Randomized controlled trial of the efficacy of short-term amitriptyline administration for treatment of acute, nonobstructive, idiopathic lower urinary tract disease in cats

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Objective—To determine whether short-term amitriptyline administration would be efficacious in the treatment of acute, nonobstructive, idiopathic lower urinary tract disease in cats.

Design—Randomized controlled trial.

Animals—31 untreated male and female cats with acute, nonobstructive, idiopathic lower urinary tract disease.

Procedures—Cats were treated with amitriptyline (5 mg/d; n = 16) or a placebo (15) for 7 days and monitored for pollakiuria, hematuria, and adverse events. Cats were reexamined 1 month after treatment, and owners were interviewed by telephone 6, 12, and 24 months after treatment.

Results—2 amitriptyline-treated cats were excluded from analyses because of acquired urinary tract infection. Clinical signs resolved by day 8 in 8 amitriptyline-treated and 10 control cats. There were no apparent differences in likelihood or rate of recovery from pollakiuria or hematuria between groups. Overall, clinical signs recurred significantly faster and more frequently in amitriptyline-treated than control cats. However, after excluding recurrences within 21 days of treatment, risk of recurrence was similar in both groups. Increasing age was significantly associated with increased likelihood and rate of recovery from hematuria and with decreased risk of recurrence of signs.

Conclusions and Clinical Relevance—Results suggest that short-term amitriptyline treatment has no benefit in terms of resolution of pollakiuria and hematuria in cats with idiopathic lower urinary tract disease and may be associated with an increased risk of recurrence. (*J Am Vet Med Assoc* 2003:222:749–758)

Cats with naturally occurring **lower urinary tract disease (LUTD)** of unknown etiology are classified as having idiopathic LUTD.[1] Idiopathic LUTD is the most common cause of hematuria, dysuria, pollakiuria, and urination in inappropriate locations (periuria) in male and female cats.[1,2] During the past 4 decades, more than 30 agents or procedures have been recommended for management of idiopathic LUTD in cats,[3,4] but few of these proposed treatments have been evaluated in controlled clinical trials.[5-7] Debate surrounding the efficacy of various treatments is complicated by the self-limiting nature of some forms of idiopathic LUTD.[5,7-10] Clinical signs of hematuria, dysuria, and pollakiuria frequently subside within 7 days in many untreated male and female cats with nonobstructive idiopathic LUTD.[5,7,8] Signs may recur after variable periods of time and again subside without treatment.[5-9]

Amitriptyline hydrochloride has been advocated for the treatment of severe recurrent idiopathic cystitis in cats.[11-13] Amitriptyline is a tricyclic antidepressant drug with anticholinergic, antihistaminic, sympatholytic, analgesic, and anti-inflammatory properties.[14,15] On the basis of studies[14-18] in humans, rodents, and cats, amitriptyline is believed to exert its effects through inhibition of serotonin and norepinephrine reuptake with subsequent changes in central amine receptor systems as well as antagonism of muscarinic, histaminic, alpha-adrenergic, N-methyl-D-aspartate, and substance-P receptors. In humans, several weeks to months of treatment are often necessary before amitriptyline's antidepressant actions are clinically evident.[14,15] In contrast, in vivo studies in humans, rodents, and cats indicate that the anticholinergic,[17,19] antihistaminic,[20] sympatholytic,[21,22] analgesic,[23-27] and anti-inflammatory[28-30] effects of amitriptyline and other tricyclic antidepressants are more rapid in onset (often within several days). Consequently, amitriptyline and other tricyclic antidepressants have been used in humans for treatment of various nonpsychiatric conditions, including long-term treatment of chronic pain and inflammatory syndromes[24,27,31-33] and short-term treatment of acute pain.[34,a]

Amitriptyline has been used extensively for treatment of human patients with interstitial cystitis,[31,35,36] a chronic idiopathic LUTD characterized by urinary urgency and frequency, pelvic or perineal pain, and

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characteristic (nonspecific) cystoscopic lesions[35] that shares many clinical features with chronic forms of idiopathic LUTD in cats.[37] Results of uncontrolled studies[31,b] suggested that amitriptyline was of benefit in reducing symptoms in 60 to 90% of humans with interstitial cystitis. Similarly, in an uncontrolled study[13] of cats with severe recurrent idiopathic cystitis, clinical signs decreased in 9 of 15 cats treated with amitriptyline for 12 months, with most cats that responded favorably doing so within the first week of treatment.

Abrupt cessation of long-term amitriptyline treatment in humans may precipitate a constellation of stereotypic clinical signs collectively referred to as the tricyclic antidepressant withdrawal syndrome.[38-43] However, tricyclic antidepressant withdrawal syndrome is rare in humans treated with amitriptyline for < 4 weeks.[38] To our knowledge, tricyclic antidepressant withdrawal syndrome has not been reported in cats.

Because of amitriptyline's potent anticholinergic and antihistaminic properties, the rapid onset of analgesic and anti-inflammatory effects, and the rapid response of cats with severe recurrent idiopathic cystitis, we hypothesized that short-term (7 day) treatment with amitriptyline may also be of benefit in reducing the duration of clinical signs in cats with acute, nonobstructive, idiopathic LUTD. The purpose of the study reported here, therefore, was to determine whether short-term amitriptyline treatment was efficacious in cats with acute, nonobstructive, idiopathic LUTD.

Materials and Methods

Study population—Forty-two cats with acute signs of pollakiuria, stranguria, dysuria, and hematuria evaluated at the Michigan State University Veterinary Teaching Hospital between October 1, 1996, and September 30, 2000, were considered for inclusion in the study. Only those cats with acute, nonobstructive, idiopathic LUTD of < 14 days' duration were eligible for inclusion in the study. The diagnosis of idiopathic LUTD was made by exclusion of other potential causes for the pollakiuria, dysuria, stranguria, and hematuria.[44] Cats were excluded from the study if any other cause of the pollakiuria, dysuria, stranguria, or hematuria was identified; clinical signs were of > 2 weeks duration; the cat had had > 1 episode of clinical signs in the preceding 3 months; the cat had received any type of treatment (including calculolytic diets) during the preceding 2 weeks; or any other major illness involving another body system was detected. Of the 42 cats evaluated, 11 were excluded because of urolithiasis (3), previous treatment (2), bacterial urinary tract infection (2), chronic renal failure (1), cardiomyopathy (1), or a lack of clinical signs (2). Owners of the 31 cats enrolled in the study provided informed consent.

