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A double-blind, placebo-controlled, randomized study to evaluate the weight gain drug, mirtazapine transdermal ointment, in cats with unintended weight loss

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Abstract

Mirtazapine is classified as a weight gain drug in cats, and the purpose of this study was to evaluate its efficacy in cats experiencing unintended weight loss. This was a multi-center, double-blind, placebo-controlled, randomized clinical study in client-owned cats ≥1 year of age, weighing ≥2 kg, with a documented loss (≥5%) in body weight. Cats were treated once daily with either 2 mg/cat mirtazapine transdermal ointment (n = 83) or placebo (n = 94) (Per Protocol population) applied to the inner surface of the pinna for 14 ± 3 days. Physical examination, body weight, complete blood count, serum chemistry, and urinalysis were performed prior to treatment and on Day 14. Changes in body weight between the mirtazapine and placebo groups were evaluated from Day 1 to Day 14 and compared using a two-sample t test. The mean percent change in body weight was +3.9% (standard deviation ±5.4%) in the mirtazapine group and +0.4% (±3.3%) in the placebo group ($p < 0.0001$). The most common adverse event was mild erythema at the application site in 17.4% of placebo and 10.4% of mirtazapine-treated cats. Application of mirtazapine transdermal ointment was well tolerated both topically and systemically and resulted in significant weight gain in cats experiencing unintended weight loss associated with various underlying diseases.

KEYWORDS
appetite, dysrexia, mirtazapine, transdermal, weight gain

1 | INTRODUCTION

Mirtazapine is classified as a weight gain drug and has been used in cats as an appetite stimulant (Agnew & Korman, 2014; Ferguson, McLean, Bates, & Quimby, 2016; Quimby & Lunn, 2013; Quimby, Summers, Benson, Herndon, & Gustafson, 2017). In cats with chronic kidney disease, mirtazapine has been shown to promote weight gain and increase food intake in addition to reducing nausea and vomiting (Quimby & Lunn, 2013). The pharmacological effects of mirtazapine are thought to be mediated via presynaptic alpha-2 antagonism,

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which enhances serotonin and noradrenaline release (de Boer, 1996), and antagonism of serotonin (5-HT) and histamine (H_1) receptors (Stahl, 2008; Stahl, Mignon, & Meyer, 2009). Inhibition of 5-HT_{2C} and H_1 receptors may account for the orexigenic effects of mirtazapine (Stahl, 1998). Reduction in nausea and vomiting observed in cats (Quimby & Lunn, 2013) is theorized to be due to antagonism of 5-HT_3 receptors (Stahl, 2008).

The mirtazapine transdermal ointment used in this study was approved by the Food and Drug Administration (FDA) on May 4, 2018 [New Animal Drug Application 141–481; https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/3487] for the management of weight loss in cats and has been shown to achieve measurable plasma concentrations of mirtazapine following single and repeat dosing in the cat (Buhles, Quimby, Labelle, & Williams, 2018). Weight loss and chronic dysrexia in cats can lead to serious complications such as hepatic lipidosis (Valtolina & Favier, 2017), altered immune function (Valtolina & Favier, 2017), delayed wound healing (Agnew & Korman, 2014), and decreased survival time (Finn, Freeman, Rush, & Lee, 2010). Appetite is considered by owners to be an important aspect of quality of life, and such secondary complications may influence an owner's decision to humanely euthanize their cat (Reynolds et al., 2010).

Administering oral medication to cats can be challenging. Topically applied medications have been used in cats due to the ease of dosing compared to orally administered medications (Hill et al., 2015) and can improve owner compliance (Hill et al., 2011). The purpose of this study was to evaluate body weight gain in cats treated with mirtazapine transdermal ointment that were experiencing unintended weight loss associated with various underlying diseases.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a multi-center, randomized, double-blind, placebo-controlled study in client-owned cats conducted at 20 veterinary sites across the United States. It was conducted according to Good Clinical Practices (FDA Center for Veterinary Medicine (CVM) Guidance 85; VICH GL9). The scientific and ethical validity of the study was reviewed by FDA prior to study conduct (Study protocol KB105, FDA protocol concurrence received on Jan 7, 2016). The protocol was approved by the East Tennessee Clinical Research Institutional Animal Care and Use Committee (IACUC) [#ETCR-18-0228]. All cat owners reviewed and signed informed owner consent forms prior to participation in the study. For the purpose of calculating study power, it was assumed that cats in the mirtazapine group would have an average of a 3% increase in body weight and cats in the placebo group would have an average of a 0% increase in body weight, a common standard deviation of 6%, and a 15% drop-out rate. The study was intended to enroll at least 100 eligible cats in each treatment group and was therefore powered at a 90% level, with a two-way p-value of 0.05, to demonstrate statistical significance of the difference in the mean percent change in body weight between mirtazapine and placebo.

