

# Identification and Prevention of Serotonin Syndrome

Mohammad Masud Iqbal<sup>1\*</sup>, Saabry Yusof Osmany<sup>2</sup>,

Mohamamd Tamzid Iqbal<sup>3</sup>

<sup>1</sup>Central New York Psychiatric Center, Marcy, NY, USA

<sup>2</sup>Paragon Medical Center, Radlink PET and Cardiac Imaging, Singapore

<sup>3</sup>University of Buffalo, Buffalo, NY, USA

**ABSTRACT:** *Serotonin Syndrome (SS) is a rare, but lethal, adverse drug reaction caused by excessive serotonin activity in the nervous system. Serotonin syndrome is more accurately described as serotonin toxicity and can be triggered by serotonergic agents either alone or in combination with monoamine oxidase inhibitors (MAOIs). It may occur after one standard therapeutic dose of a single agent, unintentional interactions between various medications, drug overdose, as well as recreational drug use. Symptoms present as alteration of mental status, abnormalities of neuromuscular tone, and autonomic hyperactivity. Although effects are usually mild and resolve with prompt recognition and supportive care, there exists a strong need for integration of these preventative measures in current clinical practice.*

**Key words:** *Serotonin syndrome, selective serotonin reuptake inhibitors, antidepressants, serotonergic agents*

## INTRODUCTION

Excessive serotonergic activity at the central and peripheral 5-hydroxytryptamine 2A (5-HT<sub>2A</sub>) and 5-hydroxytryptamine 1A (5-HT<sub>1A</sub>) receptors causes Serotonin syndrome. If gone unrecognized, this excessive serotonergic activity has the potential to become fatal (Bishop & Bishop, 2011). Serotonin Syndrome, previously referred to as Serotonin toxicity, (Sternbach, 1991) typically develops soon after initiation or dosage increase of a serotonergic agent, or a combination of agents. Nearly all medications that increase central nervous system (CNS) serotonin have been associated with cases of SS (Keck & Arnold, 2000; Boyer & Shannon, 2005; Jones & Story, 2005; Huang & Gortney, 2006). The most common agents involved in SS include: antidepressants, opiate analgesics, weight-loss medications, antibiotics, over-the-counter (OTC) drugs, street drugs, dietary supplements, antiemetic drugs, antimigraine medications, CNS stimulants and herbal products (Boyer & Shannon, 2005) (Table 1). Several medications, including meperidine, tramadol, ecstasy, dextromethorphan, SSRIs, imipramine, and MAOIs, have been observed to cause extreme cases of SS (Isbister et al., 2003; Demirkiran et al., 1996). With respect to drug overdose, it has been estimated that nearly 16% of all SSRI overdose cases result in SS (Mackay, Dunn, & Mann, 1999).

Up to 85% of general practitioners are unaware of SS (Mackay, Dunn, & Mann, 1999). Greater physician awareness, along with increased communication among physicians, and between patients and their physicians is urgently needed to promptly recognize the various autonomic, somatic, and cognitive symptoms associated with SS.

## CLINICAL FEATURES

The onset of SS symptoms is rapid, usually within 6 hours of the initial exposure, or heightened dosage to a serotonergic agent (Sternbach, 1991; Boyer et al., 2005; Birmes et al., 2003; Radomski et al., 2000; Martin, 1996). Symptoms can also be resolved rapidly,

often within 24 hours, if the offending agent(s) are identified and withdrawn at initial signs of serotonin toxicity (Gelender et al., 2011; Arora et al., 2010). The symptoms of SS are classified based on their severity as either mild, moderate or severe (full-blown form); each requiring a different level of care (Radomski, Dursun, Reveley et al., 2000) (Table 2).

Mild SS, by virtue of its reduced severity, is often unrecognized due to its time limited, afebrile, and self-resolving nature. Observed symptoms may include intermittent tremors or twitching, myoclonus, diaphoresis, restlessness, shivering, mydriasis, tachycardia, and hyperreflexia (Radomski, Dursun, Reveley et al., 2000).

