Introduction
Non-steroidal anti-inflammatory analgesics and opioids will likely remain the cornerstone drug classes to manage pain in both human and veterinary medicine. Full treatment of NSAID and opioids can be found in other sources, and this manuscript will deal with some in the feline species.

NSAID:
One unpublished case series of cats undergoing de-sexing not receiving IVF did result in many patients experiencing acute renal failure with only 1 or 2 doses of various NSAID. Case reports of ARF with meloxicam use in cats prompted the manufacturer to place a "black box" warning on the U.S. label, keeping in mind that the U.S. label for cats is different than anywhere else in the world: a single injection at 0.3 mg/kg. Elsewhere in the world, the label is for an initial oral or parenteral dose at 0.2 mg/kg, followed by oral doses at 0.1 mg/kg for 5-11 days depending on the country, and one feline study revealed no alteration in glomerular filtration rate, as measured by iothexol clearance, after 5 days of oral meloxicam. Another more recent study of cats with surgically-induced reduced renal mass revealed that meloxicam 0.2 mg/kg Day 1 and 0.1 mg/kg Days 2-7 did not elicit a measurable effect on creatinine clearance test, serum creatinine concentration, or UP:C; these results are consistent with the hypothesis that GFR of euvoletic cats with normal or reduced renal function is not dependent on cyclooxygenase function. The same may not be true for hypovolemic cats, and it may be that cats susceptible to post-meloxicam ARF may have been have had pre-existing clinical or subclinical diminished volume or other pre-existing problems with renal blood flow. Meloxicam has been shown to be superior to butorphanol in onychectomy, there were no differences in efficacy and safety parameters whether receiving 3- or 5-days of meloxicam post-sterilization + onychectomy; the patients that received meloxicam preoperatively had statistically better gait/lameness scores than those that received meloxicam postoperatively, supporting the principle of preemptive analgesia.

Robenacoxib (Onsior®): available in Europe, and approved by the FDA for post-operative pain in cats in the U.S. in 2011, this unique COX-2 selective NSAID has a short plasma half-life in this species (1.7 H), yet accumulates in inflammatory exudates for up to 24 hours. This novel “tissue-specific” character appears to fulfill the promise to provide both safety and efficacy in cats, and in fact, while approved only for 3 days post-operatively, a 6-week trial in cats revealed the drug to be well-tolerated even at 3X and 5X the labeled dose. Robenacoxib by SC injection was FDA-approved as effective and well tolerated in the control of post-operative pain associated with orthopedic, ovariohysterectomy and castration surgery in cats. In a study of cats undergoing ovariohysterectomy, robenacoxib appeared to elicit superior post-operative pain control than meloxicam, but in another study in orthopedic surgery, 1 injection of robenacoxib SC was non-inferior to 1 injection of meloxicam (0.3 mg/kg) SC, and additional PO robenacoxib did not demonstrate any additional advantage. In another OHE study, robenacoxib was a more effective analgesic drug than buprenorphine, and the addition of buprenorphine did not provide any additional analgesic effects compared to robenacoxib alone; however the pain scoring system utilized in the outcome measure was not a validated one.

It is axiomatic that patients undergoing general anesthesia should have the benefit of intravenous fluid support and blood pressure monitoring, which would further increase the safety margin of NSAID use pre-operatively. Nevertheless, many clinicians elect out of an abundance of caution to reserve NSAID for post-surgical use only.

Long-term NSAID in cats:
In the EU, meloxicam carries a label for its indefinite use in cats for musculoskeletal pain at 0.05 mg/kg. A 6-month safety of reduced-dose meloxicam (0.01-0.03 mg/kg/day) has been reported, and the results of one retrospective study suggested that a long-term maintenance low-dose of 0.02 mg/kg/day of meloxicam can be safely administered to cats older than 7 years even if they have chronic kidney disease, provided their overall clinical status is stable (in fact creatinine trended slightly lower in some cats) and patients are carefully monitored. This is important because up to 2/3 of cats with DJD have concurrent CRD. From an efficacy perspective, however these studies were not blinded, which leaves them open to caregiver placebo effect, which in OA cats is up to 63-74+% (depending on the outcome measure); and the latter (Gowan 2013) was not randomized, as only the healthiest cohort of cats was included. The exceedingly high caregiver placebo effect (in which almost any treatment might appear effective) can be offset by a different model: detecting a worsening in outcome measure after withdrawal of treatment. However, long-term daily low dose meloxicam appears to be well tolerated, including one study at 0.03 mg/kg daily for 448 days, and one retrospective study demonstrated that a cohort of older cats with IRIS II and III CRD receiving long-term low-dose meloxicam had survival times similar to historical cohorts of similar cats not receiving long-term meloxicam (1600+ days). A more recent study using objective outcome measures demonstrated improved nighttime activity (but no improvement in force plate). Lastly a recent study evaluated an oral transmucosal (OTM)
Robenacoxib has excellent, even dramatic, long-term safety data in young healthy cats, up to 6 weeks at 10 times the labeled dose,24 and 6 months at 5 times the labeled dose.25 More recently, safety was demonstrated in stable IRIS 1 & 2 chronic kidney disease cats for 1 month at the daily labeled dose.26

