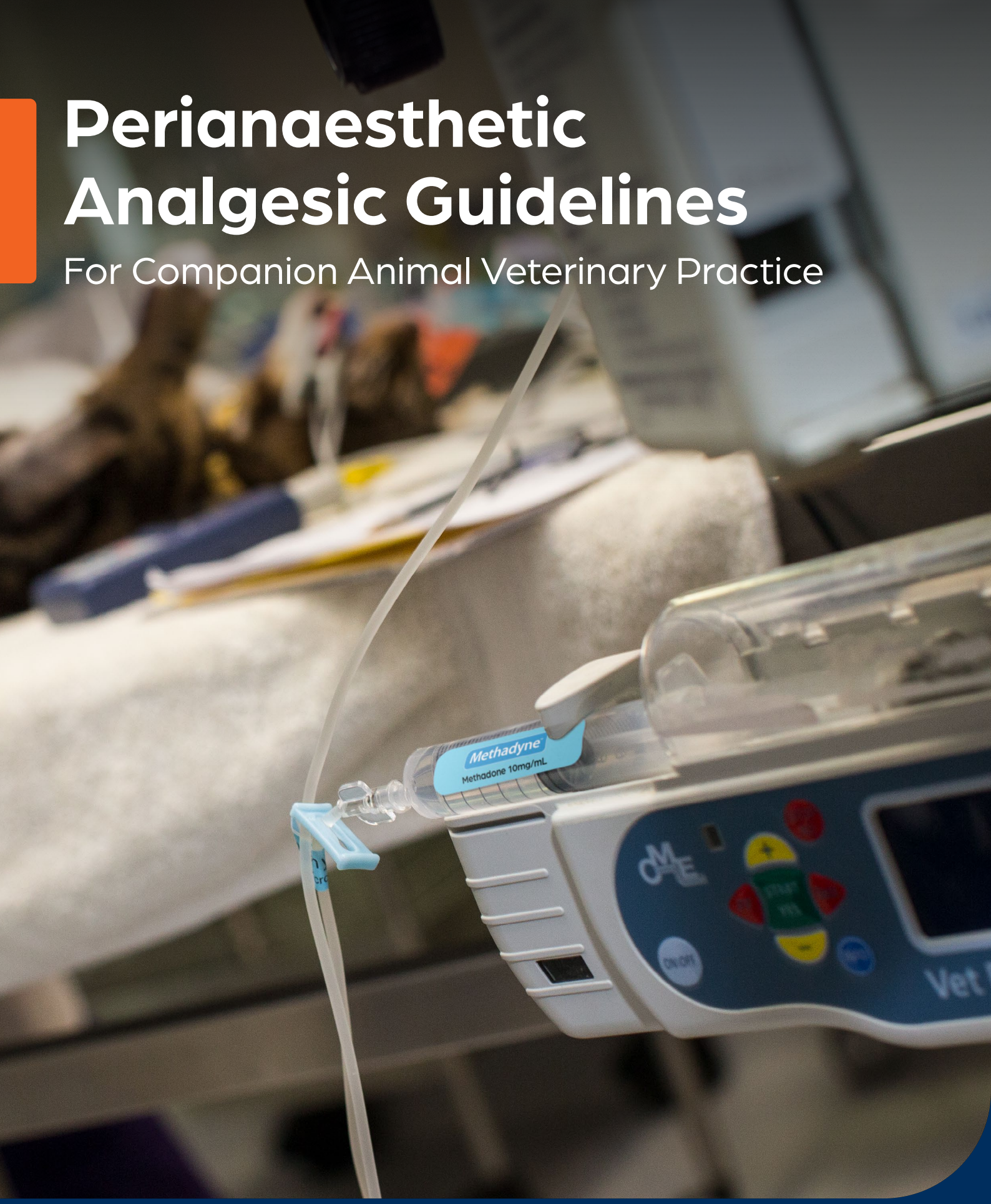
Perianaesthetic Analgesic Guidelines

For Companion Animal Veterinary Practice



AVAAAP
Australian Veterinary Anaesthesia and Analgesia Advisory Panel

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AVAAAP
Australian Veterinary Anaesthesia and Analgesia Advisory Panel

Purpose

The Australian Veterinary Anaesthesia and Analgesia Advisory Panel (AVAAAP) was formed to support veterinary practice in anaesthesia and analgesia in Australia. The AVAAAP is a committee of registered Veterinary Anaesthesia and Analgesia Specialists. The panel works together with Zoetis to assist with the ongoing understanding and advancement of knowledge of the field of veterinary anaesthesia and analgesia.

In recognition of the need to assist the veterinary community in navigating what can be a complex and confusing area of veterinary practice and advocating for best practices in anaesthesia and analgesia, the panel has crafted the AVAAAP Perianaesthetic Analgesic Guidelines for Companion Animal Veterinary Practice.

These Guidelines stem from thorough reviews of published literature, the latest research findings, and expert insights, with a focus on improving outcomes for companion animal patients undergoing painful surgical procedures by promoting the appropriate and optimal use of available products and techniques related to this therapeutic area.

The Guidelines are intended to be a quick reference guide to perianaesthetic analgesia in small animal patients. They include information on clinically relevant pharmacological characteristics of commonly used drugs, practical tips and dosages for their use in anaesthetic and surgical situations, as well as guidance on various techniques for their use.

The AVAAAP has taken the utmost care to ensure that the information contained within these Guidelines is accurate and clinically practical at the time of writing. However, given the changing nature of veterinary medicine and science in general, it is recommended that usage of the information contained herein is considered against current practices and the individual case. No liability is accepted by the AVAAAP as a result of the usage of the information contained in this publication.

Where necessary, all information is attributed to relevant sources. A full reference list can be found at the end of each chapter. Please note, these recommendations are made by the AVAAAP, and some of these recommendations include the "off-label" use of certain medications. These off-label uses are not endorsed by Zoetis.

Zoetis is proud to support this educational initiative, aligning with its broader commitment to the continuous education and professional growth of veterinarians, thereby enhancing the quality of care provided to patients.

Zoetis would like to thank the dedicated members of the AVAAAP for all their hard work and contribution towards these guidelines.

AVAAAP
Australian Veterinary Anaesthesia and Analgesia Advisory Panel

The AVAAAP consists of six panel members, all experts in Veterinary Anaesthesia and Analgesia who have substantial enthusiasm for this field of veterinary science.



Dr. Scott Cumming, BVSc (Hons) MCom MANZCVS (Anaesthesia and Critical Care) MVS (Veterinary Anaesthesia) Dip ECVAA, Registered Veterinary Anaesthesia Specialist

Dr. Scott Cumming is a Specialist Veterinary Anaesthetist and Diplomate of the European College of Anaesthesia and Analgesia. Scott is a graduate of the University of Sydney, is a member of the Australian and New Zealand College of Veterinary Scientists in Anaesthesia and Critical Care, and holds a Masters in Veterinary Anaesthesia. Scott is the founder of Sydney Veterinary Anaesthesia, providing specialist anaesthesia services and training to referral and general practices.



Dr. Jen Davis, BVMS MVSc PhD MANZCVS Dipl. ECVAA, Specialist Veterinary Anaesthetist at Animalius

Jen graduated from Glasgow University in 2005, then spent the next six years working in general veterinary practice in the UK and Australia. In 2011, Jen joined the Murdoch University anaesthesia department where she completed her specialist training in 2015, passing the European College of Veterinary Anaesthesia and Analgesia Diploma examination the same year. Between 2015-2020 Jen worked as a registrar and lecturer in anaesthesia at Murdoch University. Jen is currently working as a specialist veterinary anaesthetist at Animalius, a veterinary specialist hospital in Perth. Jen has also completed a PhD in the diagnosis of peri-operative acute kidney injury in dogs.

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Dr. Eleanor Drynan, BVSc MANZCVS DACVAA, Specialist Veterinary Anaesthetist at WAVES

Ellie graduated from the University of Sydney in 2002 and after a few years working in both mixed and small animal practices in Australia and in England, she commenced a residency in Veterinary Anaesthesia and Analgesia at Murdoch University in 2007. In 2013, she became a Diplomate of the American College of Veterinary Anaesthesia and Analgesia and a registered specialist in Veterinary Anaesthesia. Her main interests are anaesthesia for the emergency and critical care patient. She is currently an anaesthetist at WAVES, a private emergency and specialty practice in Western Australia.

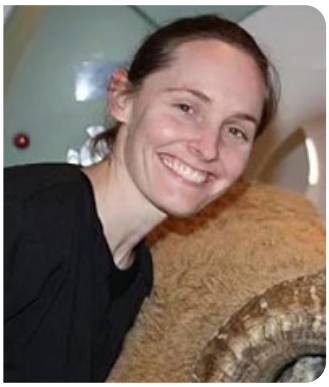


Assoc Prof. Wendy Goodwin, PhD BVSc FANZCVS Anaesthesia and Analgesia Specialist

Wendy Goodwin is a registered veterinarian in Queensland and has worked for the University of Queensland as a clinical anaesthetist since 2010. She received her veterinary degree from the University of Queensland in 2004 and in 2013 was awarded a Doctorate of Philosophy by the University of Queensland for her research thesis 'Studies of Alfaxalone in Horses'. In 2008, she was awarded Membership of the Australian & New Zealand College of Veterinary Scientists in Equine Medicine and in 2013 was awarded Membership in Veterinary Anaesthesia and Critical Care. In 2016, Wendy became a Fellow of the Australian & New Zealand College of Veterinary Scientists in Veterinary Anaesthesia and Critical Care.

Wendy is passionate about veterinary anaesthesia and analgesia and has dedicated the majority of her professional career to pursuing excellence in this field. Her clinical anaesthetic experience has covered a wide range of species including horses, small animal companion animals, farm animals, avian and exotic animals and animals used in scientific research. Wendy has a strong research interest and is keen to further explore research and development opportunities in the veterinary and medical sectors. She has papers published in peer reviewed scientific journals and presented her research findings at international conferences relating to veterinary anaesthesia and pain management.

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Dr. Eleanor Holden, BVSc MANZCVS DipECVAA, Registered Specialist in Veterinary Anaesthesia

After graduating from the University of Queensland, Eleanor spent time in mixed general practice in Lilydale followed by a small animal rotating internship at the University of Melbourne. After returning to the University of Queensland as a clinical anaesthetist for a few years, she undertook a residency in veterinary anaesthesia and analgesia at the University of Glasgow, Scotland. Eleanor became a Diplomat of the European College of Anaesthesia and Analgesia in 2017 and she now works in private practice in Melbourne.



Dr. Heidi Lehmann, BVSc (Hons), BVMS, PGCert, MVSc, MPhil, MANZCVS, DACVAA, Registered Specialist in Veterinary Anaesthesia

After completing veterinary school at Murdoch University, Heidi worked for a few years in small animal general practice south of Perth before she undertook a three-year specialty training programme in Veterinary Anaesthesia and Analgesia back at Murdoch, becoming a board-certified specialist of the American College of Veterinary Anesthesia and Analgesia. Moving to New Zealand to gain research experience in animal welfare, Heidi worked clinically in the Massey University Veterinary Teaching Hospital teaching and mentoring both undergraduate and post-graduate students. With an interest in production animals and biomedical research, she also maintained an active role in swine anaesthesia and welfare management for nutritional research projects.

In 2021, Heidi returned to home shores, working as a Senior Lecturer in Veterinary Anaesthesia at Charles Sturt University in NSW, following which she went to private practice in Melbourne, and currently WA. Heidi maintains an interest in mentoring young vets in the area of anaesthesia and analgesia, and has a particular desire to help elevate the standards of anaesthesia and analgesia in general practice.



PAIN

‘Pain is not just about *what* you feel but *how* it makes you feel’.[1]

Pain – What is it?

Pain is defined as 'An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'. More recently this definition has been updated by the International Association for the Study of Pain (IASP) to include
'...inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain'.[1]

Physiologic pain is a vital function of the body. It is an early warning system of potential or actual injury. Pain has both sensory and emotional (affective) components, making it a multi-dimensional experience that is unique to the individual. It is also affected by species, breed, environmental conditions, and psychological factors such as fear and anxiety.[1-3]

'Pain is not just about what you feel but how it makes you feel'.[1]

Why treat pain?

Untreated pain can lead to consequences including:

- Delayed postoperative recovery
- Immobility and poor appetite
- Increased stress response, leading to a catabolic state that could delay wound healing
- Immunosuppression
- Impaired organ function e.g. respiratory compromise
- Potential for development of peripheral and central sensitisation, resulting in chronic pain.[1-3]

Pain management is an ethical and professional duty of veterinarians. The alleviation of pain is essential to animal welfare and the minimisation of patient suffering. It is key to successful patient outcomes and can enrich the bond between the patient, its owner and the veterinarian.

