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Review Article

Evidence-Based Tiered Framework for Feline Pain Management: A Systematic Review

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Abstract

This systematic review developed an evidence-based framework for feline pain management. The systematic search of Scopus, ScienceDirect, and PubMed from 1980 to october 2023 found 42 eligible studies that explored pharmacological and non-pharmacological approaches to feline pain management. The outcome measures included analgesic efficacy, rescue analgesia, and adverse effects. Rescue analgesia was a key endpoint in multimodal therapies and was mostly used in severe pain models. Multimodal therapies were mainly employed in complex cases/procedures with severe pain potentials, resulting in higher rescue rate (16.6%) compared to monotherapy in routine procedures/neuter (5.29%). Pre-emptive analgesics were always associated with the best outcomes. The UNESP-Botucatu multidimensional scale was one of the most frequently used and validated pain assessment tools. The adverse effects were usually easy to manage, with the most frequent being opioid-related dysphoria and NSAID-related gastrointestinal effects. Following these results, we propose a tiered framework: a base of NSAIDs and local anaesthetics (Tier E1), supplemented with opioids for severe pain (Tier E2) and adjunctive stress-reducers (Tier E3). This is a pre-emptive, structured and severity-specific method necessary to ameliorate the cycle of treating pain insufficiently, thereby improving the welfare of cats, as well as staff safety and strengthening the veterinary practice.

Keywords: Feline pain management, Multimodal analgesia, Pre-emptive analgesia, Systematic review, Tiered framework

Introduction

Pain affects the quality of life and well-being in cats, with the potential of delaying recovery and causing enduring physiological and behavioural alterations [1]. Cats' pain and stress are often overlooked, given their inability to express feelings. Despite all the progress in veterinary medicine, studies have shown that pain management in cats is still under-addressed compared to dogs [1]. A survey by Adams and Munoz revealed that 6.7% of cats were given analgesics after surgery compared to 16% of dogs undergoing similar procedures, including ovariohysterectomy and orchiectomy [1]. Cats are generally undertreated with analgesics due to various factors, such as the absence of appropriate analgesic agents or the inability to detect pain through their distinctive behavioural patterns [2,3].

Unmanaged pain in cats poses a major safety risk. Defensive aggression is directly provoked by fear and discomfort, which significantly raises the possibility of being bitten or scratched by handlers, veterinarians, and owners [4-6]. These injuries are directly and physically harmful and may introduce the risk of contracting zoonotic diseases. Trust in the veterinary team is lost when owners feel that their cat is not receiving the attention it deserves. These events have a detrimental effect on client satisfaction, indirectly through negative word-of-mouth and decreasing the

willingness to pursue future care, including necessary follow-up visits and vaccination [7]. As a result, distrust in pain-mitigating approaches and quality of care could have a direct financial implication on pets' long-term health [8]. Meanwhile, effective care leads to high client satisfaction, which is directly proportional to better practice and financial performance. Thus, proficient pain management is a critical factor in economic viability.

Pain recognition in cats is complicated by their inherent behavioural patterns, and the challenge in developing effective screening and measurement instruments. Despite the availability of some validated pain assessment scales, only 10% of surveyed veterinary clinics use these tools for postoperative pain measurement in cats [9]. Moreover, the complex nature of validated pain assessment tools poses a hindrance to their regular use in clinics [10]. This problem is further exacerbated by the lack of pain management education in veterinary schools, gender-specific pain perception, and the limited variety of appropriate analgesics [11,12]. Several drugs used in other animals are either not licensed or off label for cats, and veterinarians are unwilling to prescribe these medications due to fears of side effects and lack of specific usage guidelines [13,14]. The undertreatment of pain in cats is also influenced by factors such as transportation stress and anxiety when managed in a new environment, confinement in a carrier and inappropriate handling [15]. These factors may cause aggressive behaviour that complicates the treatment [16,17]. Cats that had negative experiences with veterinarians are more likely to feel anxious during their next appointments [18,19]. Neglecting pain results in insufficient utilisation of analgesics and less effective pain management [20].

Effective pain management is essential in veterinary practice given its significance to animal welfare, human safety and economic efficiency. A stress and pain-free cat is easier to manage, creates confidence in the owner, and improves adherence to follow-up appointments. Therefore, a detailed review of the current evidence on pain management modalities in cats is pertinent to support clinical practice and advance feline welfare. By synthesising the available evidence, this review presents a clear and actionable framework that will enable clinicians to effectively and confidently manage feline pain. The implementation of evidence-based protocols is key to ending the vicious circle of undertreatment, thereby improving feline welfare and the relationships with clients, guaranteeing staff safety, and protecting the economic well-being of veterinary facilities. This systematic review aims to: (i) stratify the efficacy of analgesic interventions based on pain severity, (ii) analyse the effects of multimodal therapy and timing on pain-related outcomes, (iii) describe the available pain assessment tools, and (iv) to integrate the findings on efficacy, safety and global availability into a practical tiered framework for clinical decision making.

Material and Methods

Search Methods

Articles published between 1980 to October 24th, 2023, were searched across three digital databases: Scopus, ScienceDirect and PubMed. This time frame was considered to elucidate the different advanced methods and improvements in pain management in the last four decades. A methodical exploration was conducted utilising a set of predetermined terms by using the PICO tool. The keywords and search strings used in all the databases were "cat OR cats OR feline) AND (stress OR pain) AND "management". The search was restricted to articles written in English. Duplicates found across the various databases were eliminated during the article selection process *(Fig. 1)*. All the retrieved data were imported into a Microsoft Excel sheet for data cleaning, sorting and storage.

Study Selection

Inclusion and Exclusion Criteria: According to the PICO tool, this review focused on domestic cats (P) experiencing pain and stress due to some surgical, medical procedures or were in a clinical or experimental setting. We investigated a range of analgesic interventions (I), including opioids, NSAIDs, local blocks, acupuncture and their combination. These were compared with placebo, no treatment, or an alternative analgesia regimen (C). The primary outcome was analgesia efficacy, assessed using the need for rescue analgesia, stress-related measures, and adverse effects associated with each intervention (O).

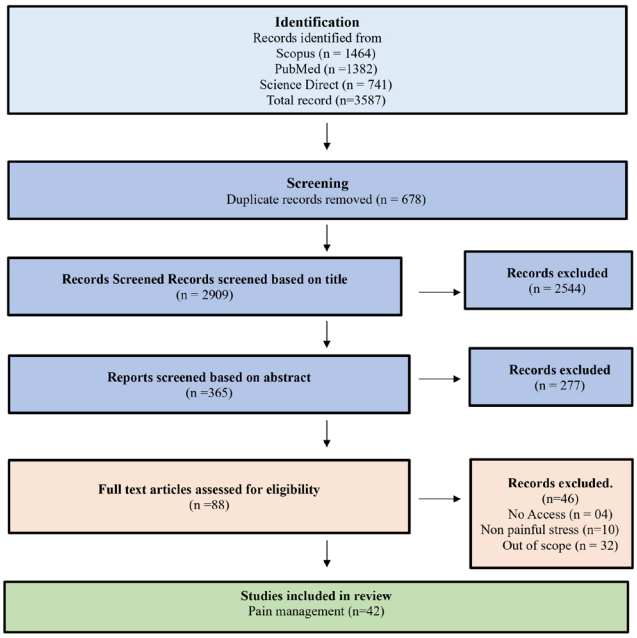

Fig 1. Flow diagram showing study selection process according to PRISMA guidelines

Studies involving the treatment of pain in client-owned or research cats with a specific surgical or medical condition were included. Meanwhile, studies that only investigated non-painful stress or anxiety (e.g. associated with transportation, hospitalisation, or unfamiliar environments) were excluded from the qualitative synthesis.

