

Serotonin Syndrome



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P Profile

- Serotonin (5-hydroxytryptamine [5-HT]) is a biogenic amine naturally present in the body and stored primarily in the presynaptic nerve terminals of the CNS, enterochromaffin cells, and platelets.
- Serotonin functions in neurotransmission, intestinal motility, regulation of vasomotor tone and blood pressure, and platelet aggregation.
 - Systemic levels in the circulation are normally low.

Definition

- Serotonin syndrome (SS) is a spectrum of clinical signs caused by the effects of elevated serotonin levels.
- Ingestion of certain medications—at therapeutic (eg, adverse effect) or toxic doses—can result in SS (see **Medications & Supplements That May Cause Serotonin Syndrome**, page 14, and the handout, **Agents Implicated in Serotonin Syndrome**, page 16).

Systems

- SS can affect multiple body systems to varying degrees, depending on medication and dose ingested (see **Table**).
- Tryptophan is converted to 5-hydroxytryptophan (5-HTP) and then to serotonin.

Table Clinical Signs of Serotonin Syndrome

Body System	Clinical Signs
Cardiovascular	Tachycardia, bradycardia, arrhythmias, hypertension
Nervous	Sedation, lethargy, recumbency, weakness, hyperexcitability, agitation, aggression, ataxia, behavioral abnormalities, hyperreflexia, hyperesthesia, vocalization, muscle rigidity, transient blindness, tremors, seizures, coma, mydriasis, nystagmus
GI	Hypersalivation, nausea, vomiting, diarrhea, abdominal pain
Metabolic/endocrine	Hyperthermia
Respiratory	Tachypnea

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- ❑ Accidental poisoning from ingestion of holistic supplements containing 5-HTP can result in significant SS.

- In humans, SS often occurs with coingestion of ≥ 2 drugs that alter serotonin metabolism via different mechanisms (eg, selective serotonin reuptake inhibitors [SSRIs], monoamine oxidase inhibitors [MAOIs]), although overdose of single agents has also been reported.¹⁻³
- In veterinary medicine, most SS cases result from accidental ingestion or overdose of 1 drug.
 - ❑ Depending on patient size and drug involved, ≥ 1 pill may be required to initiate clinical signs.

Genetic Implications

- Individual variation or deficiencies in intrinsic monoamine oxidase and cytochrome P450 enzymes may affect drug sensitivity.
- Specific implications for veterinary patients are unknown.

Incidence & Prevalence

- Prevalence of SS in humans and other animals has increased over 10–15 years with increased use of antidepressants (particularly SSRI and selective norepinephrine reuptake inhibitor [SNRI] antidepressants).²

Geographic Distribution

- There is no known specific geographic distribution associated with SS.

Signalment

- Any species or breed may be affected.
- Animal poison control helplines are most commonly contacted for SS in dogs, cats, birds, ferrets, and potbellied pigs (in order of decreasing frequency).⁴
 - ❑ Crossbreed dogs and Labrador retrievers were overrepresented in one study.⁵

- No sex or age predilections have been noted.

Causes

- The most common causes of SS include excessive ingestion of SSRIs; SNRIs; tricyclic antidepressants (TCAs); MAOIs; and dietary supplements containing tryptophan, 5-HTP, and other herbal supplements.

Risk Factors

- Risk for SS is increased in patients with underlying cardiovascular or metabolic (eg, hepatic or renal impairment) conditions, primary or secondary hypertension, and seizure disorders.
- Some neonatal and geriatric patients may be at increased risk.

Pathophysiology

- SS is caused by any substance or mechanism that increases serotonin levels in the CNS.
- To date, four major mechanisms by which these agents increase serotonin in the CNS have been identified:
 - ❑ Serotonin metabolism inhibited (eg, MAOIs, isoniazid)
 - ❑ Reuptake of serotonin by presynaptic nerve terminals (eg, SSRIs, SNRIs, TCAs) inhibited
 - ❑ Serotonin precursor and serotonin agonist (eg, tryptophan, 5-HTP, other herbals) use increased
 - ❑ Release of stored serotonin from presynaptic nerves (eg, amphetamines; 3,4-methylenedioxymethylamphetamines [eg, ecstasy]; cocaine) increased

History

- A thorough patient history should include:
 - ❑ Clinical signs
 - ❑ Signalment
 - ❑ Vaccination status
 - ❑ Heartworm prevention

- ❑ Exposure to trauma or infectious agents
- ❑ Underlying conditions
- ❑ Current and recent medications and supplements (including herbal)
- ❑ Exposure history (eg, what, when, how much [dose strength, tablet number])
- ❑ Emetic agents used at home (if any)
- ❑ Owner medications

Physical Examination

- A thorough, systematic examination should include assessment of vital signs with emphasis on the CNS and cardiovascular system.