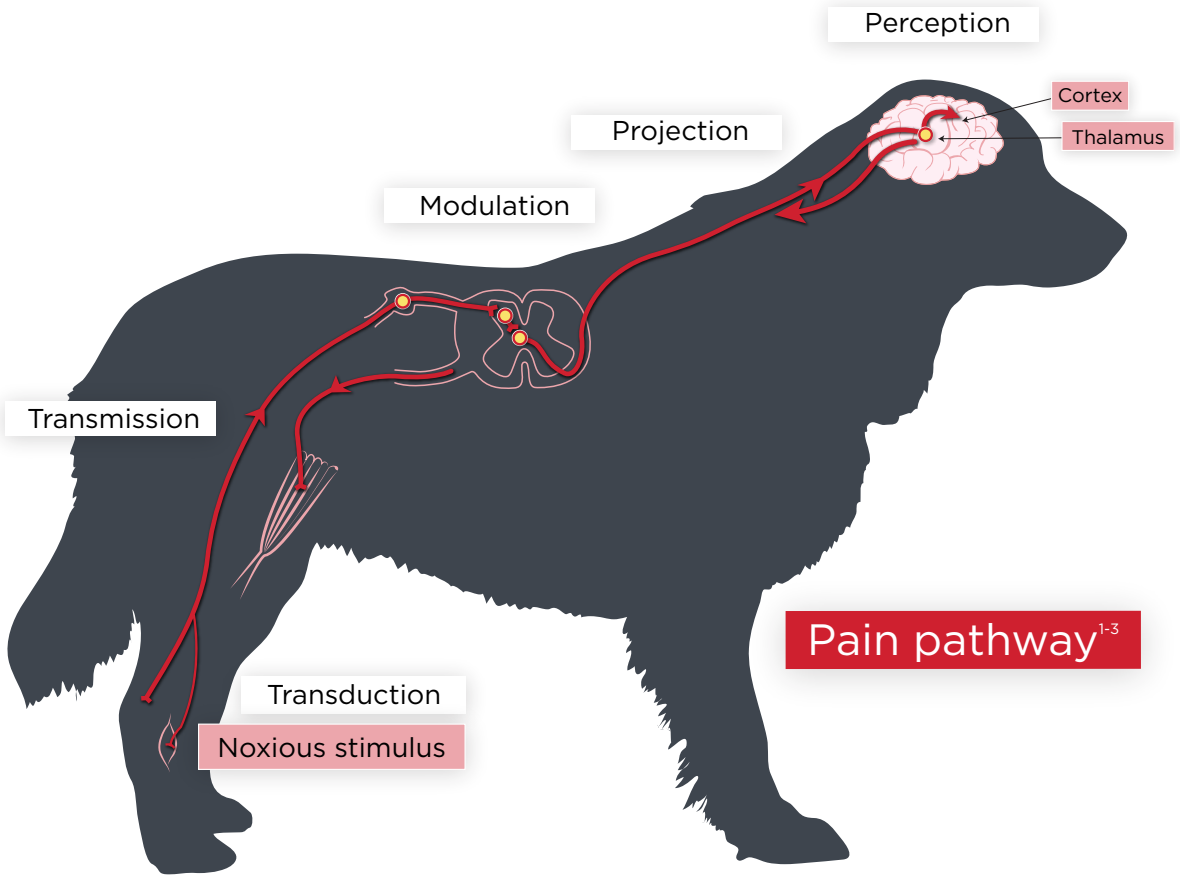


Pain Physiology

Four processes make up the pain pathway. While this may seem simplistic, the physiology of pain is by no means simple, with complex interplay between the peripheral and central nervous systems that occurs constantly.

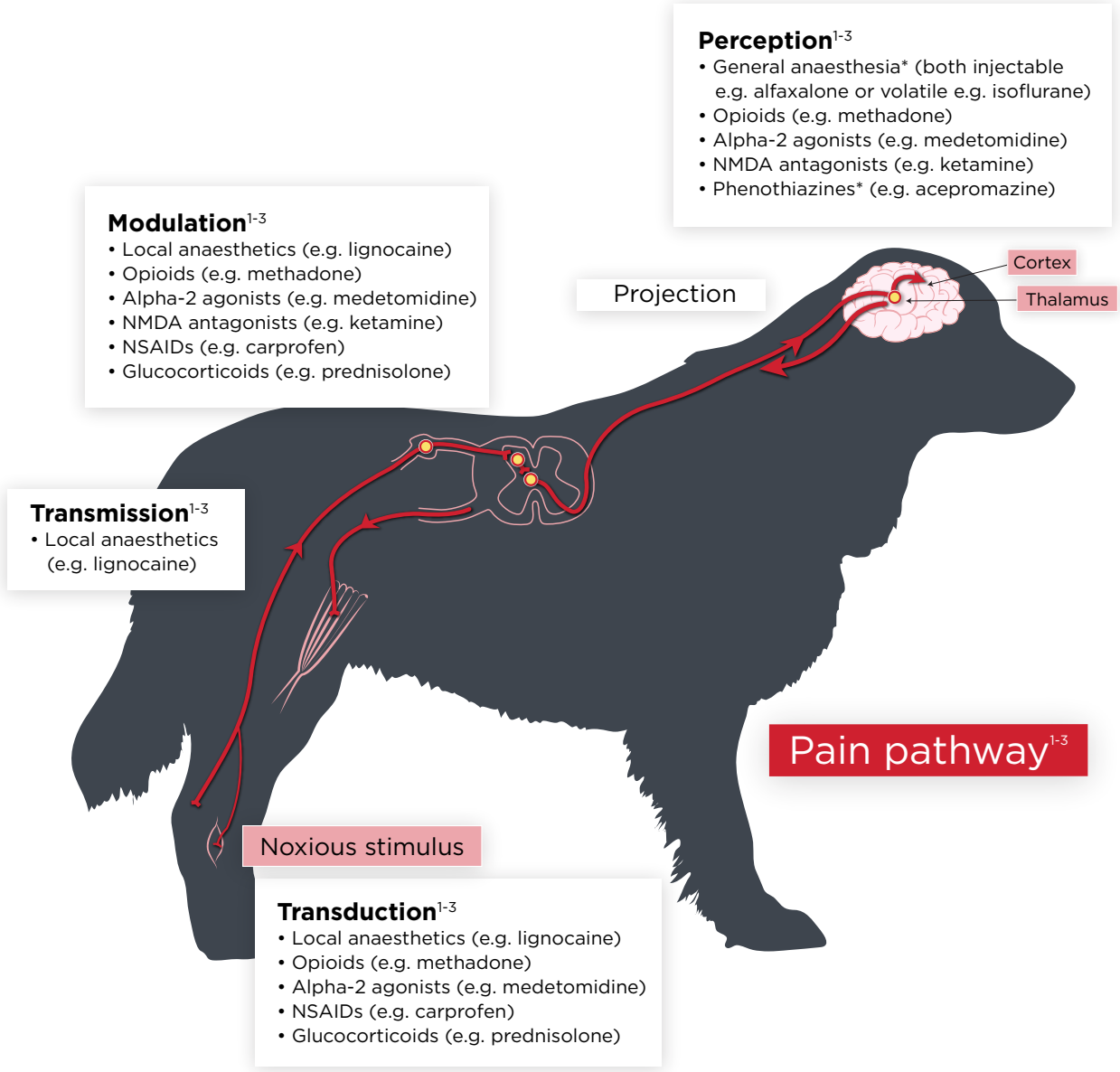
The pain pathway includes:

1. **Transduction** – Nociceptors or free nerve endings detect sensory input, a noxious stimulus, such as that from surgery or trauma. The detected stimulus is turned into a nociceptive or electrical impulse.
2. **Transmission** – The electrical impulse is transmitted by an afferent nerve such as Aδ and C-fibres to the dorsal horn of the spinal cord. From the dorsal horn, impulses are projected along special sensory tracts to higher regions such as the brain.
3. **Modulation** – The nociceptive impulse can undergo signal dampening or amplification along the pathway. This can occur in the spinal cord, thalamus or other areas of the brain.
4. **Perception** – The nociceptive impulse is carried to the brain where it is consciously perceived, resulting in the pain experience.[1-3]



Understanding the major processes in the pain pathway allows a mechanism-based approach to pain management for different disease processes.

The foundation of this is the optimisation of analgesia while minimising the side effects of each drug.



*These are **not** considered analgesics in their own right, but rather alter the perception of pain and therefore should not be used as analgesics, but rather in conjunction with multi-modal analgesia.

Types of Pain

There are different types of pain classification which may require different analgesic strategies.[1-3]

- **Acute pain** – Physiological pain in response to tissue injury. This pain is adaptive, and its purpose is to protect injured tissue. Acute pain is often nociceptive or inflammatory pain. It is commonly associated with surgery or trauma. It is typically short-lasting (days to weeks) and usually straightforward to treat.
- **Chronic pain** – This pain persists beyond the expected time frame for healing (weeks to months/years). It is often more difficult to treat.
- **Inflammatory pain** – This type of pain often occurs in association with perioperative pain and is mediated by the local release of chemicals such as prostaglandins (PGs), leukotrienes (LTs), and histamine, causing increased sensitivity to nociceptors. This pain will often resolve with healing.
- **Neuropathic pain** – Pain that is caused by a lesion or dysfunction in the peripheral or central nervous system. This type of pain can be difficult to diagnose and treat.
- **Cancer pain** – Cancer pain may have both acute and chronic pain components. Pain can arise from primary lesions or be secondary to treatment such as radiotherapy or chemotherapy.
- **Visceral pain** – Pain arising from internal organs. This pain is often dull and aching.
- **Somatic pain** – Pain arising from nociceptors in tissues such as muscle, bone, skin, ligaments, tendons, and joints.

Analgesic Strategies

Continuous, high-frequency pain signals bombarding postsynaptic receptors in the spinal cord lead to more widespread nerve activation than single, short bursts. This is known as 'dorsal horn wind-up' and results in escalated neuronal responses to stimulation, or 'central sensitisation'. Clinically, this increased activity means the patient feels more intense pain from subsequent stimuli for a variable period of time after the initial event. This occurs even in the presence of general anaesthesia.[1-4]

Analgesic strategies can include *pre-emptive* analgesia, which may result in reduced intensity of subsequent pain, thus making pain easier to manage. This is a major reason for analgesic administration prior to a painful procedure or as early as possible in the pain process. *Preventive* analgesia is the concept that there is provision and continuation of pre-emptive analgesia for as long as the pain is present.[2,4]

Underpinning these can be a ***multimodal* approach**, where drugs from different analgesic classes have effects at different levels of the pain pathway, thereby increasing their efficacy and reducing the side effects of any one drug.

There are numerous analgesic drugs available and well-described locoregional analgesic techniques that can be easily incorporated into veterinary practice. Some of these are described later in these Guidelines. Non-pharmacological and complementary strategies can also be beneficial when included in a pain management plan, but are outside the scope of these Guidelines.

Given the subjective nature of pain, there is no analgesic that will suit all patients or all types of pain. Drug class, dose rate, routes of administration and frequency should be tailored to the individual patient.

Pain Recognition and Assessment

Pain is a subjective experience and it is difficult to quantify. The lack of verbal communication in veterinary patients also means there is no gold standard for pain assessment in veterinary medicine.[1]

However, in recent years, significant developments in pain assessment have resulted in pain-scoring tools that are based on pain behaviours and/or facial expressions.

These tools are observer-based questionnaires and have been developed to be multidimensional (i.e. assess pain intensity and its emotional impact) and objective.

Pain scales that have undergone validity testing are recommended. These tools have undergone testing for effectiveness, reliability, responsiveness, and consistency between different pain assessors.

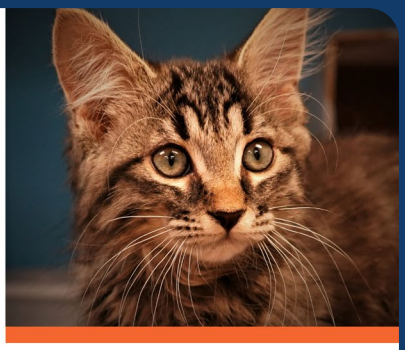
When incorporating a clinic or hospital-wide pain assessment tool, the AVAAAP recommend choosing a tool for each patient that is designed to measure what you want to assess, for example, acute versus chronic pain, dogs versus cats. Ensure the tool is user-friendly and easy to use for everyone involved and integrate it with the patient's hospital chart.

The following are some examples of validated veterinary pain-scoring tools available, which are routinely used and recommended by the AVAAAP. However, many others are available.

