Original Article

Journal of Feline Medicine and Surgery
1–7
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DOI: 10.1177/1098612X15599026
jfms.com

Mirtazapine toxicity in cats: retrospective study of 84 cases (2006–2011)

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Abstract

Objectives Mirtazapine is commonly used in veterinary medicine at doses of 1.88 or 3.75 mg as an appetite stimulant. The objectives of this study were to determine the most common adverse effects reported and the dose associated with these signs.

Methods Records of cats with mirtazapine exposure (2006–2011) were obtained from the American Society for the Prevention of Cruelty to Animals' Animal Poison Control Center. The following parameters were recorded: signalment, weight, outcome, agent ingested, amount ingested, route of exposure, clinical signs observed, intent of use, onset time of signs and duration of signs.

Results The 10 most commonly observed adverse effects reported in 84 cats exposed to mirtazapine included vocalization (56.0% of cats; mean dose 2.56 mg/kg), agitation (31.0%; 2.57 mg/kg), vomiting (26.2%; 2.92 mg/kg), abnormal gait/ataxia (16.7%; 2.87 mg/kg), restlessness (14.3%; 3.55 mg/kg), tremors/trembling (14.3%; 2.43 mg/kg), hypersalivation (13.0%; 2.89 mg/kg), tachypnea (11.9%; 3.28 mg/kg), tachycardia (10.7%; 3.04 mg/kg) and lethargy (10.7%; 2.69 mg/kg). Fifty-nine (70.2%) cases were considered accidental ingestions and 25 (29.8%) cases were given mirtazapine as prescribed. The doses associated with signs of toxicity were 15.00 mg (40 cats), 3.75 mg (25 cats), 7.50 mg (four cats), 30.00 mg (one cat), 18.75 mg (one cat), 11.25 mg (one cat), 5.80 mg (one cat) and 1.88 mg (one cat). For cats with available information, the onset of clinical signs ranged from 15 mins to 3 h, and resolution of clinical signs ranged from 12–48 h.

Conclusions and relevance The greater number of adverse effects at 3.75 mg rather than 1.88 mg suggests that the latter may be a more appropriate starting dose for stimulating appetite while limiting toxicity. The benefit of dispensing exact doses of mirtazapine is implied given the likelihood of accidental administration of a full tablet (15 mg) and the resulting toxicity.

Accepted: 12 July 2015

Introduction

Anorexia is a frequently encountered clinical sign found in cats with a variety of underlying disease processes. Regardless of the disease, nutritional support can be an important component of successful patient management. Extended inadequate nutritional intake should be avoided as it can lead to secondary complications, including reduced immunity, hepatic lipidosis and delayed wound healing.[1–3] Appetite stimulants are commonly prescribed for patients with chronic diseases or prior to placing a feeding tube in the acute setting.

Mirtazapine, an antidepressant used in humans, has gained popularity in veterinary medicine because of its antiemetic and appetite-stimulating properties. Mirtazapine is a presynaptic α_2-adrenergic receptor antagonist that increases noradrenergic and serotonergic neurotransmission by blocking presynaptic inhibitory receptors, resulting in increased norepinephrine release into the synaptic cleft

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and therefore increased postsynaptic availability.[4] This net increase in norepinephrine likely contributes to its appetite stimulating effects.[3] The serotonergic effects occur through 5-hydroxytryptamine $(HT)_1$ receptor-like activity, as well as enhancement of serotonergic transmission by norepinephrine. Mirtazapine has also been shown to antagonize the 5-HT_2 receptors, resulting in appetite stimulation by nuclei within the hypothalamus.[5] Antagonism of the 5-HT_3 receptor is responsible for its antiemetic and antinausea properties.[6]

Adverse effects associated with mirtazapine administration in cats are not well described. In humans, mirtazapine can cause signs of serotonin toxicity, sometimes called serotonin syndrome.[7] Signs of serotonin toxicity range from very mild (nausea, low-grade fever, tachycardia, diarrhea, and agitation) to life threatening (extreme hyperthermia and rigidity). Serotonin syndrome in humans can be described as clinical signs consisting of autonomic hyperactivity, neuromuscular signs and altered mental status.[6] The purpose of this study was to determine the most common adverse effects reported with mirtazapine ingestion in cats and the dose associated with these signs.

