Effects of reconcile (fluoxetine) chewable tablets plus behavior management for canine separation anxiety

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Effects of Reconcile (Fluoxetine) Chewable Tablets Plus Behavior Management for Canine Separation Anxiety*

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CLINICAL RELEVANCE

Canine separation anxiety is a common behavioral problem presented to veterinarians. Associated behaviors are distressing to both dog and owner, have the potential to disrupt the human–animal bond, and may lead to euthanasia. The results of this study demonstrate the clinical efficacy and safety of Reconcile chewable tablets (fluoxetine, 1 to 2 mg/kg/day [0.45 to 0.91 mg/lb/day]), in conjunction with behavior management, for the treatment of canine separation anxiety. The beef-flavored chewable tablets were palatable to treated dogs and easy to administer. This study provides valuable information about an effective separation anxiety treatment plan that combines the use of Reconcile with behavior modification.

■ INTRODUCTION

Canine separation anxiety (SA) occurs when a dog is separated from or denied access to familiar individuals. It is the second most frequently recorded behavioral disorder (after aggression) reported in dogs presented to referral behavior practices.[1,2] A survey of gonadectomized dogs adopted from an animal shelter in New York found a prevalence of SA ranging from 14.2% to 18.7%, a proportion similar to that identified in a survey of veterinarians in the United Kingdom (15%).[3,4] The major manifestations of SA are destructiveness or rearranging behavior and excessive vocalization. Other reported signs include inappropriate elimination in an otherwise properly housetrained pet, excessive salivation, depressed or withdrawn appearance, and restlessness manifested as repetitive activities such as pacing, circling, overgrooming, and self-mutilation.[1,5–7]

Although this disorder does not typically pose an immediate serious medical risk to affected dogs, there is the potential for grave outcomes in that owners may relinquish the pet (e.g., place the dog in an animal shelter) or request euthanasia. In fact, behavioral problems, including those related to SA, represent the most common reason given for pet relinquishment at humane shelters.[1,8–11]

SA is indicative of distress,[12] and treatment should address the anxiety problem underlying the demonstrated behaviors.[6,7] Treatment approaches include design and implementation of behavior management programs (BMPs), which may be combined with appropriate pharmacologic intervention to enhance the patient's ability to respond to a BMP.[1,3,13,14] Pharmacologic interventions typically involve drugs that enhance serotonin levels at presynaptic axon terminals, which include the tricyclic antidepressant clomipramine and selective serotonin reuptake inhibitors, such as fluoxetine hydrochloride.[7,15] However, to date, there have been no published placebo-controlled studies to allow a clinical assessment of the potential contribution of selective serotonin reuptake inhibitors in the treatment of SA.[7,16,17]

The purpose of this study was to compare the effectiveness and safety of treatment with beef-flavored fluoxetine chewable tablets (Reconcile, Lilly Animal Health), developed specifically for veterinary use, with that of a placebo, when used in conjunction with a BMP to improve signs of SA in client-owned dogs. The dose of fluoxetine used in the study, 1 to 2 mg/kg/day (0.45 to 0.91 mg/lb/day), was selected based on studies and clinical experience reported in the

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Inclusion and Exclusion Criteria for Study Enrollment of Dogs

Inclusion Criteria

- ≥6 months of age
- In acceptable physical condition
- With present owner for at least 1 month
- Housetrained
- Not pregnant or lactating; not used for breeding
- At least four separation anxiety–related departures/week
- No clinical signs of seizures or aggression
- At least one measurable SA sign (i.e., destructive/rearranging behavior, inappropriate urination or defecation, hypersalivation) exhibited for ≥1 month
- Only one dog in household exhibits signs of SA, and those signs can be clearly attributed to affected dog
- No plan to change household routine or change ownership in 60 days following enrollment
- No plan to breed dog during 60 days following enrollment
- No elective surgeries or vaccines scheduled 30 days before and 60 days after enrollment
- Allowable routine medications (heartworm, flea prophylaxis) must be started 30 days before enrollment and continue as prescribed during the trial

