Duloxetine ingestion in 364 dogs

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OBJECTIVE

To describe abnormal clinical signs following duloxetine ingestion in dogs.

ANIMALS

364 client-owned dogs that ingested duloxetine.

PROCEDURES

The American Society for the Prevention of Cruelty to Animals, Animal Poison Control Center electronic database was searched for records of dogs with duloxetine ingestion between January 2012 and December 2016. Data collected included age, body weight, breed, duloxetine exposure and dose, clinical signs, and overall outcome. Clinical signs were categorized as either neurologic, digestive, cardiovascular, respiratory, or metabolic and endocrine. Outcomes were categorized as no clinical signs, fully recovered, died, or unknown.

RESULTS

Clinical signs developed in 55 of the 364 (15.1%) dogs with known ingestion of duloxetine. The most common clinical signs were lethargy (22/55 [40%]), mydriasis (18/55 [33%]), vomiting (11/55 [20%]), and trembling (6/55 [11%]). Dogs that ingested an estimated dose of duloxetine ≥ 20 mg/kg (9.1 mg/lb) were more likely to have had abnormal clinical signs than were dogs that ingested < 20 mg/kg.

CONCLUSIONS AND CLINICAL RELEVANCE

Findings indicated that most dogs in the present study did not have clinical signs associated with ingestion of duloxetine and that development of clinical signs varied by individual dog. Further information is needed to determine toxic dose ranges for duloxetine ingestion in dogs. (*J Am Vet Med Assoc* 2019;255:1161–1166)

Pet exposure to toxic drugs by accidental ingestion of owner medication is very common, and prescription psychiatric medication is a common type of pet toxicant in households, with an estimated 1 in 6 American adults taking a psychiatric medication.[1] Duloxetine is a widely prescribed antidepressant used in treating depression, diabetic nerve pain, anxiety, fibromyalgia, and chronic musculoskeletal pain in humans, and the frequency at which antidepressants such as duloxetine are prescribed for humans may increase the likelihood of accidental ingestion and potential toxicoses in dogs and cats.

Duloxetine is a serotonin and norepinephrine reuptake inhibitor. Although the exact mechanism of action of such inhibitors is unknown, duloxetine is known to inhibit reuptake of serotonin and norepinephrine in nerve cells in the brain, resulting in higher concentrations of these substances in the brain. Duloxetine also has a limited effect on dopamine reuptake inhibition.[2] Duloxetine is well absorbed through the gastrointestinal tract in humans and dogs, with lag times to the start of absorption varying among patients.[2,3] A pharmacokinetic study[3] in 20 purpose-bred Beagles shows that the peak plasma concentration of duloxetine is achieved 2 hours after oral administration, compared with 6 hours after oral administration in humans.[2] Also in humans, plasma duloxetine is highly protein bound (> 90%) with most bound to albumin and α_1-acid glycoprotein. Duloxetine is primarily metabolized through the liver with cytochrome P450 isozymes CYP1A2 and CYP2D6, resulting in multiple metabolites, most of which are excreted in the urine. The elimination half-life of duloxetine is 12 hours in humans[2] but unknown in dogs.

Clinical signs of duloxetine toxicosis in humans include serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, vomiting, coma, and death, alone or in combination.[2] Human patients with duloxetine toxicosis should also be monitored for airway control, oxygenation, ventilation, and cardiac arrhythmias. However, to our knowledge, there have been no published reports of the clinical signs, exposure doses, or adverse effects of duloxetine ingestion or toxicosis in dogs or cats. The purpose of this report was to describe abnormal clinical signs following duloxetine ingestion in dogs.

ABBREVIATIONS

ASPCA APCC	American Society for the Prevention of Cruelty to Animals, Animal Poison Control Center
CI	Confidence interval

Materials and Methods

Animals

The ASPCA APCC electronic database was searched for medical records of dogs reported by owners and veterinarians as having ingested duloxetine (name

brand[a] or generic product) between January 2012 and December 2016 in North America. Dogs with known exposure to duloxetine were included in the study. A known exposure was defined as the owner either observing the ingestion or finding evidence of the ingestion (eg, torn packaging). Dogs were excluded from the study if the records were incomplete, multiple medications were ingested simultaneously, or exposure to duloxetine could not be determined, alone or in combination. The information for dogs that had more than 1 episode of duloxetine ingestion was not available at the time of the study and therefore was not included.

