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Original Study

Effects of Capromorelin, Mirtazapine, and Cyproheptadine on Food Intake in Budgerigars (*Melopsittacus undulatus*)

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Abstract: These studies aimed to evaluate the appetite-stimulating effects of capromorelin, cyproheptadine, and mirtazapine in budgerigars (*Melopsittacus undulatus*). The effects of a single oral dose of capromorelin (10 and 40 mg/kg), cyproheptadine (0.5 and 2.5 mg/kg), and mirtazapine (1 and 5 mg/kg) on food intake in budgerigars (n = 12 per study) were evaluated in 3 separate blinded, randomized, placebo-controlled complete crossover studies. Food intake was quantified in hourly intervals between 1 and 8 hours after administration and in a 4-hour interval between 8 and 12 hours. Both doses of capromorelin significantly increased mean food intake in the first 12 hours after administration (10 mg/kg: 66 ± 39 g/kg; 40 mg/kg: 71 ± 40 g/kg) compared with the control treatment (46 ± 30 g/kg). Administration at 10 and 40 mg/kg capromorelin resulted in a 1.5-fold increase (interval: 0.4–9) and 1.7-fold increase (interval: 0.7–5.5) in food intake, respectively. Productive and nonproductive regurgitation after administration of capromorelin at 40 mg/kg occurred in 92% of birds within 1 hour of administration, compared with 42% of birds and 25% of birds who regurgitated in the 10 mg/kg and control treatments, respectively. Cyproheptadine and mirtazapine did not have a measurable appetite-stimulating effect in this study, and no significant adverse effects were recorded.

Key words: food intake, appetite, psittacine, avian, nutrition, capromorelin, mirtazapine, and cyproheptadine

INTRODUCTION

Avian patients in veterinary practice frequently present with anorexia or hyporexia, or these conditions develop during hospitalization.[1,2] Reduced caloric intake can detrimentally affect the patient outcome and speed of recovery. In addition, caloric deficits can prolong hospitalization time, which further exacerbates the reduction in food intake and stress that the patients endure.[3] When placed in an unfamiliar environment, avian patients, which have a high metabolic rate, can become stressed and rapidly decline in health, especially if they are concurrently affected by diseases that require the diversion of calories.[4,5]

Nutritional support provided to anorexic or hyporexic patients can decrease necessary hospitalization time and improve outcomes.[3] The most common method of nutritional support for avian patients is via crop gavage.[6] These gavage feedings require trained veterinary support staff, most often at a veterinary hospital, to perform them safely and effectively. Risks associated with crop gavage include aspiration, esophageal or crop irritation or trauma, and crop burns.[6] Birds are manually restrained and often struggle during the gavage procedure, which increases the stated risks and associated stress.[6]

An alternative to force-feedings in dogs and cats includes appetite-stimulating medications to promote voluntary food intake. Common appetite stimulants include ghrelin-receptor agonists, antidepressants, antihistamines, benzodiazepines, dopamine agonists, and corticosteroids.[7] Capromorelin works as a ghrelin receptor agonist in the gastrointestinal tract of mammals and has been United States Food and Drug Administration approved for use as an appetite stimulant in dogs and cats.[8,9] Mirtazapine, an antidepressant, is a serotonin and alpha-2 receptor antagonist effective at stimulating appetite, most notably in cats.[10,11] Cyproheptadine, a serotonin receptor antagonist, is an antihistamine that increases appetite in cats.[7,10]

There are few studies evaluating the efficacy of appetite stimulants in avian species. Benzodiazepines, including midazolam and lorazepam, have been studied in psittacines and provide effective short-term appetite stimulation in budgerigars (*Melopsittacus undulatus*).[12,13] However,

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the most significant impact on food intake occurs within 1 hour with both drugs. In addition, benzodiazepines produce dose-dependent sedation, and the parenteral route is most effective.[14] Consequently, these drugs are less ideal for long-term or outpatient management of anorexia or hyporexia in avian patients. Cyproheptadine, capromorelin, benzodiazepines, and corticosteroids have shown promise as appetite stimulants in non-psittacine avian species.[15–18]