Exclusion Criteria

- Conditions identified in inclusion criteria not met
- Current treatment with psychoactive medication (must be discontinued 30 days before enrollment)
- Complicating medical disorder, including history of seizures
- History of aggressive behavior that put humans at risk for physical injury
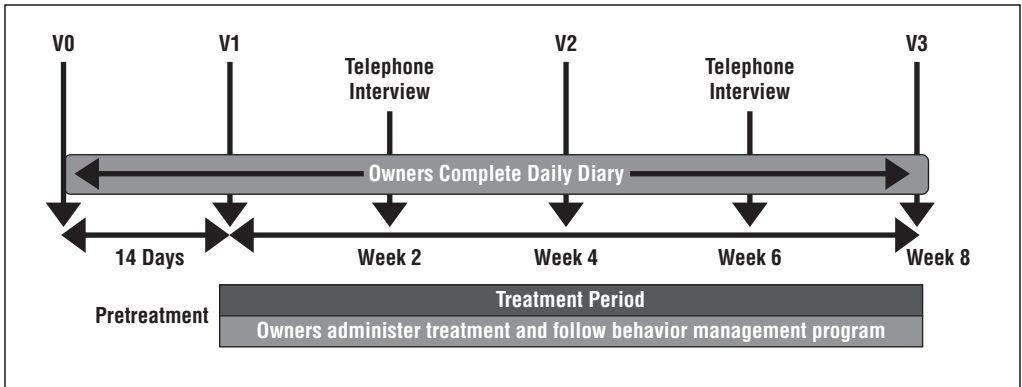
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literature.[15,18–22] The primary effectiveness measure was the incidence of dogs demonstrating improvement in the owner-provided overall severity score (OSS) for SA behaviors. A secondary measure was palatability (acceptance) of the chewable formulation. Safety was assessed by evaluation of adverse events (AEs), clinical chemistry, and hematology.

■ MATERIALS AND METHODS
Study Procedure

This was a multiple-center (35 participating veterinary clinics in the United States and Canada), placebo-controlled, double-blind, parallel-arm study. Dogs were recruited into the study based on the occurrence of one or more specific SA behaviors expressed when the dog was left alone, including destructive/rearranging behavior, inappropriate urination, inappropriate defecation, and excessive salivation. At the study enrollment visit (V0), dogs were provisionally enrolled based on a veterinarian's determination of their suitability. This decision followed an evaluation that included a prescreening questionnaire (completed by the owner), a complete history, and a physical examination (with collection of blood samples). Dogs were accepted for enrollment when the veterinarian was satisfied that the defined inclusion and exclusion criteria were met (see box, left) and informed consent was obtained from the owner.

At V0, the owner and veterinarian identified up to four separation anxiety–related departures (SARDs) that the owner identified as triggers for SA behaviors and that could be tracked by the owner. For example, SARDs for a specific owner might include departures for work, departures for evening meetings, and trips to the store. For each of 14 days following V0, the owner recorded SA behaviors associated with the identified SARDs and any observations of AEs. At the end of each week (days

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Figure 1. *Schematic of key activities. V0: prestudy visit; V1: baseline visit and study admission; V2: visit 4 weeks after starting treatment with Reconcile or placebo; V3: final visit. Owners completed daily records of separation anxiety–related behaviors and completed weekly score sheets of the severity of overall and individual behaviors.*

7 and 14), the owner assigned an OSS (0 = absent; 1 = mild; 2 = moderate; 3 = severe) for the dog's overall SA behaviors. The same scoring system was used to score the severity of the dog's individual SA behaviors, such as destructive behavior (including rearranging behaviors), excessive vocalization, inappropriate urination, inappropriate defecation, excess salivation, restlessness, shaking or shivering, excessive licking or grooming, and appearing depressed. When the owner returned for the second study visit (V1), 14 days after V0, the veterinarian collected the owner's diary information; if a diagnosis of SA was confirmed by a board-certified veterinary behaviorist, the dog was entered into the study and the test article was dispensed to the owner to begin daily treatment (Figure 1). The owner was also instructed regarding the BMP to be followed for the duration of the study (see box on page 22).

During the treatment period, owners continued to record SARDs and the behaviors that the dog exhibited as a result of the departure. Owners also recorded in their diary (Owner's Daily Diary) any problems or unusual behaviors that they observed. All such observations were assessed as mild (1), moderate (2), or se-

vere (3) and were considered owner-reported AEs. The owner also recorded the dog's acceptance of the chewable tablet. The veterinarian, who was blinded regarding treatment group assignment, called the owner for a progress check after 2 and 6 weeks of treatment; physical examinations were conducted after 4 weeks (at V2) and at the final visit (V3, which occurred after 8 weeks of treatment). At each of these visits, the veterinarian reviewed the owner-recorded data for completeness, conducted a physical examination of the dog, and recorded the dog's body weight; at the final visit, blood samples were collected for serum chemistry analysis.

