CHAPTER

36

Chronic Disease Management

OUTLINE

IMMUNOSUPPRESSIVE DRUG THERAPY

Kristin M. Lewis and Leah A. Cohn

Cats, like other animals, are protected from microbial pathogens through a combination of physical barriers, innate immune effectors (e.g., phagocytic cells, complement system) and acquired immunity (e.g., cell-mediated and humoral effectors). Although these systems do a magnificent job in protection from pathogens, the immune systems occasionally cause or worsen disease when either misdirected against self-tissues or through an overexuberant reaction to exogenous stimuli. In such cases, it is medically advisable to suppress the inflammatory or immune responses.

In an ideal world, only those components of the immune response that cause harm would be suppressed. In reality, therapeutic immune suppression usually suppresses beneficial as well as harmful components of the immune response. Therefore all immunosuppressive therapies have the potential to make manifest quiescent infections (e.g., toxoplasmosis) or increase susceptibility to newly acquired infection.

Immunosuppressive drugs can be divided into several categories, including glucocorticoids (GCs); cytostatic drugs, including alkylating agents (e.g., chlorambucil) and antimetabolites (e.g., azathioprine); immunophilin ligands (e.g., cyclosporine); antibodies (e.g., intravenous immunoglobulin, monoclonal antibodies); and miscellaneous drugs (e.g., cytokine agonists or antagonists, integrin inhibitors). This chapter will focus on those drugs that have been used therapeutically in cats. It is important to note that most immunosuppressive drugs used in feline medicine are used in an off-label fashion. Dose regimens, duration of therapy, and adverse effects are often either anecdotal, or at best, based on small published case series.

GLUCOCORTICOIDS

Glucocorticoids are by far the most commonly used immunosuppressive drugs. They affect nearly every tissue in the body to alter metabolism and suppress inflammation and immune responses in a dose-dependent fashion. Genomic transcription patterns and subsequent protein expression are altered, resulting in impaired cell-mediated immunity, and to a lesser extent, impaired phagocytic and humoral immunity.[8] A multitude of GCs are available that vary in potency and route of administration. Based on data largely derived from other species, these drugs are described as short-, intermediate-, or long-acting based on duration of suppression of the hypothalamic-pituitary-adrenal axis (HPAA; Table 36-1). Duration of action depends upon both the base compound and modifications, such as esterification, that alter GC absorption. For instance, although methylprednisolone is an intermediate-acting compound, it is a very long-acting compound as the repositol formulation methylprednisolone acetate. When used to achieve chronic immunosuppression, intermediate-acting preparations, such as prednisolone, offer the advantage of a practical dose regimen, which allows the dose to be tailored to produce efficacy while minimizing HPAA suppression and adverse effects. The most commonly prescribed GCs are prednisone or its active metabolite prednisolone. In cats, prednisolone is strongly preferred versus prednisone, because of a superior pharmacokinetic profile.[12] The mechanism behind the disparity is not entirely clear, but decreased gastrointestinal (GI) absorption of prednisone or diminished hepatic conversion of prednisone to prednisolone are suspected.

Surprisingly, there is no scientific evidence of exactly what constitutes an immunosuppressive dose of prednisolone (or any other GC) in cats. In dogs, 2 to 4 mg/kg/day has been accepted as an initial immunosuppressive dose. Recommendations for initial immunosuppression in cats range from 2 to 8 mg/kg, while antiinflammatory dosages range from 0.5 to 2 mg/kg/day of prednisolone. Compared with dogs, cats are relatively resistant to many of the effects of GC, perhaps because of lesser numbers of intracytoplasmic GC receptors.[37] However, in the authors' opinion, dosages greater than 4 mg/kg/day are not required; higher dosages recommended in years past may have been based on clinical experience using less biologically available prednisone instead of prednisolone. The initial dose is continued for several days past clinical remission and then gradually tapered over months. In general, the dose may be reduced approximately 25% every 3 to 4 weeks as long as disease remains controlled. In some cases, GCs are continued at the lowest effective dose for an indefinite (even lifelong) period. Disease control should be monitored during dose reduction, a task more easily accomplished for diseases in which there is a measurable end point (e.g., hematocrit in cats with immune-mediated anemia). Although it is tempting to reduce dosages rapidly, early withdrawal may predispose to relapse. Biologically equivalent dosages of other GCs can be used in place of prednisolone (e.g., dexamethasone at 0.3 to 0.55 mg/kg/day). Long-acting repositol formulations of GCs (e.g., methylprednisolone acetate) can be used when owners are unable to administer daily oral medications, but fine adjustments become impossible and adverse effects may be more likely.

TABLE 36-1 Comparison of Various Glucocorticoid Base Compounds

	Relative Antiinflammatory Potency	Equivalent Pharmacologic Dose (mg)	Relative Mineralocorticoid Potency	Plasma Half-Life Dogs/People (hours)	Biologic Half-Life in People (hours)
SHORT-ACTING GLUCOCORTICOIDS					
Hydrocortisone	1	20	2	1/1.5	8-12
Cortisone	0.8	25	2	?/1.5	8-12
INTERMEDIATE-ACTING GLUCOCORTICOIDS					
Prednisone	4	5	1	?/1	12-36
Prednisolone	4	5	1	1-3/2-3	12-36
Methylprednisolone	5	4	0	1.5/3	12-36
Triamcinolone	5	4	0	?/4 or more	24-48
LONG-ACTING GLUCOCORTICOIDS					
Dexamethasone	30	0.75	0	2/5 or more	35-54
Betamethasone	30	0.6	0	?/5 or more	>48

From Cohn LA: Glucocorticoid therapy. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine disease of the dog and the cat*, ed 7, vol 1, St. Louis, 2010, Saunders Elsevier.

Adverse reactions of GCs are usually associated with high-dose regimens, and extended administration protocols, such as those used in chronic immune suppression. Although cats are relatively resistant to GC, adverse effects can develop. Polyuria, polydipsia, and polyphagia are less common in cats than in dogs but do occur, while a variety of other adverse effects of GCs have been documented or suggested (e.g., alopecia, pancreatitis).[8] In addition to a stress leukogram, hyperglycemia, hyperalbuminemia, and hyperlipidemia were noted in healthy cats given prednisolone (4.4 mg/kg/day) or dexamethasone (0.55 mg/kg/day) for 56 days.[18] These same cats developed hepatic glycogen deposition as well.[18] The metabolic actions of GCs on glucose balance result in hyperglycemia in healthy cats, and some cats treated with GC develop either temporary or permanent diabetes mellitus.[19,22] The diabetogenic effects of dexamethasone may be more pronounced than those of prednisolone.[18,19] The use of high-dose, long-term systemic GC should be avoided whenever possible in diabetic cats. Cardiac disease and especially congestive heart failure are also relative contraindications to GC use, since GC-associated water retention may exacerbate congestive failure.[35] As with any immunosuppressive therapy, an additional relative contraindication is infection.

Adverse effects of GCs can be minimized by limiting systemic exposure. In addition to using the lowest effective dose of an intermediate-acting GC, this can be achieved by local application of GC whenever possible. In some cases, GCs are formulated in such a way that systemic absorption is limited after local application, and/or absorbed GC is rapidly inactivated through first-pass hepatic metabolism. For example, application of the GCs fluticasone or flunisolide by nebulization or metered dose inhaler to the airway epithelium of cats with feline reactive airway disease (e.g., asthma) delivers the drug directly to the disease site, preserving efficacy while limiting systemic GC exposure.[9,28,29] Similarly, oral budesonide has been used to treat inflammatory bowel disease in dogs, because it delivers GC to the GI epithelium but limits systemic exposure as a result of limited intestinal absorption and first-pass hepatic metabolism.[36] There are no studies showing efficacy of this agent in cats; anecdotal reports suggest variability in clinical response. When adverse effects of GC are pronounced or when GC alone fails to control disease, alternative immunosuppressive drugs may allow a decrease in GC dose or may even permit discontinuation of GC therapy.

IMMUNOPHILIN LIGANDS

The most commonly used immunosuppressive drug in this class is cyclosporine. Cyclosporine inhibits T-lymphocyte activation and inhibits synthesis of cytokines, such as interleukin-2 (IL-2) and gamma interferon, while also reducing activation of antigen-presenting cells and phagocytes.[13,30] Used extensively to prevent rejection of transplanted kidneys, cyclosporine has also been used to treat immune-mediated blood disorders in cats, including immune hemolytic anemia, pure red cell and megakaryocytic aplasia, and immune thrombocytopenia.[6,15,33,34] Cyclosporine has also been used successfully to treat a variety of feline skin diseases, including atopic dermatitis, feline eosinophilic granuloma complex, feline urticaria pigmentosa, pemphigus erythematosus, feline pruritus, atopic dermatitis, granulomatous folliculitis, and furunculosis as well as sebaceous adenitis.[24,25,38,40] Anecdotally, cyclosporine has been used to treat inflammatory bowel disease as well.[1] Cyclosporine has been explored as an additional therapy for feline asthma, with conflicting results. One experimental study suggested cyclosporine inhibited airway remodeling and inflammation, while a second study found no change in initial asthmatic response or mast cell degranulation of experimentally sensitized animals.[23,26]

Cyclosporine is poorly soluble in water. Microemulsified formulations (e.g., Neoral, Atopica) are preferred rather than the original nonaqueous suspension. An initial dose of 5 mg/kg, PO, every 12 hours is reasonable, but there is enough individual variation in absorption that dosage must be adjusted based upon measured drug concentration.[21]Fortunately, the small size of cats makes the cost of treatment reasonable.

Compared with other immunosuppressive therapies, cats tolerate cyclosporine well. Unlike cytostatic drugs, cyclosporine is not myelosuppressive. The most common adverse effect associated with cyclosporine is GI irritation. Hepatotoxicosis or nephrotoxicosis, although rare, is more serious.[24,30] Because there are multiple case reports of cats developing systemic toxoplasmosis during treatment with cyclosporine, the authors recommend that toxoplasma titers be determined prior to initiation of therapy.[2,5,17] Risk must be weighed against benefit for any cat with positive titers. Cats treated with cyclosporine should be monitored with a complete blood count (CBC) and serum chemistry profile at least 3 times per year. In a group of feline renal transplant patients treated with cyclosporine and prednisolone, malignant neoplasias occurred at more than 6 times the expected rate.[32]

Tacrolimus is an immunophilin ligand immunosuppressive agent that is available in both oral and topical formulations, and it has a mechanism of action similar to cyclosporine. It is used in humans to prevent graft rejection and has also been evaluated for prevention of renal allograft rejection in cats.[16] Tacrolimus provided marked improvement in the a small series of cats with proliferative and necrotizing otitis externa refractory to GC, antibiotic, and antifungal therapy.[20]

CYTOSTATIC DRUGS

Alkylating agents act by causing cross-linkage and strand breaks in DNA and RNA. They are commonly used as chemotherapeutic drugs, but they also act on lymphocyte populations impairing both cell-mediated and humoral immunity. Because these agents require at least several weeks to become effective, they are begun along with GC and continued after the GC is tapered or discontinued. The two alkylating agents used most often as immunosuppressant therapies in cats are chlorambucil and cyclophosphamide. Both have been used as adjunctive or alternative therapies to GC in cats with inflammatory bowel disease (IBD).[1] Occasionally, alkylating agents have been used to treat hematologic disorders as well.[34]

Many feline practitioners prefer chlorambucil to cyclophosphamide, because it seems to be better tolerated, but there is little to document an advantage of one versus the other. Chlorambucil is available in a 2-mg tablet form convenient for use in cats. Most cats can be given 2 mg, PO, every 48 hours initially. The dose frequency may be adjusted from every 24 to every 96 hours, depending on the response of the cat to treatment. Both chlorambucil and cyclophosphamide can induce myelosuppression; so, a CBC must be monitored on a regular basis. Initially a CBC should be checked 7 to 10 days after beginning therapy, and even during chronic therapy, a CBC should be monitored at least every 60 days. Additional adverse effects include GI upset and myoclonus (muscle twitching) for chlorambucil or hemorrhagic cystitis for cyclophosphamide.[4,10]

Cytostatic antimetabolite drugs mimic molecules that participate in cellular biochemical reactions but differ enough from the natural molecule to interfere with normal cell division and function. They include nucleic acid analogues as well as antifolate drugs. Most have a more profound effect on T lymphocytes (and therefore on cell-mediated immunity) than on B-lymphocytes. Azathioprine is an antimetabolite commonly used to induce and maintain immunosuppression in dogs and humans. The drug is metabolized to 6-mercaptopurine (6-MP), which interferes with de novo purine synthesis. Unfortunately, a profound and potentially fatal myelosuppression occurs more commonly in cats treated with azathioprine than in dogs or humans, preventing its routine use in felines.[3,27] This difference in the response of cats compared with other species is likely the result of a relative deficiency in the enzyme that catalyzes the conversion of 6-MP to inactive metabolites.[11,31]

Methotrexate is an antimetabolite used to treat rheumatoid arthritis in humans and is occasionally used for chemotherapy or as an immunosuppressive drug in cats. The drug has been used in combination with another antimetabolite drug, leflunomide (Arava), in a small number of cats with spontaneous erosive rheumatoid arthritis.[14] Leflunomide has been used to treat dogs with a wide variety of immune-mediated diseases, but experience in cats is more limited. Leflunomide is converted to an active metabolite that inhibits an enzyme crucial for de novo pyrimidine synthesis. There has been some interest in the use of leflunomide for immunosuppression in feline renal transplantation, since the drug also possesses antiherpesvirus activity.[39]

ANTIBODIES

Antibodies can be used to cause therapeutic immunomodulation. For instance, humanized murine monoclonal antibodies directed against the CD3 molecule on T-lymphocyte receptors are quite effective in the prevention of organ rejection in people. However, human or humanized antibodies may not be effective or safe in cats. To the author's knowledge, the single drug in this class that has been used in feline medicine is human intravenous immunoglobulin (IV-Ig). Derived from a pooled human donor population, IV-Ig contains human polyvalent antibody consisting of predominantly IgG antibodies. Originally developed to treat antibody deficiency syndromes, it has become well accepted for the acute treatment of immune-mediated disease in humans. Although the mechanisms of action are poorly understood, competitive blockade of Fc receptors on macrophages, inhibition of complement activity, and alterations in T-lymphocyte and B-lymphocyte function may each play a role.[7] In cats, IV-Ig has been used to treat severe erythema multiforme and immune-mediated erythroid and megakaryocytic aplasia with a good outcome.[7,41] Although adverse effects were not reported in the few published case reports, it is reasonable to assume that a human-derived protein may lead to anaphylactic reactions, especially with repeated use. Although IV-Ig may eventually be shown to have some utility in initial stabilization of cats with life-threatening immune-mediated disease, this expensive therapy is unlikely to have a role in chronic immunosuppression.

References

1. Allen H: Therapeutic approach to cats with chronic diarrhea. In August J, editor: *Consultations in feline internal medicine*, ed 6, St Louis, 2010, Elsevier, p 244.
2. Barrs VR, Martin P, Beatty JA: Antemortem diagnosis and treatment of toxoplasmosis in two cats on cyclosporin therapy, *Aust Vet J* 84:30, 2006.
3. Beale KM, Altman D, Clemmons RR et al: Systemic toxicosis associated with azathioprine administration in domestic cats, *Am J Vet Res* 53:1236, 1992.
4. Benitah N, de Lorimier LP, Gaspar M et al: Chlorambucil-induced myoclonus in a cat with lymphoma, *J Am Anim Hosp Assoc* 39:283, 2003.