Species	Name	Pain assessed	Website
Dogs	Glasgow Composite Measure Pain Scale (Glasgow CMPS-SF)[5]	Acute pain	http://www.newmetrica.com/acute-pain-measurement
	Liverpool Osteoarthritis in Dogs (LOAD)[6]	Chronic - OA	https://my.elanco.com/au/insights-centre/the-liverpool-osteoarthritis-in-dogs
	Canine Brief Pain Inventory (CBPI)[7]	Chronic - OA, cancer	https://www.vet.upenn.edu/docs/default-source/VCIC/canine-bpi.pdf
Cats	Glasgow Composite Measure Pain Scale (CMPS-Feline)[8]	Acute	http://www.newmetrica.com/acute-pain-measurement
	Feline Grimace Scale[9]	Acute	https://www.felinegrimacescale.com
	UNESP Botucatu Multidimensional Composite Pain Scale (MCPS)[10]	Acute	https://www.animalpain.com.br/assets/upload/escala-en-us.pdf
	Feline Musculoskeletal Pain Index (FMSPI)[11,12]	Chronic, OA	https://painfreecats.org/

FELINE GRIMACE SCALE©

FACT SHEET



WHY? Pain-induced behavioral changes are unique and can be subtle in cats

WHAT? The Feline Grimace Scale© (FGS) is a quick and reliable tool for acute pain assessment based on changes in facial expressions

WHEN? Pain assessment should be performed in all cats as often as needed on a case-by-case basis

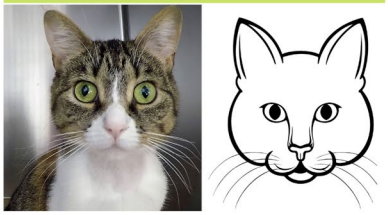
WHO? The FGS can be used by the veterinary health care team and by cat caregivers

HOW?

There are five action units (AU)

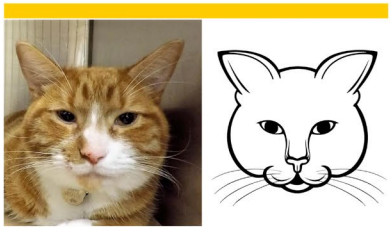
- Ear position
- Orbital tightening
- Muzzle tension
- Whiskers position
- Head position

- Each AU is scored on a 0-2 scale
- The final score is the sum of all scores
- Analgesia is suggested with final score ≥ 4/10



0 = AU is absent

- Ears facing forward
- Eyes opened
- Muzzle relaxed (round shape)
- Whiskers loose and curved
- Head above the shoulder line



1= AU is moderately present*

- Ears slightly pulled apart
- Eyes partially opened
- Muzzle mildly tense
- Whiskers slightly curved or straight
- Head aligned with the shoulder line

* The score of 1 can also be given when there is uncertainty over the presence or absence of the AU



2 = AU is markedly present

- Ears flattened and rotated outwards
- Squinted eyes
- Muzzle tense (elliptical shape)
- Whiskers straight and moving forward
- Head below the shoulder line or tilted down (chin towards the chest)

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Download the FGS App to learn more and practice your skills. Check our linktree for additional information.

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Feline Grimace Scale © Université de Montréal 2019

Effective pain management is crucial

Different situations and patients call for different approaches to analgesia.

These Guidelines provide key information veterinary teams need to make practical and informed decisions about the variety of analgesic drugs available and how best to use each, including:

- Dose and route recommendations
- Effective use of pain scoring
- Choosing the right drug(s) for each situation
- Nuances of drugs to improve analgesic efficacy
- Multimodal techniques.



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OPIOIDS

Opioids are the cornerstone of acute and perioperative pain management in dogs and cats due to their efficacy, ease of administration and relative safety.

Opioids

Opioids are listed on the World Small Animal Veterinary Association (WSAVA) list of essential medicines for cats and dogs[1] and remain the cornerstone of acute and perioperative pain management in cats and dogs due to their efficacy, ease of administration, and relative safety.

Opioids exert their effects by binding to opioid receptors in the peripheral and central nervous systems. Opioids decrease membrane excitability and may decrease both pre- and post-synaptic responses (i.e. decrease transmission of nociceptive stimuli).

Opioids are classified according to their effect at opioid receptors (mu [μ] and kappa [κ] receptors). They can be classified as follows:

Effect		Examples	Relevance
Agonist (aka Full Agonist)	Elicits a maximal response from that receptor	Morphine, methadone, fentanyl and hydromorphone are all pure agonists at the mu receptor	Suited to severe levels of pain and should be the opioid(s) of choice prior to painful surgeries
Partial Agonist	Produces a partial functional response no matter the dose used (ceiling effect)	Buprenorphine at the mu receptor provides dose related analgesia up to a ceiling, the dose beyond which analgesia is not necessarily enhanced with increasing the dose rate	Suited to moderate levels of pain
Agonist/ Antagonist	Dual functions; agonist behaviour at one receptor and antagonist at another	Butorphanol is an antagonist at the mu receptor but an agonist at the kappa receptor	Suited for use in non-painful to mildly painful procedures Note: butorphanol can partially reverse the effects of mu agonists so it should not be administered concurrently unless the goal is to reverse the mu agonist
Antagonist	Produces no functional response and prevents agonists binding to a receptor	Naloxone is an antagonist at all opioid receptors	Can be used to reverse both mu and kappa agonist opioids

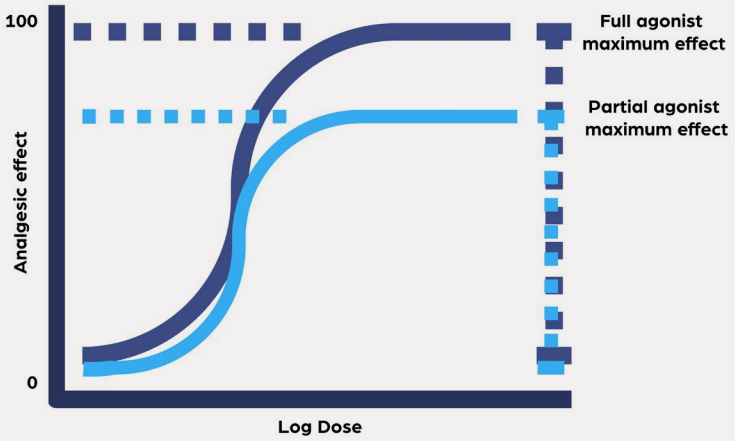


Figure 3a: Full versus Partial Agonists

Figure 3a demonstrates the difference between a full and partial (mu) agonist in terms of their analgesic effects; the full agonist elicits a maximal response from the receptor whereas the partial agonist reaches a ceiling and is only able to produce only a partial analgesic response, even with an increasing dose.

In general, pure mu agonists (e.g. morphine, methadone) provide better analgesia than partial mu agonists (buprenorphine) or mu antagonist-kappa agonists (butorphanol).

Indications

Opioids are used as part of a multimodal analgesic plan to treat acute and perioperative pain. They may also be used to treat chronic pain, but such use is outside the scope of these Guidelines.

The degree and duration of analgesia may vary between individual animals, but will largely depend on the choice of drug, dose, route and species to which they are administered.

Common indications include:

- Sedation and premedication prior to general anaesthesia (alone or combined with alpha-2 adrenoreceptor agonists, acepromazine or benzodiazepines for a synergistic effect).
- Treatment of acute pain e.g. emergency and critical care setting, pain associated with surgery.
- Administered intra-operatively to reduce the requirement for inhalational anaesthesia (less isoflurane is needed and therefore arterial blood pressure is better maintained).

Effective use of pain scoring is essential in ensuring that the dose and route of administration chosen is providing the desired level of analgesia for the individual patient.

The Opioid "Spice Scale": Which Opioid Should I Choose?

The following key has been used throughout this section to help guide the recommended opioid choice(s) based on the anticipated amount of pain, but remember regular pain scoring should always guide dosing intervals and dose rates.

		
Indicated for non-painful to mildly painful procedures	**Indicated for moderately painful procedures**	**Indicated for up to and including severely painful procedures**

"Regular pain scoring should always guide opioid dosing intervals and dose rates."

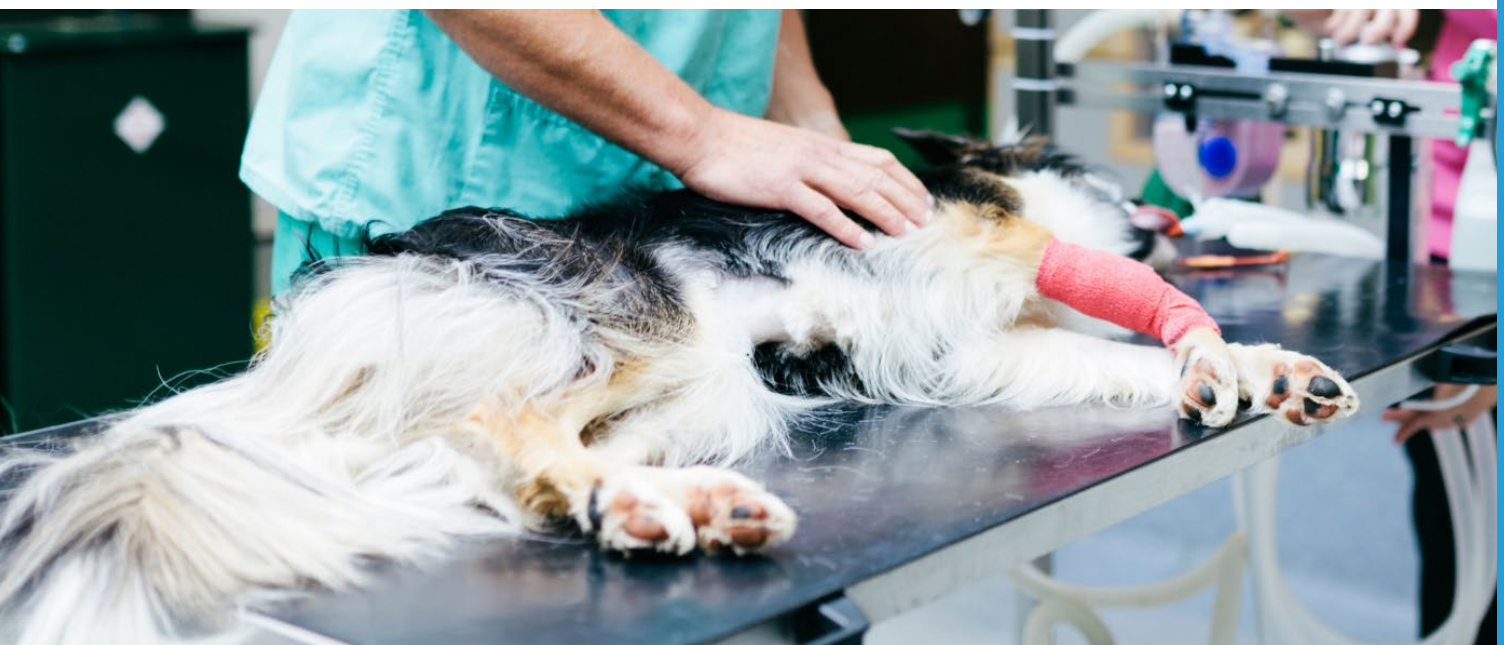
Clinical Pharmacology

Pharmacokinetics:

Measurements of serum or plasma concentrations over time after drug administration characterise absorption, distribution and elimination, and inform dosing regimens. However, plasma levels of opioids often do not match the clinical effect. It is therefore important that experimental nociceptive testing and clinical trials are considered when making recommendations regarding clinical use.

Most opioids are metabolised by the liver prior to excretion and the metabolites of some opioid drugs possess analgesic properties.

The preferred routes of administration are the intravenous (IV) or intramuscular (IM) routes; however, in cats, the oral transmucosal route (OTM) may be used for buprenorphine and methadone. Opioids should not be administered orally due their low bioavailability and therefore lack of analgesic effect.[2] Subcutaneous (SC) and transdermal are unreliable routes of administration due to variable drug absorption. The AVAAAP does not recommend routinely administering opioids via the SC or transdermal route.



Effects:

Opioids are primarily administered for their analgesic or sedative effects. Other effects, including adverse effects, are typically associated with higher doses and tend to be less prevalent in painful animals. Opioids are generally considered safe in animals as adverse effects can be reversed with titration of antagonists such naloxone.

Body system	Effect
Nervous System	Analgesia Sedation Euphoria Dysphoria Excitation Panting (due to change in thermoregulatory set point)
Respiratory System	Depression (dose dependent)¨ Antitussive effects
Cardiovascular System	Bradycardia (due to increased vagal tone) Vasodilation (due to histamine release with IV administration of morphine and hydromorphone)
Gastrointestinal System	Nausea Vomiting (more common with pure mu agonists) Inappetence Constipation Delayed gastric emptying Increased pyloric sphincter tone* and Increased tone of biliary sphincter of oddi* Gastroesophageal reflux
Ocular	Miosis (dogs) Mydriasis (cats)
Urinary System	Urinary retention (due to increased sphincter tone and inhibition of voiding reflex)
Thermoregulatory System	Hypothermia (dogs) Hyperthermia (cats)

¨This is uncommon at clinical dose rates in conscious patients but can occur when opioids are administered with other central nervous system depressants (e.g. inhalational anaesthetic agents and sedatives) and in sick or compromised patients.

*Not recommended for duodenal endoscopy or in animals with biliary obstruction.

