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Assessment of compounded transdermal mirtazapine as an appetite stimulant in cats with chronic kidney disease

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Abstract

Objectives The aim of this study was to assess the appetite stimulation properties of compounded transdermal mirtazapine (CTM) in cats with chronic kidney disease (CKD).

Methods Two sequential double-blind placebo-controlled crossover prospective studies were performed in client-owned cats with stable stage 2 or 3 CKD and a history of decreased appetite. In the first study nine CKD cats were randomized to receive 3.75 mg/0.1 ml CTM gel or placebo on the inner pinna every other day for 3 weeks, then, after a 4 day washout period, the cats were crossed over to the alternate 3 week treatment. In a second study, 10 CKD cats were randomized to receive 1.88 mg/0.1 ml CTM or placebo on the same schedule. Physical examination and serum biochemistry were performed before and after each treatment period, and owners kept daily logs of appetite, activity and eating behaviors. Mirtazapine concentrations in CTM gels and steady-state mirtazapine serum concentrations were measured using liquid chromatography/tandem mass spectrometry.

Results Administration of both 3.75 mg and 1.88 mg CTM resulted in a statistically significant increase in weight ($P = 0.002$ for both), increase in appetite ($P = 0.01$ and $P = 0.005$, respectively), and increase in rate of food consumption ($P = 0.03$ and $P = 0.008$, respectively). No significant difference in activity or vocalization was seen at either dose; however, individual cats experienced excessive meowing. Median weight increase for the 3.75 mg arm was 0.22 kg (range 0.04–0.44 kg), while median weight increase for the 1.88 mg arm was 0.26 kg (range –0.25 to 0.5 kg). Improvement in body condition score was seen in 5/9 cats in the 3.75 mg arm ($P = 0.04$) and 6/10 cats in the 1.88 mg arm ($P = 0.004$).

Conclusions and relevance CTM increased appetite and resulted in weight gain in CKD cats despite significant inconsistencies in compounding, and may benefit cats in countries where an approved product is not available.

Keywords: Renal; gel; compounding; weight

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Introduction

Dysrexia and weight loss are common in cats with chronic kidney disease (CKD).[1,2] Weight loss is associated with a poorer prognosis in CKD cats and is likely attributable to abnormal appetite and subsequent inadequate caloric intake, as well as processes such as cachexia and sarcopenia, which result in a loss of lean body mass.[1,3] Additionally, poor appetite is perceived as a significant quality of life concern in cats with chronic disease and can cause emotional distress to owners.[4–6]

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Therefore, the management of appetite is an important therapeutic goal in feline CKD patients.

Mirtazapine has been demonstrated to be an effective appetite stimulant in cats, and administration of mirtazapine at a dose of 1.88 mg PO q48h has been shown to stimulate appetite, promote weight gain and reduce vomiting in cats with CKD.[7,8] However, many feline patients are not amenable to oral administration of medications and this can become a source of frustration to owners. During the management of CKD, multiple medications may be necessary, resulting in a pill burden that may ultimately affect quality of life and the human–animal bond. In one study, the average number of medications administered to CKD cats was two (range 0–10) and 54% of owners used methods other than direct oral administration to try and administer the medication.[2]

Transdermal application of medications is of interest in feline patients owing to the ease of administration compared with the oral route,[9] and can improve owner compliance.[10] Although not all medications are amenable to transdermal application, advantages of a transdermal formulation of mirtazapine for stimulating weight gain in cats was demonstrated by the US Food and Drug Administration (FDA) approval of a commercial formulation (Miratraz; Kindred Bio).[11,12] The purpose of this study, which was performed before the FDA approval of transdermal mirtazapine ointment, was to assess the appetite stimulation properties of compounded transdermal mirtazapine (CTM) in cats with CKD in two sequential clinical trials.

Materials and methods

Cats

Client-owned cats with stable International Renal Interest Society (IRIS) stage 2 or 3 CKD and history of decreased appetite completed a double blind placebo-controlled crossover prospective study. Nine cats were enrolled in the 3.75 mg arm and 10 cats were enrolled in the 1.88 mg arm. One cat was enrolled in both arms of the study; however, more than 2 years had elapsed between enrollment episodes. Study arms were performed in a sequential manner. Diagnostics required for enrollment included serum biochemistry profile, complete blood count, urinalysis, urine culture, blood pressure and total thyroxine measurement. Exclusion criteria included concurrent systemic illness, pyelonephritis, ureteral obstruction or decompensation of CKD/recent hospitalization.