Animals

A total of 242 client-owned dogs were randomized into the study. Dogs entering the study met key inclusion and exclusion criteria (see box on page 20). Inclusion criteria included acceptable physical condition and at least one of the following SA behaviors exhibited for at least 1 month: destructive/rearranging behavior, inappropriate urination, inappropriate defecation, or excessive salivation; absence of apparent medical condition(s) or other behav-

ior disorder(s) (e.g., barrier anxiety) that could contribute to the above behaviors; and the absence of any medical regimens that could affect SA assessment. For any dog crated for control of SA behavior(s), crating was to continue throughout the study. The diagnosis of SA must have been confirmed by a board-certified veterinary behaviorist. Exclusion criteria included a history of seizures, display of any ag-gressive behavior that put humans at risk for physical injury, or treatment with psychoactive medications (including tricyclic antidepressants [i.e., clomipramine or amitriptyline], phenothiazines [including acepromazine], monoamine oxidase inhibitors [i.e., selegiline or L-deprenyl], serotonin reuptake inhibitors [i.e., fluoxetine or fluvoxamine], propranolol, and St. John's Wort [*Hypericum perforatum*]) within 30 days of the start of the prestudy period.

Treatments

On entry into the study, dogs were randomly assigned to treatment groups within blocks, with each block containing one dog from each of the two treatment groups, consisting of fluoxetine- or placebo-treated dogs. A separate randomization was generated for each veterinarian. Dogs in the fluoxetine group received Reconcile chewable tablets at a fluoxetine dosage of 1 to 2 mg/kg (0.45 to 0.91 mg/lb) once daily (Table 1). Placebo tablets matched the Reconcile tablets in size, shape, odor, and color. All tablets were formulated as beef-flavored chewables. The prandial state of the dog at the time of dosing was not specified; thus, owners could administer the tablet with or without food. As an assessment of palatability, owners were instructed to offer the tablet to their dogs and record whether the dog voluntarily ingested it within 3 minutes. If the dog rejected the tablet, it could then be offered in food or administered directly. Study medication was to be administered orally, once daily, for 56 days. Study veterinarians, monitors, and dog owners were blinded to the treatment group assignments until completion of the study.

Measurements

The incidence of improved OSS (compared with baseline scores) was the primary measure of effectiveness. The incidence of improvement

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was also calculated for the specified behaviors of inappropriate urination, inappropriate defecation, destructive/rearranging behavior, excessive salivation, excessive licking or grooming, excessive vocalization, shaking or shivering, restlessness, and depression. The "Effectiveness Evaluable Population" consisted of all dogs administered the test article for which there was at least 6 weeks of study data (2 weeks of pretreatment data and 4 weeks of treatment data) and an average pretreatment OSS of at least 1. The "Safety Evaluable Population" consisted of all dogs that were randomized into the study and received at least one dose (or a portion of a dose) of study medication (Reconcile or placebo).

Calculations

Scoring of behaviors was completed using a four-point scale:

0 = Absent

1 = Mild

2 = Moderate

3 = Severe

A binary variable was calculated to indicate whether there was improvement in a dog's OSS and individual behavior scores, with a value of 1 indicating improvement. This variable was calculated on an individual-dog basis for each treatment-period week as follows:

1 = Weekly score at least 1 point less than the average of the two pretreatment scores recorded at the end of each week of the pretreatment period

0 = Weekly score less than 1 point less than the average of the two pretreatment scores

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TABLE 1. Dosing Information for Dogs Receiving Reconcile (Fluoxetine) Chewable Tablets (1–2 mg/kg/day)

Dog Weight			Tablet
(kg)	(lb)	Tablet Size (mg)	Strength (mg)
2–8[a]	4.4–17.6[a]	200	8
>8–16	>17.6–35.2	400	16
>16–32	>35.2–70.4	800	32
>32–64	>70.4–140.8	1,600	64

[a]Dogs weighing 2–4 kg (4.4–8.8 lb) were administered one-half of an 8-mg tablet to provide a dose of 1–2 mg/kg (2.2–4.4 mg/lb). The tablets are not scored, precluding general administration to dogs less than 4 kg.