The ideal appetite stimulant in avian patients should be easily administered orally by owners or caretakers and have sustained appetite-stimulating effects to avoid frequent dosing. Capromorelin and mirtazapine provide long-term appetite stimulation, while cyproheptadine has short-term appetite-stimulating effects in mammalian species.[7,9,11] The goals of the separate studies summarized here were to evaluate the efficacy and safety of capromorelin, mirtazapine, and cyproheptadine as appetite stimulants in healthy budgerigars. We hypothesized that capromorelin, mirtazapine, and cyproheptadine would significantly increase voluntary food intake longer than benzodiazepines in budgerigars.

MATERIALS AND METHODS

Animals

This study was approved by the University of Wisconsin (Madison, WI, USA), School of Veterinary Medicine, Animal Care and Use Committee (protocol ID: V006128R1). Healthy sub-adult to adult budgerigars (n = 24 undetermined sex, variety of color morphs, and wild type) of approximately 6 months of age were obtained from a pet store for the studies. The median (interval) body weight was 33 g (26–45 g). Birds were housed in wire enclosures (76 × 46 × 46 cm) in groups of 6 birds. The animals were maintained in a climate-controlled room with a temperature set at 22°C (72°F) and a 12:12 hour light:dark cycle. The birds were fed a fortified commercial seed diet (Forti-Diet Pro Health Parakeet Food; Kaytee, Chilton, WI, USA) formulated for budgerigars and provided free-choice water and a mineral block (Zoo Med Laboratories, San Luis Obispo, CA, USA). Millet sprigs (Drs. Foster and Smith, Rhinelander, WI, USA) were offered as treats. A physical examination was performed on each bird to ensure the subjects were in good health. Daily care was provided by separate husbandry personnel who monitored the day-to-day activity, appetite, and eliminations throughout the study. The birds were acclimatized to this environment and diet for 2 months before initiating this study.

Dose-escalating pilot studies

Each drug was tested in a noncrossover, nonblinded, and nonrandomized manner to determine the highest safe dose with the least adverse effects. Expected adverse effects included regurgitation, sedation, dyspnea, and sneezing. Birds were administered a drug and then placed into individual containers for observation. The dosages of mirtazapine and capromorelin tested were based on recommendations for cats and dogs and previously tested dosages in avian species for cyproheptadine.[15,19–22]

Drugs were administered by crop gavage. Oral capromorelin (30 mg/mL, Entyce, Elanco Animal Health Inc, Greenfield, IN, USA) was evaluated at 10, 40, 50, and 200 mg/kg. Regurgitation was the most common adverse effect, occurring in 20%, 40%, 100%, and 100%, respectively. Regurgitation occurred within 10 minutes of drug administration and subsided by 60 minutes for all dosages tested. Two of the 3 budgerigars tested at 50 mg/kg also displayed a rolling behavior. Mirtazapine (20 mg/mL, compounded by the University of Wisconsin Veterinary Pharmacy using tablets and a suspension vehicle[23]) was tested at 5, 10, and 20 mg/kg. Regurgitation was also the most common adverse effect, with an occurrence of 50%, 100%, and 100%, respectively. Regurgitation occurred 5 minutes after drug administration for all dosages of mirtazapine and lasted 30 to 90 minutes. Cyproheptadine (0.4 mg/mL, Rising Pharmaceuticals Inc, East Brunswick, NJ, USA) was tested at 1, 5, and 10 mg/kg doses. Regurgitation occurred in 0%, 50%, and 100% of birds tested, respectively, and began within 1–15 minutes, with higher dosages causing an earlier onset of regurgitation. Cessation of regurgitation with cyproheptadine occurred on average at 90 minutes; however, some individuals had infrequent regurgitation up to 4 hours post-treatment administration. Other adverse effects of cyproheptadine included dose-dependent sedation ranging from mild sedation (closing eyes for a short period) to moderate sedation (wing droop, head droop) and dyspnea for all birds at the 5 and 10 mg/kg dosage (n = 6 and n = 3, respectively). The final dosages evaluated in each crossover study included the highest dosage with the least adverse events (ie, regurgitation, dyspnea, sedation) as the high dose for crossover trials and a dosage reduced by a factor of 4–5 as the low dosage evaluated.