Contraindications

Relatively few absolute contraindications to opioids exist. Careful consideration of the desirable and undesirable effects of the opioid drug and the individual needs of the patient should be considered.

Morphine

Mode of action: Pure mu agonist.

Formulation: 5, 10, or 30 mg/mL morphine. Human formulations only available.

Onset of analgesia: 10-15 minutes IV and 30 minutes IM.

Routes of administration, dose and frequency:[2,7]

Dogs	Cats
IM: 0.3-0.5 mg/kg every 2-4 hours	IM: 0.3-0.5 mg/kg every 4-6 hours
IV: 0.1-0.2 mg/kg every 2-4 hours#	IV: 0.05-0.2 mg/kg every 4-6 hours#
CRI: (0.1 mg/kg IV load) 0.1-0.3 mg/kg/hr	CRI: (0.05 mg/kg IV load) 0.05-0.2 mg/kg/hr

#Histamine release can occur after rapid IV injection. Dilution and slow IV administration is recommended.

Morphine can also be administered via the intra-articular, epidural or intrathecal route (preservative free formulations for the latter only). Doses typically range from 0.1-0.2 mg/kg. See sub-section Epidural Anaesthesia and Analgesia in Chapter entitled Local Anaesthetic Agents for further details.

Indications:

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Precautions:

Vomiting can occur after administration in dogs and cats and therefore morphine should be used with caution in animals with upper airway or oesophageal disease and raised intraocular or intracranial pressure. This can be reduced with administration of acepromazine 15 minutes prior[8] and is less likely to occur in painful animals.



Methadone

Mode of action: Pure mu agonist, non-competitive inhibitor of N-methyl-D-aspartate (NMDA) receptors and can reduce re-uptake of norepinephrine and serotonin.

Formulation: 10 mg/mL methadone, registered for use in cats, dogs and horses.

Onset of analgesia: <10 minutes IV and 15 minutes IM.

Routes of administration, dose and frequency:[3,4]

Dogs	Cats
IM: 0.3-0.5 mg/kg every 2-4 hours	IM: 0.2-0.5 mg/kg every 2-4 hours
IV: 0.1-0.2 mg/kg every 2-4 hours	IV: 0.1-0.2 mg/kg every 2-4 hours
CRI: (0.2 mg/kg IV load) 0.1 mg/kg/hr	CRI: (0.1 mg/kg IV load) 0.05-0.1 mg/kg/hr^

^Clinical recommendation as no published studies are currently available.

Methadone has been administered via the oral transmucosal (OTM) route (0.6 mg/kg) to cats experimentally and shows promise but clinical efficacy information is lacking at this time.[5]

Indications:

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Methadone has similar physiological effects in dogs and cats as other mu agonists but is less likely to cause vomiting. Therefore, methadone should be used in preference to morphine or hydromorphone in animals where vomiting is undesirable, such as dogs and cats with oesophageal or upper airway disease (e.g. brachycephalic syndrome), raised intracranial or intraocular pressure.[4]

In addition to action at the mu receptor, methadone contributes to analgesia via other pathways and may be suitable for the prevention and treatment of chronic pain.

Precautions:

Due to potential risk of serotonin toxicity, do not use in patients receiving monoamine oxidase inhibitor (MAOI) drugs and use with caution in patients receiving selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs).[6]

Fentanyl

Mode of action: Pure mu agonist.

Formulation: 50 µg/mL fentanyl. Also available in transdermal patches (25, 50, 75, 100 µg/hr). Human formulations only available.

Onset of analgesia: <10 minutes IV.

Routes of administration, dose and frequency:[2,9]

Dogs		Cats	
IV: 2-5 µg/kg every 20-30 minutes		IV: 1-3 µg/kg every 20-30 minutes	
CRI: (2-5 µg/kg IV load) 3-6 µg/kg/hr⌘		CRI: (2-5 µg/kg IV load) 2-5 µg/kg/hr⌘	
Transdermal patch:ϒ		Transdermal patch:Ñ	
<10 kg	25 µg/hr patch	<10 kg	25 µg/hr patch
10-20 kg	50 µg/hr patch		
20-30 kg	75 µg/hr patch		
>30 kg	100 µg/hr patch		

⌘Doses can be increased for inhalant anaesthetic-sparing effect or for maximum analgesia. For example, intra-operative doses of up to 20 µg/kg/hr for cats and 40 µg/kg/hr for dogs. If these higher doses are used, it is imperative that clinics use capnography and have access to ventilatory support due to the significant risk of associated respiratory depression and apnoea.

ϒTransdermal patches in dogs reach therapeutic plasma concentration in approximately 24 hours and are maintained for 72 hours following patch placement.

ÑTransdermal patches in cats reach therapeutic plasma concentration in approximately 12 hours and are maintained for 72 hours following patch placement.

Indications:

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Due to the short duration of action, fentanyl is commonly administered as an infusion.

Precautions:

Following placement of transdermal patches, absorption of fentanyl and analgesic efficacy shows wide individual variation; therefore, transdermal patches should only be used as part of a multimodal analgesic plan in conjunction with regular pain scoring.

If higher CRI dose rates are used intra-operatively for inhalational sparing effects, respiratory depression and bradycardia are likely. Dysphoria may also occur during the recovery period and additional sedation should be on hand or administered pre-emptively.

In cats, intra-operative fentanyl CRIs do not reduce inhalational anaesthetic requirements to the same extent as in dogs.

Due to potential risk of serotonin toxicity, do not use in patients receiving monoamine oxidase inhibitor (MAOI) drugs.[6]

Buprenorphine

Mode of action: Partial mu agonist, with many of the same actions as the pure mu agonists. Dose related analgesia may be provided up to a 'ceiling,' the dose beyond which analgesia is not necessarily enhanced with increasing the dose rate.

Formulation: 0.3 mg/mL buprenorphine registered for use in dogs, cats and horses.

Onset of analgesia: 30-45 minutes for IM or IV; may be slightly longer for oral transmucosal (OTM) route (in cats).

Routes of administration, dose and frequency:[2,10]

Dogs	Cats
IV or IM: 0.01-0.04 mg/kg every 4-8 hours	IV, IM or OTM[Δ]: 0.02-0.04 mg/kg every 4-8 hours

[Δ]OTM route may be suitable as "hands-off" analgesia in cats, when part of a multimodal analgesia plan with regular pain scoring.

Subcutaneous administration and the use of transdermal patches in cats is not recommended.[10,11]

Transdermal patches have been used in dogs as part of a multimodal analgesic plan for mild to moderate pain but show variable absorption and analgesic efficacy. As better alternatives are available, the use of buprenorphine transdermal patches in dogs is not routinely recommended.

Indications:

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For mild to moderate pain as part of multimodal analgesic plan. For example, in cats when combined with an NSAID, buprenorphine may provide adequate analgesia for dental and neutering procedures; however, it is not sufficient for acute pain relief following major orthopaedic procedures.[10]

Alternate buprenorphine formulations such as extended-release injectable formulations and transdermal solutions are not available in Australia at this time.

Precautions:

Dose related analgesia may be provided up to a 'ceiling,' the dose beyond which analgesia is not necessarily enhanced with increasing the dose rate.

Competitively binds to the mu opioid receptor with high affinity, displacing full mu agonists.

- May lessen the effect of full mu agonists administered prior to or concurrently, reducing the level of analgesia.

Butorphanol

Mode of action: kappa agonist and mu antagonist.

Formulation: 10 mg/mL butorphanol registered for use in dogs, cats and horses.

Onset of analgesia: <15 minutes IV (effect is mainly sedation with limited analgesia provided).

Routes of administration, dose and frequency:[7]

Dogs	Cats
IV, IM: 0.2-0.4 mg/kg every 2-4 hours CRI: (0.1 mg/kg load) 0.1-0.2 mg/kg/hr[+]	IV, IM: 0.2-0.4 mg/kg every 2-4 hours

[+]for sedation only and in dogs, not cats.

Indications:



Provides mainly sedation, with limited analgesia and is best reserved for use in non-painful to mildly painful conditions.

- Butorphanol is most often combined with other agents, such as alpha-2 agonists and acepromazine, to provide short term sedation for procedures (e.g. diagnostic imaging, bandage changes etc).

Low doses of butorphanol can be used to partially reverse pure mu agonists by blocking their action at mu receptors. Note that this will reduce the level of analgesia.



"Butorphanol provides limited analgesia and is best reserved for use in non-painful to mildly painful conditions."

Naloxone: Opioid Antagonist

Mode of action: antagonist (competitive) at mu, kappa and delta opioid receptors.

Formulation: 0.4 mg/mL naloxone hydrochloride. Human registered formulations only available. The AVAAAP recommend that all clinics who use full mu agonists should also stock naloxone.

Onset of analgesia: <2 minutes IV and duration of action approximately 20 minutes.

Routes of administration, dose and frequency:[2]

Dogs	Cats
IV, IM: 0.04 mg/kg every 20–60 minutes[Φ]	IV, IM: 0.04 mg/kg every 20–60 minutes[Φ]

[Φ]In painful patients, 1 vial (0.4 mg/mL) can be diluted in 10 mL of saline. The solution can then be titrated slowly to effect to reverse the undesirable opioid-related effects but avoiding complete antagonism of the analgesia.

Indications:

Reversal of the effects of opioids.

- Used to reverse the unwanted side effects of opioids such as central nervous system depression (over-sedation), respiratory depression, hypotension, dysphoria etc.
- **It is important to note that analgesic effects may also be reversed.**

Precautions:

Analgesic effects of opioids may also be reversed.

The short duration of effect (approximately 20 minutes) may be less than that of the opioid whose effects it is desired to counteract. Therefore, it may be necessary to administer additional doses and close monitoring of the patient is warranted.

"The AVAAAP recommend that all clinics routinely using opioids should also stock naloxone."

Tramadol

Tramadol is a centrally acting analgesic drug with a dual mechanism of action; binding at mu-opioid receptors and inhibiting noradrenaline and serotonin re-uptake (among other mechanisms). The opioid agonist effects are mediated by a metabolite of tramadol, *O*-desmethyl tramadol, which is not produced in clinically significant concentrations in dogs.[2] In fact, evidence for the analgesic efficacy of tramadol for postoperative pain management in dogs is very low.[12] The AVAAAP do not recommend the routine use of tramadol for acute pain management in dogs. In comparison, there is some evidence for the use of tramadol for multimodal analgesia in cats; however, regular pain assessment should always be performed.

Dose:[10]

Cats
PO: 4 mg/kg every 6 hours[➢]
IV, IM: 2-4 mg/kg

[➢]PO is known to be unpalatable (bitter taste) in cats; may not be a suitable route of administration in some patients.

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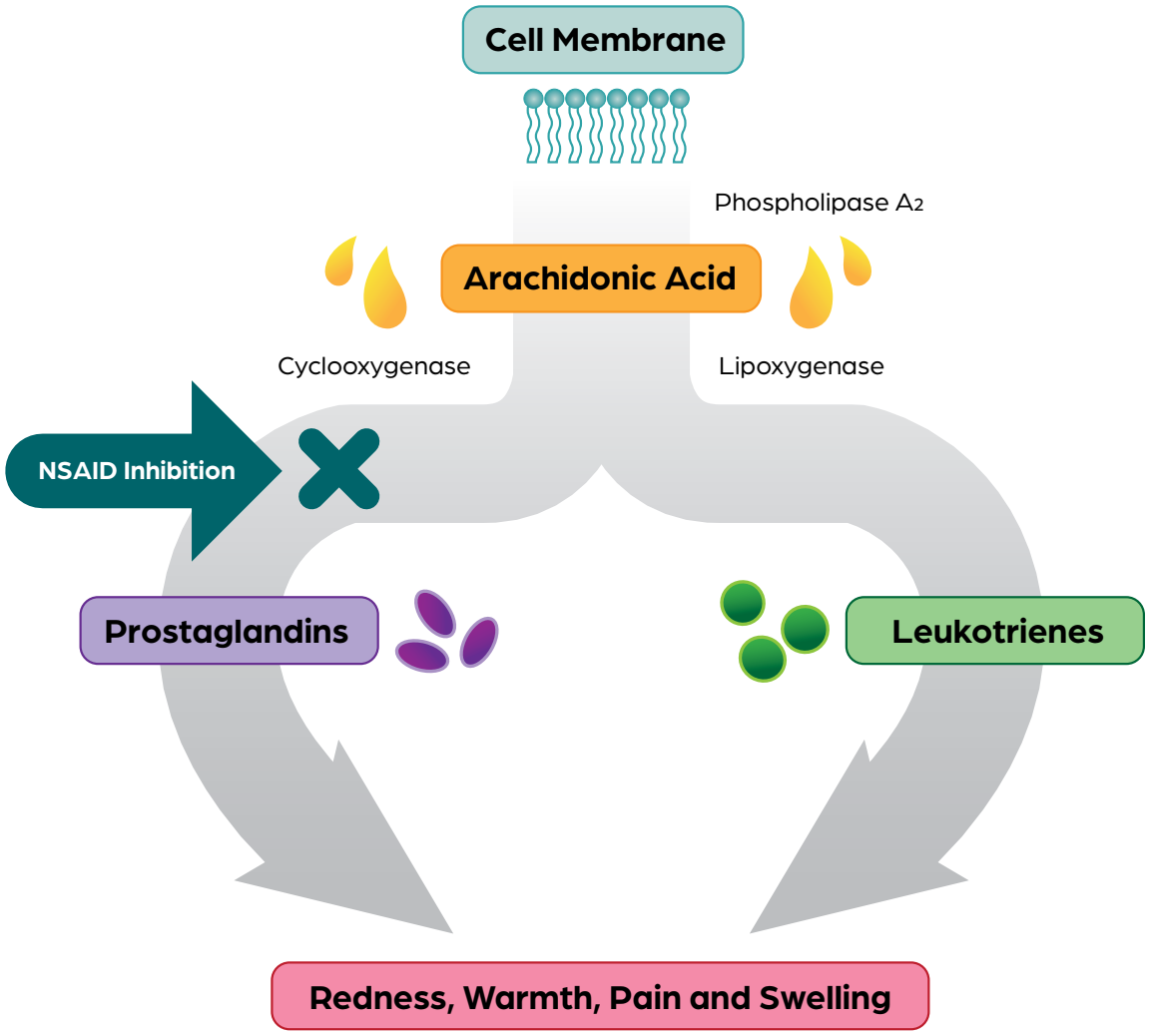
NON–STEROIDAL ANTI–INFLAMMATORY DRUGS (NSAIDS)

NSAIDs are a reliable tier 1[1] analgesic for the management of acute inflammatory pain in dogs and cats. Combining NSAIDs with opioids represents the ideal approach to multi-modal pain management in the perioperative setting.

