EAT UP. Capromorelin is the first FDA-approved appetite stimulant for dogs. Its safety and effectiveness make it a promising solution for ill pets.

FOCUS ON

The Use of Capromorelin for the Clinical Problem of Inappetence

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Inappetence is a common clinical sign that has an important influence on perceived quality of life and case management in dogs and cats. Prolonged inappetence can negatively affect patient nutritional status, clinical outcome, and, potentially, survival.

Capromorelin oral solution (Entyce®, Aratana Therapeutics, aratana.com) was approved by the Food and Drug Administration (FDA) in May 2016 for appetite stimulation in dogs and became available to veterinarians in the fall of 2017. Although further studies are needed to fully define the ideal use of this product in veterinary practice, capromorelin has the potential to positively affect the clinical management of inappetence and weight loss/cachexia in dogs (and, off-label, cats) with many different medical conditions.

This article provides an overview of capromorelin's mechanism of action, safety and efficacy data, and potential clinical roles.

BACKGROUND

Capromorelin oral solution is an orally active small-molecule ghrelin receptor agonist (GRA) that mimics the action of endogenous ghrelin, resulting in growth hormone secretion and appetite stimulation.[1-4] Given its effect on growth hormone and, subsequently, insulin-like growth factor-1 (IGF-1) levels, capromorelin may also have a clinical role in treating cachexia.[2,5]

Capromorelin is the first GRA approved by the FDA for a therapeutic purpose in any species.[6] Due to the

TABLE 1 Common Clinical Causes of Inappetence in Dogs and Cats

CHRONIC	ACUTE
Cancer	Gastroenteritis (non-specific)
Gastrointestinal/inflammatory bowel disease	Pancreatitis
Heart failure	Surgery
Chronic kidney disease	Pain
Pancreatitis	Infectious (e.g., parvovirus)
Palliative/end-of-life	Cancer (e.g., lymphoma)
Secondary to other drugs/therapies	Secondary to other drugs/therapies

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limited inappetence treatment options available for cats, it may be considered for off-label use in cats that do not respond to the FDA-approved therapy mirtazapine transdermal ointment (Mirataz®, Kindred Biosciences, kindredbio.com).[7] Ideal integration of capromorelin into clinical case management for both short- and long-term inappetence is still being defined.

CLINICAL CHALLENGE OF INAPPETENCE

Reduced appetite is a nonspecific clinical sign with myriad acute and chronic physiologic causes (**TABLE 1**). Signs are often subtle, subjective, and highly dependent on client and clinician observations. The observed decrease in appetite is often broadly described in severity along a spectrum from anorexia (complete loss of appetite) to hyporexia (decreased appetite, not consuming full caloric needs). Dysrexia—any level of altered eating pattern (e.g., eating, but not the desired diet)—can also span this clinical spectrum.[8,9] *Inappetence* is an overarching term that is used in this article to encompass decreased and/or altered appetite/food intake.

Given the wide variety of clinical conditions that can lead to inappetence, it is no surprise that inappetence has been reported as the most common presenting problem (8.5%) for patients evaluated in the small animal primary care setting.[10] This highlights the critical role that a good appetite plays when pet owners evaluate the overall quality of life for their dog or cat.[11,12] Inappetence at time of admission has been associated with a higher risk of death in hospitalized dogs,[13] and inappetence has been shown to be a key variable in a client's end-of-life decision for their dog or cat.[14]

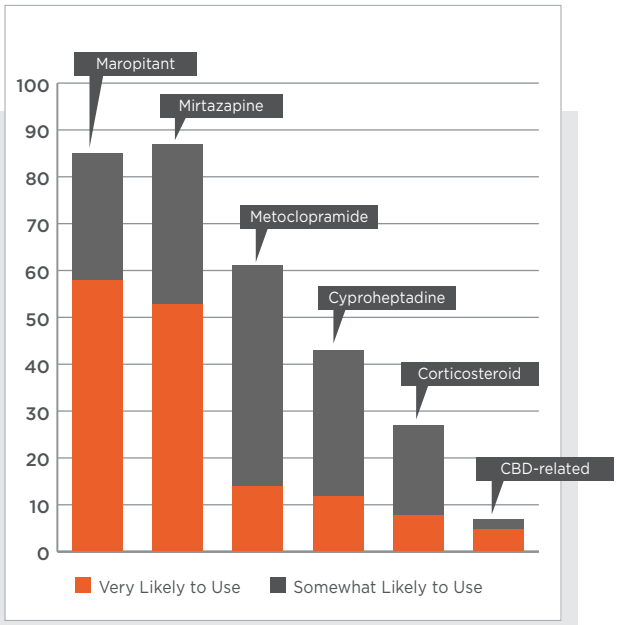

FIGURE 1. Appetite Stimulant Utilization by Specialists for Chemotherapy-Induced Signs in Dogs (April 2016)[a,15]

[a]Online survey of 85 veterinary specialists evaluating clinical appetite stimulant use before approval of capromorelin. CBD=cannabinoid.

