The Evolving Clinical Management of Chronic Inappetence

Marissa Delamarter

Newer treatments for chronic inappetence include capromorelin for use in dogs and cats and mirtazapine for use in cats.

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Chad M. Johannes

DVM, DACVIM (SAIM, Oncology)

Dr. Johannes is an associate professor and director of the James L. Voss Veterinary Teaching Hospital at Colorado State University. His industry experience includes working as the former Medical Director at Aratana Therapeutics, Inc., and coordination of the launch of Palladia, the first FDA-approved veterinary cancer therapeutic, during his time with Pfizer Animal Health (now Zoetis, Inc.). Dr. Johannes's practice experience includes primary care, specialty care, and academic settings. His areas of research interest include oncology therapeutic development, immunotherapeutics, and effective management of oncology treatment–related side effects.

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Abstract

Chronic inappetence in dogs and cats can be caused by the disease process itself, increased inflammatory cytokines, side effects of therapeutics, and/or effects of concomitant medications. Affected animals typically experience weight loss and decreased survival times.

Traditional treatment has included mirtazapine (formerly off-label), cyproheptadine, corticosteroids, and antiemetics. Newer treatments are capromorelin and mirtazapine. Capromorelin has been approved for use in dogs and cats. Mirtazapine seems to be more effective in cats than dogs and is approved for use in cats only.

Take-Home Points

The causes of chronic inappetence in dogs and cats can be multifactorial and have a substantial effect on their quality of life and clinical outcomes.

Traditional treatment has included off-label mirtazapine, cyproheptadine, corticosteroids, and antiemetics—often with little clinical data to support use.

Newer treatments with a growing body of data to guide clinical use are capromorelin (approved for use in dogs and cats) and mirtazapine (approved for use in cats).

Appetite is a key determinant often used by dog and cat owners when evaluating perceived quality of life for their dog or cat with cancer or other chronic disease. Lack of appetite is often the first sign that their pet is not feeling well and often triggers a visit to their veterinarian's office. This article briefly reviews the causes and consequences of chronic inappetence and describes some of the newer therapies available to treat inappetence.

Causes of Inappetence

Inappetence in dogs and cats with chronic disease is often multifactorial with potential contributing factors, including the disease process itself (e.g., dysphagia, pain, ascites), increased inflammatory cytokines, chemotherapy or other drug side effects (e.g., dysmotility, nausea), and effects of concomitant medications.

Although inappetence is a commonly described side effect of many chemotherapeutic agents in dogs and cats, the true incidence is not well documented. Studies focusing on the incidence of inappetence in dogs and cats receiving chemotherapy (**TABLE 1**) are limited, and methods of measuring inappetence are variable and inconsistent.

TABLE 1 Reported Incidence of Inappetence in Dogs and Cats Receiving Chemotherapy

CHEMOTHERAPEUTIC	SPECIES	INAPPETENCE PREVALENCE	REFERENCE
Vinorelbine	Dogs	17% (4/24)	Grant (2008)[1]
Epirubicin	Dogs	19% (27/139)	Marrington (2012)[2]

Carboplatin	Dogs, cats	25% (7/28)	Bowles (2010)[3]
Doxorubicin	Dogs	35–51% (n = 49)[a,b]	Rau (2010)[4]
Cyclophosphamide	Dogs	36% (15/42)[a]	Mason (2014)[5]
Toceranib phosphate	Dogs	39% (34/87)	London (2009)[6]
Vincristine	Dogs	43% (25/57)[a]	Mason (2014)[5]
Epirubicin	Dogs	44% (8/18)	Kim (2007)[7]
Lomustine	Dogs	48% (39/81)	Vail (2012)[8]
Paclitaxel	Dogs	76% (128/168)	Vail (2012)[8]

[a]Subset of dogs treated with maropitant after chemotherapy administration
[b]Crossover study

In addition to cancer,[9] other chronic conditions in dogs and cats (**TABLE 2**) associated with inappetence and related weight loss/cachexia include chronic kidney disease (CKD),[10-13] congestive heart failure (CHF),[14,15] and inflammatory bowel disease.[16]

