, hyperpathia is defined as an abnormally painful reaction to a stimulus. In animals, it is translated as a behavioural response to a stimulus, suggesting increased perception of pain. The term 'hyperalgesia' is preferred in veterinary medicine
Hyperaesthesia	Increased sensitivity to a normal level of stimulation, which manifests as a behavioural reaction (eg, an animal tensing during palpation of the spine during a physical examination)
Paraesthesia	A spontaneous or evoked, not unpleasant, abnormal sensation. Often described in humans as tingling or pricking
Dysaesthesia	A spontaneous or evoked, unpleasant, abnormal sensation associated with neuropathic pain. Humans may express difficulty describing dysaesthesia because it can be unlike any sensation they have had prior to developing neuropathic pain. The most common descriptions are 'tissue destruction' with a prominent 'burning' component. In humans, it should be specified if the sensations are spontaneous or evoked
Analgesia	Inability to feel pain
Hypoalgesia	Diminished behavioural response to a normally painful stimulus
Hypoesthesia	Decreased sensitivity to stimulation, excluding the special senses (sight, hearing, smell, taste)

From Loeser (2011)¹

with chronic pain, hypothesised because of similar changes in neuroplasticity and overlapping neurobiological mechanisms.²⁸

Pain is not just an unpleasant sensory and emotional experience, but something that requires a behavioural response to the danger to the body tissue. Due to the implications for survival, pain demands the brain's attention, affecting other cortical processing as well as other body systems, including the immune system, hypothalamus–pituitary–adrenal axis, sympathetic nervous system and reproductive system.²⁹ Consequently, pain affects cognition, and vice versa. In rodent models, chronic pain impairs learning and memory, interrupts attention and affects decision-making.³⁰ Animals in pain may be more predisposed to stress-related behavioural disorders, and the converse is also true – that is, chronic stress may trigger or worsen behavioural signs of pain.¹³ For example, in feline orofacial pain syndrome (FOPS), the expression of signs of pain is influenced by environmental stress.³¹

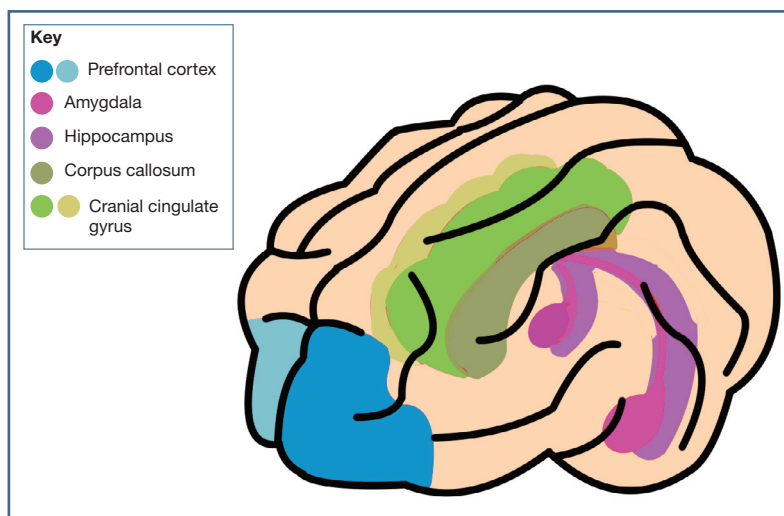


Figure 2 The corticolimbic system circuitry of the prefrontal cortex, amygdala and hippocampus. The amygdala and hippocampus lie within the medial temporal lobes and encode and consolidate the emotional memory of events (amygdala); convert short- to long-term memory and spatial memory (hippocampus); and regulate the fear–anxiety response by activating the hypothalamic–pituitary–adrenal axis (both). The prefrontal cortex and cranial cingulate gyrus receive somatosensory, visual, auditory and emotive inputs, and are involved in planning complex cognitive behaviour, personality expression, decision-making and moderating social behaviour. Image by Thomas Rusbridge

Case 1

A 5-year-old male neutered British Shorthair presented with chronic pain and self-injury to the digits following orthopaedic surgery.

History The cat had previously undergone left total hip replacement. Surgical notes indicated that the sciatic nerve was identified and retracted during the procedure. There were immediate postoperative sciatic motor and sensory deficits which gradually improved, and 4 months after surgery the cat was described as using the limb satisfactorily. However, he had frequent (daily) episodes where he would start shaking the limb, run off, and then lick and chew the paw (image a). Amantadine, gabapentin and meloxicam treatment prescribed by the veterinary orthopaedic surgeon was reported to be ineffective, although if a gabapentin dose was missed, there was more frequent or intense behaviour, suggesting limb irritation. Amitriptyline was subsequently prescribed in addition to the existing therapy, but the cat's caregivers were unable to administer this drug because of its unpalatability.

Neurological examination The cat was hyperaesthetic to touch in the distribution of the sciatic nerve. Light touching of the paw resulted in withdrawal and vigorous shaking of the limb. A behavioural reaction suggesting pain was elicited when the area of the sciatic nerve was palpated, especially behind the greater trochanter and medial to the biceps femoris muscle. Other than an inability to retract the toenails, there were no motor deficits and also no hypoalgesia. Proprioception was normal.

Diagnosis Neuropathic pain following iatrogenic sciatic nerve damage.

Management Meloxicam was discontinued and, after a 24 h washout period, prednisolone therapy was initiated at 1 mg/kg q24h in addition to the existing gabapentin at 10 mg/kg q12h. After 7 days, the prednisolone dosage was decreased to 0.25 mg/kg q24h. The amantadine was withdrawn over 2 weeks. At this time, the cat was described as considerably improved but still showing signs of pain and increased sensitivity. Topiramate, at 5 mg/kg q12h, was added, resulting in resolution of the behavioural signs of allodynia, abnormal foot sensation and self-injury (images b and c).

Outcome After 6 weeks of this combination therapy, the medication was gradually withdrawn over a 2-month period and the cat returned to normal activity, with no further signs of discomfort.



Day 0 – appearance of the left hind paw at presentation in a cat with a 4-month history of pain and self-injury



Day 20 – improvement in clinical signs following combination therapy with prednisolone, gabapentin and topiramate



Day 34 – resolution of clinical signs and almost complete healing of the wounds

Prioritising emotional health

Reduced emotional capacity hinders an individual's ability to cope with neuropathic pain, while enhanced emotional capacity can mitigate the clinical impact of neuropathic pain. The following are priorities for the veterinary clinician:

- ❖ Integrate assessment of emotional health into the diagnostic work-up of any patient with neuropathic pain
- ❖ Consider emotional bias and the arousal state of patients during assessment
- ❖ Address social and environmental factors impacting emotional wellbeing
- ❖ Focus on addressing emotional compromise to increase emotional capacity

Most drug treatments are directed towards peripheral, spinal and brainstem targets, and neglect a pivotal area in pain perception. In human medicine, it is increasingly recognised that successful management of chronic pain employs a more holistic approach that includes cognitive behavioural therapy, physical therapy and neuromodulation techniques.³² In cats, pain management should also focus on addressing emotional compromise and increasing available emotional capacity (see box 'Prioritising emotional health') to mitigate the clinical impact of neuropathic pain.^{33–35}

Confirmation of neuropathic pain

Tentative diagnosis

As discussed, neuropathic pain is characterised by abnormal hypersensitivity to stimuli (hyperalgesia) and pain due to a stimulus that does not normally provoke pain (allodynia),³⁶ and can be caused by a lesion or disease affecting central or peripheral somatosensory processing. These conditions are difficult to objectively define in animals and are subjectively assumed to be present based on behavioural responses to touch (including from collars and grooming) and occasionally other stimuli; caregivers may, for example, report a reaction to wind or draughts.

Neuropathic pain may be suggested by marked and persistent hyperaesthesia associated with nerve trauma. The first of three case vignettes included in this review (case 1) describes a cat with sciatic nerve injury following orthopaedic surgery. Note that self-injurious behaviour does not in itself imply neuropathic pain, but does suggest the animal may experience abnormal sensations that provoke self-mutilation (as illustrated by all three cases). Animals showing self-mutilation often have sensory loss (hypoesthesia or analgesia), which permits scratching or licking to continue to the point of self-injury extending into tissue below the dermis (case 2).

Definitive diagnosis

Confirming a diagnosis of neuropathic pain (Figure 3) – that is, pain originating from the nervous system – is challenging and requires:

- ❖ Demonstrating that distribution of the pain corresponds to an area of abnormal sensation (eg, decreased or increased sensitivity to touch);
- ❖ Ideally, demonstrating that the distribution of the pain corresponds to an underlying lesion or disease of the somatosensory system.²⁰ In some cases, there may be a known historical injury (eg, previous surgery). In others, further diagnostic testing is required, such as MRI to demonstrate a lesion or neuroelectrophysiology to confirm a peripheral neuropathy.

A positive response to trial treatment with drugs effective for neuropathic pain can additionally be used to support a tentative diagnosis. However, caution is advised because many drugs that are useful for treating neuropathic pain can also affect emotional state – for example, gabapentinoid drugs.^{37,38} Thus, without the above requirements having been met, a positive response to these drugs does not 'prove' a diagnosis of neuropathic pain. Given, however, that a negative emotional state can influence pain, it can be argued that the cat's quality of life is improved regardless.



Pain management should focus on addressing emotional compromise and increasing available emotional capacity to mitigate the clinical impact of neuropathic pain.