Experimental protocol—In all cats, a history was obtained, and a complete physical examination, CBC, serum biochemical profile, and urinalysis were performed. The body condition of each cat was scored on a 3-point scale (1 = thin, 2 = normal, 3 = obese). Urine samples were submitted for quantitative culture for aerobic bacteria, mycoplasmas, and ureaplasmas. Survey radiographs of the abdomen were obtained. Cats were then sedated with ketamine hydrochloride (10 mg/kg [4.5 mg/lb]) and midazolam (0.2 mg/kg [0.09 mg/lb]), IM, and double-contrast cystography and antegrade positive-contrast urethrography were performed.[45,46]

Cats were randomly assigned to 1 of 2 treatment groups with a simple blocked randomization procedure.[47] Cats in the amitriptyline group received a gelatin capsule containing 5 mg of amitriptyline[c] and lactose[c] once daily in the evening for 7 days. Cats in the control group received a placebo consisting of an identical capsule containing lactose[a] once daily in the evening for 7 days. Compounding and distribution of amitriptyline and placebo capsules were directed by a clinical pharmacologist. Neither owners nor attending clinicians knew to which group cats had been assigned. Treatment commenced within 24 hours after collection of samples for the initial database.

Clinical evaluation—All but 2 cats were hospitalized for 8 days after initiation of treatment to facilitate daily observation of clinical signs, frequency of urination and defecation, and collection of urine for detection of gross and microscopic hematuria. As a convenience to owners, 1 cat was hospitalized for 14 days, and 1 cat was hospitalized for 9 days. During the time of hospitalization, cats were fed their normal diet, as provided by their owners. Physical examinations were performed daily on all cats. Micturition frequency was quantified by observation of urine in litter trays; shredded wax paper was used in the litter trays. All cats were observed 5 to 10 times during each 24-hour period. A fresh litter tray was provided after each urination or defecation. Pollakiuria was defined as > 3 urinations per day. Urine retention was defined as no urination for 48 hours. Constipation was defined as no defecation for 48 hours. Because cystocentesis may induce transient microscopic hematuria, only naturally voided urine samples were collected. Each urine sample was examined for gross hematuria; a reagent strip[d] was used to test for occult hematuria. Hematuria was defined as grossly visible blood in the urine, > 5 RBCs/hpf in the urine sediment, or any color reaction indicating nonhemolyzed or hemolyzed occult blood on the reagent strip.

Twenty-four hours after administration of the last capsule (day 8), urine was collected for a urinalysis and quantitative bacterial culture, and a CBC and serum biochemical profile were performed. Approximately 1 month later, cats were reexamined at the veterinary teaching hospital, and a complete physical examination, CBC, serum biochemical profile, urinalysis, and quantitative bacterial culture of a urine sample were performed. Owners were contacted by telephone 6 and 12 months after the end of treatment and annually thereafter and asked whether there had been any recurrence of clinical signs of hematuria, dysuria, pollakiuria, periuria, or any episodes of urethral obstruction.

The treatment group code was broken for the first 27 cats enrolled in the study 1,162 days after the study was initiated, and interim analyses were performed. Follow-up time for these first 27 cats ranged from 17 to 870 days. The treatment code was broken for the remaining 4 cats, all of which were enrolled after the interim analyses, 342 days after interim analyses, and final analyses were performed. Follow-up time for these 4 cats ranged from 44 to 295 days.

Statistical analyses—The main factor of interest in all analyses was administration of amitriptyline. Other factors that were included in the analyses because of their possible effects on recovery and recurrences included age at the time of initial diagnosis of idiopathic LUTD, number of previous episodes of LUTD, number of days with clinical signs prior to treatment, diet moisture content during treatment, diet moisture content following treatment, and body condition score. For analysis of efficacy, outcome variables of interest included recovery from pollakiuria, hematuria, or both pollakiuria and hematuria and number of days to resolution of pollakiuria, hematuria, or both pollakiuria and hematuria. For analysis of risk of recurrence, outcome variables of interest included recurrence of clinical signs, total number of recurrences, time between recurrences, and duration of recurrences.

Descriptive statistics were generated for the outcome variables. Fisher exact 2-tailed tests[48] and Kruskal-Wallis χ^2 tests[48] were used to test categorical and continuous variables for significant differences between groups. Multivariable logistic regression was used to model the effects of treatment and other factors on recovery from pollakiuria, hematuria, or both pollakiuria and hematuria.[48] Survival analysis with multivariable proportional hazards models was used to assess the effects of treatment and other factors on number of days to recovery from pollakiuria, hematuria, or both pollakiuria and hematuria.[48] Survival analysis was also used to assess the effects of treatment and other factors on recurrence of clinical signs of LUTD. Two-way repeated-measures ANOVAs were used to compare body weight, urine specific gravity, and results of CBCs and serum biochemical analyses performed before and after treatment.[48]

Results

Mean ± SD age of the 31 cats enrolled in the study was 67 ± 39 months. Mean body weight was 5.4 ± 1.6 kg (11.9 ± 3.2 lb). Ten cats were classified as obese. Twenty-six cats were male, and 5 were female. Twenty-seven were of mixed breeding, and 4 were purebred. Twenty-three lived indoors exclusively, and 8 had access to the outdoors. Twenty-one lived with other cats. Twenty-three were fed dry cat food exclusively, 1 was fed canned food exclusively, and 7 were fed a mixture of dry and canned food. Ten cats had a history of ≥ 1 previous episodes of clinical signs compatible with LUTD (4 cats with 1 previous episode, 3 with 2 previous episodes, and 1 each with 3, 4, and 6 previous episodes). Pollakiuria was the most common clinical sign (n = 29) followed by gross hematuria (21), stranguria (19), periuria (urination outside of the litterbox, 16), and dysuria (7). Duration of clinical signs prior to treatment ranged from 1 to 10 days (mean, 3.6 ± 2.4 days). No significant differences were found between the treatment and control groups with respect to age, sex, breed, lifestyle, body weight, body condition score, diet consistency, clinical signs, duration of clinical signs, and number of previous episodes of LUTD.

