# Effects of a selective serotonin reuptake inhibitor on urine spraying behavior in cats

Patricia A. Pryor, DVM; Benjamin L. Hart, DVM, PhD, DACVB; Kelly D. Cliff, DVM; Melissa J. Bain, DVM

**Objective**—To determine the effectiveness of a readily available selective serotonin reuptake inhibitor (SSRI), fluoxetine hydrochloride, on reducing problem urine spraying in cats.

**Design**—Randomized placebo-controlled double-blind clinical trial.

**Animals**—17 neutered cats > 1 year old with objectionable urine spraying behavior.

**Procedure**—Owners recorded urine-spraying events for 2 weeks (baseline). Cats that vertically marked a mean of ≥ 3 times per week were treated for 8 weeks with fluoxetine or fish-flavored liquid placebo. If urine spraying was not reduced by 70% by weeks 4 through 5, the dosage was increased by 50% for weeks 7 and 8. After discontinuation of treatment at the end of 8 weeks, owners recorded daily urine marks for another 4 weeks.

**Results**—The mean (± SE) weekly rate of spraying episodes in treated cats was 8.6 (± 2.0) at baseline, decreased significantly by week 2 (1.7 ± 0.6), and continued to decrease by weeks 7 and 8 (0.4 ± 0.2). The mean weekly spraying rate of cats receiving placebo was 7.8 (± 1.5) at baseline, decreased only slightly during week 1 (5.5 ± 1.8), and did not decline further. When treatment was discontinued after 8 weeks, the spraying rate of cats that had received treatment varied. The main adverse reaction to the drug was a reduction in food intake, which was observed in 4 of 9 treated cats.

**Conclusions and Clinical Relevance**—Administration of fluoxetine hydrochloride for treatment of urine spraying in cats can be expected to considerably reduce the rate of urine marking. The frequency of spraying before treatment is predictive of the spraying rate when the drug is discontinued. (*J Am Vet Med Assoc* 2001;219:1557–1561)

Problem urination, especially urine spraying (also known as urine marking), appears to be the most common behavioral problem in cats for which veterinary consultation is sought.[1-3] Important inroads have been made in understanding the predisposing factors and proximate causes of the behavior.[4] Male cats are much more likely to become problem urine markers than females, and cats from multiple-cat households are more likely to be urine markers than their apparent proportional representation in the population.[5] Common proximate causes for the onset or continuation of urine marking include agonistic or unfriendly interactions with outdoor cats or with other cats in the same household and limitation of a cat's access to the outdoors.[6,7] Common targets of urine marking are walls, windows, furniture, and appliances.[6,7]

Although environmental management, such as the reduction of residual urine odors, may reduce urine marking frequency, the problem is likely to continue in many cats, and pharmacologic treatment is customarily recommended.[6,7] The drugs explored to date in open-label prospective studies have not been shown to satisfactorily resolve the problem in all cats. The administration of diazepam[8,9] and buspirone[10] resulted in considerable reduction or elimination of the behavior in 55 to 75% of cats while being treated. When the drug was withdrawn, almost all cats receiving diazepam and 50% of those receiving buspirone resumed urine marking. In another limited single-blind trial, the serotonergic tricyclic drug clomipramine appeared to reduce urine marking in some cats.[11]

The drug chosen for this trial was a **selective serotonin reuptake inhibitor (SSRI)**, fluoxetine hydrochloride,[a] which, according to 1 case report, was effective in reducing or eliminating urine marking.[12] Additionally, there is some information suggesting a wide safety margin for cats (lethal $dose_0$ > 50 mg/kg [22.7 mg/lb] of body weight).[13] Fluoxetine is a commonly used SSRI in human psychiatry[14] and is in a class of drugs not previously studied in clinical trials for effectiveness in treating feline urine marking.

The gold standard of evaluating the effectiveness of a drug on behavioral problems is the double-blind trial with randomized assignment of animals to placebo or drug treatment.[15,16] To our knowledge, this type of trial has not been reported for any drug in the treatment of urine marking in cats. The purpose of the study reported here was to perform such a trial, using cats that met specific enrollment criteria with regard to number of urine marking episodes and duration of the problem and that were screened to exclude those with medical problems that may have interfered with the conduction of the trial.