BOX 1 Nonapproved Medical Treatments Considered for Inappetence in Dogs

- Anabolic steroids (stanazol/Winstrol)
- Hemp (Canna-Pet®)
- Benzodiazepines (diazepam)
- Maropitant (Cerenia®)
- Cobalamin (vitamin B12)
- Medical marijuana
- Cyproheptadine
- Megestrol acetate (Ovaban®)
- Fish oil
- Mirtazapine
- Glucocorticoids (prednisone)
- Propofol

The importance of early and adequate enteral nutritional support in clinically ill dogs and cats has long been recognized. The challenge has been having reliably effective medical therapies to treat inappetence. **BOX 1** summarizes potential appetite stimulant therapies that have been utilized historically by veterinarians. **FIGURE 1** shows the results of an online survey of veterinary specialists asked about the most commonly used therapies for appetite stimulation in dogs (for chemotherapy-induced signs) before the approval of capromorelin.[15] Most of these therapies have variable clinical results in dogs, likely owing to the fact that any appetite stimulation component is a secondary effect of the drug.

PHYSIOLOGY OF APPETITE REGULATION

Initiation of feeding behavior and control of appetite is complicated and continues to be investigated

in hopes of identifying targets for therapeutic manipulation. A multitude of signals from peripheral tissues (gastrointestinal tract, pancreas, adipose) act on two neuronal subpopulations within the hypothalamus to influence appetite: (1) anorexigenic (suppressing) neurons and (2) orexigenic (stimulating) neurons.[16] Most of these signals (peptide YY, leptin, insulin) have a suppressant effect via a positive influence on anorexigenic neurons and/or a negative influence on orexigenic neurons.[8,16,17]

Capromorelin oral solution has demonstrated a wide margin of safety in long-term use, being well tolerated at daily doses up to 17.5 times the label dose for 12 consecutive months in healthy dogs.[21]

Ghrelin, produced predominantly by the oxyntic glands of the gastric fundus, is the only known signal with a stimulatory influence on orexigenic neurons.[6,17] For this reason, ghrelin is believed to play the primary role in initiation of feeding behavior, appetite stimulation, and food intake.[17] Consistent with findings in other species, ghrelin levels have been demonstrated to be increased in the fasting state and suppressed with food intake in both dogs[18,19] and cats.[20] Exogenous administration of ghrelin to healthy beagle dogs increased daily food intake.[18]

MECHANISM OF ACTION OF CAPROMORELIN

As a GRA, capromorelin stimulates appetite via the hypothalamus as outlined in the above paragraph. Capromorelin also causes release of growth hormone and subsequent increase of IGF-1 (produced by the liver under growth hormone stimulation) by binding the growth hormone secretagogue receptor 1a (GHS-R1a) in the pituitary gland.[1,2,6] Capromorelin administered to healthy beagle dogs for 7 days produced sustainably increased IGF-1 levels that were approximately 60% to 70% higher (4 to 8 hours post-dosing) in dogs treated with 3 mg/kg capromorelin q24h compared with dogs receiving placebo.[2] These sustained IGF-1 levels may increase lean muscle mass in dogs receiving capromorelin over extended periods of time.[2,5]

ROLES FOR CAPROMORELIN IN PRACTICE

Clinical Use for Appetite Stimulation in Dogs

Capromorelin is dosed at 3 mg/kg PO q24h, which has been shown to increase food intake and weight gain in both inappetent client-owned dogs and healthy laboratory dogs.[2-4] The pivotal field safety and effectiveness study evaluated 177 inappetent dogs (121 treated with capromorelin for 4 days, 56 with placebo). Treatment with capromorelin significantly improved appetite (68.6% versus 44.6%, respectively, $P = 0.008$) as well as mean body weight compared with placebo (1.8% versus 0.1%, respectively, $P < 0.001$). The most commonly observed adverse clinical signs included diarrhea (7.0%), vomiting (6.4%), polydipsia (4.1%), and hypersalivation (2.3%).[1,3]

Capromorelin oral solution has demonstrated a wide margin of safety in long-term use, being well tolerated at daily doses up to 17.5 times the label dose for 12 consecutive months in healthy dogs.[21] As a result of this extensive safety profile, capromorelin has no treatment duration, weight, or age restrictions on the label.[1] It can be used as chronic, long-term therapy as clinically indicated in dogs.