Mean ± SD specific gravity of urine samples obtained from cats at the time of enrollment in the study was 1.054 ± 0.011. Microscopic hematuria (> 5 RBCs/hpf) was detected in 22 of the 31 (71%) cats; pyuria (> 5 WBCs/hpf) was detected in 6 (19%). Crystalluria was observed in 15 (48%). Results of CBCs and serum biochemical profiles were unremarkable. Quantitative bacterial culture of urine samples failed to yield any growth. The most common radiographic abnormalities were generalized thickening of the urinary bladder wall (n = 20), irregular mucosa (5), and urethral dilatation (1); no radiographic abnormalities were seen in 9 cats. Treatment and control cats did not differ significantly in regard to results of pretreatment CBCs, serum biochemical analyses, urinalyses, and radiographic evaluations.

All 31 cats completed the course of treatment. However, 2 cats receiving amitriptyline were excluded from further analyses because of acquired bacterial urinary tract infection detected on day 8. Pollakiuria resolved by day 8 in 12 of the 14 amitriptyline-treated cats and 11 of the 15 control cats. Hematuria resolved by day 8 in 8 amitriptyline-treated cats and 12 control cats. Both pollakiuria and hematuria resolved by day 8 in 8 amitriptyline-treated cats and 10 (67%) control cats. There were no significant differences in the likelihood of recovery (multivariable logistic regression, $P \geq 0.1$) or rate of recovery (survival analysis, $P > 0.5$) from pollakiuria, hematuria, or both pollakiuria and hematuria between amitriptyline-treated and control cats **(Tables 1 and 2)**.

Increasing age was significantly associated with an increased likelihood of recovery from hematuria and with a more rapid rate of recovery from hematuria and both pollakiuria and hematuria. Ten of the 11 cats ≥ 6 years old recovered from both pollakiuria and hematuria by day 8 regardless of treatment, compared with 6 of 11 cats between 3 and 6 years old and 2 of 7 cats between 1 and 3 years old. Number of previous episodes of LUTD, number of days with clinical signs prior to treatment, diet moisture content, and body condition were not associated with likelihood or rate of recovery from pollakiuria, hematuria, or both pollakiuria and hematuria (Tables 1 and 2).

During the treatment and 30-day post-treatment follow-up phases, adverse events were observed in all 16 cats treated with amitriptyline and 11 of 15 control cats. Adverse events observed in both groups included urine retention (n = 1 treated, 1 control), constipation (11 treated, 10 controls), vomiting (2 treated, 2 controls), mild neutropenia (3 treated, 2 controls), and mild basophilia (3 treated, 1 control). Adverse events

Table 1—Results of multivariable logistic regression analysis evaluating the likelihood of recovery from pollakiuria, hematuria, or pollakiuria and hematuria among 29 cats with acute, nonobstructive, idiopathic lower urinary tract disease treated with amitriptyline (n = 14; 5 mg, PO, q 24 h) or a placebo (15)

	Pollakiuria			Hematuria			Pollakiuria and hematuria		
Variable	**RR**	**95% CI**	***P* value**	**RR**	**95% CI**	***P* value**	**RR**	**95% CI**	***P* value**
Amitriptyline	4.4	0.3–72.7	0.29	0.01	0.001–2.2	0.09	0.2	0.01–7.5	0.37
Age (in months)	2.1	0.8–5.3	0.12	5.0	1.3–19.7	0.02	4.4	1.0–19.2	0.057
No. of previous episodes	0.1	0.1–1.5	0.14	0.5	0.1–6.1	0.62	0.2	0.02–3.0	0.27
No. of days with signs prior to treatment	0.1	0.3–1.0	0.06	1.2	0.6–2.8	0.61	0.7	0.3–1.5	0.37
Diet moisture content[a]	1.6	0.2–13.4	0.65	0.01	0.001–3.3	0.13	0.02	0.001–1.9	0.09
Body condition[b]	0.6	0.02–25.4	0.81	144.6	0.1–999	0.18	4.1	0.04–427	0.55

RR = Risk ratio. CI = Confidence interval.
[a]Diet classified as exclusively dry, exclusively canned, or mixed dry and canned. [b]Body condition was classified as thin, normal, or obese by the attending clinician.

Table 2—Results of survival analysis evaluating the number of days to recovery from pollakiuria, hematuria, or pollakiuria and hematuria among 29 cats with acute, nonobstructive, idiopathic lower urinary tract disease treated with amitriptyline (n = 14; 5 mg, PO, q 24 h) or a placebo (15)

	Pollakiuria[a]			Hematuria[b]			Pollakiuria and hematuria[c]		
Variable	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Amitriptyline	0.7	0.3–1.8	0.51	1.2	0.4–3.3	0.76	1.0	0.3–2.7	0.94
Age (in months)	1.2	1.0–1.4	0.11	1.3	1.0–1.5	0.017	1.3	1.0–1.6	< 0.007
No. of previous episodes	0.8	0.6–1.2	0.37	0.9	0.6–1.3	0.49	0.9	0.6–1.3	0.48
No. of days with signs prior to treatment	0.9	0.8–1.2	0.56	1.1	0.9–1.4	0.27	1.1	0.9–1.4	0.38
Diet moisture content	1.0	0.3–3.0	0.96	0.7	0.2–2.5	0.61	0.6	0.2–2.0	0.37
Body condition	0.9	0.4–2.4	0.88	1.3	0.4–3.6	0.67	0.9	0.3–2.8	0.80

HR = Hazard ratio.
[a]Six cats censored from analysis. [b]Nine cats censored from analysis. [c]Eleven cats censored from analysis.
See Table 1 for remainder of key.