Clinical Effects and Mechanism of Action

Non-steroidal anti-inflammatory drugs (NSAIDs) provide analgesia through inhibition of inflammation and associated pain.

During tissue trauma, arachidonic acid in cell membranes is exposed and cyclooxygenase (COX) enzymes catalyse its conversion to prostaglandin (PG) H_2, the first step in the inflammatory cascade. Whilst intended to trigger healing of damaged tissues, this process is responsible for the production of a range of inflammatory mediators within the body, whose presence results in pain and inflammation. NSAIDs inhibit COX activity, blocking the propagation of this cascade, and production of further prostaglandins and other cytokines, resulting in anti-inflammatory, analgesic and anti-pyretic effects.



COX enzymes are also involved in many physiological and homeostatic functions, such as maintenance of renal blood flow, haemostasis and gastroprotection. As a result, the use of NSAIDs, particularly in a perioperative setting, may also result in adverse effects.

The availability of a wealth of efficacy, pharmacokinetic and safety data for veterinary registered NSAIDs makes them important first-line medications[1] for the management of acute pain in small animals. Understanding their effects and side effects enables veterinarians to determine when and how to use them perioperatively.

Adverse Effects

In addition to their role in inflammation, prostaglandins have a protective effect, regulating function and blood flow in the gastrointestinal tract and kidneys and regulating platelet activity. Most of the adverse effects of NSAIDs are due to their effect of disrupting these functions through inhibition of prostaglandin and/or thromboxane production via COX inhibition. The three main potential adverse consequences are:

- Gastric ulceration
- Renal injury
- Platelet dysfunction.

Based on the assumption that COX-1 was a "constitutive" enzyme responsible for the physiological protective functions, while COX-2 was an "induced" enzyme that produced inflammation, most NSAIDs currently registered for use in cats and dogs have been developed to inhibit COX-2 to a greater extent than COX-1 in an attempt to minimise the adverse effects.

However, the functions of the two enzymes are not as clearly demarcated as first thought; COX-2 also produces prostaglandins involved in healing of mucosal erosions, has anti-inflammatory actions, and is involved in maintenance of renal blood flow, while COX-1 may contribute to pro-inflammatory prostaglandin synthesis. Nevertheless, side effects may be less common with contemporary NSAIDs that favour COX-2 inhibition over COX-1.

Precautions

The mechanism responsible for NSAID-related kidney injury involves a reduction in renal blood flow. Any disease process that reduces cardiac output and/or blood pressure will exacerbate reductions in renal blood flow and make ischaemic nephrotoxicity more likely. Common situations where this may occur include:

- Dehydration
- Hypovolaemic shock
- Anaesthesia-related hypotension
- Congestive heart failure.

NSAIDs should be used only with great care and accompanied by diligent monitoring in these patients.

Additionally, NSAIDs should be avoided or used with extreme care in:

- Animals with pre-existing renal disease
- Animals receiving any other drugs with potential nephrotoxic effects (e.g. gentamicin, ACE-inhibitors, diuretics)
- Animals with, or at increased risk for developing coagulopathies
- Animals under 6 weeks of age due to their immature kidneys, lower concentration of circulation proteins (NSAIDs are highly protein bound) and limited drug elimination capabilities.[2]

Contraindications

NSAIDs are contraindicated for use in:

- Animals with gastrointestinal disorders such as haemorrhage or mucosal damage/irritation
- Pregnant and lactating animals, based on research in human medicine and a lack of veterinary-specific studies.[3]

When to Administer

While many NSAIDs are registered for pre-operative use, the safe and optimal timing for peri-operative NSAID administration remains controversial. Due to NSAID-induced inhibition of autoregulation of renal blood flow, hypotension during anaesthesia increases the risk of ischaemic kidney injury if NSAIDs are administered pre-operatively.

Thus, it may be more appropriate to administer NSAIDs post-operatively or immediately prior to recovery, when the anaesthetist is confident of cardiovascular stability (e.g. mean arterial blood pressure is consistently >70mm Hg). In many cases, adequate analgesia can be provided by other means (i.e. full mu-agonist opioids) pre-operatively, so there is little additional benefit to administering a NSAID at this time.



Image courtesy of Dr. Eleanor Holden

Pre-operative NSAIDs should always be avoided in animals where significant intra-operative haemorrhage is anticipated or where the risk of hypotension is expected to be increased.

In healthy, non-geriatric animals with provision of appropriate IV fluids, adequate blood pressure monitoring and the ability to respond promptly to any hypotension (through use of anti-muscarinics, inotropes and vasopressors), the risk associated with pre-operative administration may be minimised.

Tolfenamic acid and ketoprofen should not be administered pre-operatively as they may adversely affect platelet function.[4]

Changing NSAIDs

Washout periods should be observed when switching between NSAIDs or from a NSAID to a corticosteroid. Evidence-based information on ideal length of washout periods is limited, with recommended protocols including waiting a minimum of 5–7 days, depending on the half-life of the first drug, before administering the second.[4,5]

When the change is due to adverse effects, a longer washout period is recommended.

Common Non-Steroidal Anti-Inflammatory Drugs for Perioperative Use:*

Drug	COX-2 Selectivity	Dose Rate		Time to Peak Blood Levels
		Dogs	Cats	
Carprofen	Preferential COX-2 inhibition	4 mg/kg IV/SC; 2–4 mg/kg/day PO	4 mg/kg IV/SC ONCE ONLY; tablets not registered for use	1–3 hours after oral administration[9,11] ; 2.5 hours after SC injection (dog)[11]
Meloxicam	Preferential COX-2 inhibition	0.2 mg/kg SC/IV; after 24 hours can be followed with 0.1 mg/kg/day PO	0.3 mg/kg SC ONCE ONLY **OR** 0.05 mg/kg/day PO (with no SC administration)^	1.5/2.5 hours after SC injection (cat/dog)[8]
Robenacoxib	Selective COX-2 inhibition	1–2 mg/kg SC ONCE; after 24 hours can be followed on with PO dosing 1 mg/kg for up to 12 days	1–2 mg/kg SC ONCE; after 24 hours can be followed on with PO dosing 1 mg/kg for up to 6 days	90 minutes after SC injection (dogs), 30 minutes after oral administration; do not give with food[12]

*See specific product labels for further information on dosage, specific precautions and contraindications.

^Off-label dosing of meloxicam in cats at 0.2 mg/kg SC injection, followed 24 hours later by 0.05 mg/kg PO once daily for up to 4 days has been recommended by an international consensus of veterinary anaesthetists.[7]

NSAIDs are appropriate for use across the spectrum of mild to severe pain as part of a multimodal analgesia approach. Regular pain scoring should be used to assess for adequate patient response.

Atypical NSAIDs

Paracetamol (acetaminophen)

Paracetamol is often referred to as an atypical NSAID due to inhibitory effects on a variant of COX-1 known as COX-3. However, its mechanism of action is complex, with demonstrated actions at prostaglandin H_2 synthase, transient receptor vanilloid 1 (TRPV1) receptors, serotonergic inhibitory pain pathways, and the endogenous cannabinoid system.

While paracetamol may be useful in some patients, it is not recommended as a first line peri-operative analgesic due to scarcity of published species-specific pharmacokinetic and pharmacodynamic data and lack of a veterinary specific product in Australia.

Clinical investigations into the use of paracetamol as an analgesic for acute pain in dogs have produced conflicting results[13], and it is likely that plasma concentrations capable of a significant analgesic effect are not reached at commonly used dosing practices.

Nevertheless, paracetamol may be considered in animals where NSAIDs are contra-indicated, or may be used in combination with NSAIDs when an adjunct is required.

The suggested dosing range for short-term peri-operative use is 15-30 mg/kg IV or PO every 6–8 hours.[14]

Paracetamol should not be used in cats due to likelihood of severe toxicity (primarily methaemoglobinaemia and hepatotoxicity, sometimes accompanied by acute nephrotoxicity) even at low doses.[13,14]

Paracetamol use should be avoided in dogs with hepatic disease.

Grapiprant

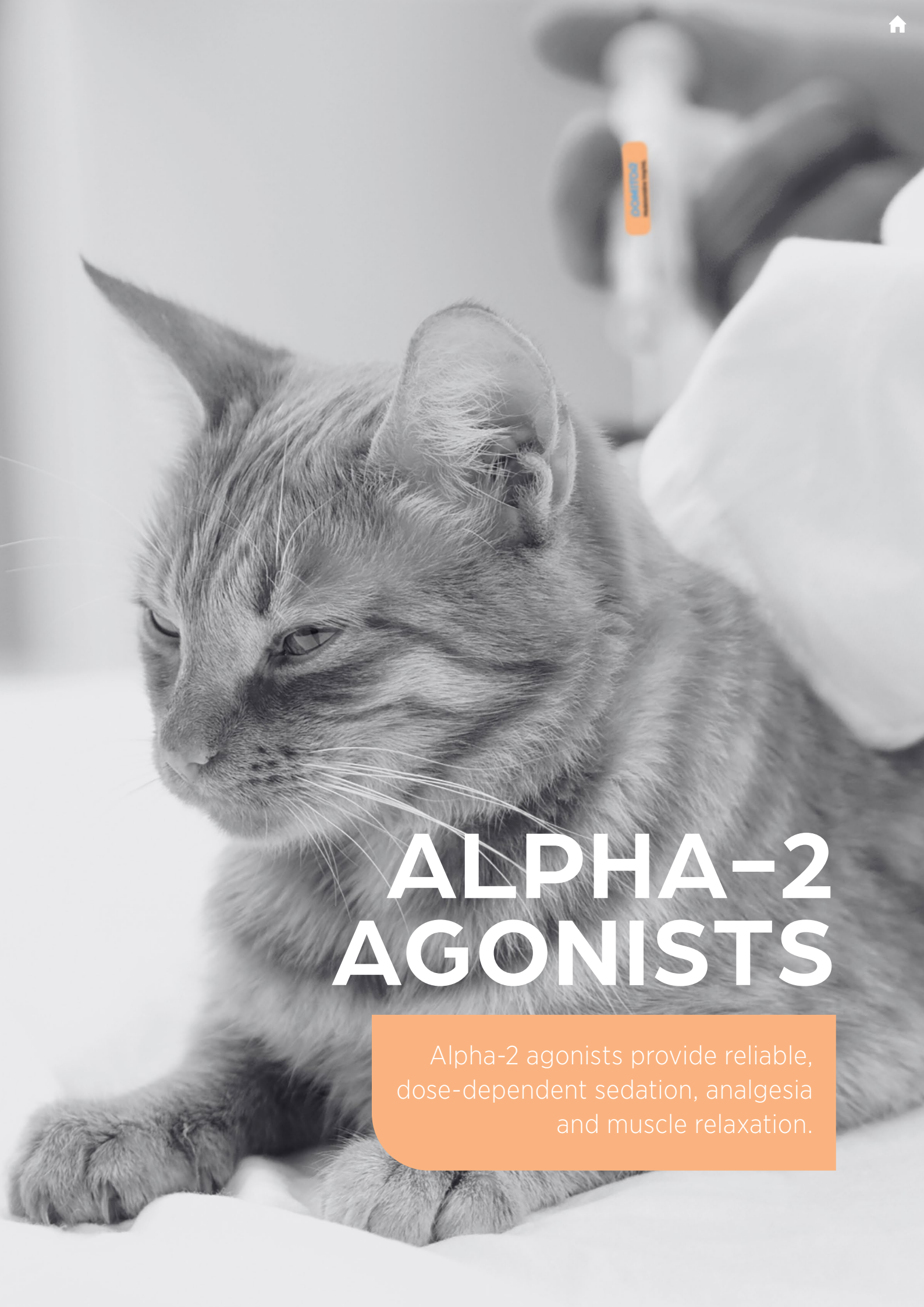
Grapiprant blocks the prostaglandin receptor EP4, rather than COX. The EP4 receptor is responsible for some nociceptor sensitisation and inflammation[14], with a minimal role in gastrointestinal, renal, and platelet functions. Grapiprant is currently registered for use in dogs with osteoarthritis in Australia.[15]

While the EP4 receptor has been identified as the primary receptor responsible for mediating pain and inflammation during osteoarthritis, other prostaglandin receptors are activated during inflammation and are expected to contribute to peri-operative pain. For this reason, while there has been some investigation into the use of grapiprant for acute post-operative pain in dogs, the AVAAAP does not currently recommend this medication as a first line treatment in place of a NSAID in this setting.

