

# Randomized, controlled clinical trial of the efficacy of fluoxetine for treatment of compulsive disorders in dogs

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**Objective**—To evaluate efficacy of fluoxetine hydrochloride for treatment of compulsive disorders in dogs.

**Design**—Randomized, controlled clinical trial.

**Animals**—63 dogs with compulsive disorders.

**Procedures**—The diagnosis was confirmed on the basis of analysis of videotapes of the dogs' behavior by 3 veterinary behaviorists, results of physical examination and clinicopathologic testing, and, when necessary, telephone interviews with owners. Dogs were randomly assigned to treatment with fluoxetine (1 to 2 mg/kg [0.45 to 0.9 mg/lb], PO, q 24 h) or a placebo. Owners did not receive any advice regarding behavioral or environmental modifications. Severity of episodes was measured through telephone interviews every 2 weeks and on the basis of a daily diary kept by each owner.

**Results**—42 days after the initiation of treatment, the proportion of dogs with a decrease in severity of the compulsive disorder, as reported by the owners, was significantly higher for dogs treated with fluoxetine than for control dogs, and dogs treated with fluoxetine were significantly more likely (odds ratio, 8.7) to have a decrease in severity of the compulsive disorder. However, mean number and duration of compulsive episodes, as determined from daily diary entries, did not differ significantly between groups. The most common adverse effects were decreased appetite and mild lethargy.

**Conclusions and Clinical Relevance**—Results suggested that fluoxetine may be efficacious in the treatment of compulsive disorders in dogs, although results were equivocal. The present study did not examine whether fluoxetine was more efficacious than or synergistic with behavioral and environment modifications. (*J Am Vet Med Assoc* 2009;235:705–709)

Obsessive-compulsive disorder is a well-known psychiatric disorder of humans characterized by recurrent intrusive thoughts and ritualistic behaviors.<sup>1</sup> Previous authors<sup>2–5</sup> have suggested that dogs may be affected by similar conditions. In most dogs with compulsive disorders, the condition is characterized by persistent, often repetitive behaviors such as tail chasing, spinning, pacing, or self mutilation. However, some affected dogs may have sustained behaviors, such as freezing or staring at and fixating on imaginary objects, shadows, and lights. In addition, it has been suggested that acral lick dermatitis may constitute a neurobiologic model of OCD in humans, given the similarity in behaviors associated with both disorders and the similar responses to SSRIs.<sup>6</sup>

Fluoxetine is an SSRI that has been widely used for treatment of OCD in humans,<sup>7</sup> and veterinary behaviorists have recommended the use of fluoxetine for treatment of

## ABBREVIATIONS

OCD	Obsessive-compulsive disorder
SSRI	Selective serotonin reuptake inhibitor

compulsive disorders in dogs. To our knowledge, however, only a single clinical study<sup>8</sup> of the efficacy of fluoxetine in dogs with a compulsive disorder has been published, and that study focused on dogs with acral lick dermatitis. Fluoxetine was found to be safe and effective for the treatment of acral lick dermatitis, but its efficacy in dogs with other compulsive disorders has not been evaluated.

The purpose of the study reported here, therefore, was to evaluate the efficacy of fluoxetine for the treatment of compulsive disorders in dogs. In addition, we wanted to identify adverse effects associated with oral administration of fluoxetine in dogs.

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## Materials and Methods

**Study design**—The study was conducted as a randomized, placebo-controlled, blinded, parallel-arm clinical trial. Multiple sites participated in the study, with data evaluated by a single coordinating investigator (MI). The experimental protocol was approved by the Purdue Animal Care and Use Committee. All owners who were interested in participating in the study were required to read and sign an informed consent form prior to enrollment of their dog in the study.

**Dogs**—From January 2001 through September 2002, dogs were recruited to participate in the study through the use of flyers distributed at veterinary continuing education meetings, veterinary technician continuing education meetings, and veterinary offices; advertisements on the Internet and in *Dog World Magazine*, *Dog Fancy Magazine*, and various newspapers; and a news story on a television news show broadcast in the Lafayette, Ind, area.

Dogs offered for inclusion in the study were screened by the coordinating investigator, and only those dogs that were > 7 months old and had exhibited a compulsive behavior on a daily basis for at least 2 months were considered for inclusion. In addition, dogs were considered for inclusion only if the owner did not have any plans to change the dog's ownership or to have elective surgery performed during the study period. Dogs were excluded from the study if they were pregnant or lactating; if they had been used for breeding; if they had received any psychoactive medications (eg, tricyclic antidepressants, St John's wort, or monoamine oxidase inhibitors) in the past 30 days; if they had any history of hepatic disease, renal disease, seizures, or diabetes mellitus; or if the owner was unwilling to comply with the study procedures.