The relative frequencies of SA behaviors were calculated for each dog by dividing the number of SARDs resulting in SA behavior by the total number of SARDs. This variable, measuring the percentage of departures that resulted in SA behavior, was calculated as an average for the 2 weeks pretreatment and weekly for each behavior and the absence of any behavior for each treatment week.

The rate of change in SA behavior scores was calculated for individual dogs for OSS and individual SA behaviors using the following regression model:

$$S_d = \alpha + \beta d$$

where S_d is the subjective score obtained from the questionnaire on specified day (day d) of the study, and the slope, β, is the rate of change in the subjective score. All data collected during the study (2-week pretreatment period plus treatment weeks 1 through 8) were used to calculate the rate of change. The average of the scores from the 2-week pretreatment period was calculated before performing the regression analysis.

Statistical Analyses

The study was powered for the primary variable, incidence of improved SA OSS. Power

TABLE 2. Characteristics of Dogs in the Study		
Factor	*Reconcile*	*Placebo*
No. of dogs (allocated)	122	120
Effectiveness Evaluable Population[a]	101	96
Mean duration of ownership (mo)	37.3	34.8
Mean age at randomization (yr)	4.0	3.6
Sex distribution		
Male	54%	44%
Female	46%	56%
Mean body weight (kg [lb])	19.7 (43.3)	20.1 (44.2)
Dogs crated	12.8%	11.6%
Early withdrawal from study	11	17
SA-related behaviors in the pretreatment period[b]		
Destructive/rearranging	82.2%	78.1%
Inappropriate urination	31.7%	38.5%
Inappropriate defecation	22.8%	32.3%
Excessive salivation	38.6%	28.1%
Owner-reported adverse events		
In the pretreatment period	54.7%	64.3%
During the treatment period	81.2%	72.3%
Investigator-reported adverse events		
In the pretreatment period	66.7%	70.5%
During the treatment period	58.1%	42.9%

[a]The Effectiveness Evaluable Population (*N* = 197) consisted of all dogs administered the test article with at least 6 weeks of study data (2 weeks of pretreatment data and 4 weeks of treatment data) and average pretreatment overall severity score ≥1.
[b]From the Effectiveness Evaluable Population.

calculations were based on a generalized linear mixed model for logistic regression. To account for veterinarian × treatment interaction, an overdispersion factor of 10% was applied to the binomial variation. Based on 100 dogs/group, this study had approximately 80% power to detect a difference of 25% between Reconcile and placebo in the incidence of improved OSS. There were no adjustments for missing data (e.g., no observations carried forward). Statistical testing was performed at the .050 level using two-tailed tests. The binary variables for improved OSS and individual SA behaviors were analyzed using generalized linear mixed models with treatment as a fixed effect and site and site × treatment interaction as random effects. Separate analyses were conducted for each treatment-period week. The relative frequencies of SA signs were analyzed using generalized linear mixed models, using the method described above except that average pretreatment score was added as a covariate. The rate of change in OSS and individual SA behavior scores were analyzed using linear mixed models. The objective SARD relative frequency variables for each behavior and for the absence of any SA behavior were used to confirm the subjective SA severity scores (OSS and the individual SA behavior scores) following Hewson et al.[23] Based on the subjective scores for each treatment-period week, dogs were assigned to one of three groups:

- **Better:** Weekly score at least 1 point less than the average pretreatment score
- **Same:** Weekly score within 0.5 points of the average pretreatment score
- **Worse:** Weekly score at least 1 point higher than the average pretreatment score

For objective relative frequency data for each dog, a ratio was calculated for OSS and indi-

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TABLE 3. Selected Normal Hematology and Blood Chemistry Ranges and Mean Changes That Occurred During the Trial in Dogs Treated Daily with Reconcile or with Placebo

Parameter	Normal Range	Mean Change (SD)	
		Reconcile	Placebo
Erythrocyte count (×10⁶/μl)	4.95–7.87	0.13 (0.57)	–0.00 (0.49)
Total leukocytes (×10³/μl)	5.0–14.1	–0.26 (2.58)	0.15 (2.25)
Blood urea nitrogen (mg/dl)	8–28	–0.58 (5.48)	0.5 (5.74)
Creatinine (mg/dl)	0.5–1.7	0.04 (0.16)	0.04 (0.13)
Alkaline phosphatase (IU/L)	36–300	–8.42 (20.28)	–4.14 (20.01)
Alanine aminotransferase (IU/L)	10–109	1.64 (36.61)	1.87 (19.58)
Total bilirubin (mg/dl)	0–0.3	0.00 (0.05)	0.01 (0.10)
Total protein (g/dl)	5.4–7.5	–0.09 (0.32)	0.06 (0.36)
γ-Glutamyl transpeptidase (IU/L)	2–16	–1.12 (11.35)	1.51 (17.53)

