Control of urine marking by use of long-term treatment with fluoxetine or clomipramine in cats

Benjamin L. Hart, DVM, PhD, DACVB; Kelly D. Cliff, DVM; Valarie V. Tynes, DVM; Laurie Bergman, VMD

Objectives—To determine whether clomipramine differs from fluoxetine in reducing feline urine marking; whether reduction of marking continues in cats treated > 8 weeks; whether recurrence of marking, after abrupt drug withdrawal, is less in cats treated > 8 weeks; and whether cats that are successfully treated but resume marking after drug withdrawal can be successfully treated again with the same drug regimen.

Design—Positive-controlled, double-masked clinical trial.

Animals—22 neutered cats (2 females, 20 males) ≥ 1 year old with objectionable urine marking.

Procedure—Cats that marked vertically ≥ 3 times/wk were treated with fluoxetine (1 mg/kg [0.45 mg/lb], q 24 h, PO) or clomipramine (0.5 mg/kg [0.23 mg/lb], q 24 h, PO) for 16 weeks, and efficacy was compared. Recurrence of marking was determined after abrupt withdrawal of fluoxetine at 16 or 32 weeks. Reduction in marking in cats treated with fluoxetine for 8 weeks after returning to marking following drug withdrawal was compared with the initial 8 weeks of successful treatment.

Results—Efficacy of fluoxetine and clomipramine was similar. Treatment > 8 weeks revealed increasing efficacy in reduction of marking. Return of marking after termination of fluoxetine administration occurred in most cats. Cats successfully treated initially with fluoxetine responded similarly to repeated treatment.

Conclusions and Clinical Relevance—Clomipramine and fluoxetine were equivalent in treating urine marking. Longer treatment increased efficacy. Most cats return to marking after abrupt drug withdrawal. A second course of treatment can be expected to be as effective as the first. (*J Am Vet Med Assoc* 2005;226: 378–382)

It is clear that antianxiety drugs will markedly reduce frequency of urine marking in most cats. Efficacy of such medication, generally administered for 8 weeks, reportedly ranges from > 90% reduction in cats treated during an 8-week period with the **selective serotonin reuptake inhibitor (SSRI)** fluoxetine hydrochloride in a placebo-controlled, double-masked trial[1] to most cats having at least partial reduction for other medications including diazepam, buspirone, and clomipramine hydrochloride in open-label trials.[2-5] The medications that have been effective in reducing urine marking have different mechanisms of influences on brain neurotransmitters.[6] The SSRIs, for example, increase serotonin concentration primarily by blocking its reuptake at the synaptic junction. Buspirone has serotonergic effects by presynaptic augmentation of serotonin release. The **tricyclic antidepressant (TCA)** clomipramine increases serotonin concentration by blocking serotonin reuptake and increases norepinephrine and dopamine concentrations by a similar mechanism. Benzodiazepines, such as diazepam, increase the effects of the inhibitory neurotransmitter γ-aminobutyric acid. These medications share the effect of reducing anxiety; this common effect may be the means through which urine marking is reduced. However, when recurrence has been evaluated, the studies also reveal recurrence of urine marking in most cats after drug withdrawal.

Further gains in the resolution of problem urine marking in cats should be attained by concentrating on treatment regimens that result in the greatest reduction of marking in the highest proportion of cats and that minimize the number of cats in which urine marking recurs after drug withdrawal. In the study reported here, these conceptual issues were examined by use of 2 drugs, rather than 1 drug and a placebo, and by use of a double-masked design for cat owners and investigators. The trial design, referred to as positive-controlled, double-masked, is standard in clinical pharmacology for testing 2 or more drugs when one of the drugs is superior to placebo.[7] The purpose of the study was to evaluate control of urine marking behavior by use of long-term treatment with fluoxetine hydrochloride and clomipramine hydrochloride. Because clinicians may wish to withdraw medication to determine whether a cat returns to urine marking, the response of cats to a second treatment after they had been successfully treated in an initial treatment was also evaluated.

