

# Serotonin Syndrome: A Concise Review of a Toxic State

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## ABSTRACT

The serotonin syndrome is a toxic state caused by increased intrasynaptic serotonin and characterized by a triad of altered mental status, autonomic instability and neuromuscular abnormalities. It can result from exposure to a single serotonergic agent but is more likely to be due to polypharmacy, often with drugs from multiple classes. It develops over a short period of time and resolves just as quickly once identified and treated. Diagnostic criteria have been developed to assist in clinical practice. Treatment is largely supportive and prognosis is generally very favorable. Pharmacologic vigilance and prevention are key.

**KEYWORDS:** Serotonin syndrome, polypharmacy, myoclonus

## INTRODUCTION

Frequently considered diagnostically but not always recognized or well understood, the serotonin syndrome (SS) is best conceptualized as a potentially life-threatening neurotoxic state rather than a distinct idiosyncratic reaction. It results from excess intrasynaptic serotonin, with symptoms developing over hours, and is characterized by the triad of mental status alteration, neuromuscular hyperactivity and autonomic instability.<sup>1,2</sup>

Initially described in 1960<sup>3</sup> and brought into mainstream awareness with the case of Libby Zion,<sup>4</sup> its true incidence is likely underestimated given the wide spread use of selective serotonin reuptake inhibitors (SSRIs) and other serotonergic drugs, and because mild cases often go undetected.<sup>2,5</sup> Serotonin syndrome occurs in approximately 14%-16% of patients who overdose with SSRIs.<sup>6</sup>

Serotonin syndrome has been reported to occur with numerous drugs and in various combinations, and is overwhelmingly the result of polypharmacy, including illicit and over-the-counter drugs (OTCs). Occurrence of SS with a single agent is unusual, though it does occur, sometimes after a single dose.<sup>7</sup> Case reports document numerous drugs from different classes as precipitants for this toxic state.<sup>8-12</sup>

In this article we review the pathophysiology, clinical presentation, differential diagnosis, precipitating drug classes, and general management of the SS. The aim of this paper is

to provide a brief review of the SS in order to promote greater awareness, increased understanding, and more effective prevention of this toxidrome.

## PATHOPHYSIOLOGY

Serotonin (5-hydroxytryptamine or 5-HT) is a product of hydroxylation and decarboxylation of L-tryptophan.<sup>8</sup> The majority of serotonin is found in the periphery where it is involved in regulation of GI motility and vasomotor function. Approximately 2% of serotonin is found in the CNS and synthesized primarily in the raphe nucleus of the brainstem.<sup>13</sup> Serotonin is involved in modulating multiple CNS functions including core body temperature, emesis, eating behavior, analgesia, wakefulness, sexual behavior, mood, affect, perception, and personality.<sup>2,8,14,16</sup>

The SS toxidrome is thought to result from hyperstimulation of postsynaptic serotonergic receptors. Clinical findings do not correlate with serum serotonin levels; it is the concentration at the nerve terminal that is most important. While 5-HT<sub>2A</sub> receptor agonism has been implicated,<sup>2,8,15,16</sup> activation of the 5-HT<sub>1A</sub> receptor is thought to be primarily responsible for the clinical syndrome.<sup>2, 8, 13-14, 16-18</sup> Increased serotonergic activity is driven by various mechanisms including increased serotonin synthesis and release, decreased catabolism and reuptake, and increased receptor agonism and sensitivity.<sup>8,14,19</sup>

Genetic variability in the activity of the monoamine oxidase (MAO) enzyme responsible for serotonin metabolism is a predisposing factor for the development of SS. Acquired defects in MAO activity and serotonin metabolism related to cardiovascular disease, liver disease, and pulmonary disease associated with chronic tobacco use are identified risk factors for SS development.<sup>18</sup>

Drugs and drug classes that can contribute to the development of this toxic state include, but are not limited to: opioids (and related agents including tramadol), antimicrobials (including antiretrovirals), SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), atypical antidepressants such as trazodone and mirtazapine, lithium, triptans, anxiolytics, antihistamines, antitussives, anti-emetics, antiepileptic drugs (AEDs), muscle relaxants, anti-obesity drugs, methylene blue, herbal preparations, OTCs, and drugs of abuse.<sup>8,19</sup>

**CLINICAL PRESENTATION AND DIAGNOSIS**

SS is a clinical syndrome that requires a careful history, complete medication reconciliation, and comprehensive physical and mental status examinations to diagnose. It presents with a triad of mental status changes (anxiety, agitation, confusion, restlessness, disorientation, coma), neuromuscular abnormalities (rigidity, tremor, nystagmus, myoclonus, hyper-reflexia, ataxia, increased tone, particularly in the lower extremities), and autonomic instability (hypertension, hypotension, tachycardia, tachypnea, mydriasis, diaphoresis, hyperthermia).<sup>5, 14-15, 17, 20</sup>