## Materials and Methods

**Recruitment and enrollment of cats**—Cats were recruited by use of newspaper advertisements announcing the study for enrollment at the University of California School of Veterinary Medicine **Veterinary Medical Teaching Hospital (VMTH)** in Davis, Calif, and the **University of California Veterinary Medical Center-San Diego (UCVMC-SD)**. Letters were also sent to veterinarians within the referral area of the VMTH and UCVMC-SD. The newspaper advertisements and letters to veterinarians listed some primary enrollment criteria: only 1 urine marking cat per household; an average of ≥ 4 vertical urine marks indoors per week for the problem cat; ≤ 4 cats per household; the cat

From the Behavior Service, Veterinary Medical Teaching Hospital, School of Veterinary Medicine, University of California, Davis, CA 95616.

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Address correspondence to Dr. Hart.

must be castrated or spayed; and the cat must not be currently receiving any medication for the problem behavior. A telephone number was listed for owners to call and leave messages. Veterinary students called back the interested owners and delivered a screening interview over the telephone. Owners were asked to explain how they determined which cat in a household was spraying (eg, owners saw only the nominated cat spraying; only the nominated cat had access to marked area), and a judgment was made as to the reliability of this claim. For owners whose cats appeared to meet enrollment criteria, an appointment was made with a veterinarian at the Behavior Service of the VMTH or UCVMC-SD. During these appointments, an extensive interview, which reviewed and confirmed the enrollment criteria and gathered information on owner-estimated urine marking frequency, location, and causative factors, was administered. A physical examination was performed, and blood was obtained for a CBC and a serum biochemical profile. Urine for urinalysis was obtained by cystocentesis, using ultrasound guidance if necessary. Cats that met the household and behavioral criteria and for which results of the CBC, serum biochemical analysis, and urinalysis were within reference ranges were selected for enrollment in the baseline phase.

**Baseline observations—**Owners of cats were asked to record, on a daily basis for 2 weeks, the number and location of all urine marks. Because of concern regarding the owner's ability to distinguish urine marking from inappropriate urination, only vertical marks were used in data analysis. The owners were instructed to institute standardized environmental management procedures that were explained to them verbally and in written form. The owners were provided with an enzymatic cleaner,[b] based on previous findings that enzymatic cleaners result in the most effective removal of urine odors.[17,18] On the first day, owners were to clean all previously urine-soiled areas of the house, using the enzymatic cleaner. Owners were also required to clean, in a specified manner, all subsequent detected vertical and horizontal urine deposits, using the same enzymatic cleaner. For households with more than 1 cat, the owner was instructed to add additional litter boxes so that the total number of boxes equaled the number of cats plus 1. Owners were also instructed to clean all feces and urine from the litter boxes once a day and to completely change the litter material and wash the litter boxes once per week; the location of the litter box was not changed. The only other standard procedure required the owner to refrain from physically or verbally punishing the cat for urine marking.

The owners were given forms for daily recording, on which they were required to enter the number of urine marks each day, using 1 sheet per 7 days. Information about urine marking frequency and location was collected from the owners by telephone on a weekly basis throughout the baseline phase. Owners were instructed to mail in their baseline daily recording forms at the end of the 2-week period.

**Drug treatment—**At the end of the baseline phase, owners whose cats marked ≥ 6 times were given an opportunity to enroll their cats in the drug treatment phase. The nature of the double-blind trial, with half of the cats receiving placebo and half receiving medication, and a description of the drug being tested were explained. Those owners who wished to proceed signed a consent form. The cats were randomly assigned to a placebo or drug group by an investigator who had no direct contact with the cat or the owner; no one who had contact with the cat or the owner was aware of the assignment. The assignment was stratified so as to approach an equal distribution of sexes, cats that received prior anxiolytic treatment for the problem, cats from single-cat households, and marking rate during baseline. The dosage of fluoxetine hydrochloride (1 mg/kg [0.45 mg/lb], PO, q 24 h), individualized for each cat by a commercial pharmacy and provided in a fish-flavored liquid vehicle, was formulated so that each cat would receive 1 ml of medication once a day. The medication was shipped to participating cat owners. The same amount (1 ml) of vehicle was used for each cat receiving placebo treatment.