Materials and Methods

Recruitment and enrollment of cats—Cats were recruited by use of newspaper advertisements announcing the study and enrollment at the **Veterinary Medical Teaching Hospital (VMTH)**, School of Veterinary Medicine, University of California, Davis, 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 UCMVC-SD. The newspaper advertisements and letters to veterinarians listed primary enrollment criteria: only 1 urine marking cat/household; mean of 3 or more vertical urine marks indoors per week for the problem cat; ≤ 4 cats/household; the cat must be castrated or spayed; and the

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

Supported by the University of California, Davis, Center for Companion Animal Health (allocation #01-47-F).

The authors thank Heather Mohan and Jennie Lane for technical assistance.

Address correspondence to Dr. Hart.

cat must not be presently receiving any medication for the problem behavior. A Web site that gave more enrollment information was listed. A telephone number was listed for owners to call and leave a message about possibly enrolling their cat. Screeners called back the interested owners and performed a screening interview that ascertained the estimated number of urine marks per week and, for multicat households, how owners determined which cat was marking. The purpose of screening was to reduce the number of cats seen in an appointment in which the owner was vague about which cat was responsible for the urine marks.

For owners whose cats appeared to meet enrollment criteria, an appointment was made with a veterinary behaviorist at the Behavior Service of the VMTH or UCVMC-SD. During these appointments, an interview was administered, which confirmed the enrollment criteria. By use of criteria of a previous study[1] (eg, owners may have only seen the nominated cat marking or only the nominated cat had access to marked area), particular attention was paid to ensure that there was only 1 urine marking cat in multicat households and that the owner knew which cat was marking. A physical examination was performed, and blood was obtained for a CBC and a serum biochemical profile. Urine for urinalysis was obtained by cystocentesis by use of ultrasound guidance if necessary. Cat owners who participated in the trial were required to sign a consent form in which they were notified that they may remove their cat from the trial at any time. They were also advised that if in the judgment of investigators they could not reliably record daily urine marking events or if there was a major change in the household that might affect urine marking, their cat could be removed from the trial.

Cats that met the household and behavioral criteria, and for which results of the CBC, serum biochemical analyses, and urinalysis were within reference ranges, were selected for enrollment in the baseline phase. Some cats that met medical criteria had been recently treated with medication by a referring veterinarian or had previously been enrolled in another trial on treatment of urine marking. If so, owners completed 4 weeks of nontreatment observations, the last 2 weeks of which served as the baseline for this trial. Twenty-two cats comprising 20 males and 2 females that satisfactorily completed baseline observations were enrolled.

Baseline observations—The owners were instructed to institute standardized daily litter box cleaning and cleaning of urine marks with an enzymatic cleaner as in a previous trial.[1] Cats in the baseline phase were assigned a treatment duration of 8, 16, or 32 weeks, and owners were given daily observation forms sufficient for the baseline phase and the anticipated duration of treatment (1 sheet/7 d). Owners of cats were asked to record, on a daily basis, the number and location of all urine marks. Because of concern regarding the owner's ability to distinguish urine marking from inappropriate urination,[1,8] only vertical marks were used in data analysis. They were also instructed to make notes about their cat's general behavior, appetite, and defecation. The owners were contacted weekly during baseline by monitors (same individuals as screeners) to transfer data to similar pages in the trial office. They were instructed to mail in their baseline daily recording forms at the end of the 2-week period.