Materials and methods

Clinical data involving exposure to mirtazapine in cats from 1 January 2006, to 31 December 2011 were retrieved from the American Society for the Prevention of Cruelty to Animals' (ASPCA) Animal Poison Control Center's (APCC) electronic medical record database. The APCC provides a 24-h telephone consulting service to support animal owners and veterinarians with the diagnosis and treatment of animal poisoning cases throughout the USA and Canada. Only incidents classified as toxicosis (high likelihood that the observed clinical signs were caused by mirtazapine) or suspected toxicosis (medium likelihood that the observed clinical signs were caused by mirtazapine), as assessed by an APCC veterinarian, were included. These classifications by the APCC veterinary staff are assigned to each incident on the basis of history of exposure; type, onset time and duration of clinical signs; information present in the literature; and previous experience dealing with the agent. A total of 106 records of cats with mirtazapine ingestion were available. Twenty-two were excluded – no monitoring or follow-up (n = 17), doubtful that mirtazapine was the cause of the signs (n = 3) and signs not related to mirtazapine (n = 2) – leaving 84 cats included in the study. For each incident, the following information was retrieved: animal signalment (age, weight and breed); intended use of mirtazapine (intentional [the product was knowingly used for treatment purposes] vs accidental [the product was used accidently]); approximate amount (mg) to which the animal was exposed; exposure certainty (observed [the exposure was witnessed] vs evidenced [there was conclusive evidence that an exposure occurred, but it was not witnessed]); route of exposure (oral or other); onset time if known, types and duration of clinical signs; severity of illness (mild, moderate or major illness); final outcome (recovered or died); and geographic location of the incident. Clinical signs that occurred in two or more cats were included in the study. Clinical signs that were similar (ie, mouth breathing and panting) were included in the same category. Adverse effects were further subdivided into three groups: (A) signs observed at <0.75 mg/kg representing what may be encountered when prescribing a dose of 1.88–2.00 mg to a cat weighing 2.5 kg; (B) signs observed in the 0.75–1.50 mg/kg category representing what may be encountered when prescribing a dose of 3.75 mg to a cat weighing 2.5 kg; (C) signs seen in a cat receiving >1.5 mg/kg, representing accidental overdose.

Results

Of the 84 cats included in the study, six were $\leqslant 5$ years of age, three were 6–9 years of age, 44 were 10–15 years of age and 31 were >15 years of age. Fifty-six cats were domestic shorthairs, 10 were domestic longhairs, six were Maine Coons, five were Siamese, three were domestic mediumhairs, and there was one of each of the following breeds: Burmese, Devon Rex, Ragdoll and unspecified. Sex and neuter status was not provided.

The adverse effects reported to be associated with mirtazapine administration listed in order of most to least common included vocalization, agitation, vomiting, ataxia/abnormal gait, restlessness, tremors/trembling, hypersalivation, tachypnea, lethargy, tachycardia, anorexia, disorientation, dyspnea, hypothermia, mouth breathing/panting, mydriasis, behavior change, depression/sedation, fasciculations, hyperactivity, hypertension, pacing, dysphoria, inappropriate elimination, polyphagia, circling, discomfort, hiding, inappetence, seizures and weakness.

