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Efficacy of fluoxetine for canine behavioral disorders

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ABSTRACT

The objectives of this retrospective descriptive study were to compare the efficacy of fluoxetine in conjunction with a behavior modification plan for the treatment of common canine behavioral disorders, and to compare the effects of other factors, including patient sex, fluoxetine dosage, and concurrent drug administration. Owners of all dogs prescribed fluoxetine through the Animal Behavior Clinic at the Cornell University Hospital for Animals in Ithaca, NY, between June 15th, 2012, and December 31st, 2016, were queried regarding their dogs' behavior after prescription of fluoxetine. Behavioral diagnosis, fluoxetine dosage, concurrently administered psychoactive medications, sex, and response to fluoxetine for each dog were recorded. Of the 134 owners contacted, 93 responded. Eighty-eight dogs met inclusion criteria and were included in the study. Overall, 59% of owners reported that their dogs showed improvement, 32% reported no appreciable response, and 9% reported negative responses. Behavioral diagnoses were grouped into three categories: "Anxiety", "Aggression", and "Other" (which included compulsive/obsessive-compulsive behavior and self-mutilation). Most dogs in each category of diagnosis responded positively to treatment: 69% of dogs diagnosed with "Anxiety", 55% of dogs diagnosed with "Aggression", and 50% of dogs with a diagnosis of "Other". A negative response to treatment was reported in 0% of dogs with a diagnosis of "Anxiety", 13% of dogs diagnosed with "Aggression", and 0% of dogs with a diagnosis of "Other". More dogs prescribed fluoxetine at a daily dose of 0.5–0.99 mg/kg and 1.0–1.49 mg/kg responded positively to treatment (63% and 64%, respectively) than did dogs prescribed fluoxetine at 1.5–1.99 mg/kg daily (31%). Sixty-seven percent (N = 14/21) of dogs prescribed only trazodone in addition to fluoxetine and 63% (N = 5/8) of dogs prescribed only clonidine concurrently with fluoxetine responded positively to treatment, as compared with 59% (N = 23/39) of dogs prescribed fluoxetine as the sole agent. However, this difference was not significant. There was no significant effect of sex on treatment efficacy (Pearson chi square; [$\chi^2 = 0.000$; $P = 0.999$]). Sixty-eight percent (N = 19/28) of spayed females responded positively to treatment and 14% (N = 4/28) responded negatively, whereas 55% (N = 31/56) of castrated males responded positively and 9% (N = 5/56) responded negatively, a nonsignificant difference (Pearson chi square; ($\chi^2 = 2.990$; $P = 0.224$). Limitations of this study included its retrospective nature, number of owners who responded (N = 93; 66%) owner recall bias, and lack of control group (i.e., dogs with the same behavioral disorders that were not prescribed fluoxetine).

Introduction

Behavior disorders can lead to disruption of daily life, owner frustration, and physical injury to humans and/or animals, all of which can be devastating to both the dog and its owner and compromise the human-animal bond. In some cases, this can lead to relinquishment or euthanasia of the affected pet. Although there is no cure for most canine behavior problems, there are several treatment options, including a combination of environmental management, behavior modification, and psychoactive medications when warranted, to make the behavior manageable for a positive, long-term outcome.

One of the most commonly prescribed medications by veterinary behaviorists at the Animal Behavior Clinic at the Cornell University Hospital for Animals for canine behavioral complaints is fluoxetine, a selective serotonin reuptake inhibitor. Like other selective serotonin reuptake inhibitors, fluoxetine acts by selectively

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Table 1
Grouping of authors' specific diagnoses into broad categories

Anxiety	Aggression	Other
Generalized anxiety	Conflict/impulse control aggression	Compulsive/obsessive-compulsive behavior;
Separation anxiety	Fear aggression	Self-mutilation
Storm phobia	Status-related interdog aggression	
	Territorial aggression	

inhibiting reuptake of serotonin and downregulating 5-HT_1 receptors, resulting in an increase in the availability of serotonin in the synaptic cleft (Papich, 2016).

