Treatment options for feline pain are definitely fewer than those available for dogs. Although this knowledge gap has narrowed in the past decade, most of the information available for pain control in cats is related to perioperative analgesia, while chronic pain conditions are still poorly treated.

**THERAPEUTIC OPTIONS FOR FELINE CHRONIC PAIN (other than NSAIDs)**

There are very few drugs approved for long-term use in cats with maladaptive pain both in Europe and in North America, and only one NSAID (meloxicam) is approved for long-term use in some parts of the world. Despite recent information suggesting that NSAID therapy can partly reverse central plasticity changes, it is generally accepted that the maladaptive component of pain conditions is poorly responsive to NSAIDs [1]. Additionally, concerns about the potential for adverse effects from NSAIDs has led to a search for alternative drug therapies. Currently, drug choices are based on published case reports or experimental studies performed in rodent models of chronic pain. Some of the drugs that have been lately being considered therapeutic options for the feline patient suffering from chronic pain include gabapentin, tramadol, amitriptyline, amantadine, tapentadol, flupirtine. Finally, a couple of very promising novel analgesic agents include grapiprant and anti-nerve growth factor antibodies, however their clinical use is not a reality yet [2].

**Gabapentin**

Neuromodulating drugs, such as Gabapentin and Pregabalin, have become the mainstay of treatment for neuropathic pain in human patients in the last decades. In people its administration is only approved for postherpetic neuralgia, and as an adjunctive therapy for partial onset seizures, which are undocumented syndromes in animals.

Both pregabalin and gabapentin have proven to have a similar mechanism of action that works through the \( \alpha_2\delta-1 \) subunit of voltage-gated calcium channels which are upregulated in the dorsal root ganglia and spinal cord after a noxious insult. Although they are structurally related to GABA, they do not bind directly to this receptor. They are believed to selectively bind to the \( \alpha_2\delta \) subunit of the voltage-gated calcium cannels, reducing the calcium influx into the presynaptic nerve terminal, and thereby inhibiting the release excitatory neurotransmitters involved in pain transmission, such as glutamate and substance P. In veterinary medicine, the most commonly reported side effects are minimal and are restricted to mild sedation and pelvic limb ataxia.

The use of gabapentin as an adjunctive analgesic agent has increased significantly in veterinary medicine over the past several years. It has anecdotally been used to treat chronic neuropathic pain, chronic cancer pain, chronic osteoarthritis pain, and, increasingly lately, perioperative pain in dogs and cats. Dosing guidelines in veterinary medicine have been largely based on human recommendations despite some key species differences in pharmacokinetics [3]. The pharmacokinetics of oral (10 mg/kg) and intravenous (4 mg/kg) gabapentin in cats has been described and a dosing regimen of 8 mg/kg every 6 h
has been suggested for antihyperalgesic effect in the cat based on pharmacokinetic–pharmacodynamic data and modeling studies from other species. However, caution is warranted when extrapolating data from other species. There is also a current lack of information on pharmacokinetics after repeated dosing. Currently, the most frequently followed dosing regimen by veterinarians ranges from 5-10 mg/Kg Q12. Additionally, there are no clinical studies evaluating the efficacy of gabapentin in chronic pain conditions in cats and only a number of case studies have reported its use in patients suffering from musculoskeletal pain and traumatic incidents. Despite the promising results reported, these case studies possess no objective or validated pain assessment method and may even suffer from the placebo effect perceived by owners and reflected in their pain assessment reports. Therefore, additional research evaluating safety and efficacy of gabapentin in the treatment of chronic pain in the feline patient is still necessary before treatment recommendations could be made.

**Tramadol**

Tramadol exerts agonist actions at all opioid receptors, but particularly at μ receptors. Additionally it inhibits the re-uptake of norepinephrine and serotonin, and stimulates presynaptic serotonin release.

Its analgesic potency is one-tenth that of morphine, and respiratory depression and constipation are milder than those produced by morphine. Its use is contraindicated in seizure-prone patients and those with hepatic insufficiency. Its main advantage remains the fact that, unlike most of opioids, it’s not a controlled drug, making it an excellent option for pain management at home once the patient is discharged.

This drug is formulated as a mixture of enantiomers, and its first metabolite M1 (o-desmethyltramadol), may be responsible for the majority of the analgesic effects of tramadol. The pharmacokinetics of oral (5 mg/kg) and intravenous (2 mg/ kg) tramadol in cats has been described [4]. While more data needs to be collected about minimum effective concentration, the pharmacokinetic data collected so far is promising. Currently, the most frequently followed dosing regimen by veterinarians ranges from 2-4 mg/Kg Q12. As for the evaluation of tramadol efficacy, a few studies have recently reported very promising reports in osteoarthritis (OA) feline patients. The most common side effects reported include mydriasis, sedation, hypersalivation, vomiting, and stomatorrhagia. The reported bitter taste of Tramadol is suspected to be responsible for most of the latter observations. While additional research would be needed, the pharmacokinetic data and the recent efficacy studies on chronic pain are very encouraging. Aversion of patients to its administration may present a problem with clinical use, and may require compounding or reformulation.

