

## ANTIDEPRESSANTS-INDUCED SEROTONIN SYNDROME: LITERATURE REVIEW

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**Summary.** The serotonin syndrome (SS) is a potentially life-threatening adverse drug reaction caused by excessive serotonergic activity in the nervous system. It is characterized by a triad of symptoms, which include mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. Numerous medications have been associated with the SS. However, most of the reported cases include antidepressants, either on their own or in combinations with drugs from different therapeutic groups, over-the-counter drugs or illicit substances. The most well-known combination resulting in SS is the selective serotonin reuptake inhibitors (SSRIs) with Monoamine oxidase inhibitors (MAOIs). Of all groups of antidepressants, the SSRIs are the most commonly implicated. The incidence of reported cases with the serotonin and noradrenaline reuptake inhibitors (SNRIs) is also increasing. Because of the widespread use of antidepressants, clinicians must maintain a high clinical suspicion for the SS. The avoidance of multidrug regimens is critical to the prevention of the SS.

**Keywords:** serotonin syndrome, antidepressants, selective serotonin reuptake inhibitors

### Introduction

The serotonin syndrome (SS) is a drug-induced condition resulting from medications that increase the level of intrasynaptic serotonin. It is characterized by a constellation of symptoms, which include mental status changes, autonomic hyperactivity and neuromuscular abnormalities [1, 2]. Many reports prefer to call this condition serotonin toxicity rather than syndrome due to its wide range of symptoms and toxicity. Also, the term “serotonin syndrome” tends to encourage the assumption that it is an idiosyncratic response, which SS is not [3, 4].

Numerous medications can lead to SS,

either alone or in combination. However, antidepressants occupy a central place. The selective serotonin reuptake inhibitors (SSRIs) are perhaps the most commonly implicated group of antidepressants associated with this syndrome [5].

Although a lot of medications can precipitate SS, life-threatening cases tend to occur with the use of drug combinations. The most well-known combination is SSRIs with Monoamine oxidase inhibitors (MAOIs) [6, 7]. The actual incidence of SS is unknown. It is often underdiagnosed because of the mild symptoms and unawareness of the syndrome [1, 2].

Oates and Sjostrand [8] first described the SS in 1960 in patients on monoamine oxidase inhibitors (MAOIs) who developed the symptoms when given tryptophan, a serotonin precursor. Since then the number of reported cases of SS has increased, probably secondary to the widespread use of antidepressants. The reported incidence may also reflect an increasing diagnostic awareness of the syndrome [1, 2]. SS has been documented in all age groups [1].

### Presentation

The presentation of SS can range from mild to life-threatening. The symptoms usually begin within 24 hours of an increased dose of a serotonergic agent, the addition of another serotonergic agent to the drug regimen, or overdosing. Most patients will seek help at a hospital within the first 6 hours [1, 3].

Altered mental status, autonomic hyperactivity, and neuromuscular abnormalities comprise the triad of clinical features seen in the SS. These symptoms could range in severity. In mild cases, patients are usually conscious and afebrile. The autonomic features presented are: mild hypertension and tachycardia, diaphoresis, shivering, and mydriasis. The neurologic examination may show tremor, myoclonus, and hyperreflexia. Patients with mild symptoms may have a more subacute or chronic presentation and usually, these cases stay unrecognized.

In moderate cases, mental status changes such as mild agitation with pressured speech may become apparent. All of the existent symptoms in mild cases are also present plus hyperthermia (40°C), hyperactive bowel sounds, and horizontal ocular clonus. As regards to the neurologic examination, it is worth mentioning that the symptoms of hyperreflexia, rigidity, and clonus tend to be more marked in the lower extremities.

In contrast to mild cases, severe cases may rapidly progress to death. Patients with severe, life-threatening cases have all of the above symptoms plus hyperthermia greater than 41.1°C, delirium, and hemodynamic instability manifested as dramatic swings in pulse rate and

blood pressure. As the syndrome progresses, the neuromuscular findings become more generalized, presented as muscle rigidity.

Severe cases may result in lethal complications, such as seizures, metabolic acidosis, rhabdomyolysis, renal failure, acute respiratory distress syndrome, and respiratory failure, diffuse intravascular clotting, coma, and death. It's essential to mention that most of these complications occur, generally as a result of inadequately treated hyperthermia [1, 3, 9].

### Diagnosis

The diagnosis of SS remains challenging since it can only be made on clinical grounds. No single diagnostic test can confirm this syndrome [10]. The suspicion of SS and diagnosis must occur rapidly so that treatment can prevent the morbidity and mortality associated with this condition [3].