vidual behaviors using the average number of SA behaviors exhibited per SARD for each 7-day period divided by the average number of behaviors for the 14-day pretreatment period. For each of the three groups (better, same, worse), the null hypothesis (i.e., median ratio = 1) was tested using the sign test. For the OSS and for each SA behavior, an indication of positive confirmation was determined based on the following:

- **For outcome = "better":** Median ratio < 1 and $P \leq .050$
- **For outcome = "same":** $P > .050$
- **For outcome = "worse":** Median ratio > 1 and $P \leq .050$

For safety, rates of treatment-emergent AEs in Reconcile- and placebo-treated dogs were compared with Fisher's exact test.

■ RESULTS

All dogs enrolled in the study were at least 6 months old (average: approximately 4 years), and both genders were approximately equally represented (6% of females and 13% of males were intact) (Table 2). The majority (64%) of dogs in the Effectiveness Evaluable Population were purebred, and no breed was predominant. Weights ranged from 2.7 to 58.4 kg (5.9 to 128.5 lb). There were 197 dogs in the Effectiveness Evaluable Population, consisting of 101 dogs given Reconcile and 96 given placebo. The most common manifestation of SA in trial dogs was destructive/rearranging behavior, occurring in 82% and 78% of dogs allocated to the Reconcile and placebo groups, respectively. Physical and laboratory evaluations were performed for all dogs that received Reconcile or placebo and compared with values collected before treatment. The mean pre- and posttreatment hematology and serum chemistry values were similar for Reconcile- and placebo-treated dogs, and there were no remarkable changes in these values between the initial and final samplings (Table 3). The average percentage of times the dogs freely accepted the study medication was 85.4% for placebo and 70.5% for Reconcile beef-flavored chewable tablets.
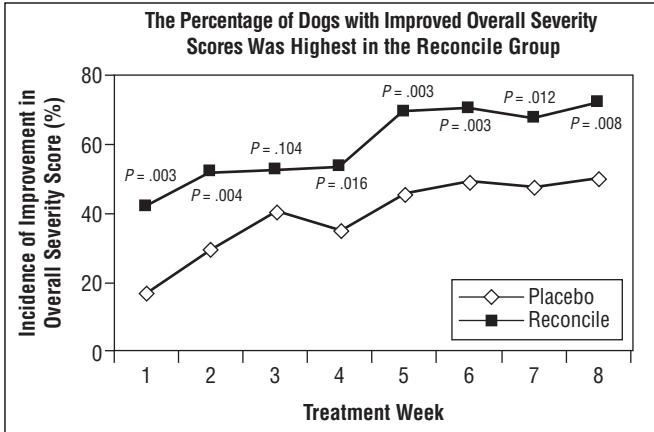
Figure 2. *Incidence of improvement in overall separation anxiety–related severity scores relative to baseline for dogs treated daily with either Reconcile or placebo; both treatment regimens were administered in conjunction with behavior modification.*

Changes in SA Scores

For the Effectiveness Evaluable Population, the incidence of improved scores generally increased over time in each treatment group. The percentage of dogs with improved OSS was higher among dogs treated with Reconcile chewable tablets than among placebo dogs at each week, with significant differences at week 1 (42% for Reconcile versus 17% for placebo; $P = .003$) and for all weeks ($P \leq .016$) except week 3 ($P = .104$) (Figure 2).

At 8 weeks after treatment, 72% of dogs treated with Reconcile had shown improvement in OSS compared with 50% of placebo-treated dogs. Trends in improvement were similar regardless of crating status, with greater OSS improvement among dogs receiving Reconcile compared with controls. For destructive behavior, excessive vocalization, and restlessness, the percentage of dogs with improved behavior was higher among dogs that received Reconcile compared with dogs receiving placebo at each week, with significant differences ($P \leq .05$) at all weeks except for destructive be-

havior at week 3 and excessive vocalization at week 1 (Figures 3 and 4).