2.2 | Inclusion/exclusion criteria

Cats were included in the study if they were ≥1 year of age, had ad libitum access to food and a documented medical history of ≥5% body weight loss without calorie restriction. Treatments (e.g., flea control, vaccinations, etc.) which had no impact on the clinical conditions being investigated were allowed during the study for both treatment groups. Cats receiving diuretics, insulin, and/or ACE inhibitors must have been on a stable regimen at Day 1. Subcutaneous fluid as supportive therapy was permitted during the study; however, it was required that body weight be measured prior to fluid administration if fluid therapy was received on a day of weighing. Systemic corticosteroids were allowed for treating any underlying illness, but the dose and schedule must have not been altered for 14 days prior to Day 1 or during the study. Cats were excluded if they were pregnant or lactating, had a body weight <2.0 kg, had been diagnosed with neoplasia or severe kidney disease (International Renal Interest Society Stage 4 or serum creatinine >5.0 mg/dl), or received any prohibited concurrent medication. Additional medications intended to stimulate appetite or cause weight gain were not allowed for 7 days prior to the study or during the study and included diazepam, oxazepam, phenothiazines, metoclopramide, cyproheptadine, maropitant, and marinol. Additional exclusion criteria included treatment within 30 days of study onset with mirtazapine, monoamine oxidase inhibitors, or other serotonergic drugs. Cats that were not expected to survive the study were also excluded.

2.3 | Animal housing and diet

Study cats remained at home with their owners. To minimize environmental factors influencing appetite, the normal environment of each cat was maintained throughout the study (indoors or outdoors and diet). Cats had ad libitum access to food, except for the two-hour period immediately preceding hospital visits on Days 1 and 14. Cats were allowed to be on special diets during the study. The cat's food type (wet, dry, mixed, special, or standard diet) was not altered for 7 days prior to the onset of the study and was maintained through the study completion.

2.4 | Treatment drug and placebo

Mirtazapine transdermal ointment contained 2% mirtazapine (1 g of ointment contained 20 mg mirtazapine, active ingredient) [Kindred Biosciences, Inc., Burlingame, CA]. The formulation contained the following inactive ingredients: polyethylene glycol (PEG) 400, PEG 3350, diethylene glycol monoethyl ether, PEG-8 caprylic/capric glycerides, oleyl alcohol, butylated hydroxytoluene, dimethicone, and Dry Flo TS. The formulation used in this study was the final commercial formulation and was stable under storage conditions of 25°C/60% relative humidity for at least 30 months which covered

the duration of the study. Mirtazapine transdermal ointment and placebo ointment were manufactured at the same facility and under the same conditions. The placebo ointment consisted of the same formulation without the active ingredient, mirtazapine.

2.5 | Dosing and application

Cats were randomized 1:1 into mirtazapine or placebo groups. A centralized block randomization was implemented with a block size of four. Cats were enrolled based on the order of presentation to the clinic; the blocking scheme was used to maintain an approximately equal number of cats per treatment arm and was not considered a factor in the statistical model. An independent third-party statistician generated the randomization list. Mirtazapine was dosed at 2 mg/cat (0.1 g of 2% ointment), regardless of body weight. Placebo was dosed at the same volume. Each cat was dosed by applying mirtazapine or placebo ointment topically to the inner surface of the pinna once daily for 14 days according to treatment assignment. A 1.5-inch ribbon of ointment (mirtazapine or placebo) constituting approximately 0.1 g was applied on the pinna and spread over the inner (anterior) surface using a gloved finger. Owners were allowed to alternate ears for dose application. A dosing card was provided to the owner to assist in determining the appropriate ribbon length (Kindred Biosciences, Inc., 2018). For all doses, the date, dose number, and ear (left or right) treated was recorded in the Owner Diary Dose Log. Compliance with treatment was evaluated via the Owner Diary Dose Log.

2.6 | Statistical analysis

Effectiveness was defined as meeting all three of the following criteria: (a) a statistically significant difference between treatment groups ($p < 0.05$) in mean percent change in body weight (Day 1 to Day 14), (b) a higher mean percent change in body weight in the mirtazapine group, and (c) a mean percent change in body weight in the mirtazapine groups ≥0. Statistical significance was tested using independent sample *t* test assuming equal variances between the two treatment groups (the TTEST procedure in SAS®, SAS Institute, Cary, NC, version 9.4). Statistical significance was set at $p < 0.05$. Study site and interactions within study site were not included in the statistical model given the objective nature of the primary outcome and the assumed trivial differences between sites in measuring body weight. Subgroup analysis based on baseline characteristics of weight category (≤4 kg or >4 kg), presence/absence of kidney disease, and administration of concurrent glucocorticoid or antithyroid medications was also performed. Kidney disease was a diagnosis made at the discretion of the clinical investigators based on clinical presentation, physical examination, and clinical pathology findings. Chi-square or Fisher's exact test was used to compare relative incidence of adverse events (AEs) between treatment groups.