Procedures

Electronic medical records from the ASPCA APCC database indicating duloxetine ingestion by dogs were reviewed. Data collected included signalment (eg, age, breed, sex, and body weight); duloxetine exposure, capsule size, and amount ingested; clinical signs; and outcome. Clinical signs were individually evaluated and categorized as neurologic (eg, lethargy, tremors, ataxia, vocalization, mydriasis, behavioral changes, and signs of anxiety), cardiovascular (eg, tachycardia, hypertension, pale mucous membranes), gastrointestinal (eg, vomiting, retching, and diarrhea), respiratory (eg, bradypnea, tachypnea, and panting), or metabolic and endocrine (eg, hyperthermia). Outcomes were categorized as no clinical signs, fully recovered, died, or unknown.

Statistical analysis

Descriptive statistics were generated for all demographic variables, clinical signs, duloxetine dose ingested, and outcome. The duloxetine dose ingested was estimated on the basis of the dog's body weight and the number and strength of duloxetine capsules ingested. The distribution of data for continuous variables was assessed for normality with the Shapiro-Wilk test. Duloxetine dose was transformed with the Johnson SU distribution. The Student *t* test or 1-way ANOVA was used to assess the respective relationships between the duloxetine dose, dog's age, and presence of clinical signs. The Tukey correction was used when multiple pairwise comparisons were indicated. The respective associations between each categorical variable and the presence of clinical signs were assessed with the Fisher exact test. Individual variables that were associated with outcome, on the basis of minimum Bayesian information criterion, were individually entered into logistic regression models for the presence of any clinical sign. Variables with collinearity were removed from the multivariate analysis. Logistic fit and inverse prediction were used to estimate the probability of any clinical sign following ingestion of various duloxetine doses. Values of $P < 0.05$ were considered significant. Data analysis and plot design were performed with commercial software.[b–d]

Results

Dogs

A search of the ASPCA APCC medical record database identified 737 dogs reported to have ingested duloxetine, and 364 dogs met the inclusion criteria. Of these, 354 dogs were reported from 40 states in the United States, and 7 were reported from Canada. Geographic information was not available for the remaining 3 dogs. Mean age was 3.4 years (range, 2 months to 18 years), with 126 of the 364 (34.6%) dogs ≤ 1 year of age (young) and 238 (65.4%) dogs > 1 year of age (adult). Mean body weight was 15.9 kg (35.0 lb; range, 1.3 to 83.8 kg [2.9 to 184.4 lb]). Sixty-nine breeds were represented, with the most common being Labrador Retriever (52/364 [14.3%]), Miniature Dachshund (18 [5.0%]), Maltese (17 [4.7%]), Yorkshire Terrier (17 [4.7%]), and Chihuahua (16 [4.4%]). Twenty-five of the 364 (6.9%) dogs did not have a specific breed described, and 115 (31.6%) were described as mixed breed.

Duloxetine exposure

Ingestion of duloxetine was observed in 161 of 364 (44.2%) dogs, and evidence of ingestion was reported for the remaining 203 (55.8%) dogs. The brand name product[a] was reported as the source of exposure in 315 (86.5%) dogs, whereas the generic form was the source in 49 (13.5%). Overall, the mean amount of duloxetine ingested was 231 mg (range, 7.5 to 5,400 mg); however, 278 of the 364 (76.4%) dogs ingested ≤ 120 mg. The most common capsule strength ingested was 60 mg (236/364 [64.8%]), with most dogs (206/364 [56.6%]) ingesting 1 capsule/episode. Mean dose ingested was 18.0 mg/kg (8.2 mg/lb; range, 0.38 to 397.4 mg/kg [0.17 to 180.6 mg/lb]), with 276 of the 364 (75.8%) dogs ingesting ≤ 16.6 mg/kg (7.5 mg/lb). The mean and median dose ingested per kilogram of body weight was significantly ($P < 0.001$, Student *t* test) higher for young dogs (28.2 mg/kg [12.8 mg/lb] and 16.6 mg/kg, respectively) versus adult dogs (12.6 mg/kg [5.7 mg/lb] and 5.0 mg/kg [2.3 mg/lb], respectively).