For inappropriate defecation, excessive licking or grooming, shaking or shivering, depression, and inappropriate urination, the incidence of improvement was consistently higher for dogs receiving Reconcile than for placebo-treated dogs. For depression, differences between groups were statistically significant at treatment week 8 ($P = .048$). For excessive salivation, there were no apparent differences between groups.

Although the relative frequency of departures that did not result in any SA behaviors was statistically similar for both groups, there were significant reductions in the group treated with Reconcile compared with the placebo group in destructive/rearranging behavior ($P \leq .035$; weeks 1, 2, 4, 5, and 7), excessive vocalization ($P \leq .043$; weeks 3, 4, 6, 7, and 8), and restlessness ($P \leq .020$; weeks 2 and 7). There were no significant differences between the two groups at any week in the relative frequency of departures that resulted in inappropriate urination or defecation, excessive salivation, excessive licking or grooming, shaking or shivering, or depression.

The weekly rate of decline in OSS was significantly more rapid for Reconcile compared with placebo ($P = .042$). For individual behaviors, the weekly rate of change in severity scores was significantly more rapid for Reconcile compared with placebo for depression ($P = .035$) and excessive vocalization ($P = .003$), but not for any of the other SA behaviors.
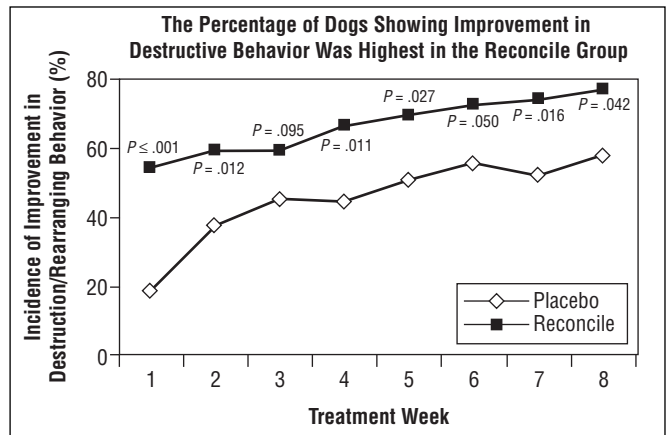
Confirmation of Subjective Scores

For dogs classified as "better," consistency

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between objective and subjective owner assessment of relative frequency of SARDs, and of all individual behaviors except inappropriate elimination at week 1, confirmed construct validity. For dogs classified as "same," construct validity was demonstrated for OSS for 2 of the 8 treatment weeks, for excessive salivation and excessive vocalization for each week, for inappropriate urination for 7 weeks, for depression for 6 weeks, for restlessness and shaking/shivering for 5 weeks, for destructive or rearranging behavior and inappropriate defecation for 4 weeks, and for excessive licking or grooming for 2 weeks. For dogs classified as "worse," construct validity was not demonstrated for OSS or any individual behavior except excessive vocalization at treatment week 1; the inability to demonstrate construct validity for "worse" was primarily related to the small number of dogs classified as "worse," limiting the ability to obtain statistical significance.

Adverse Events

There were 229 dogs in the Safety Evaluable Population (Table 4). The most commonly reported AE, which occurred at a significantly higher rate in dogs that received Reconcile, was "calm/lethargy/depression."[a] The category was applied to 53 dogs (45%) that received Recon-
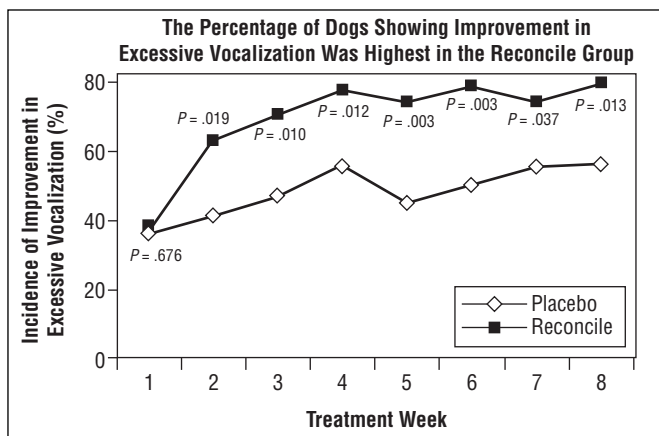

Figure 3. *Incidence of improvement in separation anxiety–related severity scores relative to baseline for destruction/rearranging behavior for dogs treated daily with either Reconcile or placebo; both treatment regimens were administered in conjunction with behavior modification.*

cile and 19 (17%) that received placebo ($P = .019$; Table 4). Most of these events resolved uneventfully, usually within 1 to 2 weeks.