Table 3—Results of survival analyses evaluating the risk of recurrence of signs of lower urinary tract disease in 29 cats with acute, nonobstructive, idiopathic lower urinary tract disease treated with amitriptyline (n = 14; 5 mg, PO, q 24 h) or a placebo (15)

	All recurrences[a]			Recurrences within 7 days after treatment[b]			Recurrences within 21 days after treatment[b]		
Variable	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Amitriptyline	0.3	0.07–0.99	0.048	0.4	0.1–1.8	0.24	0.5	0.1–1.8	0.28
Age (in months)	0.9	0.7–1.1	0.26	0.7	0.6–0.9	0.008	0.7	0.5–0.9	0.01
No. of previous episodes	1.1	0.7–1.7	0.78	2.0	1.2–3.4	0.006	2.5	1.4–4.6	0.002
Post-treatment diet moisture content	1.3	0.4–4.4	0.66	3.3	0.7–14.3	0.12	4.8	0.8–28.4	0.09
Body condition	2.7	0.9–8.1	0.08	1.5	0.4–5.9	0.61	3.2	0.8–12.8	0.10

[a]Twelve cats censored from analysis. [b]Fifteen cats censored from analysis.
See Tables 1 and 2 for remainder of key.

observed only in amitriptyline-treated cats included bacterial urinary tract infection (n = 3), sedation (4), increased serum **alanine aminotransferase (ALT)** activity (1), and increased total bilirubin concentration (1). *Staphylococcus intermedius* (> 10^3 cfus/mL) was detected in urine samples from 2 cats with bacterial urinary tract infection, and *Enterococcus* spp (> 10^5 cfus/mL) was detected in a urine sample from the third; for all 3 cats, urine samples were obtained by means of cystocentesis. Serum ALT activity in 1 cat treated with amitriptyline increased from 91 U/L prior to treatment to 182 U/L immediately after treatment (reference range, 23 to 109 U/L). Thirty days after treatment, ALT activity was 143 U/L. In another cat treated with amitriptyline, serum total bilirubin concentration increased from 0.5 mg/dL prior to treatment to 1.1 mg/dL immediately after treatment (reference range, 0.1 to 0.7 mg/dL). Thirty days after treatment, serum total bilirubin concentration was within reference limits. Prior to treatment, immediately after treatment (day 8), and 30 days after treatment, there were no significant differences between groups in regards to Hct; total WBC, segmented neutrophil, lymphocyte, and eosinophil counts; urine specific gravity; serum concentrations of creatinine, sodium, potassium, magnesium, calcium, phosphorous, total CO_2, albumin, globulin, glucose, and total bilirubin; and serum ALT and alkaline phosphatase activities.

Two cats received amitriptyline after the initial treatment period and were censored from long-term follow-up analyses. Diet moisture content changed from an exclusively dry diet to a mixed dry and canned diet during the follow-up period in 2 amitriptyline-treated cats and from a mixed diet to an exclusively dry diet in 1 control cat. Changes in diet formulation occurred in 6 of the 13 amitriptyline-treated cats available for long-term follow-up at various times after treatment. Two were switched to commercial diets specifically designed to minimize struvite crystalluria, 3 were switched to another commercial feline maintenance diet, and 1 was briefly fed a home-cooked diet before returning to its previous commercial diet. Changes in diet formulation occurred in 4 of the 14 control cats available for long-term follow-up at various times after treatment. Two were switched to a commercial diet specifically designed to minimize struvite crystalluria, 1 was switched from a diet designed to minimize struvite crystalluria to a maintenance diet, and 1 was switched to another maintenance diet.

Overall, owners of 12 of the 14 amitriptyline-treated cats and 8 of the 15 control cats reported ≥ 1 recurrence of signs compatible with LUTD. In all but 2 cats, clinical signs associated with recurrent episodes resolved spontaneously without additional treatment. A total of 28 episodes over a period of 6,456 blinded follow-up days were reported for amitriptyline-treated cats, and 22 episodes over 7,942 days were reported for control cats. Overall incidence densities of recurrent episodes of signs of LUTD were 10.5 events/1,000 d at risk for amitriptyline-treated cats and 2.6 events/1,000 d at risk for control cats. Amitriptyline-treated cats were significantly more likely to have a recurrence of signs than were control cats after controlling for age, number of previous episodes of LUTD, diet moisture content after treatment, and body condition score (**Table 3**).