Clinical pathology data (CBC, serum chemistry, and U/A) from Day 1 prior to treatment and Day 14 were analyzed using the Analysis of Covariance (ANCOVA), with treatment as a fixed effect and the baseline value as a covariate. The covariate remained in the model regardless of significance. Statistical significance was set at $p < 0.10$ (per regulatory requirements). Blood was collected for hematology (complete blood count, CBC) and serum chemistry, and urine samples for urinalysis (U/A) at Screening, Day 14, and any unscheduled visits. A centralized laboratory was utilized for all clinical pathology samples.

The Safety Population consisted of all cats randomized to either treatment group who received at least one dose of study drug. The Per Protocol (PP) population included all cats completing the study through and including Day 14. The Intent-to-Treat (ITT) population included all cats randomized and who received at least one dose of study drug and had at least one postbaseline body weight measurement. The ITT population was utilized for secondary efficacy analyses.

3 | RESULTS

3.1 | Cats

A flow diagram of study enrollment is presented in Figure 1. The signalment, baseline weight, and underlying condition for the Safety and PP populations are presented in Table 1. Breed information is presented in Supporting Information Table S1. Dose of study drug (mg/kg) is presented in Supporting Information Table S2. A listing of concurrent medications is presented in Supporting Information Tables S3 and S4.

3.2 | Compliance

Compliance was assessed by owner entries in the Owner Diary Dose Log (see sample in the Supplemental Material). One hundred and sixty-six cats received all doses of study drug, 45 cats missed one dose (23 in the mirtazapine group and 22 in the placebo group), and 14 cats missed two doses (eight in the mirtazapine group and six in the placebo group). Of the 14 cats who missed two doses, three were consecutive missed doses and 11 were nonconsecutive missed doses. Three cats missed three doses (and two cats missed four doses). Cats that missed ≥ 20% of doses of study drug were not included in the PP population for analysis.

3.3 | Effectiveness

In the PP population, the mean percent change in body weight from Day 1 to Day 14 was +3.9% in the mirtazapine group and +0.4% in the placebo group ($p < 0.0001$; Figure 2, Table 2). The effectiveness of mirtazapine versus placebo in cats with and without preexisting kidney disease, those receiving glucocorticoids, and those undergoing treatment for hyperthyroidism was evaluated separately and is presented in Table 3 (Per Protocol Population). Data for the ITT population are provided in Supporting Information Figure S1; Tables S5 and S6.