Research articles that lacked clear assessments or measurements of pain, as well as review articles, opinion pieces, editorials, case reports or case series, and commentaries were excluded. During the abstract and full-text screening, studies with significant methodological flaws were also excluded. This included studies with small sample sizes (<6 animals per group) and those employing methods that were not related to the research question.

The data screening and extraction were performed independently by two reviewers UK and MSB. Any disagreements arising between the two reviewers were resolved through a discussion leading to a consensus.

Data Extraction and Synthesis: Articles fulfilling the inclusion criteria were read thoroughly. Data were extracted systematically using a pre-established, standardised approach. Extracted data included: author name, year of publication, research objectives, pain condition (orthopaedic, ovariohysterectomy, osteoarthritis, etc.), intervention details (analgesic drugs, dosage, route of administration), pain assessment tools, comparator group, outcomes (primary and secondary), rescue analgesia (incidence and indications), adverse effects, and main findings.

A narrative and descriptive approach was used for the data synthesis and qualitative analysis. Studies were initially categorised as surgical and non-surgical. Subsequently, to enable a clinically relevant analysis, the pain in these categories was grouped by severity (severe, moderate, mild), the invasiveness of the procedure, duration of pain and potential for distress. This severity ranking was utilised to organise the synthesis of findings and guide clinical recommendations. In studies related to pain due to surgical conditions, the number of cats that required rescue analgesia in each study was recorded (where available). The data were further analysed based on the intervention strategy (e.g., multimodal vs. single therapy), drug class, and timing of administration, which assisted in identifying the most effective strategies for optimising pain control. Geographical visualisations were generated using Python mapping libraries with base map data sourced from OpenStreetMap. A formal meta-analysis was not possible given the large degree of heterogeneity between the studies, particularly in terms of study designs, interventions and outcome measures.

Results

Study Characteristics

A total of 42 studies met the inclusion criteria for the systematic review. Twenty-five studies were classified

Table 1. *Descriptive characteristics of the studies involving interventions on pain severity in surgical and non-surgical procedures*

Study	Year	Objective	Condition (n)	Treatment	Dosage	Timing	Duration	Pain Assessment	Outcome
King et al. [34]	2016	Evaluate the efficacy	Onychectomy/ OVH/ Castration (358)	Robenacoxib①	2 mg/kg SQ	Pre-op	3 days	Palpometer, behaviour view from distance/social interaction, posture score	Lower rescue analgesia
Speranza et al. [40]	2015	Compare analgesia	Orthopedic surgery (147)	G1: Robenacoxib① G2: Meloxicam②	G1: 2 mg/kg SQ + 1-2.4 mg/kg PO G2: 0.3 mg/kg SQ	Pre-op & post-op	9 days	Global investigator/ owner scale, Cortisol level	Non inferior to meloxicam
Thomson et al. [39]	2013	Evaluate the efficacy	Corneal ulceration (17)	Morphine③	1 ocular drop 50 µL	Pre-op	Once	Aesthesiometer	Not effective for corneal pain
Rufiange et al. [21]	2022	Compare analgesia	OVH (27)	OSA: Ketamine① + midazolam③ + dexmedetomidine② + buprenorphine① meloxicam②, Bupivacaine③ IP OFA: without buprenorphine	OSA: 4 mg/kg + 0.25 mg/kg + 40 µg/kg + 20 µg/kg IM + 0.2 mg/kg SQ OFA: same no buprenorphine	Pre-op	Once	FGS, DIVAS	Buprenorphine eliminated need for rescue analgesia
Corrêa et al. [22]	2021	Compare analgesia	OVH (70)	MG: Maropitant③ LG: Lidocaine③ KG: Ketamine①	MG: 1 mg/kg IV + CRI 1.67 µg/kg/min LG: 1.5 mg/kg IV + CRI 50 µg/kg/min KG: 1 mg/kg IV + CRI 10 µg/kg/min	Pre- & intra-op	Once	VAS, UNESP Batucatu scale	Individual CRI effective, combination not superior

Table 1. *Continue*

Pereira et al. [25]	2021	Compare analgesia	OVH (30)	D25: Dipyrone③ D12.5: Dipyrone M: Meloxicam②	D25: 25 mg/kg IV & q24h PO D12.5: 12.5 mg/kg IV & q24h PO M. 0.1 mg/kg IV &q24h PO	Pre & post-op	3-6 days	VAS, CSU-FAPS, Glasgow pain scales	All protocol were equally effective. No statical difference in pain score
Corrêa et al. [26]	2019	Compare analgesia	OVH (30)	GM30: Maropitant③ GM100: Maropitant	GM30: 1 mg/kg & CRI 30 µg/kg/h GM100: 1 mg/kg &CRI 100 µg/kg/h	Pre & intra-op	Once		100 ug/kg/hr decreased rescue analgesia
Vicente & Bergström [28]	2018	Compare analgesia	OVH (75)	GL: Lidocaine③ GLB: Lidocaine③ + Bupivacaine③	GL: 1.5 mg/kg GLB: 1 mg/kg + 1 mg/kg	Pre-op	Once	HR, MAP	Incisional local block significantly improved the intraoperative analgesia vs control
Ribeiro et al. [29]	2017	Evaluate efficacy	OVH (20)	Dry needle simulation③ + ketamine① +, midazolam③ + tramadol③	D points simulated 20 min preop to end of surgery + 5 mg/kg + 0.5 mg/kg + 2 mg/kg IM	Pre & intra-op	Once	UNESP Batucatu scale, VAS, Behaviour score	YNSA decreased need for rescue analgesia
Marques et al. [30]	2015	Evaluate efficacy	OVH (20)	Infrared laser acupuncture③ + ketamine① +, midazolam③ + tramadol③ Control: same drugs, no acupuncture	Laser acupuncture +5mg/kg+0.5mg/kg +2mg/kg IM	Pre-op	Once	MCPS, DIVAS	Laser acupuncture lowered the incidence of rescue analgesia.
Fudge et al. [31]	2021	Compare analgesia	OVH (151)	BUP: Bupivacaine③ BLE: Bupivacaine③ + lidocaine③ + epinephrine DEX: Dexamethasone MEL: Meloxicam②	BUP: 1 mg/kg BLE: 1 mg/kg + 2 mg/kg + 0.005 mg/kg DEX: 0.125 mg/kg MEL: 0.2 mg/kg	Intra-op	Once	NRS	MEL had significantly lower pain scores at 3h than the BLE.
Machado et al. [32]	2018	Compare dose	OVH (27)	Remifentanil③	CRI 0.1/0.2/0.4 µg/kg/min	Intra-op	Once	UNESP Batucatu scale	0.4 µg/kg/min effective; no rescue analgesia needed
Guerrero et al. [33]	2014	Comparing analgesia	OVH (21)	G1: Alfaxalone② + Meloxicam② MK: Ketamine① + Medetomidine②	G1:5 mg/kg IV & bolus 2 mg/kg MK: 5 mg/kg IV& bolus 2 mg/kg + 30 µg /kg IM	Pre & intra-op	Once	CPS, VAS, MWT	ketamine-medetomidine provide better analgesia than alfaxalone.
Teixeira et al. [24]	2020	Compare analgesia	OVH (28)	Dipyrone③ + Tramadol③	25 mg/kg + 2 mg/kg	Post-op	5 days	UNESP Batucatu scale, Glasgow pain scales, VAS, BG	No additive benefit of dipyrone with tramadol
Heo et al. [27]	2018	Compare analgesia	OVH (18)	A: Meloxicam② B: Meloxicam② + Buprenorphine①	A: 0.3 mg/kg SQ B: 0.3 mg/kg SQ + 20 µg/h patch	Pre & post-op	Once	Cortisol level, 4A-VET pain scale, VAS	Meloxicam + buprenorphine patch combination significantly reduces pain vs meloxicam alone