Clinical signs

After ingestion of duloxetine, 55 of the 364 (15.1%) dogs were noted to have developed 1 or more abnormal clinical signs. Twenty-nine different clinical signs were reported, with the most common being lethargy (22/55 [40%]), mydriasis (18/55 [33%]), vomiting (11/55 [20%]), trembling (6/55 [11%]), and vocalization (6/55 [11%]), alone or in combination **(Figure 1; Table 1)**. The odds of having abnormal clinical signs after ingestion of duloxetine were 2.1 times as high (OR = 2.1; 95% CI, 1.2 to 3.7; $P = 0.020$, Fisher exact test) for young dogs (27/126 [21.4%]) as for adult dogs (28/238 [11.8%]).

Mean ± SD ingested dose of duloxetine was significantly ($P < 0.001$, Student *t* test) higher for dogs that subsequently developed abnormal clinical signs (34.2 ± 56.6 mg/kg [15.5 ± 25.7 mg/lb]; median, 17.1 mg/kg [7.8 mg/lb]; range, 0.4 to 347.3 mg/kg [0.2 to

157.9 mg/lb]; n = 55), compared with dogs that did not develop abnormal clinical signs (12.8 ± 34.5 mg/kg [5.8 ± 15.7 mg/lb]; median, 5.5 mg/kg [2.5 mg/lb]; range, 0.4 to 397.4 mg/kg [0.2 to 180.6 mg/lb]; 309; **Figure 2**). When dogs were grouped according to whether they did or did not have signs in specific categories, the median estimated ingested dose was higher in dogs with (17.4 mg/kg [7.9 mg/lb]; n = 37)

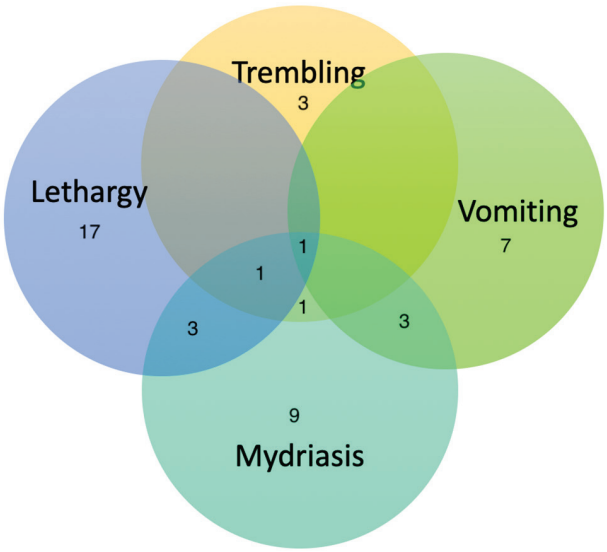

Figure 1—Venn diagram of the number of 364 client-owned dogs that ingested duloxetine between January 2012 and December 2016 and had 1 or more of the most common clinical signs reported.

