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**Common Pharmaceutical Poisonings from Adderall to Zoloft**

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**INTRODUCTION**

Over 50% of the calls received by Pet Poison Helpline involve animal exposures to human drugs. This lecture will cover the most common and potentially serious prescription pharmaceutical exposures in cats and dogs: antidepressants, sleep aids, ADD/ADHD drugs (amphetamines), baclofen, and blood pressure medications (calcium channel blockers, beta blockers and ACE inhibitors). Overdoses from the majority of these drugs can result in the rapid onset of clinical signs and life-threatening toxicity. Aggressive treatment and 24 hour monitoring is often necessary. Due to the complicated and intensive treatment of these cases, early consultation with an animal poison control center is strongly recommended.

**ANTIDEPRESSANTS**

This category of drugs encompasses many drug classes, namely selective serotonin reuptake inhibitors (SSRI), selective serotonin and norepinephrine reuptake inhibitors (SSNRI), and cyclic antidepressants. A growing number of these drugs are used in veterinary medicine. Some veterinary specific products such as Reconcile® (fluoxetine) and Clomicalm® (clomipramine) come in chewable, meat flavored tablets.

The range of toxicity varies depending on the drug and species. Cats, overall, are more sensitive to the effects of antidepressants necessitating lower therapeutic doses and exhibiting lower ranges of toxicity. This is especially true with clomipramine as cats may develop sedation, mydriasis, and urinary retention at therapeutic doses (0.25–1 mg/kg). Similar sensitivities are also seen with fluoxetine as the feline LD<sub>50</sub> is half that of dogs (>100 mg/kg in dogs, 50 mg/kg in cats). For a listing of common antidepressants and their minimum reported toxic dose for dogs, please refer to Table 1.

**Table 1. Common prescription antidepressants with correlating doses of canine toxicity.**

Generic name	Trade name	Drug class	Minimum canine toxic dose
Fluoxetine	Prozac, Reconcile	SSRI	1 mg/kg
Sertraline	Zoloft	SSRI	10–20 mg/kg
Venlafaxine	Effexor	SSNRI	1 mg/kg
Paroxetine	Paxil	SSRI	1mg/kg
Bupropion	Wellbutrin, Zyban	Monocyclic	10 mg/kg
Clomipramine	Clomicalm	Tricyclic	12 mg/kg

Small overdoses of SSRIs typically cause sedation and lethargy. Larger overdoses may cause salivation, agitation, ataxia, tremors, and seizures. Serotonin syndrome (also called “hyperactivity syndrome”) is characterized by central nervous, autonomic, and neurobehavioral signs. It may occur with SSRI overdoses and is more often seen in dogs. Overall, the true occurrence of this syndrome is relatively rare. Common signs of serotonin syndrome include GI distress, confusion, agitation, vocalization, muscle rigidity, increased reflexes tremors, seizures, hyperthermia and transient blindness.

Treatment of SSRI overdoses is largely supportive and symptomatic. For seizures in the absence of serotonin syndrome, benzodiazepines are highly effective. In cases of serotonin syndrome, benzodiazepines may exacerbate neurologic signs; barbiturates may be more effective. Cyproheptadine, a serotonin antagonist, has proven useful in reducing the severity of toxicity and can be given orally or crushed and administered rectally. Additional treatments include methocarbamol for tremors, IV fluids for thermal cooling and to maintain hydration, sedation with chlorpromazine or acepromazine, and beta blockers for tachycardia and hypertension (if this is not corrected following sedation).

Overdoses of SSNRIs such as venlafaxine (Effexor®) are similar to SSRI overdoses. However, they have the added element of increased pre-synaptic concentration of norepinephrine. This may lead to an increase the frequency and severity of sympathomimetic signs (tachycardia, hyperthermia, hypertension, etc.) Treatment is similar to SSRI overdoses but more focus on sedation may be needed. Extremely high doses of chlorpromazine (10–18 mg/kg) may be necessary.

Cyclic antidepressant overdoses such as those of the common tricyclic agents amitriptyline and clomipramine may lead to profound cardiac toxicity in addition to the previously discussed neurologic signs. Tricyclic antidepressants exhibit anticholinergic properties and also inhibit fast sodium channels in the cardiac ventricles. This slows depolarization and leads to clinical bradycardia, hypotension, and arrhythmias. Cardiac failure and collapse is the major cause of death following tricyclic antidepressant overdoses.