Table 1. *Continue*

Quarterone et al. [23]	2017	Compare analgesia	OVH, Orchiectomy (24)	Meloxicam② + Fentanyl②	0.1 mg PO + 2 µg/kg IV	Pre-op	Once	UNESP Batucatu scale	Insufficient for OVH; adequate for orchiectomy
Skouropoulou et al. [36]	2018	Evaluate the efficacy	Ovariectomy (20)	TAP: bupivacaine③ + 2% lidocaine③ Control: Saline	TAP: 1 mg /kg + 1.5 ml	Pre-op	Once	SDS	TAP effective; no rescue analgesia vs control 100% recue
Cicirelli et al. [35]	2022	Evaluate efficacy	Orchiectomy/ castration (60)	Ropivacaine③ Control: NaCl	1 mg/kg	Pre-op	Once	UNESP Batucatu scale, HR, BP, RR	Ropivacaine superior; lower pain scores vs control
Taylor et al.[37]	2010	Compare analgesia	Neutering (153)	G1: Buprenorphine① G2: Butorphanol②	G1: 10-20 µg/kg G2: 0.4 mg/kg	Pre-op	Once	SDS	Pain scores significantly lower in buprenorphine vs butorphanol
Coelho et al. [38]	2023	Evaluate the efficacy	Feline Chronic gingivitis (FCGS) (22)	CBD③	4 mg/cat bid	Preop & post op	15 days	COPS C/F, SDAI, HR, BP, WL	CBD treated cats more comfortable and active.
Adrian et al. [41]	2021	Evaluate efficacy	DJD pain (109)	RR: Robenacoxib① PP:Placebo	RR: 1 mg/kg PO	Daily	6 weeks	FMPI, CSOM, AMs Owner assessment	Improvement after 6 weeks, and not 3 weeks based on activity.
Gruen et al. [42]	2021	Evaluate efficacy	DJD associated chronic pain (126)	Frunevetmab③	1-2.8 mg/kg SQ & IV	Repeated 28 days	56 days	AMs, CSOM FMPI, Owner Global Assessment, Veterinary Assessments	Effective at day 42-56; no difference between SQ vs IV routes
Monteiro et al. [43].	2015	Compare analgesia	Osteoarthritis (15)	GM:Meloxicam② TM:Meloxicam② +Tramadol③	M. 0.05 mg/kg sid TM: 0.05 mg/kg sid + 3 mg/kg bid	Daily	25 days	Peak vertical force, RMTS, Motor activity measure	No added benefit of tramadol to meloxicam
Gunew et al. [44]	2008	Evaluate efficacy	OA (92)	Meloxicam②	0.01 - 0.03 mg/kg drops	Daily	12 months	Simple discontinuous scales	Safe and palatable for long-term osteoarthritis management
Gearing et al. [45]	2016	Evaluate efficacy	Kaolin-induced inflammatory pain (30)	Felinized anti-NGF mAb③	2 mg/kg NV-02 SQ	Pre-emptive	Once	Discontinuous scoring system	Significantly reduced lameness

Studies were categorised based on pain severity. The superscripts number following analgesics agent indicates their regulatory and evidence status. Regulatory status ① Approved for and evidence supported, ② Extra label and evidence supported, ③ Limited evidence, not recommended or investigational
4A-VET: 4A-Vet Pain Scale, CBD: Cannabidiol, CRI: Constant Rate Infusion, CSU-FAPS: Colorado State University Feline Acute Pain Scale, DIVAS: Dynamic Interactive Visual Analogue Scale, DJD: Degenerative Joint Disease, FCGS: Feline Chronic Gingivostomatitis, FGS: Feline Grimace Scale, FMPI: Feline Musculoskeletal Pain Index, MWT: Mechanical Wound Threshold, OTMS: Oral Transmucosal, RMTS: Response to Mechanical Temporal Summation, SDS: Simple Descriptive Scale, TAP: Transversus Abdominis Plane, VAS: Visual Analogue Scale, YNSA: Yamamoto New Scalp Acupunctur

based on the severity of the procedure and synthesised in *Table 1*, while 13 studies on mechanical and thermal threshold were summarised in *Table 2*. The remaining four studies which focussed specifically on the validation of pain assessment tools, are reviewed in the text below.

Of the 42 articles, 38 studies reported data on the adverse effects of various pain treatment modalities. All the studies were grouped based on context (surgical, non-surgical, experimental) and further classified by the severity of the procedure (minimal, mild, moderate and severe). Information on the animals' age, sex and bodyweight was not provided in all the studies. Global distribution of studies and year of publication are shown in *Fig. 2* and *Fig. 3*.

Surgical Versus Non-Surgical Procedures

Overall, 20 studies were related to pain arising from

Table 2. Healthy Pharmacologic Challenge (Thermal and Mechanical Threshold)