The study was approved by the Institutional Animal Care and Use Committee and the Clinical Review Board at Colorado State University, and the Clinical Research Committee at Ohio State University. Written informed consent was obtained from the owner or legal guardian of all cats described in this study for the procedures undertaken. No cats were individually identifiable within this publication and therefore additional informed consent for publication was not required.

Study design

This study had a two-treatment two-period crossover design with a predetermined sequence of AB or BA. As cats were enrolled, they were assigned consecutively to a treatment regime. The randomly predetermined gel (A or B) was administered to the inner ear pinna every other day for 3 weeks. After a 4 day washout, the other gel (B or A) was administrated every day for another 3 weeks.

Owners documented appetite, rate of food ingestion, begging behavior, activity and vocalization in the home environment as increased, decreased or unchanged in a daily log. Physical examination, body weight, World Small Animal Veterinary Association (WSAVA) body condition score (BCS), WSAVA muscle condition score (MCS) and serum biochemistry panel were performed at the end of each treatment period. Cats were not fasted prior to study visits but were seen at a consistent time of day throughout the study. Serum was collected on day 21 of CTM administration for measurement of mirtazapine steady-state drug serum concentration. Mirtazapine drug concentrations in CTM gels and steady-state mirtazapine serum concentrations were measured using liquid chromatography/tandem mass spectrometry (LC/MS-MS).

Drug preparation

Mirtazapine tablets (Aurobindo Pharma) were compounded into a 3.75 mg/0.1 ml or 1.88 mg/0.1 ml dose transdermal Lipoderm gel by the Colorado State University Veterinary Medical Center pharmacy along with an identical placebo according to Professional Compounding Centers of America (PCCA) protocol. The method used is guaranteed to produce accurate compounding to within 10% of the target dose.

Statistical analysis

To determine sample size for the study, an a priori power calculation was performed using a paired Student's *t*-test to represent the crossover design. The response was defined as 'weight change' (post–pre) and the two treatments were mirtazapine and placebo. For each cat in a previous study,[8] the difference mirtazapine – placebo was calculated, and the average difference (0.3 kg) and SD of the differences (0.2 kg) was used for the power calculation. Using Lenth's online power calculator (http://homepage.stat.uiowa.edu/~rlenth/Power/), this resulted in a power of >95% with a total of 10 cats.

Appetite, rate of food ingestion, begging behavior, activity and vocalization data from owner daily logs were converted to clinical scores; a decrease in the behavior was scored as −1, no change scored as 0 and an increase scored as 1. Daily scores for each behavior were

then summed for the 3 week treatment period. Outcomes from physical examinations (change in weight and BCS), clinicopathologic parameters (change in serum creatinine, blood urea nitrogen [BUN], phosphorus and potassium) and summed scores on owner documented logs were analyzed using the ANOVA model for a 2 × 2 crossover study estimating a treatment effect (mirtazapine vs placebo), while adjusting for the period effect. The inclusion of a period effect in the model is based on the assumption that the characteristics of the cats are not the same between period 1 and 2 owing to the weight gain property of mirtazapine, and that owner observations, although blinded, may be affected by placebo effect. Spearman's rank test was used to assess correlation between vocalization score and serum mirtazapine concentration. Analyses were performed in Prism v7 (GraphPad) or Stata v 15.1 (StataCorp). For all analyses, a P value <0.05 was considered to be statistically significant.

Mirtazapine serum and gel concentration analysis

Mirtazapine concentrations of CTM and steady-state serum samples were measured using LC/MS-MS by the Pharmacology Shared Resource at Colorado State University using a validated LC/MS-MS based assay for the analysis of mirtazapine in feline serum.[7] To measure transdermal gel concentration, approximately 10 mg dosing solution gel was diluted 1:100 with solution of 50:50, ACN:Milli-Q (v:v). Samples were vortex mixed, sonicated for 5 mins and diluted an additional 1:10,000 with 50:50, ACN:Milli-Q. In total, samples were diluted 1:1 $\times 10^6$ and quantified using a standard curve of mirtazapine prepared in 50:50, ACN:Milli-Q using the LC/MS-MS method described previously.[7] Assay performance for each batch was assessed using at least 10% quality assurance, quality control (QA/QC) samples dispersed among unknown samples at low (1 ng/ml), mid (10 ng/ml) and high (100 ng/ml) ranges of the standard curve (0.5–500 ng/ml) with batches failing if >25% of the QA/QC samples were outside of the accepted level of 85% accuracy. Accuracy of QA/QC samples among the batches analyzed for this study ranged from 89.5 ± 3.5% to 96.4 ± 1.5%. The lower limit of quantitation for this assay was based on the level of detection with >85% accuracy and a coefficient of variation (%) <15%, and was determined to be 0.5 ng/ml. Assay performance was linear to >500 ng/ml, with 500 ng/ml used as the upper limit of the assay because of a lack of samples exceeding this concentration.