Clinical Signs

- Signs of SS can vary with the toxicant ingested, ingested dose, time to decontamination, and underlying patient health (see **Table**, page 11).
- Level of concern, onset of signs, and duration of action can vary, depending on whether the drug is rapid onset, extended release, or sustained release.
 - ❑ With most rapid-onset drugs, signs may be observed as early as 30 minutes–2 hours postingestion.
 - ❑ With extended- or sustained-release formulations, signs may develop within 2–6 hours (rarely out to 12 hours) postexposure.
- SS can be seen at therapeutic doses and overdoses of veterinary-prescribed medications
 - ❑ With low doses (ie, low levels of toxicosis) or adverse effects from drugs, mild signs (eg, GI and CNS signs) are common.
 - ❑ At higher doses, SS signs may include more serious GI upset and CNS signs, as well as cardiopulmonary signs.
- Untreated, SS can result in death.

5-HTP = 5-hydroxytryptophan, MAOI = monoamine oxidase inhibitor, SNRI = selective norepinephrine reuptake inhibitor, SS = serotonin syndrome, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant

Dx Diagnosis

Definitive Diagnosis

- Over-the-counter urine drug tests may detect some (not all) agents suspected of causing SS.
 - These tests can produce false-negative and false-positive results and do not undergo strict laboratory standards.
- Urine, blood, and stomach contents can be tested through a human or veterinary diagnostic laboratory, but testing may be cost-prohibitive, and results probably will not be available in time to benefit treatment.
 - Serum levels do not often correlate consistently with clinical signs.

Differential Diagnosis

- Other exposures or toxicants that can result in similar signs include:
 - Illicit drugs
 - Sleep medications (eg, zolpidem, zopiclone, zaleplon)
 - Wild mushrooms
 - Tremorogenic mycotoxins (eg, compost, moldy food)
 - Atypical antipsychotics (SS vs neuroleptic malignant syndrome)
 - Opioids or opiates
 - Sympathomimetics
 - Anticholinergics
 - Insecticides (eg, carbamates, organophosphates)
 - Rodenticides (eg, zinc phosphide, bromethalin, strychnine)
 - Infectious diseases
 - Metabolic causes
 - Molluscicides (eg, metaldehyde)

Tx Treatment

- There is no specific antidote for SS.
- Treatment is supportive and sympto-

matic, aimed at controlling GI, CNS, and cardiovascular signs and regulating body temperature.

- Depending on when the toxicant was ingested, treatment may consist of decontamination measures followed by monitoring for clinical signs.
 - Decontamination (eg, emesis induction, administration of activated charcoal) should only be performed in the following situations:
 - *In dogs only:* At-home emesis induction can be performed safely with hydrogen peroxide only with recent ingestion (<15–30 min) in asymptomatic patients.
 - *In cats:* Immediate veterinary attention for appropriate emesis induction with xylazine should be performed in asymptomatic patients with recent ingestion (<1 hour); no at-home emetic agents are recommended.
 - At presentation, the decision regarding appropriate emesis induction should be based on whether the patient is asymptomatic and whether the benefit outweighs risk for aspiration.
 - See **Suggested Reading** for more on decontamination.

Inpatient or Outpatient

- Asymptomatic patients should be monitored for 12 hours postexposure.
- Because clinical signs may change abruptly, symptomatic patients should be monitored closely as inpatients.
 - After clinical signs have resolved (typically within 12–24 hours, rarely 48–72 hours in severe cases), the patient can be discharged.

Medical

GI Support

- Antiemetic therapy (eg, maropitant 1 mg/kg SC q24h) should be administered after emesis or gastric lavage and before activated charcoal.
- Activated charcoal with sorbitol should be administered.
 - Benefits of charcoal administration over aspiration risk should be considered in symptomatic patients.
 - Repeat doses without sorbitol can be provided for sustained- or extended-release drug exposures, TCAs, and drugs that undergo enterohepatic recirculation.

Fluid Therapy

- IV fluids (standard crystalloids) at 1.5–2 times maintenance dose may provide adequate hydration and renal perfusion.
- Diuresis typically does not enhance excretion of these drugs.

What to Monitor

- Baseline renal values, blood glucose, and electrolytes in symptomatic patients
- CNS and cardiovascular signs
- Heart rate, respiratory rate, blood pressure, and body temperature
- Continuous electrocardiographic monitoring if cardiac abnormalities develop

Symptomatic Supportive Care

- Cooling measures for body temperature >106°F should be stopped once temperature is 103.5°F.
 - Antipyretics are not recommended.
- Sensory stimuli should be minimized (if possible): no bright lights, loud noise, or sudden movements.
- Cyproheptadine (5-HT_{2A} serotonin receptor antagonist) can be used for SS, hyperesthesia, hyperreflexia, and vocalization.
 - May be used with sedation

Treatment focuses on controlling GI, CNS, and cardiovascular signs, along with regulating body temperature.