Several studies have examined the efficacy of fluoxetine for specific canine behavioral disorders. In two studies, fluoxetine, in the human formulation (Landsberg et al., 2008) or the veterinary chewable form, Reconcile® (Simpson et al., 2007), had a positive effect on separation anxiety in canine patients, especially when combined with behavior management. For the treatment of separation anxiety, 72% of dogs given Reconcile® in conjunction with a behavior modification plan showed improvement as compared with 50% of dogs given a placebo (Simpson et al., 2007). In another study, 76% of the 34 participating dogs with anxiety disorders improved when given a combination of fluoxetine and diazepam, a benzodiazepine (Ibáñez and Anzola, 2009).

Studies evaluating the effects of fluoxetine on compulsive/obsessive-compulsive disorders have generally found fluoxetine to be effective in their treatment, including for tail-chasing and fly-biting behaviors. Dogs prescribed fluoxetine were 8.7 times more likely to experience improvement in severity of their compulsive disorders than dogs given a placebo (Irimajiri et al., 2009). A study on fly-biting behavior found that 100% of the dogs treated with fluoxetine (n = 11) responded positively to treatment, whereas only 36% of the dogs treated with phenobarbital (n = 11) improved (Wrzosek et al., 2015).

To date, most studies regarding the efficacy of fluoxetine have focused on a single behavioral disorder. The objective of this retrospective study was to compare the efficacy of fluoxetine across several common canine behavioral disorders, when given in conjunction with a behavior modification plan.

Materials and methods

This study was designed as a retrospective descriptive study. Canine case records from the Animal Behavior Clinic at the Cornell University Hospital for Animals in Ithaca, NY, from June 15th, 2012, through December 31st, 2016, were reviewed. Only dogs prescribed fluoxetine as part of their treatment were included in the study. Of the 288 dogs seen in the Animal Behavior Clinic, 134 were prescribed fluoxetine as part of their treatment and, therefore, met the inclusion criterion. Dogs were primarily from New York State and Pennsylvania, between 8 months and 14 years old, and of all breeds and both sexes (56 males, 28 females). Owners were contacted by email or phone and asked if their dogs' behavior significantly improved, improved, did not change, or worsened while on fluoxetine.

Cases were sorted by diagnosis as recorded in the hospital's database. For cases with multiple diagnoses, only the primary diagnosis was recorded.

For the purpose of simplification, the diagnoses were grouped into three main categories: "Anxiety", "Aggression," and "Other" (Table 1). Owner-reported effects of the drug were similarly combined into three categories: "Positive", "Neutral", and "Negative".

Daily dosages of fluoxetine prescribed (mg/kg) were grouped into intervals of 0.5 mg/kg (0–0.49, 0.50–0.99, 1.00–1.49, 1.50–1.99, and $\geq$ 2.0 mg/kg). One case was not included in this analysis because the dog's weight was absent from its records.

Statistics

Descriptive data are presented as counts and percentages. A Pearson chi-square was used to test whether the probabilities of categorized responses (positive, neutral, and negative) were equally distributed. A Pearson chi-square was also used to test whether the response to fluoxetine (positive, neutral, or negative) was the same for dogs prescribed fluoxetine as the sole agent versus dogs prescribed fluoxetine plus other psychoactive medications. Only four dogs were sexually intact and therefore excluded from analysis. A Pearson chi-square was then used to test whether the response to fluoxetine differed between spayed females and castrated males.

Statistical analysis was performed using JMP® Pro 14.0.0 (SAS Institute, Cary, NC, USA). A two-tailed P-value $\leq$ 0.05 was considered statistically significant.

Results

Of the 134 owners contacted, 93 responded (66%). Five owners could not judge the dog's response to fluoxetine (two dogs were prescribed fluoxetine before adoption by the owners, and three dogs were not given the fluoxetine). The five cases that could not be judged were excluded from the study, resulting in a sample size of 88 dogs.