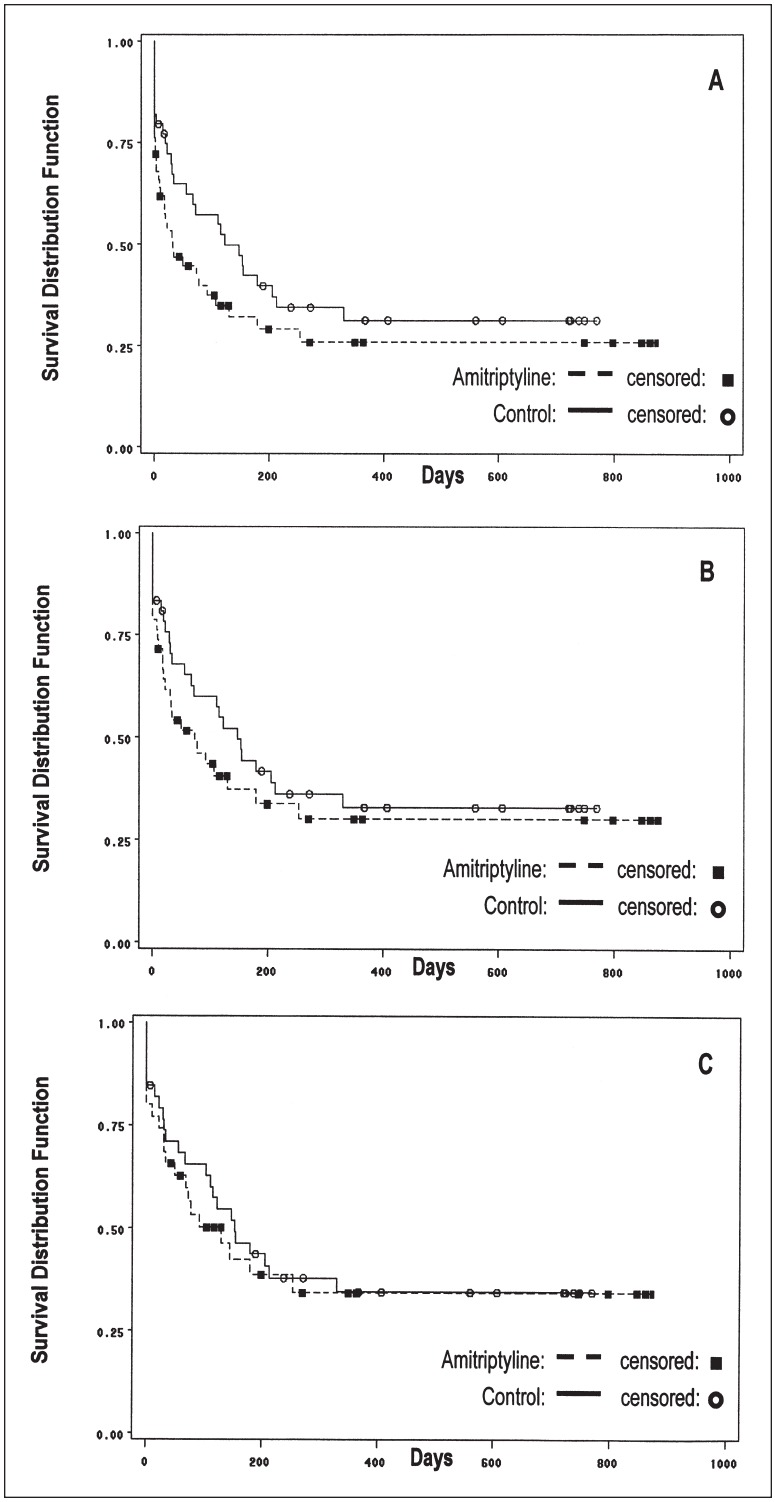

Figure 1—Survival distribution functions for the number of days to recurrence of signs of lower urinary tract disease in 29 cats with acute, nonobstructive, idiopathic lower urinary tract disease treated with amitriptyline (n = 14) or a placebo (15), controlling for age, number of pretreatment episodes of lower urinary tract disease, post-treatment diet moisture content, and body condition. The survival distribution function indicates, at a selected point in time, the probability that a cat will not have had a recurrence of signs of lower urinary tract disease. A—Overall model including all episodes of recurrent signs of lower urinary tract disease. B—Seven-day model excluding all recurrences occurring within 7 days of discontinuation of treatment. C—Twenty-one day model excluding all recurrences occurring within 21 days of discontinuation of treatment.

Signs of LUTD recurred within the first 7 days after treatment in 5 of 14 amitriptyline-treated cats but only 1 of 15 control cats, and mean time to first recurrence of signs was significantly shorter in amitriptyline-treated cats (24 days) than control cats (98; Mann-Whitney rank sum test, $P < 0.05$). Because recurrence of clinical signs shortly after discontinuation of treatment may have represented incomplete resolution of signs associated with the original episode (relapse) or a reaction to the discontinuation of amitriptyline, the risk of recurrence was reevaluated by sequentially excluding episodes occurring within 7 (7-day model) and 21 (21-day model) days of discontinuation of treatment (**Fig 1**). After exclusion of all episodes occurring within 7 days after treatment, clinical signs recurred in 9 of 13 amitriptyline-treated and 7 of 15 control cats. Survival analysis excluding recurrences occurring within 7 days after treatment did not reveal any effect of amitriptyline treatment on risk of recurrence of signs of LUTD (Table 3). In this model, however, increasing age was associated with a significantly lower risk and increasing number of previous episodes of LUTD was associated with a significantly higher risk of recurrence of clinical signs. Examination of graphs of the survival distribution functions for the 7-day model revealed evidence of a continued early post-treatment effect of amitriptyline on risk of recurrence of clinical signs (Fig 1). After exclusion of all episodes occurring within 21 days of treatment, clinical signs recurred in 7 of 13 amitriptyline-treated cats and 6 of 14 control cats. Results of survival analysis excluding recurrences occurring within 21 days of treatment were similar to those for survival analysis excluding recurrences within 7 days of treatment (Table 3).

Discussion

Only cats with acute, nonobstructive, idiopathic LUTD were included in the present study. Nonobstructive, idiopathic LUTD is more common than the obstructive form of the disease,[49,50] and it is our clinical impression that acute, nonobstructive, idiopathic LUTD is more common than the chronic and frequently recurrent forms. The demographic features, clinical signs, and clinicopathologic and radiographic findings of cats in this study were similar to those reported for cats with idiopathic LUTD in general.[1,2] Most cats were young to middle aged,

lived indoors with at least 1 other cat, and consumed a dry commercial diet. However, there were a disproportionately large number of male cats enrolled in our study. Since previous studies[1,2] have demonstrated that idiopathic LUTD tends to affect males and females equally, it is unlikely that this disparity represented a predisposition for acute, nonobstructive, idiopathic LUTD among male cats. More likely, it represented a selection bias for male cats. We speculate that owners were more willing to enroll male cats in the study because of the risk of urinary tract obstruction and the benefit of continuous monitoring during hospitalization.

Results of the present study suggest that short-term amitriptyline treatment had no apparent beneficial effect on recovery from hematuria or pollakiuria in cats with acute, nonobstructive, idiopathic LUTD. Clinical signs resolved in most cats by day 8 regardless of treatment. Our observations are consistent with those of previous clinical reports and controlled studies investigating treatments for idiopathic LUTD.[5,7-10] In those studies, clinical signs tended to resolve in most cats within 7 days regardless of treatment. Nevertheless, results of the present study should be viewed with caution. The lack of a demonstrable treatment effect could be related to subtherapeutic treatment (ie, insufficient dosage, inadequate duration of treatment, or both), possible therapeutic effects of diagnostic procedures, a placebo effect, or an insufficient sample size to detect small treatment differences.