Complete crossover studies

Three separate, randomized, blinded, balanced, complete crossover design studies were completed, with each treatment sequence and each treatment being equally represented. Animals were randomly assigned

to treatment sequences (Research Randomizer, version 4.0, randomizer.org) and a minimum washout period of 7 days between treatments. The same 12 birds were used for the capromorelin and mirtazapine studies, and 12 different birds were used for the cyproheptadine study.

Based on previous studies evaluating the effects of midazolam on food intake in budgerigars,[12–23] a difference in food intake between treatment groups and between pre- and post-treatment data of 30 ± 20% was considered clinically relevant. By using 12 budgerigars each, the study would be sufficiently powered (0.8), statistical significance between treatments could be identified ($\alpha = 0.05$), and the risk for type 2 statistical errors was minimized.

All treatments were administered between 8 AM and 10 AM, with final recordings occurring by 10 PM on the same day. The person measuring food intake and evaluating abnormal behavior was blinded to the treatments administered. Each drug was tested at 2 doses and compared with control treatment in separate complete crossover studies. The capromorelin study treatments included the following: (1) capromorelin 10 mg/kg PO; (2) capromorelin 40 mg/kg PO; and (3) tap water (control) at an equivalent volume to the higher dose of capromorelin. The mirtazapine study treatments included the following: (1) mirtazapine 1 mg/kg PO; (2) mirtazapine 5 mg/kg PO; and (3) tap water (control) at an equivalent volume to the higher dose of mirtazapine. The cyproheptadine study treatments included the following: (1) cyproheptadine 0.5 mg/kg PO; (2) cyproheptadine 2.5 mg/kg PO; and (3) tap water (control) at an equivalent volume to the higher dose of cyproheptadine. Each oral treatment was administered via crop gavage with a metal gavage needle followed by 0.25 mL of tap water. Capromorelin (30 mg/mL) and cyproheptadine (0.4 mg/mL) were available as a commercial solution. However, capromorelin was diluted (7.5 mg/mL in sterile water for injection) just before administration for accurate dosing. Mirtazapine was compounded to a stock suspension (10 mg/mL) by a licensed veterinary pharmacy using published protocols. Mirtazapine was diluted (1 mg/mL in sterile water for injection) just before administration for accurate dosing.[23] All volumes were rounded to the second decimal point for accurate dosing. Drug volumes administered in the 3 studies ranged from 0.03–0.27 mL.

Food intake and adverse effect recording

Food intake was quantified for each bird by placing the birds individually in clear plastic enclosures measuring 29 cm × 29 cm × 18 cm with access to a sprig of millet and water. Birds were not acclimatized to these containers because each trial occurred 1 week apart, and birds were not exposed to the containers at any point between trials; therefore, simulating an unfamiliar environment similar to a hospitalized setting. The amount of millet offered was weighed before each 1-hour observation period, and the amount of millet left was measured to determine the total millet eaten during that period. The same scale was used each time the millet was weighed, with all measurements made to the nearest 0.1 g. Before treatment administration, a 1-hour food intake period was recorded on unfasted birds. After treatment administration, each bird was transferred into a new, identical container with fresh, weighed millet. After each subsequent hour, birds were removed from their containers and placed into identical containers with fresh millet to measure their food intake and clean each used container. A total of eight 1-hour periods were recorded for each bird with each treatment, comprising the first 8 hours after treatment administration. Food intake between 8 and 12 hours after administration was recorded as a single 4-hour period. Visual barriers were used to prevent the birds from seeing each other and human observers in the room.

Digital video recordings were obtained for each bird during the pre-treatment period and for the first 6 hours of the post-treatment period; these were subsequently evaluated by an observer blinded to treatment. Each video was evaluated for sedation and abnormal behavior, similar to the pilot trials. Budgerigars were considered sedated if they exhibited closed eyes, head droop, wing droop, hock sitting, or sternal recumbency. The duration of sedation was recorded in seconds.