5. Bernsteen L, Gregory CR, Aronson LR et al: Acute toxoplasmosis following renal transplantation in three cats and a dog, *J Am Vet Med Assoc* 215:1123, 1999.
6. Bianco D, Armstrong PJ, Washabau RJ: Presumed primary immune-mediated thrombocytopenia in four cats, *J Feline Med Surg* 10:495, 2008.
7. Byrne KP, Giger U: Use of human immunoglobulin for treatment of severe erythema multiforme in a cat, *J Am Vet Med Assoc* 220:197, 2002.
8. Cohn LA: Glucocorticoid therapy. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine: diseases of the dog and the cat*, ed 7, St Louis, 2010, Elsevier, p 503.
9. Cohn LA, Declue AE, Cohen RL et al: Effects of fluticasone propionate dosage in an experimental model of feline asthma, *J Feline Med Surg* 12:91, 2009.
10. Crow SE, Theilen GH, Madewell BR et al: Cyclophosphamide-induced cystitis in the dog and cat, *J Am Vet Medical Assoc* 171:259, 1977.
11. Foster AP, Shaw SE, Duley JA et al: Demonstration of thiopurine methyltransferase activity in the erythrocytes of cats, *J Vet Intern Med* 14:552, 2000.
12. Graham-Mize CA, Rosser EJ, Hauptman J: Absorption, bioavailability and activity of prednisone and prednisolone in cats. In Hillier A, Foster A, Bertola G et al, editors: *Advances in veterinary dermatology*, ed 5, Ames, Iowa, 2005, Blackwell Publishing, p 152.
13. Guaguere E, Steffan J, Olivry T: Cyclosporin A: a new drug in the field of canine dermatology, *Vet Dermatol* 15:61, 2004.
14. Hanna FY: Disease modifying treatment for feline rheumatoid arthritis, *Vet Comp Orthop Traumatol* 18:94, 2005.
15. Husbands B, Smith SA, Weiss DJ: Idiopathic immune mediated hemolytic anemia (IMHA) in 25 cats [abstract], *J Vet Intern Med* 16:350, 2002.
16. Kyles AE, Gregory CR, Craigmill AL et al: Pharmacokinetics of tacrolimus after multidose oral administration and efficacy in the prevention of allograft rejection in cats with renal transplants, *Am J Vet Res* 64:926, 2003.
17. Last RD, Suzuki Y, Manning T et al: A case of fatal systemic toxoplasmosis in a cat being treated with cyclosporin A for feline atopy, *Vet Dermatol* 15:194, 2004.
18. Lowe AD, Campbell KL, Barger A et al: Clinical, clinicopathological and histological changes observed in 14 cats treated with glucocorticoids, *Vet Rec* 162:777, 2008.
19. Lowe AD, Graves TK, Campbell KL et al: A pilot study comparing the diabetogenic effects of dexamethasone and prednisolone in cats, *J Am Anim Hosp Assoc* 45:215, 2009.
20. Mauldin EA, Ness TA, Goldschmidt MH: Proliferative and necrotizing otitis externa in four cats, *Vet Dermatol* 18:370, 2007.
21. Mehl ML, Kyles AE, Craigmill AL et al: Disposition of cyclosporine after intravenous and multi-dose oral administration in cats, *J Vet Pharmacol Ther* 26:349, 2003.
22. Middleton DJ, Watson AD: Glucose intolerance in cats given short-term therapies of prednisolone and megestrol acetate, *Am J Vet Res* 46:2623, 1985.
23. Mitchell RW, Cozzi P, Ndukwu IM et al: Differential effects of cyclosporine A after acute antigen challenge in sensitized cats in vivo and ex vivo, *Br J Pharmacol* 123:1198, 1998.
24. Noli C, Scarampella F: Prospective open pilot study on the use of ciclosporin for feline allergic skin disease, *J Small Anim Pract* 47:434, 2006.
25. Noli C, Toma S: Three cases of immune-mediated adnexal skin disease treated with cyclosporin, *Vet Dermatol* 17:85, 2006.
26. Padrid PA, Cozzi P, Leff AR: Cyclosporine A inhibits airway reactivity and remodeling after chronic antigen challenge in cats, *Am J Respir Crit Care Med* 154:1812, 1996.
27. Paul AL, Shaw SP, Bandt C: Aplastic anemia in two kittens following a prescription error, *J Am Anim Hosp Assoc* 44:25, 2008.
28. Reinero CR, Brownlee L, Decile KC et al: Inhaled flunisolide suppresses the hypothalamic-pituitary-adrenocortical axis, but has minimal systemic immune effects in healthy cats, *J Vet Intern Med* 20:57, 2006.
29. Reinero CR, Decile KC, Byerly JR et al: Effects of drug treatment on inflammation and hyperreactivity of airways and on immune variables in cats with experimentally induced asthma, *Am J Vet Res* 66:1121, 2005.
30. Robson D: Review of the pharmacokinetics, interactions and adverse reactions of cyclosporine in people, dogs and cats, *Vet Rec* 152:739, 2003.
31. Rodriguez DB, Mackin A, Easley R et al: Relationship between red blood cell thiopurine methyltransferase activity and myelotoxicity in dogs receiving azathioprine, *J Vet Intern Med* 18:339, 2004.
32. Schmiedt CW, Grimes JA, Holzman G et al: Incidence and risk factors for development of malignant neoplasia after feline renal transplantation and cyclosporine-based immunosuppression, *Vet Comp Oncol* 7:45, 2009.
33. Schmiedt CW, Holzman G, Schwarz T et al: Survival, complications, and analysis of risk factors after renal transplantation in cats, *Vet Surg* 37:683, 2008.
34. Stokol T, Blue JT: Pure red cell aplasia in cats: 9 cases (1989-1997), *J Am Vet Med Assoc* 214:75, 1999.
35. Trasida P, Tobias AH, Smith SA, et al: Hemodynamic effects of methylprednisolone acetate administration in cats, *Am J Vet Res* 67:583, 2006.
36. Tumulty JW, Broussard JD, Steiner JM et al: Clinical effects of short-term oral budesonide on the hypothalamic-pituitary-adrenal axis in dogs with inflammatory bowel disease, *J Am Anim Hosp Assoc* 40:120, 2004.
37. Van den Broek AH, Stafford WL: Epidermal and hepatic glucocorticoid receptors in cats and dogs. *Res Vet Sci* 52:312, 1992.
38. Vercelli A, Raviri G, Cornegliani L: The use of oral cyclosporin to treat feline dermatoses: a retrospective analysis of 23 cases, *Vet Dermatol* 17:201, 2006.
39. Williams CR, Sykes JE, Mehl M et al: In vitro effects of the active metabolite of leflunomide, A77 1726, on feline herpesvirus-1, *Am J Vet Res* 68:1010, 2007.
40. Wisselink MA, Willemse T: The efficacy of cyclosporine A in cats with presumed atopic dermatitis: a double blind, randomised prednisolone-controlled study, *Vet J* 180:55, 2009.
41. Zini E, Hauser B, Meli ML et al: Immune-mediated erythroid and megakaryocytic aplasia in a cat, *J Am Vet Med Assoc* 230:1024, 2007.

MONITORING LONG-TERM THERAPY

Melissa Clark and Duncan C. Ferguson

Monitoring drug therapy consists of assessing both the efficacy and the safety of a medication in an individual patient. Monitoring is necessary because the safety of a particular drug may vary among patients, or in the same patient over time, resulting from differences in major organ function (e.g., age-related, breed-related, or disease-related), hydration, body condition, concurrent therapy, and susceptibility to idiosyncratic adverse drug reactions. Likewise, efficacy may be affected by individual patient physiology and disease states as well as by drug interactions, formulation, and delivery. Recognizing early signs of therapeutic failure or unacceptable drug side effects is essential to ensuring appropriate individualized treatment.

CLINICAL MONITORING

Repeated evaluation of a patient's clinical status is the cornerstone of ensuring efficacy and safety. Particularly in cats, client observations are important in making decisions about the benefits and safety of therapy. For example, because cats are often reluctant to ambulate in an exam room, monitoring the efficacy of treatments for osteoarthritis may be impossible without information about the cat's behavior at home. Suggestions for improving clinical monitoring of efficacy and safety include

1. Educating both oneself and the client about adverse effects and indicators of efficacy associated with a particular drug
2. Making follow-up calls to detect adverse effects, since clients will not necessarily report this information without prompting
3. Accurately recording physical examination findings at each recheck visit
4. Having clients keep a treatment log in order to note changes in their pets over time

Monitoring issues associated with some feline drugs for which efficacy assessment is primarily based on clinical observation are listed in Table 36-2.

TABLE 36-2 Summary of Monitoring Recommendations for Long-Term Drugs That Have Primarily Clinical Efficacy Indices in the Cat*

Drug or Drug Class	Potential Adverse Effects	Monitoring Recommendations
Antifungals (G = griseofulvin, I = itraconazole, T = terbinafine)	Bone marrow suppression; hepatotoxicity; ataxia (G)[18,26,42]; dose-dependent anorexia and vomiting (I)[27]; increased ALT(I)[57,58]; alter therapy if severe or symptomatic; rare hepatotoxicity in humans (T)[11]	CBC +/− liver enzymes before and every 1 to 4 weeks during therapy (G); liver enzymes every 2 to 4 weeks (I); consider baseline and periodic liver enzyme assessment (T)
Antihistamines (e.g., chlorpheniramine)	Transient sedation[31]	Data limited; safety monitoring is primarily clinical at this time
Antivirals	Anemia with zidovudine (AZT) in cats with FeLV[17]and FIV[16]; mild diarrhea and fatigue with feline IFN omega[10]; transient anorexia and weight loss with high-dose human IFN alpha[59]	PCV periodically (AZT); if <20%, discontinue temporarily and restart at lower dose[16]
Appetite stimulants (mirtazapine, cyproheptadine)	Anecdotally, hyperexcitability and vocalization with mirtazapine (possible serotonin syndrome)[1,40]; may respond to dose reduction or treatment with cyproheptadine[28,56]; vomiting, vocalization, and sedation with cyproheptadine (infrequent)[47]	Data limited; safety monitoring is primarily clinical at this time
Cobalamin	None documented in cats; clinical effect measured by improved appetite, weight gain, decreased GI signs[43]	Serum levels can be measured; however, dosing is usually empirical
Fluoroquinolones (long-term use not ideal)	Retinal toxicity at doses as low as 4.6 mg/kg/day (see Chapter 29 for further details)	Monitor for mydriasis or vision loss; discontinue drug if noted
Metronidazole	Neurotoxicosis at chronic doses >58 mg/kg/day[3,33]; reversible DNA disruption after 7 days of treatment (clinical significance unclear)[49]	Monitor for neurologic abnormalities; consider alternative medications for chronic therapy
Meloxicam (chronic use off label in some countries)	Renal and GI toxicity class effect; discontinue if GI upset[15]	Manufacturer recommends CBC and chemistry panel before and periodically during treatment in dogs
Serotonin selective reuptake inhibitors (e.g., fluoxetine)	Intermittent inappetence[39]; shortened REM sleep in laboratory cats at doses of 2.5 mg/kg[51]; increased liver enzymes in humans	Monitor appetite and body weight; consider baseline liver enzyme assessment
Tricyclic antidepressants (e.g., amitriptyline, clomipramine)	Lethargy[4,22,50] and diminished coat quality[4]; anticholinergic effects (urine retention)[37]; cardiac conductivity disturbances in humans (seen in healthy cats only with overdose)[13]; hepatopathy in humans	Consider baseline CBC, chemistry panel, and cardiac evaluation; consider periodic liver enzyme assessment; monitor urine and fecal output
Tramadol	Dysphoria[54]	Data limited; safety monitoring is primarily clinical at this time

*Monitoring therapy with glucocorticoids, chlorambucil, and chemotherapeutic agents is discussed above and in Chapter 28, respectively.
ALT, Alanine transaminase; *AZT,* azidothymidine; *CBC,* complete blood count; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency disease; *IFN,* interferon; *PCV,* packed cell volume; *REM,* rapid eye movement.

PHARMACODYNAMIC MONITORING

Specific physiologic end points (pharmacodynamic measures) are helpful in assessing success of therapy for certain drugs. In cats, these drugs include amlodipine, erythropoietin, methimazole, phosphate binders, and potassium supplements. Efficacy and safety monitoring for these drugs is discussed below, and recommendations are summarized in Table 36-3.

Amlodipine

The main objective of efficacy measure for amlodipine, a commonly used antihypertensive in the cat, is blood pressure measurement. Preferred methods for measuring blood pressure in cats, target ranges for blood pressure after treatment, and blood pressure reduction in special situations are discussed in the American College of Veterinary Internal Medicine (ACVIM) Consensus Statement on systemic hypertension[2] and in Chapter 20.

In humans, the effects of amlodipine increase gradually in conjunction with plasma levels during 7 to10 days of dosing.[30] Unfortunately, no specific information is available regarding the pharmacokinetics of amlodipine in cats. Rechecking blood pressure and making dosage adjustments after 7 days of treatment is probably appropriate based on published studies, although anecdotal reports[23] suggest that a clinically significant effect of amlodipine on blood pressure may be seen much sooner (24 to 48 hours). Timing of blood pressure measurement after administration does not appear to be an important factor in evaluating efficacy.[53]

Side effects reported from three studies of amlodipine in cats[8,19,53] included weakness and hypotension (in a patient also receiving propanolol), pruritus, a mild decrease in serum potassium of more than 1 to 2 months following the start of treatment, and need for initiation of potassium supplementation or increase in the dose during the treatment period. Many of the cats in these studies also had some degree of renal dysfunction. Average values for blood urea nitrogen (BUN) and creatinine did not change significantly during the first 1 to 2 months of amlodipine therapy; however, 1 of 10 cats with elevated creatinine in one study became uremic and hypokalemic while on amlodipine.[19] Hence, monitoring of serum potassium concentrations and renal values in cats receiving amlodipine is prudent, particularly if chronic renal disease (CRD) has been diagnosed. Owner monitoring for signs of hypotension may be important in cats taking multiple agents expected to lower blood pressure.[8]

TABLE 36-3 Summary of Monitoring Recommendations for Drugs with Measurable Pharmacodynamic Parameters*

Drug or Drug Class	Efficacy Monitoring	Safety Monitoring
Amlodipine	Measure blood pressure 7 days after treatment initiation or dose changes; timing of BP measurement with respect to medication not important	Measure serum K periodically during treatment, especially if concurrent CKD Monitor for clinical signs of hypotension (weakness) if cat is taking multiple agents expected to lower BP
Erythropoietin (recombinant human); darbepoetin	Measure PCV every 7-14 days until normalized (25%-30%), then monthly if patient is clinically stable	Monitor for development of anemia (due to anti-rHuEPO antibodies) every 14 days for first 60-90 days Monitor blood pressure periodically Monitor for vomiting, uveitis, or cutaneous/mucocutaneous lesions
Methimazole	Measure serum total T_4 2-4 weeks after initiating therapy or making dose adjustments, then every 6 months	Measure ALT, ALP, bilirubin, BUN, Cr, and USG periodically throughout treatment (example: every 4-6 months after initial control) Monitor CBC periodically, particularly within first 3 months of treatment, and platelet count before surgery Monitor for vomiting or facial excoriation
Phosphate binders (aluminum salts, calcium salts, chitosan/calcium carbonate, lanthanum carbonate)	Measure serum P concentration monthly until within desired range, then every 2-4 months	Monitor for signs of encephalopathy; monitor CBC periodically for microcytosis (aluminum-containing binders) Measure serum Ca periodically to detect hypercalcemia (calcium-containing products) Monitor for constipation (all)
Potassium supplements	Measure serum K 7-14 days after oral supplementation is initiated or dose changes are made	Discontinue supplementation in oliguric/anuric states (acute-on-chronic renal failure, urinary obstruction) to avoid hyperkalemia

*Monitoring insulin therapy is discussed in depth in Chapter 24.
ALP, Alkaline phosphatase; *ALT,* alanine transaminase; *BP,* blood pressure; *BUN,* blood urea nitrogen; *Ca,* calcium; *CBC,* complete blood count; *CKD,* chronic kidney disease; *Cr,* creatinine; *K,* potassium; *PCV,* packed cell volume; *rHuEPO,* recombinant human erythropoietin; *T_4,* thyroxine; *USG,* urine specific gravity.

Erythropoietin

Efficacy of therapy with recombinant human erythropoietin (rHuEPO) is documented by measuring the hematocrit (packed cell volume, PCV). This should be done every 1 to 2 weeks during initial therapy. Once PCV has reached 25% to 30% (often by week 4), the frequency of dosing can be reduced.[6,24] Thereafter, PCV should be monitored periodically (one author suggests monthly[24]) in animals receiving erythropoietin, to avoid creating polycythemia and to detect the severe anemia that can result from development of anti-rHuEPO antibodies.

Anemia secondary to antibody development occurred in of five of seven cats treated for more than 180 days in one study,[6] 4 to 16 weeks after therapy was begun. Darbepoetin, a chemically modified rHuEPO, has not been associated with antibody-positive anemia in human patients to date.[5] No data is available on the likelihood of antibody formation with this form of rHuEPO in cats.

Vomiting, uveitis, seizures, and cutaneous hypersensitivity were reported side effects in a group of 11 cats receiving rHuEPO; both cats with seizures were moderately or severely azotemic, and at least one was hypertensive at the time the seizures were noted.[6] Hypertension can result from use of erythropoietin, possibly due to increased blood viscosity.[24] Erythropoietin treatment increases the demand for iron, and iron deficiency may develop if stores are inadequate. Therefore serum iron should be measured before and during therapy with erythropoietin; supplementation with ferrous gluconate or sulfate may be indicated.

Methimazole

Methimazole therapy is usually monitored by measurement of total thyroxine (T_4) concentrations. Normalization of T_4 levels in treated hyperthyroid cats typically takes 2 to 4 weeks,[55] because the drug inhibits T_4 production but does not affect thyroid hormone that has already been synthesized and is either stored in the gland or in circulation. Timing of sampling during the day does not appear to affect results.[45] Dosage adjustments may be necessary over time, resulting from growth of the thyroid tumor. Thyroid stimulating hormone (TSH) measurement is also possible, because feline TSH shows cross-reactivity in the canine assay.[41] TSH levels are normal to low in cats with adequate thyroid function; elevated TSH levels can indicate overtreatment with antithyroid medication.

Cats with hyperthyroidism and high-normal creatinine levels may progress to mild to moderate azotemia following treatment, regardless of the treatment modality (i.e., medical, surgical, or radioiodine). Development of azotemia typically occurs within the first 30 days following initiation of therapy. Although BUN and creatinine may increase significantly, azotemia is often stable and nonprogressive.[25] It is not clear whether careful dose titration to avoid subnormal T_4 concentrations affects the development of azotemia, but such titration is possible with methimazole therapy (as opposed to radioiodine or surgery). Indicators of renal function, such as urine specific gravity (USG), urine protein:creatinine (UPC) ratio, glomerular filtration rate (GFR) (measured by exogenous creatinine or iohexol clearance), and the urinary enzyme *N*-acetyl-beta-D-glucosaminidase have been investigated as monitoring tools. Their ability to predict propensity for renal decompensation has been poor in most studies.[20] In particular, USG, although simple and noninvasive to measure, is not necessarily predictive, because some cats with renal insufficiency paradoxically retain the ability to concentrate urine to 1.045 or higher.[34]

Other reported side effects of methimazole include vomiting and anorexia (11% to 23% of cats), facial and/or cervical excoriation (2% to 15% of cats, depending on study), agranulocytosis, thrombocytopenia (epistaxis, oral hemorrhage), hepatopathy (anorexia, vomiting, icterus), lymphadenopathy, or acquired myasthenia gravis (all in < 3% of cats). The ideal time frame for monitoring blood values to detect bone marrow suppression and hepatopathy is not known, but in one large study[36] that documented these effects, bone marrow suppression occurred during the first 3 months of therapy.

