

# Serotonin Syndrome

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**A**lthough serotonin syndrome was described more than 40 years ago,<sup>1</sup> most clinicians are unfamiliar with the condition. This potentially life-threatening adverse drug reaction is a cause of current concern because of the high utilization of psychopharmacologic therapies with pro-serotonergic properties. This condition warrants prompt diagnosis and aggressive intervention to reduce morbidity and prevent fatalities.<sup>2</sup> The majority of physicians are unaware of the manifestations of severe serotonin (5-HT) toxicity, despite the fact that serotonin reuptake inhibitors (SRIs), both selective and unselective, are widely used in clinical practice. These agents include selective serotonin reuptake inhibitors (SSRIs), dual reuptake inhibitors, such as venlafaxine and duloxetine, tricyclic antidepressants (TCAs), and other pro-serotonergic drugs prescribed for mood and anxiety disorders.<sup>3</sup>

Drug interactions that result in hyperactivity of the serotonin system are the most frequent cause of serotonin toxicity, due to additive pharmacologic effects on neuronal pathways modulated by this monoamine neurotransmitter. Because serotonin syndrome is a predictable adverse occurrence, not an idiopathic adverse drug reaction, it is potentially avoidable. An accurate medication history is critical for recognition and proper diagnosis of the syndrome. However, even clinicians familiar with the syndrome may initially miss early and subtle clinical manifestations of serotonin toxicity. Prompt detection of serotonin toxicity is vital because without intervention, rapid progression to potentially life-threatening status can occur.

## THE HYPER-SEROTONERGIC STATE: CLINICAL SYNDROME

Serotonin toxicity is characterized by the triad of neuromuscular abnormalities, altered mental status, and hyperactivity of the autonomic nervous system. All of these manifestations need not be present, depending on the severity of the reaction. The clinical

picture can range from mild agitation, tremor, and gastrointestinal (GI) symptoms in less severe cases, to a state of extreme muscle rigidity with hyperthermia that demands immediate intervention.<sup>4</sup> Serotonergic neurons mediate multiple central nervous system (CNS) functions, including wakefulness, thermal regulation, food and sexual appetites, affective behavior, and motor tone. In the peripheral nervous system, serotonin induces GI motility and diaphoresis. This multiplicity of CNS and peripheral receptors accounts for the highly variable clinical manifestations of serotonin toxicity.

Analysis of an extensive series of cases of serotonin toxicity found neuromuscular abnormalities to be the most reliable diagnostic finding. Clonus, hyperreflexia, and muscle rigidity nearly always are evident, and shivering may be present.<sup>2,5</sup> The autonomic hyperactivity is reflected by diarrhea, increased bowel sounds, dilatation of the pupils (mydriasis), and sweating. CNS disturbances include akathisia, agitation, delirium, hyperthermia, and in advanced cases, coma. Extreme muscular rigidity in severe cases can obscure clonus and hyperreflexia, exacerbate the hyperthermia, and without aggressive treatment intervention, be life-threatening.

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Onset of symptoms in serotonin syndrome is typically acute and rapidly progressive, following shortly after one or two doses of offending medication. While this is usually caused by a drug interaction, it may also result from excessive dosage (or self-poisoning). Manifestations of moderate serotonin toxicity are present in approximately 15% of SSRI overdoses, but fortunately self-poisoning with a serotonergic drug by itself is rarely fatal. The most frequent cause of severe and potentially fatal reactions is co-administration of a monoamine oxidase inhibitor (MAOI) and SRI.<sup>6</sup> Life-threatening toxicity results from combination of two potent serotonergic drugs acting via differing pharmacologic mechanisms. The vast majority of drug interactions resulting in fatalities have involved MAOIs combined with either an SRI or an opioid drug with SRI- or serotonin-releasing properties.<sup>6</sup>

Patients with milder forms of serotonin toxicity can experience subacute symptoms that may not be sudden or severe enough to cause the patient to seek treatment. Clinicians may also fail to recognize these milder complaints as being manifestations of serotonin toxicity and inadvertently raise the dose of the offending agent.

