

# Antidepressant drug overdoses in dogs

by  
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With the rising number of people and animals receiving antidepressant medications, it's not surprising that the number of accidental ingestions of these drugs has also increased. Since 1998, the ASPCA Animal Poison Control Center (APCC) has received more than 1,075 calls concerning antidepressant medication ingestion by dogs. The ingestion of psychotherapeutic medications is often a true emergency because clinical signs can develop rapidly and may lead to death.

Antidepressants encompass several classes: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and novel (or atypical) antidepressants (*Table 1*). Each class differs in its effects on the central neurotransmitters serotonin, norepinephrine, epinephrine, and dopamine. Specificity for each neurotransmitter determines the antidepressant's effectiveness and potential side effects.

*Table 1*

<b>Classes of Antidepressant Drugs</b>
<b>TCAs</b>
Amitriptyline hydrochloride
Amoxapine
Clomipramine hydrochloride
Desipramine hydrochloride
Doxepin hydrochloride
Imipramine hydrochloride
Imipramine pamoate
Maprotiline hydrochloride
Nortriptyline hydrochloride
Protriptyline hydrochloride
Trimipramine maleate
<b>MAOIs</b>
Phenelzine sulfate
Tranylcypromine sulfate
<b>SSRIs</b>
Fluoxetine hydrochloride
Fluvoxamine maleate
Nefazodone hydrochloride
Paroxetine hydrochloride
Sertraline hydrochloride
Trazodone hydrochloride
Venlafaxine hydrochloride
<b>Novel Antidepressants</b>
Bupropion hydrochloride

## TCAs

TCAs are one of the largest families of psychotropic drugs. Their precise mechanism of action is unknown, but TCAs have been shown to block the reuptake of norepinephrine and serotonin at the neuronal membrane, potentiating their effects.<sup>1</sup> TCAs also have strong anticholinergic activity.<sup>1</sup> TCAs are rapidly absorbed from the digestive tract (within 30 to 60 minutes), bind to plasma proteins, and become widely distributed in tissues as a result of their lipophilic nature. The mean plasma half-lives of TCAs can vary greatly among individuals (e.g. two to 21 hours for clomipramine hydrochloride [Clomicalm-Novartis Animal Health]<sup>2</sup>) at both toxic and therapeutic doses. As a result of the anticholinergic properties of TCAs, affected animals may demonstrate delayed gastric emptying and decreased intestinal peristalsis, enhancing absorption. In addition, TCAs have been reported to undergo enterohepatic recirculation, which may prolong their half-lives.<sup>3</sup>

Clinical signs of TCA overdose can appear as early as 30 minutes after ingestion, and death can occur within one or two hours if a patient is not treated.<sup>4</sup> Lethargy and ataxia can quickly progress to tachycardia, vomiting, mydriasis, vasodilation, hypotension, cardiac arrhythmias, vocalizing, dyspnea, pulmonary edema, seizures, coma, and death.<sup>5,6</sup> Occasionally with TCA overdoses, an idiosyncratic hyperactivity may be seen. The most life-threatening effect of a TCA overdose is the slowing of cardiac conduction and the resultant arrhythmias.<sup>5,6</sup> Toxicity varies greatly for drugs in this category. The oral lethal dose for many TCAs is 15 mg/kg. But the subcutaneous lethal dose for amitriptyline hydrochloride is 50 mg/kg,<sup>7</sup> and the oral lethal dose for clomipramine is 100 mg/kg.<sup>2</sup>

In cases of recent ingestion (< 15 minutes), you can treat dogs with TCA overdoses by inducing emesis. Emesis is not recommended if clinical signs are present because of the increased risk of aspiration. Repeated doses of activated charcoal with a cathartic are recommended because they may interrupt enterohepatic recirculation. Avoid magnesium salts as cathartics because of the decreased peristalsis caused by TCAs, which can result in increased magnesium absorption. Sodium bicarbonate (2 to 3 mEq/kg slowly intravenously) is recommended if a patient is acidotic or hypotensive or if arrhythmias are present, because maintaining alkalosis (pH>7.5) in experimentally dosed dogs prevented death.<sup>4</sup> But don't administer sodium bicarbonate therapy if you can't monitor blood gases, because metabolic acidosis can be a serious complication.

## MAOIs

Two MAOIs, phenelzine sulfate (Nardil--Parke-Davis) and tranylcypromine sulfate (Parnate-SmithKline Beecham), are used to treat depression in people. Monoamine oxidase is an enzyme found mainly in nerve tissue but also in the liver, kidneys, intestines, platelets, and placenta.<sup>5,6</sup> Monoamine oxidase catalyzes the oxidative deamination of various amines, including epinephrine, norepinephrine, dopamine, and serotonin.<sup>1</sup> Although the precise mechanism is unclear, monoamine oxidase inhibition results in increased concentrations of these amines, primarily in the central nervous system. With overdoses, monoamine oxidase inhibition occurs in other tissues as well.