There are two major components in the diagnostic of SS - a complete and accurate medication history and physical examination. An accurate history of the drugs or substances administered or taken is of utmost importance. Clinicians should also inquire about any recent changes in dosing or the addition of new drugs to a drug regimen. It is crucial to note that drugs that could precipitate SS include not only prescribed drugs, such as antidepressants, but also over-the-counter drugs, illicit substances, and dietary supplements [1, 3]. Presence of any comorbidity, for example, depression and chronic pain, may also alert the clinicians to the use of drugs implicated in the development of the SS [3]. Furthermore, a higher incidence of SS has been reported in patients with end-stage renal disease who are on selective serotonin reuptake inhibitors (SSRIs) and hemodialysis [3, 11]. As regards to the physical examination, clinicians should be focused on identifying the three major features of SS - autonomic instability, neuromuscular signs, and cognitive impairment. Therefore, the neurological examination is critical when making the diagnosis [3].

Several diagnostic criteria have been proposed for SS through the years, such as

Radomski criteria [12], Sternbach criteria [13], and the Hunter Serotonin Toxicity Criteria (HSTC) [4]. The most recent diagnostic criteria are the HSTC, which have replaced the older ones in an attempt to simplify the diagnosis. When compared the HSTC are more sensitive (84% versus 75%) and specific (97% versus 96%) than the Sternbach criteria [3, 4].

The HSTC include the use of a serotonergic agent plus 1 of the 5 following criteria: spontaneous clonus, inducible clonus plus agitation or diaphoresis, ocular clonus plus agitation or diaphoresis, tremor and hyperreflexia, hypertension and a temperature above 38°C plus ocular or inducible clonus. We should emphasize that clonus and hyperreflexia are the most important findings when making the diagnosis of the SS. However, clinicians should always be aware that severe muscle rigidity may mask these symptoms [3, 4]. Some nonspecific laboratory abnormalities might be seen: elevated creatinine level, elevated transaminases and leukocytosis. Serum serotonin concentrations do not correlate with the severity of this syndrome [2, 3].

Although the HSTC are frequently thought to be the gold standard for the diagnosis of the SS, recent research has not proven that. The research conducted by Werneke et al., tested the validity of four assumptions, which have become widely accepted. One of these assumptions is that the Hunter classification performs clinically better than the Sternbach and Radomski criteria. Systematic review and meta-analysis have been conducted, and the results have shown that the Hunter criteria did not perform better than the Sternbach and Radomski criteria. Therefore, clinicians should keep an open mind about the diagnosis, even if HSTC are not met [10].

The primary differential diagnosis of SS includes neuroleptic malignant syndrome (NMS), anticholinergic syndrome and malignant hyperthermia. Other potential diagnoses may include: serotonergic discontinuation syndrome, overdose of sympathomimetic drugs, meningitis, encephalitis or heat stroke. Some diagnoses may be distinguished from the SS by the clinical

features, medication history and time course [3].

The NMS is an idiosyncratic reaction to dopamine antagonists. This condition is related to a slow onset, bradykinesia or akinesia, “lead pipe” muscular rigidity, hyperthermia, fluctuating consciousness, and autonomic instability. Symptoms of the NMS evolve during several days, in contrast to the rapid onset of the SS [1]. Although, recent research proved that not all cases of SS seem to be of rapid onset [10]. Medication history also helps in distinguishing between syndromes: dopamine antagonists produce bradykinesia, whereas serotonin agonists produce hyperkinesia.

The anticholinergic syndrome is “toxicodrome” with specific features, which include mydriasis, dry oral mucosa, hot and dry, erythematous skin, urinary retention, and an absence of bowel sounds. Hyperactive bowel sounds, diaphoresis, and normal skin color, along with neuromuscular abnormalities, distinguish the SS from the anticholinergic toxidrome.

Malignant hyperthermia is a pharmacogenetic disorder, which occurs within minutes after exposure to inhalational anesthetic agents. It is characterized by increasing concentrations of end-tidal carbon dioxide, muscle rigidity, hyperthermia, and metabolic acidosis. Mottled, often cyanotic skin and the rigor mortis-like rigidity of skeletal muscles and hyporeflexia distinguish this condition from the SS [1].