Results

3.75 mg clinical trial

A flow chart describing study enrollment, allocation, outcome and analysis is presented in Figure 1. Study discontinuation occurred in three cats (one household outbreak of gastrointestinal signs and one uremic crisis during mirtazapine treatment; and one uremic crisis/congestive heart failure during placebo). The nine cats that completed the 3.75 mg trial included six domestic shorthairs, two domestic longhairs and one Ragdoll. The median age was 15.5 years (range 12–21 years) with six spayed females and three castrated males. Six cats were classified as IRIS stage 2, and three cats were IRIS stage 3. Baseline serum creatinine, BUN, weight, BCS and MCS are presented in Table 1.

When CKD cats (n = 9; six IRIS stage 2 cats and three IRIS stage 3 cats) received 3.75 mg CTM every other day for 3 weeks a statistically significant increase in weight ($P = 0.002$), increase in BCS ($P = 0.04$), increase in appetite ($P = 0.01$) and increase in rate of food consumption ($P = 0.03$) was seen. A statistical trend for increase in begging behaviors was seen ($P = 0.06$). No significant difference in activity ($P = 0.25$) or vocalization ($P = 0.08$) was seen; however, 2/10 cats experienced excessive vocalization, as described by owners in the daily log (21/21 days and 19/21 days, respectively). Weight gain occurred in 100% of the CKD cats during CTM administration; in contrast, 67% of cats lost weight during the placebo phase. Median body weight change after CTM administration was 0.22 kg (range 0.04–0.44 kg), while median body weight change during the placebo period was –0.04 kg (range –0.6 to 0.08 kg). Improvement in BCS was seen in 5/9 cats during CTM administration and improvement in MCS was seen in 3/9 cats.

A statistically significant increase in serum BUN concentration (median increase 10 mg/dl [range –16 to 21 mg/dl]; $P = 0.01$) was seen after CTM administration, but no significant changes in serum creatinine, phosphorus or potassium were seen. Gel concentrations were available for six enrolled cats and varied by 74–122% (median 111%) of target dose, with 66% of formulations being outside 10% variability from target dose. Steady-state day 21 serum mirtazapine concentrations were available for 11 enrolled cats; median concentration was 5.5 ng/dl (range 3.3–11 ng/dl). There was no significant correlation between vocalization score and serum mirtazapine level. Serum BUN was the only parameter that displayed a significant period effect.

1.88 mg clinical trial

A flow chart describing study enrollment, allocation, outcome and analysis is presented in Figure 2. Study discontinuation occurred in two cats (one household upper respiratory outbreak, one development of tooth root abscess). The 10 cats that completed the 3.75 mg trial included four domestic shorthairs, two Siamese mixes, one Ragdoll, one British Shorthair, one Ragamuffin and one domestic longhair. The median age was 14 years (range 12–18 years) with seven spayed females and three castrated males. Six cats were classified as IRIS