All dogs considered for inclusion in the study were required to undergo a complete physical examination, including dermatologic and neurologic examinations, by their regular veterinarian and to have blood and urine samples submitted for clinicopathologic testing. Veterinarians were provided telephone instructions by the coordinating investigator with regard to how to conduct the physical examination, collect blood and urine samples, and ship samples overnight to the Purdue University Clinical Pathology Laboratory and were provided standardized forms to record their physical examination findings. Results of a CBC, serum biochemical profile, and urinalysis were examined by a board-certified veterinary clinical pathologist or a senior clinical pathology resident to determine whether dogs had any evidence of another condition that could account for the clinical signs. Additional testing was performed as needed, with results of additional tests examined by the veterinary clinical pathologist in conjunction with a board-certified small animal internist. Dogs with any evidence of a complicating condition were excluded from the study.

For all dogs included in the study, the diagnosis of a compulsive disorder was confirmed on the basis of analysis of videotapes of the dogs' behavior by 3 board-certified veterinary behaviorists, who also reviewed results of a preliminary questionnaire completed by all

owners and results of physical examinations and clinicopathologic testing. In addition, the veterinary behaviorists were allowed to contact owners by telephone to obtain additional information, if necessary, to confirm the diagnosis. The 3 behaviorists worked independently, and the diagnosis of a compulsive disorder was considered confirmed only if all 3 individuals arrived at the same conclusion. Dogs for which any 1 or more of the behaviorists questioned the diagnosis of a compulsive disorder were excluded from the study.

**Study protocol**—Dogs in which the diagnosis of a compulsive disorder was confirmed and that met all other inclusion and exclusion criteria were included in the study. Dogs included in the study were randomly assigned to treatment and control groups, with blocking on clinical diagnosis. Six clinical diagnosis categories were identified: Bull Terriers with spinning, German Shepherd Dogs with tail-chasing, Doberman Pinschers with flank-sucking, Miniature Schnauzers with hind-end checking, dogs of any breed with another oral compulsive disorder (eg, acral lick dermatitis, licking of any body part without self injury, licking objects, and licking in the air), and dogs of any breed with another locomotory compulsive disorder (eg, chasing shadows or lights, circling, spinning in dogs other than Bull Terriers, pacing, tail chasing in dogs other than German Shepherd Dogs, biting at the air, and fixation). A centralized randomization scheme was used, so that dogs of specific breeds were assigned to the treatment and control groups in approximately equal numbers. Owners, the dogs' regular veterinarians, and the investigators were all blinded to treatment group assignment until all data had been collected.

For all dogs included in the study, owners were instructed to complete a daily questionnaire on their dogs' behavior for 14 days to obtain baseline data. At the end of this 14-day period, the owner was contacted by the coordinating investigator by telephone and asked to indicate the severity of the dog's compulsive disorder as absent, mild, moderate, severe, or very severe. After this baseline telephone interview, owners were provided study drugs (fluoxetine or a placebo) and instructed to administer the assigned drug for 42 days.

Dogs in the treatment group received fluoxetine at a dosage of 1 to 2 mg/kg (0.45 to 0.9 mg/lb), PO, every 24 hours. Fluoxetine was available as 4-, 8-, 16-, and 32-mg tablets, and the appropriate tablets were dispensed on the basis of the dog's weight. Dogs in the control group received a placebo that consisted of tablets with the same ingredients as the tablets provided to the dogs in the treatment group, with the exception of the active ingredient. Fluoxetine and placebo tablets were indistinguishable from each other and were provided by Elanco Animal Health. Study medications were shipped directly from the manufacturer to the regular veterinarian for each dog enrolled in the study.

Owners of dogs included in the study were instructed to complete a daily diary for the 42 days that their dogs received the study drug. Each day's entry included questions as to whether the owner had given the dog the medication that day, whether the owner had observed any adverse effects and, if so, what effects had been seen, how many hours the owner had spent with

the dog that day, the number of episodes of compulsive behavior the owner had witnessed that day, the duration of the longest observed episode, and whether the behavior ended on its own or because it was interrupted. Owners were instructed to not change how they interacted with their dogs during the study period, and no advice was provided on behavioral or environmental modifications. Telephone interviews were conducted after study drugs had been administered for 14, 28, and 42 days, and owners were again asked to rate the severity of the dog's compulsive behavior. In addition, owners were asked whether their dog had experienced any adverse effects associated with drug administration and, if so, the type of effect and its severity. At the time of the final telephone interview, owners were asked to mail their daily diaries to the coordinating investigator.