One important consideration when incorporating capromorelin into clinical case management is setting appropriate expectations. Capromorelin has not been evaluated in clinically inappetent dogs for longer than 4 days[3]; therefore, the clinical considerations below are based on anecdotal experiences of the authors. In the clinical study, the response was 68.6% in capromorelin-treated dogs, so not all dogs may show a positive response.

As previously described, many peripheral signals cause appetite suppression. In the authors' clinical experience, dogs with severe disease and/or multiple comorbidities may take time (3 to 4 days) and clinical support of the comorbidities to see a strong appetite stimulation effect. If no significant appetite stimulation response is

noted after 24 to 48 hours of capromorelin therapy, consider increasing the dose to 4.5 mg/kg PO once daily. Given the demonstrated wide margin of safety, this increase to 1.5 times the label dose is a reasonable consideration. Once a response is noted, the dose can often be decreased back to the label dose. If no clinical response is noted within approximately 5 days of treatment, consider discontinuation of therapy.

Clinical Use for Appetite Stimulation in Cats

Capromorelin is not yet FDA approved for use in cats; however, data are available for healthy cats. A 91-day study demonstrated sustained increases in serum IGF-1 levels (similar to that seen in dogs) and increased food intake and body weight.[22] Whether the noted increase in IGF-1 levels would be enough to cause peripheral insulin resistance leading to diabetes mellitus is not yet known. However, serum fructosamine monitoring revealed that levels did not exceed the upper end of the reference range for any cat treated with capromorelin.[22]

A cat-specific formulation is currently being developed, and a pivotal effectiveness study for weight management in cats with chronic kidney disease, dosing at 2 mg/kg PO q24h, is anticipated to be complete in mid-2019.[23] Based on anecdotal experience of the authors, capromorelin treatment initiation in cats should be considered at a dose of 2 mg/kg PO q24h. As noted in dogs, if no significant appetite stimulation response is noted within the first 24 to 48 hours, consider increasing the dose to 3 mg/kg PO q24h. Once a response is noted, reduce the dose to 2 mg/kg q24h.

Beyond Appetite Stimulation

Given the physiologic functions of endogenous ghrelin and demonstrated activity of GRAs, therapeutic investigation of these molecules in human medicine has included treatment of gastroparesis associated with diabetes mellitus, growth hormone deficiency, frailty in the elderly, nutrition disorders, and cancer anorexia-cachexia syndrome (CACS).[6,17] The last indication has garnered the most attention in human drug development based on the frequency with which CACS is seen in people with advanced cancer and the impact it has on survival and quality of life. Although not yet FDA approved, anamorelin, an orally administered GRA, has been extensively evaluated in humans with advanced non-small cell lung cancer. Anamorelin treatment has demonstrated significantly increased lean body mass and meaningful improvement of anorexia and cachexia clinical symptoms in these patients.[24,25]

A cat-specific formulation is currently being developed, and a pivotal effectiveness study for weight management in cats with chronic kidney disease, dosing at 2 mg/kg PO q24h, is anticipated to be complete in mid-2019.[23]

Numerous studies in dogs with cancer (osteosarcoma, lymphoma, solid tumors) indicate that dogs experience metabolic alterations similar to those documented in human patients with cachexia.[26–29] Other common chronic medical conditions in dogs and cats documented to be associated with inappetence and related weight loss/cachexia include chronic kidney disease,[30-33] congestive heart failure,[34] and inflammatory bowel disease.[35] One of the crucial advantages of GRAs in the treatment of cachexia lies in their unique ability to stimulate appetite and food intake as well as promote anabolism and increased muscle mass without the detrimental side effects of other anabolic drugs.[25] The clinical impact that capromorelin may have in dogs and cats with acute or chronic medical conditions resulting in the metabolic changes consistent with cachexia remains to be determined, but the potential benefit and clinical role are exciting to consider. TVP

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Disclosures

Within the past 3 years, Dr. Johannes has the following disclosures relevant to this article: Aratana Therapeutics (advisory board, paid consultant, clinical trial) and Zoetis (advisory board, research grant).

Within the past 3 years, Dr. Musser has the following disclosure relevant to this article: Aratana Therapeutics (clinical trial [not related to Entyce]).