Trial procedure—Cat owners whose cats successfully completed baseline and marked a mean of ≥ 3 times/wk, were sent coded drug that was custom formulated in a tuna-flavored liquid so that 1 mL of liquid represented either 1 mg of fluoxetine/kg (0.45 mg/lb) or 0.5 mg of clomipramine/kg (0.23 mg/lb) to be administered every 24 hours. The dosage of fluoxetine was the same as that previously found to be effective in controlling urine marking.[1] Additionally, results of a preliminary trial in 5 cats indicated that increasing the dose of fluoxetine to > 1 mg/kg every 24 hours did not increase efficacy. The dosage of clomipramine was approximately the same as that found to be at least partially effective in previous open-label trials.[4,5] Also, a preliminary trial on urine marking in 4 cats indicated that clomipramine at 0.25 mg/kg (0.11 mg/lb) every 24 hours for 8 or 16 weeks was not as effective as 0.5 mg/kg every 24 hours. One female cat each was assigned to the group that received fluoxetine for 16 weeks and the group that received clomipramine for 16 weeks.

When it was evident that the effectiveness of clomipramine in cats treated for 8 and 16 weeks was no greater than that of fluoxetine, the trial involved primarily cats treated with fluoxetine with a smaller number of cats treated with clomipramine, to maintain a masked control throughout the trial. Accordingly, the main study involved 16 cats treated with fluoxetine and 6 cats treated with clomipramine, both for 16 weeks. Five of the 16 cats treated with fluoxetine were reenrolled for 32 weeks of fluoxetine treatment after being evaluated for 4 to 8 weeks after withdrawal of fluoxetine. Cat owners were called weekly to answer questions and transfer data from their daily record sheets on urine marking frequency, appetite, defecation, and general observations of cat's behavior onto similar record sheets kept in the trial office. At the end of record keeping, they were required to return original data sheets to the trial office.

One aspect of this trial involved abrupt withdrawal of fluoxetine treatment; records were kept on the cats for 8 weeks after drug administration was discontinued. This procedure involved 6 cats treated for 16 weeks and 5 cats treated for 32 weeks.

An experiment to determine whether a cat that returns to urine marking after being successfully treated will again respond to treatment used the 5 cats reenrolled for 32 weeks of fluoxetine treatment. These cats had responded satisfactorily to the initial 8-week series of treatment, and the first 8-week series of the 32-week treatment phase was compared with the initial 8 weeks.

Monitoring adverse effects—Observations by cat owners on general behavior, appetite, and defecation were recorded on daily observation forms and available for all enrolled cats. The owners were asked to schedule an appointment during the final week of treatment with their regular veterinarian for blood sampling for CBC and serum biochemical analyses as in the enrollment examination (provided at no charge). For cats enrolled for 32 weeks, these tests were requested at 16 and 32 weeks. Results were available only for cats brought in for the requested evaluations. Most, but not all, cat owners complied with these requests.

Statistical analyses—Effects on marking were evaluated on the basis of mean number of vertical marks per week during the 2 weeks of baseline and mean number of vertical marks per week during 2-week periods during treatment. Percentage improvement over baseline in marking rate during various stages of treatment (2-week means) was represented by the following formula: (baseline rate – rate during treatment week/baseline rate) × 100. All statistical procedures involved nonparametric analyses.[9] Within-group comparisons of reduction of marking were performed by use of the Wilcoxon signed rank test for related subjects. Comparisons between fluoxetine and clomipramine treatment were performed by use of the Wilcoxon-Mann-Whitney test for independent subjects. Between-treatment analysis of the percentage of cats that improved to ≥ 90% was performed by use of the χ^2 test. When treatment weeks were compared with baseline, or with the same drug for different durations, the tests were 1-tailed because improvement was predicted on the basis of results of previous studies.[1,4,5] Tests between

drugs were 2-tailed. A Spearman rank correlation test was used to examine the degree to which the marking rate after drug withdrawal was correlated with the marking rate in baseline. For all comparisons, a value of $P \leq 0.05$ was considered significant.