Alternatives for cats that develop gastrointestinal (GI) side effects include discontinuing the drug and reintroducing it gradually, changing to propylthiouracil, or using transdermal formulations of methimazole. Transdermal methimazole has been reported to cause fewer GI side effects; however, all other adverse reactions may still occur. When a cat develops allergic side effects to methimazole, such as facial pruritus and excoriation, treatment with radiocontrast agents (e.g., iopanoic acid) may be considered. These iodinated compounds inhibit the enzymes that convert T_4 to T_3 (triiodothyronine) but do not alter thyroidal secretion of T_4. Therefore the effect of these drugs is monitored by measuring T_3, not T_4, concentrations. Owners of cats with adverse reactions to methimazole should also be reminded of the options for radioiodine therapy and surgery.

Carbimazole, a prodrug for methimazole, is widely used in Europe, and is being considered for approval in the United States. A sustained-release product, Vidalta (Intervet/Schering-Plough Animal Health, Summit, NJ), allowing once-daily dosing at 10 to 15 mg/cat/day, PO, has been approved in Europe.[14] Monitoring recommendations for carbimazole are similar to those for methimazole; however, more rapid normalization of serum T_4 (mean, 5.7 days after the start of treatment) may be achieved with carbimazole at a dosage of 5 mg/cat, PO, every 8 hours.[32]

Phosphate Binders

Phosphate binders used in cats include aluminum or calcium salts, chitosan/calcium carbonate, sevelamer hydrochloride, and lanthanum carbonate. For most of these compounds, the measurable efficacy indicator is serum phosphate concentration. To date, there are no controlled studies demonstrating the most appropriate values for serum phosphate in cats with renal disease. Suggestions for target values (derived from human medicine) can be found in a recent roundtable discussion on the management of hyperphosphatemia in dogs and cats.[9] After initial achievement of target phosphate levels through dose titration, periodic reassessment is necessary because progression of renal disease or changes in diet may alter serum phosphate concentrations with time. One author recommends measuring serum phosphate concentration monthly after starting therapy until phosphate is in the lower portion of the reference range, then every 2 to 4 months.[21]

A chitosan/calcium carbonate product labeled for veterinary use as a food additive (Epakitin;Vétoquinol, Fort Worth, Tex.) has been shown to lower plasma parathyroid hormone (PTH) concentrations in cats with chronic renal disease. Titrating dose to normalize PTH levels has been recommended,[21] although a dose-response relationship of phosphate binders on PTH has not been established.

There are few studies evaluating the safety of phosphate binders in animals. In humans, all phosphate binders can cause gastrointestinal side effects (e.g., constipation, GI upset). In addition, aluminum-containing phosphate binders are no longer used in human medicine because of occurrences of aluminum toxicity. This complication has also been reported in two dogs with renal disease, after 2 to 6 weeks on doses of 126 to 200 mg/kg/day of aluminum hydroxide. Both dogs had elevated serum aluminum levels; signs of toxicity included lethargy progressing to obtundation and recumbency, with decreased reflexes.[48] Progressive microcytosis preceded the development of neurologic signs in these dogs. For this reason, and because microcytic anemia is also associated with aluminum toxicity in humans, one clinician has advocated serial evaluation of red blood cell (RBC) indices in all animals receiving aluminum-containing phosphate binders.[12]

Hypercalcemia is a concern with calcium-containing phosphate binders and has been observed in cats taking Epakitin.[21] Sevelamer or lanthanum salts may be alternatives in cats with hypercalcemia, although sevelamer has not been used extensively in cats. No adverse effects were observed with administration of a liquid formulation of lanthanum carbonate to 10 cats with renal disease during a 6-month period.[46]

Potassium Supplements

Therapy with oral potassium supplements (potassium gluconate, potassium citrate) is very safe and can be monitored by sequential measurement of serum potassium concentration. One author[38] suggests rechecking potassium concentrations every 7 to 14 days during initial therapy. Once potassium concentration has normalized, frequency of rechecks depends on the severity of concurrent disease. The development of hyperkalemia in cats on potassium supplements is reportedly rare as long as urine production (and, therefore, urinary potassium excretion) is adequate.[7]

PHARMACOKINETIC MONITORING

Measurement of plasma drug concentration is indicated for those drugs that

1. Exhibit inconsistent absorption, elimination, or interaction characteristics, leading to variation in plasma concentration among individuals
2. Show a correlation between drug concentration and toxicity and/or efficacy
3. Have a commercially available assay, validated for veterinary patients, through which results can be obtained in a timely manner[52]

Among drugs used in cats, aminoglycosides, cyclosporine, theophylline, and anticonvulsants satisfy these criteria.

Aminoglycosides are not commonly used long term in the cat. However, assays for measuring serum concentrations are available, and may be useful in certain situations (e.g., treatment of sepsis during protracted hospitalization of a patient with panleukopenia). Aminoglycosides are associated with dose-dependent nephrotoxicity. Monitoring of serum drug concentrations, along with frequent in-hospital testing (e.g., BUN, creatinine, examination of urine sediment for casts) may aid in avoiding this complication.

Cyclosporine is gaining popularity as a treatment for allergic and immune-mediated diseases. As in other species, cyclosporine absorption is unpredictable in the cat.[29] Theophylline has been a recommended treatment for feline bronchitis. For both cyclosporine and theophylline, measurement of plasma drug concentrations may be indicated when lack of efficacy or toxicity is suspected, despite an adequate dose, or when the formulation of the drug is changed.

The main utility of therapeutic drug monitoring in cats at this time is in monitoring therapy with anticonvulsants, particularly phenobarbital. Monitoring of anticonvulsant therapy is discussed in depth in Chapter 27. Recommendations for measurement of aminoglycoside,

TABLE 36-4 Therapeutic Drug Monitoring in Cats

Drug	Sample Preparation and Timing[35]*	Target Plasma Concentrations[35]
Aminoglycosides	0.5 mL serum or plasma, shipped on ice; sample at 1, 2, and 4 hours after dose for clearance measurements	Amikacin: peak 40 µg/mL; trough <0.8 µg/mL Gentamicin: peak 20 µg/mL; trough <0.27 µg/mL
Cyclosporine	1 mL whole blood in EDTA tube, shipped on ice; sample at least 48 hours after beginning or altering therapy; trough or peak (2 hours after dosing) samples may be appropriate	Depends on disease; in general, trough should be 300-600 ng/mL
Phenobarbital	0.5 mL serum or plasma; sample at steady state (7-14 days after first dose), any time during dosing interval	15-40 µg/mL (extrapolated from dogs); one author recommends 20-30 µg/mL for cats[44]
Theophylline	0.5 mL serum, shipped on ice; sample at trough; add peak sample for assessment of clearance (timing of peak varies with formulation)	5-20 µg/mL expected to be therapeutic (extrapolated from humans)

*Verify specific instructions for sample handling with laboratory.
EDTA, Ethylenediaminetetraacetic acid.

cyclosporine, phenobarbital, and theophylline levels are found in Table 36-4.

References

1. Adams LG: Updates in management of chronic kidney disease, Western Veterinary Conference 2009 [proceedings online]. Available at http://www.vin.com/Members/Proceedings/Proceedings.plx?CID=wvc2009&PID=pr50998&O=VIN. Accessed February 11, 2009.
2. Brown S, Atkins C, Bagley R et al: Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats, *J Vet Intern Med* 21:542, 2007.
3. Caylor KB, Cassimatis MK: Metronidazole neurotoxicosis in two cats, *J Am Anim Hosp Assoc* 37:258, 2001.
4. Chew DJ, Buffington CA, Kendall MS et al: Amitriptyline treatment for severe recurrent idiopathic cystitis in cats, *J Am Vet Med Assoc* 213:1282, 1998.
5. Cournoyer D, Toffelmir EB, Wells GA: Anti-erythropoietin antibody-mediated pure red cell aplasia after treatment with recombinant erythropoietin products: recommendations for minimization of risk, *J Am Soc Nephrol* 15:2728, 2004.
6. Cowgill LD, James KM, Levy JK et al: Use of recombinant human erythropoietin for management of anemia in dogs and cats with renal failure, *J Am Vet Med Assoc* 212:521, 1998.
7. Dow SW, Fettman MJ: Chronic renal disease and potassium depletion in cats, *Sem Vet Med Surg* 7:198, 1992.
8. Elliott J, Barber PJ, Syme HM et al: Feline hypertension: clinical findings and response to antihypertensive treatment in 30 cases, *J Sm An Pract* 42:122, 2001.
9. Elliot J, Brown SA, Cowgill LD et al: Phosphatemia management in the treatment of chronic kidney disease, a roundtable discussion, January 10, 2006. Available at http://www.vetoquinol.ca/documents/Quoi%20de%20neuf/Articles/Round%20table%20discussion.pdf. Accessed January 15, 2010.
10. European Medicines Agency, Veterinary Medicines: European Public Assessment Report, Virbagen Omega. Available at http://www.ema.europa.eu/vetdocs/PDFs/EPAR/virbagenomega/V-061-en1.pdf. Accessed January 15, 2010.
11. Fernandes NF, Geller SA, Fong T: Terbinafine hepatotoxicity: case report and review of the literature, *Am J Gastroenterol* 93:459, 1998.
12. Fischer J: Dealing with renal hyperphosphatemia: the good, the bound, and the ugly, Veterinary Information Network Rounds transcript, June 22, 2008 [website]. Available at http://www.vin.com/Members/CMS/Rounds/default.aspx?id=887. Accessed February 1, 2010.
13. Follmer CH, Lum BK: Protective action of diazepam and of sympathomimetic amines against amitriptyline-induced toxicity, *J Pharm Exp Ther* 222:424, 1982.
14. Frenais R, Rosenberg D, Burgaud S et al: Clinical efficacy and safety of a once-daily formulation of carbimazole in cats with hyperthyroidism, *J Small Anim Pract* 50:510, 2009.
15. Gunew MN, Menrath VH, Marshall RD: Long-term safety, efficacy, and palatability of oral meloxicam at 0.01-0.03 mg/kg for treatment of osteoarthritic pain in cats, *J Feline Med Surg* 10:235, 2008.
16. Hartmann K, Donath A, Kraft W: AZT in the treatment of feline immunodeficiency virus infection, part 2, *Feline Pract*, 23:13, 1995.
17. Haschek WM, Weigel RM, Scherba G et al: Zidovudine toxicity to cats infected with feline leukemia virus, *Fund Appl Toxicol* 14:764, 1990.
18. Helton KA, Nesbitt GH, Caciolo PL: Griseofulvin toxicity in cats: literature review and report of seven cases, *J Am Anim Hosp Assoc* 22:453, 1986.
19. Henik RA, Snyder PS, Volk LM: Treatment of systemic hypertension in cats with amlodipine besylate, *J Am Anim Hosp Assoc* 33:226, 1997.
20. Jepson RE, Brodbelt D, Vallance C et al: Evaluation of predictors of the development of azotemia in cats, *J Vet Intern Med* 23:806, 2009.
21. Kidder A, Chew D: Treatment options for hyperphosphatemia in feline CKD: what's out there? *J Feline Med Surg* 11:913, 2009.
22. King JN, Steffan J, Heath S et al: Determination of the dosage of clomipramine for the treatment of urine spraying in cats, *J Am Vet Med Assoc* 225:881, 2004.
23. Kittleson MD, Kienle RD, editors: *Small animal cardiovascular medicine*, ed 1, St Louis, 1998, Mosby, p 445.
24. Langston CE, Reine NJ, Kittrell D: The use of erythropoietin, *Vet Clin North Am Small Anim Pract* 33:1245, 2003.
25. Langston CE, Reine NJ: Hyperthyroidism and the kidney, *Clin Tech Sm Anim Pract* 21:17, 2006.
26. Levy JK: Ataxia in a kitten treated with griseofulvin, *J Am Vet Med Assoc* 198:105, 1991.
27. Mancianti F, Pedonese F, Zullino C: Efficacy of oral administration of itraconazole to cats with dermatophytosis caused by *Microsporum canis*, *J Am Vet Med Assoc* 213:993, 1998.
28. McDaniel WW: Serotonin syndrome: early management with cyproheptadine, *Ann Pharmacother* 35:1672, 2001.
29. Mehl ML, Kyles AE, Craigmill AL et al: Disposition of cyclosporine after intravenous and multi-dose oral administration in cats, *J Vet Pharmacol Therap* 26:349, 2003.
30. Michel T: Treatment of myocardial ischemia. In Brunton LL, editor: *Goodman and Gilman's the pharmacological basis of therapeutics*, ed 11, Chicago, 2006, McGraw-Hill, p 823.

31. Miller WH, Scott DW: Efficacy of chlorpheniramine maleate for management of pruritus in cats, *J Am Vet Med Assoc* 197:67, 1990.
32. Mooney CT, Thoday KL, Doxey DL: Carbimazole therapy of feline hyperthyroidism, *J Sm Anim Pract* 33:228, 1992.
33. Olson EJ, Morales SC, McVey AS et al: Putative metronidazole toxicosis in a cat, *Vet Pathol* 42:665, 2005.
34. Osborne CA, Stevens JB, Lulich JP et al: A clinician's analysis of urinalysis. In Osborne CA, Finco DR, editors: *Canine and feline nephrology and urology*, ed 1, Baltimore, 1995, Williams & Wilkins, p 141.
35. Papich MG: Therapeutic drug monitoring. In Papich MG, Riviere JE, editors: *Veterinary pharmacology and therapeutics*, ed 9, Ames, Iowa, 2009, Wiley-Blackwell, p 1323.
36. Peterson ME, Kintzer P, Hurvitz AI: Methimazole treatment of 262 cats with hyperthyroidism, *J Vet Intern Med* 2:150, 1988.
37. Pfeiffer E, Guy N, Cribb A: Clomipramine-induced urinary retention in a cat, *Can Vet J* 40:265, 1999.
38. Plotnick A: Feline chronic renal failure: long-term medical management, *Compend Contin Educ Pract Vet* 29:342, 2007.
39. Pryor PA, Hart BL, Cliff KD et al: Effects of a selective serotonin reuptake inhibitor on urine spraying behavior in cats, *J Am Vet Med Assoc* 219:1557, 2001.
40. Quimby JM, Gustafson DL, Samber BJ et al: The pharmacokinetics of mirtazapine in healthy cats [abstract], *J Vet Intern Med* 23:767, 2009.
41. Rayalam S, Eizenstat LD, Davis RR et al: Expression and purification of feline thyrotropin (fTSH): immunological detection and bioactivity of heterodimeric and yoked glycoproteins, *Dom Anim Endocrin* 30:185, 2006.
42. Rottman JB, English RV, Breitschwerdt EB et al: Bone marrow hypoplasia in a cat treated with griseofulvin, *J Am Vet Med Assoc* 198:429, 1991.
43. Ruaux CG, Steiner JM, Williams DA: Early biochemical and clinical responses to cobalamin supplementation in cats with signs of gastrointestinal disease and severe hypocobalaminemia, *J Vet Intern Med* 19:155, 2005.
44. Rusbridge C: Diagnosis and control of epilepsy in the cat, *In Practice* 27:208, 2005.
45. Rutland BE, Nachreiner RF, Kruger JM: Optimal testing for thyroid hormone concentration after treatment with methimazole in healthy and hyperthyroid cats, *J Vet Intern Med* 23:1025, 2009.
46. Schmidt BH, Murphy M: A study on the long-term efficacy of Renalzin™ (Lantharenol® suspension 20%) in cats with experimentally induced chronic kidney disease [poster], *Proc 19th Eur Coll Vet Intern Med Congress*, 2009.
47. Scott DW, Rothstein E, Beningo KE et al: Observations on the use of cyproheptadine hydrochloride as an antipruritic agent in allergic cats, *Can Vet J* 39:634, 1998.
48. Segev G, Bandt C, Francey T et al: Aluminum toxicity following administration of aluminum-based phosphate binders in 2 dogs with renal failure, *J Vet Intern Med* 22:1432, 2008.
49. Sekis I, Ramstead K, Rishniw M et al: Single-dose pharmacokinetics and genotoxicity of metronidazole in cats, *J Feline Med Surg* 11:60, 2009.
50. Seksel K, Lindeman MJ: Use of clomipramine in the treatment of anxiety-related and obsessive-compulsive disorders in cats, *Aust Vet J* 76:317, 1998.
51. Slater IH, Jones GT, Moore RA: Inhibition of REM sleep by fluoxetine, a specific inhibitor of serotonin uptake, *Neuropharmacology* 17:383, 1978.
52. Smith JA: What is the role of therapeutic drug monitoring in antifungal therapy? *Curr Infect Dis Rep* 11:439, 2009.
53. Snyder PS: Amlodipine: a randomized, blinded clinical trial in 9 cats with systemic hypertension, *J Vet Intern Med* 12:157, 1998.
54. Steagall PV, Taylor PM, Brondani JT et al: Antinociceptive effects of tramadol and acepromazine in cats, *J Feline Med Surg*, 10:24, 2008.
55. Trepanier LA: Pharmacologic management of feline hyperthyroidism, *Vet Clin North Am Small Anim Pract* 37:775, 2007.
56. Veterinary Information Network discussion: mirtazapine toxicity? September 14, 2009 [website]. Available at http://www.vin.com/Members/boards/discussionviewer.aspx?DocumentId=4113030. Accessed January 15, 2010.
57. Vlaminck KM, Engelen MA: An overview of pharmacokinetic and pharmacodynamic studies in the development of itraconazole for feline *Microsporum canis* dermatophytosis. In Hillier A, Foster AP, Kwochka K, editors: *Advances in veterinary dermatology*, vol 5, Ames, Iowa, 2005, Blackwell Publishing, p 130.
58. Whitney BL, Broussard J, Stefanacci JD: Four cats with fungal rhinitis, *J Feline Med Surg* 7:53, 2005.
59. Zeidner NS, Myles MH, Mathiason-DuBard CK: Alpha interferon (2b) in combination with zidovudine for the treatment of presymptomatic feline leukemia virus-induced immunodeficiency syndrome, *Antimicrob Agents Chemother* 34:1749, 1990.