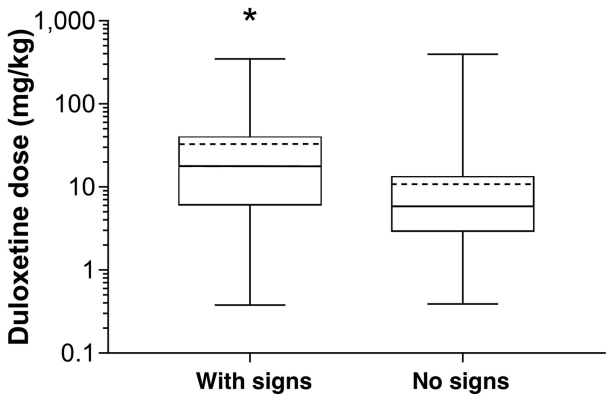

Figure 2—Box-and-whisker plots of duloxetine dose ingested by 364 client-owned dogs between January 2012 and December 2016 grouped according to whether the duloxetine-exposed dogs did (n = 55) or did not (309) develop abnormal clinical signs. In each plot, the box represents the first to third quartiles, the solid horizontal line in the box represents the median, the dashed horizontal line in the box represents the mean, and the whiskers represent the range. *Mean ingested dose of duloxetine was significantly ($P < 0.001$) higher for dogs that subsequently developed abnormal signs than for dogs that did not develop abnormal signs.

Table 1—Summary of abnormal clinical signs* observed in 364 client-owned dogs that ingested duloxetine between January 2012 and December 2016.

Clinical sign	Sign category	No. of dogs reported*	Percentage of all dogs (n = 364)	Percentage of dogs with signs* (n = 55)
Lethargy	Neurologic	22	6.0	40
Mydriasis	Neurologic	18	5.0	33
Vomiting	Gastrointestinal	11	3.0	20
Trembling	Neurologic	6	1.7	11
Vocalization	Neurologic	6	1.7	11
Behavior change	Neurologic	5	1.4	9.1
Ataxia	Neurologic	5	1.4	9.1
Tachycardia	Cardiovascular	4	1.1	7.3
Hyperesthesia	Neurologic	4	1.1	7.3
Panting	Respiratory	3	0.8	5.5
Hyperthermia	Metabolic and endocrine	2	0.6	3.6
Hypertension	Cardiovascular	2	0.6	3.6
Hyperactivity	Neurologic	2	0.6	3.6
Hypersalivation	Gastrointestinal	2	0.6	3.6
Diarrhea	Gastrointestinal	1	0.3	1.8
Anorexia	Gastrointestinal	1	0.3	1.8
Bradypnea	Respiratory	1	0.3	1.8
Wheezing	Respiratory	1	0.3	1.8
Nasal discharge	Respiratory	1	0.3	1.8
Stupor	Neurologic	1	0.3	1.8
Absent pupillary light reflex	Neurologic	1	0.3	1.8
Glazed eyes	Neurologic	1	0.3	1.8
Facial tremors	Neurologic	1	0.3	1.8
Tense abdomen	Neurologic	1	0.3	1.8
Bradycardia	Cardiovascular	1	0.3	1.8
Pale mucous membranes	Cardiovascular	1	0.3	1.8
Tacky mucous membranes	Metabolic and endocrine	1	0.3	1.8
Adipsia	Metabolic and endocrine	1	0.3	1.8
Death	—	1	0.3	1.8

*Some dogs developed > 1 abnormal clinical sign.
— = Not categorized.

Table 2—Summary of duloxetine dose ingested by 364 client-owned dogs described in Table 1 stratified according to the category of abnormal clinical signs (none, neurologic, gastrointestinal, or cardiovascular) that developed at any ingested duloxetine dose and at duloxetine doses ≥ 20 mg/kg.

	Any dose of duloxetine ingested					Duloxetine doses ≥ 20 mg/kg ingested		
Sign category	No. of dogs	Mean ± SD (mg/kg)	Median (mg/kg)	IQR (mg/kg)	*P* value*	No. of dogs	OR (95% CI of OR)	*P* value†
Neurologic					< 0.001			< 0.001
Yes	37	33.2 ± 56.3	17.4	6.1–40.1		16	3.5 (1.8–6.8)	
No	327	17.2 ± 40.5	6.0	2.9–14.1			Referent	
Gastrointestinal					0.012			< 0.001
Yes	15	62.7 ± 93.1	28.5	6.6–79.5		11	13 (4.0–42.1)	
No	349	16.2 ± 34.2	6.5	2.9–14.3			Referent	
Cardiovascular					< 0.001			0.031
Yes	7	73.5 ± 121.5	28.3	17.2–52.6		4	5.6 (1.2–25.9)	
No	357	16.9 ± 35.4	6.5	2.98–15.2			Referent	
No abnormal signs	309	12.8 ± 34.5	5.5	2.9–13.2	—		—	—