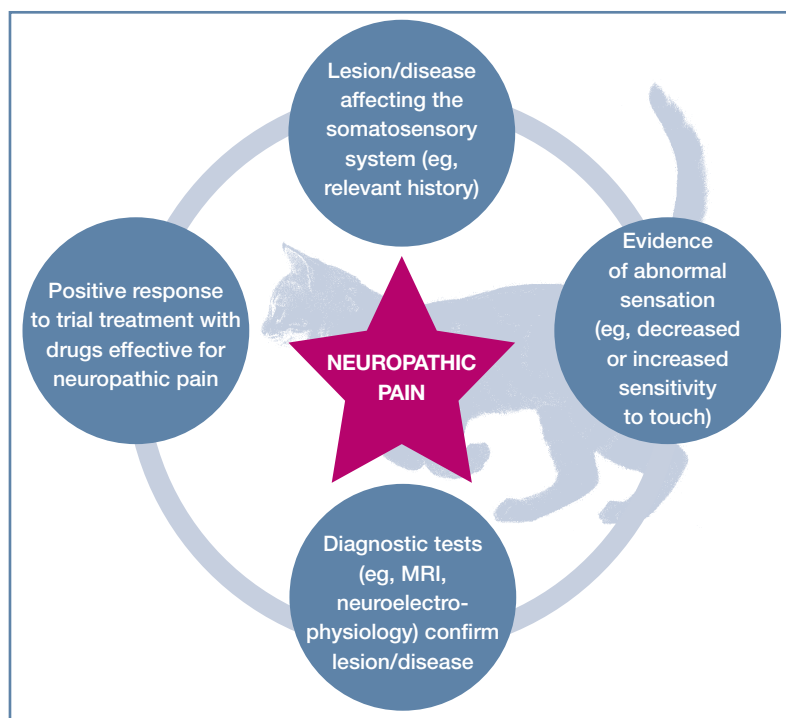


Figure 3 Diagnosis of neuropathic pain in the cat

Case 2

A 10-year-old male neutered domestic shorthair cat presented with distress and tail stump mutilation.

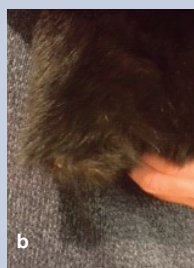
History Nine months earlier, the cat had presented to the primary veterinary surgeon with an analgesic flaccid tail following a presumed 'tail pull injury' (sacroccygeal luxation). With no apparent recovery in tail sensation or motor function after 6 weeks, the tail was amputated. The cat started traumatising the stump within a week of the surgery, before the sutures were removed. Initially, signs were controlled with 3-weekly parenteral methylprednisolone acetate, but, about 4 months after the amputation, there was an acute deterioration in the cat's condition, characterised by distress and attempts to traumatise the stump. Gabapentin (20 mg/kg q12h) and transdermal tramadol (2 mg/kg q24h, applied to the ear) were prescribed, without positive effect. Despite using a variety of Elizabethan collars, the cat succeeded in severely traumatising the stump, with the caregivers describing his behaviour as suggesting considerable periodic distress. The caregivers and primary veterinarian had discussed euthanasia but decided against it because, in between the periods of distress, the cat was deemed to be happy and enjoyed a good quality of life.

Neurological examination The tail stump was covered with raw granulating tissue (image a) and was analgesic below the level of the first coccygeal vertebra. However, the cat was noted to be hyperaesthetic just above that line of analgesia. Aside from tail stump motor and sensory deficits, there were no other neurological deficits.

Diagnosis Neuropathic pain following coccygeal nerve trauma and exacerbated by tail amputation. In hindsight, tail amputation had been performed when coccygeal nerve function was returning.

Management Topiramate (approximately 5 mg/kg q12h) was added to the existing medication, and a several-week course of cephalosporin was prescribed owing to the high risk of ascending meningitis. Methylprednisolone acetate was discontinued. At examination 2 weeks later, the caregivers reported that the cat appeared to be in less distress but there had been no change in the frequency or intensity of the attempts to injure the tail stump. Despite the use of an Elizabethan collar, these attempts at self-injury were often successful. Neurological examination found that tail stump voluntary movement and pain perception had returned and that the hyperaesthesia was now at the level of the lumbosacral junction. Topiramate was continued, gabapentin was switched to pregabalin (approximately 5 mg/kg q12h) and tramadol was tapered and then withdrawn over 2 weeks. Over the next 4 months, clinical signs were improved, such that when the cat did gain access to his tail stump, he would lick rather than bite. However, there were periods of anorexia associated with pancreatitis and, at those times, the caregivers struggled to give medication and signs would recur.

At 1 year after the original trauma, the tail stump moved normally but the tail could not be handled (eg, groomed) without causing distress. There was still an open wound because, despite a constant 'comfy' collar and supervision, the cat would succeed in reaching and removing the scab every 3–4 days. An increase in the evening dose of topiramate to 10 mg/kg (morning dose unchanged), with pregabalin continuing at the original dose, resulted in improvement to the extent that, over the next 4 weeks, the collar could be removed and the tail stump wound healed (image b).



Tail stump finally showing healing 13 months after tail amputation, and following a dose adjustment of the topiramate and pregabalin therapy

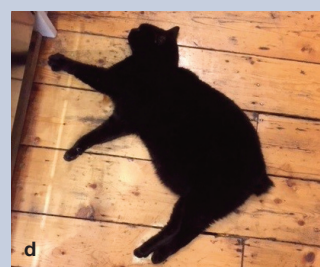
At an examination approximately 12 months after starting topiramate and pregabalin combination therapy (20 months after tail amputation), the cat was described as having mostly controlled signs. However, any minor touch to the stump and tailhead area could aggravate signs; moreover, shaving of matted fur triggered self-injury (image c).



Shaving of matted fur triggered a recurrence of mutilation 20 months after tail amputation

The cat re-presented just over a year later (34 months after tail amputation), because he was paying increased attention to the stump. He was described as licking the tail stump rather than biting, but approximately once a month the caregivers needed to place a comfy Elizabethan collar to stop self-trauma. Diabetes mellitus had developed in the interim that was described as difficult to control. On neurological examination, there was evidence of weakness and a decreased pelvic limb withdrawal reflex, consistent with a diabetic neuropathy. Clinical signs improved when diabetes management was optimised.

Outcome Four years after the original injury, the caregivers reported that the cat had not tried to mutilate the tail stump for well over a year, and that the stump could be touched and groomed without causing distress (image d). On attempting to reduce the medication, signs had recurred and so treatment was continued at the same doses, in addition to injectable insulin for diabetes mellitus. Signs of weakness relating to (presumed) diabetic neuropathy were improved. There were no further signs suggesting tail stump discomfort until the cat's death at the age of 16 years.



Four years after the original injury, the cat showed no signs of tail stump discomfort unless topiramate or pregabalin were withdrawn



Appearance of the tail stump at presentation in a cat with an 8-month history of tail stump pain and self-injury following tail amputation performed 6 weeks after a tail pull injury

Pharmacological management of neuropathic pain

Treatment of neuropathic pain depends on the aetiology, with humans recognised to respond best to multimodal therapy. This multimodal approach is required because single agents have poor success. For example, if effective treatment is defined as a 50% reduction in pain, the average number of human patients with neuropathic pain who need to be treated for just one person to benefit has been shown in a controlled clinical trial to be 7.7 for pregabalin and 7.2 for gabapentin.³⁹ Also, it is

important to address the underlying cause of neuropathic pain and, furthermore, to consider the impact of emotional health on chronic pain (as discussed earlier).

There are no licensed preparations for the management of feline neuropathic pain and many of the agents referred to in this article are adjuvants – that is, medications that are not primarily designed to relieve pain but are used alongside primary pain-relieving drugs (eg, opioids or non-steroidal anti-inflammatory drugs [NSAIDs]) to enhance their effectiveness or address specific aspects of pain or its management.

Case 3

A 5-month-old female Burmese kitten presented with acute-onset orofacial discomfort.

History Investigation under anaesthetic on initial presentation to the primary veterinary surgeon did not reveal significant findings other than that the permanent canines were erupting. Liberal spraying of the oral mucosa with lidocaine was not effective in alleviating the problem. The kitten had injured her face and tongue and, in an attempt to prevent this, her feet were bandaged.

Examination On referral, the kitten's behaviour suggested severe tongue/oral discomfort. She made exaggerated tongue movements and was pawing at her mouth continuously (images a–d show similar behaviour in an older cat with feline orofacial pain syndrome [FOPS]). Touching her face was tolerated, but touching the oral mucosa was not. Serum biochemistry, haematology, retroviral titres, brain MRI, cerebrospinal fluid analysis and dental examination (by a diplomate of both the American and European Veterinary Dental Colleges) were unremarkable.

Diagnosis FOPS – breed related; triggered by teething and subsequent periodontitis, as well as stress related to attending cat shows and cattery stays.

Management Clinical signs improved after phenobarbital treatment was instituted (3 mg/kg IV, continued at 3 mg/kg q12h PO). For a few days, the kitten tended to paw at the mouth when emotionally aroused (eg, during handling), but the signs then resolved completely and, after 1 month, the phenobarbital was slowly withdrawn.

The cat re-presented with a recurrence of clinical signs aged 5 years old. The primary veterinary surgeon found oral ulceration, and the signs resolved with antibiotic, buprenorphine and meloxicam therapy.

At 7 years of age, the cat was presented with more sustained signs and examination revealed extensive periodontal disease. She was prescribed antibiotics and phenobarbital (same oral dose as above) and referred to a veterinary dental specialist. Dental radiography confirmed odontoclastic resorptive lesions on a premolar and molar tooth. In addition, there was marked gingival recession, horizontal bone loss and a periapical abscess of the rostral root of the third right premolar. Treatment included surgical extraction of all cheek teeth distal to the canines under a local anaesthetic block and general anaesthesia. Phenobarbital was continued until 2 weeks postoperatively and then slowly withdrawn.

For the next 2 years, the cat had a tendency to exhibit brief episodes of mouth pawing when attending cat shows and when staying in a cattery. For the former, the caregiver gave buprenorphine and meloxicam. For the latter, a short course of phenobarbital (as above) was prescribed.