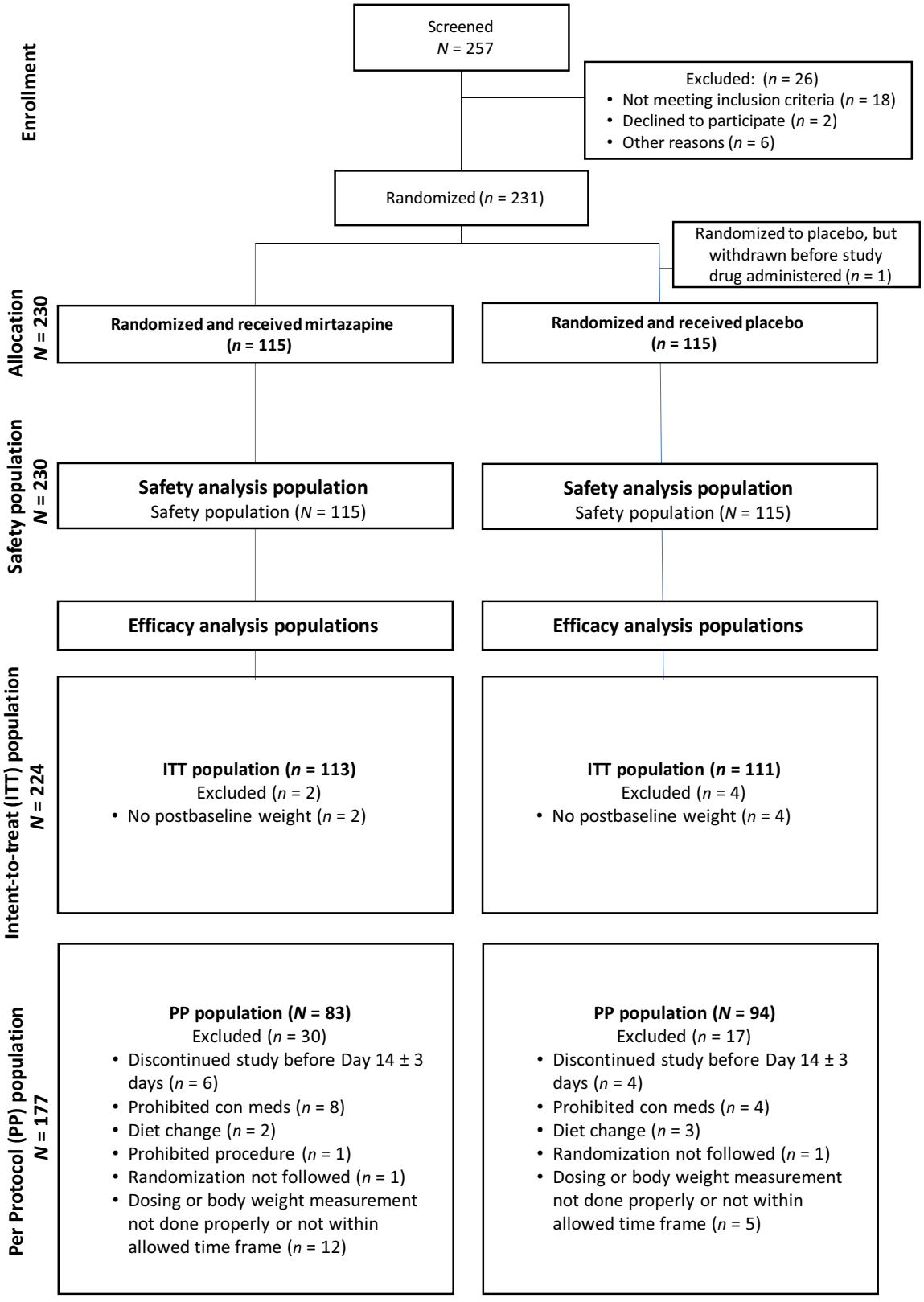

FIGURE 1 Disposition. Disposition is depicted in this figure. In this study, there were 257 cats screened; 26 were excluded and ultimately 231 were randomized to treatment. The Safety Population consisted of all cats randomized to either treatment group who received at least one dose of study drug. The Intent-to-Treat (ITT) population included all cats randomized and who received at least one dose of study drug and had at least one postbaseline body weight measurement. The Per Protocol (PP) population included all cats completing the study through and including Day 14. One cat with preexisting dental disease underwent dental prophylaxis, and this cat was not included in the effectiveness population [Colour figure can be viewed at wileyonlinelibrary.com]

3.4 | Safety

In the 230 cat Safety Population, no significant difference was seen in the percentage of cats in each group that were reported to have experienced an AE. A summary of AEs that occurred in greater than 5% of cats in the Safety Population is presented in Table 4. Incidence of behavioral adverse events (vocalization and hyperactivity) in the overall population as well as in subgroups based on weight and presence/absence of kidney disease are presented in Table 5.

Nine cats discontinued the study early due to a reported AE or serious adverse event including four placebo-treated cats and five mirtazapine-treated cats, regardless of causality to treatment. Eight cats were euthanized due to progression of their underlying disease, and one cat in the placebo group with preexisting cardiac disease, inflammatory bowel disease, and hyperthyroidism died at home. Of the three cats that were euthanized in the mirtazapine group, two had necropsies performed. In both cases, there were multiple findings related to underlying conditions and no causal relationship to mirtazapine was established.

3.5 | Clinical pathology

There were significant differences ($p < 0.10$) in several mean clinical pathology parameters at Day 14 compared to Day 1 (Supporting Information Table S7); however, each of these parameters was within the normal laboratory reference range and not considered clinically relevant except for BUN. The mean BUN concentration for the mirtazapine group was slightly above the reference range (LS mean 43.6 mg/dl, reference range 16–37 mg/dl) whereas the mean BUN concentration for the placebo group was within the normal range (LS mean 36.1 mg/dl). There was no significant difference in serum creatinine between mirtazapine- and placebo-treated cats.