TABLE 2 Common Clinical Causes of Inappetence in Dogs and Cats

CHRONIC	ACUTE
Cancer	Gastroenteritis (nonspecific)
Gastrointestinal/inflammatory bowel disease	Pancreatitis
Heart failure	Surgery
Chronic kidney disease	Pain
Pancreatitis	Infection (e.g., parvovirus)
Palliative treatments	Cancer (e.g., lymphoma)
Secondary to other drugs/therapies	Secondary to other drugs/therapies

Clinical Effects of Inappetence

In human patients, weight loss is frequently associated with several types of cancer as well as reduced survival times and quality of life.[17] There are multiple causes of weight loss in cancer patients, key among them inappetence along with numerous catabolic drivers (e.g., direct tumor metabolism, systemic inflammation, insulin resistance).[18] This phenomenon is referred to as cancer-related anorexia/cachexia syndrome (CACS), a metabolic, paraneoplastic syndrome characterized by decreased food intake, involuntary weight loss, and altered body composition (loss of fat and muscle).[18] Cachexia is reported for 15% to 40% of human cancer patients and approaches 80% for those with advanced illness.[18]

For decades, whether CACS develops in veterinary patients has been debated. Debate may be attributed in part to veterinarians not recognizing the syndrome due to a lack of awareness and/or absence of established diagnostic criteria. Information about the incidence of CACS in pets is limited, partly because some veterinary patients may be humanely euthanized before the syndrome becomes clinically evident. A study by Michel et al reported that 37% of dogs with cancer had lost 5% or more

of their body weight at the time of cancer diagnosis.[19] A number of studies in veterinary medicine have indicated that dogs with cancer experience metabolic alterations similar to those observed in human patients with cachexia: increased resting energy expenditure and decreased rates of protein synthesis in dogs with osteosarcoma,[20] altered carbohydrate metabolism in dogs with solid tumors,[21] and different serum cytokine profiles in dogs with lymphoma compared with healthy controls.[22] Survival times have been shown to be significantly shorter for dogs that are underweight at the time of lymphoma diagnosis.[23]

Beyond cancer, studies in veterinary medicine have further indicated that weight loss not only is an early indicator or predictor of underlying CKD in cats [11-13] but is also associated with survival.[13] Survival times have been shown to be longer for dogs with CHF gaining body weight than for those losing or maintaining weight[24] and shorter for those with cardiac cachexia.[15] Similarly, cats with CHF and low body weight experienced shorter survival times compared with cats with moderate or high body weight.[25]

Emerging Treatments for Inappetence

If weight loss/cachexia affects survival times for dogs and cats as it does for humans with cancer, CHF, and other chronic illnesses, management may improve survival times and quality of life for pets with similar conditions. The challenge for veterinarians lies in having effective, proven therapies available for clinical use. The list of drugs used to stimulate appetite in dogs and cats is quite extensive; common choices include mirtazapine (formerly used off-label), cyproheptadine, corticosteroids, and antiemetics. The challenge with these drugs is that none stimulates appetite as a primary mechanism. Appetite stimulation is a secondary or side effect for these drugs, which explains the lack of reliability from patient to patient. Except for mirtazapine in cats, additional challenges arise from limited data on dosing and pharmacokinetics and sparse to nonexistent data on efficacy for appetite stimulation in dogs and cats. New options are available and outlined below.

Capromorelin Oral Solution

General Information

Capromorelin is sold as Entyce (dogs; Elanco, elanco.com) and Elura (cats; Elanco, elanco.com).

Capromorelin is an orally active small molecule that mimics the action of ghrelin, which causes growth hormone secretion and appetite stimulation.

Capromorelin oral solution dosed at 3 mg/kg PO q24h has been shown to cause increased food intake and weight gain in healthy laboratory dogs and inappetent client-owned dogs.[26-28]

Margin of safety is wide; capromorelin oral solution is well tolerated at daily doses up to 40 mg/kg q24h for 12 consecutive months in dogs.[29]