Outcome When the cat was around 9 years old, episodes suggestive of oral pain became more frequent and were managed, according to the caregiver, with gabapentin at 5 mg/kg q12h and 2 mg/kg phenobarbital q72h. The caregiver increased medication dosages during prolonged episodes and also gave parenteral buprenorphine. Subsequently, when the cat was 14 years old, she re-presented because of increasingly severe oral pain associated with a period of anorexia that had hampered giving medication. The caregivers and primary veterinarian had eventually controlled signs with phenobarbital at approximately 8.5 mg/kg q24h, but the medication had adverse effects of sedation and ataxia. Examination revealed sensitivity and gum recession around the right upper canine tooth and she was again referred to a specialist dentist. Signs improved following canine extraction and the cat remained on daily phenobarbital treatment before being lost to further follow-up.



Video stills of a 13-year-old Singapura cat with FOPS displaying mouth and tongue movements suggesting discomfort, with attempts to paw at the mouth. The episodic behaviour was triggered by mouth or tongue movements, especially eating, grooming and sometimes yawning. During the episodes, the caregiver attempted to restrain the paws to prevent tongue injury

The implications of using a non-licensed drug should be discussed with the client. It should also be remembered that licensed NSAIDs can still have a role in the management of a cat with neuropathic pain, especially as they do not have a sedative adverse

effect and/or may allow a reduction in the dose of a drug with sedative effects. Cyclooxygenase (COX-2) mediated prostaglandins, such as prostaglandin E₂ (PGE₂), contribute to the development of neuropathic pain.⁴⁰ In the central nervous system, PGE₂

Table 3 Drugs and other treatment modalities for management of neuropathic pain in cats, categorised according to anatomical target (continued on page 11)

Drug/treatment modality	Mechanism of action and clinical application
Peripheral afferent nerve (nociceptors, afferent fibres and dorsal root ganglion)	
Anti-NGF monoclonal antibody	Chronic painful stimuli (eg, within joints) increase NGF, a neurotrophin that binds to TKA on the nociceptor. The NGF-TKA complex is translocated to the dorsal root ganglion cell body nucleus where it induces gene transcription resulting in, among other changes, overexpression of substance P and calcitonin gene-related peptide, leading to central and peripheral sensitisation and neurogenic inflammation. ⁴³ Antagonists against NGF or TKA are potentially useful in managing pain associated with osteoarthritis; for example, frunevetmab – a monoclonal antibody that targets NGF. ⁴⁴ In cats, frunevetmab is licensed for osteoarthritis but hypothetically (and based on studies in humans) may be useful for other chronic peripheral neuropathic pain, such as radicular pain, ⁴⁵ diabetic neuropathy ⁴⁶ and, anecdotally, FOPS ⁴⁷
Glucocorticoids	Glucocorticoids block transcription of inflammatory genes, upregulate anti-inflammatory genes and have excitatory and inhibitory effects on a variety of neuronal systems. They can have benefit in traumatic peripheral nerve injury by reducing ectopic discharges. ⁴⁸ Glucocorticoids can be applied locally (eg, epidural methylprednisolone in the management of radicular pain due to lumbosacral disc herniation) or given systemically
NSAIDs	Prostaglandins such as PGE ₂ contribute to the development of neuropathic pain. ^{40,41} NSAIDs are unlikely to be sufficient as monotherapy for neuropathic pain, but selective COX-2 inhibitors or EP receptor antagonists may be useful in combination with other agents (not glucocorticoids). At the time of writing, there are no EP receptor antagonists available for cats, but there are for dogs
Local anaesthetics (lidocaine)	Topical lidocaine (lidocaine plaster) is used for the management of chronic peripheral neuropathic pain in humans, ⁴⁹ but is less practical for animals. However, lidocaine can have a role in the short term; for example, cats with FOPS undergoing dental treatment should have dental blocks to reduce the likelihood that the procedure will facilitate central sensitisation ^{50,51}
Topiramate	Topiramate is an antiepileptic drug that may be useful for the management of feline neuropathic pain and self-mutilation. ^{52,53} Apart from some isolated case reports, ⁵⁴ it is not generally useful for human neuropathic pain, although it is a first-line drug for migraines ⁵⁵ and the mechanism for this has been investigated in feline laboratory models. ^{56–58} It is neuroprotective and anti-inflammatory in some neuropathy models, especially diabetic neuropathy. ^{59–62} For neuropathic pain, topiramate is often classified as a voltage-dependent sodium channel blocker, resulting in a reduction of ectopic firing in the peripheral nerves and dorsal root ganglion. However, it has several other central mechanisms of action, including potentiation of GABA _A neurotransmission, inhibition of glutamate neurotransmission through its effects on kainate-evoked currents, inhibition of voltage-activated calcium channels and inhibition of carbonic anhydrase ⁶³
Carbamazepine, oxcarbazepine	These are the most common drugs for treating human trigeminal neuralgia, and have been used successfully in feline experimental models of neuropathic trigeminal pain ^{64–66} and peripheral neuropathic pain. ⁶⁷ The author has successfully used carbamazepine in a single cat with FOPS when other treatment modalities failed (unpublished data); these drugs should only be considered when all other options have been explored (see Table 4). The main mechanism of action is voltage-sensitive sodium channel antagonism, which inhibits high-frequency repetitive neuronal firing and the release of glutamate ^{68,69}
TENS	TENS is a non-invasive method for alleviating pain. Pulsed electrical currents are applied to the skin's surface to activate the nerves beneath. In the case of conventional TENS, the goal is specifically to stimulate larger diameter, low-threshold sensory nerves (A-β fibres) within the pain-related dermatomes. This stimulation helps to reduce the activity of second-order pain transmission neurons within the CNS, thereby inhibiting pain signals (gate control theory of pain – see Table 1). ⁷⁰ TENS is considered a first-line adjuvant therapy for the management of human peripheral neuropathic pain and, although there are no clinical studies in cats, there are many experimental feline studies suggesting effect. ^{71,72} However, given that hyperaesthesia is associated with neuropathic pain, it may not be a practical treatment modality in many cats. Nonetheless, a multimodal approach to neuropathic pain is standard practice in human medicine, and so alternative therapy modalities like this should be considered
Acupuncture/electroacupuncture	Electroacupuncture (frequency 2–10 Hz) is widely used in the multimodal management of neuropathic pain in humans. The mechanistic basis involves many receptors at multiple levels of the CNS (for a review, see Zhou et al [2023] ⁷³), including the endogenous opioid pathway, excitatory amino acid neurotransmitters, serotonin/norepinephrine signalling pathway, endocannabinoid system pathway, purinergic signalling pathway, glial cells and cytokine signalling pathway. ⁷³ Electroacupuncture as a component of a multimodal treatment regimen for neuropathic pain has been described in a single cat, ⁷⁴ and, together with manual acupuncture, is performed as part of pain management in many veterinary practices (Figure 4)
Dorsal horn neurotransmitters and receptors	
Gabapentin, pregabalin (gabapentinoids)	All nociceptor afferents release the excitatory neurotransmitter glutamate. Gabapentinoids prevent the release of glutamate through interaction with the α ₂ δ subunit of voltage-gated calcium channels. The gabapentinoids also have supraspinal sites of action; for example, at the locus coeruleus, influencing descending inhibitory noradrenalin control by reducing presynaptic GABA release and inducing glutamate release from locus coeruleus astrocytes. ^{75–77} This may be the mechanism by which gabapentinoids have an anxiolytic effect, ⁷⁵ although there is also insula and amygdala activation. ⁷⁸ Pregabalin (and probably gabapentin) inhibit dopaminergic function in the hypothalamus, increasing food intake. ⁷⁹ The gabapentinoids also reduce formation of new excitatory CNS synapses via an action on the astrocyte-secreted protein thrombospondin. ⁸⁰ Pregabalin is five times as potent as gabapentin ^{81,82} and the elimination half-life in cats suggests q12h rather than q8h medication (as for gabapentin) is appropriate. This makes it an attractive first- or second-line medication for neuropathic pain in the cat. ⁸³ The oral route is preferred as transdermal absorption is unpredictable

For footnotes, including with regard to the unlicensed nature of the listed medications for the management of feline neuropathic pain, see page 11

Table 3 Drugs and other treatment modalities for management of neuropathic pain in cats, categorised according to anatomical site (continued from page 10)