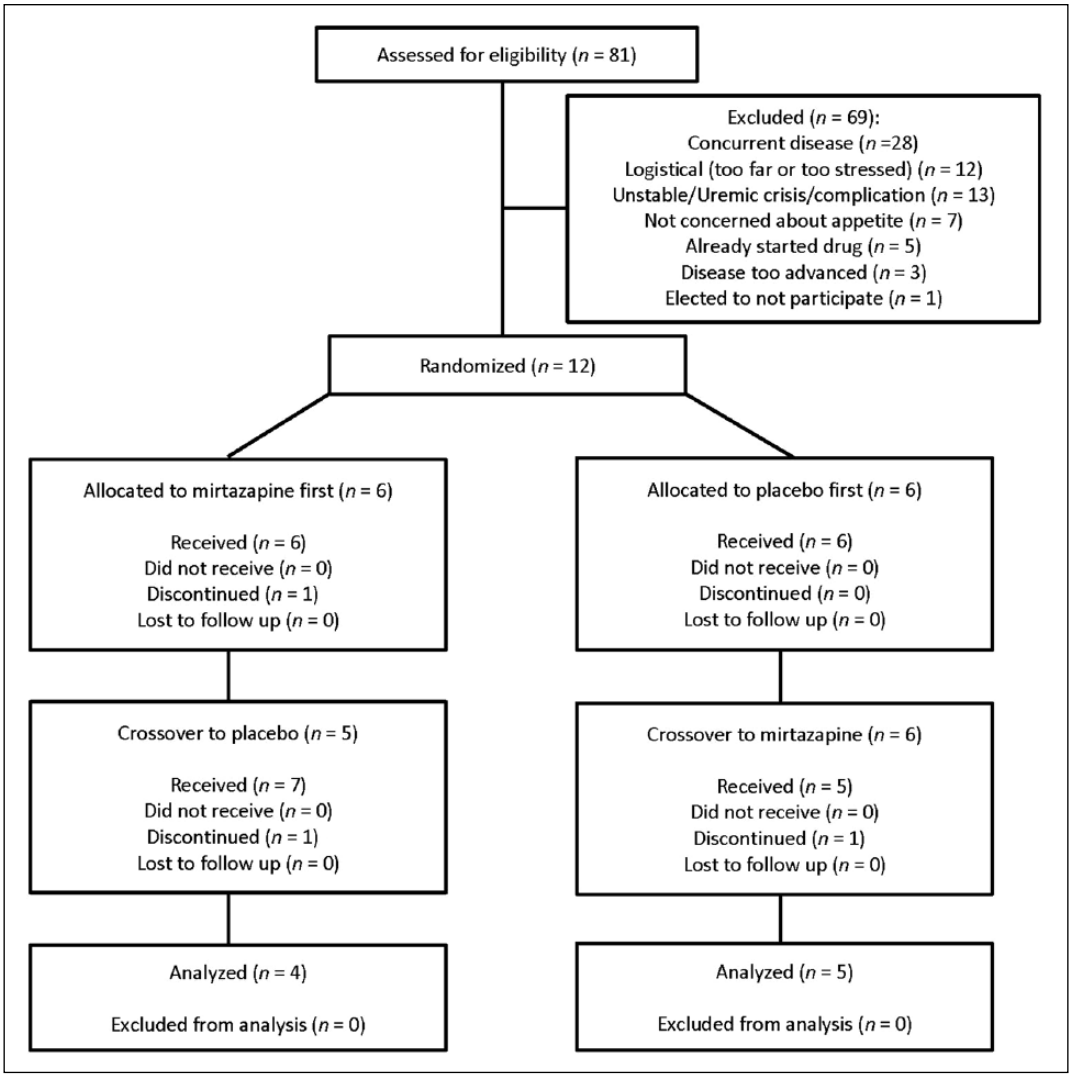

Figure 1 Consort diagram for 3.75 mg compounded transdermal mirtazapine clinical trial

stage 2 and four cats were IRIS stage 3. Baseline serum creatinine, BUN, weight, BCS and MCS are presented in Table 1.

When CKD cats received 1.88 mg CTM every other day for 3 weeks a statistically significant increase in weight ($P = 0.002$; Figure 3), increase in BCS ($P = 0.004$), increase in appetite ($P = 0.005$; Figure 4), increase in rate of food consumption ($P = 0.008$; Figure 5) and increase in begging behaviors ($P = 0.003$; Figure 6) was seen. No significant difference in activity ($P = 0.10$) or vocalization ($P = 0.08$; Figure 7) was seen; however, 2/10 cats experienced excessive vocalization as described by owners in the daily log (19/21 days and 16/21 days, respectively). Weight gain occurred in 90% of the CKD cats during CTM administration; in contrast, 70% of cats lost weight during the placebo phase. Median body weight change after CTM administration was 0.26 kg (range –0.25 to 0.50 kg), while median weight change during the placebo period was –0.05 kg (range –0.2 to 0.01 kg). Improvement in BCS was seen in 6/10 cats during CTM administration and improvement in MCS was seen in 4/10 cats.