## Mechanism

Serotonin (5-hydroxytryptamine [5-HT]) is a monoamine neurotransmitter. It is formed from the decarboxylation and hydroxylation of the amino acid L-tryptophan. The serotonin is stored in vesicles and released into the synaptic cleft when there is stimulation. 5-HT is metabolized by monoamine oxidase-A (MAO-A) into 5-hydroxyindoleacetic acid, which is then excreted in the urine. Serotonin receptors are divided into seven families (5-HT<sub>1</sub> to 5-HT<sub>7</sub>), several of which have multiple members. No single receptor is responsible for the development of SS. However, several studies provide evidence that the 5-HT<sub>2A</sub> receptors mediate the

most important consequences of SS [1, 3, 14].

Serotonin has both central and peripheral effects. In the central nervous system (CNS), serotonergic neurons are found in the midline raphe nuclei of the brainstem from the midbrain to the medulla. In the CNS serotonin plays a role in numerous functions: regulation of wakefulness, food intake, thermoregulation, affective behavior (anxiety and depression), sexual behavior, nociception and motor tone. Outside of the CNS, the serotonin is synthesized in the enterochromaffin cells of the gastrointestinal (GI) tract. Peripheral 5-HT is involved in stimulation of vasoconstriction, GI motility, bronchoconstriction, uterine contraction and platelet aggregation [1, 3, 14].

SS is a result of increased intrasynaptic levels of serotonin, caused by overstimulation of both the central and peripheral 5-HT receptors. Several animal studies show that other neuromediators, such as noradrenaline, N-Methyl-D-aspartate (NMDA), gamma aminobutyric acid (GABA), and dopamine may also play a role in SS, but their impact is still unclear [1, 3].

Drugs, which raise the intrasynaptic serotonin, are known as serotonergic drugs. The complete list of the serotonergic drugs is long but is important to note that it includes over-the-counter drugs, illicit substances, and diet supplements. However, as major representatives, antidepressants take a central place.

Antidepressants that have been reported to cause SS and the mechanism of each are as follows [3, 14]:

#### 1. Inhibit serotonin metabolism:

- MAOIs: *Tranlycypromine, Phenelzine, Isocarboxazid, Nialamid, Iproniazid, Pargyline, Clorgiline, Moclobemide, Toloxatone*

#### 2. Increase serotonin release: *Mirtazapine*

#### 3. Inhibit serotonin reuptake:

- Selective serotonin reuptake inhibitors (SSRIs): *Paroxetine, Sertraline, Fluoxetine, Fluvoxamine, Citalopram, Escitalopram*

- Serotonin and noradrenaline reuptake inhibitors (SNRIs): *Venlafaxine, Desvenlafaxine, Duloxetine, Milnacipran*

- Tricyclic antidepressants (TCAs):

*Imipramine, Clomipramine, Desipramine, Doxepin, Amitriptyline, Amoxapine, Maprotiline, Nortriptyline, Protriptyline, Trimipramine*

- *Bupropion, Nefazodone, Trazodone*

4. **Activate serotonin receptors:** *Mirtazapine, Trazodone*

5. **Inhibit CYP2D6 enzyme (pharmacokinetic mechanism):**

- Inhibitors: *Fluoxetine, Sertraline*

- Substrates: *Dextromethorphan, Oxycodone, Tramadol, Phentermine, Risperidone*

Although numerous antidepressants can precipitate SS, most of the cases tend to occur when antidepressants are combined with other serotonergic medications. The reported drug interactions that have caused SS continue to increase and include interactions on both pharmacodynamic and pharmacokinetic level. Some of the reported drug combinations include [3, 7, 14, 15, 16, 17, 18]:

- MAOIs: alone or with SSRIs; SNRIs; TCAs; opiates; Amphetamine or Ecstasy (3,4-methylenedioxymethamphetamine)

- SSRIs: alone or with MAOIs; SNRIs; TCAs; opiates; triptans; Dextromethorphan; Linezolid or L-tryptophan

- Citalopram with: Fluconazole or Olanzapine and Lithium

- Fluoxetine with: Risperidone; Carbamazepine; Phentermine or Fentanyl

- Sertraline with Fentanyl
- Paroxetine with: Risperidone or Methylene blue

- Clomipramine with Methylene blue

- Amitriptyline with: Dextromethorphan or Dextromethorphan and Risperidone

- SNRIs with: MAOIs; TCAs or opiates

- Venlafaxine with: Lithium or calcineurin inhibitors; Mirtazapine and Tramadol; Amitriptyline and Meperidine; Mirtazapine or Tranlycypromine; Methadone and Fluoxetine; Methadone and Sertraline; Tramadol; Trazodone and Quetiapine; Ciprofloxacin and Methadone; Co-amoxiclav

- Mirtazapine with SSRIs or Tramadol and Olanzapine

- Trazodone with Amitriptyline

and Lithium

As demonstrated above, antidepressants can lead to SS when they are combined with each other or when they are combined with other medications from different groups. Such groups include opiates (Tramadol, Fentanyl), triptans, atypical antipsychotics (Olanzapine, Risperidone), antibiotics (Ciprofloxacin, Co-amoxiclav), some illicit substances (Amphetamine, Ecstasy) and over-the-counter drugs (Dextromethorphan).