Study	Year	Objective	Condition(n)	Intervention	Dosage	Timing	Pain Assessment	Outcome
Ambros & Duke [49]	2013	Determine thermal and mechanical antinociceptive effects	Healthy-Analgesic Testing (24)	Ketamine low vs high dose	LD 0.5 mg/kg + CRI 5 µg/kg/min vs 0.5 mg/kg + CRI 23 µg/kg/min	Pre-stimulus +CRI	TT, MT	High dose of ketamine increases thermal and mechanical threshold vs low dose
Simon et al. [50]	2016	Evaluate antinociceptive effects opioids combination	Healthy-Analgesic Testing (6)	H-Sal: Hydromorphone H-Bupre: Hydromorphone + buprenorphine H-Butor: Hydromorphone + butorphanol	H-Sal: 0.1 mg/kg IV H-Bupre: 0.1 + 0.02 mg/kg IV H-Butor: 0.1 mg/kg + 0.2 mg/kg IV	Pre-stimulus	TT	Hydromorphone + buprenorphine longer duration (2-3 h) Butorphanol decreased hydromorphone antinociception
Wegner & Robertson [52]	2007	Dose-related thermal antinociceptive effects of hydromorphone	Healthy-Analgesic Testing (21)	Hydromorphone	0.025, 0.05, 0.1 mg/kg IV	Pre-stimulus	TT	0.1 mg/kg dose provided most potent analgesia
Ferreira et al. [51]	2011	Compare IV vs OTM methadone	Healthy-Analgesic Testing (8)	IV group: Methadone OTM group: Methadone	IV group: 0.3 mg/kg IV OTM group: 0.6 mg/kg	Pre-stimulus	MT	OTM; significant antinociception from 10 min to 6 h; longer duration than IV
Doodnaught et al. [53]	2017	Evaluate oral tapentadol analgesic effect	Healthy-Analgesic Testing (6)	BUP: Buprenorphine Low TAP: Tapentadol High TAP: Tapentadol	BUP: 0.02 mg/kg IM Low TAP: 25 mg PO High TAP: 50 mg/kg PO	Pre-stimulus	TT	Higher dose tapentadol: prolonged effect for 2 h like buprenorphine; no significant TT increases vs placebo
Pypendop et al. [54]	2016	Determine the antinociceptive effects of IV/ buccal opioids	Healthy-Analgesic Testing (6)	Morphine, Methadone Hydromorphone Oxymorphone	Morphine: 0.2 mg/kg IV or 0.5 mg/kg buccal Methadone: 0.3 mg kg IV or 0.75 mg/kg buccal Hydromorphone: 0.1 mg/kg IV or 0.25 mg/kg buccal Oxymorphone: 0.1 mg/kg IV or 0.25 mg/kg buccal	Pre-stimulus	TT	Significant thermal antinociception: IV hydromorphone/ methadone, and buccal methadone only
Carrozzo et al. [55]	2018	Determine the effects of fentanyl CRI on thermal thresholds.	Healthy-Analgesic Testing (6)	F3: Fentanyl low dose F5: Fentanyl high dose	F3: 3 µg/kg + CRI 3 µg/kg/h F5: 5 µg/kg + CRI 5 µg/kg/h	Pre-stimulus + CRI	TT	5 µg /kg/h increased TT during infusion.
Farnworth et al. [58]	2015	Assess thermal CO_2 laser as analgesia measure tool	Healthy-Analgesic Testing (60)	Saline Morphine, Buprenorphine, Medetomidine, Tramadol, Ketoprofen	Saline: 0.2 mL Morphine: 0.5mg/kg Buprenorphine: 20 µg/kg Medetomidine: 2 µg/kg Tramadol: 2 mg/kg Ketoprofen: 2 mg/kg	Pre-stimulus	TT	Morphine and Tramadol significantly increased response time; others non-significant
Steagall et al. [57]	2007	Evaluate a prototype pressure stimulus device	Healthy-Analgesic Testing (8)	Carprofen, Buprenorphine Normal saline	Carprofen: 4 mg/kg, Buprenorphine: 0.01 mg/kg Normal saline 0.3 mL SQ	Pre-stimulus	TT, MT	Buprenorphine: longer duration than carprofen (up to 8 h)
Dixon et al. [56]	2007	Development of a pressure nociceptive threshold testing device	Healthy-Analgesic Testing (11)	Butorphanol	0.4 mg/kg SQ	Pre-stimulus	MT	Increased pressure threshold from the baseline

Table 2. Continue

Briggs [48]	1998	To determine the antinociceptive effects	Healthy-Analgesic Testing (8)	Oxymorphone, Butorphanol (individual and combination) ± acepromazine	Oxymorphone: 0.025-0.20 mg/kg IV Butorphanol: 0.025-0.20 mg/kg IV Combinations at 0.1 mg/kg total ACE: 0.05 mg/kg IV	Pre-stimulus	MT (rectal balloon catheter)	Oxymorphone + butorphanol combinations superior to alone; adding ACE further enhanced antinociception
Taylor et al. [46]	2007	Evaluate TT testing for NSAID analgesia investigation	Healthy-Analgesic Testing (26)	Ketoprofen	2 mg/kg SQ	Pre-stimulus	TT	Insufficient sensitivity for NSAID analgesia study
Taylor et al. [47]	2007	Evaluate MT for NSAID analgesia testing	Healthy-Analgesic Testing (8)	Group C: Carprofen Group B: Buprenorphine	Group C: 4 mg/kg SQ Group B: 0.01 mg/kg SQ	Pre-stimulus	MT	Carprofen and buprenorphine, prevented inflammatory hyperalgesia

Summary of the studies that applied thermal and mechanical threshold in healthy cats to evaluate the pharmacodynamics of the analgesic agents

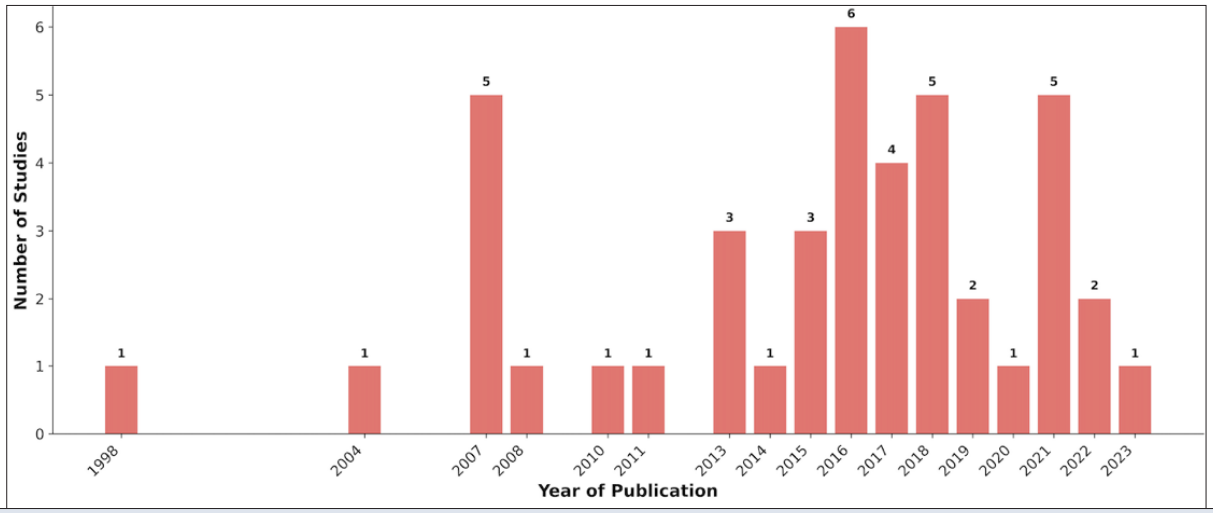

Fig 2. Year-wise distribution of studies on pain included in this systematic review, showing publication trends from 1998 to 2023