Data analysis

Data were analyzed using statistical software (SigmaPlot 13, Systat Software Inc, San Jose, CA, USA). The food intake data were evaluated for normal distribution using the Shapiro-Wilk test and equal distribution using the Brown-Forsythe test. Total food intake differences between treatments and control for each study were evaluated using 1-way repeated-measures ANOVA. Two-way repeated-measures ANOVAs were used to evaluate the effects of treatment and time on cumulative food intake and associated interactions. The Holm-Sidak method was used for post-hoc analysis. A χ^2 test was used to determine if there was an association between group and regurgitation. A value of $P < 0.05$ was considered statistically significant. Data are reported as mean ± SD or as median (range).

RESULTS

Both doses of capromorelin significantly increased total food intake in the 12 hours after administration

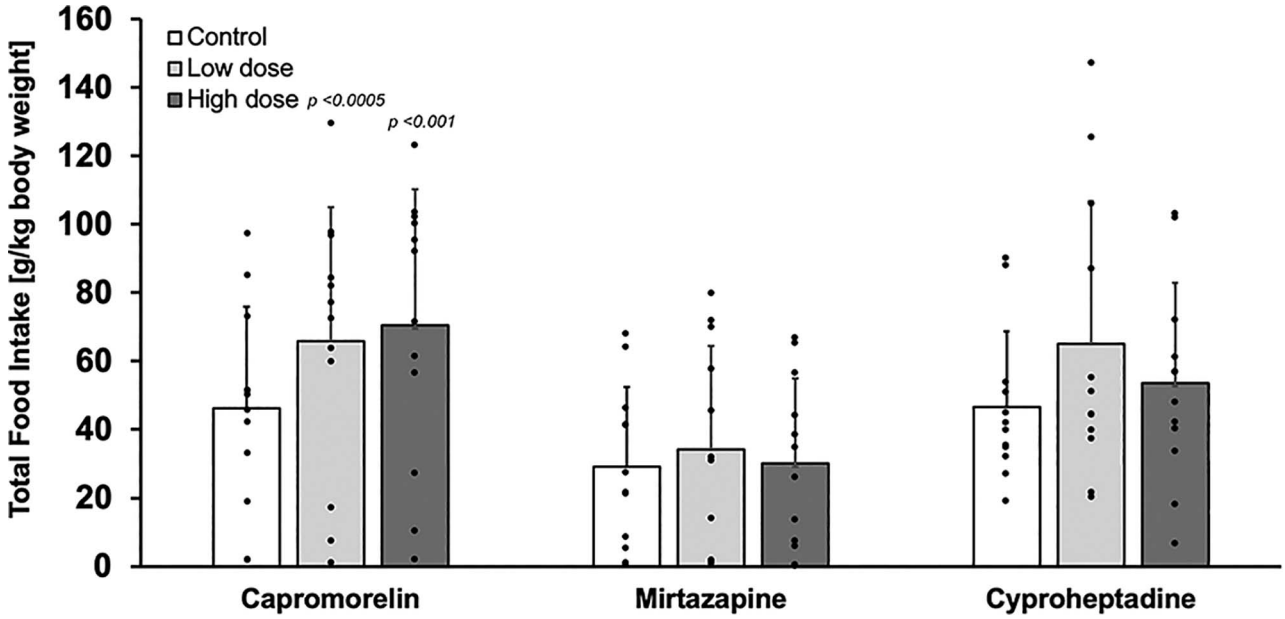

Figure 1. Total food intake (mean [SD], with individual data points) of budgerigars (*Melopsittacus undulatus*) (n = 12 per study) in a 12-hour period after administration of a single oral dose of capromorelin (10 and 40 mg/kg), mirtazapine (0.5 and 2.5 mg/kg), and cyproheptadine (1 and 5 mg/kg). The drugs were evaluated in 3 separate blinded, randomized, placebo-controlled, complete crossover studies with a 7-day washout period. Food intake was measured hourly during the first 8 hours after drug administration. Between 8 and 12 hours after administration, food intake was measured at a single 4-hour interval. Only capromorelin resulted in a significant non–dose-dependent increase in food intake compared with the control treatment ($P < 0.001$) at both doses evaluated.