MAOI overdoses may cause either hypotension or hypertension, depression, ataxia, restlessness, tachycardia, arrhythmias, coma, seizures, respiratory depression, fever, and shock (ASPCA APCC Database: Unpublished data, 2000). Signs are usually seen within one or two hours but can be delayed 12 to 24 hours. No lethal doses in dogs have been published for phenelzine or tranylcypromine, but a review of the ASPCA APCC database (1995 to present) shows that dogs have exhibited tremors with oral doses as low as 5.5 mg/kg of phenelzine and 2.2 mg/kg of tranylcypromine.

Treatment for MAOI overdoses includes emesis (if the animal is asymptomatic) or gastric lavage and administration of activated charcoal with a cathartic and intravenous fluids. Monitor the patient's body temperature, respiration, and blood pressure closely. Avoid administering pressors (e.g. norepinephrine), phenothiazines, and central nervous system stimulants because their cardiovascular effects may be potentiated.<sup>1</sup> MAOIs interfere with the hepatic metabolism of many drugs and may potentiate the actions of agents such as general anesthetics, barbiturates, morphine, alcohol, corticosteroids, and atropine.<sup>1</sup> Obtain baseline liver enzyme (e.g. alanine transaminase, alkaline phosphatase) activities on admission, and recheck them four to six weeks after exposure since liver enzymes may become elevated after MAOI ingestion.<sup>1</sup> If these activities are elevated, they should return to normal in four to six

weeks. These elevations are rarely accompanied by clinical illness, but avoid administering other drugs that undergo hepatic metabolism, if possible.

## **SSRIs and novel antidepressants**

### **SSRIs**

SSRIs all differ structurally but have the same ability to inhibit presynaptic neuronal reuptake of serotonin. Fluoxetine hydrochloride (Prozac-Dista Products), paroxetine hydrochloride (Paxil-SmithKline Beecham), and sertraline hydrochloride (Zoloft-Pfizer) are the most commonly encountered SSRIs. They have little to no effect on nonserotonin neurotransmitters and, thus, have less anticholinergic, sedative, and cardiovascular side effects than TCAs or MAOIs.<sup>1</sup> Fluoxetine, paroxetine, and sertraline are all well-absorbed and highly protein-bound.<sup>1</sup> The half-lives of sertraline and fluoxetine in dogs are 26 and 20 hours, respectively.<sup>8</sup> The half-life of paroxetine is 20 hours, but it increases in cases of overdose because the metabolic pathway is saturable. Clinical signs of an SSRI overdose, which include lethargy or agitation, vomiting, ataxia, tremors, seizures, hypertension, and tachycardia, are due to increased serotonin in the central nervous system (ASPCA NAPCC Database: Unpublished data, 2000).

In one study, dogs given 10 to 20 mg/kg sertraline orally developed mydriasis and became transiently anorectic; at 30 to 50 mg/kg dogs developed increased salivation and muscle tremors.<sup>9</sup> At 50 mg/kg orally of sertraline no marked effects on blood pressure or heart rate or on the electrocardiogram (ECG) were elicited.<sup>9</sup> The minimum lethal oral dose of sertraline in dogs is reported as 80 mg/kg.<sup>7</sup> Paroxetine causes mild depression starting at oral doses of 1 mg/kg (ASPCA APCC Database: Unpublished data, 2000) but has no effect on heart rate with doses up to 3 mg/kg intravenously and only mild ECG changes at 10 mg/kg intravenously.<sup>10</sup> The lethal dose for paroxetine is unknown. Fluoxetine causes mild depression at oral doses of 1 mg/kg (ASPCA APCC Database: Unpublished data, 2000). The minimum lethal dose of fluoxetine in dogs is greater than 100 mg/kg.<sup>11</sup>

Fluvoxamine maleate (Luvox-Solvay Pharmaceuticals) is another SSRI that inhibits reuptake of serotonin at the presynaptic membrane. But its full mechanism of action is not understood. Fluvoxamine has little to no effect on dopamine and norepinephrine concentrations.<sup>1</sup> The half-life of fluvoxamine in dogs is 15 hours.<sup>12</sup> The most common clinical signs seen in an overdose are lethargy, vomiting, tremors, and bradycardia. Depression and tremors are seen with oral doses of 10 mg/kg (ASPCA APCC Database: Unpublished data, 2000).

Nefazodone hydrochloride (Serzone--Bristol-Myers Squibb) blocks serotonin reuptake at the presynaptic neuronal membrane but is also a serotonin-2 receptor antagonist. Peak plasma concentrations are reached within 20 to 40 minutes. The half-life in dogs is 6.8 to 14.2 hours, but it can increase in overdose situations because of a saturable metabolic pathway.<sup>13</sup> Doses of up to 100 mg/kg given orally twice a day in dogs have not proved lethal.<sup>14</sup>

Trazodone hydrochloride (Geneva Pharmaceuticals) acts in a manner similar to that of nefazodone, but trazodone can have a dual effect on the central serotonergic system; it's a serotonin agonist at high (6 to 8 mg/kg) doses and a serotonin antagonist at low (0.05 to 1 mg/kg) doses.<sup>1</sup> The oral LD<sub>50</sub> in dogs is 500 mg/kg.<sup>1</sup> Common overdose effects include sedation and hypotension. Neurologic signs (*e.g.* ataxia, tremors, seizures) are seen when the dosage reaches the serotonin agonist range (ASPCA APCC Database: Unpublished data, 2000).