Statistically significant increases in serum BUN concentration (median increase 9.5 mg/dl, range –5 to 22 mg/dl; $P < 0.001$) and serum phosphorus (median increase 0.8 mg/dl [range –0.3 to 2.8 mg/dl]; $P = 0.009$) were seen after CTM administration. No significant changes in serum creatinine or potassium were seen. Gel concentrations were available for 11 enrolled cats and varied by 76–107% (median 97%) of target dose, with 18% of formulations being outside 10% variability from target dose. Steady-state day 21 serum mirtazapine concentrations were available for six enrolled cats; median concentration was 2.5 ng/dl (range 0.97–6.4 ng/dl). There was no significant correlation between vocalization score and serum mirtazapine level. Serum BUN was the only parameter that displayed a significant period

Table 1 Comparison of results for two doses of compounded transdermal mirtazapine administered every other day for 3 weeks

	1.88 mg trial (n = 10 cats)	3.75 mg trial (n = 9 cats)
Baseline creatinine (mmol/l)	221 (186–327)	221 (141–407)
(mg/dl)	2.5 (2.1–3.7)	2.5 (1.6–4.6)
Baseline BUN (mmol/l)	17 (11–28)	17 (10–27)
(mg/dl)	48 (31–79)	47 (27–77)
Baseline weight (kg)	4.0 (3.0–5.8)	3.8 (3.0–6.8)
Weight change drug (kg)	0.26 (–0.25 to 0.5)	0.22 (0.04–0.44)
Weight change placebo (kg)	–0.05 (–0.2 to 0.01)	–0.04 (range –0.6 to 0.08)
Baseline WSAVA BCS	4 (3–5)	4 (4–7)
Change in BCS	6/10 improved	5/9 improved
Baseline WSAVA MCS	Moderate (mild–severe)	Moderate (mild–severe)
Change in MCS	4/10 improved	3/9 improved
Serum mirtazapine concentrations (ng/ml)	2.5 (0.97–6.4)	5.5 (3.3–11)
Gel mirtazapine concentrations (% of target dose)	97 (range 76–107)	111 (range 74–122)

Data are median (range)
BUN = blood urea nitrogen; WSAVA = World Small Animal Veterinary Association; BCS = body condition score; MCS = muscle condition score