compared with the control treatment (Figs 1 and 2). By 12 hours, birds receiving capromorelin had ingested, on average, 66 ± 39 g/kg (10 mg/kg dose, $P = 0.005$) or 71 ± 40 g/kg (40 mg/kg dose, $P = 0.001$) of millet compared with 46 ± 30 g/kg of millet in the control treatment. (Figs 1 and 2A). Administration of capromorelin at 10 and 40 mg/kg resulted in a 1.5-fold increase (interval: 0.4–9) and 1.7-fold (interval: 0.7–5.5) increase in food intake, respectively, over the 12 hours. No significant dose-dependent effect on food intake was present after administration of the higher 40 mg/kg dose of capromorelin (Fig 1, $P = 0.43$). However, a significant ($P = 0.003$) dose-dependent increased likelihood for regurgitation was observed with the 40 mg/kg dose. Productive and non-productive regurgitation was significantly more likely within the first hour in 92% (11/12) of the budgerigars treated with 40 mg/kg of capromorelin compared with 42% (5/12, $P = 0.01$) of birds administered 10 mg/kg of capromorelin and 25% (3/12, $P = 0.001$) of birds with the control treatment.

The administration of a single oral dose of cyproheptadine or mirtazapine at any of the evaluated doses had no statistically significant (all $P > 0.05$) or clinically relevant effect on food intake at any time point in the budgerigars in this study (Figs 1 and 2B and 2C). Mirtazapine caused no birds to regurgitate with the low dose, 16% (2/12) of birds to regurgitate at the high dose, and 16% (2/12) of birds to regurgitate with the tap water. Cyproheptadine caused 16% (2/12) of the birds to regurgitate at the low dose, 8% (1/12) to regurgitate at the high dose, and 8% (1/12) to regurgitate with the tap water.

DISCUSSION

Capromorelin was the only drug with a measurable appetite-stimulating effect in budgerigars in the studies presented here. It significantly increased the cumulative amount of food consumed in the first 12 hours after drug administration. Capromorelin's prolonged positive effects on food intake are in contrast to previous studies evaluating the effects of midazolam and lorazepam in budgerigars, which showed that these benzodiazepines had a significant effect on food intake only in the first 1–2 hours after drug administration.[12,13] It remains unknown if capromorelin has sustained appetite-stimulating effects beyond the 8–12 hours since food intake was not measured further, and the dark phase of the photoperiod and sleeping behavior would have limited food intake. No dose-dependent effect on food intake was found for capromorelin in this study, and both doses tested (10 and 40 mg/kg) resulted in a

