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FEATURE ARTICLE

PEER REVIEWED

Recognizing Dangerous Poisonings in Primary Care: Part 6, Serotonin Syndrome

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The 5 most common causes of poisoning-related fatalities in the United States are antidepressants, antihistamines, cardiovascular drugs, opioids, and pesticides.[1] Drug poisonings, particularly mild cases, are often exceptionally difficult to recognize. Slightly dilated pupils, mild tachycardia and hypertension, slight fever, and tachypnea are all constitutional symptoms that fit myriad working diagnoses, but autonomic instability is a hallmark of drug poisonings. Motor stiffness and hyperreflexia are frequently seen with a number of drug poisoning syndromes, although not with pesticide poisoning.[2,3]

This 6-part review article series helps sort out some of the more common symptoms, interactions, and therapeutic considerations in the clinical approach to a patient whom you suspect may be experiencing the effects of the most common types of poisoning.

This article, the sixth in the series, specifically covers serotonin syndrome (SS). Other articles in the series cover antidepressants, antihistamines, cardiovascular drugs, opioids, and pesticides.

In the early 1960s, researchers described symptoms of euphoria, hyperreflexia, clonus, and drowsiness after administration of high doses of serotonin precursor L-tryptophan to 7 patients being treated with a monoamine oxidase inhibitor.[4] Sternbach first described SS as a distinct clinical entity in humans in 1991.[5,6] In his paper, Sternbach reviewed 38 case reports and described the most common features of the disorder. He also found that nearly all of the patients reported use of antidepressants and other psychotropic agents.[6]

SS, also known as serotonin toxicity, is a potentially fatal adverse drug reaction resulting in excessive 5-HT stimulation.[7] SS is diagnosed clinically, and therefore a detailed history, a comprehensive physical examination, and a neurologic examination are necessary. SS is classically characterized by the triad of altered mental status (lethargy, confusion, coma, agitation), autonomic hyperactivity (nausea, vomiting, diarrhea, mydriasis, hyperthermia, tachycardia), and neuromuscular abnormalities (hyperreflexia, myoclonus, trismus, rigidity).[8,9] The Hunter Serotonin Toxicity Criteria (HSTC) can be used to determine whether a patient who has overdosed on a serotonergic has significant serotonin toxicity.[10,11] The HSTC requires the following variables to predict serotonin toxicity: spontaneous clonus, inducible clonus, ocular clonus, agitation, diaphoresis, tremor, and diaphoresis.[11]

SS can range in severity from mild to potentially life-threatening. Patients exhibiting mild toxicity may be afebrile but tachycardic and manifesting autonomic signs of diaphoresis, shivering, or mydriasis. Patients with moderate toxicity can be tachycardic, hypertensive, and hyperthermic (**Table**).

Table. Serotonin Syndrome: Signs and Symptoms[8]

Acuity	Autonomic Dysfunction	CNS Signs	Mental State
Mild	Usually afebrile or low-grade fever; tachycardia; mydriasis; diaphoresis or shivering	Mild hyperreflexia; periodic tremor; akathisia; myoclonus	Anxious; restless
Moderate*	Fever (≤41°C); ↑ tachycardia; ↑ bowel sounds and diarrhea; diaphoresis	↑ hyperreflexia; induced clonus; ocular clonus; ↑ myoclonus	Easily startled; confused; agitated; hypervigilant
Severe*	Fever (≥41°C)	Increased muscle tone (lower extremity > upper extremity); spontaneous clonus; ↑↑ hyperreflexia	Delirious; comatose

*Moderate and severe toxicity may also present with disseminated intravascular coagulation, acute kidney Failure, metabolic acidosis, and severe rhabdomyolysis.