**Amitriptyline**

Amitriptyline is a tricyclic antidepressant (TCA) that exerts its pharmacologic effect by inhibiting serotonin, norepinephrine, and dopamine reuptake. While its use in veterinary medicine has been limited primarily to behavioral disorders, in human medicine it has been widely used to provide analgesia in cases of neuropathic pain and interstitial cystitis. Due to the similarity of interstitial cystitis in humans and idiopathic cystitis (IC) in cats (as both seem to have a neuropathic pain component), amitriptyline has been evaluated for efficacy in IC with very promising results. Also, the effect of amitriptyline on segmental inhibition has been studied in cats and its administration significantly increased its occurrence. This results particularly interesting for the treatment of chronic pain states where inhibitory processes of the CNS may be pathologically altered. There are currently no data on the pharmacokinetics of amitriptyline in the cat, which would be important for making dosing recommendations. However, currently, the most frequently followed dosing regimen by veterinarians ranges from 0.5-1 mg/Kg Q24. The drug’s reported bitter taste, and potential side effects such as reduced grooming, sedation, and weight gain may limit its clinical use [5].
Amantadine

Amantadine is an antiviral agent that is also prescribed for treatment of Parkinson disease in human patients. Its mechanism of action seems to be related to its modulatory effects on CNS dopamine concentrations. However, Amantadine has also been described as an N-methyl-D-aspartate (NMDA) antagonist, and that characteristic seems to be responsible for its analgesic properties. In fact, it has been proven that both the NMDA receptor and its ligand, glutamate, have been involved in the development and maintenance of central plasticity through the increase and maintenance of neuronal excitation and subsequent modifications of gene and receptor expression. Blockade of these receptors with NMDA antagonists has been shown to both prevent the development of central plasticity, as well as to provide analgesia to affected animals.

Amantadine’s use in cats stems from anecdotal reports of efficacy, or from extrapolation of treatment efficacy in dogs when used in conjunction with NSAIDs. In this study, amantadine was evaluated in dogs with OA that were not fully responsive to NSAID therapy and found to be beneficial. While this study is not indicative of amantadine’s efficacy as a sole analgesic, these data were promising when amantadine is considered a part of a multimodal therapeutic strategy when NSAIDs are not an effective option.

The pharmacokinetics and efficacy studies on amantadine administration in feline chronic pain patients have shown inconclusive results since amantadine was tested on thermal threshold animal models and this agent may require changes present in chronic pain state in order to be able to exert appreciable effects. No dosing recommendations can be made from these studies’ results, as no data exists for minimum effective concentrations. However, currently the most frequently followed dosing regimen by veterinarians ranges from 3-5 mg/Kg Q24 (a dosing regimen likely extrapolated from the canine literature). Amantadine’s mechanism of action makes it an attractive candidate for further evaluation in cats. However, clinical data showing efficacy of amantadine is currently lacking.

Flupirtine

Flupirtine is an aminopyridine that acts as a selective neuronal potassium channel opener (SNEPCO). Its mechanism of action is based on the interaction with G-protein-regulated, inwardly rectifying K+ channels (GIRKs) (a class of potassium channels that do not belong to the voltage-gated family). Activation of GIRKs by flupirtine results in a hyperpolarizing current that stabilizes the membrane potential and therefore, decreases neuronal excitability. Additionally, it also indirectly inhibits the NMDA receptor due to its role as an oxidizing agent at the receptor’s redox site, maintaining the magnesium block on the NMDA receptor.

Flupirtine has been historically used in Europe for a range of painful conditions in humans, including musculoskeletal back pain, migraines, chronic pain, postoperative pain, and myofascial pain. Opioid-sparing effects have also been demonstrated in human patients. However, acute hepatotoxicity has been reported in humans. Unfortunately, there is only one pharmacokinetic study available in cats and the evidence of efficacy is very limited to only non-companion animal models or pain models that do not allow for evaluation of chronic or maladaptive pain [6]. However, its novel mechanism of action makes it an attractive candidate for evaluation, although the drug is only available in certain parts of the world at the moment.

