CASE STUDY: Stimulating the appetite of a geriatric dog with chronic comorbidities

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In this case, the owners knew their longtime companion was frail, and they were addressing his multiple health concerns. But when the dog quit eating, they knew something more needed to be done to bring him comfort.

Presenting complaint and history
Nikki, a 14-year-old, castrated male rat terrier, was admitted to the Emergency Service at Texas A&M's Veterinary Teaching Hospital. He had exhibited a decreased interest in food for two days and then anorexia for three days. The referring veterinarian had examined the dog a few days prior and had noted dental disease; tramadol and amoxicillin/clavulanate potassium were prescribed, and a professional dental cleaning was scheduled for the following week.

The owners wanted Nikki to be as comfortable as possible, and his hyporexia/anorexia was a substantial concern to them. They reported that Nikki was still drinking water, and that he was routinely fed a low-fat diet because of a history of pancreatitis. Nikki was also receiving pimobendan because of an undefined heart murmur.

Referral evaluation
On presentation, Nikki was lethargic. Physical examination revealed Nikki weighed 6 kg, had a body condition score of 5 (on a scale of 1 to 9) with moderate muscle loss and exhibited mild dehydration (5%). His temperature was 99.1 F, his pulse was 160 beats/min., and his respiratory rate was 20 breaths/min. He had moderate dental disease and a grade V/VI left-sided apical systolic murmur.

Initial diagnostic testing revealed azotemia with poorly concentrated urine. Further evaluation established concurrent severe chronic kidney disease and stage B2 chronic valvular heart disease (see Table 1 for diagnostic findings).

Treatment
Day 1
Nikki was admitted to the hospital and received intravenous fluids to replace the fluid deficit (300 ml) over 12 hours with careful monitoring. Warmed oats were used to address hypothermia. A proton-pump inhibitor (pantoprazole) and an antiemetic (maropitant) were administered parenterally, along with ampicillin-sulbactam for possible pyelonephritis or leptospirosis.

Day 2
On the second day, Nikki was transferred to the Internal Medi-
The intravenous fluids and other medications were continued, and because Nikki was still refusing food, capromorelin oral solution (ENTYCE®) was administered at 3 mg/kg to stimulate his appetite.

A few hours after receiving capromorelin, Nikki began eating a low-fat, canned food, despite persistent severe azotemia (creatinine concentration of 6.4 mg/dl). Because Nikki’s hydration status was normal, and he was alert, responsive and drinking water, the intravenous fluids were tapered and discontinued during the next 24 hours.

**Day 3**
Nikki continued to eat well. Since the urine culture and leptospirosis titers were negative, the antibiotic was discontinued. Sevelamer was prescribed to mitigate hyperphosphatemia, and the proton pump inhibitor was switched to an oral product (omeprazole).

Nikki was discharged from the hospital on Day 3, with instructions to continue capromorelin long-term at home. Oral maropitant (3 days’ worth) was dispensed, and the owner was instructed to restart the pimobendan and continue with a low-fat diet. The owners were advised to schedule a follow-up appointment with Nikki’s primary care veterinarian in a few days, so that his body weight, overall condition, azotemia and hyperphosphatemia could be reassessed.

Because of chronic kidney disease and heart disease, Nikki’s long-term prognosis was guarded, but getting him home, eating and comfortable was a positive outcome for the owners.

**The consequences of dysrexa**
Patients develop anorexia or dysrexa for a number of reasons, and it typically reflects a primary disease. For example, if a dog has ascites due to cancer or heart failure, the fluid can make eating uncomfortable. Patients that develop encephalopathy with liver failure do not eat well. Pain from pancreatitis, a fracture, kidney failure/uremia, ketosis, acute infection—all can inhibit appetite. Diseases that result in inflammation or other changes in the gastrointestinal tract can delay emptying and cause anorexia.

Extensive research exists in human medicine about the impact of dys-

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**Table 1. Selected diagnostic test results**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum chemistry panel</td>
<td>Severe azotemia (BUN 166 mg/dl; creatinine 7.1 mg/dl; phosphorus &gt;13.0 mg/dl)</td>
</tr>
<tr>
<td>Leptospirosis titer</td>
<td>Negative (results reported on Day 3)</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Specific gravity of 1.010; trace protein; unremarkable sediment</td>
</tr>
<tr>
<td>Urine bacterial culture</td>
<td>Negative (results reported on Day 3)</td>
</tr>
<tr>
<td>Abdominal ultrasonography</td>
<td>Degenerative changes in both kidneys</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Mitral valve endocardiosis; stage B2 chronic degenerative valve disease</td>
</tr>
</tbody>
</table>

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**Earn CE and learn more about dysrexia and appetite stimulation**

Attend the 1-hour “Dealing with Dysrexia” webinar, which is now available for free and on-demand. Sponsored by Aratana Therapeutics, Inc.

In this presentation by Dr. Audrey Cook, you will gain a greater understanding of dysrexia, its various causes and clinical impact on dogs, as well as the available treatment options for appetite stimulation.