Moderate SS may require treatment of symptoms such as tachycardia, hypertension, hyperthermia (up to 40 degrees C or 104 degree F), hyperactive bowel sounds, diaphoresis, hyperreflexia/clonus (both greater in lower extremities than upper), horizontal ocular clonus, tremors (greater in lower extremities), and altered mental status (mild agitation, hypervigilance, peculiar head turning).

Severe SS, or serotonin crisis, is treated as a medical emergency that requires immediate hospitalization and Intensive Care Unit (ICU) support. Symptoms include life threatening hyperthermia, generalized tonic-clonic seizures, shock, rapid changes in blood pressure (either marked as severe hypertension or hypotension), tachycardia, tachypnea, hypertonicity, increase rigidity and muscle tone (greater in lower extremities), multiple organ failure and mental status changes, such as elevated mood, confusion and agitated delirium that may ultimately end as coma (Radomski, Dursun, Reveley et al., 2000).

The classic SS triad of neuroexcitatory features includes altered mental status, neuromuscular hyperactivity and autonomic instability. The symptoms are categorized in table 3 (Boyer et al., 2005; Keegan et al., 2006; Birmes et al., 2003; Gelender et al., 2011; Walse, 2010; Bodner et al., 1995; Woollorton, 2006; Dvie et al., 2008; Thanacoody, 2007).

## DIAGNOSIS

There is no conclusive laboratory test. Diagnosis of SS is clinical, relying on patient history and presentation, history of medication

\*Correspondence regarding this article should be directed to: mmqbal569@gmail.com

**Table 1.**

A Striking Number of Drug Combination have been Associated with the Serotonin Syndrome (Sternbach, 1991; Keck & Arnold, 2000; Boyer & Shannon, 2005; Isbister et al., 2003; Gelender et al., 2011; Hall, 2003)

<b>Antidepressants</b>	MAOI A: Irreversible: Phenelzine, Tranylcypromine, Isocarboxazid Reversible: Moclobemide. MAOI B: Selegiline  TCA: Nortriptyline, Protriptyline, Imipramine, Desipramine, Doxepine, Clomipramine, Amitriptyline  SSRIs: Fluoxetine, Citalopram, Sertraline, Paroxetine, Escitalopram  SNRI's: Venlafaxine, Duloxetine  Other : Bupropion, Trazodone, Serzone, Nefazodone, Mirtazepine
<b>Opiate analgesics/pain medications</b>	Tramadol, Fentanyl, Meperidine, Morphine, Pethidine, Pentazocine, Buprenorphine, Oxycodone, Hydrocodone, Cyclobenzaprine
<b>Over the counter (OTC) cough medication</b>	Dextromethorphan
<b>Antimigraine agents/Tryptans (5-HT<sub>1</sub> agonists):</b>	Triptans: Almotriptan, Dihydroergotamine, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan, Zolmitriptan Others: Carbamazepine, Valproic acid.
<b>Psychedelics (drugs of abuse/street drugs)</b>	Lysergic acid diethylamide (LSD), MDA, Methylenedioxymethamphetamine (MDMA: ecstasy), Cocaine, Amphetamine, 5-methoxy-diisopropyltryptamine, foxy methoxy, Syrian rue (Peganum harmala) seeds
<b>Weight reduction agents/appetite suppressant (bariatric medications)</b>	Sibutramine (Meridia), Phenylpropanolamine
<b>Herbal products</b>	St. John's wort, Syrian rue (Peganum harmala) seeds, Panax ginseng, Nutmeg, Yohimbe
<b>Antibiotics</b>	Linezolid (Zyvox)
<b>Antiemetics</b>	Droperidol, Metoclopramide, Ondansetron, Granisetron
<b>Others Tryptophan</b>	L-Dopa, Valproate, Buspirone, Lithium, Dextromethorphan, 5-hydroxytryptophan, Certain foods (cheese and red wine)
<b>CNS Stimulants</b>	Phentermine, Diethylpropion, Amphetamine, Subutramine, Methylphenidate, Methamphetamine, Cocaine
<b>Anticonvulsant</b>	Valproic acid, Carbamazepine
<b>Antiviral</b>	Ritonavir
<b>Others</b>	Chlorpheniramine, Risperine, Olanzapine