Results

Comparison of fluoxetine with clomipramine— For the fluoxetine- and clomipramine-treated groups, the mean weekly baseline rate of marking was 9.9 and 12.8 events, respectively. By the end of week 1, there was a significant ($P < 0.02$) reduction in weekly mean number of marks in cats treated with clomipramine. By the end of week 2, cats treated with fluoxetine had a significant ($P < 0.01$) reduction. Thereafter, urine marking continued to improve with both treatments (**Figure 1**). As evident by the percentage improvement at weeks 7 to 8 and weeks 15 to 16, the reduction of urine marking for cats treated with either fluoxetine or clomipramine was approximately the same and not significantly different. The time course of change was also approximately the same. Improvement was characterized by pronounced improvement within 2 weeks followed by gradual improvement. In fluoxetine-treated cats, 7 of 16 reached the criterion of ≥ 90% improvement by 8 weeks and 11 of 16 reached the criterion by 16 weeks. Of clomipramine-treated cats, 2 of 6 reached this criterion at both 8 and 16 weeks. A significant difference between treatments with regard to this criterion was not found.

Among 16 fluoxetine-treated cats, improvement at weeks 7 to 8 ranged from 0 (n = 1) to 100% (3); 9 cats had improvement < 90%. Six cats continued to improve from weeks 7 to 8 to weeks 15 to 16, whereas 3 declined in improvement. Two of the cats with a decline in improvement were treated for 32 weeks, and by weeks 31 to 32, urine marking in these cats improved to > 90%, along with the other 3 cats treated for 32 weeks (**Figure 2**). Thus, all 5 cats treated for 32 weeks met the ≥ 90% improvement criterion with a mean improvement of 96%. Among the 6 clomipramine-treated cats, improvement at weeks 7 to 8 ranged from 0% (n = 1) to 100% (2). In 1 cat, there was a decline in improvement from weeks 7 to 8 to weeks 15 to 16; all of the other cats improved unless they were already 100% improved.

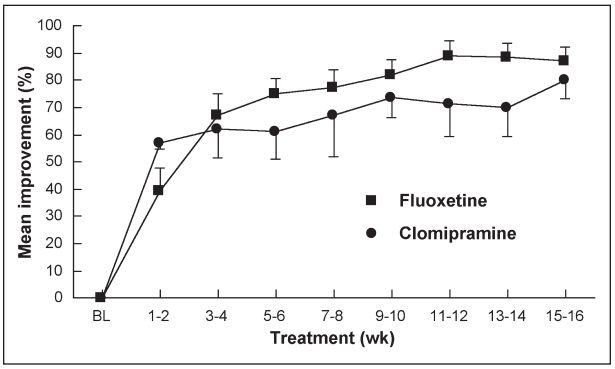

Figure 1—Comparative efficacy of fluoxetine (n = 16 cats) and clomipramine (6 cats) in reducing urine marking during a 16-week treatment period. Values are mean ± SEM improvement over baseline (BL) marking rate. Significant ($P \leq 0.05$) improvement was detected for both treatments by 2 weeks, and no significant differences were found between the 2 groups. Notice rapid improvement followed by gradual improvement.

Recurrence of urine marking after withdrawal of treatment—Most cats treated with fluoxetine for 16 and 32 weeks returned to some level of urine marking after abrupt drug withdrawal, although there was individual variability. Following withdrawal after 16 weeks of treatment in 6 cats, the marking rate increased in all cats and exceeded baseline in 4 cats. Among cats treated for 32 weeks, 1 had no recurrence of marking during treatment withdrawal; the other 4 cats returned to marking, reaching 25% to 80% of the baseline marking rate. There was a significant positive correlation (r^2 = 0.81) between the number of marks at baseline and the number of marks recorded at 8 weeks after treatment for cats treated 32 weeks. There was, however, no such correlation for cats treated for 16 weeks.

Response to second series of treatment—Five cats treated with fluoxetine that had ≥ 70% improvement before treatment was discontinued were then treated again with the same dosage of fluoxetine after marking returned to ≥ 70% of the baseline rate. A comparison was made between the first 8 weeks of the initial treatment and first 8 weeks of the second treatment. Approximately the same response was detected for the 2 periods regarding group mean values and individual patterns of response during the course of treatment (**Figure 3**).