Piprant anti-inflammatory/analgesic
In 2014, the FDA designated a new “piprant” class (for Prostaglandin receptor antagonists, non-prostanoids, PRAs) of “non-COX-inhibiting anti-inflammatory, analgesic drug.” It represents a new targeted inhibition of strictly the EP4 G-protein coupled receptor of PGE2. It is the EP4 receptor of PGE2 binding that appears responsible for pain, inflammation and hypersensitization,27,28 while EP1, EP2, EP3 receptors are responsible for promoting normal tissue (especially GI) homeostasis. Thus antagonizing EP4 while sparing the other EP4 receptors holds the promise of achieving a clinically anti-inflammatory and analgesic effect in osteoarthritis29,30,31 (and anti-hyperalgesia32) while minimizing the well-described gastrointestinal adverse effect profile common to COX-inhibiting NSAIDs. The first drug in this class, grapiprant, achieved approval in the U.S. for dogs in March 2016. Pharmacokinetics of oral grapiprant has been studied in cats, and if the minimal effective concentration in dogs (164 ng/ml) also applies in cats, 2 mg/kg PO might be effective for 10 hr.33 Toxicokinetic profiles of grapiprant in cats reveals a wide safety margin; administered at up to 15 mg/kg PO (>7X the prospective therapeutic dose) for 28 days, with no adverse effects were detected and no changes in body weight, food consumption, clinicopathologic variables, or gross or histologic necropsy findings.34

Opioids
Synthetic opioids are the most powerful tools to manage acute pain.

Full mu agonists:
Morphine: Cats lack glucoronate metabolism, resulting in minimal production of the analgesic M6G metabolite35, therefore morphine may not be the ideal opioid for use in this species. However, the clinical utility of morphine of cats has been reported at 0.1-1.0 mg/kg SQ, IM, IV36
Hydromorphone: In cats, hydromorphone may have a longer duration of action than in dogs (>7 hours in one thermal threshold model37) and is implicated more than other opioids in episodes of hyperthermia in this species.38 0.05-0.2mg/kg SQ, IM, IV38
Methadone: Methadone may also be an attractive opioid alternative in animals,40 in part due to its additional effect as an NMDA antagonist and evidence of effectiveness in rodent models of neuropathic pain.41 Its utility as a premedication has been demonstrated in cats.42 The utility of oral [transmucosal???} methadone has been reported in cats but it is distasteful and elicits drooling. 0.05 – 0.5 mg/kg SQ, IM, IV43
Fentanyl is a short-acting opioid preparation (Sublimaze®) with a potency of 80-100x that of morphine. It has a very short half-life that generally limits its use as an intravenous constant rate infusion 0.1-0.7 ug/kg/min44. A commercial transdermal fentanyl patch (Duragesic®), labeled for breakthrough cancer pain in humans, has been used in cats 1-2 ug/kg/hr.45 While clinical utility has been demonstrated in these species,46,47 plasma levels appear to be highly variable in cats38,49, (and dogs) under the best of circumstances. A strong argument can be made that liability exists with regards to human exposure (using it on a non-indicated species, for a non-indicated purpose).
Recently the anesthesia-sparing30 and dose-titration studies in cats has been performed for another ultra-short-acting opioid preparation, remifentanil (0.4 µg/kg/min in cats undergoing OHE).51

Partial mu agonist:
Buprenorphine (Buprenex®) is a partial agonist on the mu receptor though it has greater affinity than morphine (and will displace it if given together, although this effect may be clinically significant only at higher doses). It does have a ceiling effect meaning the analgesic effect does not become more pronounced at higher doses (and may actually become diminished at higher doses as it displaces endogenous opioids off mu receptors). Customary dose is 0.02 mg/ kg IM, IV preferred52 (PK superior to SC and OTM, with the former being highly erratic).53 Its superiority at this dose to butorphanol has been demonstrated in feline OHE,54 but another study found the analgesia for feline OHE inadequate at the same dose.55 A benefit of the drug in had been thought to be because pKa (8.4) closely matches the pH of the feline oral mucosa (9.0), this allows for nearly complete absorption when given buccally in that species56 and kinetics nearly identical to IV and IM administration.57 More recent work however (collecting non-jugular blood, demonstrates approximately 50% of previously reported bioavailability.58 While there is apparent clinical utility of OTM buprenorphine in cats, the kinetic data above explains why IV or IM administration appears to be superior to OTM.59 Oral transmucosal absorption in the dog appears to be similar to cats and humans (25-40%).60 All of the above studies utilize the commercially available form of buprenorphine (Buprenex); compound solutions of OTM buprenorphine derived from sublingual tablets are available. While stability of up to 90 days has been demonstrated,61 the extent of absorption is significantly less than that of Buprenex®.62
Buprenorphine is recently available for humans as a transdermal patch (Transtec®, BuTrans®, Buprederm®). Rabbits and rodents achieved rapid plasma levels (1-24 hours) with peak analgesic activity with the tail-flick and writhing model at 3-4 hours and sustained for 72 hours of the study.53 However in one feline study using a 35 mcg/h patch, plasma levels were negligible and there were no changes in thermal thresholds.54