**Table 2.**

Symptoms of Serotonin Syndrome- Classified based on their Severity

Mild	Moderate	Severe
<input type="checkbox"/> Often unrecognized and self resolving in nature. <input type="checkbox"/> Afebrile <input type="checkbox"/> Intermittent tremors or twitching <input type="checkbox"/> Myoclonus <input type="checkbox"/> Diaphoresis <input type="checkbox"/> Restlessness <input type="checkbox"/> Shivering <input type="checkbox"/> Mydriasis <input type="checkbox"/> Tachycardia <input type="checkbox"/> Hyperreflexia	<input type="checkbox"/> May require treatment <input type="checkbox"/> Tachycardia <input type="checkbox"/> Hypotension <input type="checkbox"/> Hyperthermia <input type="checkbox"/> Hyperactive bowel sounds <input type="checkbox"/> Diaphoresis <input type="checkbox"/> Hyperreflexia/clonus <input type="checkbox"/> Horizontal ocular clonus <input type="checkbox"/> Tremors <input type="checkbox"/> Altered mental status	<input type="checkbox"/> Treated as a medical emergency. <input type="checkbox"/> Threatening hyperthermia <input type="checkbox"/> Generalized tonic-clonic seizures <input type="checkbox"/> Shock <input type="checkbox"/> Rapid changes in blood pressure <input type="checkbox"/> Tachycardia <input type="checkbox"/> Tachypnea <input type="checkbox"/> Hypertonicity <input type="checkbox"/> Multiple organ failure <input type="checkbox"/> Increase muscular rigidity and tone <input type="checkbox"/> Mental status changes <input type="checkbox"/> Delirium <input type="checkbox"/> Coma

use, physical examination, and ruling out other neurologic disorders such as neuroleptic malignant syndrome, malignant hyperthermia, sympathomimetic toxicity, anticholinergic poisoning, meningoencephalitis, severe sepsis, delirium tremens and heat stroke (Garside & Rosebush, 2003; Adnet et al., 2000).

The most common symptoms of SS are widespread myoclonus, tremor, hyperreflexia, diaphoresis, flushing and clonus (Gelender et al., 2011; Hall, 2003). Physical examination should include assessment of deep-tendon reflexes, muscle rigidity, oral mucosa, size and reactivity of pupils, intensity of bowel sounds, skin color and the presence or absence of sweating.

## MANAGEMENT AND PREVENTION OF SEROTONIN SYNDROME

Typical SS management involves agitation control, autonomic and neuromuscular stabilization, and hyperthermia control (Sporer, 1995). Ingestion of large doses of serotonergic agents can be treated

by gastrointestinal decontamination with activated charcoal (Isbister, Buckley, & Whyte, 2007).

The aggressiveness and intensity of SS therapy depends on the severity of the symptoms. The initial management and treatment for all forms of SS are supportive care and cessation of any serotonergic medications. Mild cases may only require cessation of offending agents and supportive care. Supportive care can prevent secondary complications, such as rhabdomyolysis, renal failure and disseminated intravascular coagulation.

Patients with moderate SS may show progressively increasing toxicity a number of hours after ingestion of serotonergic drugs. Moderate cases of SS should be observed for a period of 6 hours, and up to twelve hours if a slow or extended release formulation has been ingested (Isbister, Buckley, & Whyte, 2007). Mild to moderate cases are largely self-limiting and symptoms generally resolve within 24 to 72 hours after the administration of offending agent(s) are decreased or terminated (Mir & Taylor, 1999).