Adverse effects—No cat was withdrawn from the trial because of adverse effects. Of 16 cats treated with fluoxetine for 16 weeks, decreased activity was noted in 1 cat and decreased aggression towards other cats was noted in 1 cat. Vomiting during 1 of the weeks, which resolved with no intervention, was noted in 2 cats. Otitis, which was resolved, occurred in 1 cat. Results of CBCs and serum biochemistry profiles, available for 15 cats, were within reference limits in 13 cats; in the 2 instances in which 1 or more variables were outside reference limits, the values had returned to reference ranges when evaluated 1 to 3 months later. Of the 5 cats treated for 32 weeks with fluoxetine, decreased aggression was noted in 1 cat and vomiting, which resolved, was noted in 1 cat. Conjunctivitis, which resolved, was also noted in 1 cat. In another cat, some variables of the biochemistry profile at week 32 were outside reference ranges, but these were within reference ranges at a later date.

Of 6 cats treated with clomipramine for 16 weeks, vomiting was noted during 1 week in 1 cat and decreased activity during 1 week in another. These signs resolved

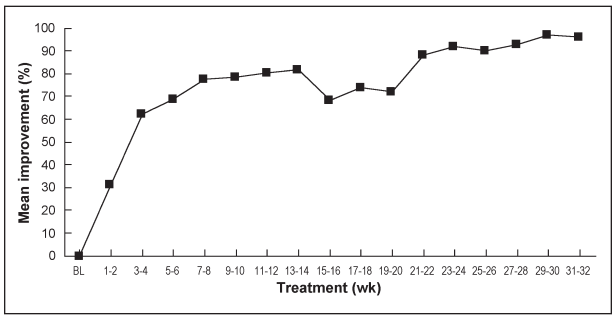

Figure 2—Mean improvement over BL urine marking rate in 5 cats treated with fluoxetine for 32 weeks.

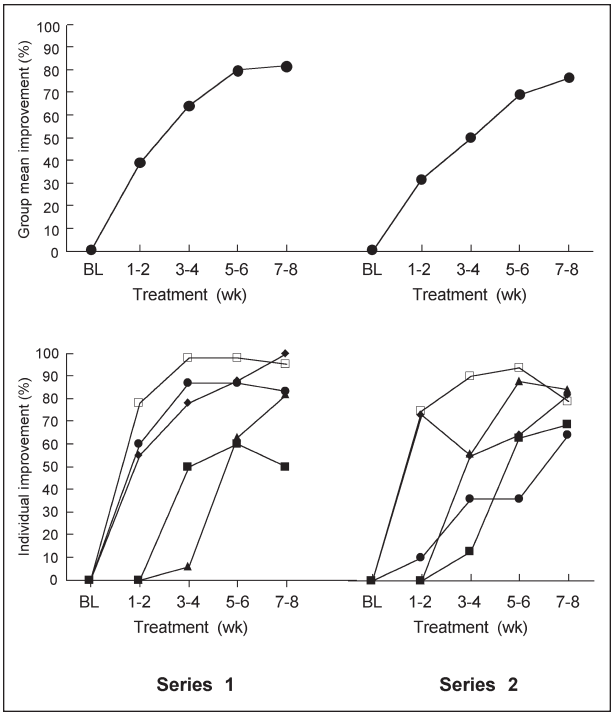

Figure 3—Comparison of mean improvement over BL weekly urine marking rate of 5 cats during 8 weeks of fluoxetine treatment (Series 1); drug administration was withdrawn until marking returned to that of approximately the BL rate, followed by a second series of identical treatments for 8 weeks (Series 2). The top panel represents the group mean; the lower panel represents responses of individual cats (identified by the same symbol between Series 1 and 2).

with no intervention or adjustment of drug dosage. Only 2 clomipramine-treated cats received CBC and serum biochemical analyses at the end of 16 weeks of treatment. In both instances, all variables were within reference limits.

