

Serotonin Syndrome/Serotonin Toxicity

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Objective: This review of serotonin syndrome or serotonin toxicity covers the years 2014 to 2019, including information on pathophysiology, etiology, and diagnosis, 3 criteria for diagnosing serotonin syndrome, and criteria for neuroleptic malignant syndrome.

Importance: The review highlights the potential lethal

combinations of commonly prescribed medications used to treat both veteran and nonveteran patients and includes the latest information on offending medications.

Conclusions: Prevention of serotonin toxicity includes informed clinicians, patient education, careful prescribing and monitoring, and avoidance of multidrug regimens.

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Serotonin, or 5-hydroxytryptamine (5-HT), is a chemical neurotransmitter in the central and peripheral nervous systems that was discovered in 1940s.¹ One of the most widely studied chemical messengers, serotonin influences many physiologic functions in humans, including regulation of mood, sleep-wake cycle, appetite suppression, memory, emesis, breathing, cognition, blood coagulation, libido, and many other functions.² In 1992, Insel and colleagues first documented the toxic symptoms produced from too much serotonin in the central and peripheral nervous systems, naming it serotonin syndrome.^{3,4}

SEROTONIN SYNDROME

Experts in the fields of psychiatry, pharmacy, and toxicology refer to these symptoms as serotonin toxicity, because the symptoms result from the toxic effects of too much serotonin.⁵⁻⁹ The term *toxicity* instead of *syndrome* “clarifies that it is a form of poisoning, just as lithium toxicity is a form of poisoning.”⁶ Therefore, serotonin toxicity (ST) can develop with administration of any serotonin-enhancing medication, including therapeutic use, polypharmacy, or accidental/intentional drug overdose.

The incidence of ST has increased over the past decade.^{5,6,10,11} Several reasons explain this increase: (1) ST mirrors the increase in depression in the US populations^{10,12,13}; (2) There has been an increase in off-label antidepressant prescribing by both primary care and mental health providers¹⁴⁻¹⁶; (3) the increased use of illicit drugs¹³; (4) an increase in suicide attempts with antidepressants¹⁷; and (5) increased use of opioids for pain management, including both prescription and illicit use.^{11,14}

This paper reviews the potential lethal combinations of commonly prescribed medications used to treat both veteran and nonveteran patients and includes the latest information on offending medications; a presentation of symptoms from in utero to adult; diagnostic criteria; and recommended treatments.

The Veterans Health Administration (VHA) and non-VHA health care providers can play a key role in identifying and preventing serotonin syndrome/ST by keeping abreast of the latest updates of potentially lethal drug combinations. Commonly prescribed medications with the potential for a reaction include antidepressants, anxiolytics, pain medications, anti-nausea medications, herbal medications, and over-the-counter (OTC) medications, such as cough suppressants. Patients may be at increased risk for ST due to the growth of polypharmacy management of comorbidities.

Antidepressants

Over the past decade, antidepressant use has increased substantially in the US, United Kingdom, and Canada.¹⁴ Also the types of antidepressants prescribed has changed and been replaced with the newer agents. The selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) have replaced the older tricyclics (TCAs) and monoamine oxidase inhibitors (MAOIs) as first-line treatments for depression due to their improved comparative efficacy, reduced mortality following overdose, adverse effects (AEs) that are more tolerable for most patients, and the SSRIs have no anticholinergic properties (except paroxetine) (Table 1).¹⁸