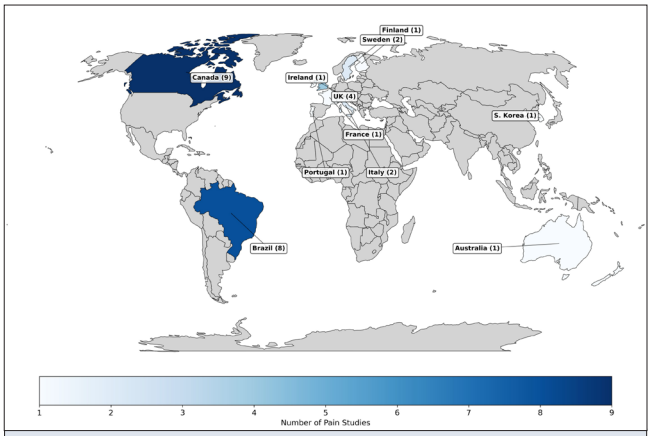

Fig 3. Global distribution of studies on pain in cats included in the systematic literature review. The map displays the number of studies per country using a color gradient (darker colors indicate more studies). Base map data from OpenStreetMap

surgical procedures such as ovariohysterectomy, ovariectomy, orchiectomy [21-37], dental problems [38], ocular issues [39] and orthopaedics [40]. The identified pain-related studies for non-surgical conditions primarily investigated on chronic degenerative disease and osteoarthritis [41-44], as well as kaolin-induced inflammatory pain model [45]. *Table 1* depicts the severity of the interventions and their regulatory status for these studies. *Table 2* summarises the research conducted on healthy cats. These studies focused on pain due to kaolin injection [46, 47], noxious visceral pain stimuli [48] and evoked thermal and mechanical threshold model for different drugs comparison [49-58].

The remaining four studies [59-62] focused specifically on validation of pain assessment tools. Among the included studies, the UNESP-Batucatu multidimensional composite pain scale was the most frequently applied validated tool, demonstrating significant efficacy in surgical condition.

Other commonly employed outcomes included the Visual Analogue Scale, physiological parameters, mechanical and thermal threshold, which were predominantly used in the experimental setting *(Table 1, Table 2)*.

For severe pain models like orthopaedic surgeries, results strongly recommend the use of multimodal analgesia approaches. King et al. [34] and Speranza et al. [40] concluded that the use of preoperative NSAIDs such as robenacoxib significantly reduced the need for rescue analgesia compared to a placebo. Furthermore, Speranza et al. [40] found robenacoxib to be non-inferior to meloxicam for postoperative pain control.

Most of the included studies focused on moderate pain models such as ovariohysterectomy. A multimodal analgesia approach involving the opioid-sparing protocol, combined with dexmedetomidine, ketamine, and local anaesthesia, was effective in managing moderate pain. However, the addition of buprenorphine provided stronger analgesic effects, thereby further reducing the rescue rate [21]. A few studies highlighted the importance of a local anaesthesia. For example, a Transversus Abdominis Plane (TAP) block [36] and incisional block with buprenorphine and lidocaine [28], both yielded good intra-and postoperative analgesic effects. New emerging techniques, along with local anaesthesia like laser and scalp acupuncture, demonstrated good potential in reducing the need for rescue analgesia [29,30]. Unlike the other effective options, dipyrone's efficacy was limited. Results demonstrated little to no advantage over placebo and other analgesics like meloxicam and tramadol [21,22].

For moderate chronic pain conditions such as osteoarthritis, degenerative joint disease (DJD) and feline chronic gingivitis (FCGS), long-term management protocols were evaluated. NSAIDs were the cornerstone of these protocols. Both meloxicam and robenacoxib improved comfort and activity level, demonstrating effectiveness for long-term use [41,44]. A single injection of frunevetmab (anti-nerve growth factor) was also effective in ameliorating DJD pain for several weeks [42]. In FCGS, cannabidiol (CBD) improved outcomes, including activity and comfort, compared to placebo [38].

Several studies investigated the use of thermal threshold (TT) and mechanical threshold (MT) devices, along with their subtypes, to characterise analgesic pharmacodynamics in healthy cats *(Table 2)*.

Butorphanol, hydromorphone, buprenorphine and methadone significantly increased the withdrawal threshold [50,52,57]. In contrast the model showed little to no efficacy for tapentadol, reflecting its underperformance and poor performance in clinical trials [53]. The types of analgesia used in all 38 studies are summarised in *Table 3*.

Table 3. *Frequency of analgesic modalities reported across all 38 studies*

Type of analgesia	Studies	Percentage (%)
Opioids	12	31.6
NSAIDs	5	13.2
Opioids and NSAIDs combination	6	15.8
Local Analgesics	7	18.4
Acupuncture	2	5.3
Anti-Nerve Growth Factor (NGF)	2	5.3
Miscellaneous	4	10.5
Total	38	100.0

Miscellaneous category includes the following single-agent therapies: cannabidiol, NMDA antagonists, alpha-2 adrenergic agonists, and neurokinin-1 receptor antagonists

Proportion of Cats Subjected to Rescue Analgesia and the Effectiveness of Different Drug Protocols

A total of 924 cats were recruited in studies reporting rescue analgesia following pain intervention. Descriptively, 18.9% of the cats required rescue analgesia, especially those in the control group (61.4%) compared to cats in the treatment group (38.9%). Specifically, 10.2% and 41.6% of cats in the treatment and control groups received rescue analgesia.

The occurrence of rescue analgesia was 16.6% (95% CI 12.7-21.3) in multimodal arms, 5.3% in individual therapy arms (95% CI 3.5-8.0) and 41.6% in control arms (95% CI 35.8-47.7) as described in *Table 4*.

The frequency of rescue analgesia requirement by category arms was highest for NSAIDs (12.9%; 95% CI 9.9-16.7), followed by opioids (3.1%; 95% CI 1.4-6.6), opioids and NMDA agonists (26.2%; 95% CI 15.3-41.1), acupuncture (5.0%; 95% CI 0.9-23.6) and miscellaneous (4.9 %; 95% CI 1.4-16.4) as described in *Table 5*.

The occurrence of rescue analgesia based on the timing of drug administration arms is depicted in *Table 6*. The highest incidence was observed postoperatively (19.6%;

Table 4. *Rescue analgesia by drug protocol*

Category	Rescue Required (n)	Total Cats (N)	Rescue Rate (%)	95% CI (%)
Multimodal therapy	48	289	16.6%	12.7-21.3
Individual therapy	20	378	5.3%	3.5-8.0
Control/ Placebo	107	257	41.6%	35.8-47.7
Total	175	924		

Rescue analgesia rates categorised by analgesic protocol. A lower percentage indicates better outcomes. The 95% confidence interval (CI) was calculated by the Wilson method. n: number of cats required rescue analgesia, N: total number of cats in that category

Table 5. Comparison of rescue analgesia among the different pharmacological classes and therapeutic categories.					
Analgesic Category	**Studies**	**Rescue Required (n)**	**Total Cats (N)**	**Rescue Rate (%)**	**95 % CI (%)**
NSAIDs	4	48	371	12.9	9.9-16.7
Opioids	3	6	193	3.1	1.4-6.6
Opioids+NMDA antagonists	2	11	42	26.2	15.3-41.1
Acupuncture	2	1	20	5.0	0.9-23.6
Miscellaneous (CBD, LA)	2	2	41	4.9	1.4-16.1
Total	13	68	667		