MANAGING ADVERSE DRUG REACTIONS

Sidonie Lavergne

Adverse drug reactions (ADR) are a common collateral damage of practicing medicine. They are responsible for high morbidity and even mortality in both human and veterinary medicine every year. The previous chapters and sections have already described numerous adverse drug reactions, well characterized or not, that could be associated with prescribing the therapy options available for the discussed diseases. This chapter section will focus on the general principles and specific aspects that were not already presented earlier.

INCIDENCE OF ADVERSE DRUG REACTIONS

There is no fully established estimate of ADR in veterinary medicine.[3,4,6] Cats, however, appear to have a similar overall incidence of ADR as dogs and humans. The most commonly reported are dose-dependent ADR related to the properties of the drugs (type A). Drugs that are most often associated with adverse events are those that are also the most commonly prescribed: antiparasitic agents, antiinflammatory drugs, antimicrobials, and finally, drugs acting on the neurologic system.

CLASSIFICATION OF ADVERSE DRUG REACTIONS

Type A

Type A adverse drug reactions are dose-dependent and are secondary to the drug characteristics. They will occur in any cat beyond a certain dose. These reactions are predictable and therefore avoidable. There are three different subtypes of type A reactions:

1. Those related to the pharmacologic interaction of the drug with a cell receptor
   a. On-target: for instance, barbiturate- and benzodiazepine-induced sedation, loperamide-associated constipation, immunosuppression from immunosuppressive therapy associated with risks of sepsis
   b. Off-target: for instance, nonsteroidal antiinflammatory drug (NSAID)–associated gastrotoxicity and nephrotoxicity; beta-lactam–induced seizures at high concentrations, erythromycin-induced vomiting, morphine-induced central nervous system stimulation at high doses (greater than 5 mg/kg), xylazine-induced emesis, reversible and dose-dependent bone marrow suppression in cats treated with chloramphenicol
2. Those related to the chemical and/or physical properties of the drug (e.g., most nausea and vomiting reactions, esophageal lesions secondary to tablets or capsules, especially doxycycline and clindamycin)
3. Those related to the toxic properties of a drug metabolite: for instance, metabolite-associated methemoglobinemia and hepatotoxicity with acetaminophen (see Chapter 31), azathioprine-associated bone marrow toxicity (potentially exacerbated in cats by a much lower thiopurine methyltransferase activity compared with humans and dogs); bone marrow toxicity with high doses of griseofulvin in cats infected with feline immunodeficiency virus[8]

The risk of type A ADR increases with the dose and the duration of the treatment, because they are dose-dependent. In addition, drugs can become toxic when used in combination, despite each agent being used at the recommended dosage regimen. Drug interactions are of three types:

1. Pharmaceutical interactions when drugs are not compatible on a chemical or physical level (e.g., diazepam precipitation in lactated Ringer solution or adsorption to plastic, complexation of tetracycline with calcium or magnesium)
2. Pharmacokinetic interactions (e.g., bicarbonates in IV fluids decrease the renal elimination of weak bases; ketoconazole inhibits the metabolism of cyclosporine)
3. Pharmacodynamic interactions during which drugs can synergize their toxic effects (e.g., nephrotoxicity from NSAIDs and aminoglycosides, bleeding risk from aspirin and heparin) or antagonize their therapeutic effects (e.g., immunosuppressive agents with antimicrobials, antiemetic agents with emetic drugs)

Some intrinsic factors may also increase the risk for type A adverse drug reactions, such as age (neonate vs. kitten vs. elderly), percentage of body fat (cachectic vs. normal weight vs. obese), hydration status; and any underlying diseases (especially renal and severe liver dysfunction or meningitis). These factors should always be taken into consideration before deciding on a dosage regimen for any given cat. See type A and type B adverse drug reactions algorithm on page 1164.

Type B

Type B adverse drug reactions are not usually dose-dependent and are secondary to features of the patient rather than the drug. They will not be seen in all cats, even at very high doses, and are sometimes called "idiosyncratic." They are therefore neither predictable nor avoidable (at least before the first episode).

Many type B reactions are thought to be immune mediated and are called "drug allergies" or "drug hypersensitivity reactions." The reaction can be immediate and usually quite severe in cases of anaphylactic or anaphylactoid reactions. Anaphylactic reactions are truly immune mediated, involving immunoglobulin E (type I hypersensitivity), and require a previous exposure. Anaphylactoid reactions, on the other hand, result from the release of powerful inflammatory mediators and can occur at the first exposure. Delayed reactions can be antibody mediated, involving IgG and IgM (type II hypersensitivity) or immune complexes and/or the complement cascade (type III hypersensitivity), or can be cell-mediated, involving T-lymphocytes (type IV). No data have been generated in feline patients, with the exception of propylthiouracil-associated blood dyscrasias, that were shown to involve several antibody markers (antinuclear, anti–red blood cells, and anti-neutrophil).[1,7,9]

Involvement of the immune system has not been confirmed for all type B reactions. The nature of these uncharacterized reactions remains unknown. This was the case for "ivermectin hypersensitivity" in Collies until the *MDR1* genetic mutation was identified in these dogs. It was also the case with fluoroquinolone-induced retinal degeneration until it was shown to be a dose-dependent phenomenon that can happen in all cats with high enough dosages and might involve a drug metabolite (see Chapter 29). It remains the case for carprofen-associated hepatotoxicity in dogs and for diazepam- and glipizide-associated hepatotoxicity in cats.[2,5]

PREVENTING ADVERSE DRUG REACTIONS

Type B reactions are by definition unpredictable, at least until the first episode. Any suspected episode of drug allergy needs to be carefully recorded in the medical

record to prevent re-exposure. Type A reactions are, on the other hand, predictable and therefore avoidable. Preventing them, however, requires being aware of their existence. This awareness should be reflected in multiple steps of daily practice through the following protocols:

- Choose drugs with the lowest possible toxicity profile.
- Adjust the dose according to the life stage and health of the patient (especially in very young and old cats, or in cats with renal or severe liver insufficiency).
- Use drugs approved for cats in the disease of interest whenever possible, or research off-label dosage regimen information carefully in the literature before use.
- Try to limit polypharmacy (to decrease the risk of negative drug interactions).
- Realize that most drugs can induce side effects and ALL drugs can be associated with allergic reactions; therefore always warn owners about potential side effects of drugs and nutraceuticals (e.g., SAMe, *N*-acetylcysteine, vitamin C).
- Never prescribe a drug without being perfectly aware of its potentially toxic effects in cats, but also in other species (in case it has not been reported in cats yet), and always use appropriate monitoring tools (e.g., physical examination, CBC, serum chemistry panels, and, when available, drug plasma concentrations).
- Try to limit the use of drugs in sensitive populations, such as kittens, older cats, or pregnant queens.

There is a very limited amount of information on the carcinogenic and/or teratogenic effects of drugs in cats. Metronidazole is thought to be potentially teratogenic in laboratory animals and was shown to be genotoxic in cats. It is recommended, however, to always assume that potential teratogenicity and/or genotoxicity or carcinogenicity demonstrated in other species could occur in cats too. Furthermore, any highly liposoluble drug (e.g., phenobarbital) that will most likely reach the fetus and be excreted in milk, as well as any drug interacting with hormones (e.g., methimazole) or developmental signaling pathway (e.g., cyclooxygenase 2 and kidney development) should not be used in pregnant queens or neonatal kittens, unless strictly necessary and no other treatment alternatives are available.

DIAGNOSING ADVERSE DRUG REACTIONS

A key component of managing an ADR is first to recognize it. This seems like an obvious statement, but most clinicians forget to include ADR in their differential list. Adverse drug events can mimic most diseases, with rare exceptions such as bone fractures, abscesses, or tooth resorption lesions.

Diagnostic Steps for All Adverse Drug Reaction Types

The diagnosis of any ADR involves the following steps:

1. Collection of a complete medical history (previous and present drug exposure and timing); a thorough physical examination; a CBC and serum chemistry panel; +/– a tissue aspirate/biopsy, which should show some specific signs of drug or chemical toxicity but is more important in severe cases.
2. Discontinuation of the drug suspected (a "de-challenge"). If the drug was responsible for the clinical signs, they should resolve when administration of the drug is ceased and the drug has been cleared. Re-challenges are considered unethical, especially in cases of drug allergy, because the next exposure could be associated with much more severe clinical signs.
3. It is critically important to contact and consult with the pharmaceutical company and/or the American Society for the Prevention of Cruelty to Animals (ASPCA) Animal Poison Control Center if necessary (1-888-426-4435; http://www.aspca.org/pet-care/poison-control/).

ADR diagnosis is rendered very challenging by the fact that these drug reactions can mimic miscellaneous non–drug-related diseases. Only the combination of drug exposure and the right timing of events with a given set of clinical signs will allow a clinician to conclude that the patient suffered from a probable adverse drug reaction. Beyond that, there are a very limited number of laboratory tests that a clinician can use to confirm the diagnosis.

Diagnostic Steps for Type A Reactions

Because Type A drug reactions are dose-dependent, and secondary to known features of the drug, getting the following information is useful:

- History: doses and intervals prescribed, but also those that were actually given to the cat by the owner
- Drug plasma concentration, although these tests are not always readily available for the drug of interest (see Table 36-4)
- Specific organ function monitoring depending on the toxicity profile of the suspected drugs, for instance, liver enzymes for diazepam toxicity (see Table 36-2)

Diagnostic Steps for Type B Reactions

Confirming a diagnosis of drug allergy can be difficult. Because they are usually not dose-related, and are often thought to involve a drug metabolite rather than the parent drug, the drug plasma concentration will not be useful. The hematopoietic system, the liver, and the skin are the most common targets of immune-mediated drug reactions, but reports have been published involving miscellaneous organs, such as the lungs, the kidneys, the pancreas, and even the central nervous system. A diagnosis of immune-mediated drug reaction can be suggested by

- The timing of the reaction: occurring immediately after the initial exposure (anaphylactoid reaction), immediately after previous exposure(s) (anaphylaxis), or delayed (usually after at least 5 days of drug administration for the first course); this requires that the clinician inquire about drugs that the cat has been taking within the past month, even if the cat has stopped receiving them at the time of the reactions.
- Clinical signs that may include skin lesions (such as pruritic urticaria-angioedema, maculopapular dermatitis, erythema multiforme, pemphigus foliaceus, vasculitis, and toxic epidermal necrosis), as well as purpura, pale mucosa, jaundice, fever, or polyarthropathy.
- Typical findings from complementary clinical tests that may include blood cytopenia involving one or several cell lines or increased liver enzymes.

When a clinician suspects a drug-induced immune-mediated reaction, some tests specific to the organ targeted by the reaction can be useful: for instance, skin biopsy, liver biopsy, bone marrow aspirate, antinuclear antibody test, and Coombs' test. Some veterinary schools also offer research tests (often free of charge) to help confirm the diagnosis by looking for specific anti-drug antibodies, antitissue antibodies, or drug-specific lymphocytes (lymphocytes recognizing the drug as their target and as their stimulating antigen).

MANAGING ADVERSE DRUG REACTIONS

Fortunately, most adverse drug reactions involve mild clinical signs, and most animals will recover without requiring any specific treatment other than drug discontinuation. The clinical management of some ADR will, however, be more challenging.

Managing Type A Reactions

Because type A reactions are dose-dependent and related to the drug features, the clinician will have to consider either modifying the dosage regimen or discontinuing the drug all together. There is no specific rule in making that decision, but severe clinical signs should probably lead to discontinuing any drug or nutraceutical the cat could be receiving at the time of the reaction. Non–life-threatening reactions can probably be managed by decreasing the dose or increasing the dosing interval.

Type A reactions result from a negative characteristic of the drug that can sometimes be counteracted by antidotes (e.g., folic acid or folinic acid for bone marrow suppression secondary to high doses and long-term trimethoprim/ormetoprim, atipamezole for medetomidine reversal, protamine for heparin overdose, antioxidants when oxidative stress has been proved to be part of the pathogenesis). Some dose-dependent ADR will require complementary organ support (e.g., fluid therapy for hypotension or nephrotoxicity, erythropoietin for anemia, gastroprotectants for NSAID-induced ulcers, antiemetics for vomiting).

Pharmaceutical companies and the ASPCA Animal Poison Control Center (see above) will provide information regarding the treatment of specific dose-dependent ADR.

Managing Type B Reactions

When an idiosyncratic drug reaction is suspected, all drugs and nutraceuticals should be withdrawn, since even a minute amount of drug could elicit an allergic reaction. Most cases of drug allergy are mild, but some allergic reactions can be life threatening, and their clinical management should start as soon as possible and be aggressive. This is the case for anaphylaxis and anaphylactoid drug reactions, blood dyscrasias, liver toxicity, or severe skin reactions, such as Stevens-Johnson syndrome and erythema multiforme majus (approximately 50% survival in humans), and toxic epidermal necrolysis (less than 30% survival in humans).

Anaphylaxis and anaphylactoid reactions are the only true emergency in ADR. Their treatment includes the following steps:

- Ensure patent airway and IV access (central venous access is ideal)
- IV fluids (monitor the rate carefully to avoid pulmonary edema)
- Epinephrine: slow IV if possible (0.1 mL of a 1:1,000 solution per cat, or 1 mL/10 kg of a 1:10,000 dilution or 0.01 mg/kg); or 0.02 mg/kg endotracheal when the cat is intubated or 0.01 mg/kg, SC or IM, in less severe cases, to be repeated as needed every 5 to 15 minutes
- +/– Short-acting water-soluble corticosteroids (prednisolone 50 to 100 µg/cat, IV)

TABLE 36-5 **Examples of Regulatory Agencies Recording Adverse Drug Reaction Reports**

Country	Agency	Website
United States	Federal Drug Administration: Center for Veterinary Medicine (FDA-CVM)	http://www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm055305.htm
United Kingdom	Veterinary Medicine Directorate: Suspected Adverse Reaction Surveillance Scheme (VMD-SARSS)	http://www.vmd.gov.uk/General/Adverse/adverse.htm
Canada	Health Canada: Veterinary Pharmacovigilance	http://www.hc-sc.gc.ca/dhp-mps/vet/advers-react-neg/index-eng.php

- +/− Antihistamines: anti-H1 receptors (e.g., diphenhydramine 2 mg /kg, IM, every 12 hours) alone or in combination with anti-H2 receptors (e.g., ranitidine 1 to 3.5 mg/kg, IV or SC or PO, every 12 hours; there are reports of hemolytic anemia with famotidine given IV)

It is important to remember that some type I hypersensitivity reactions involve the mucocutaneous system (urticaria and angioedema) without the respiratory and cardiovascular system. These reactions are less severe and can probably be managed with corticosteroids and/or antihistamines alone, under careful surveillance until complete resolution.

Discontinuing any drug and implementing aggressive organ support are the cornerstones of treating all drug allergies. Immunosuppressive therapy (e.g., corticosteroids, human intravenous IgG, cyclosporine) is sometimes included in the management of drug allergies. There is no strong evidence in human medicine, however, and none in feline drug allergies, that they improve the outcome.

If the idiosyncratic reaction is thought to be immune mediated, the cat should never receive the culprit drug again, because the clinical signs could be much more severe at the next exposure. Sometimes, another member of the same drug class may be substituted (e.g., midazolam in cats with a history of diazepam-associated hepatotoxicity, propyluracil in propylthiouracil-sensitive cats). In cases of drug allergies, some clinicians will prefer to use a different drug class to avoid any risk of cross-reactivity (e.g., avoiding all penicillins after amoxicillin allergy). If some of the drugs that were discontinued when the episode started were essential to the cat's survival or quality of life, the clinician should use the following precautions:

- Reintroduce each drug one-by-one, starting with those that are the least likely to have caused the incident.
- Start at a low dose (lower than the therapeutic dose) and increase it very gradually, with strict clinical surveillance and with all the emergency supplies and drugs ready in case of an allergic reaction.

REPORTING ADVERSE DRUG REACTIONS

Reporting an ADR is part of managing the event, even if the clinical signs were only mild, predictable, and/or could have been avoided. The reactions should be reported to the pharmaceutical company (using the phone number on the drug package). The manufacturer is required by law to pass this information on to the necessary governmental agency (Table 36-5). Only cases involving human drugs should be reported directly to a regulatory agency by the veterinarian. The clinician needs to report the adverse drug event as soon as possible, to avoid forgetting important details and to potentially receive key information about managing the reaction and helping the patient.

CONCLUSION

It is important to recognize that ADRs are not uncommon in cats, even though they are less often the subject of publications on ADR than are dogs or humans. The management of an ADR requires being aware of the risks, recognizing reactions promptly, and reporting them.