Tapentadol

Tapentadol is part of a new class of drugs known as MORphine receptor agonist-Noradrenaline Reuptake Inhibitors (MOR-NRI), and shares a common structure with tramadol. Tapentadol’s affinity for morphine
receptor is 50-fold less than that of morphine, which appears to translate into a decrease in the characteristic opioid related adverse effects (such as vomiting or decreased GI motility). It also only exists as a single enantiomer, and only the parent compound exerts the MOR-NRI effects (unlike tramadol, where the metabolite is the pharmacologically active form).

Tapentadol’s pharmacokinetics has been characterized in cats, as well as its side effects (similar to those previously reported in dogs, such as salivation and panting, although agitation has also been seen in some cats). Additionally, there are some data evaluating the efficacy of orally administered tapentadol in healthy adult cats. Currently, only parenteral routes of administration have been evaluated, with no data on potential efficacy in the cat. Oral pharmacokinetics and analgesic efficacy in the cat are needed before any treatment recommendations can be made.

**Maropitant**

Maropitant is a potent and selective neurokinin-1 receptor (NK1R) antagonist that acts as a central and peripheral antiemetic. However, this receptor is also shared by Substance P (SP), which is known to be involved in inflammatory and nociceptive processes. Although the pharmacologic properties of the drug seem very promising, it is also true that NK-1 receptor antagonists have failed clinical trials for multiple painful conditions in humans (possibly due to the existence of parallel pathways in the transmission of pain).

The pharmacokinetics of maropitant administered intravenously, orally and subcutaneously has been evaluated in cats. And, while initial pharmacological data are available, there is currently insufficient data for pain therapeutic recommendations to be made due to lack of efficacy data (data available so far is only related to its MAC sparing properties).

**FUTURE THERAPEUTIC OPTIONS (what the future brings…)**

**Grapiprant**

Grapiprant is a selective prostaglandin E receptor 4 (EP4) antagonist that belongs to a new class of drugs, the piprants, which work by blocking prostaglandin E2 (PGE2) receptors. Different studies have proven that EP4 receptor is involved in the occurrence of rheumatoid and osteoarthritis associated pain, as well as with inflammation in general. However, this mechanism of action can be considered similar to that of traditional NSAIDs and grapiprant may not be efficacious for pain syndromes with a primarily maladaptive drive.

While pharmacokinetic and clinical data of efficacy is available for dogs with osteoarthritis, only safety and toxicokinetic data are available in cats [7], [8]. Minor clinical pathological abnormalities have been reported in cats (such as changes in clotting times and hemoglobin), however, they are not considered clinically relevant. And, most importantly, no GI or renal abnormalities were among the abnormalities observed, in contrast to the most frequent concerns when COX-inhibiting NSAIDs are administered in cats.

While the drug is still in early stages of evaluation in the cat, its potential as an anti-inflammatory and analgesic drug with an apparently good safety profile is very promising. More solid pharmacokinetic and pharmacodynamic data will be hopefully available in the future, particularly studies of clinical efficacy in chronic pain conditions in feline patients.
Anti-nerve growth factor antibodies

Nerve Growth Factor (NGF) is a protein that regulates the growth, maintenance, and survival of neurons in the developing animal and a recent interest in its inhibition has been growing. It is known that NGF levels are increased within the joints of humans and dogs affected by osteoarthritis, where it increases sensitivity and excitability of nociceptors, as well as stimulates the growth of new nerve fibers into inflamed tissue. NGF exerts its actions by activation of a specific tyrosine kinase receptor that leads to a signaling cascade that increases both excitability the TRPV1 channels as well as the production of other pro-excitation proteins. Additionally, NGF is also known to activate mast cells, whose cellular products can increase sensitization of neurons. Both dog-specific and cat-specific (ranvetmab and frunevetmab, respectively) monoclonal antibodies against NGF have been developed, evaluated in pilot trials, efficacy has been proven and no adverse effects have been reported. Currently, the role of anti-NGF antibody in treating central processes is unclear, however there are indications that there may be some modulation of central processes as well. Pharmacokinetic data for NV-02 (the felinizied antibody) is available for doses ranging from 2 mg/kg to 28 mg/kg SQ in 8 healthy cats.

The data available so far for the felinizied anti-NGF antibody, including a long duration of action with few adverse effects, is promising [9][10]. Its actions would be particularly interesting in cats in which oral administration of medications is not possible, or in cats where NSAIDs are not indicated. However more pharmacologic and efficacy data are needed.

Finally, another novel agent is being currently developed: anti-TNFa antibodies. Given the role of TNFa in chronic pain, it may also exert beneficial effects in maladaptive pain states. However, insufficient data is currently available and it cannot be considered as a clinical therapeutic option at this point.

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