Drug/treatment modality	Mechanism of action and clinical application
Dorsal horn neurotransmitters and receptors (continued)	
Ketamine, amantadine (NMDA receptor antagonists)	Treatment of chronic neuropathic pain is challenging because central sensitisation has already occurred. As this is mediated through the NMDA receptor, an ideal medication protocol would include an NMDA receptor antagonist. Ketamine non-competitively antagonises NMDA receptors and interacts with multiple receptor systems within the CNS (eg, opioid receptors, sigma receptor, dopamine D₂ receptors, muscarinic acetylcholine receptor, innate repair receptor, HCN1 cation channels, astrocytes).^{84,85} In humans, ketamine can be administered by intranasal, sublingual, subcutaneous, rectal, transcutaneous and intravenous routes. For the intravenous route, it is often combined with a magnesium infusion as magnesium increases ketamine's binding affinity.⁸⁴ Perioperatively, ketamine has been shown to be useful in a range of surgeries to reduce persistent postoperative pain in humans.⁸⁴ Subanaesthetic dosages do not produce anaesthesia but may play a role in analgesia and limit development and advancement of neuropathic pain in cats, either as a one-off intravenous infusion over several hours or as a one-off or monthly subcutaneous injection.⁸⁶ The scientific rationale for this is based on a meta-analysis in human patients that suggested a maximum analgesic effect between 48 h and 2 weeks postinfusion. In general, the longer the infusion, the more sustained the response; for example, in humans, a 100 h infusion gives a 4–8 week response and 12–24 h give 7–10 days.^{85,87} In addition to being an NMDA receptor antagonist, amantadine potentiates dopaminergic neurotransmission and has anticholinergic activity. Although widely used, there has only been one small trial (13 cats) of amantadine for feline osteoarthritis, with owners reporting improvement in their cat's mobility and quality of life. However, the cats had a significantly reduced activity, presumably due to sedative effects of the drug.⁸⁶
Phenobarbital	Phenobarbital reverses hyperalgesia in rodent and cat trigeminal neuropathic pain models. ^{66,88} and in FOPS. ³¹ Its pharmacological effect is mediated via action at the GABA receptor, in addition to other sites/mechanisms, including the excitatory neurotransmitter glutamate, calcium channels, sodium channels and voltage-dependant potassium currents. ^{88,89}
Corticolimbic system (pain matrix)	
See earlier discussion of the 'Interplay between chronic pain and emotional health'. Chronic stress or fear-anxiety can potentiate pain via the limbic system and the central stress response (hypothalamic-pituitary-adrenal axis). Spending time establishing the cat's environment and social interactions, especially with other cats, is paramount. Using a questionnaire ⁹⁰ is a useful means of ensuring the correct information is obtained. Cats have a fundamental need to be in control and able to access vital resources freely and immediately, without conflict with other cats, humans or other pets. ³⁴	
Descending control of pain and dorsal horn inhibitory interneurons	
Amitriptyline (tricyclic antidepressant)	Amitriptyline has multiple mechanistic actions on neuropathic pain, including blocking the reuptake of serotonin and norepinephrine neurotransmitters, ⁹¹ alpha-adrenergic antagonism, ⁹² glutamate receptor antagonism, ⁹³ modulating dorsal horn neuron voltage-gated ion channels ⁹³ and nociceptor sodium channels, ⁹⁴ and stabilising mast cells via H1 receptor antagonism. ⁹⁵ In humans, topical preparations are favoured for management of peripheral neuropathic pain as there is direct action on nociceptor sodium channels and systemic adverse effects are reduced. ⁹⁴ The patient applies the preparation directly to the painful area (eg, foot). In cats, transdermal absorption is poor and, unless intended as topical (vs systemic) therapy, this route is not appropriate. ⁹⁶ Oral amitriptyline has been used most commonly for idiopathic feline lower urinary tract disease. ⁹⁷ This is extrapolated from human medicine as amitriptyline is a common treatment for interstitial cystitis (bladder pain syndrome). Mast cell degranulation within the bladder wall, possibly related to histamine release, has been proposed as a contributing factor in the inflammatory process and amitriptyline can give rapid relief because of its multiple mechanisms of action, including blockade of histamine H1 receptors. ⁹⁸ Amitriptyline, in combination pharmacotherapy, has also been reported in the management of FHS. ⁵³
Selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors	These drugs have a role in the management of human neuropathic pain and fibromyalgia, especially the serotonin noradrenaline reuptake inhibitors venlafaxine and duloxetine. ⁹⁹ Fluoxetine, a selective serotonin reuptake inhibitor, is used extra-label for behavioural disorders in cats. However, fluoxetine is considered less useful for the management of human neuropathic pain syndromes, although it has been shown to improve pain relief, function and quality of life in fibromyalgia. ⁹⁹ Anecdotally, fluoxetine can be useful in the management of FHS, especially if there is tail mutilation. ⁵³ However, it is difficult to know if a positive response is due to its effect on abnormal sensations or in reducing anxiety.
Tramadol	Tramadol, a serotonin noradrenaline reuptake inhibitor and centrally acting opioid, is occasionally prescribed for chronic pain management in the cat (osteoarthritis, ¹⁰⁰ FHS ⁵³). In humans, there is only weak evidence to support the use of tramadol for neuropathic pain, and only as a second-line drug. ³⁹ In a study involving eight healthy cats, transdermal application of compounded tramadol gel did not yield clinically relevant plasma tramadol concentrations. ¹⁰¹
Neuroinflammation – glial cell activation (eg, microglia and astrocytes), with enhanced interaction between neurons, glial cells and mast cells	
Cannabinoids (CBD oil)	Veterinary surgeons are often asked about the value of hemp-based cannabinoids (CBD oil) for treating chronic pain. Giving accurate advice to clients about CBD oil is hampered by highly variable preparations, absorption and bioavailability, and inconsistent pharmacokinetics. ^{102,103} Adverse effects, including emesis, hypersalivation, head shaking, lethargy and increased serum ALT activity, can be observed in cats given dosages of 0.5 mg/kg q12h and above. ^{104,105} The effectiveness of lower dosages has not been proven. There is one case report citing benefit for feline osteoarthritis. ¹⁰⁶ In humans, although there is some evidence suggesting benefit for chronic pain, more robust studies are required. ¹⁰⁷
Palmitoylethanolamide	Palmitoylethanolamide (PEA) is an endocannabinoid-like compound found in several food sources that reduces neuroinflammation. ¹⁰⁸ Micronised and ultra-micronised palmitoylethanolamide has higher bioavailability and is a proposed nutraceutical for chronic pain, but rigorous clinical trials have yet to be performed. ¹⁰⁸

Note: All the medications listed are unlicensed for the management of feline neuropathic pain. The implications of using a non-licensed drug should be discussed with the client

ALT = alanine transaminase; CBD = cannabidiol; CNS = central nervous system; COX = cyclooxygenase; EP = E-prostanoid; FHS = feline hyperaesthesia syndrome; FOPS = feline orofacial pain syndrome; GABA = gamma-aminobutyric acid; NGF = nerve growth factor; NMDA = *N*-methyl-D-aspartate; NSAIDs = non-steroidal anti-inflammatory drugs; TENS = transcutaneous electrical nerve stimulation; TKA = tyrosine kinase A

modulates pain sensitivity and, in the peripheral nervous system, PGE₂ sensitises nociceptive afferent neurons through E-prostanoid receptors.⁴¹ Further information is provided in the '2024 ISFM and AAFP consensus guidelines on the long-term use of NSAIDs in cats'.⁴²

Table 3 details possible treatment options (pharmacological and non-pharmacological) for neuropathic pain in cats and describes where they are effective in the anatomical pathway. Dose rates, monitoring recommendations and adverse effects of commonly used adjuvant analgesic drugs are provided in Table 4.

Table 4 Adjuvant analgesics commonly used for neuropathic pain in cats (continued on page 13)

Drug	Dose	Common (dose-related) adverse effects	Less common adverse effects	Monitoring
Gabapentin	10–20 mg/kg PO q8–12h	❖ Sedation, ataxia ❖ Gabapentin has minimal hepatic metabolism and is excreted unchanged by the kidney. Reduce the dose (amount and frequency) in cats with CKD (IRIS stage 2 or 3)¹⁰⁹ ❖ Polyphagia and weight gain	❖ Gastrointestinal signs (hypersalivation, emesis, diarrhoea) ❖ Tremor, myoclonus ❖ Respiratory depression (caution if respiratory function is compromised)	Haematology, serum biochemistry (baseline, then every 6–12 months). Dose is adjusted based on efficacy or adverse effects, but serum concentrations can be measured using human epilepsy therapeutic range* as a guide, especially for cats with CKD
Pregabalin	2–10 mg/kg PO q8–12h If switching from gabapentin, halve the current gabapentin mg/kg dose and give q12h (eg, a gabapentin dose of 50 mg q8h becomes a pregabalin dose of 25 mg q12h)	❖ Sedation, ataxia ❖ Like gabapentin, pregabalin is excreted unchanged by the kidney. For cats with IRIS stage 2 or 3 CKD, reduce the dose (amount and frequency) ❖ Polyphagia and weight gain	❖ Gastrointestinal signs (hypersalivation, diarrhoea) ❖ Tremor, myoclonus ❖ Respiratory depression (caution if respiratory function is compromised) ❖ Superficial dermatitis¹¹⁰	Haematology, serum biochemistry (baseline, then every 6–12 months). Dose is adjusted based on efficacy or adverse effects, but serum concentrations can be measured using human epilepsy therapeutic range* as a guide, especially for cats with CKD
Topiramate	2.5–10 mg/kg PO q12h	❖ Sedation, ataxia ❖ Gastrointestinal signs (inappetence, nausea, diarrhoea)	❖ Anaemia (reported with extended-release formulation dosed at 10 mg/kg q24h)¹¹¹ ❖ Renal tubular acidosis with hypokalaemia (single case report – dose 11.9 mg/kg q8h)¹¹²	Haematology, serum biochemistry (baseline, 1 month after initiating, and then every 6–12 months). Dose is adjusted based on serum concentrations using human epilepsy therapeutic range* as a guide
Amantadine	3–5 mg/kg PO q12–24h At least 3 weeks of therapy is required to assess effect on neuropathic pain	❖ Sedation, ataxia ❖ For cats with IRIS stage 2 or 3 CKD, reduce the dose (amount and frequency)	❖ Gastrointestinal signs (emesis, diarrhoea) ❖ Overdosing leads to agitation, tremors and hypersalivation	Haematology, serum biochemistry (baseline, then every 6–12 months). Dose is adjusted based on efficacy or adverse effects
Amitriptyline	0.5–4 mg/kg PO q12–24h At least 3 weeks of therapy is required to assess effect on neuropathic pain	❖ Unpalatable – can be difficult to administer or may induce hypersalivation (compounding can help) ❖ Sedation, ataxia	❖ ECG changes (widened QRS complexes, prolonged PR intervals, flattened T waves) and ventricular arrhythmia ❖ Gastrointestinal signs (nausea, emesis) ❖ Haematological (bone marrow suppression, thrombocytopenia, neutropenia) ❖ Anticholinergic effects (constipation, urinary retention, hyperexcitability, seizures) ❖ Reduced grooming behaviour (unkempt coat) ❖ Reduced thyroid hormone concentrations	Baseline ECG prior to therapy. Haematology, serum biochemistry and thyroid function (baseline, 1 month after initiating, and then every 6–12 months). Dose is adjusted based on efficacy or adverse effects
Phenobarbital	1–3 mg/kg PO/IM q12–24h	❖ Sedation, ataxia ❖ Polydipsia, polyuria, polyphagia	❖ Haematological (bone marrow suppression, anaemia, thrombocytopenia, neutropenia) ❖ Facial pruritis ❖ Pseudolymphoma ❖ Phenobarbital-induced fever ❖ Phenobarbital-induced hypersensitivity syndrome ❖ Hepatotoxicity	Haematology, serum biochemistry (baseline, 1 month after initiating, and then every 6–12 months). Phenobarbital does not induce liver enzymes in the cat and increases should prompt investigation. Dose is adjusted based on serum concentrations using human epilepsy therapeutic range* as a guide