The doses reported to be associated with adverse effects were 15.00 mg (40 cats) followed by 3.75 mg (25 cats), 7.50 mg (four cats), 30.00 mg (one cat), 18.75 mg (one cat), 11.25 mg (one cat), 5.80 mg (one cat) and 1.88 mg (one cat) (Figure 1). The dose associated with adverse effects was not known in four cats. Six of the 84 cats exposed to mirtazapine did not develop any adverse effects (7%). The cats that did not develop clinical signs received an average mirtazapine dose of 3.25 mg/kg (range 0.75–5.50 mg/kg). Adverse effects that occurred in two or more of the 84 cats and the average mg/kg dose and dose range that caused each clinical sign are shown in Table 1. These ranges are presented in comparison with the mg/kg range that would result from administering 1.88 mg to a cat weighing 2.5–6.0 kg (Figure 2).

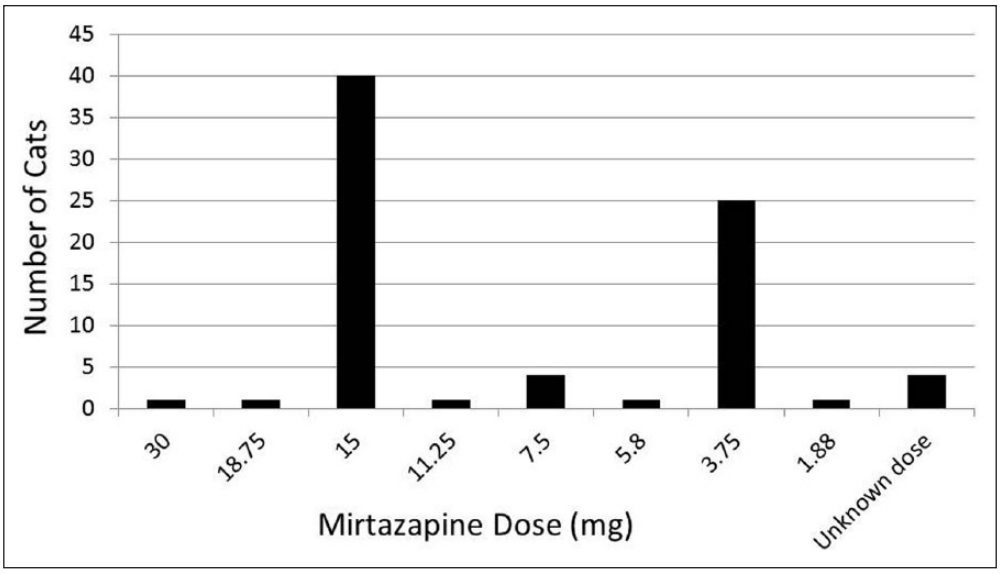

Figure 1 The number of cats reported to have received each intentionally or accidentally administered dose of mirtazapine (mg). The doses most commonly associated with reported adverse effects were intentionally administered 3.75 mg and accidentally administered 15.00 mg

Table 1 Adverse effects reported to the Animal Poison Control Center in two or more of 84 cats exposed to mirtazapine and the percentage of cats experiencing each adverse effect, average mg/kg dose and dose range that caused each clinical sign