Rescue analgesia rates categorised by different pharmacological classes and therapeutic categories. A lower percentage indicates better outcomes. The 95% confidence interval (CI) was calculated by using the Wilson method. n: number of cats required rescue analgesia, N: total number of cats in that category

Table 6. Comparison of rescue analgesia between the timing of drug administration					
Timing of Administration	**Studies**	**Rescue Required (n)**	**Total Cats (N)**	**Rescue Rate (%)**	**95% CI (%)**
Pre-operative	6	11	238	4.62	2.6-8.1
Postoperative	2	10	51	19.61	11.0-32.5
Pre + post-operative	3	38	331	11.48	8.5-15.4
Pre + Intra-operative	2	9	47	19.15	10.4-32.5
Total	13	68	667	10.19	

Comparison of rescue analgesia rates between the timing of analgesic and the time of administration. A lower percentage indicates better outcomes. The 95% confidence interval (CI) was calculated by using the Wilson method. n: number of cats required rescue analgesia, N: total number of cats in that category. Timing refers to primary analgesia administration rather than the rescue analgesia

95 % CI 11.0-32.5), followed by pre- and intraoperative (19.2%; 95 % CI 10.4-32.5), and pre- and postoperative (11.5%; 95 % CI 8.5-15.4). The lowest incidence was recorded preoperative alone (4.6%; 95% CI 2.6-8.1).

Side Effects of Different Drugs Used for Feline Pain Management

Adverse effects associated with analgesic interventions were reported in 20 studies. The frequency and nature of these effects were varied by drug class, as summarised in *Table 7*. The most reported side effects were gastrointestinal symptoms (e.g. vomiting, diarrhoea) associated with NSAIDs and behavioural symptoms (e.g. euphoria, dysphoria, mydriasis) with opioids. Other significant effects included salivation with CBD and dipyrone, and neurological signs in cats administered robenacoxib.

Synthesis of Evidence and Clinical Framework

To establish a practical framework for clinical practice, data regarding efficacy *(Table 1, Table 2, Table 3)*, rescue analgesia *(Table 4, Table 5, Table 6)* and safety *(Table 7)* were synthesised. The resulting Evidence-Based Tired Framework for feline pain management is presented in *Table 8*, classifying interventions according to their recommended hierarchy and supporting evidence.

Table 7. Side effects related to different analgesics					
Compound	**Dose & Route**	**Treated Cats**	**Cats with Side Effects**	**Side Effect**	**Reference**
Cannabidiol (CBD)	4 mg/kg PO	22	08	Salivation, licking, headshaking (5); diarrhoea (1); vomiting (2)	Coelho et al. [38]
Ketamine	LD 0.5mg + CRI 5-23 µg/kg/min IV	16	16	Mydriasis	Ambros & Duke [49]
Ketamine + Midazolam +Dexmedetomidine + Buprenorphine + Meloxicam + Bupivacaine (OSA multimodal)	4 mg/kg + 0.25mg/kg + 40 µg/kg + 20 µg/kg IM + 0.2 mg/kg SQ + 2 mg/kg IP	13	2	Tachypnoea	Rufiange et al. [21]
Robenacoxib	1 mg/kg PO	37	5	GI emesis (3); neurological (1); skin (1)	Adrian et al. [41]
Robenacoxib	2 mg/kg SQ	173	26	Incision site infection, dehiscence, bleeding; vomiting; decreased appetite; lethargy	King et al. [34]

Table 7. *Continue*					
Robenacoxib	2 mg/kg SQ	101	30	Diarrhoea, emesis	Speranza et al. [40]
Meloxicam	0.3 mg SQ	46	12	Diarrhoea, emesis	Speranza et al. [40]
Frunevetmab (NGF)	1.0-2.8 mg/kg SQ, IV	64	5	Renal Insufficiency	Gruen et al. [42]
Dipyrone	12.5 and 25 mg/kg PO	20	20	Sialorrhea	Pereira et al. [25]
Hydromorphone + Buprenorphine or + Butorphanol	0.1 mg/kg + 0.02 mg/kg or + 0.2 mg/kg IV	6	6	Euphoria (rolling, kneading, vocalising, and purring)	Simon et al. [50]
Hydromorphone	0.1 mg/kg IV	7	7	Hyperthermia	Wegner & Robertson [52]
Methadone	0.3 mg/kg IV or 0.6 mg/kg OTM	16	16	Mydriasis	Ferreira et al. [51]
Oxymorphone	0.1 mg/kg IV or 0.5 mg/kg buccal	12	6	Restlessness (4), vomiting (1), muscle rigidity (1)	Pypendop et al. [54]
Tapentadol	25-50 mg/kg PO	12	11	Salivation	Doodnaught et al. [53]
Butorphanol	0.4 mg IV	70	2	Dysphoria	Taylor et al.[37]
Tramadol + Meloxicam	3 mg/kg + 0.05 mg/kg OTM	8	5	Mydriasis, decreased appetite, hypersalivation, vomiting	Monteiro et al. [43]
Meloxicam	0.01 - 0.03 mg/kg drops in feed PO	46	4	Vomiting	Gunew et al. [44]
Morphine	1 drop (50 µL) Ocular	17	3	Blepharospasm, hyperaemia, chemosis	Thomson et al. [39]
Oxymorphone	0.2 mg/kg	8	8	Restlessness	Briggs [48]
Alfaxolone	5 mg/kg IV	10	5	Opisthotonus, limb stiffness, shivering, excitation, myoclonus, vocalisation	Guerrero et al. [33]

Summary of the reported adverse effects of analgesic interventions reported in 38 studies. OTM: oral transmucosal; PO: per os, IV: intravenous, SQ: subcutaneous, IM: intramuscular

Table 8. *An Evidence-Based Tiered Framework for Feline Analgesia and Integrated Patient Care*				
Evidence-based Tier	**Recommendation**	**Agent Example**	**Rationale**	**Availability**
E1	Foundational analgesics	Robenacoxib, Meloxicam, Bupivacaine, lidocaine	Strong evidence, core of therapy	Widely available globally
E2	Potent analgesic add-ons	Buprenorphine, Hydromorphone, Ketamine	High efficacy; logistical constraints	Variable (often controlled substances)
E3	Adjunct for stress and anxiety	Synthetic facial pheromones (Feliway), Pregabalin	Reduces non-painful stress; supports welfare	Feliway: globally available. Pregabalin: controlled in the USA and the UK
E4	Not recommended	Dipyrone, Tramadol	significantly lower palatability and safety concerns	Banned or restricted in major jurisdictions (USA, Canada, Japan)

E1-E4 indicates the recommended order of intervention, from foundational (E1) to not recommended (E4)

Discussion

This review concludes that available evidence strongly supports the use of multimodal analgesia, with drug selection tailored according to the nature of individual cases. For severe acute pain cases, a combination of NSAIDs (meloxicam/robenacoxib), full opioid agonists (hydromorphone) and local anaesthesia is effective in ameliorating pain. For moderate pain such as routine ovariohysterectomy (OVH) procedures, a comprehensive multimodal approach encompassing opioid-sparing adjuvants and local analgesia is indicated.

