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Invited Review

# State of the art analgesia- recent developments in pharmacological approaches to acute pain management in dogs and cats. Part 1

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ABSTRACT

There has been considerable interest in acute pain management over recent years, focusing on pain assessment, pharmacological and non-pharmacological interventions. The evidence base for our clinical decision making and treatment of patients is increasing and becoming more robust. There is still a tendency to base some aspects of pain management on poor quality evidence and this requires further input in years to come. With new literature come new ideas and this review will detail the current knowledge base behind pharmacological management of acute pain in dogs and cats. The known mechanisms of action of each analgesic and its evidence will be considered. The first part of this review will consider the opioid and anti-inflammatory analgesics, describing their component drugs individually, thereby focusing on their mechanisms of action and the current evidence for their use in acute pain management.



## Introduction

The aim of this review is to assess recent developments in pharmacological approaches to acute pain management in cats and dogs, which has seen considerable recent interest. This has been centered around the use of the non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics. A recent review (Gurney, 2012) described new concepts in acute pain management, highlighting the investigating authors use of new analgesic medications as well as re-focusing on currently utilized classes of analgesics. For information on other, non-pharmacological methods of pain management the reader is directed towards the other reviews in this special edition.

Appropriate analgesia should be used in combination with adequate and effective pain assessment. A multi-modal approach to good pain management is essential to ensure a successful outcome and avoid over reliance on pharmacotherapy. The reader is referred to elsewhere in this special edition for information on pain assessment.

The literature search was performed for the preceding 5-year period (2012–2017) and appropriate studies on acute pain management in dogs and cats were selected and a narrative review style decided upon, due to the evidence available being of insufficient quality to permit a systematic review. In addition to this 5-year period, key references from earlier in the literature were also included when considered appropriate, i.e. to illustrate an analgesic mechanism of action.

Acute pain management has been and continues to be a challenging area of veterinary medicine and historically, clinicians have been faced with a limited number of available interventions. Recent years have seen an increase in the use of non-traditional analgesics such as tramadol and paracetamol, despite limited evidence of their efficacy. A 2013 survey (Hunt et al., 2015a) assessed use of perioperative analgesics by UK small animal veterinary surgeons. The results showed an increase in the number of UK veterinary surgeons prescribing perioperative analgesia compared to a previous study in 1999 (Capner et al.) and increase in the classes of analgesic available within veterinary practice. The authors concluded that this increase in analgesic use is a positive step for animal welfare.

The American Animal Hospital Association published guidelines in 2015 (Epstein et al.) highlighting recent advances in pain management, namely since the last publication of their guidelines in 2007. They focus on the recognition and assessment of pain, pharmacological intervention, non-pharmacological interventions and the importance of a team approach and education of the client. The WSAVA Global Pain Council has also published guidelines for recognition, assessment and treatment of pain (Matthews et al., 2014) which embody the Global Pain Council vision to empower the veterinary profession to “effectively recognize and minimize pain prevalence and impact”.

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As a profession we continue to draw information from our colleagues in the human medical field. The Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine published their acute pain management: scientific evidence fourth edition in 2015 (Schug et al.), which is a comprehensive review addressing the importance of effective pain management and the consequences of inadequately treated acute pain. An area that veterinary medicine is yet to move into, but one that is of increasing interest is the discipline of acute pain medicine as its own entity.

The first part of this review will consider the opioid and anti-inflammatory analgesics, describing their component drugs individually, thereby focusing on their mechanisms of action and the current evidence for their use in acute pain management. In the second part the non-traditional analgesics will be considered.

## Opioid analgesics

### *Methadone*

Methadone is most commonly presented as a racemic mixture and is a synthetic full mu opioid receptor agonist and reported to be an antagonist at the *N*-methyl D-aspartate (NMDA) receptor and inhibit norepinephrine reuptake. These properties are linked to the action of each of the enantiomers. In dogs and cats' absorption is rapid following intra-muscular administration, with variable absorption from the subcutaneous route in dogs and poor absorption from this route in the cat. Clearance is longer in the cat than the dog (Ingvast-Larsson et al., 2010; Slingsby et al., 2016).

There are many clinical studies examining the use of methadone, showing positive results when assessing its analgesic efficacy. Hunt et al. (2013) compared premedication with acepromazine in combination with buprenorphine (0.02 mg/kg) or methadone (0.5 mg/kg) on postoperative analgesia in dogs undergoing orthopaedic surgery. Methadone produced superior analgesia for eight hours postoperatively than buprenorphine. Monteiro et al. (2016b) showed a greater reduction in MAC isoflurane requirements in dogs undergoing ovariohysterectomy when acepromazine was combined with methadone compared to morphine. Pain assessment was not recorded preventing evaluation of MAC reduction in respect to analgesia. In a study comparing medetomidine (2.5 mcg/kg IV) in combination with either IV morphine (0.3 mg/kg) or methadone (0.3 mg/kg) for laparoscopic surgery in dogs, methadone resulted in lower isoflurane requirements and better analgesia three hours post-operatively than morphine, although both protocols provided adequate analgesia (Raillard et al., 2017). Amengual et al. (2017) demonstrated that pain scores, assessed using the Glasgow short form pain scale, did not differ following spinal surgery in dogs with either a fentanyl infusion or intermittent bolus administration of methadone.