References

1. Aucoin DP, Peterson ME, Hurvitz AI et al: Propylthiouracil-induced immune-mediated disease in the cat, *J Pharmacol Exp Ther* 234:13, 1985.
2. Center SA, Elston TH, Rowland PH et al: Fulminant hepatic failure associated with oral administration of diazepam in 11 cats, *J Am Vet Med Assoc* 209:618, 1996.
3. Dyer F, Mulugeta R, Spagnuolo-Weaver M et al: Suspected adverse reactions, 2004, *Vet Rec* 156:561, 2005.
4. Hampshire VA, Doddy FM, Post LO et al: Adverse drug event reports at the United States Food and Drug Administration Center for Veterinary Medicine, *J Am Vet Med Assoc* 225:533, 2004.
5. Levy JK, Cullen JM, Bunch SE et al: Adverse reaction to diazepam in cats, *J Am Vet Med Assoc* 205:156, 1994.
6. Maddison JE: Adverse drug reactions: report of the Australian Veterinary Association Adverse Drug Reaction Subcommittee, 1994, *Aust Vet J* 73:132, 1996.
7. Peterson ME, Hurvitz AI, Leib MS et al: Propylthiouracil-associated hemolytic anemia, thrombocytopenia, and antinuclear antibodies in cats with hyperthyroidism, *J Am Vet Med Assoc* 184:806, 1984.

8. Shelton GH, Grant CK, Linenberger ML et al: Severe neutropenia associated with griseofulvin therapy in cats with feline immunodeficiency virus infection, *J Vet Intern Med* 4:317, 1990.
9. Waldhauser L, Uetrecht J: Antibodies to myeloperoxidase in propylthiouracil-induced autoimmune disease in the cat, *Toxicology* 114:155, 1996.

PALLIATIVE MEDICINE: PAIN ASSESSMENT AND MANAGEMENT

Sheilah Robertson

Pain is a component of many chronic diseases and is an important welfare issue. However, it is often overlooked and therefore undertreated. Recognizing long-standing pain and its impact on quality of life is challenging. Some of the behavior changes associated with pain may be mistaken for normal aging. The prevalence of chronic pain in the cat population is unknown, but in one study, 33.9% of cats between 6 months and 16.4 years of age had degenerative joint disease.[9] There is very little scientific evidence on the subject of chronic pain in cats, including treatment options and outcomes, in the veterinary literature.

POTENTIAL CAUSES OF LONG-TERM PAIN AND DISCOMFORT

Clinical conditions likely to result in long-term pain and discomfort in cats include interstitial cystitis, neoplasia, dermatologic diseases, dental and oral diseases, gastrointestinal disease, degenerative joint disease, slow-healing wounds, and diabetic neuropathy. Other causes include treatment-related pain, for example, radiation damage or chemotherapy-induced neuropathy. These conditions can afflict cats of any age, breed, or sex. In these patients, both the disease itself and the pain that is associated with it must be addressed. For example, it is important to regulate blood glucose in a diabetic cat, but the associated pain from neuropathy must also be addressed and often by different methods. In some cases, such as degenerative joint disease, there is little that can be done to halt the disease process, so the focus is to relieve pain.

PATHOPHYSIOLOGY

Defining pain is not a simple matter. It is a multifactorial experience with sensory (how much does it hurt), affective or emotional (how does it make the cat feel), and functional (can the cat still perform normal daily activities) components. Pain can result from obvious causes (e.g., trauma) and last an expected time period, but sometimes pain persists after the original injury or wound appears to be healed. In diseases such as interstitial cystitis, the underlying mechanisms that cause pain are poorly understood, and classical analgesics, such as opioids and anti-inflammatory agents, do not consistently relieve the cat's pain.

In some cases, pain has no obvious cause and is sometimes classified as "idiopathic" or dysfunctional.[10] Dysfunctional pain serves no purpose—it is neither protective nor does it support healing. Historically, pain has been labeled as acute or chronic based solely on its duration; however, this is not a helpful classification. It has been suggested that the terms adaptive and maladaptive be adopted. The term adaptive infers a normal response to tissue damage and involves an inflammatory component (for example, a surgical incision) that is reversible and disappears over a predictable and relatively short time period. Maladaptive pain results from changes in the spinal cord and brain that result in abnormal sensory processing and is usually persistent. Nerve damage results in neuropathic pain that is maladaptive and often persistent, for example after limb amputation. Maladaptive pain can develop if adaptive pain is not quickly and aggressively treated, emphasizing the importance of good pain management for all painful procedures.

Ideally, pain should be classified by the underlying mechanism[31]; for example, inflammatory or neuropathic. Knowing and understanding the underlying cause guides the practitioner in the choice of treatment; otherwise treatment will be empirical. A diagnosis of "cancer" pain is not very helpful, since the cause could be mechanical compression of a nerve, inflammation from tissue necrosis, or mechanical distension of an organ. The underlying cause may be complex, and some mechanisms of pain can co-exist, requiring several different treatment strategies. This approach is discussed in the American Animal Hospital Association (AAHA)/American Association of Feline Practitioners (AAFP) pain management guidelines.[14]

Another challenge to the practitioner is that even if the underlying cause or mechanism is identified, the disease process and associated pain may not be static; "good" days and "bad" days are common in cats with long-term disease. A cat that has good pain management for a tumor can have acute exacerbations if the tumor grows rapidly or becomes necrotic. A concurrent disease condition, such as inflammatory bowel disease, may also change the processing of noxious signals and the pain that the cat perceives.

CLINICAL SIGNS AND DIAGNOSIS

Because of the nature of long-term pain, which is sometimes slow and insidious in onset, the accompanying behavioral changes can be subtle and easily missed. Asking the owner the correct questions about changes in behavior (loss of normal behaviors [e.g., grooming] or

appearance of new behaviors [e.g., seeking solitude, aversion to being stroked]) and changes in lifestyle are key to establishing a suspicion of underlying pain. Mobility, activity, grooming, and temperament improve with analgesic intervention in cats with degenerative joint disease.[2,19] It is likely that these four major behavior domains are also altered in other chronic pain states. Keeping track of these questions and answers is also important for evaluating response to therapy. In addition, it can be useful if the owner keeps a diary, noting things such as appetite, playing, hiding, socialization, or interaction with other pets, and to compare current to previous entries. Having a written account can show the owner which therapies appear to help and show when bad days are outnumbering the good days, helping them make decisions on whether or not to continue treatment.

Painful diabetic neuropathy occurs in some but not all human diabetics and can be seen at different times after diagnosis and can resolve as nerves degenerate, but when present is distressing and has a significant impact on quality of life.[30] This component of the disease is less well described in cats; however "irritability, especially when touching the feet" is reported in the literature[21] and by many owners and veterinarians. In humans, sensory changes start in the feet and hands. Unlike humans, changes in sensation to thermal and tactile stimuli have not yet been documented in cats[6]; however, only a very small number of cats have been tested, and only at one time point in the disease process. Clues as to whether diabetic cats are painful include reports by the owner that the cat has recently started to dislike being touched, especially around the distal extremities. Licking of the feet leading to discoloration of the fur can sometimes be seen in light colored cats and suggests tingling or other sensory changes.

Clinical examination by the veterinarian is also an important part of the assessment process.[25] Questioning the owner and performing a comprehensive examination will take time and so should be planned outside of a busy schedule.

TREATMENT

At the outset, some clear treatment goals should be established. In many cases, we are not dealing with curable diseases; quality of life, not quantity of life is the focus of treatment. The aim of treatment is to normalize pain sensitivity.[31] Our goals are to make cats comfortable so that they can perform normal daily activities and to prevent any marked changes in their normal behavior or personality.

The level of treatment must be matched to the level and complexity of the pain present. However, some cats are difficult to medicate, and compliance with a recommended treatment is often poor; therefore the route of administration, number of drugs, and dosing schedules should be carefully evaluated for feasibility in each patient. As previously discussed, chronic diseases are not static and neither is the pain associated with them; therefore frequent modification of the treatment plan may be needed to maintain a constant level of comfort.

Because treatment will often be for a prolonged period of time, it is important to have a discussion with the owner at the outset about the financial, time, and emotional commitment involved and to point out that treatment may require considerable trial and error, with associated disappointment and frustration. It is important to be realistic about what can be achieved and not give false hope or allow the owner to embark on treatment pathways with no scientific basis and with little chance of success.

Drug Therapy

Sometimes it can be difficult to be certain a cat is in pain based on a clinical assessment, or an owner may be convinced that some of the behavioral changes seen are just part of "slowing down and getting old." In these cases, an analgesic trial can be helpful and often results in the owner claiming they did see a change in behavior and the cat is now "like its old self."[2]

Most drugs used for the alleviation of maladaptive pain are used "off label" for the feline species, and doses and dosing intervals are not well established (Table 36-6).

Psychoactive Drugs

Drugs in this category include the selective serotonin reuptake inhibitors (SSRIs [e.g., fluoxetine]), monoamine oxidase inhibitors (MAOIs [e.g., selegiline]), and tricyclic antidepressants (TCAs [e.g., amitriptyline]). These drugs act to alter reuptake, release, and deactivation of catecholamines and serotonin, neurotransmitters known to be involved in pain transmission in the spinal cord. Psychoactive drugs, in particular the TCAs, are used in people for the treatment of chronic and neuropathic pain, often at doses lower than those used to treat depression. Amitriptyline has been used successfully for interstitial cystitis in some cats.[8] The TCAs should not be used concurrently with drugs that also modify the serotonergic system, such as tramadol (also see Drug Interactions below).

Antiepileptics

Gabapentin and pregabalin have been effective in various neuropathic pain states in people. Information on the kinetics of gabapentin in cats is available[27] but there are no scientific publications demonstrating its efficacy for alleviation of long-term pain in this species. However, this author finds gabapentin a particularly useful drug for so-called neuropathic or neurogenic

TABLE 36-6 Suggested Doses of Analgesics That May Be Used for the Alleviation of Long-Standing Pain in the Cat*

Drug and Class	Dose (mg/kg)	Comments
Amantadine (NMDA antagonist)	3.0-5.0 mg/kg, PO, q24h	This drug has not been evaluated for toxicity in the cat. It may be a useful adjunct to NSAIDs in the treatment of cancer-related pain and degenerative joint disease.
Amitriptyline (TCA)	0.5-2.0 mg/kg, PO, q24h	This drug appears to be well tolerated in cats. It has been used for interstitial cystitis. Somnolence (<10% of cats), weight gain, decreased grooming, and transient cystic calculi were observed during treatment in some cats.[8]
Buprenorphine (opioid)	0.01-0.02 mg/kg, oral transmucosal, q8h, or "as needed"	The oral transmucosal route is well tolerated by most cats.
Gabapentin (antiepileptic)	5-10 mg/kg, PO, q12h	Appears to be effective in cats where the underlying cause of pain is neuropathic.
Meloxicam (NSAID)	Oral formulation: Approval was gained in Europe (June 2007) for long-term (unlimited) use of meloxicam in the cat at 0.1 mg/kg, PO, on day 1, followed by 0.05 mg/kg, PO, every 24 hours Lower doses and "every other day" dosing can also be effective Injectable formulation available	This drug is particularly well received by cats, because of its formulation as a liquid. The formulation makes it very easy to gradually and accurately decrease the dose. Meloxicam should be dosed accurately using syringes. Careful titration and monitoring allows the "lowest effective dose" to be reached, thereby avoiding potential side effects. Give with food. Labeled for acute perioperative pain.
Tramadol (mixed analgesic)	1-2 mg/kg, PO, every 12 to 24 hours	Published data suggests the metabolism of tramadol is slower in the cat than in the dog, and the production of the M1 metabolite is very much greater, leading to a greater tendency to see "opioid"-like side effects (pupil dilation euphoria).[24] Very unpalatable even when compounded. Do not use in cats receiving psychoactive drugs.
Transdermal fentanyl patch (opioid)	25 µg/hour patch	A 25 µg/hour patch can be applied to an "average" cat (3.5-5.0 kg, 7.7-11 lb). Uptake is highly variable. Time to onset of action is 6-12 hours. The patches may provide 3-5 days of analgesia in some cases. Following removal at 3 days, the decay in plasma levels following patch removal is slow. Liability issues should be considered when these are used in a home setting. Do not use in cats receiving psychoactive drugs. Do not use in combination with tramadol.
	12.5 µg/hour patch	Smaller cats.

*See text for details. In most cases these drugs are used "off label" for cats, and doses are not well established.
M1 metabolite, *O*-desmethyl-tramadol; *NMDA, N*-methyl-D-aspartate; *NSAID,* nonsteroidal antiinflammatory drug, *TCA,* tricyclic antidepressant.

pain, at starting doses of 10 mg/kg, PO, every 12 hours. Sedation and ataxia are the main side effects seen in cats.

Sodium Channel Blockade

Although not a convenient mode of delivery for most patients with neuropathic pain, intravenous lidocaine has proven effective for neuropathic pain in humans with single treatments, sometimes offering long-term relief.[7] However, the intravenous administration of lidocaine to cats is associated with cardiovascular depression and is not recommended.[23] There is increasing interest in transdermal lidocaine patches, and a recent study reported on the absorption and kinetics of lidocaine from transdermal patches in cats; plasma lidocaine concentrations remained well below systemically toxic concentrations, and skin concentrations of lidocaine were high.[15] The transdermal technique may prove useful for alleviating pain originating from long-standing wounds and scar tissue.

N-*Methyl-D-Aspartate (NMDA) Inhibitors*

Preclinical evidence indicates that hyperalgesia (an exaggerated and prolonged response to a noxious stimulus) and allodynia (pain that can be elicited by normally innocuous stimuli) following peripheral tissue or nerve injury depends on NMDA receptor–mediated central

changes in synaptic excitability, and also shows quite clearly that NMDA antagonists can attenuate hyperalgesia and allodynia in animal models of neuropathic pain. The NMDA antagonist amantadine (3 to 5 mg/kg, PO, every 24 hours), as an adjunct to NSAID use, is effective in dogs with osteoarthritis.[18] There are no pharmacokinetic studies of amantadine in the cat, and although there are anecdotal reports of use for chronic pain, there are no well-controlled published studies.

In some cats with maladaptive pain, the author has observed improvement after they have been sedated with ketamine for diagnostic tests. Ketamine, as a bolus (2 mg/kg, IV), or as a constant rate infusion (2 to 5 µg/kg/minute) for several hours, may have a role to play in "resetting" the central nervous system in some pain states.

Mixed Analgesics

Although not classified as a true opioid, tramadol has weak binding affinity at OP3 (mu) opioid receptors but also acts at serotonin and adrenergic receptors. There has been considerable interest in evaluating tramadol in cats. Pharmacokinetic evaluation of intravenous and oral tramadol found a relatively long half-life and rapid and significant formation of the M1 metabolite (*O*-desmethyl-tramadol) when compared with use in dogs.[24] The M1 metabolite is considered to be the active metabolite, responsible for analgesia. Tramadol can provide analgesia in the cat, at least in the acute setting (see Chapter 6). As yet, there is no work evaluating the analgesic action of tramadol in chronic or maladaptive scenarios. One of the biggest drawbacks with oral tramadol is its bitter taste, and even with flavoring, this drug can be difficult to administer to cats. The development of palatable formulations that allow high compliance will be essential to future studies. Tramadol should not be given to cats receiving psychoactive drugs (see above, Adverse Drug Reactions).

Opioids

Opioids have variable efficacy in the treatment of maladaptive pain in humans, and their role in this setting is not well defined in cats. Transdermal fentanyl can be an effective way of providing perioperative analgesia in the cat (see Chapter 6). Buprenorphine, given by the oral transmucosal route (OTM), is highly bioavailable, easy to administer, and is antinociceptive in the cat.[26] The major physical side effect of continuous opioid use for weeks or months in humans is constipation, but there are no similar reports in cats. There are anecdotal reports of appetite loss in cats after several days of opioid use, which usually resolves when the dose is lowered or its use is discontinued. Opioid-related euphoria can occur and is undesirable to some owners.

There is no information on dependence or withdrawal with long-term use of opioids in cats. Opioids may have a role to play in controlling "break-through" pain, for example, when a cat whose pain is well controlled with amitriptyline or meloxicam has a "bad day." In this author's experience, OTM buprenorphine can be helpful given in the evening to ensure overnight sleep; the restorative powers of sleep should not be underestimated. In addition, a restless cat can be upsetting and disruptive to the owner. Opioids may also be used in "end-of-life" situations. As discussed below, amitriptyline and fentanyl should not be used concurrently. The liability issues surrounding the use of transdermal patches are discussed in Chapter 6.

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are the foundation of a treatment plan for many long-term pain patients. The mode of action and use of NSAIDs in cats has been comprehensively reviewed.[17] Meloxicam is approved in Europe and other countries, including Australia, for the treatment of chronic musculoskeletal pain. This approval is for an unlimited time at a dose of 0.05 mg/kg, PO, every 24 hours. A study of 40 cats with degenerative joint disease (DJD)–associated pain suggested that a dose of 0.01 to 0.03 mg/kg, PO, every 24 hours, with mean treatment duration of 5.8 months, was well tolerated.[12] Gastrointestinal upset in 4% of cats was the only adverse effect noted. The first drug in the coxib class of NSAIDs, robenacoxib (Onsior),[11] has been granted approval in Europe for use in cats. In cats with musculoskeletal pain, the indication is for as many as 6 days of therapy at a dose of 1 mg/kg, PO, every 24 hours. Oral NSAIDs should be administered with food.

Adverse Drug Interactions

There is potential for adverse drug interactions when patients with behavioral problems are prescribed psychoactive drugs and require treatment for pain. The main concern is precipitation of serotonin toxicity, sometimes referred to as "serotonin syndrome." This is well recognized in humans[4] and is now reported in animals.[22] Serotonin toxicity results from overdose with one serotonergic drug or by the use of a combination of drugs that influence serotonin levels. Serotonin toxicity resulting from multidrug therapy is not well documented in the veterinary literature but is an increasing concern as treatment strategies become more complex.