Findings from the rescue analgesia analysis provide strong, empirical and evidence-based data with qualitative and severity-based insight. The need for rescue analgesia clearly indicates inadequate pain management, and the analyses assist in identifying effective strategies. The rescue analgesia analysis depicted a subtle image determined by the intensity of pain models and sample sizes. The low pooled rescue rate in individual therapy

arms (5.3%) is diluted primarily by multiple large-scale trials (n >100) of effective single agents. Some of these agents include the use of robenacoxib in normal procedures like ovariohysterectomy. A single effective drug is often adequate in these controlled environments with a predictable pain burden, leading to few rescue events in a large population of animals. In contrast, the multimodal therapy arms were frequently used in more complicated cases or studies with a small sample size (n=10 per arm). Under such circumstances, characterised by a more intense or unpredictable pain, the objective of a multimodal protocol is to offer a strong analgesic base. Although this approach results in an increased pooled rescue rate (16.6%) compared to idealised single-agent cases, it offers a significant improvement over the rescue rate recorded in the control group (41.6%).

Thus, the available data provides no evidence on the superiority of monotherapy. Instead, these findings support the selection of a multimodal therapy when dealing with complex or severe pain, given its ability to address the situation reliably [21,63,64]. On the other hand, monotherapy can be very useful in moderate pain models [21]. The substantial difference in the rescue rates between both treatment groups (multimodal and monotherapy) and the control group underscores the necessity of active analgesic intervention.

The drug-class analysis provided a well-defined hierarchy of the efficacy of monotherapy options. The very low rescue rate for opioids (3.11%) confirms their strong analgesic activity as a group of drugs [21,37]. The low rate in the miscellaneous category (4.9%), which incorporates local anaesthetics and other adjuncts, indicates the definitive effect of these interventions. While the average rate of NSAIDs (12.9%) confirms their effectiveness, it also depicts their limitations as a monotherapy approach, particularly in more painful procedures. The high rescue rate observed for the opioids and NMDA agonists groups (26.2%) does not indicate a regimen failure. Instead, it reflects this combination's use in models with extreme pain burden, and it still resulted in better outcomes [21].

Based on the rescue data from this review, the timing of analgesia administration is significant factors. The results strongly support the use of pre-emptive analgesia. The lowest rescue rate was, by far, for the pre-operative administration (4.6%). This reflects the effectiveness of administering analgesia before surgical intervention and the onset of pain (central sensitisation). It is more effective to prevent pain in this way than attempting to ameliorate pain once it occurs [22,65,66]. The higher rescue rates in post-operative (19.6%) and pre- and intra-operative (19.2%) groups indicate that delaying intervention until the activation of pain results in poor control, despite subsequent usage of other effective drugs. This confirm that time of administering the drug is as critical as the drug itself.

This review also described the topography of pain assessment tools applied in feline research, due to their direct influence on intervention efficacy. The UNESP-Botucatu multidimensional composite pain scale and its subtypes [22-25,29,30,32,35,59,62] were the most frequently applied tools in surgical studies, especially for ovariohysterectomy and castration. These tools have been proven effective, demonstrating significant results compared to controls in various acute surgical conditions. These scales are designed to be comprehensive, incorporating behavioural observations, physiological parameters, and direct palpation to gauge discomfort. This tool assesses patient's behaviour both spontaneously and in response to interaction, incorporating features from established clinical pain measurement [67]. Its widespread use reflects a paradigm shift towards standardised, validated tools that assess multiple behavioural parameters, making them more sensitive and reliable than unidimensional scales.

The visual analogue scale (VAS) was also a frequently used [22,24-27,29,33], particularly in conjunction with other tools such as the UNESP-Botucatu, the Feline grimace scale, the Glasgow composite measure pain scale and physiological parameters. While its subjectivity is a limitation, its ongoing use highlights the continued need for tools that are practical for clinical application. However, the variability emphasises the significance of using VAS in conjunction with more objective measures or specific behavioural scales.

Physiological indicators like heart rate, blood pressure, respiratory rate [28,35,38], blood glucose [24] and cortisol level [27,40] are also used in assessing pain and stress in cats. Postoperative physiological parameters (HR, BP, and RR) and different biochemical markers (blood glucose and cortisol level) are inconsistent and unreliable for pain assessment, as evidenced in the reviewed studies [27,38,40]. These parameters and markers are often affected by different factors such as stress, fear, discomfort and anaesthesia recovery [27,35,38,40], thus contributing to their limitations in explaining significant differences between treatment groups as compared to validated pain scales. This implies that although physiological parameters are important in pain assessment, they are not adequate to be used as individual tools in explaining feline pain.

Mechanical Threshold (MT) [33,43,48,51,56] and Thermal Threshold (TT) [50,52-55,57] testing was generally used for quantitative, objective data. These tools were helpful in studies on healthy cats in establishing the pharmacodynamic profile of drugs, such as buprenorphine and hydromorphone [52,57]. They also yield a precise measure of efficacy that is less susceptible to observer bias. However, their use is limited to research settings because of the equipment and cooperation required from the patient. These instruments have their own advantages; however, drawbacks relating to habituation in

cats following their repeated usage remain a big challenge. Despite their effectiveness in identifying nociceptive pain and hyperalgesia, their focus on sensory reaction may not fully reflect the animal's pain. They may overlook other aspects of the animals' experience, such as their behaviour and perception of pain. Overall, the common choice of tool was determined by the pain model. Activity monitors (AMs) and owner-completed questionnaires such as the Feline Musculoskeletal Pain Index (FMPI) were valuable and valid endpoints for chronic OA studies [41,42]. These tools provide a real-life measure of improvement that is unachievable by pure threshold testing. Overall, a universally optimal pain assessment technique for cats has not yet been established. Nevertheless, veterinary medicine is progressively embracing a flexible, multimodal methodology. Within this approach, validated composite scales such as the UNESP-Botucatu remain the most reliable in clinical settings.

Every analgesic protocol should be considered in view of its safety and tolerability profile. The analysis of adverse effects from this review identified significant trends to guide clinical decision-making. Opioids were commonly associated with dysphoric behaviours of euphoria (vocalising and rolling), and mydriasis [50,51]. While these effects are typically brief and rarely harmful, they can be unpleasant for owners and make post-operative monitoring more challenging. This emphasises the significance of patient monitoring and owner education when administering these potent medications. NSAIDs, especially robenacoxib and meloxicam, were linked to gastrointestinal effects such as vomiting and diarrhoea. However, the incidence was generally low and within acceptable limits for peri-operative use [40,41]. Dipyrone was consistently and significantly associated with ptyalism (excessive salivation) [25]. Despite not being life-threatening, dipyrone has significant detrimental effects on patient and owner comfort, thereby constituting a considerable limitation to its use.

The accumulated evidence from this review demonstrates that with multimodal therapy, effective analgesia could be achieved without a concomitant rise in severe adverse events. By leveraging synergistic pharmacological benefits, lesser doses of each individual agent can be employed, potentially reducing the adverse effects associated with greater doses of individual treatments. The observed adverse effects were largely predictable and manageable. Opioid related dysphoria and GI effects from NSAIDs were the most common considerations. This information is crucial in making informed choices, preparing owners for what to expect and choosing the appropriate drug for a patient.