Methadone use in cats has also produced many analgesic studies, particularly comparing its effects with other opioid analgesics. Warne et al. (2013) demonstrated methadone to be superior to butorphanol for perioperative analgesia, with lower pain scores (utilizing a multi-dimensional composite pain scale) and less requirement for rescue analgesia. In a similar study Bortolami et al. (2013) showed no difference between groups when methadone, buprenorphine or butorphanol were used as premedication prior to neutering in cats in combination with acepromazine. An interactive visual analogue scale and mechanical threshold testing were used as objective scoring measures. The same group utilized the same opioid analgesics in combination with medetomidine, and although they once again found no significant differences between groups, more cats in the butorphanol group required rescue analgesia than the other two opioid groups (Slingsby et al., 2015). Fernandez-Parra et al. (2017) compared the use of IV methadone, intratesticular lidocaine and sacrococcygeal epidural lidocaine prior to castration in cats. All techniques provided adequate analgesia for castration, assessed post-operatively using a validated pain assessment tool.

The use of methadone for acute pain management in both the dog and cat is recommended, based on current literature.

### *Fentanyl*

Fentanyl in dogs has been the subject of numerous recent analgesia and MAC reduction studies. Williamson et al. (2017) studied the effect of "low" and "high" dose fentanyl on MAC (Isoflurane). Administration of a "low dose" (33 μg/kg loading dose and 0.2 μg/kg/min) resulted in an average MAC reduction of 42.3 ± 9.4% and a "high dose" (102 μg/kg loading dose, 0.8 μg/kg/min) a MAC reduction of 76.9 ± 7.4%. The anaesthetic sparing effect of fentanyl was also evaluated by Suarez et al. (2017), who demonstrated a mean MAC (Sevoflurane) reduction with fentanyl (loading dose, 15 μg/kg; constant rate infusion, 6 μg/kg/h) of 39% and Simões et al. (2016) who reported that fentanyl bolus (5 μg/kg) and CRI (9 μg/kg/h) reduced MAC (Isoflurane) by approximately 50% which was stable for 300 min suggesting no opioid accumulation. Atropine administration did not influence MAC reduction. Becker et al. (2013) demonstrated that dysphoria was observed in the post-operative period in 23.9% (22 out of 92) of dogs following infusion of fentanyl during anaesthesia for pelvic limb orthopaedic surgery. The incidence of dysphoria was not statistically different between the three fentanyl infusion rates and all cases responded to the administration of naloxone alone, or in combination with a sedative.

The use of intranasal fentanyl administration has been described in a single case report in the dog (Micieli et al., 2017). When comparing the respiratory effects of intravenous fentanyl or methadone in dogs following spinal surgery, neither fentanyl constant rate infusion (5 μg/kg/h) or methadone boluses (0.2 mg/kg, every 4 h) caused respiratory depression (Amengual et al., 2017).

Ambros et al. (2014) demonstrated that fentanyl (5 μg/kg) followed by fentanyl infusion (5 μg/kg/h, IV) for 2 h increased mechanical and thermal thresholds in cats. During the fentanyl CRI, mean ± SD plasma fentanyl concentration decreased from 4.41 ± 1.86 ng/mL to 2.99 ± 1.28 ng/mL and was correlated with antinociception; plasma concentrations < 1.33 ± 0.30 ng/mL were not associated with antinociception. Further Ambros (2016) showed that when administered to cats, buprenorphine did partially inhibit the antinociceptive action of subsequently administered fentanyl, and that pre-treatment with hydromorphone did inhibit the antinociceptive action of fentanyl at one single time point.

Fentanyl has a useful role to play in the management of acute pain in both dogs and cats.

### *Alfentanil*

Montefiori et al. (2016) documented that addition of alfentanil to propfol target controlled infusion sedation resulted in no cardiovascular benefits and only a dose related increase in the incidence of hypoxaemia.

Further research is required to allow more recommendations to be made regarding the use of alfentanil.

### *Hydromorphone*

The efficacy of liposomal hydromorphone (0.2 mg/kg) was demonstrated in dogs undergoing limb amputation with a multi-modal analgesic approach. The authors concluded that

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