The dosage of amitriptyline used in this study corresponded to 0.55 to 1.16 mg/kg (0.25 to 0.53 mg/lb) once daily. A daily amitriptyline dosage of 0.33 to 1.0 mg/kg has been effective in the treatment of interstitial cystitis in some human beings,[31,35,d] and the empirically recommended dosage for treatment of cats with chronic idiopathic cystitis is between 2.5 and 12.5 mg, every 24 hours, adjusted to achieve a barely perceptible calming effect on the cat.[12] A dosage of amitriptyline of 5 to 10 mg every 24 hours has also been used to treat cats with severe recurrent idiopathic cystitis.[13] Although a higher dosage of amitriptyline may have been more effective in the present study, the risks of adverse effects and the short duration of treatment precluded use of a higher initial dosage or titration to a higher dosage during the treatment period. It is also possible that a longer duration of treatment would have influenced outcome. In an uncontrolled study[13] of 15 cats with severe recurrent idiopathic cystitis treated with amitriptyline for 12 months, clinical signs resolved in 9 cats despite persistent cystoscopic urinary bladder lesions.

Conversely, the lack of difference between responses of amitriptyline-treated and control cats in the present study could have represented a therapeutic effect resulting from diagnostic interventions that were performed prior to treatment. Controlled hydraulic distension of the urinary bladder (therapeutic urohydrodistension) has been known for > 70 years to be of transient therapeutic value in human patients with interstitial cystitis,[51] and approximately 30% of human patients with interstitial cystitis experience substantial but temporary relief of symptoms after urohydrodistension.[52] Similarly, controlled distention of the urinary bladder during cystoscopy reportedly has been associated with a reduction in the severity of clinical signs in some cats with idiopathic cystitis.[11] Although the exact mechanism is unknown, urohydrodistension may induce increased urothelial glycosaminoglycan production, depletion of bladder sensory nerve neuropeptides, or mechanical or ischemic degeneration of sensory nerve endings in the bladder wall.[11,52,e] It is conceivable that urinary bladder distension during double-contrast cystography had a therapeutic effect in cats in the present study. Until other, more specific and less invasive markers of idiopathic LUTD are identified, it will be difficult to isolate the beneficial effects of bladder distension for diagnostic purposes from those induced by various forms of treatment.

A placebo effect may account, at least in part, for the lack of apparent difference between responses of amitriptyline-treated and control cats in the present study. Although studies in cats are lacking, studies[53] in other animal species have documented beneficial physiologic and health effects resulting from visual and tactile contact with humans. Frequent animal contact was a necessary part of the present study, but may itself have had a role in recovery from idiopathic LUTD. Future clinical trials incorporating a control group given a placebo should take into account the potential for a placebo effect when evaluating therapeutic responses in cats with idiopathic LUTD.

Lack of a demonstrable beneficial effect of short-term amitriptyline administration may represent a type II statistical error (ie, failure to reject the null hypothesis when it is false). A type II error can occur when the sample size is inadequate to detect small but clinically meaningful treatment effects.[54] Based on the sample size in the present study, the probabilities (power) of detecting a clinically meaningful change in the rate of recovery from pollakiuria, hematuria, or both pollakiuria and hematuria were estimated to be 26, 13, and 14%, respectively.[55] To achieve a statistical power of 80%, the study would have required a sample size of > 150 cats. Consequently, the apparent lack of a beneficial response of short-term amitriptyline administration on amelioration of clinical signs of acute, nonobstructive, idiopathic LUTD must be interpreted within this context. Although a larger sample size would have facilitated detection of more subtle beneficial therapeutic effects, the trial was terminated early because of the increased risk of recurrence of clinical signs after discontinuation of amitriptyline administration in treated cats. Because of the increased risk of relapse, any benefit of short-term amitriptyline administration that might be detected in a larger sample would have to be weighed against the risk of potential adverse effects that may be encountered during or after treatment. The apparent lack of beneficial effects of short-term administration in cats with acute disease does not preclude the possibility that long-term amitriptyline administration may be of value for cats with more severe or persistent forms of idiopathic LUTD.[13] However, proof of this hypothesis would require controlled clinical trials of amitriptyline in cats with chronic or frequently recurrent forms of idiopathic LUTD.

Increasing age was significantly associated with an increased likelihood of recovery from hematuria and an increased rate of recovery from hematuria and both pollakiuria and hematuria. In contrast, we were unable to identify associations between other factors (number of previous episodes, number of pretreatment days, diet moisture content, and body condition) and recovery from hematuria or pollakiuria. Lack of association of these variables with recovery must be interpreted within the context of the small sample size. The effect of increasing age on recovery is consistent with previous observations that idiopathic LUTD tends to affect young to middle-aged cats[1,2,50] and with clinical impressions that recurrent episodes of acute, idiopathic LUTD tend to decrease in frequency and severity over time.[8,9] Mechanisms responsible for age-related effects on the biological behavior of acute, idiopathic LUTD are unknown. Age-related changes in immunologic or inflammatory responsiveness may alter host reactions to etiopathologic agents involved in idiopathic LUTD. Alternatively, age-related physiologic or metabolic changes may alter composition of the urine, resulting in changes in concentrations of substances that may promote or inhibit signs of idiopathic LUTD. The finding that increasing age significantly modulated recovery from some signs of acute idiopathic LUTD suggested that future studies evaluating treatments for idiopathic LUTD should incorporate controls for age effects.

In our study, adverse events observed in cats treated with amitriptyline short-term included sedation, bacterial urinary tract infection, and transient increases in serum ALT activity and total bilirubin concentration. Adverse events were similar to those previously reported[13] for 15 cats with severe recurrent idiopathic cystitis treated for 1 year with amitriptyline and those reported[14] for humans treated with amitriptyline at higher dosage for depression. In our study, bacterial urinary tract infections were detected in 3 amitriptyline-treated cats. Although specific risk factors for urinary tract infection were not identified in affected cats in the present study, observations in cats and humans suggest that decreased frequency of urination, increased urinary bladder capacity, and incomplete urinary bladder emptying associated with administration of amitriptyline and related drugs may be potential risk factors for development of bacterial urinary tract infection.[31,56,57] In a previous study,[13] bacterial urinary tract infection was detected in 1 of 15 cats with severe recurrent idiopathic cystitis treated with amitriptyline for 1 year, and uroliths were detected in 4. In that study, investigators hypothesized that amitriptyline may be a contributing factor in urinary tract infection and urolithiasis. Although insufficient numbers in our study preclude statistical evaluation, our observations suggest that amitriptyline treatment may predispose cats to other lower urinary tract disorders and that further study is warranted.