Clinical sign	Cats affected, n (%)	Average dose (mg/kg) associated with effect	Dose range (mg/kg) associated with effect
Vocalization	47 (56.0)	2.56	0.61–5.38
Agitation	26 (31.0)	2.57	0.82–5.38
Vomiting	22 (26.2)	2.92	0.73–5.38
Ataxia/abnormal gait	14 (16.7)	2.87	0.7–5.38
Restlessness	12 (14.3)	3.55	1.8–5.38
Tremors/trembling	12 (14.3)	2.43	1.05–5.38
Hypersalivation	11 (13.1)	2.89	0.73–5.38
Tachypnea	10 (11.9)	3.28	1.0–5.38
Lethargy	9 (10.7)	2.69	0.83–5.38
Tachycardia	9 (10.7)	3.04	1.54–5.38
Anorexia	8 (9.5)	2.65	0.75–5.38
Disorientation	7 (8.3)	3.24	0.87–5.38
Dyspnea	7 (8.3)	1.99	0.73–4.10
Hypothermia	6 (7.1)	2.86	1.00–4.40
Mouth breathing/panting	6 (7.1)	3.69	1.54–5.38
No clinical signs	**6 (7.1)**	**3.25**	**0.75–5.50**
Mydriasis	5 (6.0)	2.84	1.00–4.10
Behavior change	4 (4.8)	2.20	0.78–3.50
Depression/sedation	4 (4.8)	1.85	0.70–3.00
Fasciculations	4 (4.8)	2.27	1.03–5.80
Hyperactivity	4 (4.8)	1.26	0.91–1.60
Hypertension	4 (4.8)	1.65	0.70–3.30
Pacing	4 (4.8)	1.48	0.82–2.60
Dysphoria	3 (3.6)	1.12	0.61–1.63
Inappropriate elimination	3 (3.6)	0.95	0.87–1.10
Polyphagia	3 (3.6)	2.39	0.87–3.90
Circling	2 (2.4)	2.75	2.75
Discomfort	2 (2.4)	3.40	2.40–4.40
Hiding	2 (2.4)	3.13	2.75–3.50
Inappetence	2 (2.4)	2.82	2.14–3.50
Seizures	2 (2.4)	1.80	1.80
Weakness	2 (2.4)	2.23	0.75–3.70

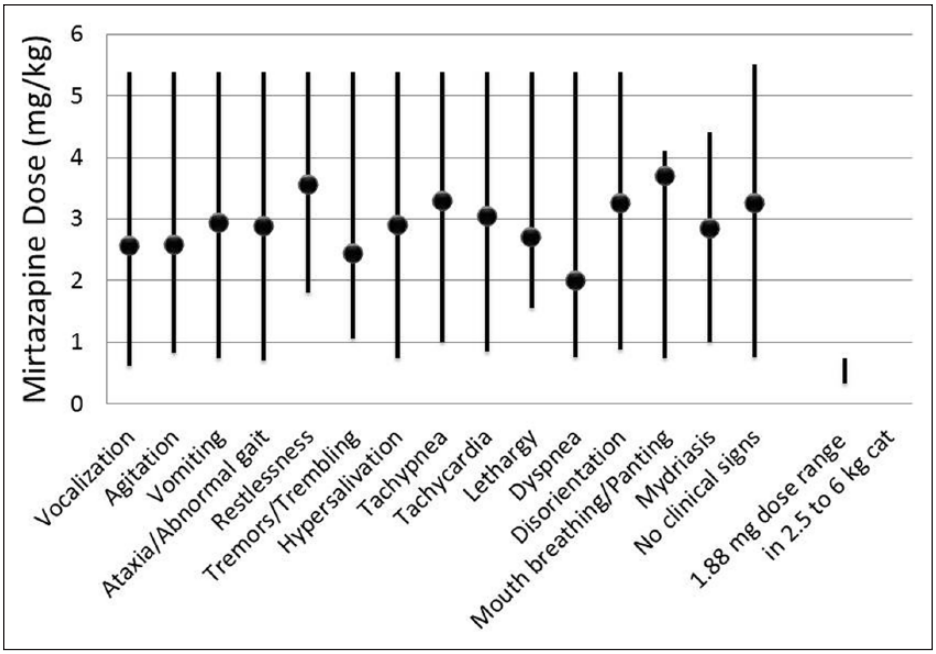

Figure 2 The average mirtazapine dose (mg/kg) and dose range (mg/kg) associated with reported adverse effects in comparison with a 1.88 mg dose range for a cat weighing 2.5–6.0 kg. The circles represent the average mirtazapine dose associated with each clinical sign. Note that the dose range for cats weighing 2.5–6.0 kg and administered a 1.88 mg dose of mirtazapine is lower than the majority of dose ranges reported to be associated with adverse effects