Buprenorphine is also available in a compounded (non-FDA approved) sustained-release formulation. Unpublished PK data in dogs report plasma levels adequate for analgesia for over 72 hours,65 but there are anecdotal reports of prolonged and in some cases dramatic sedation especially at the higher end of the dosage range in larger dogs.56 There are no published PK data for this Bup-SR product, but unpublished PK data in cats superior maintenance of plasma levels adequate for analgesia over 3 days when compared to repeated OTM dosing.67 68 One published PD study in cats found SR buprenorphine to be non-inferior to Q 12 H OTM dosing for three days post-ovariohysterectomy, with minimal adverse effects69 (however, as mentioned OTM dosing of buprenorphine may nor may not be optimal). The FDA's Animal Drug Use Clarification Act’s statement on Extra-label Drug Use does not endorse the use of compounded medications when an equivalent FDA-Approved commercial product is on the market (in this case, another long-acting buprenorphine, in the form of Simbadol®).

In July 2014, a new veterinary formulation of buprenorphine was FDA-approved and introduced into the marketplace (Simbadol™, Zoeitis). At 1.8 mg/ml it is 6 X more concentrated than the human commercial product Buprenex® (0.3 mg/ml). It is labeled for post-surgical pain in cats, a 24-hours duration with one injection at 0.24 mg/kg SC; it can be given daily for up to 3 days. The labeled dose is 0.24 mg/kg, approximately 12x historically recommended. The operating premise is that the ceiling effect of buprenorphine limits adverse effects while allowing the extended analgesic duration. Each 10 ml vial allows for approximately 15 doses. The shelf-life of an unopened vial is 21 months, and once opened, is now 56 days. Safety was studied at up to 0.20 mg/kg/day for 9 consecutive days – 5 x the labeled dose or 60x the historically customary dose of 0.02 mg/kg. Adverse effects included hyperactivity, difficulty in handling, disorientation, agitation and dilated pupils but there were no drug-related effects on survival, injection response, injection site inspections, body weight, food or water consumption, bleeding time, urinalysis, respiration rate, heart rate, ECGs, blood pressures, body temperatures, macroscopic examinations or organ weights, and overall was considered well-tolerated.70 Experientially some owners do report unacceptable withdrawal or diminished appetite at home, and dose reduction (50% adopted by author) appears to alleviate this likelihood and supported by pharmacokinetic data as well.71

A recent comparison of utilizing Simbadol™ via the IV (0.12 mg/kg), SC (0.24 mg/kg), and OTM (0.12 mg/kg) routes. The SC route was affirmed to have a prolonged plasma T ½ (11.2 H) with >24 hours of anti-nociception, while anti-nociception for IV and SC was 8 hours and 12 hours respectively. However, bioavailability was only 24% via the OTH route (SC 94%, IV 100%).72 As the peak plasma concentration of Simbadol can take 1-2 hours, if used in combination with ketamine and dexmedetomidine, the Simbadol should precede the latter two drugs by that length of time; as buprenorphine has less sedative properties than butorphanol (Torbugesic™), the “DKS” may have a less immobilizing effect than “DKT.” A recent study affirms that IM buprenorphine-dexmedetomidine provides inferior sedation and a higher incidence of vomiting than butorphanol-dexmedetomidine in cats, and the authors concluded that butorphanol-dexmedetomidine may be preferred for feline sedation, especially where vomiting is contraindicated.73

Butorphanol is a weak mu antagonist and a kappa agonist; this feature makes it a poor choice for an analgesic in this species for any kind of significant or prolonged pain states, though used parenterally it has utility as an adjunct with other medications such as alpha-2 agonists. It comes as both a parenteral and oral formulation. 0.2-0.4mg/kg SQ, IM, IV74

References
24 Clark, P., Rowland, S. E, Denis, D., Mathieu, MC, Stocco, R, Poirier, H, . . . Xu, D. MF948 [N-[4-(5,9-Diethoxy-6-oxo-6,8-dihydro-7H-pyrrolo[3,4-g]quinolin-7-yl)-3-m ethylbenzyl]sulfonyl]-2-(2-methoxyphenyl)acetamide], a selective E prostanoid receptor 4 antagonist, relieves joint inflammation and in rodent models of rheumatoid arthritis. The J Pharm Exp Ther, 2008; 326(2), 425-434.
38 ibid
39 ibid
40 ibid
41 ibid
42 ibid
43 ibid