## DRUGS IMPLICATED IN SEROTONIN TOXICITY

The Table<sup>2,6</sup> provided lists medications possessing serotonergic activity that have been implicated in causing severe serotonin toxicity or serotonin syndrome, either administered individually in high dosage, or in combination.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of serotonin syndrome spans anticholinergic overdose (insecticide poisoning), malignant hyperthermia, and neuroleptic malignant syndrome (NMS). While these medical emergencies share similarities, they should be readily distinguishable from serotonin syndrome based on a careful history and physical exam. Documenting the medication history is extremely helpful in making a diagnosis. If exposure to a serotonergic agent within the previous month can be reliably ruled out, serotonin syndrome is extremely unlikely. Malignant hyperthermia is an anesthesia-related event, occurring acutely during induction with an inhalational agent. Unlike serotonin syndrome, it is manifested by hyporeflexia. History of exposure to insecticide use or spraying immediately preceding onset of signs of anticholinergic poisoning can

usually be readily established. Anticholinergic poisoning is characterized by hot dry skin, normal reflexes, and absent bowel sounds, in contrast to serotonin toxicity.

NMS is the condition most easily confused with serotonin syndrome because of the presence of hyperthermia and altered mental status. “Lead pipe” muscular rigidity and bradykinesia, not the hyperkinesia of serotonin toxicity, are characteristic signs. NMS is an idiopathic reaction to a dopamine antagonist drug, not a pharmacologically predictable and dose-related phenomenon like serotonin toxicity. NMS typically involves gradual onset of symptoms over several days in a patient receiving psychotic drug treatment, while sudden onset of symptoms with rapid progression suggests serotonin syndrome.

## TREATMENT OF SEROTONIN SYNDROME

Management of serotonin syndrome includes withdrawal of the precipitating drug(s), supportive care and control of agitation, administration of a 5-HT<sub>2A</sub> antagonist, and use of neuromuscular-blocking drugs if the muscle rigidity and hyperthermia are severe.<sup>2</sup> Milder cases with akathisia or agitation can usually be managed with benzodiazepines and intravenous fluids to normalize vital signs. Control of agitation with benzodiazepine administration is advisable regardless of

**TABLE**  
**DRUGS THAT HAVE BEEN ASSOCIATED WITH SEROTONIN SYNDROME<sup>2,6</sup>**

Antidepressants	SSRIs, MAOIs, TCAs, venlafaxine, duloxetine, bupropion, mirtazapine, trazodone, nefazodone, buspirone
Analgesics	Meperidine, fentanyl, tramadol, pentazocine, propoxyphene
Anti-emetics	Ondansetron and others
Anti-migraine drugs	Sumatriptan
Antibiotics	Linezolid
Anticonvulsants	Valproate
Illicit drugs	Amphetamines, MDMA
OTC cold and cough preparations	Oral decongestants, dextromethorphan
Weight-loss drugs	Sibutramine
Others	Lithium, St. John's wort, dietary supplements containing tryptophan

SSRIs=selective serotonin reuptake inhibitors; MAOIs=monoamine oxidase inhibitors; TCAs=tricyclic antidepressants; MDMA=methylenedioxymethamphetamine; OTC=over-the-counter.

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severity because animal studies have shown improved survival rates and amelioration of autonomic hyperactivity with use of these agents. More severe cases benefit from treatment with a 5-HT<sub>2A</sub> antagonist, such as cyproheptadine. Hyperthermia >41°C and extreme muscle rigidity demand aggressive intervention with sedation, neuromuscular paralysis, and orotracheal intubation. Control of hyperthermia may necessitate inhibiting muscle rigidity using a non-depolarizing agent. Presence of extreme muscular rigidity also can obscure hyperreflexia and clonus, signs pathognomonic of serotonin syndrome. The clinical status of patients with serotonin syndrome can deteriorate rapidly so it is important to initiate therapy promptly. If the diagnosis is unclear initially, supportive care and administration of benzodiazepines should not be withheld, especially when there is agitation.

## CONCLUSION

Despite widespread use of SRIs and other potent serotonergic agents, a majority of clinicians are unfamiliar with the signs and symptoms of severe serotonin toxicity. Serotonin syndrome is an acute, potentially fatal condition, most fre-

quently a result of a drug-drug interaction. The interaction of an MAOI with a potent serotonergic agent is the most common cause of serotonin syndrome. SRIs, including venlafaxine and duloxetine, as well as the opioid analgesic meperidine, have the capacity for lethal reactions in combination with an MAOI. When discontinuing a drug with the potential for interaction, the agent should be washed out for at least five elimination half-lives, ordinarily 1 week (4 weeks for fluoxetine) prior to starting an MAOI. On discontinuing MAOI therapy, at least 2 weeks should elapse before initiating treatment with another serotonergic agent, since this is the minimum time required to regenerate sufficient levels of MAO enzyme and avoid this interaction. **PP**

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