For footnotes, including advice regarding dosing and legal compliance, see page 13

Table 4 Adjuvant analgesics commonly used for neuropathic pain in cats (continued from page 12)

Drug	Dose	Common (dose-related) adverse effects	Less common adverse effects	Monitoring
Tramadol	1–2 mg/kg PO q12–24h	❖ Unpalatable – can be difficult to administer or may induce hypersalivation ❖ Sedation, ataxia	❖ Gastrointestinal signs (emesis, diarrhoea, constipation) ❖ CNS effects (sedation, mydriasis, dysphoria or euphoria) ❖ Serotonin syndrome¹¹³ (mental status changes, myoclonus, hyper-reflexia, diaphoresis, shivering, tremor, diarrhoea, incoordination, pyrexia) ❖ Respiratory depression	Dose is adjusted based on efficacy or adverse effects
Carbamazepine	5 mg/kg q12h (100 mg/5 ml solution)	❖ Sedation, ataxia ❖ Pharmacokinetics and toxicity of carbamazepine when used therapeutically in the cat have not been investigated. Use of this drug can be justified only after all other options have failed	❖ This drug carries two ‘black box’ warnings in humans alerting to the possibility of serious dermatological and haematological (agranulocytosis, aplastic anaemia) adverse effects ❖ Other adverse effects seen in humans include hyponatraemia, gastrointestinal disturbances (nausea, emesis, diarrhoea), hepatotoxicity, renal toxicity and anticholinergic effects (delirium, urinary retention, increased intraocular pressure, constipation)	Haematology, serum biochemistry including sodium (baseline, 1 and 6 months after initiating, and then annually; or at any signs of malaise). Dose is adjusted based on serum concentrations using human epilepsy therapeutic range* as a guide
Ketamine	0.5 mg/kg SC as a ‘one-off’ or every 4 weeks. 24–48 h CRI (0.5 mg/kg IV loading dose, then 0.1–0.6 mg/kg/h) for initial management or during acute exacerbation (can be combined with dexmedetomidine or an opioid)	❖ Emesis ❖ Salivation ❖ Vocalisation	❖ CNS effects (hyperthermia, nystagmus, tremors, myoclonus, hypertonicity, seizures) ❖ Respiratory depression ❖ Acute congestive heart failure	Monitor for adverse effects (for at least 30 mins) following SC administration
Prednisone/ Prednisolone	0.5–1 mg/kg PO q24h, then decrease to lowest possible (ideally alternate-day) dose that controls signs. Long-term therapy (>3 months) is not advised	❖ Polydipsia, polyuria, polyphagia ❖ Weight gain	❖ Adverse effects associated with long-term administration include, in particular, iatrogenic hyperadrenocorticism and potentially a predisposition to diabetes mellitus	Haematology, serum biochemistry (baseline)
Methylprednisolone acetate	1 mg/kg lumbosacral or sacrococcygeal epidural instillation (depending on site of termination of spinal cord – see footnote [†] regarding epidural needle placement)	❖ Systemic signs of corticosteroids, including polydipsia, polyuria and polyphagia	❖ Intrathecal injection[†] may result in spinal cord or cauda equina dysfunction, arachnoiditis, meningitis and neurotoxicity from additives such as polyethylene glycol or miripirium chloride	ECG and blood pressure monitoring during epidural procedure performed under anaesthesia
Cannabinoids (CBD oil/hemp extract)	0.25–3 mg/kg PO q12h. Absorption is improved in oil or with fatty food. Adverse effects can be observed in cats given doses of 0.5 mg/kg q12h and above. ^{104,105} The effectiveness of lower doses has not been proven	❖ Sedation, ataxia ❖ Emesis and hypersalivation (associated with medium-chain triglyceride oil preparation)	❖ Products with THC are more likely to cause adverse CNS signs ❖ Gastrointestinal signs (hypersalivation, diarrhoea, emesis) ❖ Increased serum ALT activity	Serum liver enzymes (baseline, 1 month after initiating, and then every 6–12 months). In humans with hepatic impairment, a dose reduction of 50% (moderate) to 80% (severe) is recommended ¹¹⁴

Note: In each case, start at the low end of the dose range/frequency and titrate up. Be sure to fully understand and comply with national/regional regulations for controlled or other drugs, especially gabapentinoids, ketamine and CBD oil

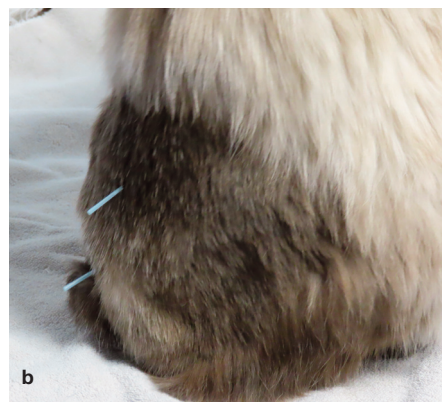
*For information see: epilepsysociety.org.uk/what-we-do/medical-services/therapeutic-drug-monitoring and epilepsysociety.org.uk/sites/default/files/2020-08/2019%20Therapeutic-Drug-Monitoring-of-Antiepileptic-Drugs-Table_0.pdf

[†]In cats, the dural sac extends beyond L6. Diagnosis of lumbosacral disc disease and the site of termination of the thecal sac should be confirmed by MRI to avoid making an intrathecal injection. Correct epidural needle placement should be confirmed by the loss-of-resistance technique with saline and absence of blood or cerebrospinal fluid in aspirate

ALT = alanine transaminase; CBD = cannabidiol; CKD = chronic kidney disease; CNS = central nervous system; CRI = constant rate infusion; ECG = electrocardiogram; IRIS = International Renal Interest Society; THC = tetrahydrocannabinol

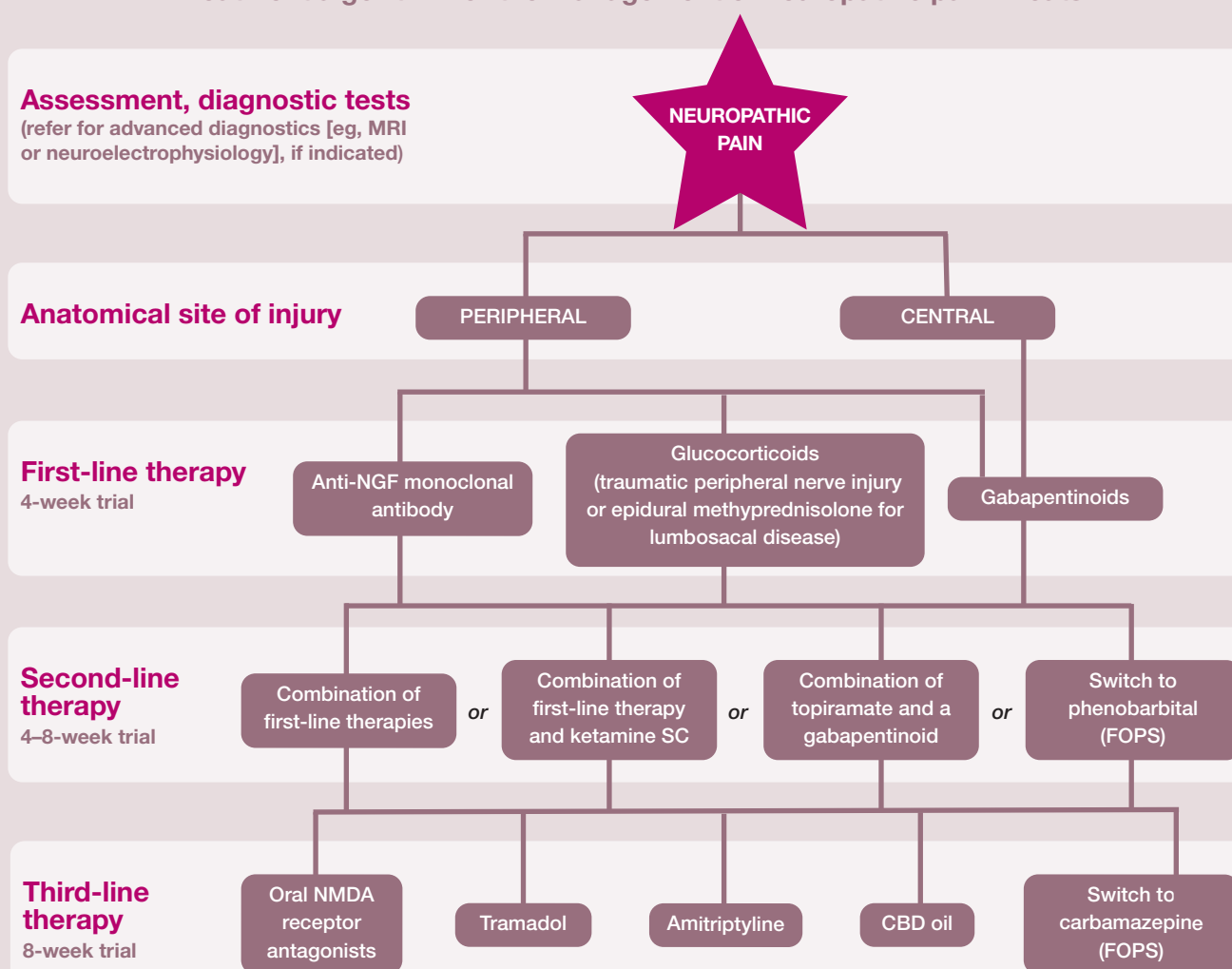


Figure 4 (a,b) A 3-year-old male neutered Ragdoll cat receiving acupuncture as part of multimodal therapy for neuropathic pain secondary to sacroccygeal luxation and surgical tail amputation. The cat was hyperaesthetic to touch in an area approximately 2.5 cm around the tailhead, and particularly on the right side. If the cat's Elizabethan collar was removed, he would self-traumatise this region. Medication with gabapentin did not improve the signs. The cat made a gradual improvement after being switched from gabapentin to a 5-week course of pregabalin therapy and undergoing two sessions of acupuncture (detailed below). Images courtesy of Dietrich Graf von Schweinitz (pictured)