Grapiprant may be considered in dogs where NSAIDs are contraindicated due to adverse gastrointestinal effects (noting that vomiting, diarrhoea, and inappetence have been reported with grapiprant). Grapiprant is only available in an oral formulation at this time.[15]

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ALPHA-2 AGONISTS

Alpha-2 agonists provide reliable, dose-dependent sedation, analgesia and muscle relaxation.

Alpha-2 Adrenoreceptor Agonists (aka Alpha-2 Agonists or α-2 Agonists)

Alpha-2 adrenoreceptor agonists are used in small animal patients to induce sedation, muscle relaxation and analgesia. These effects are achieved through activation of the alpha-2 receptors, part of the sympathetic branch of the autonomic nervous system.[1-5]

The sedation provided by these agents is reliable, with predictable timing and often a significant reduction in consciousness.

These drugs act on alpha-2 receptors found throughout the body, including in the central nervous system, cardiovascular, respiratory, gastrointestinal and genitourinary systems.

At the cellular level, the primary mechanism of action is the coupling of the alpha-2 receptor to an inhibitory G-protein.[4,7] This interaction down-regulates intracellular activity, particularly in the CNS, leading to the clinical effects of sedation and pain relief.



Medetomidine and Dexmedetomidine

Mode of action:

Medetomidine and dexmedetomidine have an approximately 1620:1 ratio of action on alpha-2 receptors versus alpha-1.[1,2,16]

Formulations:

Medetomidine: 1 mg/mL (1000 µg/mL) preserved injectable solution, registered for use in cats and dogs.

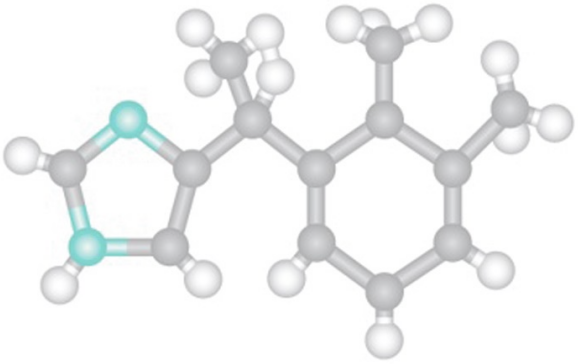
- Medetomidine is a racemic solution consisting of two optical isomers in equal parts – dexmedetomidine and levomedetomidine. Levomedetomidine is considered to be a pharmacologically inactive component.[1]

Dexmedetomidine: 0.5mg/mL (500 µg/mL) preserved injectable solution, registered for use in cats and dogs.~

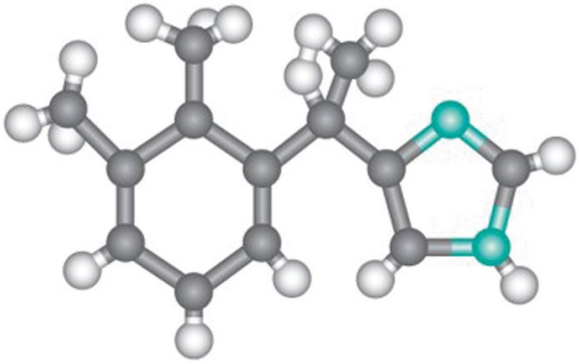
- Contains only the active dexmedetomidine isomer.[1]

~0.1mg/mL (100 µg/mL) preserved injectable solution, registered for use in cats and dogs is available overseas, but not in Australia currently.

Levomedetomidine: inactive



Dexmedetomidine: active



Pharmacokinetics & Pharmacodynamics

Onset:

IV: Within 5 minutes (both medetomidine and dexmedetomidine in dogs and cats); peak effects in 15-30 minutes.

IM: Within 10-15 minutes (medetomidine > dexmedetomidine); peak effects within 30 minutes.[10,13-15,17]

Elimination:

Medetomidine: Metabolised by the liver; elimination half-life of ~1 hour in dogs and 1.5 hours in cats.

Dexmedetomidine: Slightly shorter half-life, leading to a reduced duration of effect.[17-21]

During the first 30 minutes after IM administration, both sedation scores and analgesic response were greater following medetomidine compared with dexmedetomidine.[10,13-15,17]

Clinical Effects

Sedation:



Dose and sedation level can be tailored for the patient and procedure, ranging from mild to deep: depth of sedation is dose-dependent, but there is a ceiling effect whereby increasing doses do not increase sedation depth.[1-5,12,14,15,18] Muscle relaxation accompanies sedation.[1-3,10,18]

Opioid combinations enhance sedation quality and consistency.

Duration: 30-90 minutes; full recovery to standing within 180 minutes in dogs and cats.[4,14,15]

Analgesia:

Analgesia is dose-dependent, lasting 50-80% of the duration of sedation for both medetomidine and dexmedetomidine: they provide similar analgesia at equipotent doses.[7,11,12,15,18,20-23]

They interact synergistically with opioid receptors in the CNS, enhancing analgesia when combined with opioids and provide effective analgesia for major surgeries when combined with pure mu-agonist opioids.[1-5,7,10]

Anaesthetic-sparing effects:

Alpha-2 agonists reduce the required doses of induction and maintenance agents by up to 70%, including reducing isoflurane MAC requirements.[1,2,5]



Cardiovascular effects:

A bi-phasic effect on blood pressure occurs:[1-5,8]

Contraction of vascular smooth muscle (peripheral vasoconstriction)



Increase in systemic vascular resistance



Increase in mean arterial pressure (initial hypertension)



Baroreceptor reflex-induced bradycardia



Reduction in cardiac output



Gradual reduction in blood pressure back to normal levels (normotension); bradycardia may persist

Cardiovascular effects occur even at low doses of 1 µg/kg of medetomidine in dogs.

- More pronounced at doses >2 µg/kg.[8]

Reductions in cardiac index occur across a wide dose range, in a non-linear manner.[8] Higher doses may cause mucous membrane pallor or cyanosis; less likely with typical clinical doses.

- Oxygen supplementation via face mask or endotracheal tube is recommended, should this occur.

Effects on other body systems:[1-3,5,10]

Body system	Effect
Respiratory System	Slight decrease in respiratory rate, offset by increased tidal volume
Nervous System	Intracranial pressure reduced through decreased cerebral blood flow
Gastrointestinal System	Reduced motility, blood flow and gastric acid secretion Vomiting (cats>dogs)
Hepatic System	Reduction in blood flow, slowing drug metabolism
Reproductive System	Modification of uterine contractility
Endocrine System	Decreased ACTH secretion, lowering cortisol and the stress response Reduced ADH release; can lead to diuresis Reduced insulin release; can lead to hyperglycaemia
Thermoregulatory System	Depressed thermoregulation (but peripheral vasoconstriction helps limit heat loss)

Clinical Considerations

Patient selection:

Alpha-2 agonists are best suited to patients with an ASA Status Classification of I or II.[1-3] Use in patients with ASA >II should be evaluated individually, considering specific pathophysiology:

- **Age:** Dose adjustments may be needed, but age alone does not preclude use.[1-7]
- **Cardiovascular considerations:**
  - > Caution is advised in patients where increased systemic vascular resistance is contra-indicated (e.g. mitral valve disease, dilated cardiomyopathy).[1-3]
  - > May be contraindicated in patients with limited cardiac output.[1]
  - > Medetomidine has been used in felines with left ventricular outflow obstructions due to hypertrophic cardiomyopathy.[28]
- **Hepatic/renal impairment:** Use is feasible due to rapid clearance and available antagonists;
  - > Dexmedetomidine may be preferable for patients with hepatic disease.
- Note that safety has not been established during pregnancy and lactation.

Administration:

Preferred routes: Intravenous (IV) and intramuscular (IM); reduced dose for IV administration.

Repeat dosing (e.g. intraoperative) is possible, with timing guided by drug duration and cardiovascular effects.

Infusion can be started anytime, usually after induction of anaesthesia.

Suggested Dosing (Analgesic Doses)

Note: both medetomidine and dexmedetomidine exhibit allometric scaling, whereby larger animals require lower doses for equivalent effects compared with smaller animals.

Medetomidine:[2,3]

Dogs*	Cats*
IM: 3-15 µg/kg	IM: 5-20 µg/kg
IV: 2-10 µg /kg	IV: 5-10 µg/kg
CRI: 0.5-1 µg/kg/hr^	CRI: 0.5-1 µg/kg/hr^
Intraoperative IV bolus: 1-2 µg/kg#	Intraoperative IV bolus: 1-2 µg/kg#

Dexmedetomidine:[2,3,24]

Dogs*	Cats*
IM: 2-10 µg/kg	IM: 2.5-10 µg/kg
IV: 1-5 µg/kg	IV: 2.5-6 µg/kg
CRI: 0.25-0.5 µg/kg/hr^	CRI: 0.25-0.5 µg/kg/hr^
Intraoperative IV bolus: 0.5-1 µg/kg#	Intraoperative IV bolus: 0.5-1 µg/kg#

*Note these are not the recommended label doses for these medications. Alpha-2 agonists are best suited to allometric dosing, that is dosing on a body surface area basis rather than a bodyweight basis, such that large dogs are given a relatively lower dose than smaller dogs.

^Dilution with sterile water for injection is required and a syringe driver is highly recommended. Diluting medetomidine to 5 µg/mL for cats and small dogs and 10 µg/mL for larger dogs and dexmedetomidine to 2.5 µg/mL for cats and small dogs and 5 µg/mL for larger dogs is useful.

#If IM boluses are being used intraoperatively, rather than IV boluses, the lower end of the IM ranges listed above are recommended.

Anticholinergics and Alpha-2 Agonists:

Current research does not demonstrate a clear improvement in cardiovascular function with concurrent use of these two medications. More concerningly, the anticholinergic-induced increase in heart rate combined with the alpha-2 agonist mediated hypertension may increase myocardial oxygen tension, oxygen demand, and cardiac workload and promote dysrhythmias, which is undesirable.[10]

Atipamezole: an Alpha-2 Reversal Agent

Formulation:

5 mg/mL atipamezole in an aqueous preserved formulation, registered for use in cats and dogs.[1,2]

Mode of action:

Atipamezole is a competitive antagonist of centrally and peripherally located alpha-2 adrenoreceptors.[23,29] It has a high degree of alpha-2 versus alpha-1 selectivity.[10]

Pharmacokinetics and pharmacodynamics:

Onset of action: IM: ~6 minutes.[23]

Dogs typically start recovering from sedation within 3-30 minutes.[22,29]

Half-life is twice that of medetomidine:[10]

- Reduces the likelihood of re-sedation;
- May impair repeat dosing with medetomidine or dexmedetomidine.

Effectively reverses sedative and analgesic effects of medetomidine or dexmedetomidine, but only partially reverses cardiorespiratory effects.[14,15]

Clinical considerations:

The decision to use atipamezole should factor in the removal of all medetomidine or dexmedetomidine effects, including analgesia.

- Reversal may increase nociception and reduce the anaesthetic plane;
- Alternative pain management may be required to maintain patient comfort, especially during anaesthesia.
- Not all patients receiving medetomidine or dexmedetomidine will need atipamezole for recovery, particularly with low doses or if sufficient time has passed since administration of the alpha-2 agonist.