In the present study, the effect of short-term amitriptyline administration on recurrence of clinical signs of LUTD was also investigated. Evaluations consisted of clinical reexamination 1 month after the end of treatment and telephone interviews of owners at 6- to 12-month intervals until the study treatment code was broken. In 2 amitriptyline-treated cats and 2 control cats, results of urinalyses, bacterial culture of urine samples, and radiographic studies performed at the time of recurrence of clinical signs were consistent with a diagnosis of idiopathic LUTD. However, because most cats were not comprehensively reevaluated at the time of recurrence, it cannot be concluded that recurrent signs were solely the result of relapsing idiopathic disease. Recurrent signs could also represent the onset of a different disease (eg, bacterial urinary tract infection or urolithiasis) or combinations of LUTDs. However, in nearly all cases, owners reported that clinical signs associated with recurrent episodes resolved spontaneously without treatment.

Results of an interim analysis to monitor for early beneficial and harmful effects of short-term amitriptyline administration suggested that clinical signs of LUTD recurred significantly faster in amitriptyline-treated than control cats.[58] Because rapid recurrence represented a potentially serious adverse effect, the study was terminated earlier than scheduled. When all recurrent episodes were included, the overall risk of recurrence was significantly greater in amitriptyline-treated cats. However, it was also apparent after excluding recurrent episodes occurring within 7 and 21 days after treatment that the number of cats with recurrences, the total number of recurrent events, and the risk of recurrence in amitriptyline-treated cats were similar to those for control cats. The reasons for more rapid relapse of clinical signs in cats receiving amitriptyline short-term are unknown, but this may represent a direct exacerbating effect of amitriptyline on idiopathic LUTD or a drug discontinuation reaction. In humans, abrupt withdrawal from antidepressants may be associated with 2 distinct sets of symptoms: those directly associated with withdrawal of the drug (so-called tricyclic antidepressant withdrawal syndrome) and those related to relapse of the underlying illness the drug was used to treat.[40,43] The tricyclic antidepressant withdrawal syndrome is a constellation of stereotypic clinical signs characterized by gastrointestinal tract abnormalities (eg, nausea, vomiting, abdominal cramps, or diarrhea), general somatic abnormalities (eg, headache, lethargy, sweating, anorexia, or tremor), sleep disturbances (eg, insomnia, excessive dreaming, or nightmares), affective symptoms (eg, irritability, anxiety, agitation, or low mood), movement disorders (eg, akathisia or parkinsonism), behavioral activation (eg, hypomania or mania), and cardiac arrhythmias.[38,40,43] Most clinical signs related to tricyclic antidepressant withdrawal syndrome are believed to be the result of rebound excess of cholinergic activity (cholinergic overdrive) after prolonged exposure to the anticholinergic effects of tricyclic antidepressants.[38] Signs of tricyclic antidepressant withdrawal syndrome typically begin within a few days after treatment is discontinued, are usually mild, and usually resolve spontaneously within 3 weeks or immediately after recommencement of antidepressant administration.[40,42] The severity of signs of antidepressant withdrawal syndrome is proportional to daily dose and duration of treatment.[38,43] Signs of tricyclic antidepressant withdrawal syndrome have

not been reported in humans treated for < 14 days and are uncommon in patients treated for < 8 weeks.[38,39,41,42] Conversely, signs of a relapse of the original disease after discontinuation of drug administration follow the characteristic illness pattern. Stereotypic signs of tricyclic antidepressant withdrawal syndrome were not observed in any of the amitriptyline-treated cats in the present study. In 1 amitriptyline-treated cat, clinical signs of LUTD recurred 2 days after completion of initial treatment. Administration of amitriptyline was restarted 3 days later with no apparent immediate benefit on resolution of clinical signs. Considering the short duration of treatment, lack of stereotypic signs of tricyclic antidepressant withdrawal syndrome, lack of a recommencement response in 1 cat, and recurrence of clinical signs of the original disease, it seems unlikely that signs of hematuria, pollakiuria, and periuria observed after discontinuation of amitriptyline administration were due to tricyclic antidepressant withdrawal syndrome.

In humans, rodents, and cats, administration of amitriptyline results in acute inhibition of central presynaptic neuronal reuptake of norepinephrine and serotonin.[14-16] Increased synaptic availability of norepinephrine activates α_2-adenoreceptor-mediated negative-feedback mechanisms resulting in decreased firing rates of noradrenergic neurons ascending and descending from the locus ceruleus in the brainstem.[14,59] However, over 1 to 2 weeks, α_2-adrenoreceptor responsiveness decreases, allowing presynaptic neuronal synthesis and action potential-induced release of norepinephrine to return to or exceed pretreatment levels.[14,59,60] Following discontinuation of amitriptyline administration, presynaptic monoamine reuptake recommences. Lower synaptic norepinephrine concentrations and reduced inhibitory α_2-adrenoreceptor activity could promote increased norepinephrine release and neuronal firing rate.[59] In rodents, rebound increases in locus ceruleus neuron firing rate and central norepinephrine turnover were observed 1 to 3 days after abrupt discontinuation of long-term tricyclic antidepressant administration.[61,62] Similarly, increased central norepinephrine turnover was observed in human patients for up to 21 days after abrupt discontinuation of long-term (> 4 weeks) amitriptyline, imipramine, and despramine administration.[59] However, increased central turnover of norepinephrine was not observed in rodents after discontinuation of tricyclic antidepressant administration of only 5 to 9 days' duration.[61] Although similar studies have not been performed in cats following cessation of amitriptyline administration, results of studies in other species raise the possibility that abrupt discontinuation of short-term amitriptyline administration may be associated with rebound excess adrenergic function.