Dogs were considered to have completed the study after the final telephone interview. No attempts were made to perform posttreatment CBCs, serum biochemical analyses, or urinalyses.

**Statistical analysis**—Outcome measures of interest consisted of the change in owner-reported severity of the dog's compulsive disorder and the change in frequency and duration of episodes of the compulsive disorder. For each of the 3 evaluation times (ie, after 14, 28, and 42 days of treatment), the change in owner-reported severity of the compulsive disorder was assigned a score of 1 if severity was less than severity reported during the baseline telephone interview and a score of 0 if severity was unchanged from or worse than severity reported during the baseline telephone interview. At each time, a  $\chi^2$  test was then used to determine whether change in owner-reported severity (1 vs 0) was significantly associated with treatment (fluoxetine vs placebo). Logistic regression analysis was used to obtain the odds ratio for decreased disease severity in the treatment group.

To determine the change in frequency and duration of episodes of the compulsive disorder, data for the owner-maintained daily diaries were summarized for each 14-day period (including the baseline period) as mean number of episodes per day and mean duration of the longest episode each day. Number of episodes on any given day was right censored at 10, and duration of the longest episode on any given day was right censored at 10 minutes. Mean number of episodes per day and mean duration of the longest episode each day were analyzed by means of a linear, mixed-model technique for repeated measures. Fixed factors included in the analysis consisted of treatment group, mean number of episodes and mean duration during the baseline period, clinical diagnosis category, treatment week, and relevant interaction terms. To facilitate analyses, clinical diagnosis categories were collapsed as needed. Specifically, the 1 Bull Terrier with spinning was included in the category with all breeds with other locomotory compulsive disorders and the 1 Doberman Pinscher with flank-sucking was included in the category with all breeds with other oral compulsive disorders. A random effect for individual dog was included in the model to account for confounding associated with multiple measurements obtained over time for each dog.

All analyses were performed with standard software.<sup>a,b</sup> Values of  $P \leq 0.05$  were considered significant.

## Results

**Dogs**—Sixty-three dogs met the criteria for inclusion in the study. However, 1 dog was subsequently excluded because of missing baseline interview data and noncompliance with the treatment schedule. Data from the remaining 62 dogs were included in the statistical analyses.

There were 6 sexually intact males, 4 sexually intact females, 24 castrated males, and 28 spayed females included in the study. Ten of the 62 (16%) dogs were of mixed breeding, and the remaining 52 represented 29 breeds, including German Shepherd Dogs (12 [19%]); English Springer Spaniels, Jack Russell Terriers, Shetland Sheepdogs, and West Highland White Terriers (3 [5%] each); Cairn Terriers, Dalmatians, Labrador Retrievers, and Vizslas (2 [3%] each); and an Australian Cattle Dog, Belgian Malinois, Border Collie, Bull Terrier, Cavalier King Charles Spaniel, Chesapeake Bay Retriever, Chinese Crested, Dachshund, and Doberman Pinscher (1 [2%] each). The largest number of dogs were from Indiana (22 [35%]), although dogs from 20 states were included in the study. Median age was 42 months (range, 13 to 111 months), and median body weight was 19.1 kg (42 lb; range, 3.8 to 54.1 kg [8.4 to 119 lb]). Veterinarians who conducted physical examinations on the dogs rated 50 (81%) of the dogs as having normal body condition, 8 (13%) as thin, and 4 (6%) as obese. Of the 62 dogs included in the study, 1 (2%) was a Bull Terrier with spinning, 1 (2%) was a Doberman Pinscher with flank-sucking, 12 (19%) were German Shepherd Dogs with tail-chasing, 15 (24%) were dogs of other breeds with oral compulsive disorders, and 33 (53%) were dogs of other breeds with locomotory compulsive disorders.

Thirty-one dogs were treated with fluoxetine, and the other 31 were treated with the placebo. Dogs that received fluoxetine included the Bull Terrier with spinning, 6 German Shepherd Dogs with tail-chasing, 7 dogs with oral compulsive disorders, and 17 dogs with other locomotory compulsive disorders. Dogs that received the placebo included the Doberman Pinscher with flank-sucking, 6 German Shepherd Dogs with tail-chasing, 8 dogs with other oral compulsive disorders, and 16 dogs with other locomotory compulsive disorders.