The IM route is generally preferred due to the rapid changes in cardiovascular parameters, e.g. reduced systemic vascular resistance (easing of vasoconstriction); but

- In emergency situations, the IV route may be used.[10]

Antagonism of medetomidine or dexmedetomidine with atipamezole will negate analgesic properties as well as tranquilisation. Antinociceptive properties may decline more rapidly than sedation.[23]

Clinical Application:

Dose:[31]

	Dogs*	Cats*
Medetomidine reversal	5x that of medetomidine dose OR equal volume#	2.5x that of medetomidine dose OR half the volume#
Dexmedetomidine reversal	10x that of dexmedetomidine dose OR equal volume%	5x that of dexmedetomidine dose OR half the volume%

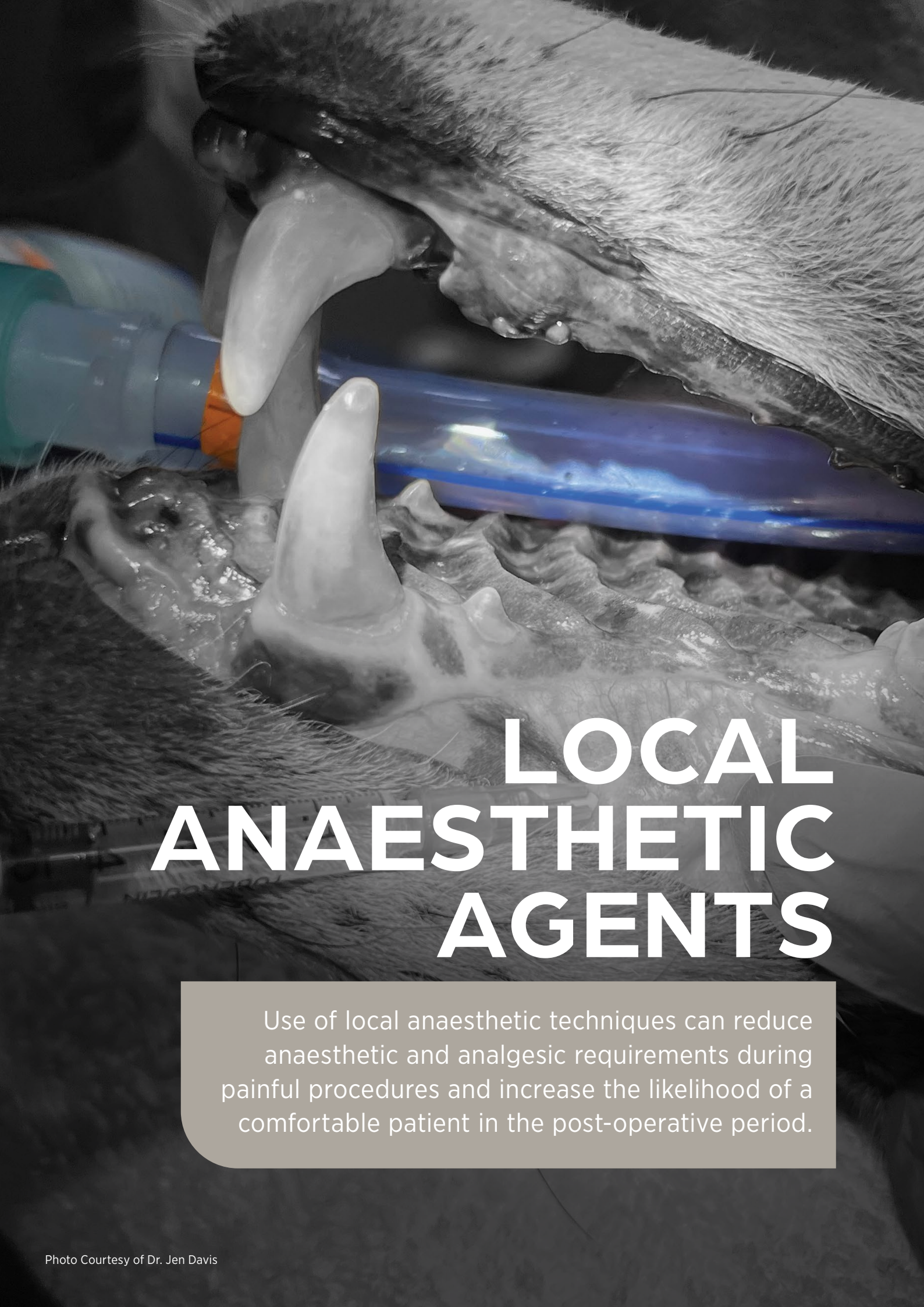
#When formulated at 1 mg/mL medetomidine. %When formulated at 0.5 mg/mL dexmedetomidine.

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LOCAL ANAESTHETIC AGENTS

Use of local anaesthetic techniques can reduce anaesthetic and analgesic requirements during painful procedures and increase the likelihood of a comfortable patient in the post-operative period.

Photo Courtesy of Dr. Jen Davis

Local Anaesthetic Agents

Local anaesthesia provides a pharmacological blockade of pain signal transmission at the level of (usually) peripheral nerves. These agents cross cell membranes and block sodium channels in the nerve, stabilising the membrane and preventing depolarisation and thus the transmission of nociceptive signals to the central nervous system. For the duration of a local anaesthetic agent's action, pain signals will not be transmitted to the spinal cord. This prevents the risk of central sensitisation, dorsal horn wind up and the physiological responses that accompany pain.

These agents may be used at the site of pain, by local infiltration in the area of an incision, in the mass or tissue to be excised or by topical application in mucosa or skin. They can also be used epidurally and perineurally to block a nerve "upstream" of the site of trauma, allowing a small amount of local anaesthetic to block pain over a wider region than by local infiltration.

Absorption of local anaesthetics depends on the site of injection, dose and patient. Generally, vascular absorption is not the desired effect. Rather, uptake and binding in nerve fibres at the site of injection is the goal. Nerve blocks can be utilised in a wide range of procedures and are commonly employed for orthopaedic procedures and dental extractions, and more recently, abdominal and thoracic procedures.



Photo Courtesy of Dr. Jen Davis

Lidocaine [Lignocaine]

Formulation:*

1% (10 mg/mL) and 2% (20 mg/mL) injectable; some formulations contain adrenaline [epinephrine]

2% gel for topical skin application

5% cream combined with prilocaine (EMLA)

5% spray combined with or without phenylephrine for intubating

5% topical patches.

*Note: some of these formulations are not registered for use in animals and therefore use would be considered off-label.

Onset of action:

2-5 minutes.[1,2]

EMLA: Applied topically to clipped fur, 20 minutes for cats,[3] 60 minutes for dogs,[4] with the area protected by an occlusive dressing.

Duration:

40–120 minutes depending on site and dose administered.[1,2]

The addition of a vasoconstrictor such as adrenaline [epinephrine] can prolong the duration of action due to delayed systemic absorption.

Dose:

Safe dose: 2–4 mg/kg. Recommended maximum safe doses vary, ranging from 6–10 mg/kg in dogs and 3–6 mg/kg in cats.[1,2-6]

The dose will be dependent on type of block being performed: 0.25–1 mL of 2% (20 mg/mL) lidocaine for dental blocks, depending on the site and the size of animal.

Indications:

Infiltration and topical anaesthesia, peripheral nerve blocks, epidural blocks and as an intravenous analgesic adjunct (see Additional Analgesic Techniques chapter for further information).

It can also be used for intravenous regional anaesthesia (IVRA), where a tourniquet is placed for a surgical procedure of the distal limb and lidocaine administered intravenously distal to the tourniquet. Doses of 2.5-5 mg/kg are reported for lidocaine IVRA.[9]

Other non-anaesthetic indications include: treatment of ventricular arrhythmias, and MAC-sparing[5], it may also have some prokinetic[8] and anti-inflammatory effects, which may be advantageous in some situations.

Precautions:

Cats may be more sensitive to CNS and cardiac effects of lidocaine, so high doses should be avoided in this species.

Contraindications:

Do not use in patients with known hypersensitivity to amide-class local anaesthetics or with severe heart blocks.

Adverse effects:

CNS signs occur at lower plasma concentrations than cardiac depression, although this is a more reliable finding in dogs than cats.[9]

Bupivacaine

Formulation:^

0.5% injectable solution.

^Note: there are no registered bupivacaine formulations for animal use and therefore use is considered off-label.

Onset of action:

20-30 minutes.[1,5,6]

Duration:

3-8 hours depending on site and dose administered.[1-5]

Dose:

Do not exceed a maximum dose of 2 mg/kg in dogs. Recommended maximum doses in cats vary, ranging from 1-2 mg/kg.[2-6]

Dose will depend on the block being performed. Some blocks may require dilution of the local anaesthetic to achieve an appropriate volume to be administered without surpassing the toxic dose.

For dental blocks, a volume of 0.25-1 mL of 0.5% (5 mg/mL) bupivacaine for each block is normally adequate.

Indications:

Infiltrative anaesthesia, peripheral nerve blocks and epidurals.

Precautions:

Cats may be more sensitive to CNS and cardiac effects of bupivacaine.

Not appropriate for IVRA.

Contraindications:

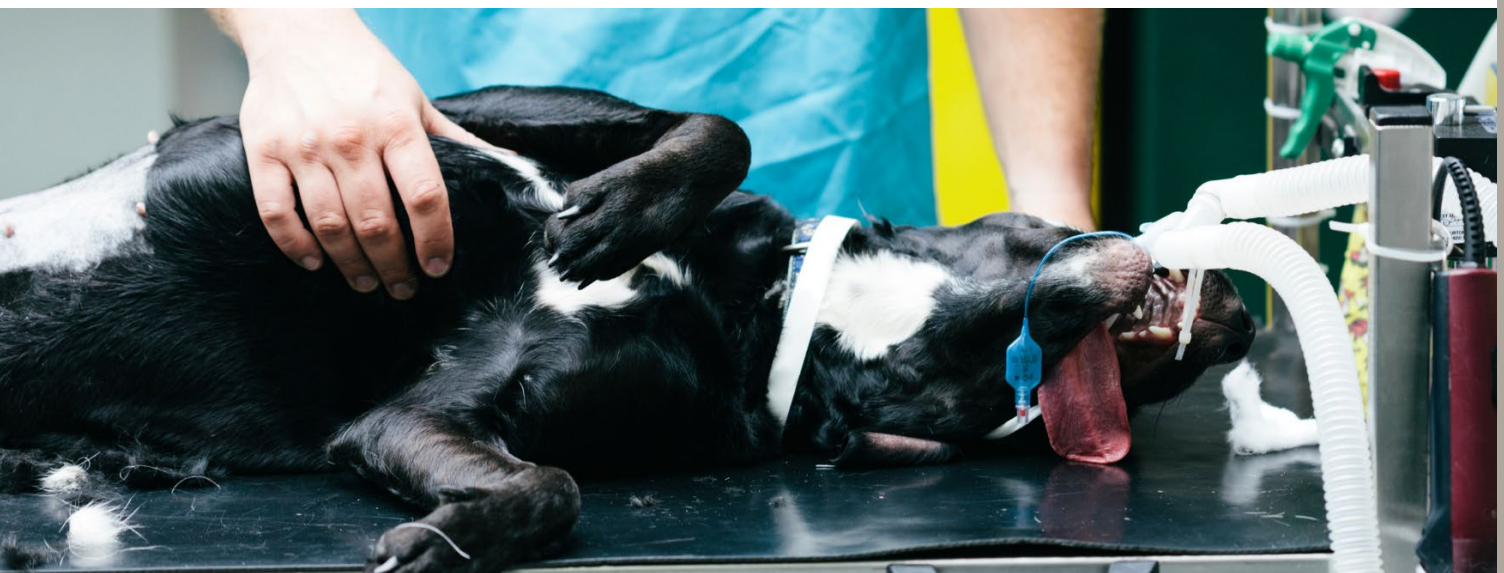
Bupivacaine has a narrower safety margin than lidocaine and should not be administered intravenously.

It is not used for topical anaesthesia.[6]

Adverse effects:

CNS signs and cardiovascular collapse occur at similar blood concentrations of bupivacaine.

Seizures may be observed at the same time as cardiovascular collapse, rather than preceding it, as with lidocaine.



Ropivacaine

Formulation:#

0.2% injectable

0.75% injectable

1% injectable

Note: there are no registered ropivacaine formulations for animal use and therefore use is considered off-label.

Onset of action:

5-10 minutes.[9]

Duration:

2.5–4 hours,[12] 5–8 hours.[9]

Dose:

1-3 mg/kg in dogs.[9]

1-2 mg/kg in cats.

Indications:

Local and regional anaesthesia.

Ropivacaine has a lower potential for inducing cardiovascular and CNS toxicity when compared with bupivacaine.

Contraindications:

Ropivacaine should not be administered intravenously.[5]

Adverse effects:

Cardiovascular collapse can occur at very high doses,[12] but ropivacaine still appears to have increased safety and decreased cardiovascular adverse effects when compared to lidocaine or bupivacaine.

How to Minimise the Risk of Toxicity

- Always check the total calculated safe dose for the animal.
- Aspirate before any nerve block injection to avoid intravascular injection.
- Monitor for any change in heart rate and blood pressure such as arrhythmias, bradycardia or vasodilation.
- Monitor for any change in neurological status such as sedation or seizures.

Examples of Commonly Used Blocks

Dental Blocks

1. Maxillary Nerve Block

Desensitises maxilla and incisor bone and associated soft tissue, hard and soft palate, upper dental arcade, upper lip and nostrils.