[dvm360.com/dealing-with-dysrexia](dvm360.com/dealing-with-dysrexia)
Dysrexia may result in delayed wound healing, decreased immune responses and decreased musculoskeletal strength. Weight loss also occurs, but it may take several days to become apparent. The health problems listed above may be well-established before weight loss is observed, thus we shouldn’t wait for it to occur in patients with dysrexia.

A dog’s inappetence may also adversely affect the owners. If a dog doesn’t eat, owners perceive it to be suffering, raising questions about quality of life. When I call owners to give them an update on a hospitalized patient, the first question they ask is, “Did he eat today?” The same thing is true when a patient is at home. I use food intake as a measure of comfort and well-being when I discuss how the patient is doing with the owners.

Good evidence exists that nutrition has a marked impact on gastrointestinal tract health. A lack of nutrients in the intestinal lumen compromises mucosal function. Enterocyte turnover slows, the intestinal villi become blunted, and permeability increases. Metabolic derangements can occur, such as hepatic lipidosis (although the effects are less dramatic in dogs than in cats). Anorexia also impacts the gastrointestinal microbiome. The predominant bacterial species may shift to less-friendly bacterial species. All of these processes combine to impact patient survival. In short, patients need adequate nutrition if they are to survive.

Stimulating the appetite
Veterinarians should consider every reason an animal may not be eating enough—pain, psychological stressors or physiologic issues (including gastric stasis, ulceration or esophageal reflux). Dysrexia is often a problem with several contributing factors, and it is likely that multimodal management will be necessary. Addressing as many of the factors as you can is the best way forward.

In a given case, if you determine that part of the problem is inadequate food intake, then you will want to stimulate the dog’s appetite. Several drugs have traditionally been used as appetite stimulants, though they are not designed for this purpose. These include mirtazapine, cyproheptadine, diazepam, tetrahydrocannabinol and glucocorticoids. These drugs have different mechanisms of action, but none of them are FDA-approved as an appetite stimulant for dogs, and their efficacy and safety profiles are uncertain.

Ghrelin’s role
In 1999, the “hunger hormone” known as ghrelin was discovered. It is made primarily in the stomach, with levels rising during the interprandial interval. Ghrelin’s function in the body is complex. It is integral to not only the regulation of appetite but also to the maintenance of homeostasis and energy metabolism. Besides stimulating food intake, ghrelin stimulates growth hormone secretion, decreases energy expenditure, reduces gastric acid stimulation, accelerates gastric emptying, impacts glucose homeostasis and modulates cardiovascular function, inflammation, reproductive function and bone formation.*

Ghrelin achieves its ability to stimulate appetite through activation of the orexigenic neurons and suppression of the anorexigenic neurons in the hypothalamus. (Orexigenic means

When to use appetite stimulation

At the Texas A&M College of Veterinary Medicine & Biomedical Sciences Veterinary Teaching Hospital, we use capromorelin in dogs recovering from an acute illness, those with chronic illness, those recovering from surgery or trauma and those transitioning to a therapeutic diet that may be less palatable.

Acute conditions
In acute illness such as acute hemorrhagic diarrhea or nonspecific acute gastritis, we provide supportive care for the dog as the disease takes its natural course. We prefer not to discharge these patients until they are eating, as they may otherwise be quickly readmitted by an anxious owner. Capromorelin can stimulate these patients to begin eating and allow us to administer oral medications as needed. We usually recommend that the owner finish giving the bottle of capromorelin at home, particularly if the dog is being fed a bland food for a few days.

Chronic illnesses
We also prescribe capromorelin for dogs with chronic conditions, such as chronic kidney disease. My colleagues in oncology and cardiology use it in many of their long-term cases, too. Keeping these dogs eating makes it easier for owners to administer oral medications. In addition, the quality of life is much better for both the dog and the owner if the dog is eating well.

Postoperative recovery or healing after trauma
We also use capromorelin in postoperative or trauma patients. These dogs may be receiving multiple medications, such as analgesics and antibiotics, and may be subject to repeated sedation for bandage changes or wound management. All of these factors can markedly impact appetite, just when the dog needs more calories for healing. Capromorelin can be a valuable tool in these cases, as it increases food intake which supports healing and the preservation of muscle mass.

Diet transitions
We also use capromorelin to help patients with pancreatitis or gastrointestinal diseases, such as inflammatory bowel disease or lymphangiectasia, transition to a therapeutic diet. I use capromorelin as soon as possible in these cases, before food aversion arises or the owner gives in to the dog when it begs for its old food.
Turn on appetite

Finally, appetite stimulation is in your control

Until now, there have been limited therapeutic options to restore appetite. That's why we created ENTYCE® (capromorelin oral solution), the only FDA-approved therapeutic designed to safely and effectively stimulate appetite in dogs.

ENTYCE works by mimicking the hunger hormone ghrelin. Administered orally once a day, ENTYCE is appropriate to treat inappetence caused by chronic and acute conditions.