On the basis of results of previous open-label studies of drug treatment for urine marking (needed for comparison of effectiveness), 8 weeks of treatment was scheduled.[9,10] During the treatment phase, owners were instructed to continue daily recording of urine marks and to continue the environmental management procedures. Although a treatment phase beyond 8 weeks may have been desirable, there is a risk of increasing noncompliance with increasing trial duration. The treatment phase was initiated after the owners had received the medication. At the end of week 5, if the mean marking rate for weeks 4 through 5 had not been reduced by 70%, the previous dose was to be replaced by an increased dose (1.5 mg/kg [0.68 mg/lb], PO, q 24 h), which was formulated to be given as 1 ml/d during weeks 7 and 8. To maintain blinding, cats on placebo were also given an increased dose (vehicle only) if this criterion was met. Cats were excluded during the study if the owner could not reliably administer the medication to the cat or if there was a major change in the household, such as removal or addition of another cat or household relocation or remodel. Information regarding urine marking frequency and location was collected weekly by telephone, and cat owners were reminded weekly that their cat was on the drug or placebo and that the caller, as well as the owner, was unaware of which cats were on which treatment.

At the end of week 8, owners were instructed to discontinue administering the medication. If the mean marking rate for weeks 7 and 8 had not been reduced by 70%, treatment was decoded. If the mean marking rate for weeks 7 and 8 was reduced by 70%, treatment was not yet decoded, and the owners were asked to continue the environmental management procedures and daily recording of urine marks for 4 weeks. During this posttreatment phase, owners were called once weekly to obtain data regarding urine marking. Following the 4 weeks of posttreatment phase, treatment was decoded. Owners of cats receiving placebo were offered 8 weeks worth of the drug. All owners were instructed to work with their family veterinarian for further administration of the drug and follow-up. At the completion of each cat's participation in the trial, owners were asked to mail in their data forms for confirmation of data collected previously over the telephone.

**Data analyses—**The mean weekly number of marks during the 2-week baseline period was used as a reference with which to compare the marking rate of cats throughout 8 weeks of treatment and 4 weeks of posttreatment drug withdrawal. Thus, each cat served as its own control. A *t*-test was used to evaluate the overall effects of treatment against baseline, followed by an analysis of each treatment compared with baseline by use of ANCOVA, taking into account previous treatment with an anxiolytic drug and household status (single- vs multiple-cat household). Sex was not taken into account, because there was only 1 female. During treatment, the drug and placebo groups were compared on a weekly basis by use of a *t*-test. Log or square-root transformations were used when necessary to achieve normality. A linear correlation analysis was performed, correlating the baseline weekly marking rate with the marking rate of week 4 after discontinuation for the treated group. Statistical procedures followed standard established methodology,[19] and a model or variable was considered statistically significant if $P < 0.05$.

## Results

In correspondence to the target enrollment, 20 cats that marked ≥ 6 times during baseline were entered into the treatment phase and were assigned

evenly to the drug and placebo groups. Of these, 1 cat was excluded, because the owner could not successfully administer the liquid formulation, and 2 were excluded because of a major change in household during the treatment phase. Of the 17 cats being analyzed for response to treatment, 9 cats had been assigned to the drug group, of which 1 was a female from a multiple-cat household and 1 was a male from a single-cat household; the remaining cats were males from multiple-cat households. The female and 1 male from a multiple-cat household had previously received anxiolytic treatment for the problem behavior. Mean age and weights for cats in the treated group were 6.3 years (range, 3 to 10 years) and 5.3 kg (range, 3.7 to 7.1 kg [11.7 {8.2 to 15.6} lb]), respectively. Eight male cats remained assigned to the placebo group; 1 was from a single-cat household, and the rest were from multiple-cat households. Two cats from multiple-cat households had received prior anxiolytic treatment for the problem behavior. The mean age and weights of cats in the placebo group were 4.9 years (range, 1 to 8 years) and 6.1 kg (range, 5.0 to 7.2 kg [13.4 {11.0 to 15.8} lb]), respectively.

In the treated group, there was a mean (± SE) of 8.6 (± 2.0) marks per week during the baseline period; the placebo group had a mean of 7.8 (± 1.5) marks per week for the same period. There was a significant decrease in marking episodes with both groups when the rate during the treatment phase was compared with that during the baseline phase ($P < 0.001$). There was no statistically significant interaction of prior anxiolytic treatment or household status with response to drug treatment versus placebo. Thus, the overall decline in marking rate was attributed to drug treatment, where the change in urine marks, compared to baseline, for the treated group was significant ($P < 0.005$); the change in urine marks from baseline for the placebo group was not significant ($P = 0.25$).