Mirtazapine, often used as an appetite stimulant and antiemetic, may cause serotonin syndrome in susceptible individuals. Because of this, other agents may be better choices, should a patient require one of the following drugs with similar serotonin effects. Some opioids, including meperidine, methadone, pentazocine and fentanyl, and tramadol impair reuptake of serotonin, and tramadol may also increase serotonin release. These drugs have precipitated serotonin toxicity when given to humans taking SSRIs, MAOIs, and TCAs. Buspirone

is a partial serotonin agonist and could lead to problems when combined with these analgesics.

Before designing a plan for treating long-term pain in a patient, it is important to know which drugs have been prescribed but also what is being given by the owner. Herbal supplements, such as *Hypericum perforatum*, or St. John's Wort, and ginseng have been linked to serotonergic intoxication in humans and dogs.[22] Transdermal fentanyl patches and tramadol should not be used in cats receiving behavior-modification drugs. Buprenorphine does not cause serotonin reuptake inhibition and so can be used as previously described.

Nonpharmacologic Therapies

Environmental Enrichment

Environmental enrichment is important for all cats, especially those confined indoors; however, it may be a critical component of treatment for cats with long-standing disease. Cats with degenerative joint disease (DJD)–associated pain will benefit from exercise, which can be increased by a complex environment, for example, by using cat towers/climbing trees, toys, and hiding food to encourage foraging and hunting behavior. In people, a stimulating environment or being engaged in activities distracts the patient from focusing on their pain, and these techniques could be applied to animals. Environmental enrichment strategies are discussed in detail in Chapter 46.

Physical Therapies

Physical rehabilitation techniques, including controlled exercise, passive range-of-motion (ROM) exercises, and massage can all be incorporated into a treatment plan. The benefits of these treatment strategies are just beginning to be defined in canine medicine but have not yet been evaluated in feline medicine. However, it is likely the same basic principles and benefits will apply to feline patients. ROM and massage techniques can be taught to owners, and these techniques can both help to alleviate muscle pain and also contribute to "environmental" enrichment for the cat; there is more interaction between the owner and cat, and this can use up otherwise empty "time budgets." It also empowers the owner by involving them in treatment. When used as an adjunct to conventional therapy, massage improved pain, discomfort, mood, tension, and stress in human pediatric patients with chronic pain.[29] Similar to massage and ROM exercises, other modalities, such as shock wave therapy, laser therapy, and heat and cold therapy, may well be of benefit in certain circumstances in feline patients, but no well-controlled scientific studies of these modalities in cats have been published.

Gingivostomatitis is challenging to treat in cats and may require several approaches, including multiple tooth extractions, corticosteroids, NSAIDs, antiviral and immunomodulatory drugs, and laser resection.[20] Pain and a poor quality of life are major features of this disease in many cats. Although lasers are widely used for oral surgery, they may also have a potential role in healing and analgesia. In humans with recurrent stomatitis, carbon dioxide (CO_2) laser irradiation provided excellent and rapid pain relief.[32] In cancer patients with mucositis, specific laser phototherapy protocols had a positive effect on pain and healing.[16,28] Once again, clinical studies are lacking in feline medicine.

Complementary Therapies

In recent years, the popularity of more "holistic" or "natural" approaches to medicine for both people and pets has increased. The legitimacy of acupuncture has been questioned because of a lack of well-controlled scientific and clinical trials, and although this is still largely true, in a review of the animal specific acupuncture literature, Habacher[13] stated that there were enough promising results to support pursuing acupuncture as a viable treatment in veterinary patients. However, none of these studies have involved cats.

FUTURE DIRECTIONS IN LONG-TERM PAIN MANAGEMENT

Regenerative Medicine

Regenerative medicine is an emerging area of research as diseases of aging that involve the loss or dysfunction of specific cells become more common. One approach to preventing or treating these diseases is to use autologous adult stem cells, which differentiate into several tissue types and supply trophic factors concurrently. Currently, autologous adipose-derived mesenchymal stem cell therapy is available in the United States (Vet-Stem, Poway, Calif.) for use in animals, primarily for the treatment of osteoarthritis (OA) and tendon injuries. Adipose tissue is surgically harvested from the patient, sent for processing, and several days later, the stem cells are injected into the affected tissue or joints, although intravenous injection is also reported. There are encouraging published results in dogs with OA.[3] Although this treatment modality has been used in cats with osteoarthritis, with anecdotal reports of improvement, there are currently no published studies.

Neurotrophic Agents

ProsaptideTX14 (A) is an exogenous neurotrophic agent given by subcutaneous injection that prevents and reverses neuronal damage and sensory changes in rat models of diabetes. Clinical trials with ProsaptideTX14 (A) have been conducted in cats with naturally occurring diabetes mellitus. Cats that were enrolled

underwent a full clinical examination, nerve conduction testing, and collection of a nerve, muscle, and skin biopsy prior to and following 6 months of treatment with either a placebo or Prosaptide injection; results of this study are expected in the near future.[6]

Neurotoxins

Resiniferatoxin, a capsaicin analog, has been injected intrathecally in dogs with severe pain related to osteosarcoma and provided good analgesia.[5] The proposed mechanism of action is a selective effect at the vanilloid receptors in nociceptive neurons, primarily C-fiber afferents of the dorsal horn; motor function and normal nociception are left intact. Other agents, such as substance P-saporin combinations, have been investigated in dogs as potential selective neuroablative agents for managing severe pain.[1] No reports of use of these agents in cats currently exist.

CONCLUSION

There is a growing awareness and concern among practitioners about long-term pain and its impact on quality of life in cats. We are in need of more evidence on the prevalence, recognition of, etiology, treatment protocols, and treatment outcomes of long-term pain issues in cats. The strong desire to help these cats will hopefully pave the way for formulating well-conducted research and clinical trials.

References

1. Allen JW, Mantyh PW, Horais K et al: Safety evaluation of intrathecal substance P-saporin, a targeted neurotoxin, in dogs, *Toxicol Sci* 91:286, 2006.
2. Bennett D, Morton C: A study of owner observed behavioural and lifestyle changes in cats with musculoskeletal disease before and after analgesic therapy, *J Feline Med Surg* 11:997, 2009.
3. Black LL, Gaynor J, Adams C et al: Effect of intraarticular injection of autologous adipose-derived mesenchymal stem and regenerative cells on clinical signs of chronic osteoarthritis of the elbow joint in dogs, *Vet Ther* 9:192, 2008.
4. Boyer EW, Shannon M: The serotonin syndrome, *N Engl J Med* 352:1112, 2005.
5. Brown DC, Iadarola MJ, Perkowski SZ et al: Physiologic and antinociceptive effects of intrathecal resiniferatoxin in a canine bone cancer model, *Anesthesiology* 103:1052, 2005.
6. Calcutt NA, Mizisin AP, Shelton GD: The diabetic cat as a model for diabetic neuropathy—developing therapeutics for neuropathy in companion animals, IASP Special Interest Group: measuring nociception and pain in non-human species: beyond the hot plate and paw pressure test. From the 12th World Congress on Pain, August 2008, Glasgow, Scotland, p 60.
7. Challapalli V, Tremont-Lukats IW, McNicol ED et al: Systemic administration of local anesthetic agents to relieve neuropathic pain, *Cochrane Database Syst Rev* (4):CD003345, 2005.
8. Chew DJ, Buffington CA, Kendall MS et al: Amitriptyline treatment for severe recurrent idiopathic cystitis in cats, *J Am Vet Med Assoc* 213:1282, 1998.
9. Clarke SP, Mellor D, Clements DN et al: Prevalence of radiographic signs of degenerative joint disease in a hospital population of cats, *Vet Rec* 157:793, 2005.
10. Costigan M, Scholz J, Woolf CJ: Neuropathic pain: a maladaptive response of the nervous system to damage, *Annu Rev Neurosci* 32:1, 2009.
11. Giraudel JM, King JN, Jeunesse EC et al: Use of a pharmacokinetic/pharmacodynamic approach in the cat to determine a dosage regimen for the COX-2 selective drug robenacoxib, *J Vet Pharmacol Ther* 32:18, 2009.
12. Gunew MN, Menrath VH, Marshall RD: Long-term safety, efficacy and palatability of oral meloxicam at 0.01-0.03 mg/kg for treatment of osteoarthritic pain in cats, *J Feline Med Surg* 10:235, 2008.
13. Habacher G, Pittler MH, Ernst E: Effectiveness of acupuncture in veterinary medicine: systematic review, *J Vet Intern Med* 20:480, 2006.
14. Hellyer P, Rodan I, Brunt J et al: AAHA/AAFP pain management guidelines for dogs and cats, *J Feline Med Surg* 9:466, 2007.
15. Ko JC, Maxwell LK, Abbo LA et al: Pharmacokinetics of lidocaine following the application of 5% lidocaine patches to cats, *J Vet Pharmacol Ther* 31:359, 2008.
16. Kuhn A, Porto FA, Miraglia P et al: Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in children, *J Pediatr Hematol Oncol* 31:33, 2009.
17. Lascelles BD, Court MH, Hardie EM et al: Nonsteroidal anti-inflammatory drugs in cats: a review, *Vet Anaesth Analg* 34:228, 2007.
18. Lascelles BD, Gaynor JS, Smith ES et al: Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs, *J Vet Intern Med* 22:53, 2008.
19. Lascelles BD, Hansen BD, Roe S et al: Evaluation of client-specific outcome measures and activity monitoring to measure pain relief in cats with osteoarthritis, *J Vet Intern Med* 21:410, 2007.
20. Lyon KF: Gingivostomatitis, *Vet Clin North Am Small Anim Pract* 35:89, 2005.
21. Mizisin AP, Nelson RW, Sturges BK et al: Comparable myelinated nerve pathology in feline and human diabetes mellitus, *Acta Neuropathol* 113:431, 2007.
22. Mohammad-Zadeh LF, Moses L, Gwaltney-Brant SM: Serotonin: a review, *J Vet Pharmacol Ther* 3:187, 2008.
23. Pypendop BH, Ilkiw JE: Assessment of the hemodynamic effects of lidocaine administered IV in isoflurane-anesthetized cats, *Am J Vet Res* 66:661, 2005.
24. Pypendop BH, Ilkiw JE: Pharmacokinetics of tramadol, and its metabolite O-desmethyl-tramadol, in cats, *J Vet Pharmacol Ther* 31:52, 2008.
25. Robertson S, Lascelles D: Long-term pain in cats: what do we know about this important welfare issue? *J Feline Med Surg* 12:188, 2010.
26. Robertson SA, Lascelles BD, Taylor P M et al: PK-PD modeling of buprenorphine in cats: intravenous and oral transmucosal administration, *J Vet Pharmacol Ther* 28:453, 2005.
27. Siao KT, Pypendop BH, Ilkiw JE: Pharmacokinetics of gabapentin in cats, *Am J Vet Res* 71:817, 2010.
28. Simoes A, Eduardo FP, Luiz AC et al: Laser phototherapy as topical prophylaxis against head and neck cancer radiotherapy-induced oral mucositis: comparison between low and high/low power lasers, *Lasers Surg Med* 41:264, 2009.
29. Suresh S, Wang S, Porfyris S et al: Massage therapy in outpatient pediatric chronic pain patients: do they facilitate significant reductions in levels of distress, pain, tension, discomfort, and mood alterations? *Paediatr Anaesth* 18:884, 2008.
30. Veves A, Backonja M, Malik RA: Painful diabetic neuropathy: epidemiology, natural history, early diagnosis, and treatment options, *Pain Med* 9:660, 2008.

31. Woolf CJ: Pain: moving from symptom control toward mechanism-specific pharmacologic management, *Ann Intern Med* 140:441, 2004.
32. Zand N, Ataie-Fashtami L, Djavid GE et al: Relieving pain in minor aphthous stomatitis by a single session of non-thermal carbon dioxide laser irradiation, *Lasers Med Sci* 24:515, 2009.

PALLIATIVE MEDICINE, QUALITY OF LIFE, AND EUTHANASIA DECISIONS

Margie Scherk and Bernard E. Rollin

> "The death we fear most is dying in pain, unnoticed, and isolated from loved ones. Concern about such an undignified and difficult death has engendered the debate over authorizing voluntary active euthanasia and physician-assisted suicide. Death is fundamental to the nature of being human."
> —***Anonymous***

It is the rare adult who does not have an emotional response to thoughts of dying. Once we reach our mid-thirties, we are all inherently aware of our mortality and that of those around us. No different from our clients, despite being veterinary health care providers, we fear the pain and suffering of friends and companions, human or nonhuman, too. Nor do we become elated when considering the probabilities of terminal illness and long-term nursing care.

What is aging? To paraphrase from Robbins[5]: Aging begins at the moment of conception, involves differentiation and maturation and, at some point, leads to the progressive loss of functional capacity characteristic of senescence, ending in death. This occurs at an organismal level as well as at a cellular level. The former may be affected by genetics, social environment, nutrition, and the occurrence of age-related diseases. Cellular aging, on the other hand, includes progressive accumulation of sublethal injury (e.g., from free radical damage), resulting in either cell death or diminished capacity of the cell to repair itself.

Why should we consider this? Home care and end-of-life issues inherently encompass matters of age-related and age-appropriate illnesses. In cats, these include, most significantly, renal insufficiency progressing to failure, hyperthyroidism, diabetes mellitus, degenerative joint disorders, neoplasia, and chronic digestive disorders, including inflammatory bowel disease, pancreatitis, and cholangiohepatitis. In some cases, by addressing organ and cell function, we can have an impact on well-being.

Just as we match nutritional and preventative medical recommendations to life stage, so too can we match stages and types of care to the final stages of life. These roles include providing supportive care; alleviating pain, discomfort, and distress; preparing the animal and client for the end, while ensuring death with dignity intact; and caring for the caregivers.

PROVIDING SUPPORT FOR THE FUNCTION OF CELLS AND ORGANS

Hydration

Hydration is of utmost importance and should be included in any home care program. Most clients are able to give fluids subcutaneously at home if the care team believes in their importance and knows that the client is capable of doing so. Fluids improve well being. Dehydration at a cellular level results in headaches, nausea, sluggishness, inappetence, lethargy, malaise, and constipation. When cells are not getting enough fluid, they take it from urine and feces. In fact, this change is more reliably evaluated than changes in skin elasticity in the early stages of dehydration, and is one that clients can easily monitor. Dehydration results in hard fecal balls rather than the normal log-shaped feces. Inadequately hydrated cells are not able to function adequately, cannot transport toxins or nutrients well, and are not well oxygenated, thereby suffering further damage and lethal changes.

Daily subcutaneous fluid requirements should be calculated in the same manner that intravenous requirements are calculated, namely deficit (as a percentage of ideal body weight in kg) plus maintenance (60 mL/kg [ideal weight]/day) plus ongoing losses sustained by diarrhea or vomiting (Box 36-1).

If this volume is too large for administration at a single time, it may be divided into multiple treatments

BOX 36-1

Example of Subcutaneous Fluid Calculation for a Dehydrated Cat

Ideal, healthy, hydrated weight: 4 kg
Ill, dehydrated, inappetent weight: 3.2 kg
Estimated deficit (assessed by firm feces, delay in skin elasticity, slightly dry oral mucous membranes, normal eye position): 8%

Deficit 8% × 4 kg = 320 mL
Maintenance (60 mL/kg/day) × 4 kg = 240 mL
Ongoing losses unknown at present = ? mL
Fluid requirement in first 24 hours = 560 mL

The 560 mL can be given IV at 23 mL/hour, or, were this to be given SC for some reason, as three boluses of 185 mL during the 24-hour period. After the patient is rehydrated, a dose of 60 mL/kg/day (based on ideal weight) = 240 mL is needed daily to maintain hydration.

BOX 36-2
Sample Client Handout Instructions on Subcutaneous Fluid Administration

To Connect a New Line to a Bag

1. Prepare the line by rolling the wheel to a closed position.
2. Take the sterile cap off the line and place it somewhere where it will stay clean.
3. Remove the white/blue end from the bag of fluids.
4. Insert the white/blue end of the IV line into the bag firmly; squeeze the bulb of the IV line to fill the bulb half full.
5. Open the line by rolling the wheel to the open position and fill the line with fluids.

To Give a Kitty Fluids

1. Wrap your kitty in a towel so his/her shoulder area is exposed.
2. Place an unused needle on the IV line.
3. Make a tent in kitty's skin over his/her shoulders.
4. Holding the needle parallel to your cat's backbone, insert the needle into the tent of skin.
5. Open the IV line and administer the volume of fluids directed by the doctor.
6. Close the IV line by rolling the wheel to the closed position, remove and discard the used needle; place the sterile cap back on the IV line.
   CONGRATULATIONS! You've done it!

Notes

1. Your kitty will look like s(he) is wearing shoulder pads. The fluid will droop to one side and down a leg so that it looks like a water wing and then a fat foot. This is normal and will resolve as the fluids are absorbed during 12 to 24 hours.
2. If some of the fluids, or even a bit of blood, leak out of the injection site, there is no need to worry.
3. Warming the fluid bag before giving the fluids may help your kitty be more comfortable. Invert the fluid bag in a warm water bath, being careful to keep the connection between the bulb and the line out of the water. Leave in for 5 minutes, massaging the bag to distribute the warmer portions before you start.
4. Please call us at any time. We are happy to demonstrate again and guide you through this process. We know you CAN do it. Your cat will feel a lot better because of your persistence.

during the day. Warming the fluids may make the experience more pleasant for some cats. Some people prefer to administer the fluids as rapidly as possible using gravity feed and an 18-gauge needle; others prefer a slower delivery rate (resulting in less rapid skin stretch) using a 20-gauge needle. Teflon-coated needles are another available option. A sample client handout for subcutaneous fluid administration is shown in Box 36-2.