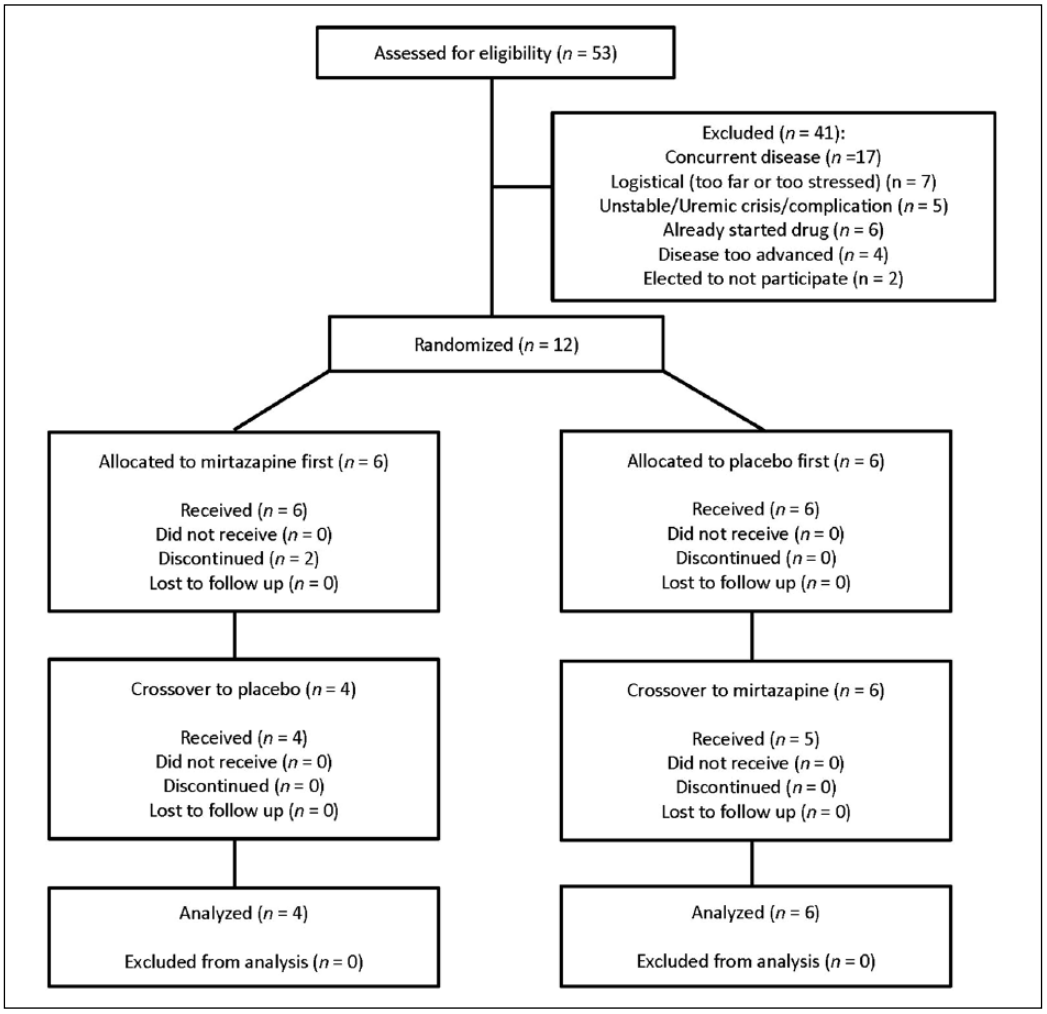

Figure 2 Consort diagram for 1.88 mg compounded transdermal mirtazapine clinical trial

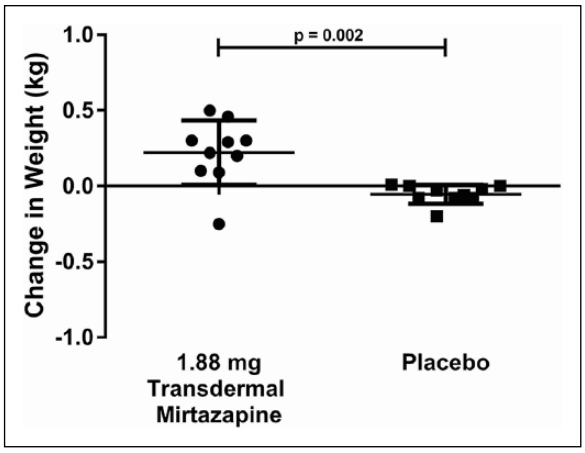

Figure 3 Change in weight after administration of 1.88 mg compounded transdermal mirtazapine or placebo every other day for 3 weeks. A statistically significant increase in weight was seen ($P = 0.002$)

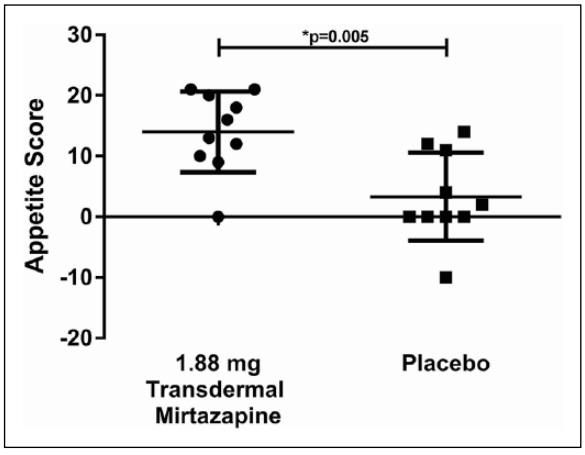

Figure 4 Appetite score based on daily owner assessment after administration of 1.88 mg compounded transdermal mirtazapine or placebo every other day for 3 weeks. A statistically significant increase in appetite score was seen ($P = 0.005$)

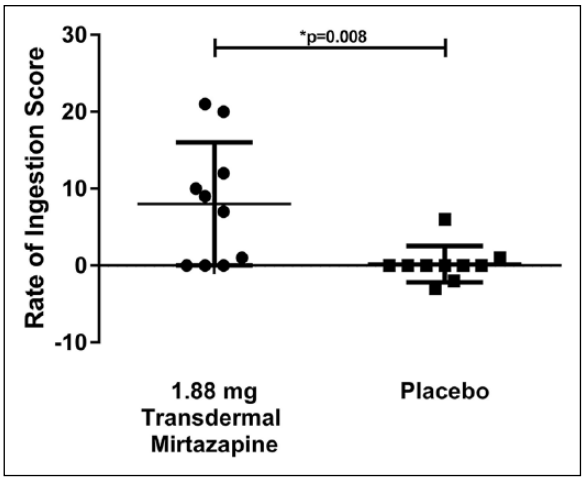

Figure 5 Rate of ingestion score based on daily owner assessment after administration of 1.88 mg compounded transdermal mirtazapine or placebo every other day for 3 weeks. A statistically significant increase in rate of ingestion was seen ($P = 0.008$)