Another AE that occurred at a significantly higher rate in dogs treated with Reconcile was anorexia/decreased appetite, for which the majority of episodes (12 of 19; 63%) lasted longer than 8 days; of these 12 events, eight (67%) began within the first 8 days of initiating treatment. Four of seven occurrences of anorexia/decreased appetite (57%) that lasted less than 8 days began within the first 8 days of treatment. Overall, 32% of the Reconcile-treated dogs and 16% of the placebo-treated dogs lost 5% or more of initial body weight. Excessive vocalization (including whining) was also significantly higher in the Reconcile-treated dogs. Destructive/rearranging behavior was reported to occur as an AE significantly more often in placebo-treated dogs.

In 25 dogs (20 that received Reconcile and five that received placebo), a reduction in dose was implemented to resolve observed AEs of anorexia and vomiting and owner descriptions

[a]Owner's Daily Diaries were reviewed in detail, separately from SA behaviors, to identify possible AEs. In some cases, there was overlap between the owner AE descriptors and the SA behavior descriptors. Hence, one or more of the terms "calm," "lethargy," and "depression" were used by owners to describe an AE based on their observed change in the dog's behavior. Such observations have accordingly been recorded as an owner-reported AE.

Figure 4. *Incidence of improvement in separation anxiety–related severity scores relative to baseline for excessive vocalization behavior for dogs treated daily with either Reconcile or placebo; both treatment regimens were administered in conjunction with behavior modification.*

dog's seizure activity increased from single seizures to cluster seizures, despite increasing doses of phenobarbital and the addition of oral potassium bromide and rectal diazepam. The third of these seizure dogs experienced one seizure 24 days after the start of therapy; no anticonvulsant therapy was initiated, and no further seizures were reported. The placebo-treated dog experienced one seizure 35 days after the start of placebo administration; no anticonvulsant therapy was initiated, and no further seizures were reported.

of depression. The dose reduction resulted in elimination of the AE or in a reduction of its severity. Resumption of the full dose of fluoxetine was uneventful in approximately half of these dogs. The effects that recurred in the remaining dogs were generally less severe, with the exception of one dog in which a second dose reduction was necessary.

There were four serious AEs reported: three seizures in dogs that received Reconcile and one seizure in a placebo-treated dog. One of the three dogs treated with Reconcile experienced two seizures 10 days after the end of fluoxetine therapy; despite escalating phenobarbital doses, the seizures continued and this dog died in status epilepticus approximately 6 months after the first seizure. The second of the three dogs treated with Reconcile had suffered a seizure immediately after experiencing head trauma approximately 1.5 years before study enrollment. This dog did not experience any additional seizures until 45 days after the end of therapy with fluoxetine. During the 1.5-year period since that second seizure, the

■ DISCUSSION

This study demonstrates that dogs with SA treated once daily with Reconcile beef-flavored chewable tablets (fluoxetine dose of 1 to 2 mg/kg [0.45 to 0.91 mg/lb]) had a greater incidence of improvement in OSS compared with dogs treated with placebo when the treatments were administered in conjunction with a BMP. Approximately 42% of dogs treated with Reconcile improved within 1 week of treatment initiation, which was significantly greater (P = .003) than the 17% of placebo-treated dogs that improved within 1 week. Both Reconcile and placebo-treated dogs continued to improve over the course of the 8-week treatment period; at the end of the study, dogs treated with Reconcile demonstrated a significant (P = .008) and substantial improvement in OSS compared with placebo-treated dogs (72% improvement in OSS versus 50%, respectively). For all weeks except week 3, the incidence of improvement in OSS was significantly greater with Reconcile than with placebo.

Palatability, measured by the percentage of dogs that freely accepted Reconcile, exceeded

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70%. The ease with which owners were able to administer the medication is important in helping to reduce a barrier to compliance and demonstrates the value of this beef-flavored chewable for inclusion in a canine SA management plan.