Two surgically placed administration options exist. The fenestrated tube implant has been anecdotally reported to have problems, including infection, resulting from movement of the tube at the stoma site. The second option, a skin button or port, shows promise.

Nutrition

Attention to nutrition is of paramount importance in order to provide calories from fat and protein and to supply antioxidants and other micronutrients (Figure 36-1). Carbohydrates are less essential for cats as obligate carnivores; however, they can be a good source of energy. The goal is to have a cat eat 50 kcal/kg (ideal weight)/day on its own. When illness interferes with meeting this goal, we have to assist. It is always important to monitor

FIGURE 36-1 As cats get older, they may become cachectic. Careful consideration for muscle wasting and weight loss starts with determining whether the cat has a good appetite or a poor appetite. This patient is manifesting protein:calorie malnutrition caused by inadequate protein in the diet.

that the amount of food being eaten is adequate, even when appetite stimulants are being used. Aversion to a new diet is readily developed when a therapeutic or other new diet is offered in a clinic setting or when an individual feels ill. Thus it may be advisable to find a

food appealing to the patient rather than to insist on a particular dietary formulation.

Pharmacologic agents such as cyproheptadine (Periactin) at 1 mg/cat, PO, q12h or mirtazapine (Remeron) at 2 to 3 mg/cat, PO, q72h can be used. Discontinue cyproheptadine if it is ineffective after four doses. Mirtazapine has the added benefit of being an antiemetic as well as an appetite stimulant. Should disorientation or mania occur with mirtazapine ("serotonin syndrome"), time and a dose of cyproheptadine will resolve the adverse reaction. Although some clinicians view diazepam as an option for appetite stimulation, because of the unnecessary sedative action and the possibility of inducing irreversible, life-threatening toxic hepatopathy, it is contraindicated.

Feeding tubes save lives by making the administration of nutrients and medications less stressful for the client and for the patient. Nasoesophageal tubes can be used short term and require a liquid diet, such as Clinicare Feline or Rebound (1.0 kcal/mL). Human enteral diets are too low in protein for long-term use and have a high osmolarity, resulting in diarrhea. Oral syringe feeding can be performed with minimal stress if several tips are considered. Face the cat away from you and use small volume syringes to ensure that the oral capacity of a cat (approximately 1 mL) is not exceeded. Place the tip of the syringe at the back of the mouth to make it more difficult for the cat to spit out the food. Room- or body-temperature food is less unpleasant. A cat's stomach can hold up to 100 mL when healthy; so, starting with 6 mL and increasing in 6 mL increments to 48 mL total per feeding is realistic with most cats.

Use of large-bore (14- to 16-Fr) feeding tubes is preferable, because a wider variety of diets can be used. Placement of esophagostomy tubes requires only brief anesthesia and eliminates the postoperative risk of peritonitis that a gastrotomy tube (G-tube) might entail (Figure 36-2). These tubes allow for the use of specially formulated, calorically dense, syringeable diets. If the client wants to dilute the diet for ease of syringing, Clinicare or Rebound should be used as the diluent rather than water to prevent loss of caloric density. G-tubes must be aspirated before infusing food to determine residual gastric volume. Either type of tube must be flushed with water following feeding to prevent clogging. Regardless of the method used for assisted feeding, including pharmacologic approaches, the daily caloric needs must be met; this is easily determined by converting to milliliters using the data in Table 36-7.

Pain may interfere with eating. There may be oral pain from periodontal disease, from a tooth resorption lesion, or from a mass (Figure 36-3). Dental health should be optimized wherever possible. Musculoskeletal pain makes crouching or bending the neck uncomfortable. Shape and placement of bowls should be taken into consideration in the ill or older individual, especially if joint pain is present. Nausea associated with uremic gastritis or renal disease may be lessened with famotidine (Pepcid) 5 mg, PO, q24h or another H2 antagonist.

Declining senses (hearing, vision, smell) may result in lack of awareness of food. Warming food to the temperature of freshly killed prey increases its palatability. Small, more frequent meals may suit the older patient better than two meals a day. The texture of the food may play an important role. Canned foods are preferable, should the cat like them, because they contain significantly more water. Practitioners often recommend feeding a prescription diet for a specific ailment. However, cats being the selective creatures they are, as mentioned earlier, it is more important that they eat, than what they eat, and that they eat enough of it.

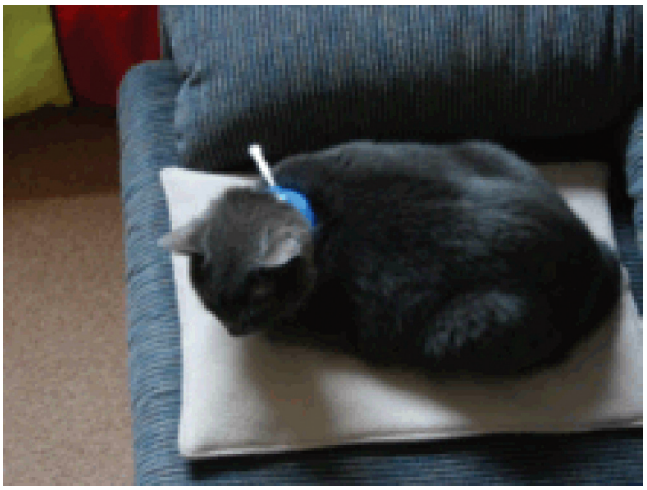


FIGURE 36-2 Supportive feeding helps provide adequate nutrition to slow and possibly reverse catabolic changes. Large-bore feeding tubes, such as the esophageal tube shown here, allow for easy administration of many medications and water for hydration, reducing stress on both the cat and its caregiver.

TABLE 36-7 Caloric Densities of Convalescent Diets, for Calculating Feeding Volumes

Product Name	Caloric Density
Rebound	1 kcal/mL
Clinicare	1 kcal/mL
Royal Canin/MediCal Recovery RS	1.23 kcal/mL
Hill's Prescription Diet a/d Canine/Feline	1.3 kcal/mL
Eukanuba Maximum Calorie	2.1 kcal/mL
Purina Veterinary Diets CV	1.3 kcal/mL when one can is blended with 170 mL Rebound/Clinicare 0.7 kcal/mL when one can is blended with 170 mL water

FIGURE 36-3 Working up a patient with a decrease in appetite or weight loss must include evaluation of the dentition and the mouth. Oral lesions, such as this squamous cell carcinoma, may hide under the tongue.

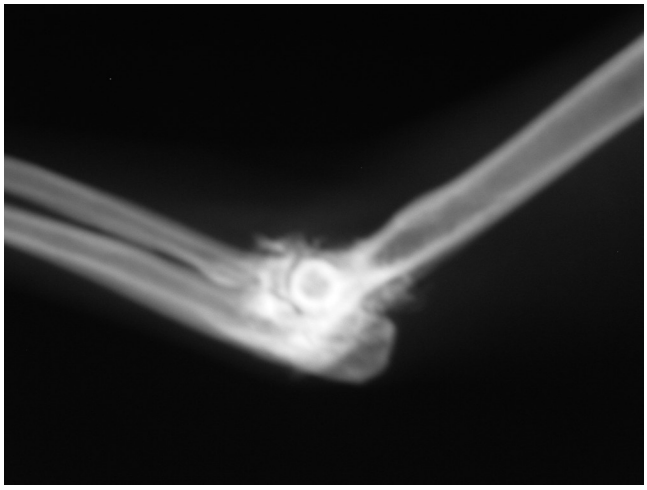


FIGURE 36-4 Proliferative changes of the elbow in a cat with degenerative joint disease. This cat will have difficulty jumping up and climbing down. Appropriate analgesia and environmental modification will allow this patient to have a more comfortable existence. Dietary changes and disease-modifying agents may also be of benefit long term.

Mobility

Mobility often declines in older or ill cats. During the past several years, numerous papers have been published regarding arthritis and degenerative joint disease in our feline patients (Figure 36-4).[9,12] Although estimates vary regarding the frequency of joint disorders, all experts agree that older cats have a greater incidence of joint problems that are clinically underdiagnosed, either because cats are not an exercised species or because they hide their discomfort well. In one paper,[12] a startling 90% of cats over 12 years of age were found to have radiographic evidence of degenerative joint disease, regardless of the reason for which they were presented to the veterinary hospital. Lameness is rarely noted; cats are seen to be "just slowing down" when they jump shorter heights and move less/rest more. If specific questions are asked about movement, one can often determine that there is stiffness or discomfort. "Have you noticed a change in how he jumps/climbs up? Jumps down? Walks?" A useful mobility questionnaire is found in Box 37-4. A recently published study includes another list of useful client evaluation questions suitable for clinic or home use.[3] Care of the older cat must include attention to mobility.

Manifestations of mobility problems include retention constipation, defecating outside of the litter box, falling when jumping onto or off of furniture, inability to climb stairs, and inability to crouch to eat, resulting in weight loss. Regular nail trimming helps by maintaining proper joint relationships. Ramps and steps onto favorite sleeping spots are thoughtful aids. Numerous websites feature ideas for steps and ramps for cats. Warm, soft, padded sleeping places for stiff, painful, possibly bony joints should be considered. Adding another litter box so that the cat does not have to walk as far may reduce inappropriate elimination as well as encourage regular voiding and defecation. Making sure that the rim of the box is not too high, and the opening into the box is not too small is helpful for older cats. Scooping the litter several times a day and making sure that the litter is not too deep or too sparse will encourage regular use.

ALLEVIATING DISCOMFORT AND OPTIMIZING COMFORT

Optimizing cellular function may require medications and supplements. Compliance is best achieved through helping the client understand the cat's illness and how the medication helps. In *Feline Oncology: a Comprehensive Guide to Compassionate Care*,[15] there are excellent handouts for clients that explain cancer terminology, treatment, and help clients to make difficult decisions.

Grooming may be neglected by the cat that has stiffness or one that is simply elderly and less attentive, possibly because of cognitive dysfunction. Diligent patient grooming by the owner may be necessary to help keep a cat's coat clean and healthy. Massage of stiff muscles may be appreciated, and if not, warm soft padded places on which to lie may be.

Cat owners may ask about nighttime yowling. Differential diagnoses include loss of special senses, hypertension, hyperthyroid agitation, pain, and cognitive dysfunction. The first may be discerned and alleviated by simply calling out to the cat so that it is able to locate the client. Hypertension and hyperthyroidism are readily

FIGURE 36-5 This cat appears to be in pain, as evidenced by the strained expression around the eyes. The spiky coat suggests dehydration as well as decreased attention to grooming. Dehydration, along with metabolic acidosis, a very common finding in ill cats, results in what humans experience as a "hangover."

diagnosed and controlled medically. Pain may be difficult to assess (see above, Palliative Medicine: Pain Assessment and Management). Often the best way to determine if pain is present is to administer analgesia and see if behavior normalizes. Cognitive dysfunction becomes a diagnosis by exclusion; it has been found that cats with cognitive dysfunction have brain changes similar to humans with dementia.[10]

The American Veterinary Medical Association (AVMA) Veterinarian's Oath states: "I solemnly swear to use my scientific knowledge and skills for … the relief of animal suffering …" Above all else, owners have the right to expect that our focus is going to be on alleviating (and preventing) pain (Figure 36-5). Fortunately, during the past decade, cats have received more attention than they did previously in this regard so that we now have a slightly wider menu from which to create our analgesic protocols. Use of a multimodal approach is often preferable in order to minimize the potential adverse effects of a single agent by using lower doses of several agents. Often a narcotic, such as buprenorphine, hydromorphone, butorphanol or fentanyl, is combined with a nonsteroidal antiinflammatory (NSAID), such as meloxicam or aspirin, or, for a single dose, ketoprofen or carprofen. Topical and local analgesia may also be provided either with EMLA cream (emulsion of lidocaine and prilocaine), a local nerve block, or acupuncture. Corticosteroids should not be combined with NSAIDs but can be used in conjunction with the other drugs.

Because of concern about possible effects on renal function, the general recommendation is to avoid NSAIDs in patients with renal disease. Having said this, at the final stages of life, as long as the owner has been fully informed about the risk, quality of life without arthritic pain may well be preferable to a painful, risk-free existence. As mentioned above, the clinical signs of arthritis include weight loss, anorexia, depression, elimination outside the litter box, poor grooming, and lameness. Meloxicam is licensed in some countries for long-term use for the alleviation of inflammation and pain in chronic musculoskeletal disorders. The registered dose in the European Union is 0.1 mg/kg on the first day, followed by 0.05 mg/kg, PO, every 24 hours, for as long as necessary. In patients with concurrent renal insufficiency, the use of an NSAID is an added reason to recommend daily home subcutaneous fluid therapy. In addition to analgesics, nutraceuticals, and chondroprotectants (such as glucosamine and chondroitin sulfate), may play a role in the management of degenerative joint disease.[2,11] Although efficacy has been shown for acupuncture in a few conditions in people, there is no solid scientific evidence at the time of writing that points to efficacy in cats.[19] For more information on analgesia, refer to the International Veterinary Academy of Pain Management website at http://www.cvmbs.colostate.edu/ivapm/.

Many patients in the later stages of life require numerous medications. The number and frequency of administration is a source of stress for both the patient and the owner. Thus, whenever possible, the importance of the particular agents should be prioritized to ensure that the most important ones are given diligently. If the less critical ones cannot be avoided, perhaps they can be administered in a different, less psychologically distressing manner. Feeding tubes are a tool that allows most oral medications to be given with minimal patient handling. Many clients are comfortable giving subcutaneous injections of agents that can be administered by this route.

PREPARING FOR AN ENDING: DYING WITH DIGNITY

Cats are living longer because of better health care, nutrition, dental care, and immunization to prevent many infectious diseases. We have the wonderful opportunity to know our patients from cradle to grave, often knowing their owners for even more years through numerous companion animals. As a preemptive measure, as a cat reaches its middle to older years, it may help to encourage owners to give consideration to introducing another companion, not only for themselves, but also for other animals that will be left alone. Should they want a kitten, adopting a pair is better for the older cat in order to avoid some of the indignities of kitten behavior. If they are considering adopting another single cat, then a young adult that has learned manners is more suitable than a kitten.

It is tempting as a clinician to treat illnesses as bodily malfunctions requiring politely caring and competent applied scientists. In human medicine, a great deal has been written about the tendency of physicians to forget that patients are persons and to designate patients by such locutions as "the kidney in room 422," "the osteosarcoma," or "the brain-dead." We may also forget that the neutered male, black and white domestic shorthair cat with renal insufficiency has his own experience of the world and the things we are doing to and for him. Although this is an issue affecting all aspects of medicine, it is especially important when we provide palliative care.

Palliative care must not be forgotten in the zeal to preserve life. In 1972, psychiatrists Marks and Sacher were called into the Sloan-Kettering Cancer Center to consult on an outbreak of "insanity," characterized by patients engaging in extreme and emotional behavior.[14] They soon realized that the issue was not madness but, rather, patient response to extreme and untreated cancer pain. Even in human medicine, as recently as 1991, it was reported that although 90% of cancer pain was manageable with available modalities, 80% was not controlled.[7] If pain was ignored as scientifically unreal, what hope was there for other negative sequelae to be treated, such as loss of dignity? Many, if not most, patients fear pain, and the suffering and degradation that extreme pain inflicts on patients and families, more than they fear death; this has resulted in a worldwide movement in favor of voluntary euthanasia and assisted suicide.

Although there are still many instances of animal patients being viewed as disposable property, there are also many in which the cat is viewed as a beloved family member. This has lead to a paradigm shift within veterinary medicine, whereby the practitioner, previously pleading for the chance to treat, may now need to advise discontinuation of treatment. There are several societal reasons for this. In many countries, more than half of marriages end in divorce. People are more separated from extended family, and making friends, particularly in urban areas, is notoriously difficult. Thus the companion animal assumes greater prominence in people's emotional lives, with upwards of 85% of the United States public affirming that their animals are "members of the family."[13] There has been an explosion of veterinary specialty practices, making treatment options previously available only through the limited number of academic institutions much more accessible, even mainstream. As early as 1980, the *Wall Street Journal* reported that clients were spending more than six figures to treat their animals at the Colorado State University Cancer Center (S. Withrow, personal communication to BR, June 2008). Many clients with companion animals will fight their pet's cancer or other terminal illness as aggressively as they would fight their own. For such people, euthanasia is a last resort option. Given this mindset, the cost of treatment is far less of a deterrent to treating animal disease than it once was; many animals that would historically have been euthanized now regain extended and good quality lives.

There is, however, a negative aspect to this for some veterinary patients. Some individuals that should receive the grace of euthanasia are denied it for too long, sometimes resulting in extended unnecessary suffering. With new modalities readily available and a sincere desire on the part of veterinarians to help their patients, it is easy to fall into the trap of doing more. The practitioner may have to guard against overzealous diagnostic and treatment plans to avoid losing sight of the well-being of the individual patient in question. "*Just because we can, doesn't mean we should*."

Similarly, the owner may struggle with assessing their companion's quality of life. When someone is in denial over the need to euthanize their "best friend" or "family member," their despair and hope may result in willingness to "try anything" to save the animal, however deteriorated or suffering it may be. They may reach out to try evidentially baseless, unproven "complementary and alternative medicine."[16] Access to the Internet assures that desperate owners can find an inexhaustible number of allegedly therapeutic modalities to pursue.