TABLE 1 Study population demographics and baseline characteristics

	Safety population			Per Protocol population		
	Mirtazapine (*n* = 115)	Placebo (*n* = 115)	All (*n* = 230)	Mirtazapine (*n* = 83)	Placebo (*n* = 94)	All (*n* = 177)
Age, years						
Mean (±*SD*)	14.2 (3.7)	13.4 (3.0)	13.8 (3.4)	14.4 (3.5)	13.5 (2.9)	13.9 (3.2)
Median (range)	14.8 (2.8, 24.6)	13.9 (6.0, 20.6)	14.2 (2.8, 24.6)	14.9 (4.8, 24.6)	14.0 (6.0, 19.0)	14.3 (4.8, 24.6)
Sex, *n* (%)						
Male neutered	53 (46.1)	53 (46.1)	106 (46.1)	42 (50.6)	41 (43.6)	83 (46.9)
Female intact	1 (0.9)	0	1 (0.4)	1 (1.2)	(0.0)	1 (0.6)
Female spayed	61 (53.0)	62 (53.9)	123 (53.5)	40 (48.2)	53 (56.4)	93 (52.5)
Baseline weight (kg)						
Mean (±*SD*)	4.1 (1.2)	4.3 (1.0)	4.2 (1.1)	4.1 (1.1)	4.3 (1.0)	4.2 (1.1)
Median (range)	3.9 (2.1, 9.2)	4.2 (2.3, 7.5)	4.1 (2.1, 9.2)	3.9 (2.1, 7.0)	4.3 (2.3, 7.5)	4.2 (2.1, 7.5)
Preexisting conditions and relevant medical history at enrollment >10% in overall population						
	Safety population			**Per Protocol population**		
Description of condition[a]	**Mirtazapine (*n* = 115) *n* (%)**	**Placebo (*n* = 115) *n* (%)**	**All (*n* = 230) *n* (%)**	**Mirtazapine (*n* = 83) *n* (%)**	**Placebo (*n* = 94) *n* (%)**	**All (*n* = 177) *n* (%)**
Any preexisting condition	109 (94.8)	107 (93.0)	216 (93.9)	78 (94.0)	87 (92.6)	165 (93.2)
Kidney disease[b]	49 (42.6)	35 (30.4)	84 (36.5)	36 (43.4)	28 (29.8)	64 (36.2)
Vomiting	32 (27.8)	28 (24.3)	60 (26.1)	23 (27.7)	23 (24.5)	46 (26.0)
Hyperthyroidism	21 (18.3)	15 (13.0)	36 (15.7)	15 (18.1)	12 (12.8)	27 (15.3)
Dental disease	15 (13.0)	15 (13.0)	30 (13.0)	8 (9.6)	11 (11.7)	19 (10.7)
Heart murmur	15 (13.0)	13 (11.3)	28 (12.2)	10 (12.0)	11 (11.7)	21 (11.9)
Arthritis	15 (13.0)	11 (9.6)	26 (11.3)	9 (10.8)	10 (10.6)	19 (10.7)
Periodontal disorder	12 (10.4)	15 (13.0)	27 (11.7)	7 (8.4)	11 (11.7)	18 (10.2)
Elevated BUN	13 (11.3)	12 (10.4)	25 (10.9)	10 (12.0)	10 (10.6)	20 (11.3)

Note. BUN: blood urea nitrogen; kg: kilogram; *SD*: standard deviation.
[a]Cats could present with more than one preexisting condition. [b]Kidney disease was determined at the clinical investigator's discretion.

4 | DISCUSSION

The mirtazapine transdermal ointment used in this study is FDA approved for the management of weight loss in cats. As a new animal drug, the formulation is produced according to cGMP regulations to ensure quality, strength, purity, and stability. In this double-blind, placebo-controlled study, daily topical mirtazapine ointment applied to the inner pinna of the cat's ear effectively increased body weight within 14 days in client-owned cats experiencing unintended weight loss associated with a variety of underlying diseases.

To be included in this study, cats had to have a clinical history of decreased food consumption and ≥ 5% loss in body weight. Weight loss of ≥ 5% in a cat with comorbidities is considered clinically relevant and should signal the clinician to evaluate nutrition and health status (Brooks et al., 2014; Laflamme & Hannah, 2005). Although few studies have characterized appropriate weight gain in cats, recommendations for intentional weight loss indicate that the loss not exceed 1%–2% of body weight per week and that all changes should be slow and incremental (Brooks et al., 2014; Laflamme & Hannah, 2005). In this study, population of cats experiencing weight loss associated with various underlying conditions, the 3.9% weight gain observed in cats receiving topical mirtazapine for 14 consecutive days represents significant weight gain, that is, clinically relevant.