The initial acupuncture session involved placement of needles at specific acupuncture points along the spinal midline, including those along the governing vessel, such as the lumbosacral area, L2/L3 and the cervicothoracic junction. Additionally, needles were inserted at the Yin Tang acupuncture point, located between the superciliary whiskers (above the eyes). For the second treatment, acupuncture points along the spinal midline were addressed once again, covering the sacroccygeal region, lumbosacral area and cervicothoracic junction. Furthermore, the Gan Shu (BL 18) acupuncture point was targeted bilaterally along the border between the longissimus and iliocostalis muscles at the T7 and T8 levels. In both sessions, fine acupuncture needles measuring 0.2 x 13 mm were inserted to a depth of approximately 10 mm, targeting interspinous spaces, muscles at the BL 18 point and subcutaneous tissue at the Yin Tang point

Treatment algorithm for the management of neuropathic pain in cats



Carbamazepine is recommended as a monotherapy. All other agents are usually added in combination with first- or second-line therapies. It may be possible to reduce or withdraw the initial drugs

Note: All the medications listed are unlicensed for the management of neuropathic pain. The implications of using a non-licensed drug should be discussed with the client and it should be remembered that licensed NSAIDs may still have a role, especially as they do not have a sedative adverse effect or, when given in combination, may allow a reduction in the dose of a drug with sedative effects. CBD = cannabidiol; FOPS = feline orofacial pain syndrome; NMDA = *N*-methyl-D-aspartate; NGF = nerve growth factor

Caregiver burden

- ❖ Managing neuropathic pain carries a significant caregiver burden because, in many instances, multiple oral treatments are required for many weeks or even the remainder of the cat's life
- ❖ Humane euthanasia of the cat may be the best option if the caregiver is unable to give medication or if the medication is not adequately controlling clinical signs

Treatment algorithm

See 'Treatment algorithm for the management of neuropathic pain in cats' for a summary of the author's recommended therapeutic approach.

Conclusions

Unravelling the intricacies of feline neuropathic pain demands understanding of nociception, pain perception and emotional health, coupled with the application of personalised multimodal interventions. The dynamic field of veterinary pain management is evolving, emphasising the pressing need for sustained research and collaborative efforts. By advancing our knowledge and refining treatment strategies, we pave the way to elevate the quality of life for cats with this potentially life-limiting condition.

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KEY POINTS

- ❖ Neuropathic pain arises from aberrant processing of sensory signals within the nervous system, resulting in chronic discomfort.
- ❖ Nociception involves the detection of noxious stimuli by specialised receptors, while pain perception encompasses the interpretation of these signals in the brain.
- ❖ Cats with neuropathic pain may have hyperaesthesia (increased sensitivity to a normal level of stimulation) or allodynia (pain from a stimulus that does not normally provoke pain, such as light touch).
- ❖ The diagnosis of neuropathic pain requires demonstrating that the distribution of pain corresponds to a lesion within the somatosensory system, supported by evidence of abnormal sensation, diagnostic (eg, MRI) test results and a positive response to trial treatment with drugs effective for neuropathic pain.
- ❖ Reduced emotional capacity hinders an individual's ability to cope with neuropathic pain. Social and environmental factors impacting emotional wellbeing must be addressed.
- ❖ Neuropathic pain responds best to a multimodal approach and pharmacotherapy including adjuvant analgesic drugs.



Conflict of interest

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This work did not involve the use of animals and therefore ethical approval was not specifically required for publication in *JFMS*.

Informed consent

This work did not involve the use of animals (including cadavers) and therefore informed consent was not required. For any animals or people identifiable within this publication, additional informed consent for publication was obtained.

References

- Loeser JD. Pain terms and definitions. Washington, DC: International Association for the Study of Pain. <https://www.iasp-pain.org/resources/terminology/> (2011, accessed 29 September 2023).
- Lindsay NM, Chen C, Gilam G, et al. **Brain circuits for pain and its treatment.** *Sci Transl Med* 2021; 13. DOI: 10.1126/scitranslmed.abj7360.
- Garland EL. **Pain processing in the human nervous system: a selective review of nociceptive and biobehavioral pathways.** *Prim Care* 2012; 39: 561–571.
- Krames ES. **The dorsal root ganglion in chronic pain and as a target for neuromodulation: a review.** *Neuromodulation* 2015; 18: 24–32.
- Hachisuka J, Omori Y, Chiang MC, et al. **Wind-up in lamina I spinoparabrachial neurons: a role for reverberatory circuits.** *Pain* 2018; 159: 1484–1493.
- Woolf CJ. **Central sensitization: implications for the diagnosis and treatment of pain.** *Pain* 2011; 152: S2–S15.
- Nalborczyk ZR, McFadyen AK, Jovanovik J, et al. **MRI characteristics for 'phantom' scratching in canine syringomyelia.** *BMC Vet Res* 2017; 13: 340. DOI: 10.1186/s12917-017-1258-2.

- 8 Willis WD and Westlund KN. **Neuroanatomy of the pain system and of the pathways that modulate pain.** *J Clin Neurophysiol* 1997; 14: 2–31.
- 9 Wu D, Wang S, Stein JF, et al. **Reciprocal interactions between the human thalamus and periaqueductal gray may be important for pain perception.** *Exp Brain Res* 2014; 232: 527–534.
- 10 de Lahunta A, Glass E and Kent M. **General sensory systems: general proprioception and general somatic afferent.** In: de Lahunta A, Glass E and Kent M (eds). *de Lahunta's veterinary neuroanatomy and clinical neurology*. 5th ed. Philadelphia: WB Saunders; 2021, pp 246–266.
- 11 Iannetti GD and Mouraux A. **From the neuro-matrix to the pain matrix (and back).** *Exp Brain Res* 2010; 205: 1–12.
- 12 Clauw DJ and Ablin JN. **The relationship between 'stress' and pain: lessons learned from fibromyalgia and related conditions.** In: Castro-Lopes J (ed). *Current topics in pain, 12th World Congress on Pain*; Seattle: IASP Press, 2009, pp 245–270.
- 13 Boadas-Vaello P, Homs J, Reina F, et al. **Neuroplasticity of supraspinal structures associated with pathological pain.** *Anat Rec (Hoboken)* 2017; 300: 1481–1501.
- 14 Guo D and Hu J. **Spinal presynaptic inhibition in pain control.** *Neuroscience* 2014; 283: 95–106.
- 15 Amir R and Devor M. **Functional cross-excitation between afferent A- and C-neurons in dorsal root ganglia.** *Neuroscience* 2000; 95: 189–195.
- 16 Melzack R and Wall PD. **Pain mechanisms: a new theory.** *Science* 1965; 150: 971–979.
- 17 Adrian D, Papich M, Baynes R, et al. **Chronic maladaptive pain in cats: a review of current and future drug treatment options.** *Vet J* 2017; 230: 52–61.
- 18 Treede RD, Rief W, Barke A, et al. **A classification of chronic pain for ICD-11.** *Pain* 2015; 156: 1003–1007.
- 19 Harrison JE, Weber S, Jakob R, et al. **ICD-11: an international classification of diseases for the twenty-first century.** *BMC Med Inform Decis Mak* 2021; 21: 206. DOI: 10.1186/s12911-021-01534-6.
- 20 Scholz J, Finnerup NB, Attal N, et al. **The IASP classification of chronic pain for ICD-11: chronic neuropathic pain.** *Pain* 2019; 160: 53–59.
- 21 Costigan M, Scholz J, Woolf CJ. **Neuropathic pain: a maladaptive response of the nervous system to damage.** *Annu Rev Neurosci* 2009; 32: 1–32.
- 22 Woolf CJ and Mannion RJ. **Neuropathic pain: aetiology, symptoms, mechanisms, and management.** *Lancet* 1999; 353: 1959–1964.
- 23 Herrero JF, Laird JM and López-García JA. **Wind-up of spinal cord neurones and pain sensation: much ado about something?** *Prog Neurobiol* 2000; 61: 169–203.
- 24 Woolf CJ, Shortland P, Reynolds M, et al. **Reorganization of central terminals of myelinated primary afferents in the rat dorsal horn following peripheral axotomy.** *J Comp Neurol* 1995; 360: 121–134.
- 25 Swartz JR and Monk CS. **The role of cortico-limbic circuitry in the development of anxiety disorders in children and adolescents.** *Curr Top Behav Neurosci* 2014; 16: 133–148.
- 26 Bergstrom HC and Pinard CR. **Corticolimbic circuits in learning, memory, and disease.** *J Neurosci Res* 2017; 95: 795–796.
- 27 Vachon-Presseau E, Centeno MV, Ren W, et al. **The emotional brain as a predictor and amplifier of chronic pain.** *J Dent Res* 2016; 95: 605–612.
- 28 Yang S and Chang MC. **Chronic pain: structural and functional changes in brain structures and associated negative affective states.** *Int J Mol Sci* 2019; 20. DOI: 10.3390/ijms20133130.
- 29 Moseley GL. **A pain neuromatrix approach to patients with chronic pain.** *Man Ther* 2003; 8: 130–140.
- 30 Low LA. **The impact of pain upon cognition: what have rodent studies told us?** *Pain* 2013; 154: 2603–2605.
- 31 Rusbridge C, Heath S, Gunn-Moore DA, et al. **Feline orofacial pain syndrome (FOPS): a retrospective study of 113 cases.** *J Feline Med Surg* 2010; 12: 498–508.
- 32 Ong WY, Stohler CS and Herr DR. **Role of the prefrontal cortex in pain processing.** *Mol Neurobiol* 2019; 56: 1137–1166.
- 33 Heath S, Dowgray N, Rodan I, et al. **A new model and terminology for understanding feline emotions.** *J Feline Med Surg* 2022; 24: 934–935.
- 34 Ellis SLH, Rodan I, Carney HC, et al. **AAFP and ISFM feline environmental needs guidelines.** *J Feline Med Surg* 2013; 15: 219–230.
- 35 Rodan I, Dowgray N, Carney HC, et al. **2022 AAFP/ISFM cat friendly veterinary interaction guidelines: approach and handling techniques.** *J Feline Med Surg* 2022; 24: 1093–1132.
- 36 Cavalli E, Mammana S, Nicoletti F, et al. **The neuropathic pain: an overview of the current treatment and future therapeutic approaches.** *Int J Immunopathol Pharmacol* 2019; 33. DOI: 10.1177/2058738419838383.
- 37 van Haaften KA, Forsythe LRE, Stelow EA, et al. **Effects of a single preappointment dose of gabapentin on signs of stress in cats during transportation and veterinary examination.** *J Am Vet Med Assoc* 2017; 251: 1175–1181.
- 38 Lamminen T, Korpivaara M, Suokko M, et al. **Efficacy of a single dose of pregabalin on signs of anxiety in cats during transportation – a pilot study.** *Front Vet Sci* 2021; 8. DOI: 10.3389/fvets.2021.711816.
- 39 Finnerup NB, Attal N, Haroutounian S, et al.

- Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis.** *Lancet Neurol* 2015; 14: 162–173.
- 40 Mebane H, Turnbach ME and Randich A. **Spinal EP receptors mediating prostaglandin E2-induced mechanical hyperalgesia, thermal hyperalgesia, and touch-evoked allodynia in rats.** *J Pain* 2003; 4: 392–399.
 - 41 Kanda H, Kobayashi K, Yamanaka H, et al. **Localization of prostaglandin E2 synthases and E-prostanoid receptors in the spinal cord in a rat model of neuropathic pain.** *Brain Res* 2021; 1750. DOI: 10.1016/j.brainres.2020.147153.
 - 42 Taylor S, Gruen M, KuKanich K, et al. **2024 ISFM and AAFP consensus guidelines on the long-term use of NSAIDs in cats.** *J Feline Med Surg* 2024; 26. DOI: 10.1177/1098612X241241951.
 - 43 Wise BL, Seidel MF and Lane NE. **The evolution of nerve growth factor inhibition in clinical medicine.** *Nat Rev Rheumatol* 2021; 17: 34–46.
 - 44 Gruen ME, Myers JAE, Tena JS, et al. **Frunevetmab, a felinized anti-nerve growth factor monoclonal antibody, for the treatment of pain from osteoarthritis in cats.** *J Vet Intern Med* 2021; 35: 2752–2762.
 - 45 Schmelz M, Mantyh P, Malfait AM, et al. **Nerve growth factor antibody for the treatment of osteoarthritis pain and chronic low-back pain: mechanism of action in the context of efficacy and safety.** *Pain* 2019; 160: 2210–2220.
 - 46 Dong X, Li H, Pei M, et al. **Analgesic effects of nerve growth factor-directed monoclonal antibody on diabetic neuralgia in an animal model.** *FEBS Open Bio* 2022; 12: 1325–1335.
 - 47 Bonomini F, Favero G, Castrezzati S, et al. **Role of neurotrophins in orofacial pain modulation: a review of the latest discoveries.** *Int J Mol Sci* 2023; 24. DOI: 10.3390/ijms241512438.
 - 48 Rijsdijk M, van Wijck AJ, Kalkman CJ, et al. **The effects of glucocorticoids on neuropathic pain: a review with emphasis on intrathecal methylprednisolone acetate delivery.** *Anesth Analg* 2014; 118: 1097–1112.
 - 49 Voute M, Morel V and Pickering G. **Topical lidocaine for chronic pain treatment.** *Drug Des Devel Ther* 2021; 15: 4091–4103.
 - 50 Aguiar J, Chebroux A, Martinez-Taboada F, et al. **Analgesic effects of maxillary and inferior alveolar nerve blocks in cats undergoing dental extractions.** *J Feline Med Surg* 2015; 17: 110–116.
 - 51 Watanabe R, Doodnaught G, Proulx C, et al. **A multidisciplinary study of pain in cats undergoing dental extractions: a prospective, blinded, clinical trial.** *PLoS One* 2019; 14. DOI: 10.1371/journal.pone.0213195.
 - 52 Grant D and Rusbridge C. **Topiramate in the management of feline idiopathic ulcerative dermatitis in a two-year-old cat.** *Vet Dermatol* 2014; 25: 226–e60.
 - 53 Amengual Batle P, Rusbridge C, Nuttall T, et al. **Feline hyperaesthesia syndrome with self-trauma to the tail: retrospective study of seven cases and proposal for an integrated multidisciplinary diagnostic approach.** *J Feline Med Surg* 2019; 21: 178–185.
 - 54 Fowler JA, Shen JY and Bettinger TL. **Successful use of topiramate in a patient with severe postherpetic neuralgia.** *Ann Pharmacother* 2009; 43: 139–142.
 - 55 Khalil NY, AlRabiah HK, Al Rashoud SS, et al. **Topiramate: comprehensive profile.** *Profiles Drug Subst Excip Relat Methodol* 2019; 44: 333–378.
 - 56 Storer RJ and Goadsby PJ. **Topiramate inhibits trigeminovascular neurons in the cat.** *Cephalalgia* 2004; 24: 1049–1056.
 - 57 Akerman S and Goadsby PJ. **Topiramate inhibits cortical spreading depression in rat and cat: impact in migraine aura.** *Neuroreport* 2005; 16: 1383–1387.
 - 58 Storer RJ and Goadsby PJ. **Topiramate is likely to act outside of the trigeminocervical complex.** *Cephalalgia* 2013; 33: 291–300.
 - 59 Attia MA, Soliman N, Eladl MA, et al. **Topiramate affords neuroprotection in diabetic neuropathy model via downregulating spinal GFAP/inflammatory burden and improving neurofilament production.** *Toxicol Mech Methods* 2023; 33: 563–577.
 - 60 Shafik AN. **Effects of topiramate on diabetes mellitus induced by streptozotocin in rats.** *Eur J Pharmacol* 2012; 684: 161–167.
 - 61 Boyd AL, Barlow PM, Pittenger GL, et al. **Topiramate improves neurovascular function, epidermal nerve fiber morphology, and metabolism in patients with type 2 diabetes mellitus.** *Diabetes Metab Syndr Obes* 2010; 3: 431–437.
 - 62 Bischofs S, Zelenka M and Sommer C. **Evaluation of topiramate as an antihyperalgesic and neuroprotective agent in the peripheral nervous system.** *J Peripher Nerv Syst* 2004; 9: 70–78.
 - 63 Bai Y-F, Zeng C, Jia M, et al. **Molecular mechanisms of topiramate and its clinical value in epilepsy.** *Seizure* 2022; 98: 51–56.
 - 64 Kiguchi S, Ichikawa K and Kojima M. **Suppressive effects of oxcarbazepine on tooth pulp-evoked potentials recorded at the trigeminal spinal tract nucleus in cats.** *Clin Exp Pharmacol Physiol* 2001; 28: 169–175.
 - 65 Fromm GH, Terrence CF and Chattha AS. **Differential effect of antiepileptic and non-antiepileptic drugs on the reticular formation.** *Life Sci* 1984; 35: 2665–2673.
 - 66 Fromm GH, Chattha AS, Terrence CF, et al. **Role of inhibitory mechanisms in trigeminal neuralgia.** *Neurology* 1981; 31: 683–687.
 - 67 Ichikawa K, Koyama N, Kiguchi S, et al. **Inhibitory effect of oxcarbazepine on high-frequency firing in peripheral nerve fibers.** *Eur J Pharmacol* 2001; 420: 119–122.
 - 68 Preuss CV, Randhawa G, Wy TJP, et al. **Oxcarbazepine.** Treasure Island, FL: StatPearls, 2023.