On physical examination, these patients can have hyperactive bowel sounds, diaphoresis, and mydriasis. Of note, the hyperreflexia and clonus seen in moderate cases can be significantly greater in the lower extremities than in the upper extremities. Patients with severe SS may have severe tachycardia and hypertension that can suddenly deteriorate into shock. These patients may have agitated delirium, as well as increased muscle tonicity and rigidity, more pronounced in the lower extremities than the upper extremities. The increased muscle tone may lead to core temperatures of more than 41°C in life-threatening cases.[8]

Numerous receptors are involved in the pathogenesis of SS. Stimulation of 5-HT_{2A} receptors contributes substantially to this condition, specifically mediating the hyperthermic and rigidity responses. Stimulation of the 5-HT_{1A} receptors may contribute to the hyperactivity and anxiety associated with SS.[5,8]

The mainstay of treatment of SS is removal of the serotonergic agent and supportive care, which involves intravenous administration of fluids and correction of vital signs. Mild cases usually can be managed with supportive care and administration of benzodiazepines. Patients with moderate SS additionally may benefit from serotonin antagonism, specifically of 5-HT_{2A} receptors. Cyproheptadine is the drug of choice, although research definitively establishing its effectiveness is lacking. Cyproheptadine can only be administered orally, but tablets may be crushed and administered through a nasogastric tube if necessary. Patients with hyperthermia (temperature above 41°C) should receive all of the aforementioned therapies along with

neuromuscular paralysis, immediate sedation, and tracheal intubation. Aggressive cooling of hyperthermic patients may reduce complications associated with excessive muscle activity and hyperthermia. Clinicians should avoid paralysis with succinylcholine, because arrhythmias may result from rhabdomyolysis-induced hyperkalemia. SS typically resolves within 24 hours of discontinuation of the serotonergic agent and management with supportive care.[5,7,8]

The diagnosis of mild SS may be easily missed for 2 reasons. First, many physicians are unaware of SS as a clinical entity, and second, the symptoms are mild and for the most part not alarming to either patient or physician. Thorough physical examinations are often omitted by physicians in the presence of such nonspecific symptoms. A high degree of suspicion and an understanding of SS is essential for early diagnosis, and quick discontinuation of the offending drug(s) also is essential, since every patient with mild SS is a potential candidate to develop severe SS. The diagnosis is made clinically and depends on a physical examination that demonstrates neuromuscular irritability (hypertonia, clonus, hyperreflexia, tremor, ocular clonus), autonomic hyperactivity (sweating, elevated pulse, elevated blood pressure), and mental status changes.

References:

1. Bronstein AC, Spyker DA, Cantilena LR Jr, Rumack BH, Dart RC. 2011 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th annual report. *Clin Toxicol (Phila).* 2012;50(10):911-1164.

2. Pierre JM. Extrapyramidal symptoms with atypical antipsychotics: incidence, prevention and management. *Drug Saf.* 2005;28(3):191-208.

3. Thiermann H, Seeger T, Gonder S, et al. Assessment of neuromuscular dysfunction during poisoning by organophosphorus compounds. *Chem Biol Interact.* 2010;187(1-3):265-269.

4. Oates JA, Sjoerdsma A. Neurologic effects of tryptophan in patients receiving monoamine oxidase inhibitor. *Neurology.* 1960;10:1076-1078.

5. Isbister GK, Buckley NA. The pathophysiology of serotonin toxicity in animals and humans: implications for diagnosis and treatment. *Clin Neuropharmacol.* 2005;28(5):205-214.

6. Sternbach H. The serotonin syndrome. *Am J Psychiatry.* 1991;148(6):705-713.

7. Martin TG. Serotonin syndrome. *Ann Emerg Med.* 1996;28(5):520-526.

8. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;352(11):1112-1120.

9. Mason PJ, Morris VA, Balcezak TJ. Serotonin syndrome: presentation of 2 cases and review of the literature. *Medicine (Baltimore).* 2000;79(4):201-20

10. Isbister GK, Buckley NA, Whyte IM. Serotonin toxicity: a practical approach to diagnosis and treatment. *Med J Aust.* 2007;187(6):361-365.

11. Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM.* 2003;96(9):635-642.