### **SLEEP AIDS**

Sleep aids are typically short-acting benzodiazepines such as temazepam (Restoril®) or non-benzodiazepine hypnotic agents such as zolpidem (Ambien®) and eszopiclone (Lunesta®). Non-benzodiazepines are chemically unrelated to benzodiazepines but still potentiate gamma-aminobutyric acid(A)-mediated (GABA) neuronal inhibition.

Though the exact range of toxicity for these drugs is not well reported in veterinary medicine, the drugs have a fairly wide margin of safety. It is unlikely that the ingestion of 1–2 pills will lead to life-threatening toxicity in most healthy adult animals. However, larger ingestions may be highly problematic and aggressive care may be necessary.

Animals, especially dogs, develop one of two clinical syndromes when exposed to these medications, each occurring about 50% of the time. Animals will either become sedate, lethargic, dull and depressed or exhibit paradoxical CNS stimulation evidenced by agitation, vocalization, panting, hyperesthesia and hyperactivity. The reason for this remains unknown. Animals exhibiting CNS stimulation should not be treated with benzodiazepines.

This class of drugs is designed to be rapidly absorbed and rapidly excreted. Therefore, the onset of clinical signs is typically 15–60 minutes and resolution is typically seen within 12 hours. Because the onset of neurologic signs can appear so quickly, it is often inadvisable to have emesis induced at home. Activated charcoal may help decrease the amount of drug absorbed.

Treatment is largely focused on symptomatic and supportive care and may include IV fluids to maintain perfusion and increase drug excretion, sedation, and (rarely) cardiac or respiratory support. Most ingestions can be easily managed and relatively little intervention is necessary. If sedation is needed, phenothiazines or barbiturates are recommended. Benzodiazepines should be avoided as they may potentiate CNS excitement. Flumazenil, a benzodiazepine antagonist, is available and may be used in cases of severe toxicity. It has demonstrated efficacy with non-benzodiazepines as well.

### **ADD/ADHD Rx DRUGS (AMPHETAMINES)**

Prescription CNS stimulants are often used for the treatment of Attention Deficit Disorder, narcolepsy and obesity in humans. Examples of amphetamine containing drugs include Adderall®, Dexedrine®, Desoxyn® and Vyvanse®. Methylphenidate (Ritalin® and Concerta®) and dexamethylphenidate (Focalin®) are also commonly prescribed CNS stimulants. Exposures to these drugs make up a large number of the prescription drug calls managed by Pet Poison Helpline. Unfortunately, these drugs have narrow margins of safety and signs of toxicity are frequently noted following exposure.

Amphetamines are sympathomimetic compounds. Although structurally related to norepinephrine, amphetamines are more potent. They stimulate the release of norepinephrine from stores in adrenergic nerve terminals. They also directly stimulate alpha and beta adrenergic receptors.

While the range of toxicity varies amongst these drugs, clinical signs are typically begin at the dose of 1 mg/kg. These drugs are rapidly absorbed and clinical signs often occur 20–30 minutes after ingestion. Sustained-release products and dermal patches (if swallowed whole) may result in a slower onset of action as well as a prolonged duration of clinical signs. Signs of toxicity involve CNS over

stimulation and excessive sympathomimetic effects such as agitation, vocalization, hyperactivity, hypertension, head bobbing, hyperthermia, tachycardia, tremors, and seizures.

Treatment is primarily symptomatic and supportive. Emesis is not often recommended due to the rapid onset of clinical signs. Gastric lavage and activated charcoal may be helpful. Maintaining control of hyperthermia, tachycardia and tremors are key elements in these cases. Chlorpromazine (up to 10-18 mg/kg) has been successfully used in a number of cases. Benzodiazepines are typically avoided as they have a propensity to increase CNS excitement in these cases. Other commonly used interventions include injectable methocarbamol, injectable beta-blockers, and IV fluids. In severe cases, general anesthesia is necessary. Additionally, serotonin syndrome may occur and can be treated with cyproheptadine (orally or as a retention enema).

### **BACLOFEN**

Baclofen is a centrally acting skeletal muscle relaxant (GABA-B receptor agonist) commonly used for the symptomatic relief of painful muscle spasms in patients with spinal cord injury, multiple sclerosis, Parkinson's and Huntington's disease. This drug is rarely used in veterinary medicine to reduce canine urinary sphincter tone. The range of toxicity for dogs and cats is quite small. In dogs, signs of toxicity in adult animals have been noted as low as 3 mg/kg with death resulting from doses of 8-16 mg/kg.