Of the 84 cats included in the study, 59 (70.2%) cases were considered accidental ingestions and 25 (29.8%) cases were given as prescribed. Of the 59 accidental ingestions, 40 cats received more mirtazapine than instructed, and two of those were actually due to a mislabeled bottle. Seven cats were given mirtazapine at the correct amount, but more frequently than prescribed. Ten cats were not actually prescribed mirtazapine, but the owner had it in the home and it was given accidently. Two cats were given a higher dose and more frequent administration than prescribed. Table 2 represents the adverse effects encountered in cats when cats were divided into subgroups based on the dose that was received (<0.75 mg/kg, 0.75–1.50 mg/kg and >1.5 mg/kg) and the adverse effects that occurred at each of those dose ranges. More adverse effects were seen with higher exposure doses.

Thirty cats had more detailed records available for review: 23 of those cats were provided with further treatment for mirtazapine toxicity, five did not receive treatment and were monitored, and information regarding further treatments could not be found in two of the records. Some of the cats only received one type of treatment and other cats received multiple treatments. The treatments that were utilized included: intravenous fluids (n = 13), cyproheptadine at a dose range of 2–4 mg/cat either orally or rectally (with number of repeat doses not specified; n = 12), subcutaneous fluids (n = 7), activated charcoal (n = 3), induction of emesis (n = 2), acepromazine (n = 2), oxygen cage (n = 2) and diazepam (n = 1). It was difficult to determine the time of onset for development of clinical signs related to mirtazapine toxicity; however, 11 cats developed clinical signs within 15 mins up to 3 h. The remainder of the records did not provide a time frame in which signs were noted. Information regarding the time to resolution of clinical signs was available in 18/30 cats; however, it was unknown in 12 cats. Six cats experienced resolution of clinical signs by 12 h, five cats within 1–4 h, one cat at 24 h, two cats at 48 h and four cats did not develop clinical signs of mirtazapine toxicity.

Discussion

In this retrospective study, records of cats exposed to mirtazapine as reported to the APCC were reviewed for the most commonly reported adverse effects and the doses associated with development of those effects. Adverse effects reported in two or more cats included vocalization, agitation, vomiting, ataxia/abnormal gait, restlessness, tremors/trembling, hypersalivation, tachypnea, lethargy, tachycardia, anorexia, disorientation, dyspnea, hypothermia, mouth breathing/panting, mydriasis, behavior change, depression/sedation, fasciculations, hyperactivity, hypertension, pacing, dysphoria, inappropriate elimination, polyphagia, circling, discomfort, hiding, inappetence, seizures and weakness. Over 70% of the cats reported to have adverse effects secondary to mirtazapine

Table 2 Adverse effects encountered in cats that received mirtazapine in three dose ranges: <0.75 mg/kg, 0.75–1.50 mg/kg and >1.50 mg/kg