All but 1 treated cat had a decrease in urine marking during week 1. By week 2, marking had declined from baseline in all treated cats ($P = 0.003$) and continued to decline throughout the treatment phase, reaching a mean of 1.4 (± 0.4) marks per week for weeks 4 through 5. In 2 cats, there was not a 70% reduction in marking for weeks 4 through 5, so they received the increased dose during weeks 7 and 8. The mean number of marks per week in weeks 7 and 8 for all 9 cats decreased to 0.4 (± 0.2). By the end of the trial, all treated cats had > 90% reduction in urine marking per week, with 6 of 9 cats marking zero times during weeks 7 and 8, and the other 3 cats were marking a mean of 0.5, 1.5, and 2.0 times per week in this period (**Fig 1**). The cat that had a mean of 2 marks per week in weeks 7 and 8 had a mean of 21.5 marks per week during the baseline period. On a week-by-week basis, there was no difference in week 1 between the drug-treated and placebo groups ($P = 0.26$), but the groups differed significantly from weeks 2 through 8, with $P$ values between 0.004 and < 0.001.

In contrast to the treated group, during week 1 the 8 cats receiving placebo had a slight decrease in numbers of marks per week to 5.5 (± 1.8), but they did not decline in frequency of marking any further. In 7 of 8 cats, there was not a 70% reduction in marking for weeks 4 and 5, so they received an increased dose of placebo, but there was no further decline in mean marking rate for weeks 7 and 8 (Fig 1). The mean marking rate of the placebo group increased to the baseline rate by week 8, with 5 cats increasing marking over baseline and 3 cats having a reduction ranging from 27 to 60%.

At the end of week 8 of treatment, only cats in the drug group met the > 70% reduction in marking criterion; at this time, owners continued environmental management procedures and recording of urine marks. With regard to the return of urine marking after drug withdrawal, there was a great deal of variability. In 2 cats the marking remained at 0 for all 4 weeks, and in others marking returned to the baseline rate (**Fig 2**). However, cats that marked the most often during the baseline period were also often those marking the most during week 4 after drug withdrawal. Of the 3 cats with the lowest rate of marking in week 4 after treatment withdrawal (0 to 1 marks), the mean rate of marking during baseline was 7.2 (range, 4.5 to 9.5). Of the 3 cats with the highest marking rate in week 4 after treatment withdrawal (8 to 16 marks), the mean baseline rate was 15.2 (range, 7.5 to 16.5). A linear correlation analysis revealed a significant correlation coefficient of 0.82 between marking rate during baseline and marking rate during posttreatment week 4 ($F = 14.7$, $P$

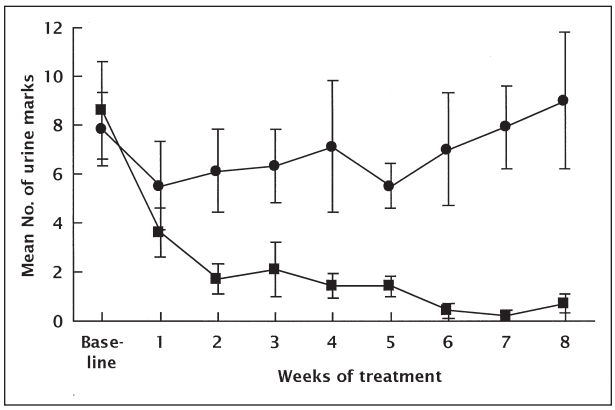


Figure 1—Mean (± SEM) number of urine marks per week during 2 weeks preceding and after initiation of treatment (baseline) and during 8 weeks of treatment with fluoxetine hydrochloride (n = 9; squares) or placebo (n = 8; circles) for urine marking in cats.

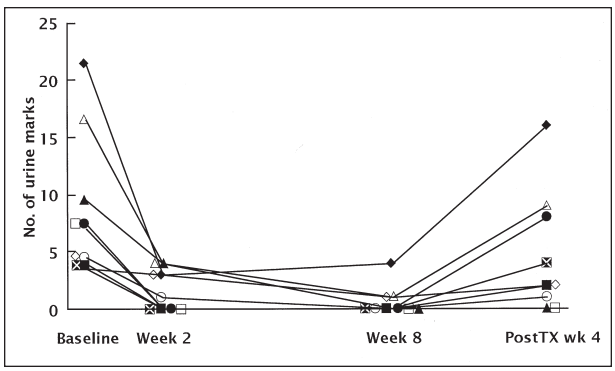


Figure 2—Weekly number of urine marks for 9 cats receiving fluoxetine hydrochloride during baseline, at weeks 2 and 8, and at posttreatment (post-TX) week 4.