Incidence of behavioral AEs of vocalization (including crying and meowing) and hyperactivity (including pacing, restlessness, and sleeplessness) were significantly more common in mirtazapine-treated cats compared to placebo-treated cats but affected a small number of cats (Table 5). In a previous study, treatment with high-dose (3.75 mg) oral mirtazapine in healthy young cats was associated with an increase in behavior such as vocalization (Quimby, Gustafson, Samber, & Lunn, 2011b). Additionally, a previous retrospective study of orally administered mirtazapine demonstrated significant behavioral adverse effects with accidental administration of an entire 15 mg tablet (Ferguson et al., 2016). Conversely, the same mirtazapine transdermal ointment as studied here reported no significant change in animal behavior when applied topically to the inner pinna at approximately 5–10X the recommended dose (range 15.8–22.0 mg) to healthy cats for 28 days, (Avenatti, Buhles, Quimby, Labelle, & Poole, 2017). For cats experiencing either reduced elimination due to disease state or behavioral effects, dose alteration may be considered (Quimby & Lunn, 2013; Quimby et al., 2017).

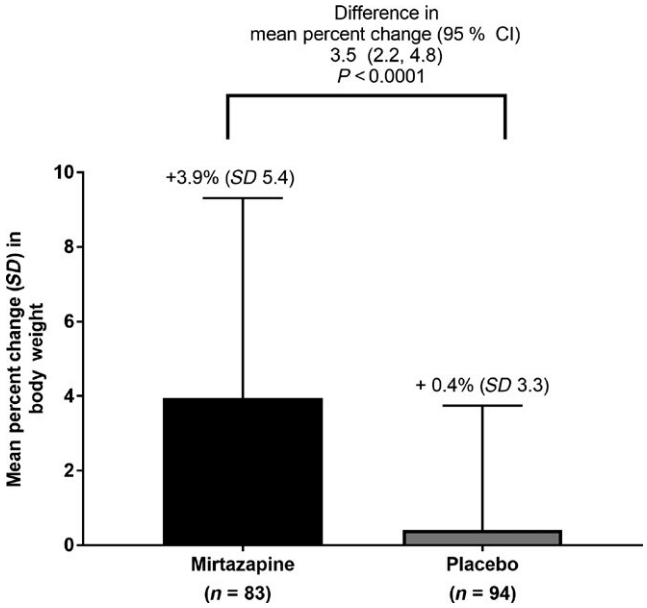

FIGURE 2 Mean Percent Change in Body Weight from Baseline (Per Protocol population). CI: confidence interval; *SD*: standard deviation. Application of transdermal mirtazapine ointment for 14 days resulted in a significant increase in body weight in comparison to placebo ($p < 0.0001$)

Cats weighing both ≤4 kg and >4 kg had significant body weight gain when treated with mirtazapine compared to placebo despite a wide range in starting body weights (2.1–9.2 kg). No significant difference was seen when incidence of behavioral AEs of vocalization and hyperactivity were compared between mirtazapine and placebo groups in the population of cats <4 kg (Table 5). These findings support the use of 2 mg/cat of mirtazapine transdermal ointment for all cats, irrespective of body weight at the start of treatment.

Cats with kidney disease have been shown to have delayed clearance of oral mirtazapine (Quimby, Gustafson, & Lunn, 2011a). In the present study, approximately 50% of cats in the mirtazapine group and 60% of cats in the placebo group were diagnosed with preexisting kidney disease at the discretion of the clinical investigator. The criteria used to diagnose renal disease were not specified

TABLE 2 Effectiveness outcomes

	Per Protocol population			
	Mirtazapine (*n* = 83)		Placebo (*n* = 94)	
	Mean (±*SD*)	Median (range)	Mean (±*SD*)	Median (range)
Baseline weight (kg)	4.09 (1.09)	3.9 (2.1, 7.0)	4.33 (1.01)	4.3 (2.3, 7.5)
Weight change (kg)	0.15 (0.22)	0.2 (−0.6, 0.5)	0.01 (0.14)	0 (−0.7, 0.3)
Weight change (%)	3.94 (5.37)	4.5 (−10.7, 16.7)	0.41 (3.33)	0 (−14.6, 7.7)

Note. *SD*: standard deviation.

TABLE 3 Sub-analysis of effect of body weight, kidney status or concurrent medications on body weight change (Per Protocol population)