- 69 Maan JS, Duong TVH and Saadabadi A. **Carbamazepine**. Treasure Island, FL: StatPearls, 2023.
- 70 Johnson M. **Transcutaneous electrical nerve stimulation: mechanisms, clinical application and evidence**. *Rev Pain* 2007; 1: 7–11.
- 71 Garrison DW and Foreman RD. **Effects of transcutaneous electrical nerve stimulation (TENS) electrode placement on spontaneous and noxiously evoked dorsal horn cell activity in the cat**. *Neuromodulation* 2002; 5: 231–237.
- 72 Garrison DW and Foreman RD. **Effects of transcutaneous electrical nerve stimulation (TENS) on spontaneous and noxiously evoked dorsal horn cell activity in cats with transected spinal cords**. *Neurosci Lett* 1996; 216: 125–128.
- 73 Zhou M, Zhang Q, Huo M, et al. **The mechanistic basis for the effects of electroacupuncture on neuropathic pain within the central nervous system**. *Biomed Pharmacother* 2023; 161. DOI: 10.1016/j.biopha.2023.114516.
- 74 Goich M, Bascuñán A, Faúndez P, et al. **Multimodal analgesia for treatment of allodynia and hyperalgesia after major trauma in a cat**. *JFMS Open Rep* 2019; 5. DOI: 10.1177/2055116919855809.
- 75 Di Cesare F, Negro V, Ravasio G, et al. **Gabapentin: clinical use and pharmacokinetics in dogs, cats, and horses**. *Animals (Basel)* 2023; 13. DOI: 10.3390/ani13122045.
- 76 Hayashida KI and Eisenach JC. **Descending noradrenergic inhibition: an important mechanism of gabapentin analgesia in neuropathic pain**. *Ad Exp Med Biol* 2018; 1099: 93–100.
- 77 Suto T, Severino AL, Eisenach JC, et al. **Gabapentin increases extracellular glutamatergic level in the locus coeruleus via astroglial glutamate transporter-dependent mechanisms**. *Neuropharmacology* 2014; 81: 95–100.
- 78 Aupperle RL, Ravindran L, Tankersley D, et al. **Pregabalin influences insula and amygdala activation during anticipation of emotional images**. *Neuropsychopharmacology* 2011; 36: 1466–1477.
- 79 Ikeda H, Yonemochi N, Ardianto C, et al. **Pregabalin increases food intake through dopaminergic systems in the hypothalamus**. *Brain Res* 2018; 1701: 219–226.
- 80 Eroglu C, Allen NJ, Susman MW, et al. **Gabapentin receptor $\alpha 2\delta 1$ is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis**. *Cell* 2009; 139: 380–392.
- 81 Shamsi Meymandi M and Keyhanfar F. **Relative potency of pregabalin, gabapentin, and morphine in a mouse model of visceral pain**. *Can J Anaesth* 2013; 60: 44–49.
- 82 Ifuku M, Iseki M, Hidaka I, et al. **Replacement of gabapentin with pregabalin in postherpetic neuralgia therapy**. *Pain Med* 2011; 12: 1112–1116.
- 83 Esteban MA, Dewey CW, Schwark WS, et al. **Pharmacokinetics of single-dose oral pregabalin administration in normal cats**. *Front Vet Sci* 2018; 5. DOI: 10.3389/fvets.2018.00136.
- 84 Kamp J, Van Velzen M, Olofsen E, et al. **Pharmacokinetic and pharmacodynamic considerations for NMDA-receptor antagonist ketamine in the treatment of chronic neuropathic pain: an update of the most recent literature**. *Expert Opin Drug Metab Toxicol* 2019; 15: 1033–1041.
- 85 Culp C, Kim HK and Abdi S. **Ketamine use for cancer and chronic pain management**. *Front Pharmacol* 2020; 11. DOI: 10.3389/fphar.2020.599721.
- 86 Gurney M. **Subcutaneous ketamine for analgesia**. <https://www.zeropainphilosophy.com/post/subcutaneous-ketamine-for-analgesia> (2023, accessed 29 September 2023).
- 87 Orhurhu V, Orhurhu MS, Bhatia A, et al. **Ketamine infusions for chronic pain: a systematic review and meta-analysis of randomized controlled trials**. *Anesth Analg* 2019; 129: 241–254.
- 88 Finamor F, Scarabelot VL, Medeiros LF, et al. **Involvement of GABAergic, glutamatergic, opioidergic, and brain-derived neurotrophic factor systems in the trigeminal neuropathic pain process**. *Neurosci Lett* 2023; 793. DOI: 10.1016/j.neulet.2022.136970.
- 89 Tremont-Lukats IW, Megeff C and Backonja MM. **Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy**. *Drugs* 2000; 60: 1029–1052.
- 90 Freeman LM, Rodenberg C, Narayanan A, et al. **Development and initial validation of the Cat Health and Wellbeing (CHEW) questionnaire: a generic health-related quality of life instrument for cats**. *J Feline Med Surg* 2016; 18: 689–701.
- 91 Thour A and Marwaha R. **Amitriptyline**. Treasure Island, FL: StatPearls, 2023.
- 92 Huang Y, Chen H, Chen SR, et al. **Duloxetine and amitriptyline reduce neuropathic pain by inhibiting primary sensory input to spinal dorsal horn neurons via $\alpha 1$ - and $\alpha 2$ -adrenergic receptors**. *ACS Chem Neurosci* 2023; 14: 1261–1277.
- 93 Farghaly HSM, Elbadr MM, Ahmed MA, et al. **Effect of single and repeated administration of amitriptyline on neuropathic pain model in rats: focus on glutamatergic and upstream nitrergic systems**. *Life Sci* 2019; 233. DOI: 10.1016/j.lfs.2019.116752.
- 94 Genevois AL, Ruel J, Penalba V, et al. **Analgesic effects of topical amitriptyline in patients with chemotherapy-induced peripheral neuropathy: mechanistic insights from studies in mice**. *J Pain* 2021; 22: 440–453.
- 95 Gurgel JA, Lima-Júnior RC, Rabelo CO, et al. **Amitriptyline, clomipramine, and maprotiline attenuate the inflammatory response by**

- inhibiting neutrophil migration and mast cell degranulation. *Braz J Psychiatry* 2013; 35: 387–392.
- 96 Mealey KL, Peck KE, Bennett BS, et al. **Systemic absorption of amitriptyline and buspirone after oral and transdermal administration to healthy cats.** *J Vet Intern Med* 2004; 18: 43–46.
 - 97 Kraijer M, Fink-Gremmels J and Nickel RF. **The short-term clinical efficacy of amitriptyline in the management of idiopathic feline lower urinary tract disease: a controlled clinical study.** *J Feline Med Surg* 2003; 5: 191–196.
 - 98 Generali JA and Cada DJ. **Amitriptyline: interstitial cystitis (painful bladder syndrome).** *Hosp Pharm* 2014; 49: 809–810.
 - 99 Lee YC and Chen PP. **A review of SSRIs and SNRIs in neuropathic pain.** *Expert Opin Pharmacother* 2010; 11: 2813–2825.
 - 100 Guedes AGP, Meadows JM, Pypendop BH, et al. **Evaluation of tramadol for treatment of osteoarthritis in geriatric cats.** *J Am Vet Med Assoc* 2018; 252: 565–571.
 - 101 Aldrich LA, Roush JK and KuKanich B. **Plasma concentrations of tramadol after transdermal application of a single metered dose of a compounded tramadol gel to cats.** *Am J Vet Res* 2021; 82: 840–845.
 - 102 Verrico CD, Wesson S, Konduri V, et al. **A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain.** *Pain* 2020; 161: 2191–2202.
 - 103 Wang T, Zakharov A, Gomez B, et al. **Serum cannabinoid 24 h and 1 week steady state pharmacokinetic assessment in cats using a CBD/CBDA rich hemp paste.** *Front Vet Sci* 2022; 9. DOI: 10.3389/fvets.2022.895368.
 - 104 Kulpa JE, Paulionis LJ, Egli GM, et al. **Safety and tolerability of escalating cannabinoid doses in healthy cats.** *J Feline Med Surg* 2021; 23: 1162–1175.
 - 105 Deabold KA, Schwark WS, Wolf L, et al. **Single-dose pharmacokinetics and preliminary safety assessment with use of CBD-rich hemp nutraceutical in healthy dogs and cats.** *Animals (Basel)* 2019; 9. DOI: 10.3390/ani9100832.
 - 106 Gutierrez E, Crosignani N, García-Carnelli C, et al. **A case report of CBD and THC as analgesic therapy in a cat with chronic osteoarthritic pain.** *Vet Med Sci* 2023; 9: 1021–1025.
 - 107 Coelho MP, Duarte P, Calado M, et al. **The current role of cannabis and cannabinoids in health: a comprehensive review of their therapeutic potential.** *Life Sci* 2023; 329. DOI: 10.1016/j.lfs.2023.121838.
 - 108 Della Rocca G and Gamba D. **Chronic pain in dogs and cats: is there place for dietary intervention with micro-palmitoylethanolamide?** *Animals (Basel)* 2021; 11. DOI: 10.3390/ani11040952.
 - 109 Quimby JM, Lorbach SK, Saffire A, et al. **Serum concentrations of gabapentin in cats with chronic kidney disease.** *J Feline Med Surg* 2022; 24: 1260–1266.
 - 110 Clark L, Doyle RS and Shroeder S. **Skin lesions following pregabalin administration in a cat.** *Vet Anaesth Analg* 2017; 44: 383–385.
 - 111 Graham LT, Foss KD, Reinhart JM, et al. **The pharmacokinetics of single oral dose extended-release topiramate and adverse effects after multi-dose administration in healthy cats.** *J Vet Pharmacol Ther* 2023; 46: 218–228.
 - 112 Centola SJ, Kaiman G, Rizzo K, et al. **Presumptive renal tubular acidosis secondary to topiramate administration in a cat.** *J Vet Emerg Crit Care (San Antonio)* 2022; 32: 420–425.
 - 113 Indrawirawan Y and McAlees T. **Tramadol toxicity in a cat: case report and literature review of serotonin syndrome.** *J Feline Med Surg* 2014; 16: 572–578.
 - 114 Plumb's. **Cannabidiol (CBD).** <https://app.plumbs.com/drug/1zvENnoNgv0V4WuK8v3dGI> (2022, accessed 29 September 2023).