Dose range (mg/kg)					
<0.75 mg/kg		0.75–1.50 mg/kg		>1.50 mg/kg	
Cats affected*		Cats affected†		Cats affected‡	
Ataxia/abnormal gait	1 (50.0)	Vocalization	9 (45.0)	Vocalization	31 (50.0)
Circling	1 (50.0)	Agitation	7 (35.0)	Agitation	17 (27.4)
Dyspnea	1 (50.0)	Fasciculations	3 (15.0))	Vomiting	16 (25.8)
Hypersalivation	1 (50.0)	Tremors/trembling	3 (15.0)	Ataxia/abnormal gait	11 (17.7)
Lethargy	1 (50.0)	Anorexia	2 (10.0)	Restlessness	11 (17.7)
Vocalization	1 (50.0)	Behavior change	2 (10.0)	Tremors/trembling	9 (14.5)
Vomiting	1 (50.0)	Disorientation	2 (10.0)	Tachycardia	8 (12.9)
		Dyspnea	2 (10.0)	Tachypnea	8 (12.9)
		Inappropriate elimination	2 (10.0)	Mouth breathing/ panting	6 (9.7)
		Lethargy	2 (10.0)	Anorexia	6 (8.1)
		Pacing	2 (10)	Lethargy	5 (8.1)
		Vomiting	2 (10.0)	Hypersalivation	4 (6.5)
		Ataxia/abnormal gait	1 (5.0)	Disorientation	3 (4.8)
		Hyperactivity	1 (5.0)	Hypothermia	3 (4.8)
		Hypersalivation	1 (5.0)	Mydriasis	3 (4.8)
		Hypertension	1 (5.0)	Behavior change	2 (3.2)
		Hypothermia	1 (5.0)	Discomfort	2 (3.2)
		Mydriasis	1 (5.0)	Dyspnea	2 (3.2)
		Polyphagia	1 (5.0)	Hiding	2 (3.2)
		Tachycardia	1 (5.0)	Hypertension	2 (3.2)
		Tachypnea	1 (5.0)	Pacing	2 (3.2)
		Weakness	1 (5.0)	Circling	1 (1.6)
				Depression/sedation	1 (1.6)
				Dysphoria	1 (1.6)
				Fasciculations	1 (1.6)
				Inappetence	1 (1.6)
				Seizure(s)	1 (1.6)
				Weakness	1 (1.6)

Data are n (%). Note that the lowest dose has the least adverse effects associated with it, while the number of adverse effects increases with the dose. Signs observed at <0.75 mg/kg are more typical of what may be encountered when prescribing a dose of 1.88 mg vs signs in the 0.75–1.50 mg/kg category, which may be more typical of what would be encountered if a cat received 3.75 mg. Signs seen in a cat receiving >1.5 mg/kg are more likely to be associated with prescribing an excessive dose or accidental overdose

*n = 2

†n = 20

‡n = 62

were due to accidental ingestion; the majority of these cats received more medication than actually prescribed. It was found that cats have a greater number of reported adverse effects secondary to mirtazapine prescribed at a dose of 3.75 mg rather than 1.88 mg.

Owing to its serotonergic activity, significant overdosage of mirtazapine can result in serious adverse effects consistent with serotonin syndrome. In humans, serotonin syndrome typically has three forms of symptoms, including neuromuscular hyperactivity (tremor, clonus, hyperreflexia, rigidity), autonomic hyperactivity (pyrexia, tachycardia, tachypnea) and altered mental status (agitation, excitement).[8,9] In cats, serotonin syndrome has been reported in conjunction with tramadol and selective serotonin reuptake inhibitor (SSRI) toxicity.[8,10] In cats with SSRI-induced serotonin syndrome clinical signs consisted of sedation, gastrointestinal signs (vomiting, diarrhea, nausea, drooling), central nervous stimulation (vocalization, hyperactivity, hyper-reflexia, agitation, tremors), cardiovascular signs (tachycardia,

bradycardia, hypertension) and hyperthermia.[10] In a case of tramadol-induced serotonin syndrome clinical signs consisted of agitation, hypersalivation, jerky head movements and hypertension, which progressed to the cat being obtunded, laterally recumbent, tachycardic and normotensive.[8] Clinical signs for mirtazapine as described in this study appear to be similar to those reported for other drugs that cause serotonin syndrome in cats.

Cyproheptadine is a non-selective serotonin antagonist that is used as an antidote for serotonin syndrome.[8,9,11] It has also been used as an appetite stimulant in cats; however, it is not recommended to use this medication with mirtazapine as it appears to cancel the effects of mirtazapine, making it ineffective.[3] Cyproheptadine is recommended in cats that develop adverse effects consistent with serotonin syndrome, which can occur with mirtazapine toxicity. A dose of 2–4 mg per cat by mouth or per rectum every 4–8 h until adverse effects abate has been described, but no clinical studies have been performed to validate this dosing regimen.[8,12] Twelve cats in this study were given cyproheptadine; however, given the retrospective nature it was difficult to determine how many doses each cat required and how long it took for clinical signs of mirtazapine toxicity to resolve.