Baseline characteristic	Placebo Mean percent change (±*SE*)	Mirtazapine Mean percent change (±*SE*)	Difference in mean percent change (95% CI)	*p*-Value
Weight				
≤4 kg	(*n* = 38) 0.97 (0.57)	(*n* = 42) 4.30 (0.86)	3.33 (1.23, 5.42)	0.0022
>4 kg	(*n* = 56) 0.03 (0.42)	(*n* = 41) 3.57 (0.82)	3.55 (1.86, 5.24)	<0.0001
Kidney status				
Kidney disease[a]	(*n* = 39) 0.65 (0.52)	(*n* = 43) 3.83 (0.87)	3.18 (1.11, 5.24)	0.0030
No kidney disease	(*n* = 55) 0.24 (0.46)	(*n* = 40) 4.07 (0.80)	3.83 (2.10, 5.55)	<0.0001
Glucocorticoids (PO)				
No glucocorticoids	(*n* = 89) 0.45 (0.34)	(*n* = 75) 4.12 (0.62)	3.66 (2.32, 5.00)	<0.0001
Methimazole				
No methimazole	(*n* = 88) 0.34 (0.36)	(*n* = 75) 3.88 (0.65)	3.54 (2.13, 4.94)	<0.0001
Glucocorticoids (PO) or methimazole				
No glucocorticoids or methimazole	(*n* = 84) 0.43 (0.36)	(*n* = 67) 4.07 (0.68)	3.64 (2.20, 5.08)	<0.0001

Note. CI: confidence interval; PO: oral; *SE*: standard error.
[a]Kidney disease was a diagnosis made at the discretion of the clinical investigators based on clinical presentation, physical examination and clinical pathology findings.

TABLE 4 Total incidence of adverse events occurring in > 5% in either treatment group (Safety population)

Adverse event	Mirtazapine (*n* = 115) *n* (%)	Placebo (*n* = 115) *n* (%)	*p*-Value[b]
Total incidence	70 (60.9)	75 (65.2)	0.4946
Vomiting	13 (11.3)	15 (13.0)	0.6867
Vocalization (including crying, meowing)	13 (11.3)	2 (1.7)	0.0033
Application site erythema[a]	12 (10.4)	20 (17.4)	0.1275
Hyperactivity (including pacing, restlessness, sleeplessness)	8 (7.0)	1 (0.9)	0.0354
Hematuria	7 (6.1)	1 (0.9)	0.0656
Diarrhea or soft stool	6 (5.2)	7 (6.1)	0.7752
Dehydration	6 (5.2)	5 (4.3)	0.7573
Elevated BUN (without creatinine)	6 (5.2)	0	0.0292
Heart murmur	5 (4.3)	7 (6.1)	0.5532
Lethargy (including depressed, sedation, weakness)	4 (3.5)	9 (7.8)	0.1534
Anemia	3 (2.6)	8 (7.0)	0.1224
Application site residue	3 (2.6)	8 (7.0)	0.1224
Application site crust/scab	3 (2.6)	6 (5.2)	0.4990
Application site dermatitis or irritation[a]	1 (0.9)	9 (7.8)	0.0097

[a]Application site dermatitis as defined by the clinical investigator and application site erythema as defined by reddening or discoloration not classified by the clinical investigator as dermatitis or irritation. [b]*p*-Value is based on a chi-square test. If any AE has expected counts less than 5 per treatment group, then the Fisher's exact test is used instead.

TABLE 5 Behavioral adverse events of vocalization and hyperactivity (Safety population, *n* = 230)

	Vocalization (including crying and meowing) *n* (%)	Hyperactivity (including pacing, restlessness, and sleeplessness) *n* (%)
All Cats (*n* = 230)		
Mirtazapine (*n* = 115)	13 (11.3)	8 (7.0)
Placebo (*n* = 115)	2 (1.7)	1 (0.9)
p-value	0.0033	0.0354
Cats with kidney disease[a]		
Mirtazapine (*n* = 58)	5 (8.6)	5 (8.6)
Placebo (*n* = 48)	2 (4.2)	1 (2.1)
p-value	0.4525	0.2181
Cats without kidney disease		
Mirtazapine (*n* = 57)	8 (14.0)	3 (5.3)
Placebo (*n* = 67)	0	0
p-value	0.0015	0.0943
Cats ≤4 kg		
Mirtazapine (*n* = 60)	7 (11.7)	5 (8.3)
Placebo (*n* = 50)	1 (2.0)	1 (2.0)
p-value	0.0693	0.2176
Cats > 4 kg		
Mirtazapine (*n* = 55)	6 (10.9)	3 (5.5)
Placebo (*n* = 65)	1 (1.5)	0
p-value	0.0468	0.0934

[a]Kidney disease was a diagnosis made at the discretion of the clinical investigators based on clinical presentation, physical examination and clinical pathology findings.

by the study protocol and is a limitation of the study. Both populations of cats (those with and without kidney disease) demonstrated significant body weight gain with the application of topical mirtazapine compared to placebo-treated cats (Table 3 and Supporting Information Table S6). This study was not designed to assess the effect of clearance by the kidneys on the safety of mirtazapine in cats with suspected kidney disease. However, no significant difference was seen when incidence of behavioral AEs of vocalization and hyperactivity were compared between mirtazapine and placebo groups in the population of cats with kidney disease (Table 5).