Some of these interactions occur on a pharmacokinetic level [3, 7, 14, 15, 16, 17]. The inhibition of CYP 450 enzymes results in the accumulation of certain serotonergic drugs that are usually metabolized by these enzymes. Antidepressants can play the role of both inhibitors and substrates. As inhibitors of CYP2D6, SSRIs increase the concentration of Dextromethorphan which is a substrate of the same enzyme. In other cases, the inhibition of CYP2C19 by Fluconazole results in the accumulation of its substrate Citalopram [3].

The most well-known combination associated with the SS is an SSRI with an MAOI. However, life-threatening cases tend to occur with the use of an irreversible MAOI or with combinations of serotonergic drugs rather than with just the use of an SSRI alone [1, 3, 4, 6, 7].

Of all SNRIs, Venlafaxine has been associated with SS the most, even more than SSRIs. Evidence suggests that it may act other than as a re-uptake inhibitor, possibly as a serotonin releaser [14]. Furthermore, it has been suggested that the risk of inducing SS might be higher with SNRIs rather than with SSRIs, especially when these are combined with a 5-HT<sub>1A</sub> antagonist.

It is important to note that Fluoxetine interactions have been reported up to 6 weeks after discontinuation of the antidepressant. Fluoxetine and its metabolite Norfluoxetine have longer half-lives (1 week and 2.5 weeks, respectively) than the other SSRIs [3]. Therefore, clinicians should be cautious when prescribing another serotonergic agent to the same patient.

Some authors suggest that critical value of serotonin is necessary for the development of SS [3, 4, 17]. Despite that, several case reports show that the critical value is likely different for each patient. The possible mechanisms of individual variability include genetic differences in the SERT gene (a serotonin transporter), polymorphisms of CYP2D6 or of the 5HT<sub>2A</sub> and 5HT<sub>3B</sub> receptors [3, 6].

### Management

When SS is recognized promptly and treated appropriately, the prognosis is generally favorable [19]. First-line management involves discontinuing the offending drugs and providing supportive care via stabilizing vital signs. The intensity of treatment depends on the severity of the symptoms. Treatment for mild cases includes removal of the causative drugs, sedation with benzodiazepines, and observation for at least 6 hours [1, 2, 3]. Most patients with mild cases do not require hospitalization [19].

Patients with moderate to severe cases require hospital admission. These patients should be treated as above with addition of serotonergic antagonist [3]. Cyproheptadine, a selective serotonin 2A antagonist, is usually recommended. Body et al. reported a sublingual use of 5-HT<sub>2</sub> receptor antagonist - Olanzapine in the treatment of serotonin syndrome [20].

The managing of the hyperthermia and the muscle rigidity in severe cases requires neuromuscular paralysis with nondepolarizing agent such as Vecuronium, sedation, and possible intubation [3, 19].

Although, SS usually resolves within 24 hours, in some cases symptoms may persist for a longer period of time. Usually, these cases involve drugs with long duration of action or active metabolites with long half-lives [1, 3, 14].

### Conclusion

The SS is an underreported, underdiagnosed and potentially life-threatening condition which requires heightened clinical awareness. The early recognition and prompt treatment are vital for the favorable prognosis of the

syndrome. Therefore, physicians should maintain a heightened clinical scrutiny for the SS, especially in the mild cases, which often remain not diagnosed. If SS is recognized, treatment should start with a prompt cessation of the offending drug.

However, SS prevention takes a central place in reducing the morbidity and mortality associated with this condition. The avoidance of multidrug regimens is critical to the prevention of the syndrome, because of the widespread use of antidepressants and numerous drug combinations implicated with it.

Increased patient awareness may also reduce the incidence of the SS. Patients should be educated on the early signs and symptoms of the syndrome. They should also be warned about the usage of some over-the-counter medications and illicit substances associated with the serotonin syndrome.

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