MORE ►



Medications & Supplements That May Cause Serotonin Syndrome

- Human prescription medications
 - SSRI and SNRI antidepressants
 - MAOIs
- Veterinary medications for behavioral modification
 - Clomipramine
 - Fluoxetine
- Mirtazapine (for appetite stimulation in cats)
- Illicit drugs (eg, amphetamines, NMDA-agonists)
- Holistic supplements
 - Serotonin
 - Tryptophan
 - St. John's wort *Hypericum perforatum*
- Atypical antipsychotics
- Miscellaneous drugs
 - Tramadol
 - Dextromethorphan
 - Sumatriptan
 - Amantadine
 - Levodopa
 - Carbidopa

Neurologic Support & Sedation

- Sedatives may be used as needed for CNS excitation.
 - The goal is to calm the patient without causing excessive sedation.
- Muscle relaxants (eg, methocarbamol) may be used for muscle fasciculation or tremors.
- Anticonvulsants may be given for seizures.
- Benzodiazepines (eg, diazepam, midazolam) are not generally recommended.
 - May increase CNS excitation



Medications

- Agitation
 - Acepromazine at 0.05–0.1 mg/kg IV, IM, or SC
 - Chlorpromazine at 0.5–1 mg/kg slow IV or IM
 - Some serotonin receptor antagonist activity
- SS
 - Cyproheptadine
 - Dogs: 1.1 mg/kg PO or PR q4–8h
 - Cats: 2–4 mg PO or PR q4–8h as needed
- Tremors
 - Methocarbamol at 55–220 mg/kg slow IV to effect
 - Note risk for CNS/respiratory depression with high doses.
- Seizures
 - Phenobarbital at 4–16 mg/kg IV as needed
 - Propofol at 2–6 mg/kg IV or 0.1–0.6 mg/kg/min CRI
 - Can decrease dose by 25% if acepromazine or chlorpromazine has been administered
 - General anesthesia
- Arrhythmias
 - In tachycardic patients (dogs, >180

bpm; cats, >220–240 bpm) not responsive to sedation, use of β -blockers may be necessary.

- Propranolol
 - 0.02–0.06 mg/kg slow IV
 - Dogs: 0.1–0.2 mg/kg PO q8h
 - Cats: 2.5–10 mg total dose PO q8–12h
- In bradycardic patients (dogs, <50–60 bpm; cats, <120 bpm), blood pressure should be checked immediately to monitor for reflex bradycardia secondary to severe hypertension.
- Antihypertensives as needed (systolic blood pressure >180 mm Hg)
- If patient is normotensive and bradycardic, treat with atropine at 0.01–0.02 mg/kg IM or IV
- Antihypertensive (eg, nitroprusside) can be considered for hypertensive patients (systolic blood pressure >180–190 mm Hg).
- Heart rate and blood pressure should be checked before administering any cardiac drugs; monitoring should be attentive and frequent.

Contraindications

- Based on human extrapolations, benzodiazepines should be avoided, as they may increase CNS excitation.
- S-adenosylmethionine (SAMe) may increase serotonergic effects.
- Magnesium-containing cathartics in TCA exposures
 - Decreased GI motility may increase serum magnesium levels.

Precautions & Interactions

- Drugs that may exacerbate signs of SS (eg, tramadol, SSRI antidepressants, MAOIs, ketoconazole, cimetidine, amitraz) should be avoided.

DIC = disseminated intravascular coagulation, MAOI = monoamine oxidase inhibitor, NMDA = N-methyl-D-aspartate, SNRI = selective norepinephrine reuptake inhibitor, SS = serotonin syndrome, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant



Follow-up

Patient Monitoring

- During monitoring, any signs should be addressed symptomatically.
- Symptomatic patients should be monitored closely until signs resolve.

Complications

- Complications include rhabdomyolysis, myoglobinuria, disseminated intravascular coagulation (DIC), renal hypoxia/failure, and respiratory/CNS depression, any of which can lead to death.

Future Follow-up

- Depending on the toxicant ingested, baseline biochemical evaluation may

need to be performed then rechecked within days of hospital discharge.



In General

Relative Cost

- \$\$-\$\$\$\$

Cost Key

\$ = up to \$100
 \$\$ = \$101–\$250
 \$\$\$ = \$251–\$500
 \$\$\$\$ = \$501–\$1000
 \$\$\$\$\$ = more than \$1000

Prognosis

- Prognosis for SS is generally good unless severe signs (eg, arrhythmias, seizures, hyperthermia, DIC) occur.
- Signs are potentially more severe with ingestion of TCAs and MAOIs.