Mirtazapine transdermal ointment applied topically at 2 mg/cat was well tolerated both locally and systemically in this study. The differences found in clinical pathology parameters between placebo and mirtazapine-treated cats in clinical pathology parameters were not considered clinically relevant. The elevated BUN levels observed in the mirtazapine-treated cats could be explained by the increased incidence of kidney disease as diagnosed by the clinical investigators in the mirtazapine group at the time of enrollment. The most common finding in both mirtazapine and placebo groups was erythema of the pinna. Other signs of irritation at the site of application included crusting and scabbing which were also more frequent in the control group.

In the diverse clinical population of cats with unintended weight loss seen in veterinary practices, there can be a variety of concurrent medications administered for underlying diseases. While this study was not designed to assess drug interactions, use of concurrent medications (including glucocorticoids and antithyroid medications) did not appear to impact the safety or efficacy of mirtazapine transdermal ointment (Table 3).

The inner surface of the pinna was chosen as the application site due to ease of application. It is less haired, highly vascular, and thinner than other anatomical locations which may improve transdermal absorption (Hill et al., 2015) and is a common site of application for other topical ointments in the cat. (Bennett, Papich, Hoenig, Fettman, & Lappin, 2005; Benson et al., 2017; Ciribassi et al., 2003; Hill et al., 2011; Mealey et al., 2004; Miller, Schick, Boothe, & Lewis, 2014).

The mirtazapine transdermal formulation used in this study was supplied in a 5 g tube and the dose was a 1.5-inch ribbon (2 mg mirtazapine) per cat, which is approximately 0.1 ml. As with any topical medication, there is a possible risk of exposure to family members or other individuals handling the cat. Visual inspection to determine how quickly the ointment was absorbed was not performed in this study. However, in a previous study conducted to evaluate dislodgeable residues of the mirtazapine transdermal ointment following repeated application, it was found that for body petting, dislodgeable residues were very low (lower than 1.0%) from 0.5 hr after the last application (Williams, Quimby, Poole, & Lee, 2017). Therefore, body petting is unlikely to result in

significant human mirtazapine exposure, but should be avoided for 2 hr following application.

Although cats can groom their ears, they cannot directly lick their inner pinna which may allow the ointment to remain in contact with the skin for a longer period, thus improving absorption and minimizing potential oral ingestion of the medication. Pharmacokinetic studies have been performed with this formulation of mirtazapine ointment in cats with e-collars and have demonstrated transdermal absorption without oral ingestion (Buhles et al., 2018). However, as cats in the present study did not wear e-collars, some degree of oral ingestion may have occurred in addition to transdermal absorption.

In order to be included in PP population, cats had to have 80% compliance. For cats that missed 1–2 doses, the effect on serum concentrations is unknown as the pharmacokinetic/pharmacodynamic relationship for transdermal mirtazapine has not been clearly established and clinical effectiveness may not be linear to plasma concentrations. A statistically significant increase in weight was still seen in the mirtazapine group regardless of an occasional missed dose in a small number of cats.

It is expected that cats with chronic disease associated with dysrexia will need therapy beyond 14 days to maintain body weight. A limitation of this study is that it did not evaluate the long-term effect of weight gain with mirtazapine. Regardless, short-term use would be an important aspect of clinical management in ill cats as nutritional intake and support of body weight is imperative while an accurate diagnosis and treatment plan is developed to avoid negative sequela such as immune dysregulation, multi-organ failure, and ultimately, decreased survival time. Cats in this study presented with a variety of underlying diseases which may be perceived as a limitation. However, these results support use of mirtazapine transdermal ointment to increase body weight in cats with various diseases associated with unintended weight loss. The client-owned cats studied are representative of what is seen in veterinary practices.

In this study, mirtazapine transdermal ointment applied topically to the inner surface of the pinna was effective for increasing body weight following 14 days of daily treatment in cats with unintended weight loss associated with a variety of underlying diseases. Topical application of mirtazapine transdermal ointment was well tolerated both locally and systemically.

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CONFLICTS OF INTEREST

Jessica M. Quimby is a consultant for Kindred Biosciences, Inc, and consulted on the data and assisted with manuscript preparation.

Melinda Poole and Tianhua Hu are employees of Kindred Biosciences, Inc.

William Buhles and Daizie Labelle are former employees of Kindred Biosciences, Inc.

AUTHOR CONTRIBUTIONS

Hypothesis generation and experimental design: MP, DL, WB. Organizing and conducting the experiments: DL, WB. Interpreting and analyzing the results: MP, JMQ, TH, DL, WB. Writing and revising the manuscript: MP, JMQ, TH, DL, WB. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for author contributions for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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