Various dosages of mirtazapine have been described for cats (ie, 3.75 mg every 3 days), but initial recommendations were not based on pharmacologic data. More recently, studies have been completed and demonstrated a significant increase in food consumed after administration of mirtazapine to healthy young cats with minimal side effects when a low dose was used (1.88 mg/cat).[13] In that study a 9 h elimination half-life was demonstrated at this therapeutic dose range leading to a recommendation of once-daily dosing in healthy cats. Cats with chronic kidney disease have been shown to have reduced clearance of mirtazapine and require an extended dosing regimen (ie, every 48 h).[14,15] Previous pharmacodynamic studies have indicated that adverse effects are dose related, with more adverse effects occurring with 3.75 mg than 1.88 mg and no increase in efficacy of appetite stimulation at the higher dose.[13] In the present study findings were similar when adverse effects were subgrouped by dose range (Table 2); the lowest dose range (representing administration of 1.88 mg to cats ranging in weight from 2.5 to 6.0 kg) had the fewest adverse effects associated with it. The number of adverse effects increased substantially in dose ranges representing administration of 3.75 mg to cats ranging in weight from 2.5 to 6.0 kg, and even more so in the dose range representing accidental overdose.

The majority of the cases (70.7%) included in this study were due to accidental ingestion/administration, with 40 cats accidently receiving a 15 mg tablet. In the USA, mirtazapine is typically obtained in a 15 mg tablet and recommendations to give one-quarter (3.75 mg) or one-eighth (1.88 mg) of a tablet are commonly made, but owners may inadvertently administer a full tablet. The importance of having mirtazapine compounded into a 1.88 mg capsule/tablet is emphasized by this study given the low frequency of adverse side effects at this dose and the alarming number of cats that were accidently given a full 15 mg tablet of mirtazapine. In the UK and Europe mirtazapine is, fortunately, available as a 2 mg tablet so this is less of a concern.

Limitations of this study include its retrospective nature, where not all information could be gathered from all the medical records available. This made it difficult to determine whether the adverse effects reported by owners were truly related to mirtazapine or due to the underlying disease process causing anorexia and for which mirtazapine was prescribed. Whether doses were single or multiple cannot be definitively determined from the data. Some cats were reported to have been given mirtazapine more frequently than recommended, but information regarding how often it was given before the owner noted clinical signs were not known. Only the most recent dose was recorded by ASPCA APCC. Multiple cats (28.2%) experienced vomiting; however, mirtazapine has been reported to have antiemetic and antinausea properties. It is possible that these cats were vomiting owing to an underlying disease and not as a result of mirtazapine, or vomiting could have actually have been regurgitation from eating quickly, but this cannot be determined based on the information obtained. Another limitation is the lack of complete records available for all cats included in the study. It was also difficult to determine whether a cat had been treated and improved or did not respond to treatment based on the records that were available.

Conclusions

In this retrospective study, records of cats exposed to mirtazapine as reported to the APCC were reviewed for the most commonly reported adverse effects and the doses associated with development of those effects. The most commonly reported adverse effects included vocalization, agitation, vomiting, ataxia/abnormal gait, restlessness, tremors/trembling, hypersalivation, tachypnea, tachycardia and lethargy. The greater number of adverse effects reported when cats received 3.75 mg rather than 1.88 mg advocates the latter is a more appropriate starting dose for stimulating appetite while limiting adverse effects. The benefit of dispensing exact doses of mirtazapine is implied given the likelihood of accidental administration of a full tablet (15 mg) and resulting toxicity.

Acknowledgements We would like to thank the veterinary hospitals approached in this study for inclusion of their cases. We would also like to thank the American Society for the

Prevention of Cruelty to Animals' Animal Poison Control Center for providing the records included in this study.

Conflict of interest The authors do not have any potential conflicts of interest to declare.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for profit sectors.

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