Venlafaxine hydrochloride (Effexor--Wyeth-Ayerst Laboratories) is another SSRI that is structurally unrelated to other antidepressants. Venlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak inhibitor of dopamine reuptake.<sup>5,6</sup> It's well-absorbed and not highly protein-bound. The half-life in dogs is two to four hours.<sup>15</sup> Mild depression is seen at doses of 1 mg/kg given orally, and tremors are seen at 10 mg/kg (ASPCA APCC Database: Unpublished data, 2000).

### **Novel antidepressants**

Bupropion hydrochloride (Wellbutrin, Zyban-Glaxo Wellcome), a novel antidepressant, is unrelated to any other currently available psychotropic drug. It's used in human medicine as an antidepressant and for smoking cessation. Bupropion's precise mechanism of action is unknown, but it's thought to selectively inhibit firing of noradrenergic neurons.<sup>1</sup> It inhibits neuronal reuptake of dopamine and, to a lesser extent, norepinephrine.<sup>5,6</sup> Bupropion is quickly

absorbed in dogs, and peak plasma concentrations are reached in 26 to 32 minutes.<sup>16</sup> The half-life of bupropion in dogs is also relatively short at 1.73 hours.<sup>16</sup> After an overdose, tremors and seizures can be seen within one to four hours; however, signs may be delayed with extended-release products. Clinical signs of bupropion overdose include vomiting, dyspnea, salivation, ataxia, seizures, arrhythmias, tremors, and hypotension. Depression can occur at 10 mg/kg orally (ASPCA APCC Database: Unpublished data, 2000).

## **Treatment**

Toxicoses from SSRIs and novel antidepressants require similar treatment. Treatment recommendations include emesis or gastric lavage and activated charcoal every six hours with a cathartic. Only attempt emesis in asymptomatic animals. An enema is recommended if sustained-release products are consumed. Activated charcoal binds tightly to these drugs and can be used as the only decontamination procedure.<sup>1</sup> Diuresis does not enhance excretion because SSRIs and novel antidepressants are highly protein-bound. But consider administering fluid therapy to help support blood pressure and maintain renal function. Treatment is otherwise symptomatic and supportive.

## **Serotonin syndrome**

When dogs ingest more than one type of antidepressant medication, the likelihood of serotonin syndrome increases. Serotonin syndrome in people is characterized by mental status and behavioral changes (*e.g.* agitation, depression), altered muscle tone or neuromuscular activity (*e.g.* myoclonus, hyperreflexia, shivering, tremors, ataxia, seizures), autonomic instability, hyperthermia, and diarrhea.<sup>17</sup> The syndrome most commonly occurs when two or more serotonergic agents with different mechanisms of action are ingested either concurrently or in close succession, leading to excessive serotonin concentrations in the central nervous system.<sup>5,6</sup> Other drugs such as 5-hydroxytryptophan, dextromethorphan hydrobromide, and lithium act synergistically with TCAs, MAOIs, SSRIs, and novel antidepressants and can lead to serotonin syndrome. Because of the severity of the signs, serotonin syndrome is much more difficult to treat than a simple overdose. Signs generally resolve over 12 to 24 hours, but you must closely monitor affected dogs.

Treatment is symptomatic and supportive. You can use activated charcoal, but the risk of aspiration needs to be considered in a vomiting patient or one with neurologic signs. Seizures often abate with diazepam or barbiturate therapy. Metabolic acidosis may occur and can be treated with sodium bicarbonate as indicated by blood gas analysis. You can administer propranolol hydrochloride (0.02 mg/kg slowly intravenously; titrate up as needed), a serotonergic receptor antagonist, to counter tachycardia.<sup>5,6</sup> Cyproheptadine hydrochloride (1.1 mg/kg orally) is a nonspecific serotonin antagonist that has been used successfully in people and, more recently, in dogs (ASPCA APCC Database: Unpublished data, 2000).<sup>5,6</sup> Although there are no controlled studies, cyproheptadine may be given rectally at the same dose.<sup>18</sup> Phenothiazines are serotonergic antagonists that also have antimuscarinic and antihistaminic effects; however, they should be avoided or used with caution because of their ability to lower the seizure threshold and cause hypotension.

## **Conclusion**

Overdoses of SSRIs have fewer cardiac effects and are much less likely to be fatal than overdoses of TCAs or MAOIs. However, the outcome of an antidepressant toxicosis depends on the dose ingested, treatment, and exposure to other highly protein-bound medications (*e.g.* anticonvulsants, thyroid medications, nonsteroidal anti-inflammatory drugs). The prognosis also depends on the dog's overall health, especially if there is a history of liver or renal disease. Liver disease can inhibit metabolism of these drugs, and renal disease can delay excretion. The prognosis is generally good with rapid and aggressive therapy.

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