**Table 3.**

Classic triad manifestations of Serotonin Syndrome (Keck & Arnold, 2000; Boyer & Shannon, 2005; Keegan et al., 2006; Birmes et al., 2003; Gelender et al., 2011; Walse, 2010; Bodner et al., 1995; Wooltorton, 2006; Dvie & Smallwood, 2008; Thanacoody, 2007)

<b>Mental Status Changes/Cognition</b>	<ul style="list-style-type: none"> <li>• Agitation, irritability, excitement, nervousness, anxiety, insomnia, vigilance, hypomania</li> <li>• Hyperactivity, restlessness, intermittent headache, dizziness</li> <li>• Hallucination, lethargy, confusion, disorientation, delirium, seizures, drowsiness to coma.</li> </ul>
<b>Autonomic Hyperactivity or instabilities</b>	<ul style="list-style-type: none"> <li>• Hyperthermia (mild: &lt;38.5 degree C; severe: &gt;38.5 degree C), profuse sweating, shivering, flushed skin</li> <li>• Tachycardia, tachypnea, dyspnea</li> <li>• Changes (unstable) in blood pressure               <ul style="list-style-type: none"> <li>- In moderate cases: severe hypertension</li> <li>- In severe cases: hypotension.</li> </ul> </li> <li>• Mydriasis (dilated pupil) and unreactive pupils</li> <li>• Presence of bowel sounds, abdominal cramps, diarrhea, nausea, vomiting, salivation</li> </ul>
<b>Neuromuscular abnormalities</b>	<ul style="list-style-type: none"> <li>• Hyperreflexia (common-over reactive reflexes),</li> <li>• Clonus (inducible/spontaneous/ocular-more especially in lower extremities/ankles than upper), myoclonus (muscle twitching), hypertonia (increase tone in lower extremities), peripheral hypertonia</li> <li>• Ataxia, loss of coordination, tremor (greater in legs), muscular rigidity, Babinski's sign (bilateral)</li> <li>• Chills, shivering</li> <li>• Nystagmus, trismus, teeth chattering or grinding, Seizures</li> </ul>

Note: Hypertonia and Clonus are always symmetrical and are often much common in the lower extremities

Patients presenting with severe SS should be admitted immediately to intensive care where neuromuscular complications may be treated with pharmacotherapy and artificial ventilation (Boyer & Shannon, 2005; Isbister et al., 2007; Mir & Taylor, 1999).

SS is highly preventable (Boyer & Shannon, 2005) and prevention practices should start with increased education for both physicians and patients. Since there is currently no laboratory test to confirm a diagnosis, physicians should carefully monitor patients for symptoms of SS when administering drugs that have the possibility to trigger excess serotonergic activity (Isbister, Buckley, & Whyte, 2007). The interplay between serotonergic drugs is complex, and the risk of serotonin toxicity increases with the use of multiple agents (Zagaria, 2007). Thus it is imperative that physicians are aware of their patient's current medications, as well as previous medication history.

Physicians must also be knowledgeable of what drugs, and combinations of drugs, may result in serotonin toxicity. This will prevent physicians from administering drugs that have a high possibility of inducing SS, as well as encouraging the use of alternate drug options. Furthermore, patients should be forthcoming regarding their health, diet, and lifestyle habits to avoid drug treatments that may augment proper serotonin activity.

## CONCLUSION

The current trends in increased use of offending agents like SSRIs, and the associated life threatening complications of SS is a major concern for clinicians. The failure to quickly recognize symptoms of hyper serotonergic activity, and the subsequent continuation of the offending agents, may result in progression towards a very severe state of SS. Since serotonin toxicity arises from combinations or high doses of serotonergic medications, it is highly preventable. Both physicians and patients need to be aware of the potential for SS, its preventability, symptoms, and treatment.

## REFERENCES

Adnet, P., Lestavel, P., & Krivosic-Horber, R. (2000). Neuroleptic malignant syndrome. *British Journal of Anaesthesia*, 85(1), 129-135.

Arora, B., & Kannikeswaran, N. (2010). The Serotonin syndrome- the need for physician's awareness. *International Journal of Emergency Medicine*, 3(4), 373-377.

Birmes, P., Coppin, D., Schmitt, L., et al. (2003). Serotonin Syndrome. A brief review. *Canadian Medical Association Journal*, 168(11), 1439-1442.

Bishop, J., & Bishop, S.L. (2011). How to prevent serotonin syndrome from dug-drug interactions. *Current psychiatry*, 10(3), 81-83.

Bodner, R.A., Lynch, T., Lewis, L., et al. (1995). Serotonin syndrome. *Neurology*, 45(2), 219-223.