**Efficacy**—After 14 days of treatment, 15 of the 31 (48%) dogs treated with fluoxetine and 6 of the 31 (19%) dogs treated with the placebo had a decrease in owner-reported severity of the compulsive disorder, compared with severity during the baseline period; these proportions were significantly ( $P = 0.015$ ) different. Similarly, after 28 days of treatment, 18 of the 31 (58%) dogs treated with fluoxetine and 8 of the 30 (27%) dogs treated with the placebo had a decrease in owner-reported severity of the compulsive disorder; these proportions were significantly ( $P = 0.013$ ) different. After 42 days of treatment, the proportion of dogs in which severity of the compulsive disorder was decreased was significantly ( $P < 0.005$ ) higher for dogs treated with fluoxetine (19/27 [70%]) than for dogs treated with the placebo (6/28 [21%]). Thus, after 42 days of treatment, dogs given fluoxetine were 8.7 times (95% CI, 2.56 to 29.60) as likely to have a decrease in severity of the compulsive disorder, com-

pared with severity during the baseline period, as were dogs given the placebo.

For the entire 42-day treatment period, mean number of compulsive episodes per day, as determined from analysis of owner diaries, was not significantly ( $P = 0.096$ ) different between dogs treated with fluoxetine (least squares mean, 4.5 episodes/d) and dogs treated with the placebo (6.5 episodes/d). The difference in mean number of compulsive episodes per day was 2.0 episodes/d (95% CI,  $-0.4$  to 4.3 episodes/d). Similarly, for each of the 2-week periods during the study, mean number of compulsive episodes per day did not differ significantly between treatment groups. Mean duration of the longest compulsive episode each day was not significantly different between treatment groups, regardless of whether data were analyzed for the entire 42-day study period or for each 2-week evaluation period.

**Adverse effects**—For the 31 dogs in the fluoxetine group, the most commonly reported adverse effects were lethargy (12 [39%]) and decreased appetite (7 [23%]). In most instances, lethargy and decreased appetite were considered mild and resolved within 2 weeks. However, 2 dogs were lethargic until the end of the study period. Other adverse effects in dogs treated with fluoxetine included aggression (4 [12%]) and vomiting, excessive vocalization, excessive licking, and anxiety (2 [6%] each). Adverse events in the 31 dogs given the placebo included vomiting (3 [10%]), aggression (2 [6%]), and excessive vocalization (1 [3%]).

## Discussion

Results of the present study suggested that fluoxetine, at the dosage used, may be efficacious in the treatment of compulsive disorders in dogs, although results were equivocal. Specifically, owner-reported severity of the compulsive disorder was more likely to have decreased, compared with baseline severity, in dogs treated with fluoxetine than in dogs treated with a placebo. However, mean number and duration of compulsive episodes, as determined from daily diary entries, did not differ significantly between groups. Administration of fluoxetine appeared to be safe for dogs in the present study, in that adverse effects that were reported were generally mild and self-limiting. Similarly, a previous study<sup>8</sup> reported that fluoxetine was efficacious for the treatment for acral lick dermatitis in dogs. The present study, however, was more extensive, in that dogs with a variety of compulsive disorders were included. The dosage of fluoxetine used in the present study was selected on the basis of the dosage used in a previous clinical trial<sup>9</sup> and dosages that have been recommended in the literature.<sup>3,10</sup>

Determining efficacy of various treatments in dogs with compulsive disorders is difficult because there currently is no gold standard method for establishing the diagnosis other than expert opinion.<sup>11–13</sup> Thus, dogs were included in the present study only if the diagnosis had been confirmed by 3 independent, board-certified veterinary behaviorists and were excluded if even 1 of the behaviorists questioned the diagnosis. The use of 3 experts is an accepted means of confirming a diagnosis in the absence of a gold standard,<sup>14</sup> and the method of using 3 experts working independently to confirm the diagno-

sis was incorporated in a previous study<sup>13</sup> of compulsive disorders in dogs. Differential diagnoses for dogs with clinical signs of a compulsive disorder include conflict behavior (eg, displacement activity, redirected activity, vacuum activity, and stereotypic activity),<sup>15–17</sup> learned behavior, and various physiologic abnormalities, including neurologic and endocrinologic diseases.<sup>3</sup> Only accepting dogs into the study if all 3 behaviorists agreed on the diagnosis did make it difficult to recruit cases. However, if dogs with disorders other than compulsive disorder (eg, redirected behavior, stereotypies, or replacement behavior) had been included in the study, it would have been more difficult to identify efficacy. Thus, the inclusion criteria were kept high to ensure that only dogs with compulsive disorders were included.

In human medicine, the Yale-Brown Obsessive Compulsive Scale has been used to measure changes in severity for patients with OCD.<sup>18,19</sup> For the present study, we used a previously validated,<sup>20</sup> 5-point Likert scale to identify changes in severity of compulsive disorders. Theoretically, use of trained observers to record each dog's behavior would have been the best way to obtain data on disease severity. However, because dogs included in the study were privately owned and located across the United States, this was not practical. Thus, we elected to use a single telephone interviewer reading from a predetermined script to obtain owner assessments of disease severity every 14 days and to have owners maintain a daily diary of number and duration of compulsive episodes.