= 0.006). A perusal of the history of each cat receiving treatment and analyzing factors such as the presumed causation factors and targets of the marking did not provide any further predictive information relating to the degree of recurrence of the marking behavior.

The main adverse effect recorded by owners was a decreased food intake, noted ≥ 1 times during at least 1 week for 4 of the 9 treated cats. In 3 cats, the decreased food intake was primarily during weeks 4 through 8, where the effect was seen at least once per week in 4 to 5 consecutive weeks. In 1 cat, the decreased food intake was only during week 1 of treatment. In 3 of the 8 cats on placebo, decreased food intake was noted ≥ 1 times during 1 of the weeks for each cat. In no instance was the decrease in food intake considered clinically significant. The only other adverse effects reported were vomiting and lethargy, both of which were rare. Vomiting was reported once in 1 cat receiving treatment and in 2 cats receiving placebo. Lethargy was reported once in 3 cats receiving treatment and in 2 cats receiving placebo.

## Discussion

The difference between the responses of cats receiving fluoxetine versus placebo was strikingly clear; our results revealed an overall significant and pronounced difference between groups. The lack of response of the placebo group was remarkable, given a rather large placebo response of animals in other trials involving drug treatment for problem behavior.[20-23] By the end of our study, the mean urine marking rate of the placebo group was increased to that during the baseline period. The lack of a major placebo response may be a reflection of the implementation of standardized environmental management procedures introduced during the baseline period. The low response observed in cats receiving placebo may also have been attributable to the fact that owners were counting urine marks and could see there was no decline.

The psychiatric literature stresses that the SSRI may require a lead-in time of 3 weeks or more to achieve full effectiveness.[14,24] The delay of full effect is theoretically explained by the molecular action of fluoxetine, which inserts itself into the serotonin reuptake pump. Initially the drug causes serotonin to increase primarily in the somatodendritic area, and the somatodendritic 5HT1A serotonin autoreceptors are downregulated or desensitized. The time course of this desensitization correlates with the onset of the therapeutic actions of the SSRI in people. Once these autoreceptors are desensitized, 5HT can no longer effectively inhibit its own release, and the serotonin neuron is therefore disinhibited.[24] In this study on cats, there was a significant reduction in urine marking in the treated cats, compared with placebo-treated cats, by the second week after initiation of treatment, and the difference between the treated and placebo groups increased from weeks 2 through 8. Whether the mechanisms of SSRI effects in cats are different from those in humans is unknown. The response of cats to fluoxetine in this study was greater than that observed in cats in open-label studies on diazepam[8,9] and buspirone,[10] which may reflect differences in effectiveness of the drugs or the small sample size (n = 9) we used, compared with treatment of 62 cats used in the buspirone study. The response of the cats when the drug was withdrawn was variable, as has been reported,[10] with some cats not resuming any marking and others resuming marking behavior.

A clinical protocol can be recommended for a pharmaceutical approach for control of urine marking in cats. The cat owners should first identify the problem cat (if the cat is in a multiple-cat household). Owners in the current study were apparently reliable in determining which cat was marking, because if a cat had been misidentified, the results would not have been so clear. Secondly, environmental management procedures, including daily cleaning of urine marks with an enzymatic cleaner, cleaning the litter box at least once a day, and changing the litter and washing the litter box at least once a week, should be implemented. Increasing the number of litter boxes in a multiple-cat household may be necessary to achieve a number of boxes equaling the number of cats plus 1. Reducing the opportunity for agonistic interactions with other cats inside or outside the home is also recommended. For example, one may block visual areas where an indoor cat may interact with outdoor cats in an unfriendly or agonistic fashion. These environmental management procedures should be implemented for at least 1 week, while marking events are recorded on a daily basis. This exercise will provide predictive information as to the degree of recurrence of the problem if treatment is discontinued after 8 weeks.

For those cats that continue to urine mark after implementation of environmental management, treatment with fluoxetine hydrochloride (1 mg/kg [0.45 mg/lb], PO, q 24 h) can be expected to cause a considerable reduction in urine marking, with positive results evident within 2 weeks. Presumably, other SSRI drugs would also be effective. The duration of treatment can be arranged on a case-by-case basis, guided by the principle that most cats should be treated more than 8 weeks before treatment is withdrawn.

[a]Fluoxetine hydrochloride (Prozac), Eli Lilly & Co, Indianapolis, Ind.
[b]Anti-Icky-Poo, Mister Max Quality Products, Lakeside, Calif.

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