2. Mandibular Nerve Block

Desensitises the mandibular teeth, rostral lower lip and rostral intermandibular region.

Desensitises the soft tissue and periosteum of the lingual side of the mandible and floor of the mouth. Rostral two-thirds of the tongue may also be desensitised if the lingual nerve is affected due to diffusion.[2,8]

Note: for most dental nerve blocks, appropriate needle sizes are 22–25 G. Volumes of bupivacaine or lidocaine administered for nerve blocks can be approximately considered as follows, always remembering to calculate the total appropriate dose of local anaesthetic for the animal:

- Cat or small dog = 0.1-0.3 mL
- Medium-sized dog = 0.5 mL
- Large dog = 1 mL
- Extra-large dog = 1.5 mL.

Testicular Block for Castration

Areas desensitised are the spermatic cord in addition to associated structures. Use of this block will provide analgesia during a castration.[13]

Needle size: 22-25G depending on the size of the patient.

Ovarian Splash Block for Ovariohysterectomy

Absorption of the local anaesthetic through mucosal surfaces, desensitising the ovarian pedicle provides pain relief during an ovariohysterectomy.

Alternative method is to infiltrate the mesovarium: inject directly into or drip over the mesovarium ligament.

Line Block

Also known as field or incisional nerve block.

Desensitises dermal, hypodermal, and potentially muscular layers along the line of injection depending on the depth administered.

Indications: Can be used for any surgery.

Needle size: variable, will depend on size of area to be desensitised and the size of patient.

Epidural Anaesthesia and Analgesia

A commonly used technique in small animal medicine, epidural anaesthesia and analgesia provides regional anaesthesia and analgesia for painful procedures in the caudal body. Depending on the volume and drug administered, in addition to gravity, epidural anaesthesia can be successfully used to provide complete analgesia to abdominal, pelvic, hindlimb, perineal and tail regions.

Epidurals are usually performed with animals either anaesthetised or heavily sedated. The most common position used is with the patient placed in sternal recumbency and the hind legs extended forward under the body. This positioning facilitates palpation of landmarks and opens the lumbosacral space for injection. It is referred to as the lumbosacral approach.[14]



Volume of epidural injection:

For regional anaesthesia, the volume administered determines the cranial spread and thus the area anaesthetised. A volume of 0.1 mL/kg of either 2% lidocaine or 0.5% bupivacaine is appropriate for procedures involving the tail or perianal region, while 0.2 mL/kg, up to a maximum volume of 6 mL is usually sufficient for procedures involving the pelvic limbs.[2,6,16]

The volume required can be made up with 0.9% sodium chloride.

Animals should be kept in sternal recumbency for 2-5 minutes after administration to ensure bilateral spread of epidural anaesthesia.

Use of other medications via epidural administration:

Ketamine, alpha-2 agonists and other medications have been trialled for epidural use, both alone and in conjunction with local anaesthetics or opioids. These agents may increase the magnitude or duration of analgesia above that offered by previously discussed options.

Opioids in epidurals:

Morphine is commonly used for epidural analgesia due to its low lipophilicity (compared with methadone) giving a slow onset but long duration of analgesia. Additionally, it is available as a preservative-free formulation. When administered epidurally, morphine provides analgesia for 6–24 hours, compared to 4 hours when administered intravenously. The onset of analgesia following an epidural infusion is approximately 20 minutes. Morphine is often administered in conjunction with a local anaesthetic to produce effective regional anaesthesia, followed by long-lasting analgesia.[6]

Doses for epidural anaesthesia and analgesia:[2,6,16]

Drug	Class	Dose	Duration of Effect
Lidocaine 2%	Local anaesthetic	0.1-0.2 mL/kg	1–2 hours
Bupivacaine 0.5%	Local anaesthetic	0.1-0.2 mL/kg	4–6 hours
Morphine	Opioid	0.1 mg/kg	6–24 hours

The maximum volume administered should not exceed 6 mL.[2]

Preservatives in many drug formulations may be neurotoxic if administered epidurally, so preservative-free options and further information should be sought for this use.[17,18]

Epidural administration can markedly reduce anaesthetic requirements and improve muscle relaxation during a procedure due to the potent analgesia.

Potential complications:

- Hypotension: use of intravenous fluid therapy, anticholinergics and vasopressors should be used as indicated.[6,15]
- Pelvic limb ataxia: may impact neurological assessment.
- High (cranial) spread of local anaesthetic: may block the intercostal or phrenic nerves causing hypoventilation or apnoea.[6]
- Dural puncture (indicated when CSF backflow is noted): higher risk in cats; a sacrococcygeal approach may help to reduce risk.[6,14]
- Vasodilation to caudal sites: promoting hypothermia and increased risk of bleeding during surgery to these areas.
- Toxicity (local anaesthetics): with inadvertent injection into a blood vessel.
- Spinal cord damage.
- Iatrogenic introduction of infection.
- Pruritus at site of injection.
- Delayed or abnormal hair growth over the site of injection.
- Poor results / incomplete blockade: there often can be a small window of sensation in the blockade produced by epidural anaesthesia.
- Urinary retention: urine output should be monitored and a urinary catheter placed or bladder nursing if necessary.

Contraindications:

Relative:

- Inability to locate landmarks (e.g. pelvic injuries, obesity).
- Hypovolaemia or hypotension: due to possible sympathetic blockade.
  > It is important to monitor blood pressure closely.
  > If there is refractory hypotension present prior to the administration of the epidural, it is recommended to remove the local anaesthetic component. The opioid may still be administered.

Absolute:

- Coagulopathies: may result in uncontrollable haemorrhage.
- Infection, particularly of the skin at site of needle placement.

For more information on specific local block techniques including epidurals, the AVAAAP recommend the following resources:

- Campoy L et al. Small animal regional anesthesia and analgesia 1st Edition 2013. © Wiley-Blackwell
- Lerche P et al. Handbook of small animal regional anesthesia and analgesia techniques 1st Edition 2016. Kindle Edition. © Wiley-Blackwell
- Read MR et al. Small animal regional anesthesia and analgesia 2nd Edition 2024. © Wiley-Blackwell
- Lamont L et al. Lumb and Jones Veterinary Anaesthesia and Analgesia 6th Edition 2024. © John Wiley and Sons.

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ADDITIONAL ANALGESIC TECHNIQUES

Further analgesic options include analgesic-dose ketamine and multi-agent infusions.



Additional Analgesic Techniques

Additional analgesic medication administration via single boluses and infusions can both be part of successful perioperative pain management.

The medications and methods discussed in this section may be useful in a variety of cases, including when other analgesics are providing insufficient pain relief, are not available, are being avoided or when there is increased risk of intractable pain and central sensitisation.

Each of the analgesic options presented here have demonstrated dose-sparing effects on inhalant anaesthetics.[1,2] This can help reduce the incidence of adverse effects associated with inhalant agents while facilitating smooth anaesthesia with a comfortable recovery period in animals undergoing general anaesthesia.



Ketamine

Ketamine is a NMDA receptor antagonist. These receptors are implicated in central sensitisation and the wind-up phenomenon, therefore NMDA receptor antagonists may be useful in both acute and chronic pain therapy.[1]

Ketamine can be used for analgesia, sedation and anaesthesia depending on the dose administered. Analgesic doses are significantly lower than those used for anaesthesia and can provide adjunctive analgesia, anti-hyperalgesia and may prevent the development of neuropathic or maladaptive pain.[1]

Ketamine also potentiates the antinociceptive effects of opioids and alpha-2 agonists.

Ketamine alone is not adequate for surgical pain relief but can be a useful adjunct to other analgesics.[3]

*Note that use of ketamine as an analgesic is off-label.

An analgesic-dose ketamine infusion offers ongoing analgesia with less risk of adverse effects than higher single doses.

Mode of action:

NMDA receptor antagonist and dissociative anaesthetic.

Formulation:

100 mg/mL injectable solution, registered for use in a wide variety of animal species including cats, dogs and horses.

Duration:

5-15 minutes of anaesthesia following higher, anaesthetic induction doses.[5]

Dose:[1,4,5]

Dogs*	Cats*
CRI: (0.1-0.5 mg/kg IV load) 0.6-1.2 mg/kg/hr^	CRI: (0.1-0.5 mg/kg IV load) 0.6-1.2 mg/kg/hr^

^Doses at the higher end of the infusion range are recommended intra-operatively and 0.3mg/kg/hr or below post-operatively, in conscious animals.

Pharmacokinetics:

Metabolism occurs in the liver, through demethylation to its active metabolite norketamine. Norketamine undergoes further biotransformation via glucuronidation prior to excretion in dogs. In cats, norketamine is excreted unchanged in the urine,[6] and therefore ketamine must be used with caution in cats with renal failure.

Indications:

As a peri-operative adjunct to provide multi-modal analgesia; the additional analgesia provided reduces the maintenance agent requirements and helps to prevent NMDA receptor-mediated central sensitisation.[7]

Precautions:

Ketamine, at (higher) anaesthetic doses, can cause an increase in heart rate and blood pressure due to sympathetic stimulation. This may be detrimental in animals with heart disease or hypertension, so ketamine should be used with caution in such patients. Analgesic doses may show a similar response, though with less intensity and tend to be dose-dependent.

Salivation may indicate nausea. Decreasing the infusion rate or the addition of ananti-emetic (e.g. maropitant) may be of benefit.[7]

Undesirable behavioural effects may be seen while the animal is conscious. Reducing the post-operative dose may help abate these effects.

Contraindications:

Anaesthetic doses of ketamine are often avoided in animals with increased intraocular pressure, open globe injuries or suspected raised intracranial pressure. This has not been studied at analgesic doses, but is not considered to be of concern when using the lower doses recommended for this indication.

Adverse effects:

At the doses of ketamine used for analgesia, few adverse effects are seen.



Analgesic Infusions

Full Mu Opioid – Lidocaine – Ketamine Infusions

These combinations of analgesic medications provide potent analgesia and have a significant dose-sparing effect on inhalant anaesthetic agents.

Indications:

- When severe or intractable pain is occurring or expected.
- Where a reduction in the side effects of inhalant anaesthetic, such as hypotension, is desired.

The combinations include a full mu opioid plus ketamine, and, depending on species, lidocaine may also be added.

Morphine is the traditional opioid included in these infusions, though fentanyl is readily used also. Methadone is less commonly used as less data is available on its use during infusions, however recent descriptions have indicated it may be used.

All agents need to have a loading dose administered prior to the infusion commencing. This can either be included in premedication, be administered as a co-induction or once the animal is anaesthetised.

Using infusions in practice:

If suitable equipment is available, it is recommended each infusion is administered separately using syringe drivers. However, it may be more practical to use a combined diluted infusion which can be utilised in multiple cases via a single fluid pump.



Photo Courtesy of Dr. Jen Davis

Example recipe:[7]

Remove 46 mL from a 500 mL bag of IV fluids (saline or similar) and add:

- 50 mg morphine
- 760 mg lidocaine (without adrenaline)
- 300 mg ketamine.

Once thoroughly mixed, this can be infused at a rate of 1–2 mL/kg/hr intraoperatively*, which will provide;

- 1.7-3.3 µg/kg/min morphine
- 25-50 µg/kg/min lidocaine
- 10-20 µg/kg/min ketamine.

*post-operatively this rate should be tapered down slowly, additional analgesia may need to be provided through this process with close attention paid to pain scoring.

Using dilutions such as the above to enable infusions to be administered at 0.5-2 mL/kg/hr makes this very useful across a range of differently sized patients and allows the combination to be set irrespective of fluid requirements.

The lower end of the infusions is applicable when the animal is conscious, while during anaesthesia, the higher end is applicable.

Adverse effects:

During infusions of the higher dose ranges, hypoventilation may be seen, and intermittent positive pressure ventilation (IPPV) may be required. It is recommended to use capnography to evaluate ventilation in anaesthetised animals.

Use in cats:

When using in cats, lidocaine should be omitted from these combinations due to the increased risk of toxicity. The infusion may be prepared and administered with the same doses of morphine and ketamine as in dogs.

The following table indicates dose rates that may be used. Additional resources may be utilised for specific recipes.

Morphine/Methadone – Lidocaine – Ketamine (MLK)

Dose rate – Dogs:[1]

	Morphine	Lidocaine	Ketamine
Loading dose	0.2-0.5 mg/kg IM or slow IV	0.5–2 mg/kg ***slow IV***	0.25-0.5 mg/kg IM or IV
Infusion rates	0.1-0.2 mg/kg/hr	25–50 µg/kg/min	0.3-0.6 mg/kg/hr

Fentanyl - Lidocaine - Ketamine (FLK) Infusion

Fentanyl may be used in place of morphine/methadone in a combination infusion.

Dose rate:[2]

3-10 µg/kg/hr fentanyl, following a 2-5 µg/kg loading dose, with the above doses of lidocaine (in dogs only) and ketamine.[2]



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