*Value of *P* determined with the Student *t* test. †Value of *P* determined with the Fisher exact test.
— = Not calculated. IQR = Interquartile (25th to 75th percentile) range.

versus without (6.0 mg/kg [2.7 mg/lb]; 327) neurologic signs, dogs with (28.5 mg/kg [13.0 mg/lb]; 15) versus without (6.5 mg/kg [3.0 mg/lb]; 349) gastrointestinal signs, and dogs with (28.3 mg/kg [12.9 mg/lb]; 7) versus without (6.5 mg/kg; 357) cardiovascular signs **(Table 2)**. In addition, when dogs were grouped according to whether they ingested duloxetine at a dose ≥ 20 mg/kg (9.1 mg/lb) versus < 20 mg/kg, the odds of developing neurologic, cardiovascular, or gastrointestinal signs were 3.5, 5.6, and 13 times as high, respectively, for dogs that ingested ≥ 20 mg/kg of duloxetine.

Of the 364 dogs that ingested duloxetine, only 30 (8.2%) had > 1 concurrent clinical sign. When dogs were grouped according to the number of concurrent abnormal clinical signs (no abnormal signs [n = 309], 1 to 3 abnormal signs [45], or 4 to 6 abnormal signs [10]), the mean estimated dose ingested was significantly (*P* < 0.001, 1-way ANOVA) higher in dogs with 4 to 6 concurrent signs (65.5 mg/kg [29.8 mg/lb]) than in dogs with 1 to 3 signs (23.3 mg/kg [10.6 mg/lb]) and in dogs with no signs (13.4 mg/kg [6.1 mg/lb]; **Figure 3**). Results of the logistic fit and inverse prediction model indicated that a duloxetine dose of 225.0 mg/kg (102.3 mg/lb; 95% CI, 137.0 to 741.0 mg/kg [62.3 to 336.8 mg/lb]) had a 50% probability of causing any 1 of the 29 clinical signs reported. Therefore, a dog ingesting ≥ 225.0 mg/kg of duloxetine had a 50% chance of developing clinical signs.

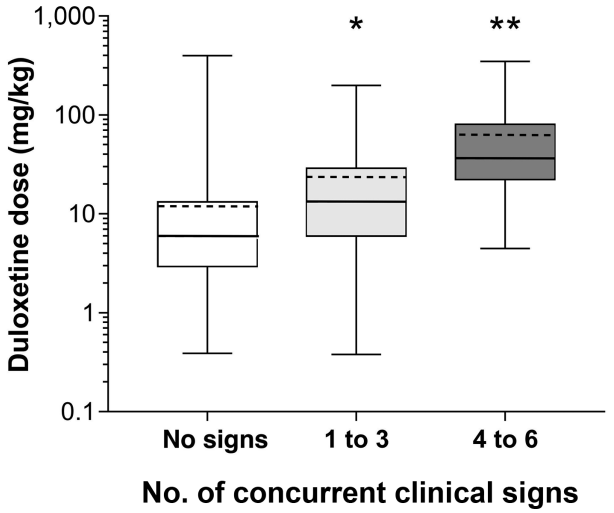

Figure 3—Box-and-whisker plots of duloxetine dose ingested by the dogs described in Figure 2 grouped by the number of abnormal concurrent clinical signs reported for each dog (no signs [no shading; n = 309], 1 to 3 signs [light gray shading; 45], or 4 to 6 signs [dark gray shading; 11]). *Mean ingested dose of duloxetine was significantly (*P* = 0.003) higher in dogs with 1 to 3 abnormal signs than in dogs with no abnormal signs. **Mean ingested dose of duloxetine was significantly (*P* < 0.001 and *P* = 0.024, respectively) higher in dogs with 4 to 6 concurrent abnormal signs than in dogs with no or 1 to 3 concurrent abnormal signs. **See** Figure 2 for remainder of the key.