Prevention

- Owners should be counseled on the importance of keeping prescription medications, drugs, and herbal supplements out of reach.
- Anecdotally, cats seem to preferentially ingest venlafaxine hydrochloride (Effexor XR, effexorxr.com) more often than most other medications; extra caution is advised. ■ **cb**

See **Aids & Resources**, back page, for references & suggested reading.



WEIGHT EXCHANGE: Feeding the neutered patient

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Why should pets maintain a healthy weight over a lifetime?

Clients sometimes are not aware of how important weight and body condition score (BCS) are to pet health. It's important to talk with them early about proper nutrition, optimal weight and ideal BCS. The Purina® Life Span Study showed that feeding to an ideal body condition over a lifetime can significantly extend a dog's healthy years — by an average of 1.8 years for dogs in this study! These dogs also had a later onset of clinical signs of age-related chronic conditions.



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How is metabolism altered after pets are neutered, and how can obesity be avoided?

Neutering often can reduce a pet's metabolic rate and may increase food intake. Several studies have shown that neutering can decrease a dog's or cat's maintenance energy requirement by 25 to 35 percent.^{2,3} Adjusting feeding amounts and/or recommending a lower-calorie food may help reduce the risk of weight gain.

Any tips for discussing feeding after neutering?

During well-puppy and well-kitten visits, talk with clients about the importance of body condition scoring. Then, at the spay or neuter appointment, discuss how the procedure will likely affect metabolic rate and feeding behaviors, and adjust food amounts accordingly, being as specific about

feeding portions and frequency as possible. Offer to do a weight and BCS check monthly, if necessary. This will help young pets transition into adulthood at a healthy weight.

Of course, the nutritional needs of growing pets should not be sacrificed. If a dog or cat is spayed or neutered during the growth period, he needs a diet formulated for growth to get needed nutrients — not a reduced-calorie adult food. Purina offers a downloadable Feeding Guide application that lets veterinarians quickly calculate an appropriate feeding recommendation for any Purina® diet.

1. Kealy RD, Lawler DF, Ballam JM et al. Effects of diet restriction on life span and age-related changes in dogs. *J Am Vet Med Assoc.* 2002 May 1;220(9):1315–20.
2. Jeusette I, Detilleux J, Cuvelier C, Istasse L, Diez M. Ad libitum feeding following ovariectomy in female Beagle dogs: Effect on maintenance energy requirement and on blood metabolites. *J Anim Physiol Anim Nutr.* (Berl). 2004 Apr;88:117–21.
3. Belsito KR, Vester BM, Keel T, Graves TK, Swanson KS. Impact of ovariectomy and food intake on body composition, physical activity, and adipose gene expression in cats. *J Anim. Sci.* 2009 Feb;87(2):594–602.

Visit PurinaVeterinaryDiets.com/NutritionExchange

Agents Implicated in Serotonin Syndrome

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This syndrome refers to the multiple signs caused by excess serotonin (see **Serotonin Syndrome**, page 11). Following is a partial list of agents that, if accidentally ingested or overdosed, can result in serotonin syndrome:

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Citalopram
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Nefazodone
- Paroxetine
- Sertraline
- Trazodone

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

- Desvenlafaxine
- Duloxetine
- Milnacipran
- Sibutramine
- Venlafaxine

Atypical Antipsychotics

- Aripiprazole
- Asenapine
- Bupropion
- Clozapine
- Lurasidone
- Olanzapine
- Quetiapine
- Risperidone
- Ziprasidone

Tricyclic Antidepressants (TCAs)

- Amineptine
- Amitriptyline
- Clomipramine
- Desipramine
- Dosulepin or dothiepin
- Doxepin
- Imipramine
- Imipraminoxide
- Iprindole
- Nortriptyline
- Opipramol
- Protriptyline
- Quinupramine
- Tianeptine
- Trimipramine

Nonselective MAO-A/MAO-B Inhibitors (Hydrazines)

- Hydralazine
- Isocarboxazid
- Isoniazid
- Phenelzine
- Phenoxypropazine
- Safrazine

Nonselective MAO-A/MAO-B Inhibitors (Nonhydrazines)

- Caroxazone
- Furazolidone
- Linezolid
- Tranlycypromine

Selective MAO-A Inhibitors

- Brofaromine
- Metralindole
- Minaprine
- Moclobemide
- Pirlindole
- Toloxatone

Selective MAO-B Inhibitors

- Rasagiline
- Selegiline

Miscellaneous Agents

- 5-hydroxytryptophan (5-HTP)
- Amphetamines
- Chlorpheniramine
- Cocaine
- Dextromethorphan
- Ecstasy (MDMA)
- Lithium
- Methamphetamine
- Metoclopramide
- Mirtazapine
- Olanzapine
- Ondansetron
- Tramadol and other opioids
- Tryptophan