The most common primary diagnoses for which fluoxetine was prescribed were fear aggression (44% of all dogs) and generalized anxiety (22%). The probabilities of categorized responses (positive, neutral, and negative) were not equally distributed ($\chi^2 = 33.96$; $P < 0.001$). Overall, 52 (59%) dogs showed a positive response, 28 (32%)

Table 2
Number and percentage of responses to treatment by diagnosis and broad diagnosis category

Primary diagnosis		Response counts				Response percentages		
Broad category	Specific	Positive	Neutral	Negative	Total	Positive (%)	Neutral (%)	Negative (%)
Anxiety	Generalized anxiety	13	6	0	19	68	32	0
	Separation anxiety	3	2	0	5	60	40	0
	Storm phobia	2	0	0	2	100	0	0
	Total anxiety	18	8	0	26	69	31	0
Aggression	Conflict/impulse control aggression	4	1	1	6	67	17	17
	Fear aggression	23	9	7	39	59	23	18
	Status-related interdog aggression	6	5	0	11	55	45	0
	Territorial aggression	0	4	0	4	0	100	0
	Total aggression	33	19	8	60	55	32	13
Other	Compulsive/Obsessive compulsive behavior	1	0	0	1	100	0	0
	Self-mutilation	0	1	0	1	0	100	0
	Total other	1	1	0	2	50	50	0

Table 3
Number of responses to treatment by dosage of fluoxetine prescribed

Fluoxetine dose (mg/kg)	Response counts			Response percentages		
	Positive	Neutral	Negative	Positive (%)	Neutral (%)	Negative (%)
0–0.49	1	1	0	50	50	0
0.5–0.99	15	8	1	63	33	4
1.0–1.49	29	12	4	64	27	9
1.5–1.99	4	6	3	31	46	23
≥2.0	2	0	1	67	0	33

showed no appreciable response, and 8 (9%) showed a negative response. The only diagnoses for which no dogs showed improvement were territorial aggression and self-mutilation. However, four or fewer dogs were diagnosed with each of these diagnoses.

Table 2 shows responses of dogs to fluoxetine treatment by diagnosis. Of the 26 dogs with a diagnosis of "Anxiety", 18 (69%) showed a positive response to fluoxetine treatment, 8 (31%) a neutral response, and 0 (0%) a negative response. Of the 60 dogs with a diagnosis of "Aggression", 33 (55%) showed a positive response, 19 (32%) a neutral response, and 8 (13%) a negative response. However, most of the subcategories of aggression had at least a 59% positive response rate; the exception was territorial aggression (0% positive response rates). Of the 2 dogs with a diagnosis of "Other", one (50%) showed a positive response and one (50%) a neutral response; no dogs showed a negative response.

The dosage of fluoxetine prescribed (in intervals of 0.5 mg/kg) and the percentages of dogs that responded positively, negatively, or neutrally are tabulated in Table 3. A higher percentage of negative responses was reported in dogs with higher dose levels of fluoxetine. Owing to the small numbers of dogs in some categories of dose range by response, statistical analyses were not performed. Of the dose ranges prescribed to more than three dogs, the highest percentage of positive responses was seen at doses of 0.5–0.99 mg/kg (N = 24; 63%) and 1.0–1.49 mg/kg (N = 45; 64%) and the lowest percentage of positive responses was seen at a dose of 1.5–1.99 mg/kg (N = 13; 31%). There was also a positive response rate of 50% or greater at doses less than 0.5 mg/kg and doses greater than 2.0 mg/kg, but there were only two and three dogs in each group, respectively.

Figure 1 shows responses of dogs to treatment categorized by concurrently prescribed medications. Only three groups contained more than five dogs and thus can be reasonably compared. There were 39 dogs prescribed fluoxetine only, 21 dogs prescribed trazodone with fluoxetine, and 8 dogs prescribed clonidine in conjunction with fluoxetine. Of the 21 dogs prescribed trazodone concurrently with fluoxetine, 14 (67%) responded positively and 1 (5%) responded negatively. Of 8 dogs prescribed clonidine in addition to fluoxetine, 5 (63%) responded positively and 1 (13%) responded negatively. Of the 39 dogs prescribed fluoxetine only, 23 (59%) responded positively and 4 (10%) responded negatively. However, there was no difference in response (positive, neutral, or negative) according to whether or not dogs received other psychoactive medications in conjunction with fluoxetine ($\chi^2 = 0.000$; $P = 0.999$).