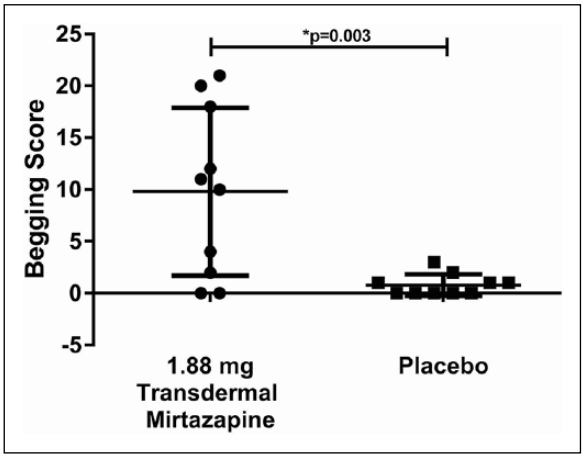

Figure 6 Begging score based on daily owner assessment after administration of 1.88 mg compounded transdermal mirtazapine or placebo every other day for 3 weeks. A statistically significant increase in begging was seen ($P = 0.003$)

effect. A comparative summary of pertinent findings from both clinical trials is provided in Table 1.

Discussion

The purpose of these two sequential clinical trials was to demonstrate that application of CTM was effective in stimulating appetite in cats with CKD and promoting weight gain. Results indicated that administration of 1.88 mg CTM every other day for 3 weeks resulted in a significant increase in appetite and weight gain in cats with IRIS stages 2 and 3 CKD. Furthermore, some cats experienced an increase in BCS and MCS.

The decision to perform a clinical trial at 3.75 mg was based on preliminary data collected in a previous study in young, normal cats.[11] However, after the conclusion of the current 3.75 mg study, it was noted that some individual cats displayed excessive vocalization, and as these types of behavioral side effects have been demonstrated to be dose related,[7,13] a follow-up study at the 1.88 mg dose was initiated. Data indicate that CTM is effective at the lower 1.88 mg dose, similar to a previous study in oral mirtazapine.[8] However, it should be noted that these data cannot be compared with Mirataz, the FDA-approved mirtazapine transdermal ointment for the management of unintended weight loss in cats, as it is a formulation that is of better quality, which meets United States Pharmacopeia (USP) standards and for which a

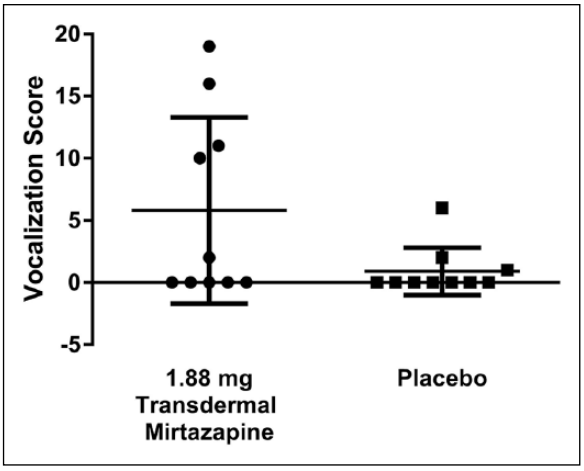

Figure 7 Vocalization score based on daily owner assessment after administration of 1.88 mg compounded transdermal mirtazapine or placebo every other day for 3 weeks. Although no statistically significant difference in vocalization was seen ($P = 0.08$), individual cats had excessive vocalization as reported by owners

dose of 2 mg has been approved by the FDA after extensive study in a large, pivotal trial.[12]