One other aspect of veterinary care and caring for animals that risks abuse is animal hospice, sometimes known as "pawspice." In some cases, when an owner wishes to pursue palliative care and legitimate treatment for the cancer patient, and has money but no time to provide care, pet hospice can fulfill a valuable function. But just as often, the hospice can allow the owner to dodge the issue of euthanasia for termination of suffering while endless new treatments are pursued. Catering to an owner's unwillingness to let go can occur in general veterinary practice as well when the needs of the individual animal are not maintained as priority. This occurs as a result of sympathy and empathy for the owner rather than empathy for the patient, along with a belief that one must cater to the desires of the person who is paying the bill. Thus, paradoxically, the rise of love for companion animals can cause new sources of uncontrolled suffering, buttressing the dictum that loving something is neither necessary nor sufficient for ensuring that one provides the beloved with good care. The question to bear in mind is, "At what cost additional life?" It is essential that veterinary medicine learn from the mistakes of human medicine and not sacrifice quality of life to quantity of life.[8]

Aesculapian authority is the unique authority possessed by physicians and veterinarians by virtue of being medical professionals.[18] To deploy such authority on behalf of the animal to end suffering is not only permissible but obligatory. When owners ask, "What would

you do if it were your cat, Doctor?", they are appealing to our Aesculapian authority. Part of a veterinarian's job as an animal advocate is to respond to such a cry for exoneration under difficult circumstances, providing the sincere guidance that our training, knowledge, and experience enable us to offer.

This means that we have an obligation to explain to owners some fundamental differences between human and animal mental life that have major and radically distinct implications for quality of life in people versus companion animals. These authors do not deny the richness and moral relevance of animal mental life. There are, however, striking differences between humans and animals facing life-threatening illnesses, even as the tools of medicine dealing with such crises converge in the two areas. Human cognition is such that it can value long-term future goals and endure short-term negative experiences for the sake of achieving them. As humans, we can therefore, rationalize and endure the excruciating pain of cosmetic surgery in order to look better. And we similarly endure chemotherapy, radiation, dialysis, physical therapy, and organ transplants to achieve longer life and a better quality of life than we would have without it, or, in some cases, merely to prolong the length of life to see our children graduate, to complete an opus, or fulfill some other goal.

In the case of animals, however, there is no evidence, either empirical or conceptual, that they have the capability to weigh future benefits or possibilities against current misery. They live in the present moment. To treat our patients morally and with respect, we need to keep in mind their mentational limits. To the animal mind, in a real sense, there is only quality of life, that is, whether experiential content is pleasant or unpleasant in all of the modes it is capable of—bored or occupied, fearful or not fearful, lonely or enjoying companionship, painful or not, hungry or not, thirsty or not, and so forth, at this time. We have no reason to believe that an animal can grasp the notion of extended life, let alone choose to trade current suffering for it.

This, in turn, demands that we realistically assess, as far as possible, what animals are experiencing. An animal cannot weigh being treated for cancer against the suffering that entails. An animal cannot affirm or even conceive of a desire to endure current suffering for the sake of future life, cannot choose to lose a leg to preclude metastasis. We must remember that an animal *is* its pain, and is incapable of anticipating or even *hoping* for cessation of that pain. Thus when we are confronted with life-threatening illnesses that afflict our animals, it is not axiomatic that they be treated at whatever qualitative, experiential cost that may entail. The owner may consider the suffering a treatment modality entails a small price for extra life, but the animal neither values nor comprehends "extra life," let alone the trade-off this entails. Treatment for minor illnesses or injuries can be justified by the virtual certainty of a long pleasant life thereafter. The owner, in turn, may ignore the difference between the human and animal mind and choose the *possibility* of life prolongation at any qualitative cost. It is at this point that the morally responsible veterinarian is thrust into his or her role as animal advocate, speaking for what matters to the animal.

The best way to accomplish this sort of advocacy is to set up the type of relationship with an owner from the outset that has both the owner and the veterinarian agreeing to keep the best interests of the animal in view as the paramount goal of treatment. In this way, the clinician can educate the owner on the nature of animal mentation, suffering, and what matters to the animal. Such education should begin along with treatment, as should the veterinarian's claim for advocacy for animal quality of life. Quality-of-life considerations should be introduced at the beginning of a veterinarian–owner relationship, not suddenly sprung on an owner when treatment is over. In particular, it is useful to recall Plato's dictum that, when dealing with ethics and adults, it far better to *remind* than to teach. For this reason, the owner, who after all knows the animal better than the veterinarian, should be encouraged from the beginning to help define quality of life for that animal.

One of the most troubling things for owners is wondering how they will know "when it is the right time." As veterinary doctors, we try to not take time away from an individual's life or from the time that that cat and its people can spend together and balance that with trying to avoid going beyond the point that the cat has enjoyment of life.

One author (MS) encourages the caregivers to imagine being inside their cat's skin and try to imagine what it is experiencing. Some people are very clear in their assessment of how a cat is doing, others less so. Using a scale of 1 to 10, with 10 being the best day of their life and 1 being equivalent to agony and hopelessness, most of us live at around a 6 or 7. If clients use this as a means to score a given day or part of a day, it allows them an objectivity that is an emotional buffer from the roller coaster of emotions they are living in. (Or, for those who are hiding or numb, it adds content to their cat's experience.) When the scores are mostly 2s and 3s, that is the time to consider helping the cat pass on. This is very helpful when a person is afraid that they allowed their last companion to suffer too long and also encourages the person who cannot let their friend go that it is the right time.

The other author (BR) recommends advising an owner to write a list, that is as long as possible, of the things their cat enjoys doing while the cat is still well or at the beginning of treatment, as might be the case in cancer. This list is then kept in a drawer at home as well as becoming part of the medical record. As the cat becomes

more debilitated, the owner can review their reflective and personal criteria and see what changes have occurred despite wishful thinking and potential selfish desires. This objective reality check provides a gauge of progression and reassurance that the decision to euthanize is appropriate while, conversely, also helping the individual who is considering further treatment out of hope and denial.

To help reduce the emotional effects of this period of uncertainty, it is often helpful for owners to feel that they have some control should their cat's condition deteriorate quickly. Things that support this include

- Making sure that they have appropriate emergency care phone numbers and knowing where the emergency facility is.
- Giving them a photocopy of the most recent medical record and laboratory data to keep by their car keys in case they need to go to the emergency clinic. Owners often forget the names of medications and doses that they are giving when they are upset.

Let people know what euthanasia entails beforehand. In a report published in 2001, the AVMA states that "The term euthanasia is derived from two Greek words—*eu*, which means good, and *thanatos*, which means death." They define this "good death" as follows: "Euthanasia is the act of inducing humane death in an animal. It is our responsibility as veterinarians and human beings to ensure that if an animal's life is to be taken, it is done with the highest degree of respect, and with an emphasis on making the death as painless and distress-free as possible."[1]

Communication is critical. Reassure the owner that the dose of barbiturate is painless. One author (MS) places the patient on a thick towel on the owner's lap, informing them that cats generally keep their eyes open and that because muscles relax, the cat may empty its bladder or bowels. Also let them know that some cats may still make breathing movements as death occurs. Although intravenous administration is the most common route for euthanasia agents, unless a cat is agonal, an alternative option, preferred by MS, is to administer a euthanasia solution intraperitoneally (IP), just caudal to a kidney. This avoids restraint and the accompanying fear for the patient. Additionally, the transition from life to death is less sudden: It may take 2 minutes or 20. As soon as the cat is anaesthetized, should the owner want to "hasten the end," a vein can be readily accessed for an additional dose. The time of waiting gives them a good opportunity to remember and cry and laugh. This helps the clinician know that they are working through their grieving normally and are going to be okay. In this author's (MS) experience, owners who have witnessed intravenous euthanasia have said that they prefer the more "natural" passing with the IP route.

CARING FOR THE CAREGIVERS

Most people are able to cope with a loss if they know it is imminent and if they have a support network. Too often, in our modern life, the veterinary team may be the only support the owner has. This is especially sad when friends and family do not appreciate the attachment the person has for their cat. Along with sending a personal card, it is usually greatly appreciated when we check in on the person after a few days. If there is any concern about the owner's emotional security and you are concerned that they might be suicidal, be sure to get help from the human health care system.

In general, however, it helps people to know that they may go through a whole range of emotions, from grief to guilt to anger to uncertainty and emptiness. This is normal and healthy. The practitioner may help an owner understand with an explanation such as, "It is even normal for these feelings to overwhelm you days or weeks after the death of a beloved companion. This reflects the unconscious mind working through things and letting go a little bit at a time. What is NOT normal or healthy is when you get stuck in one emotion." There are also instances in which the death of a cat companion is a reminder of unfinished grieving for another person or pet. There are numerous grief support networks available through veterinary school telephone hotlines, such as Cornell University: http://www.vet.cornell.edu/Org/Petloss/. Some may prefer the electronic support group found at the Rainbow Bridge (http://www.petloss.com).

If owners have not already adopted a new pet, they should give thought to that. Everyone recognizes that the new cat is not a replacement for the one that has died, but by adopting, the newcomer receives a wonderful home and a heart to fill, to ease grief, and bring joy. When the time is right, that new cat will show up.

Finally there is the "cost of caring."[17] We, the care team, experience dying and recovering from it approximately 5 times as often as our human health care equivalents. "Compassion fatigue" goes beyond just normal burnout. Compassion fatigue is a type of physical, emotional, and spiritual exhaustion that comes with frequent exposure to death and having to offer support to owners in highly emotional situations during long periods of time.[6] This is a matter of such importance that there exists a prominent group, The Compassion Fatigue Awareness Project (http://www.compassionfatigue.org). They espouse a series of recommendations, the so-called Eight Laws, regarding healthy caregiving, healthy change, self-care, and a healthy workspace.

Some of the issues that have been associated with compassion fatigue in veterinary medicine include[8]

- Difficulty accepting that the patient's physical problems cannot always be controlled

- Frustration at having invested large amounts of energy in caring for a patient that then dies, taking this investment with them
- Disappointment if expectations for patients to die a "good death," however this may be defined, are not met
- Difficulty ending a life you once saved
- Difficulty establishing realistic boundaries and expectations on veterinary care
- Caring for an animal more than the owner does
- Guilt arising from a cat's death

Without risking the tragedy of arms-length detachment, it is possible to take care of yourself. Suggestions for dealing with and protecting yourself proactively from compassion fatigue include[6]

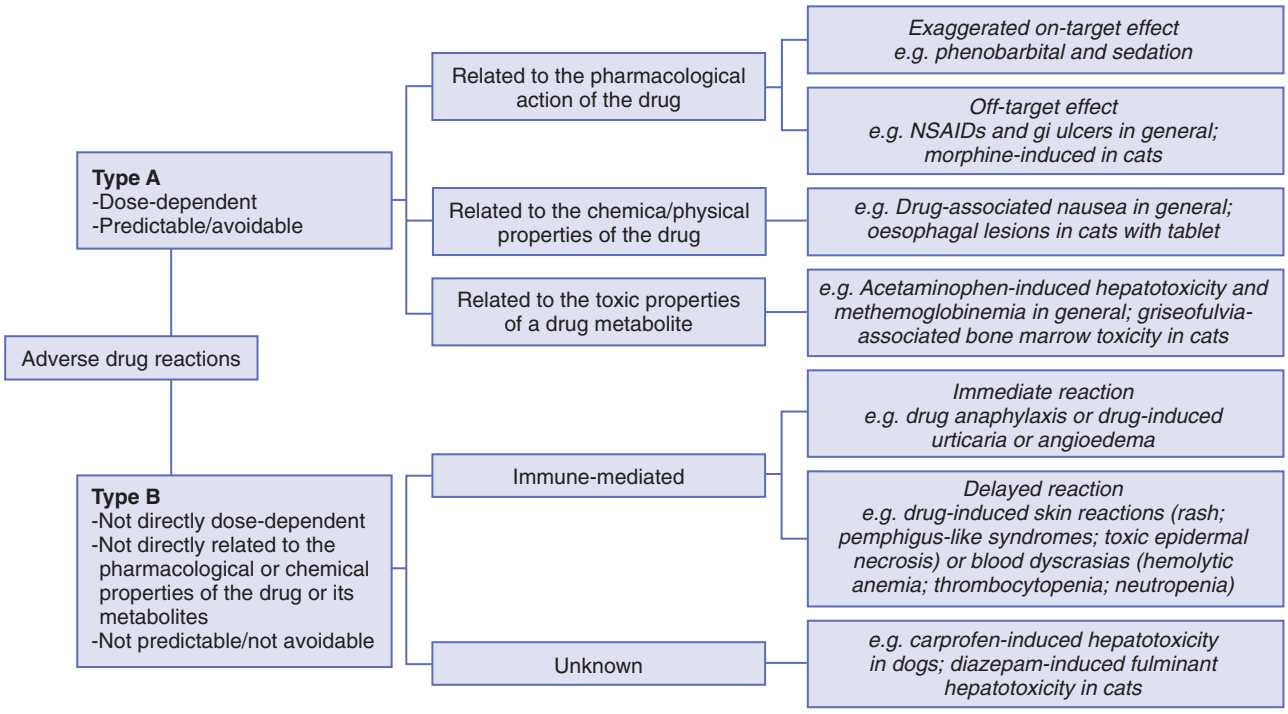
- Allow yourself to be human
- Acknowledge and honor your own grief and emotions
- Embrace your personal life away from work
- Allow time to debrief and support other team members
- Say your own private "good-bye" to your patients
- Believe in your ability to provide comfort and love to your patients
- Redefine death not as a failure but as an inevitable part of the life cycle
- After euthanasia, know that the individual is no longer suffering
- Think of euthanasia as a gift that owners want and appreciate
- With euthanasia, realize that you are providing a loving and caring time for your patients and owners

CONCLUSION

The end of life is, without a doubt, filled with losses. Although one cannot prevent the loss of function and abilities, their decline can be tempered by addressing cellular needs to some degree, as well as focusing on comfort, prevention, and alleviation of pain and ensuring dignity. When these are no longer possible, we can provide the grace of a good death. This final act holds an inherent responsibility that we do not abuse it or dispense it without the best interests of the patient at heart. So used, it is a gift that provides release for the cat and peace for all remaining.

References

1. AVMA Panel on Euthanasia: 2000 Report of the AVMA panel on euthanasia, *J Am Vet Med Assoc* 218:669, 2001.
2. Beale BS: Use of nutraceuticals and chondroprotectants in osteoarthritic dogs and cats, *Vet Clin North Am Small Anim Pract* 34:271, 2004.
3. Bennett D, Morton C: A study of owner observed behavioural and lifestyle changes in cats with musculoskeletal disease before and after analgesic therapy, *J Feline Med Surg* 11:997, 2009.
4. Clarke SP, Mellor D, Clements DN et al: Prevalence of radiographic signs of degenerative joint disease in a hospital population of cats, *Vet Rec* 157:793, 2005.
5. Cotran RS, Kumar V, Robbins SL: Cellular injury and cellular death. In Cotran RS, Kumar V, Robbins SL, editors: *Robbins' pathologic basis of disease*, ed 5, Philadelphia, 1994, Saunders, p 32.
6. Durrance D: Compassion fatigue, *Proceedings of the 2005 Western Veterinary Conference*, February 20-24, 2005, Las Vegas, Nev.
7. Ferrell BR, Rhiner M: High-tech comfort: ethereal issues in cancer pain management for the 1990s, *J Clin Ethics* 2:108, 1991.
8. Folger W, Addleman R, Rodan I et al: AAFP position statement: end of life issues in feline medicine, *J Feline Med Surg* 12:421, 2010.
9. Godfrey DR: Osteoarthritis in cats: a retrospective radiological study, *J Small Anim Pract* 46:425, 2005.
10. Gunn-Moore DA, McVee J, Bradshaw JM et al: Ageing changes in cat brains demonstrated by beta-amyloid and AT8-immunoreactive phosphorylated tau deposits, *J Feline Med Surg* 8:234, 2006.
11. Hardie EM: Management of osteoarthritis in cats, *Vet Clin North Am Small Anim Pract* 27:945, 1997.
12. Hardie EM, Roe SC, Martin FR: Radiographic evidence of degenerative joint disease in geriatric cats: 100 cases (1994-1997), *J Am Vet Med Assoc* 220:628, 2002.
13. Harris Poll #120: Pets are members of the family, and two-thirds of pet owner buy their pets holiday presents, December 4, 2007. Available at http://www.harrisinteractive.com/harris_poll/index.asp?PID=840. Accessed January 14, 2010.
14. Marks RM, Sacher EJ: Undertreatment of medical inpatients with narcotic analgesics, *Ann Intern Med* 78:173, 1973.
15. Ogilvie GK, Moore AS, editors: *Feline oncology: a comprehensive guide to compassionate care*, Trenton, NJ, 2001, *Veterinary Learning Systems*.
16. Ramey DW, Rollin BE, editors: *Complementary and alternative medicine considered*, Ames, Iowa, 2004, Blackwell.
17. Rollin BE: Euthanasia and moral stress, *Loss Grief Care* 1:115, 1987.
18. Rollin BE: The use and abuse of Aesculapian authority in veterinary medicine, *J Am Vet Med Assoc* 220:1144, 2002.
19. The National Institutes of Health (NIH) Consensus Development Program: Acupuncture. Available at http://consensus.nih.gov/1997/1997Acupuncture107html.htm. Accessed January 8, 2010.



Type A and Type B Adverse Drug Reactions