The majority of cases present within 24 hours, and most within six hours of starting, changing, adding, and even withdrawing a drug.<sup>21</sup> Clinical presentation varies across a spectrum of severity. Mild cases can present with only anxiety and tremor and often go undetected. When severe, SS can present with hyperthermia, rhabdomyolysis, acute renal failure, metabolic acidosis, disseminated intravascular coagulation, respiratory failure, seizure and coma. Fatalities associated with SS are often the result of poorly treated hyperthermia.<sup>11,12,19</sup> Associated laboratory findings are non-specific, and can include elevated aminotransferases, creatinine, serum potassium, and creatinine phosphokinase (CPK), as well as leukocytosis, and myoglobinuria.<sup>12,19</sup>

The differential diagnosis of SS is broad and includes malignant hyperthermia, anticholinergic toxicity, opioid withdrawal, CNS infection, delirium tremens, non-convulsive seizures, sympathomimetic toxicity, stiff man syndrome, and heat stroke, but diagnostic consideration of neuroleptic

malignant syndrome (NMS) in patients treated simultaneously with dopamine blocking agents is most common and challenging.<sup>8,14</sup> A number of findings aid in the differentiation between SS and NMS including abrupt onset, rapid resolution, mydriasis, myoclonus, hyper-reflexia, and clonus (especially in the lower extremities) in SS.<sup>2,14</sup> (Table 1).

Several diagnostic criteria have been developed for the accurate identification of SS.<sup>17, 22</sup> The Hunter criteria<sup>20</sup> provide decision rules that are simple to apply and have been shown to have good sensitivity (75%) and specificity (86%) (Table 2).

**TREATMENT**

Successful treatment is based on prompt recognition, after which the offending drug(s) are removed and supportive treatment instituted. Serotonin syndrome has a generally favorable prognosis and often resolves without specific intervention, other than supportive measures, including intravenous hydration and provision of a safe environment for the management of delirium.<sup>24, 25</sup> Most cases resolve within 24 hours. In approximately 30%-40% of cases, however, symptoms persist beyond 24 hours and may require more intensive care.<sup>16</sup>

Beyond supportive measures in mild cases, level of intervention is based on severity of presentation. Agitation is treated with benzodiazepines and external cooling is used to prevent complications of hyperthermia.<sup>14</sup> Moderate symptoms may be treated pharmacologically with cyproheptadine, a 5-HT<sub>2A</sub> antagonist and nonselective H<sub>1</sub> antagonist.<sup>23,25</sup> Chlorpromazine, a 5-HT<sub>2A</sub> antagonist and dopamine antagonist, is a second-line agent, but caution is advised due to the risk of hypotension and the drug's ability to decrease the seizure threshold. In cases where NMS is a diagnostic consideration, chlorpromazine and other dopamine blocking agents should be avoided so as to minimize diagnostic confounding.

Significant neuromuscular hyperactivity and autonomic instability suggest a severe course of illness and require aggressive treatment that may include sedation, intubation, and paralysis. Succinylcholine should not be used in cases of rhabdomyolysis to avoid exacerbation of hyperkalemia. Restraints should be avoided as they are associated with isometric muscle contraction that can drive lactic acidosis and worsen hyperthermia. Bromocriptine and dantrolene sodium, used in cases of severe NMS, have no proven role in the treatment of SS. Antipyretics are not indicated as hyperthermia in SS is thought to be due to excessive muscle contraction rather than to a change in hypothalamic set point.

Reinstitution of serotonergic drugs and other potentially offending agents needs to be carefully considered according to specific clinical indications and risk of recurrent toxicity. Serotonin syndrome is much easier to prevent than to treat.

**Table 1.** Differentiating SS from NMS.

	SS	NMS
<b>Onset</b>	Abrupt > gradual	Gradual > abrupt
<b>Course</b>	Rapid resolution	Prolonged
<b>Neuromuscular findings</b>	Myoclonus + tremor	Diffuse rigidity
<b>Reflexes</b>	Increased	Decreased
<b>Pupils</b>	Mydriasis	Normal

**Table 2.** The Hunter criteria for serotonin syndrome.

<b>Presence of a serotonergic agent plus one of the following:</b>
Spontaneous clonus.
Inducible clonus + agitation or diaphoresis.
Ocular clonus + agitation or diaphoresis.
Tremor + hyperreflexia.
Hypertonia + temperature >38°C + ocular or inducible clonus.

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