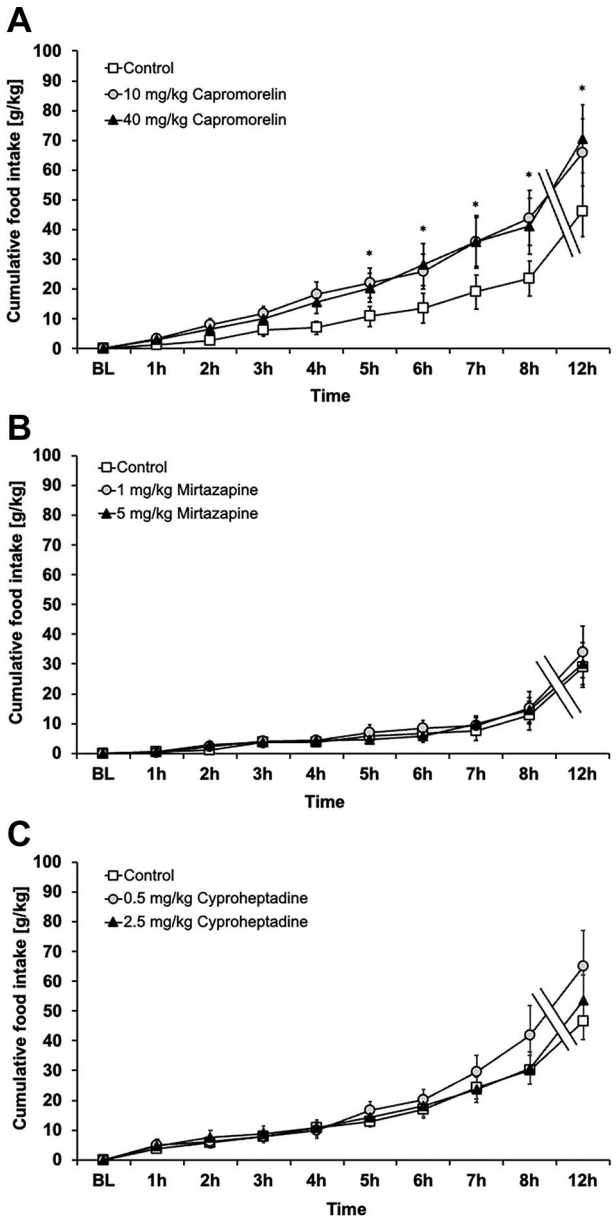

Figure 2. Mean cumulative food intake (grams per kilogram body weight) of budgerigars (*Melopsittacus undulatus*) (n = 12 per study) following single oral dose administration of (A) capromorelin (10 and 40 mg/kg), (B) mirtazapine (0.5 and 2.5 mg/kg), and (C) cyproheptadine (1 and 5 mg/kg) and tap water (control) in 3 separate blinded, randomized, placebo-controlled, complete crossover studies with a 7-day washout period between treatments. Food intake was measured hourly and during the first 8 hours after drug administration. Between 8 and 12 hours after administration, food intake was measured at a single 4-hour interval. *Statistically significant difference between food intake at a specific time point. BL indicated baseline.

similar increase in food intake. As a ghrelin receptor agonist, capromorelin mimics the effect of ghrelin and causes physiologic changes normally seen with increased endogenous ghrelin.[9] In mammals, high ghrelin levels are associated with pre-prandial periods and low ghrelin levels are associated with post-prandial periods,[18,24] which makes ghrelin agonists like capromorelin increasingly popular appetite stimulants for dogs and cats. In Japanese quail (*Coturnix japonica*) and chickens (*Gallus gallus domesticus*), exogenous ghrelin has been associated with variable effects on appetite.[25,26] In the current study, only a single oral dose of capromorelin was evaluated in budgerigars, and the effects of multiple doses were not assessed. In chickens, capromorelin (6 and 12 mg/kg) administered consecutively for 5 days significantly increased daily food intake and daily weight gain with no adverse effects reported.[18]

Mirtazapine and cyproheptadine had no measurable appetite-stimulating effects at any time with any dose tested in budgerigars. Mirtazapine is typically used as an antidepressant in human medicine and cyproheptadine as an antihistamine; however, both are administered in veterinary medicine for their secondary hyperphagic effect.[7,10] The hyperphagic effects of mirtazapine and cyproheptadine noted in multiple mammalian species are absent in budgerigars at the dosages tested in this study. In cats, cyproheptadine was found to increase appetite and reach a steady state after multiple days of q12h oral dosing, suggesting multiple doses may be required to reach the full clinical effect for either drug.[10,27] Chickens treated with cyproheptadine (0.15 and 0.32 mg/kg) q24h for 20 and 10 days, respectively, ate more food daily compared with controls, further supporting the need for repeated dosing of cyproheptadine in avian species to produce a hyperphagic response.[15] Mirtazapine, however, was found to have a peak concentration 1 hour after administration and a half-life of 9 hours in healthy young cats while increasing food intake with no significant drug accumulation over a 6-day treatment period and dosing at q24h.[11] In geriatric cats and cats with chronic kidney disease, peak mirtazapine concentrations also occurred at 1 hour. However, the median half-life was between 12 and 15 hours while effectively increasing appetite.[28] This indicates that, in cats, mirtazapine does not require multiple doses to achieve a peak concentration, but metabolism and health status impact clearance and dosing frequency recommendations. Therefore, a measurable effect on food intake could have been expected in the budgerigars following a single dose of mirtazapine. Still, no significant difference from the control treatment was found for either dose evaluated, which may suggest that this drug is metabolized differently in avian species, and pharmacokinetic properties need to be investigated further.