Because there was no placebo-treated group, no statistical tests were conducted on the observations of potential adverse effects. The behavioral observations of transient episodes of vomiting or infection were considered unrelated to drug treatment. The observations of decreased activity and decreased aggression were attributed to possible effects of the antianxiety medication. The changes in CBC and serum biochemical values may have been incidental to or related to the effects of drug treatment.

Discussion

A marked decline in urine marking from baseline in cats treated with either fluoxetine or clomipramine was evident, and significant, by the end of the second week of treatment. Thereafter, a more gradual decline occurred, as evident in cats treated with either fluoxetine or clomipramine for 16 weeks and with fluoxetine for 32 weeks. There was no difference in overall response between fluoxetine and clomipramine after either 8 or 16 weeks of treatment. Only 6 cats were treated with clomipramine, so the possibility remains that a larger sample might reveal differences between the 2 drugs. However, the similar mean response level and time course with the 2 drugs suggest that major differences would not be found with a larger sample. Given that the treatment with fluoxetine and clomipramine was double masked and that a previous masked study[1] revealed much greater efficacy of fluoxetine, compared with placebo, the effects of fluoxetine and clomipramine in our study cannot be attributed to placebo.

The 16 fluoxetine-treated cats in our study varied more in response to drug treatment than those of the previous trial, in which all 9 fluoxetine-treated cats had ≥ 90% reduction in marking by the end of 8 weeks. The ≥ 90% criterion was reached by 7 of 16 fluoxetine-treated cats in our study at 8 weeks and by 11 of 16 cats at 16 weeks. During the course of treatment, improvement in some cats temporarily declined before improving again later. Only at 32 weeks did all fluoxetine-treated cats reach the ≥ 90% reduction criterion. The results suggest that with sufficiently prolonged treatment, almost all cats will reach the ≥ 90% improvement level. The delay in achieving full effect of the drug treatment could reflect the possibility that the full effect of treatment does not occur until 5-hydroxytryptamine 1a autoreceptors are downregulated.[6] The long-term treatment and efficacy of fluoxetine, with no cat appearing to become resistant to the dosage used, was noteworthy. It was also noteworthy that in the 5 cats that returned to urine marking after being successfully treated, response to a second treatment series was similar to that of the first treatment series. This is useful information for veterinarians when they wish to discontinue treatment to determine whether marking returns, knowing that they can expect to again control the marking, if it does return.

The major challenge in treating urine marking cats with an antianxiety drug is the recurrence of marking after drug withdrawal. Whether treated for 16 or 32 weeks, as in our study, or 8 weeks, as in a previous study,[1] almost all cats in which fluoxetine treatment was abruptly withdrawn returned to urine marking ranging from 25% to > 100% of the baseline marking rate. Whether this high proportion of recurrence would occur with gradual drug withdrawal requires further investigation. Also still to be investigated is whether the recurrence after drug withdrawal might differ between clomipramine and fluoxetine treatment.

Data from 2 studies[10,11] reveal that urine marking does not involve a lower urinary tract disorder. The findings suggest that in neutered males, problem urine marking is a manifestation of normal marking behavior that can be activated without hormonal support. The persistence of urine marking in adult male cats castrated in an attempt to resolve this problem is approximately 10%.[12] A similar phenomenon occurs with the persistence of sexual behavior, which is also androgen dependent.[13,14] One way of evaluating problem urine marking, which draws on the model of hormonal control of male-typical behavior, is that the neural circuitry, which usually requires androgen to be activated, can, in a few male cats, be activated without this hormonal support, provided that an evoking stimulus is present.[14] Fortunately, at least with urine marking, antianxiety medications seem to reliably suppress this normal behavior. In spayed females, which also have a neural basis for urine marking,[14] appropriate stimuli can occasionally provoke urine marking.[14]