Based on the evidence on efficacy, safety, and assessment, the following levels of evidence-based tier (E1-E4) were suggested to range clinical practice despite the fluctuating international drug availability. This framework ranks interventions in order of strong evidence, high safety profiles, and wide regulatory acceptability to offer a flexible approach to international veterinarians *(Table 8)*.

Tier E1: Fundamentally Recommended and Accessible; this tier includes agents having strong evidence for efficacy and a well-established safety profile in cats and having a widespread registration across major international regions (EU, North America, Australia). The cornerstone in managing the most painful conditions should be the pre-emptive administration of an NSAID (i.e., robenacoxib or meloxicam) combined with local anaesthetic techniques (i.e., lidocaine or bupivacaine nerve blocks or incisional infiltration). This multimodal approach produces effective, cost-effective analgesia with minimal dependence on controlled substances.

Tier E2: Strong but Complex from a Logistical Perspective; This tier contains drugs with strong evidence of efficacy, but the use is complicated by international controlled substance regulations, requirements for intensive monitoring or limited formulation availability. The combination of superior efficacy and a growing license for use in cats globally, buprenorphine, a partial opioid agonist, is the analgesic of choice in this tier. Where legal and under appropriate surveillance, full μ-opioid agonists (hydromorphone, methadone) and low-dose ketamine infusions are pivotal in severe pain or as part of balanced treatment regimens. The application is often limited to environments that allow for addressing their side effects and regulatory requirements.

Tier E3: Adjunct for stress and anxiety: Tier E3 adds a very important aspect to the overall care of the patient, which is the management of non-painful stress and anxiety. It has been well established that stress may reduce pain thresholds and complicate recovery. Thus, the agents at this level are considered treatment adjuncts, which include synthetic feline facial pheromones (e.g. Feliway) and nutraceuticals. They produce a well-being by alleviating anxiety in hospitalised cats. This led to more accurate pain assessment, better adherence to treatment and possibly even more effective core analgesics. Their presence raises the level of care beyond mere alleviation of a symptom of pain to a proactive support of the overall patient's well-being.

Tier E4: Not Recommended for Clinical Use; This tier contains drugs limited or inconsistent evidence regarding their efficacy. It also includes drugs with significant safety concerns that have led to restrictions or bans in key jurisdictions. Dipyrone (metamizole) is banned in the United States, Canada, and Japan. Tramadol has poor oral bioavailability and inconsistent analgesia in cats and is a controlled drug in many areas. These agents cannot be recommended as reliable analgesics.

This framework emphasises that excellent analgesia can be achieved even in resource-limited environments if the

Tier E1 foundation of an NSAID and local anaesthetic block is used as a pre-emptive measure. The main challenge is in the Tier E2 group, where strong agents such as full μ-opioid agonists are often limited by controlled substance legislation, which differs markedly between countries. This requires clinicians to be familiar with their local laws and use the best available agents, especially buprenorphine, which is becoming more widely available worldwide. This tiering provides a clear rationale for not using drugs such as dipyrone, moving clinical practice in line with available evidence and with international safety standards.

While this review has been focused on direct pharmacological control of pain, optimal patient care requires a holistic approach. Given the strength of the supporting evidence, we recommend formally integrating stress management as Tier E3 in our clinical framework. Although 10 studies on non-painful stress management [68-77] were not included in the main analysis, their results revealed an important adjacent field. These studies demonstrated that non-pharmacological treatments (e.g., synthetic pheromones; Feliway, nutraceuticals; alpha-casozepine, and environmental manipulation) and pharmacological agents like pregabalin can effectively reduce anxiety related to transportation, hospitalisation, and novel environments.

The relationship between stress and pain is well-documented [78,79]; stress can exacerbate pain perception and delay recovery [80]. Therefore, a key direction for future research is to investigate the synergy between evidence-based analgesic protocols and stress-reduction strategies. Although the tiered framework offers a definite route to pharmacological analgesia, its efficacy can be significantly enhanced by concurrently applying the Tier E3 stress reduction interventions. Uncontrollable pain is a profound stressor, and pain-related behaviour can be exacerbated by stress response. Consequently, agent such as synthetic feline facial pheromones (Feliway), alpha-casozepine, and pregabalin should not be considered independent of pain management but rather as integral component of it. Implementing these modalities to create a less stressful environment helps achieve a calmer patient. This, in turn, facilitate a more successful pain assessment, easier administration of medications and reduced requirement for systemic analgesics. Future studies should quantitatively explore this multimodal synergism by determining whether the combination of stress-reduction interventions directly improves pain scores or less analgesic requirement in a clinical setting.

Looking beyond the existing evidence, several emerging methods have the potential to transform feline pain management. Targeted therapies such as the monoclonal antibodies like frunevetmab have a good safety profile and long duration of action, suggesting potential for widespread use. Cannabidiol (CBD), which represent a novel mechanism of action for conditions like feline chronic gingivitis (FCG), requires validation through more robust clinical trials. Future studies should investigate into long-acting formulations and localised delivery systems (e.g., extended-release local anaesthetics) to provide sustained analgesia from a single dose, thereby enhancing patient compliance and comfort. Lastly, the integration of precision medicine, such as genetic or biomarker testing to predict individual analgesic response, is a pertinent frontier of maximising efficacy and minimising adverse effects.

Furthermore, the application of objective neurophysiological biomarkers should be considered in future work to overcome the subjectivity intrinsic to behavioural scales. Methods, including electroencephalography (EEG) with well-established potential in identifying neurophysiological signals of pain and stress in other animals, are to be confirmed in cats. On the same note, the search for pain-specific plasma biomarkers is a crucial direction towards a blood-based objective test. Combining these objective measures with fine behavioural scales is pertinent for accurate and reliable pain assessment.

The relatively low number of studies (n=42) included in this systematic review reflecting the stringent inclusion and exclusion criteria required to address a specific research question. While this ensures the conclusions are based on high quality, relevant evidence, it also limits the generalisability of the findings and underscore the need for more primary research in this field. Furthermore, the review scope is constrained by the available research. The marked heterogeneity in study designs, pain models, and outcome measures precluded meta-analysis and prevented formal evaluation of publication bias. The accumulated evidence focused on acute peri-operative pain, with limited studies on chronic conditions. Finaly, comparability between studies was influenced by the substantial inter-study differences in pain-assessment tools.

Conclusion

This systematic review confirms that multimodal analgesia, founded on appropriate pre-emptive analgesia, is the cornerstone of effective feline pain management. The current evidence supports well-defined protocols based on NSAIDs and local anaesthetics, with addition of potent opioids for severe pain. A tiered system for global application is therefore suggested: a Tier E1 core of readily available NSAIDs and local anaesthetics, supported by Tier E2 opioids, such as buprenorphine, for more severe cases and Tier 3 stress-reducing agents as adjuncts. Drugs with limited efficacy or suboptimal safety profiles, such as dipyrone and tramadol, are not recommended. Future work should include further standardisation of outcomes, chronic pain management and investigation of synergies

with stress reduction. This synthesis provides a concise, evidence-based roadmap to enhance feline analgesia, highlighting critical areas for translational research.

Declarations

Availability of Data and Materials: All the generated data are included in the manuscript.

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