Please see the full Prescribing Information in more detail on page 6.
The following adverse reactions were reported in < 1% of dogs administered ENTYCE:

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ENTYCE (n = 171)</th>
<th>Vehicle Control (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (7.0 %)</td>
<td>5 (6.8 %)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (6.4 %)</td>
<td>4 (5.5 %)</td>
</tr>
<tr>
<td>Hyper salivation</td>
<td>4 (2.3 %)</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (1.2 %)</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2 (1.2 %)</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1.2 %)</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td><strong>CLINICAL PATHOLOGY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated blood urea nitrogen</td>
<td>7 (4.1 %)</td>
<td>2 (2.7 %)</td>
</tr>
<tr>
<td>Elevated phosphorus</td>
<td>4 (2.3 %)</td>
<td>1 (1.4 %)</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>1 (0.6 %)</td>
<td>1 (1.4 %)</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyuria</td>
<td>7 (4.1 %)</td>
<td>1 (1.4 %)</td>
</tr>
<tr>
<td>Lethargy/depression</td>
<td>2 (1.2 %)</td>
<td>0 (0.0 %)</td>
</tr>
</tbody>
</table>

The mean absolute oral bioavailability of capromorelin was 44%. The mean total plasma clearance and volume of distribution was 18.9 mL/min/kg and 2.0 L/kg, respectively. Capromorelin was not highly bound (unbound fraction 51%) to plasma protein. The protein binding was concentration-independent over the range of 10 to 1000 ng/mL. In vitro (human liver microsomes) and in vivo (rats) metabolism studies suggest that capromorelin is metabolized by hepatic enzymes, mainly CYP3A4 and CYP3A5. Therefore, drugs that inhibit CYP3A4 and CYP3A5 activity may affect capromorelin metabolism. Following oral administration of radio-labelled capromorelin to dogs, capromorelin was excreted in urine (37%) and in feces (62%) within 72 hours.

**Effectiveness:**

**Laboratory Effectiveness Study:** Twenty four healthy Beagle dogs (6 dogs per sex in each group) with normal appetite were randomized into two groups and dosed daily with ENTYCE (capromorelin oral solution) at 3 mg/kg/day or vehicle control (solution minus capromorelin) to compare food intake over a 4-day period. The dogs were 13 months of age and weighed between 6.5 and 12.5 kg at the time of randomization. Six dogs administered ENTYCE repeatedly exhibited salivation post dosing and two dogs administered vehicle control exhibited salivation only once on study day 0. Emesis was observed in one dog administered ENTYCE on study day 1. Dogs administered ENTYCE at a dose of 3 mg/kg/day for 4 consecutive days had statistically significantly increased food consumption compared to the vehicle control group (p = 0.001).

**Clinical Field Study:** Effectiveness was evaluated in 177 dogs (121 dogs in the ENTYCE group and 56 dogs in the vehicle control group) in a double-masked, vehicle controlled field study. Dogs with a reduced appetite or no appetite with various medical conditions, for a minimum of 2 days prior to day 0 were enrolled in the study. The dogs ranged in age from 4 months to 18 years. Dogs were randomized to treatment group and dosed once daily for 4 days with ENTYCE at 3 mg/kg or vehicle control. Dogs were assessed for appetite by owners on day 0 and day 3 ± 1 using an “increased”, “no change” or “decreased” scoring system. Dogs were classified as a treatment success if the owner scored their dog’s appetite as “increased” on day 3 ± 1. The success rates of the two groups were significantly different (p = 0.0078). 68.6% (n = 83) of dogs administered ENTYCE were successes, compared to 44.6% (n = 25) of the dogs in the vehicle control group.

**Animal Safety:**

In a 12-month laboratory safety study, 32 healthy Beagle dogs (4 dogs per sex per group) approximately 11-12 months of age and weighing 9-13 kg were dosed orally with capromorelin in deionized water daily at 0X (placebo), 0.3 (0.13X), 7 (2.07X), and 40 (17.5X) mg/kg/day. Administration of capromorelin was associated with increased salivation and reddening/swollen paws, increased liver weights and hepatocellular cytoplasmic vacuolation. Treatment related decreases were seen in red blood cell count, hemoglobin and hematocrit in the 40 mg/kg group. Pale skin, pale gums, and decreased red blood cell count, hemoglobin and hematocrit were observed in one dog administered 40 mg/kg/day. Increases were seen in cholesterol, high density lipoproteins, and the liver specific isozyme of serum alkaline phosphatase in the 40 mg/kg group. Growth hormone and insulin-like growth factor 1 plasma levels were increased in all groups administered capromorelin. There were no effects noted on gross necropsy. Capromorelin levels were similar in plasma collected on days 90, 181, and 349 indicating no accumulation of drug.

**Storage Conditions:** Store at or below 86° F (30° C)

**How Supplied:**

30 mg/mL flavored solution in 10 mL, 15 mL and 30 mL bottles with measuring syringe

NADA 141-457, Approved by FDA
US Patent: 6,673,929
US Patent: 9,700,591
Made in Canada

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Additional information is available at www.aratana.com or by calling Aratana Therapeutics at 1-844-272-8262.

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