Increased rebound adrenergic activity following cessation of short-term amitriptyline administration could affect recovery from or relapse of clinical signs of idiopathic LUTD. Findings of increased plasma concentrations of norepinephrine,[63] increased tyrosine hydroxylase immunoreactivity in the locus coeruleus,[64] and decreased sensitivity of inhibitory central α_2-adenoreceptors[f] in cats with chronic forms of idiopathic LUTD are indicative of increased activity of the sympathetic nervous system. Similar studies have not been performed in cats with acute, idiopathic LUTD. However, increases in plasma norepinephrine concentrations and adrenergic activity of the locus ceruleus have been detected in cats following short-term administration of other forms of stressful stimuli.[65] We hypothesize that adrenergic excess resulting from the underlying disease processes, compounded by rebound adrenergic activity following discontinuation of short-term amitriptyline administration, could exacerbate urinary bladder inflammation and nociceptive sensory afferent neuron activity and cause recrudescence of signs of LUTD.[66,67] However, proof of this hypothesis requires further investigations.

It is also conceivable that short-term amitriptyline administration may directly exacerbate preexisting disease, interfere with beneficial host responses to urinary bladder injury, or compromise host lower urinary tract defense mechanisms. In rodents with carrageenan-induced inflammation, administration of a single low dose of the tricyclic antidepressant clomipramine appeared to have a proinflammatory effect following a period of analgesia.[28] However, proinflammatory responses were not observed with higher doses of clomipramine in other rodents with experimentally induced inflammation.[29,30] Whether short-term amitriptyline administration induces similar proinflammatory reactions and recrudescence of clinical signs in cats with idiopathic LUTD is unknown. Regardless, our observations suggest that discontinuation of even short-term treatment with amitriptyline may precipitate sudden relapse of clinical signs in cats with acute, idiopathic LUTD and emphasize the need for close clinical monitoring of cats receiving amitriptyline for management of urinary and nonurinary tract disorders.

It is possible that differences between groups in the present study in regard to other factors may account for the differences in recurrence of clinical signs. Unfortunately, there are few studies[5,6,68] investigating risk factors for recurrence of signs following episodes of acute, nonobstructive, idiopathic LUTD. In 1 study,[5] clinical signs recurred in 13 of 33 (39%) nonobstructed cats with clinical findings consistent with idiopathic LUTD within 1 year, regardless of treatment. There was no apparent association between diet moisture content and recurrence of clinical signs. In a subsequent uncontrolled study,[68] clinical signs recurred in 5 of 10 nonobstructed cats with unspecified LUTD within 2 years. Recurrent episodes occurred shortly after dietary changes in at least 2 cats. In another study[6] of 48 cats with nonobstructive idiopathic cystitis fed a dry or canned acidifying diet, clinical signs recurred in 11 (39%) fed a dry diet and 2 (11%) fed a canned diet. Other epidemiologic studies[50,69-71] of cats with nonspecific signs localizing to the lower urinary tract (ie, hematuria, pollakiuria, dysuria, or urethral obstruction) have implicated Persian breed, long hair coats, younger age, castration, obesity, inactivity, restricted access to outdoors, indoor litter trays, and stress (eg, multiple cat households, moving, and inclement weather) as risk factors. In our study, there

was no significant association between risk of recurrence of signs of LUTD and body condition or diet moisture content. However, this lack of an association must be interpreted within the context of the limited sample size and the fact that the study was not designed to critically evaluate all risk factors involved in recurrence of clinical signs.

Despite limitations of our study, the finding that increasing age significantly modulated the rate of recurrence of signs of LUTD reinforces our observation that increasing age influences recovery from some signs of acute, idiopathic LUTD. These observations are also consistent with clinical impressions that recurrent episodes of acute, idiopathic LUTD tend to decrease in frequency and severity over time.[8,9] The reasons for the association between the number of previous episodes and increased risk for recurrent episodes of signs of LUTD are unknown. It is possible that cats with a history of LUTD represent a population of cats with more severe disease. Consequently, these cats may be more susceptible to external or internal factors that may precipitate recurrent episodes of LUTD. Regardless, further well-controlled longitudinal studies incorporating more comprehensive follow-up evaluations and larger sample sizes are essential to identify external and internal risk factors that may influence recurrent idiopathic LUTD.

In conclusion, there was no apparent benefit of short-term amitriptyline administration on resolution of hematuria and pollakiuria in cats with acute, nonobstructive, idiopathic LUTD in the present study. Furthermore, short-term amitriptyline administration was associated with a significantly increased risk of recurrence of signs of LUTD immediately following cessation of treatment. Because of limitations in sample size, we cannot exclude the possibility that short-term amitriptyline administration in cats with acute, nonobstructive LUTD may have some modest beneficial effect on ameliorating clinical signs of hematuria or pollakiuria. Likewise, we cannot exclude the possibility that diet changes, obesity, or other risk factors may have influenced recurrence of clinical signs. However, any potential benefits of short-term amitriptyline administration must be weighed against the risk of relapse of clinical signs. Increasing age was significantly associated with an increased likelihood and rate of recovery from some signs of acute idiopathic LUTD and with a decreased risk of long-term recurrence of signs of LUTD after treatment. These findings may have important long-term prognostic implications for the management of cats with acute, nonobstructive, idiopathic LUTD. The observations that clinical signs of idiopathic LUTD are often self-limiting, that increasing age significantly modulates the rate of recovery and the incidence of recurrence of clinical signs, and that some forms of treatment may be detrimental underscore the need for appropriately controlled clinical trials when investigating the efficacy of putative therapeutic agents for management of cats with idiopathic LUTD.

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[b]Kirkemo AK, Miles BJ, Peters JM. Use of amitriptyline in interstitial cystitis (abstr). *J Urol* 1990;143:279A.

[c]Sigma-Aldrich Co, St Louis, Mo.

[d]Hemastix, Bayer Corp, Elkhart, Ind.

[e]Hurst RE, Roy JB, Young JL. Increased urinary glycosaminoglycan excretion after bladder distension in interstitial cystitis patients (abstr). *J Urol* 1989;141:269A.

[f]Buffington CAT. Functional assessment of a-2 adrenoreceptor sensitivity in cats with interstitial cystitis (abstr). *Soc Neurosci Abstr* 2001;24:595.

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