Baclofen is rapidly absorbed from the GIT and the onset of clinical signs may occur as early as 15 minutes following ingestion. Thus, the induction of vomiting at home is not often recommended due to the risk of aspiration. Decontamination should take place under the supervision of veterinary staff to reduce the risk of aspiration. The most common initial clinical signs include vocalization, disorientation, vomiting, and ataxia. As toxicity progresses, life-threatening respiratory depression, hypotension, coma and seizures develop. It is common for clinical signs to last for several days. Fortunately, if treated appropriately, many animals survive without residual CNS effects. The prognosis is guarded for those animals with persistent seizures.

As no antidote exists specifically for baclofen toxicity, treatment is largely supportive and symptomatic. Seizures may be treated with benzodiazepines but long-acting barbiturates should be avoided as they may prolong CNS depression. Bradycardia may respond to atropine, while hypotension may respond to intravenous fluid therapy, volume resuscitation, or vasopressor support. IV fluids should be used to maintain hydration and tissue perfusion. In severe cases where the patient is hypoventilating or very sedate, endotracheal intubation and mechanical ventilation may be needed for several (5-7) days. Additional therapies that have shown success or have anecdotal support include cyproheptadine for disorientation and vocalization, and naloxone for CNS depression.

The use of hemodialysis has been successful in severe cases of toxicity with dogs making a full recovery in 3-4 days. However, the availability of hemodialysis is limited in veterinary medicine. Anecdotally, Intravenous Fat Emulsion (IFE) therapy (the direct administration of intravenous intralipid) has been used in a small number of cases. The use of IFE therapy for the treatment of fat-soluble drug toxicities in veterinary medicine is an emerging, readily available therapy. While the exact mechanism of IFE is not fully understood, the primary theory is that the intralipid emulsion acts as a "pharmacological sink" for fat soluble drugs. Intralipid can be easy to obtain from a human hospital or a veterinary supply company, and provides a cost-effective method of treatment with minimally recognized veterinary or human adverse events. Reported human side effects include fat emboli, hyperlipidemia, hepatosplenomegaly, jaundice, seizures, hemolytic anemia, prolonged clotting time, and thrombocytopenia. For additional information please visit the website <http://www.lipidrescue.org/>.

### **BLOOD PRESSURE MEDICATIONS (CALCIUM CHANNEL BLOCKERS, BETA BLOCKERS, ACE INHIBITORS)**

Companion animal exposure to prescription anti-hypertensive agents represents a large number of the prescription drug calls received by Pet Poison Helpline. Given the common occurrence of these drugs in the home, this is not surprising. The primary agents of concern are calcium channel blockers (such as amlodipine, diltiazem and verapamil) and beta-adrenergic blockers (such as atenolol, propranolol and sotalol). The ability of these drugs to cause life-threatening toxicity is great and all overdoses should be

regarded with concern. ACE inhibitors, such as benazepril and enalapril, do not typically lead to significant toxicity unless very large quantities are ingested or the animal has compromised health.

While the range and clinical manifestation of toxicity varies depending on the drug, the target organ of toxicity for these agents is the cardiovascular system. Bradycardia, hypotension, and heart block are common sequela of overdoses.

Aggressive treatment is often necessary in overdose cases involving calcium channel and beta blockers. Animals that develop signs of toxicity often need 24 hour support for one or more days. Treatment is focused on cardiovascular support and may include aggressive intravenous fluid therapy, atropine and calcium supplementation. Vasopressors must be used with extreme caution. Frequent monitoring of blood pressure, heart rate and rhythm (via ECG), electrolytes, renal indices, and urinary output are necessary.

Emerging therapies such as High Dose Insulin (HDI) and Intravenous Fat Emulsion (IFE) are showing great promise for the treatment of specific anti-hypertensive agents. HDI involves the administration of large doses of intravenous insulin (1–10 units/kg/hr) with the concurrent administration of dextrose. The exact mechanism by which HDI works is unknown. However, it is believed to promote the uptake and utilization of carbohydrates by the myocardium. Additionally, it may increase the concentration of myocardial cytosolic calcium, thus enhancing cardiac output and contractility. The enhancement of cardiac function is also due to the positive inotropic effects of insulin. IFE was briefly covered in the baclofen section of these notes. Due to the life-threatening nature of anti-hypertensive drug overdoses and because full descriptions of HDI and IFE treatments are beyond the scope of these conference notes, consultation with an animal poison control center regarding the management of these patients is strongly recommended.

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