In the present study, when data from the owner-completed daily diaries were analyzed, we did not detect any significant difference in mean number of compulsive episodes per day or mean duration of the longest episode each day between treatment groups. However, it is possible that owners were not always observing their animals or were not accurately counting numbers of episodes. Also, some owners indicated that they did not complete all entries on a daily basis, and some participants had multiple family members completing diary entries. Thus, we believe that the daily diaries may have been a good way to remind owners to administer the study drug each day and to record adverse effects associated with drug administration but may not have been a sensitive method of identifying changes in severity of the dog's condition.

Owners of dogs included in the study were asked to not change their dogs' daily interactions or environments because we wanted to determine the effect of fluoxetine alone. No advice on behavioral or environmental modifications was given during the interview period, even if the owner inquired about such modifications, as we were concerned that particular behavioral or environmental modifications might affect different dogs in different ways, introducing additional variability into the outcome. Therefore, results of the present study do not allow us to comment on whether fluoxetine was more efficacious than or synergistic with behavioral and environment modifications. Nevertheless, we believe that behavioral and environmental modifications are an important adjunct to pharmacologic treatment of dogs with compulsive disorders. Although medication alone might reduce the overall severity of compulsive episodes, environmental modifications to decrease the dog's stress level and behavioral modifications to teach the dog acceptable

behaviors as an alternative to compulsive behaviors during stressful situations will likely provide a better overall result and should be incorporated in the treatment plan.

In the present study, we used the  $\chi^2$  method to test for an association between a change in owner-reported severity of the compulsive disorder (decreased severity, compared with baseline, vs no change or increased severity) and treatment group because our null hypothesis was that the probability that dogs would improve would be the same, regardless of whether they were treated with fluoxetine or the placebo. Data obtained from a Likert scale cannot be treated as a continuous variable because this would imply that the difference between any 2 adjacent data points is equal (eg, the change between mild and moderate is the same as the change between moderate and severe). Therefore, a simple binary variable (improved or not improved) was chosen as the outcome.

Loss of appetite and anorexia were reported as common adverse effects in a study<sup>21</sup> of the use of clomipramine, another SSRI, in dogs. Selective serotonin reuptake inhibitors such as fluoxetine may mildly disturb the serotonin system in the gastrointestinal tract and may also disturb the serotonergic projection to the thalamus that regulates appetite and eating behavior. Thus, fluoxetine might lead to a change in an animal's appetite.<sup>22</sup> Overall, adverse effects reported by owners in the present study were mild and generally self limiting, suggesting that fluoxetine at this dosage is well-tolerated by dogs.

Although lethargy was reported as an adverse effect in the present study, most often the lethargy was mild and signs resolved within 2 weeks in all but 2 dogs. Dogs reported to have lethargy were not so severely affected that they were sleeping or unable to move, and owners did not report that lethargy was severe enough to prevent compulsive episodes. In 1 dog that received fluoxetine at a dosage of 2 mg/kg/d, the lethargy was severe enough to necessitate a reduction in dosage and resolved after the dosage was reduced to 1 mg/kg/d. The dog completed the remainder of the study without additional problems.

It is known that there are breeds that are predisposed to certain types of compulsive behavior.<sup>2,3,23</sup> In the present study, random assignment to the treatment and control groups was performed after blocking on clinical diagnosis. Unfortunately, we did not have sufficient numbers of dogs for a statistical evaluation to be conducted on the effectiveness of fluoxetine for each clinical diagnosis category.

In the present study, a significant difference in the proportion of dogs with an improvement in disease severity was identified after 2, 4, and 6 weeks of treatment. Because the medication period was only 6 weeks, we could not determine whether the effect would have been more pronounced after a longer treatment period. However, it has been suggested that there is a time delay in the effect of SSRIs on human patients with OCD because therapeutic effects are a result of downregulation of the expression of serotonin receptors in pre- or postsynaptic membranes.<sup>22,24</sup> It is likely that the effects of SSRIs in dogs with compulsive disorders are attributable to a similar physiologic mechanism. Thus, it would be beneficial to conduct a study on the efficacy of fluoxetine over a longer period. A long-term medication study could also examine long-term safety of fluoxetine in dogs.

- a. SPSS for Windows, version 11.5.0, SPSS Inc, Chicago, Ill.  
b. SAS, version 8.2, SAS Institute Inc, Cary, NC.

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