Outcome

Follow-up information with outcome was available for 18 of the 364 dogs. Of these 18 dogs, 13 did not have abnormal clinical signs on initial examination after ingestion of duloxetine but 5 dogs did. Of these 5 dogs, 4 fully recovered after ingesting a mean estimated duloxetine dose of 8.3 mg/kg (3.8 mg/lb; median, 8.3 mg/kg; range, 5.9 to 10.7 mg/kg [2.7 to 4.9 mg/lb]); however, 1 dog died after ingesting an estimated duloxetine dose of 19.1 mg/kg (8.7 mg/lb). Before this dog died, its abnormal clinical signs included lethargy, hyperthermia, panting, agitation, and tremors. The abnormal clinical signs of the dogs that fully recovered included lethargy, mydriasis, vocalization, trembling, vomiting, diarrhea, and regurgitation.

Discussion

Duloxetine use in people from households with dogs poses a potential risk for accidental ingestion of the drug by dogs. Although not all dogs represented in

the present study became clinically ill after ingesting duloxetine, dogs that did develop abnormal clinical signs varied in body weight and dose ingested, and no definitive dose-dependent range for the development of clinical signs could be established from the data. It was unclear what factors resulted in affected dogs developing clinical signs. In addition, because the clinical signs reported in our study appeared largely idiosyncratic and patient dependent, it was unclear as to which of duloxetine's proposed mechanisms of action (ie, inhibition of serotonin and norepinephrine reuptake and limited inhibition of dopamine reuptake[2]) contributed to the development of the clinical signs reported; however, potentially higher concentrations of serotonin, norepinephrine, and to some extent dopamine, alone or in combination, within the CNS and peripheral tissues could have contributed to abnormal clinical signs reported in the present study.

In humans and dogs, the neurohormonal physiologic processes of the CNS is controlled by serotonin, norepinephrine, and dopamine. Serotonin is an inhibitory neurotransmitter in the CNS, platelets, and enterochromaffin cells. Most of the serotonin is stored intracellularly, with approximately 90% to 95% of serotonin stored peripherally in platelets and enterochromaffin cells (allowing for tight regulation of its release) and the remaining 5% to 10% stored in the CNS at the level of the presynaptic neuron.[4] Serotonin concentration in the CNS contributes to the regulation of body temperature, appetite, vomiting, sleep cycles, and neuromuscular tone.[4] Peripherally, serotonin is involved in platelet aggregation, vascular tone, and gastrointestinal tract peristaltic activity.[4] Serotonin selective transporters on presynaptic membranes allow for reuptake of serotonin from synaptic clefts, preventing the metabolism of serotonin by monoamine oxidase and allowing for recycling of serotonin for future use.[4] Serotonin released from enterochromaffin cells into plasma is eliminated through reuptake by platelets or being metabolized in the liver or lung.[4] Norepinephrine is an endogenous neurotransmitter that, unlike serotonin, functions as an excitatory hormone in the body. Norepinephrine is synthesized by hydroxylation of dopamine and removed from the body by reuptake into adrenergic nerve terminals, diffusion into tissues, or enzymatic metabolism (eg, monoamine oxidase).[5] The excitatory effects of norepinephrine as the sympathetic neurotransmitter result in positive chronotropic and inotropic effects on the heart, dilation of bronchi, decreased peristalsis and urine production, and shunting of blood to muscles.[5] Although norepinephrine has a short half-life, the inhibitory effect of duloxetine on norepinephrine reuptake could have extended norepinephrine activity in tissues and thereby led to the variety of abnormal clinical signs reported in dogs of the present study. This was not a point of research in the present study and would require additional research to explore. Similarly, because it is unclear how dopamine function is affected by duloxetine, we were unable to attribute findings in dogs of the present study to effects of duloxetine on dopamine.