Boyer, E.W., & Shannon, M. (2005). The Serotonin syndrome. *New England Journal of Medicine*, 352, 1112-1120.

Demirkiran, M., Jankovic, J., Dean, J.M. (1996). Ecstasy intoxication: an overlap between serotonin syndrome and neuroleptic malignant syndrome. *Clinical Neuropharmacology*, 19(2), 157-164.

Dvie, Y., & Smallwood, P. (2008). Serotonin Syndrome: a complex but easily avoidable condition. *General Hospital Psychiatry*, 30(3), 284-287.

Garside, S., & Rosebush, P.I. (2003). Serotonin syndrome: not a benign toxidrome. *Canadian Medical Association Journal*, 169(6), 543.

Gelender, P., Gorgulu, U., Kutlu, G., et al. (2011). Serotonin Syndrome due to duloxetine. *Clinical Neuropharmacology*, 34(3), 127-128.

Hall, M. (2003) Serotonin Syndrome. *Australian Prescriber*, 26(3), 62-63.

Huang, V., & Gortney, J.S. (2006). Risk of serotonin syndrome with concomitant administration of linezolid and serotonin agonists. *Pharmacotherapy*, 26(12), 1784-1793.

Isbister, G.K., Bowe, S.J., Dawson, A., et al. (2004). Relative toxicity of selective serotonin reuptake inhibitor (SSRIs) in overdose. *Journal of Clinical Toxicology*, 42(3), 277-285.

Isbister, G.K., Buckley, N.A., & Whyte, I.M. (2007). Serotonin syndrome: a practical approach to diagnosis and treatment. *Medical Journal of Australia*, 187(6), 361-365.

Isbister, G.K., Hackett, L.P., Dawson, A.H., et al. (2003). Moclobemide poisoning: toxicokinetics and occurrence of serotonin toxicity. *British Journal of Clinical Pharmacology*, 56, 441-450.

Jones, D., & Story, D.A. (2005). Serotonin Syndrome and the anaesthetist. *Anaesthesia and Intensive Care*, 33(2), 181-187.

Keck, P.E. Jr., & Arnold, L.M. (2000). Serotonin Syndrome. *Psychiatric Annals*, 30, 333-343.

Keegan, M.T., Brown, D.R., & Rabinstein, A.A. (2006). Serotonin syndrome from the interaction of cyclobenzaprine with other serotonergic drugs. *Anesthesia & Analgesia*, 103(6), 1466-1468.

Mackay, F.J., Dunn, N.R., & Mann, R.D. (1999). Antidepressants and the serotonin syndrome in general practice. *British Journal of General Practice*, 49(448), 871-874.

- Martin, T.G. (1996). Serotonin Syndrome. *Annals of Emergency Medicine*, 28(5), 520-526.
- Mir, S., & Taylor, D. (1999). Serotonin Syndrome. *Psychiatric Bulletin*, 23, 742-747.
- Radomski, J.W., Dursun, S.M., Reveley, M.A., et al. (2000). An exploratory approach to the serotonin syndrome: an update of clinical phenomenology and revised diagnostic criteria. *Medical Hypotheses*, 55(3), 218-224.
- Sporer, K.A. (1995). The serotonin syndrome. Implicated drugs, pathophysiology and management. *Drug Safety*, 13(2), 94-104.
- Sternbach, H. (1991). The serotonin syndrome. *American Journal of Psychiatry*, 148, 705-713.
- Thanacoody, H.K.R. (2007). Serotonin Syndrome. *Australian Adverse Drug Reactions Bulletin*, 243, 931-934.
- Walse, J. (2010). Serotonin syndrome. *Anaesthesia Tutorial of the Week*, 166, 1-5.
- Wooltorton, E. (2006). Triptan migraine treatments and antidepressants: risk of serotonin syndrome. *Canadian Medical Association Journal*, 175(8), 874.
- Zagaria, M.E. (2007). Serotonin Syndrome: Identification, Resolution, and Prevention. *U.S. Pharmacist*, 32(11), 20-23.