When administered to healthy dogs for 7 days, capromorelin produces increased insulin-like growth factor 1 (IGF-1) concentrations on days 1 through 7.[26] IGF-1 may potentially play a role in cellular proliferation and increased metastatic ability in humans with a number of cancers.[30,31] It is unclear what role, if any, the increased IGF-1 levels produced by capromorelin could play on the clinical progression of various cancers of dogs. A recent systematic literature review in human medicine of 61 in vivo studies found that most (74%) studies evaluated showed a null or inverse association of ghrelin with risk and progression of most cancers, indicating a favorable safety profile for use as treatment for CACS.[32] Anamorelin, a therapeutic with similar mechanism, is currently being studied for treatment of CACS in humans with non–small cell lung cancer.[33,34]

Capromorelin has been shown to increase IGF-1, food intake, and body weight in cats.[35] In a study of cats with CKD, there was a significant difference in the percent change in body weight for the capromorelin-treated group (+5.2%) versus the control group (-1.6%) at day 55. The most common side effects noted (>10%) were vomiting (29.6%), hypersalivation (21.2%), inappetence (18.6%), behavior change (14.4%), and lethargy (13.6%).[36]

Product-Specific Information

Entyce was approved by the U.S. Food and Drug Administration (FDA) for appetite stimulation in dogs in May 2016 and became available to veterinarians in the fall of 2017.

Elura was approved for management of weight loss in cats with CKD in October 2020.[36]

Entyce and Elura have potential to positively affect the clinical management of inappetence associated with chemotherapy/cancer and other chronic medical conditions in dogs and cats.

Mirtazapine

General Information

Mirtazapine is a human generic tetracyclic antidepressant with ancillary properties including anxiolytic, sedative, antiemetic, and appetite-stimulant effects. It is a 5-HT3 receptor antagonist with appetite stimulant properties documented in healthy young cats dosed at 1.88 mg PO q24h.[37] Additional studies have shown that for cats with CKD, the same dose given q48h is more appropriate.[38] A double-masked, placebo-controlled crossover clinical trial in cats with CKD demonstrated that mirtazapine administration at 1.88 mg PO q48h for 3 weeks resulted in significantly increased appetite and activity and significantly decreased vomiting compared with

placebo. Mirtazapine-treated cats also experienced significant weight gain (median gain 0.18 kg) compared with cats that received placebo.[39] The specific mechanism of appetite stimulation is not well documented. Mirtazapine is also sometimes used in human patients for refractory chemotherapy-induced nausea and vomiting, and an antiemetic effect in cats with CKD has been noted.

Clinical experience would indicate that mirtazapine is a less reliable/predictable appetite stimulant in dogs. A small pilot study evaluating the pharmacokinetics in healthy beagle dogs indicated that mirtazapine is metabolized much more quickly in dogs and that twice-daily dosing may be more appropriate for canine patients.[40] Because the appetite stimulation component is essentially a side effect of mirtazapine rather than a primary mechanism, it is not surprising that its clinical effect is variable and rather unpredictable.

Product-Specific Information

Mirtazapine transdermal ointment (Mirataz; Dechra, mirataz.com) is indicated for the management of weight loss in cats. Mirataz received FDA approval in May 2018. It is administered topically (inner pinna) as a transdermal ointment at 2 mg/cat (1.5-inch ribbon) q24h for 14 days.[41]

The pivotal efficacy study included 177 cats: 83 received Mirataz and 94 received vehicle control. Primary efficacy endpoint was percent change in body weight at 14 days. At 14 days, the mean percent increase in body weight from day 1 was 3.94% in the mirtazapine group and 0.41% in the vehicle control group. The difference was significant ($p<0.0001$).[41]

The most common side effects reported in cats (>10%) treated with Mirataz include vocalization (11.3%), vomiting (11.3%), and erythema at application site (10.4%).[41]

Summary

Capromorelin has a wide margin of safety and is approved for long-term use in dogs and cats. The null or inverse association of this category of therapeutic with risk and progression of most cancers in humans indicates its likely safety for treatment of cancer cachexia in dogs and cats. In cats, it is now approved for weight management in those with CKD. Although additional peer-reviewed data will be valuable in understanding how to best incorporate capromorelin into daily clinical practice, the potential benefit to dogs and cats with chronic disease may be profound. Transdermal mirtazapine is also approved for shorter-term (14-day) use in cats. However, because the mechanism of appetite stimulation is not well defined and is most likely a side effect of mirtazapine, clinical effects can be more variable.

Note: This article is adapted and updated from the NAVC's 2021 VMX Conference Proceedings.

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