Activating stimuli for urine marking in gonadectomized cats have been identified. Most important seem to be agonistic interactions between cats of the same household or with cats outside the household.[8] Because this type of environmental management could be difficult to standardize, cat owners were expressly told to not change the environment of the cat. One would expect that in clinical practice, managing the environment to reduce intercat aggressive encounters (in addition to managing environmental hygiene, as in the present study) would increase the likelihood of reducing urine marking by use of antianxiety medications and reduce the chances of recurrence of marking after drug withdrawal.

Monitoring of adverse effects revealed no indication of medically important effects other than some serum biochemical and CBC values outside reference limits in 2 of 15 cats treated with fluoxetine; the values returned to reference limits after drug withdrawal. Because long-term treatment of urine marking cats with antianxiety medication is likely, it is becoming apparent that planning for periodic health monitoring will be essential. Drug treatment is not likely to be useful for another type of problem urination in cats, inappropriate urination. As reported elsewhere,[15] an appreciable percentage of veterinarians do not seem to correctly differentiate urine marking from inappropriate urination, which is critical in designing a treatment plan.

References

1. Pryor PA, Hart BL, Cliff KD, et al. Effects of a selective serotonin reuptake inhibitor on urine spraying behavior in cats. *J Am Vet Med Assoc* 2001;219:1557–1561.
2. Cooper L, Hart BL. Comparison of diazepam with progestin for effectiveness in suppression of urine spraying behavior in cats. *J Am Vet Med Assoc* 1992;200:797–801.
3. Hart BL, Eckstein RA, Powell KL, et al. Effectiveness of buspirone on urine spraying and inappropriate urination in cats. *J Am Vet Med Assoc* 1993;203:254–258.
4. Dehasse J. Feline urine spraying. *Appl Anim Behav Sci* 1997; 52:365–371.
5. Landsberg G. Effects of clomipramine on cats presented for urine marking, in *Proceedings*. 3rd Int Cong Behav Med 2001;186–189.
6. Stahl SM. *Essential psychopharmacology*. 2nd ed. New York: Cambridge University Press, 2000;222–234.
7. Hart BL, Cliff KD. Interpreting published results of extra-label drug use with special reference to reports of drugs used to correct problem behavior in animals. *J Am Vet Med Assoc* 1996;209:1382–1385.
8. Pryor PA, Hart BL, Bain MJ, et al. Causes of urine marking in cats and effects of environmental management on frequency of marking. *J Am Vet Med Assoc* 2001;219:1709–1713.
9. Seigel S, Castellan NJ. *Nonparametric statistics for the behavior sciences*. 2nd ed. Boston: McGraw-Hill Book Co, 1988;111–124.
10. Tynes VV, Hart BL, Pryor PA, et al. Evaluation of the role of lower urinary tract disease in cats with urine-marking behavior. *J Am Vet Med Assoc* 2003;223:457–461.
11. Frank DF, Erb HN, Houpt KA. Urine spraying in cats: presence of concurrent disease and effects of a pheromone treatment. *Appl Anim Behav Sci* 1999;61:263–272.
12. Hart BL, Barret RE. Effects of castration on fighting, roaming, and urine spraying in adult male cats. *J Am Vet Med Assoc* 1973; 163:290–292.
13. Hart BL. Gonadal androgen and sociosexual behavior of male mammals. A comparative analysis. *Psychol Bull* 1974;81:383–400.
14. Hart BL, Eckstein RA. The role of gonadal hormones in the occurrence of objectionable behaviours in dogs and cats. *Appl Anim Behav Sci* 1997;52:331–344.
15. Bergman L, Hart BL, Bain M, et al. Evaluation of urine marking by cats as a model for understanding veterinary diagnostic and treatment approaches and client attitudes. *J Am Vet Med Assoc* 2002;221:1282–1286.