There were more castrated males in this study (n = 56) than spayed females (n = 28). Only four dogs were sexually intact at the time of treatment (three females and one male). Figure 2 displays the responses of dogs to fluoxetine according to sex and neuter status. Among neutered animals, a greater percentage of spayed females (19/28; 68%) responded positively to fluoxetine treatment than castrated males (31/56; 55%). A greater percentage of spayed females (4/28; 14%) also responded negatively than did castrated males (5/56; 9%). Nonetheless, the response distributions did not differ among neutered animals ($\chi^2 = 2.990$; $P = 0.224$).

Two dogs (of 88) experienced tremors and stopped receiving fluoxetine. These dogs were prescribed fluoxetine for fear aggression at 1.41 mg/kg and 1.56 mg/kg.

Discussion

In this study, 59% of owners reported that their dogs responded "positively" to treatment with fluoxetine. Similar percentages of dogs in the three categories of diagnosis (Anxiety, Aggression, and Other) responded both positively (69%, 55%, and 50%, respectively) and negatively (0%, 13%, and 0%, respectively) to treatment with

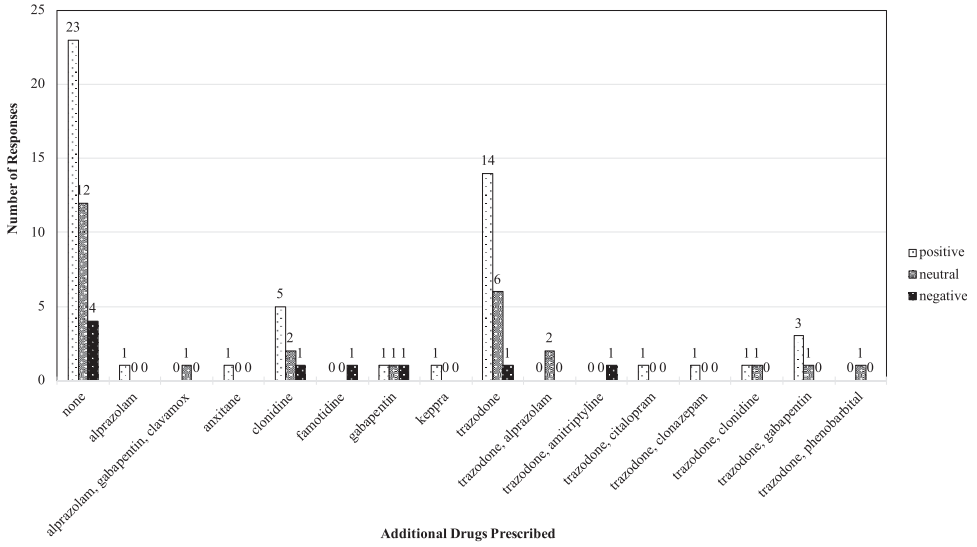

Figure 1. Responses of dogs to treatment, categorized by other medications prescribed concurrently with fluoxetine at the most recent appointment at which fluoxetine was prescribed.

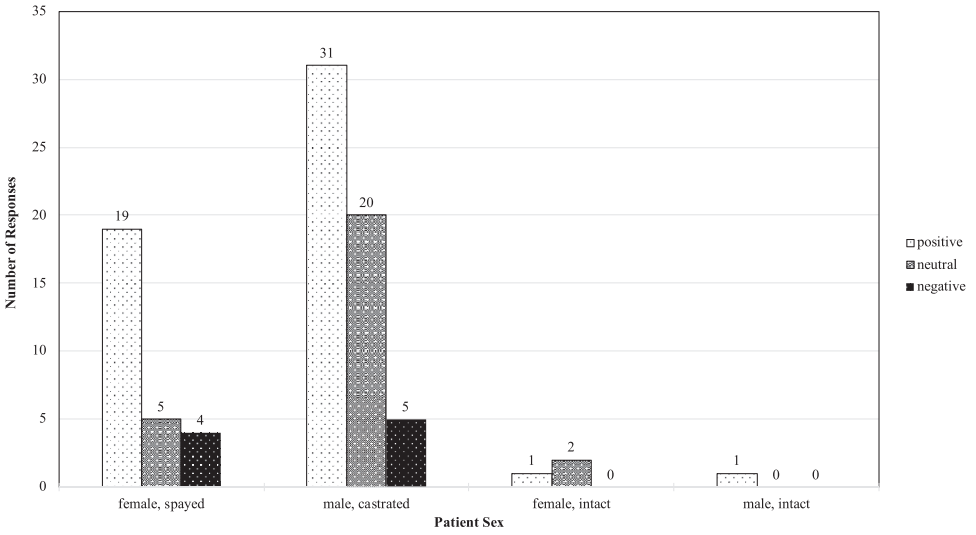

Figure 2. Responses of dogs to fluoxetine categorized by sex and neuter status.

fluoxetine. Reasons given for negative responses included worsening of the behavior and development of tremors.