Nonetheless, clinical signs reported in dogs of the present study were consistent with previously reported clinical signs of serotonin syndrome in dogs.[6–9] Serotonin syndrome is defined by a variety of clinical signs attributed to an increased concentration of serotonin in the CNS and peripheral tissues. Dogs with serotonin syndrome may have changes to mentation (eg, vocalization, lethargy, and signs of anxiety, agitation, or somnolence), altered neuromuscular activity (eg, myoclonus, shivering, trembling, mydriasis, ataxia, and seizures), and autonomic dysfunction (eg, vomiting, diarrhea, hyperthermia, arrhythmias, hypertension, and tachypnea), alone or in combination.[7,8] The abnormal clinical signs reported in dogs of the present study aligned closely with those of serotonin syndrome in dogs. However, no samples were collected for confirmation of serotonin concentration in dogs of the present study; therefore, we could not determine whether serotonin syndrome was the primary cause of the abnormal clinical signs reported.

Treatment information for dogs in the present study was not available. It was therefore unclear how many dogs did not develop clinical signs because of prompt decontamination and supportive care. Of the 364 dogs in our study, only 1 was reported to have died. It was not known whether this dog received treatment or whether the dog was euthanized before, during, or after supportive care was initiated. Treatment for dogs with serotonin syndrome generally consists of decontamination when appropriate; administration of a serotonin receptor antagonists (eg, cyproheptadine or chlorpromazine), IV lipid emulsion, and fluid therapy; and supportive care.[9] Decontamination may include induction of emesis with or without the administration of activated charcoal. The administration of serotonin receptor antagonists, such as cyproheptadine or chlorpromazine, may be beneficial because of the resulting blockade of serotonin receptors.[4] Administration of IV lipid emulsion has been used to treat humans with serotonin syndrome and animals with a variety of toxicoses in effort to bind tissue-bound drugs and neutralize them within the lipid matrix.[9] Supportive care for animals exhibiting signs of serotonin syndrome may include administration of diazepam for neurologic signs (eg, agitation, tremors, and seizures), cooling methods for pyretic patients, monitoring for arrhythmias, treatment of hypo- or hypertension, and protection of patients' airways.[7,9] Although dogs in the present study did not have confirmed serotonin syndrome, our findings suggested that dogs with duloxetine ingestion may benefit from the same decontamination and supportive care protocol as used in treating serotonin syndrome. However, decontamination practices after duloxetine ingestion has not been studied in veterinary medicine.

There were several limitations of the present study. First, information pertaining to dog sex, geographic location, whether treatment was sought and initiated prior to development of clinical signs, and outcome was inconsistently available in the database. Therefore, it was unknown how this information if complete could have affected the results. For

instance, outcomes were available for only 18 dogs, and the lack of information on the outcomes for the remaining dogs may have been because they were treated on an outpatient basis, were lost to follow-up, or had incomplete or missing medical records. Second, the information pertaining to the dose of duloxetine ingested by each dog came from estimations provided by owners' recall and was subject to error. Third, the sample size was small in that of the 364 dogs included, only 55 reportedly developed abnormal clinical signs. Finally, the abnormal clinical signs reported were broad, with most exhibited by only 1 or 2 dogs, likely because of the small sample size.

Nonetheless, our findings suggested that duloxetine ingestion in dogs may result in clinical signs consistent with serotonin syndrome. When treating dogs that have ingested duloxetine, we recommend veterinarians consider decontamination when possible, supportive care, and patient monitoring. Further studies are indicated to determine the toxic dose range and pathophysiologic effects of duloxetine in dogs and to further characterize clinical signs of duloxetine toxicosis in dogs.

Acknowledgments

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Footnotes

a. Cymbalta, Eli Lilly and Company, Indianapolis, Ind.
b. Microsoft Excel for Office 365, version 1810, Microsoft Corp, Redmond, Wash.
c. JMP Pro, version 13, SAS Corp, Cary, NC.
d. GraphPad Prism, version 7, GraphPad Software Inc, Calif.

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