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

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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 open-label trials. The medications that have been effective in reducing urine marking have different mechanisms of influences on brain neurotransmitters. The SSRIs, for example, increase serotonin concentration primarily by blocking its reuptake at the synaptic junction. Buspiron 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. 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 UCVMC-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...
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 the test for independent subjects. Between-treatment analysis of the Wilcoxon signed rank test for related subjects. Proportions of reduction of marking were performed by use of the chi-square test for independent subjects. Between-treatment analysis of the percentage of cats that improved to ≥ 90% was performed by use of the Wilcoxon signed rank test for related subjects. Comparisons between fluoxetine and clomipramine treatment was 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 χ² 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.13 Tests between

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.5-7 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 marking frequency, appetite, defecation, and other observations of cats’ 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 daily on a daily observation forms 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 treated with fluoxetine, both for 16 weeks. Five of the 16 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 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.

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 frequency 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. 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 was 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 χ² 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.13 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 13 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 followed by gradual improvement. The time course of change was also approximately the same and not significantly different.

**Recurrent 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 $\geq 70\%$ improvement before treatment was discontinued were then treated again with the same dosage of fluoxetine after marking returned to $\geq 70\%$ 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...
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the time course with the 2 drugs suggest that major differ-

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tion. The observations of transient episodes of vomiting or infection were con-

sidered unrelated to drug treatment. The behavioral observations

of 2 clomipramine-treated cats received CBC and serum bio-

chemical 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 con-

sidered unrelated to drug treatment. The observations of decreased activity and decreased aggression were

attributed to possible effects of the antianxiety medica-

tion. The changes in CBC and serum biochemical val-

ues 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 treat-
ed 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 differ-

ces 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

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, improve-

ment 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 treat-

ment, almost all cats will reach the ≥ 90% improve-

ment 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-hydroxy-

tryptamine 1a autoreceptors are downregulated.8 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 suc-

cessfully 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 studies10,11 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 behav-

ior 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 approximatley 10%.12 A similar phenomenon occurs

with the persistence of sexual behavior, which is also

androgen dependent.13,14 One way of evaluating prob-

lem urine marking, which draws on the model of hor-

monal 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 stim-

ulus is present.19 Fortunately, at least with urine mark-

ing, antianxiety medications seem to reliably suppress

this normal behavior. In spayed females, which also

have a neural basis for urine marking,16 appropriate

stimuli can occasionally provoke urine marking.31


Figure 3—Comparison of mean improvement over BL weekly urine marking rate of 5 cats during 8 weeks of fluoxetine treat-

ment (Series 1); drug administration was withdrawn until mark-

ing 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 repre-

sents responses of individual cats (identified by the same sym-

bol between Series 1 and 2).
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. 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, 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