Productive and non-productive regurgitation was the most prevalent adverse effect noticed after the

administration of capromorelin in budgerigars. It occurred approximately 10 minutes after administration and subsided by 1 hour, as recorded by video. For the lower dose, 42% of the birds regurgitated, while 92% regurgitated at the higher dose. However, regurgitation also occurred in 25% of the birds in the control treatment (tap water). Regurgitation is a common complication of crop gavage of medications and food in psittacines, and early recognition is recommended to prevent aspiration or tracheal obstruction.[6] None of the budgerigars displayed signs of aspiration or difficulty breathing after treatment administration or after regurgitating. Although unlikely, one plausible cause for regurgitation could be crop irritation from the gavage needle because regurgitation occurred in the control treatment. However, the likelihood of regurgitation increased with higher dosages of capromorelin, suggesting a dose-dependent drug effect. For mirtazapine and cyproheptadine, regurgitation after treatment administration was similar to the control treatment, and no dose-dependent increase in regurgitation was noted. Regurgitation may have also led to incomplete drug absorption due to partial loss due to regurgitation, which may have affected the evaluation of dose-dependent effects. Nevertheless, quantification of potential drug loss was not feasible in this study. Future studies should evaluate oral administration versus crop gavage in birds to evaluate if crop gavage was a factor in the observed regurgitation. The birds used in this study were healthy. It is unknown if the drug's adverse effects would be different in clinically ill birds receiving this medication.

The dosages evaluated for all drugs were based on dose-escalating pilot studies. These pilot studies highlighted regurgitation as an adverse event after crop gavage of the medication, with more events (eg, dyspnea, sedation, and rolling behavior) occurring at higher dosages. Therefore, evaluation of all 3 drugs at higher dosages than evaluated should be cautiously considered. Considerations in such evaluation should include concentration, compound vehicle, and route of administration.

Although capromorelin, mirtazapine, and cyproheptadine are generally safe in veterinary patients, and no major complications were noted with the budgerigars throughout the study period, there is little safety information for these drugs in psittacine birds.[8,29–31] In addition, few to no complete pharmacodynamic and pharmacokinetic studies exist in psittacine birds for these drugs, which limits our understanding of the mechanisms by which each drug can affect appetite and the prediction of responses in a clinical setting. Pharmacokinetic studies may assist in determining appropriate dosage and frequency but are beyond the scope of this study, in addition to limited blood volume due to the size of the study species. Evaluating the efficacy of these appetite-stimulating medications should be performed in conjunction with assessing plasma concentrations in larger species. The budgerigars used in this study were healthy and young, and capromorelin, mirtazapine, or cyproheptadine administered to older or ill birds may produce different results in food intake or adverse effects. The observed variable responses to each drug in this study indicate likely variation of effects in a clinical setting. Therefore, clinical trials in hospitalized patients of varying ages and species are recommended.

Mirtazapine is not commercially available in a liquid form, and tablet administration is not feasible in budgerigars or other small pet birds. Therefore, a licensed veterinary pharmacy compounded the mirtazapine suspension administered to the birds in this study using commercial United States Food and Drug Administration–approved tablets and following United States Pharmacopeia protocols. Veterinarians should adhere to compounding regulations and be aware that pharmacokinetic properties may differ between compounded and United States Food and Drug Administration–approved products.

Further investigation of capromorelin at doses $<$ 10 mg/kg should be considered to evaluate if regurgitation can be reduced while maintaining appetite-stimulating effects. Additionally, repeated dosing of capromorelin at q24h intervals should be evaluated. Further studies evaluating repeated dosing of mirtazapine and cyproheptadine may also be indicated based on the recommendations and efficacy in mammals.[10,32]

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