Of dogs prescribed fluoxetine at 1.5–1.99 mg/kg once daily, 31% were reported to have responded positively as compared with 63% and 64% of dogs prescribed fluoxetine at 0.5–0.99 or 1.0–1.49 mg/kg once daily, respectively. A lower percentage of dogs responded positively and a higher percentage responded negatively at doses of 1.5–1.99 mg/kg daily compared with other dose ranges. At doses above 2 mg/kg, there was also a higher percentage of positive responses, but too few cases ($n = 3$) for comparison.

Dogs prescribed trazodone or clonidine concurrently with fluoxetine were reported to have the highest percentage of positive responses (67% and 63%, respectively) and a small percentage of negative responses (5% and 13%, respectively). Dogs treated with fluoxetine alone also had a high percentage of positive responses (59%) and a low percentage of negative responses (10%). It had been hypothesized that the use of multiple drugs together may achieve greater clinical response than with a single agent. However, in testing the use of multiple medications (yes or no) versus response to treatment, the distributions did not differ ($\chi^2 = 0.000$; $P = 0.999$). A higher percentage of spayed females responded positively (68%) than castrated males (55%); however, the response distributions did not differ among sex categories ($\chi^2 = 2.990$; $P = 0.224$).

This study had several limitations. First, it relied on owner reports of dogs' responses to fluoxetine, which in some cases were several years after the drug was originally prescribed. This may have led to recall bias, that is, each owner may have remembered the response to fluoxetine differently. Furthermore, the data may be biased due to cases lost to follow-up ($n = 41$). It is possible that this group included a higher percentage of cases that were relinquished or euthanized, were treatment failures, or whose owners were less compliant than owners who did respond. In that case, the percentages of dogs found in this study to have improved with fluoxetine treatment may have been overestimated.

It should be noted that fluoxetine was only one component of the treatment plan for all dogs in this study; each owner was also instructed to implement a behavior modification plan, which may have contributed to the success attributed to fluoxetine. Behavior modification is a crucial component of the treatment plan for any behavior disorder, with fluoxetine used only as an adjunct (Papich, 2016). Behavior modification recommendations included counterconditioning to aversive stimuli, avoidance of situations that trigger the behavior, environmental management (e.g., preventing access to the targets of the behavior), and enrichment (e.g., providing long-lasting food-dispensing toys). The degree to which owners followed or ignored this advice was not assessed but may have influenced outcomes.

Limitations of this study included its retrospective nature, which may introduce owner recall bias as well as misclassification bias. In addition, this study did not use a control group (i.e., dogs with behavioral disorders who were not prescribed fluoxetine), which limited the use of statistical analyses, particularly with regard to whether dogs prescribed fluoxetine had significantly more positive responses than dogs not given fluoxetine.

In conclusion, 59% of dogs prescribed fluoxetine as part of a comprehensive treatment plan for behavior problems in this study were reported to respond positively. This supports the continued use of fluoxetine in conjunction with a behavior modification plan in the treatment of canine behavioral disorders. Dosage of fluoxetine at 0.5–1.49 mg/kg once daily, as well as concurrent treatment with trazodone alone, may be more likely to have a positive effect on behavior than other doses or drug combinations. Fluoxetine appeared to be effective for all diagnoses and had few adverse effects.

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Authors' contributions: M.C. performed the study, analyzed the data, and wrote the paper. P.P. conducted the appointments for many of the patients in the study, provided some of the data, performed statistical analysis on the data, and extensively edited the paper. K.H. designed the study and reviewed the paper.

Ethical considerations

No animals were used in this study; it was based entirely on their records and owner reports.

Conflict of interest

There is no conflict of interest.

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