SA-associated behaviors, such as destructiveness, are distressing and costly to owners and can disrupt the human–animal bond. Rapid improvement in SA behavior can therefore be especially important if the patient is to be saved from relinquishment or even euthanasia. To that end, it is extremely relevant that the rate of decrease in severity of the overall SA score was more rapid when Reconcile was administered compared with placebo, with a significance difference ($P = .003$) developing within the first week of the study. Between-group differences were then maintained throughout the duration of treatment. Similarly, individual SA behaviors benefited rapidly from treatment with Reconcile, with early significant differences seen between groups for destructive behavior, excessive vocalization, and restlessness ($P \leq .019$). For other behaviors, including inappropriate defecation, excessive licking or grooming, shaking or shivering, depression, and inappropriate urination, the improvement over placebo-treated dogs was less marked and generally did not achieve significance. This may be associated with the relative lower incidence of these behaviors and the re-

TABLE 4. Treatment-Emergent Adverse Events Occurring in ≥3% of Dogs in a Group[a]

Adverse Event	Reconcile (n = 117) (No.)	(%)	Placebo (n = 112) (No.)	(%)
Calm/lethargy/depression[b]	53	45.3	19	17.0
Anorexia/decreased appetite	34	29.1	12	10.7
Shaking/shivering/tremor	19	16.2	4	3.6
Vomiting	17	14.5	10	8.9
Restlessness/hyperactivity	16	13.7	7	6.3
Excessive vocalization (including whining)	13	11.1	7	6.3
Anxiety	8	6.8	8	7.1
Diarrhea[c]	7	6.0	7	6.3
Attachment to owner	6	5.1	3	2.7
Disruptive/destructive behavior	6	5.1	8	7.1
Aggression	5	4.3	9	8.0
Excessive licking	5	4.3	6	5.4
Otitis externa	5	4.3	1	0.9
Tartar	5	4.3	5	4.5
Disorientation/confusion	4	3.4	1	0.9
Submissive/fearful behavior	4	3.4	1	0.9
Disobedience	4	3.4	2	1.8
Incoordination	4	3.4	0	0.0
Inappropriate defecation	3	2.6	5	4.5

[a]An adverse event was considered treatment emergent if the maximum severity score recorded during the treatment period was greater than the maximum severity score during the pretreatment period or if the event was recorded only during the treatment period.
[b]Dog-owner descriptions of posttreatment attitudinal changes ranged from their dog being calm to sleeping more than usual to appearing lethargic to being depressed. These terms were combined for overall analysis of study results.
[c]Includes diarrhea, soft stool, and bloody diarrhea.

sulting lack of statistical power.

The frequency of AEs was generally similar for fluoxetine- and placebo-treated dogs. For

some reports of AEs, there appears to have been overlap between the signs of SA and the AE observation. For instance, there were significantly more AE reports of excessive vocalization (including whining), calm/lethargy/depression, and decreased appetite and significantly fewer AE reports of disruptive/destructive behavior in Reconcile-treated dogs than in placebo-treated dogs. Although some of these events, described in the owner diaries as calmness and lethargy, may be a side effect of treatment, the fact that the large majority were recorded in the early part of the trial and subsequently resolved suggests that, in both treatment groups, they may be manifestations of SA that improve with pharmacologic treatment and/or BMP implementation. In some cases, AEs were eliminated or reduced by a reduction in the dose rate of fluoxetine.

These findings suggest that each case in which side effects occur needs to be individually managed, with consideration being given to an initial reduction in dose rate; if successful, dose reductions may be followed by a return to the full dose of 1 to 2 mg/kg/day. In all such cases, dogs should be monitored closely to quickly detect any reemergence of clinical signs or side effects. If a dog is insufficiently managed at the dose of 1 mg/kg, without AEs, our clinical experience suggests that the dose should be increased.

Four dogs (one in the placebo group and three in the Reconcile group) had AEs of seizures. Although none of the seizures could be definitively associated with fluoxetine administration, the results do not preclude the possibility that seizures may occur in dogs administered 1 to 2 mg/kg/day of fluoxetine and may occur after fluoxetine therapy has been discontinued. However, given the potential gravity of the outcome of SA (e.g., possible euthanasia), the benefits of Reconcile therapy may exceed the potential risks.

■ CONCLUSION

These data demonstrate that the oral administration of 1 to 2 mg/kg/day of a flavored, chewable formulation of fluoxetine (Reconcile) is palatable and effective for the treatment of canine separation anxiety when administered in conjunction with a behavior management plan. The most common adverse events were transient lethargy and decreased appetite. Reconcile is a palatable, well-tolerated pharmacologic agent that can be dispensed by veterinarians and easily administered by owners to increase the effectiveness of a canine separation anxiety treatment plan.

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