In the second CTM clinical trial, at 1.88 mg q48h, two CKD cats still experienced excessive vocalization, in one case termed 'unbearable' in the owner's daily log. The clinical trial included a provision for dose reduction in circumstances of excessive vocalization or activity, but the owner did not contact the investigators during the trial to report the concern during the study. Although there was no correlation between serum mirtazapine concentration and vocalization score, this observation implies that for individual cats receiving CTM further dose reduction may be warranted. Additionally, these data imply that, similar to oral mirtazapine, the lowest effective dose of CTM should be used, and the 3.75 mg dose is not recommended. However, again these data cannot be compared with the FDA-approved product, Mirataz, as it is a better-quality formulation that meets USP standards and, as a result, clinical studies with Mirataz are more predictable and repeatable than the current study. In contrast to the data presented for CTM in the current, small study, no significant difference in incidence of behavioral adverse events (vocalization and hyperactivity) was seen between cats with and without CKD in the large pivotal clinical trial where 2 mg Mirataz was administered daily to cats.[12]

Although CTM was effective at stimulating appetite and promoting weight gain, concerns regarding the consistency of the compounded product still remain and are a major limitation of the current study. Although the compounded gel was formulated by a pharmacy following instructions provided by PCCA compounding guidelines, analysis of the gels revealed that concentrations varied widely from target (>10% at times), an observation that is similar to that of a previous study.[11] A compounded version of an FDA-approved drug must meet the standards of the USP with assurance that the strength is within 10% of the target dose. Therefore, the compounded formulation used in this study did not reliably meet compendial standards, despite concerted effort to do so, and probably should not be recommended for future clinical use, serving as a caution for the use of compounded transdermal medications.

Furthermore, the availability of the FDA-approved mirtazapine transdermal ointment (Mirataz) for the management of unintended weight loss in cats now makes it unnecessary (and illegal) to compound the medication in the US.[12,14] The efficacy of Mirataz has been documented in pharmacokinetic and pharmacodynamics studies, confirming the viability of the transdermal route of administration for this drug.[12,14] Specifically, a large multi-center, double-blind, placebo-controlled, randomized pivotal clinical trial was performed in cats with >5% unintended weight loss.[12] Daily application of 2 mg Mirataz to the inner ear pinnae for 14 days resulted in cats in the mirtazapine group gaining significantly more weight compared with baseline (mean gain 3.94 ± 5.37%) than the cats in the placebo group (mean gain 0.41 ± 3.33%).[12] Taken overall, the information provided in the current study may be of benefit to patients in geographical areas where an approved product is not available, and an inferior formulation is the only option.

Significant increases in serum phosphorus and BUN were observed after administration of CTM to cats with CKD. The median increase in serum phosphorus was 0.8 mg/dl and was seen only in the 1.88 mg trial; therefore, this finding may not be of clinical significance and could represent type I statistical error. The significant increase in serum BUN was observed in both trials and was of a more clinically significant magnitude. Both parameters have been observed to increase in malnourished human renal disease patients when enteric nutrition was increased, so one possible explanation is an increase in food consumption and a concomitant increase in consumption of protein and phosphorus.[15,16]

Serum BUN was the only parameter to display a significant period effect, and this was likely because if it became elevated with CTM administration in the first treatment, it then subsequently decreased in the second period when placebo was administered. A significant increase in BUN was not seen subsequent to oral mirtazapine administration in a previous clinical trial in CKD cats;[8] however, in this study, the statistical analysis of the data was performed differently (ie, not based on change in BUN) so a direct comparison may not be appropriate. Changes in hydration status and muscle mass could also

play a role in the observation regarding BUN, but as serum creatinine was not significantly different, this explanation seems less supported by accompanying data.

Conclusions

Transdermal application of CTM was effective in stimulating appetite in cats with CKD and promoting weight gain, and agreed with efficacy studies performed in a much larger population of cats by the sponsor of the FDA-approved product. Individual cats may require CTM dose reduction if side effects such as excessive vocalization are noted. Inconsistencies in compounded formulations exist and the CTM formulation as prepared for this study did not always meet USP standards for compounded products, and thus should not be used when an approved product is available.

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Author note The results of this study were presented in part, as a research report, at the American College of Veterinary Internal Medicine Annual Forum, National Harbor, MD, 2017.

Conflict of interest Jessica Quimby is an advisory board member and consultant for Kindred Bio; however, this company was not involved in the funding, design or execution of this study.

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Ethical approval This study involved the use of experimental or client-owned animal(s) in addition to internationally recognized high standards ('best practice') of individual veterinary clinical patient care. The study therefore had ethical approval from an established committee as stated in the manuscript.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal guardian of all animal(s) described in this study for the procedure(s) undertaken. No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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