TABLE 1 Serotonin-Elevating Medications

| SRI | SGA | Opioids | Illicit Drugs | OTC/Herbals | Disputed ^a |
|--|-------------|---|---|---|---|
| SSRIs (es)citalopram Fluoxetine Fluvoxamine Paroxetine Sertraline Vilazodone Vortioxetine | Ziprasidone | Meperidine Methadone Pentazocine Pethidine Tramadol | MDMA/Ecstasy Cocaine Amphetamines Methamphetamine Phentermine LSD (lysergic acid diethylamide) Bath salts | St. John's Wort L-tryptophan Ginseng Dextromethorphan S-adenosyl-L-methionine (SAME) Chlorpheniramine Brompheniramine | Antidepressants Amitriptyline Mirtazepine Trazodone Nefazodone Bupropion Antiemetics Ondansetron Metoclopramide Tryptans Buspirone Olanzapine Lithium Fentanyl Methylphenidate Cyclobenzaprine |
| SNRIs (des)venlafaxine Duloxetine (levo)milnacipran | | | | | |
| TCAs Clomipramine Imipramine | | | | | |
| MAOIs Moclobemide Isocarboxazid Phenelzine Tranylcypromine Methylene blue Linezolid (weak) Isoniazid (weak) Metaxalone (weak) | | | | | |

Abbreviations: LSD, lysergic acid diethylamide; MAOIs, monoamine oxidase inhibitors; MDMA, methylenedioxyamphetamine; OTC, over-the-counter; SGA, second-generation antipsychotics; SNRIs, selective norepinephrine reuptake inhibitors; SRI, serotonin reuptake inhibitor; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

^aDisputed-experts disagree on these medications causing serotonin syndrome/toxicity because of their mechanisms of action.

In 2017 the National Institute of Mental Health reported that about 17 million adults and 3 million adolescents (aged 11-18 years) experienced at least 1 episode of major depression.¹⁹ About 40% of US veterans will experience depression, which is 3 times higher than the rate of the general US population.¹² A random sampling survey conducted of about 17,000 active-duty service members by the US Department of Defense (DoD) from November 2015 to April 2016 revealed 9.4% reported depression.²⁰ Antidepressant usage in the US and among veterans continues to increase.^{12,16} In 2018, the list of top US prescribed drugs, included sertraline (14th), citalopram (21st), trazodone (24th), and escitalopram (26th).²¹ Antidepressant prescribing in the US increased 18% from 2012 to 2017.²² This trend also continues within the military with a 40% increase of antidepressant use in the past decade.¹⁶

One reason for the increase in antidepressant use is off-label prescribing.^{14,23} A sampling of about 2 billion psychiatric out-

patient visits in a western portion of the US found 12.9% of the prescriptions filled were off-label.¹⁵ In Minnesota, off-label prescribing of antidepressants was found to contribute to an increase in drug interactions in elderly nursing home residents.²⁴ An investigation by the *Military Times* of the military community revealed off-label prescribing occurs not only with antidepressant medications, but also with anticonvulsants, antipsychotics, anti-anxiety drugs, and antiepileptic medications.¹⁴

A case report that brought ST to the forefront occurred in the 1980s and involved a college student.²⁵ She was initially diagnosed with the flu. Her symptoms progressed over a 24-hour period despite treatment, leading to seizures, hyperthermia, generalized clonus, muscle rigidity, respiratory failure, and death because of unrecognized ST. Her combination of serotonin-elevating drugs included meperidine, phenelzine, chlorpheniramine, and haldol. On autopsy, there were traces of cocaine found in some of her tissue samples.

TABLE 2 Drugs Causing Moderate to Severe ST Symptoms⁴

| Drug Classes | Drug Combinations |
|-------------------------|---|
| MAOIs | MAOIs + SSRIs or SNRIs or TCAs or opiates Imipramine + tranylcypromine Phenelzine + meperidine Methylene blue + clomipramine or paroxetine |
| SSRIs | SSRIs + MAOIs or TCAs or SNRIs or opiates or triptans Fluoxetine + carbamazepine or phentermine or fentanyl |
| SNRIs | SNRIs + TCAs or MAOIs or opiates or triptans Fluoxetine + mirtazapine or phentermine or fentanyl |
| Other antidepressants | Mirtazapine + SSRIs Trazodone + amitriptyline + lithium |
| Opiates | Opiates + MAOIs or SSRIs or SNRIs or triptans |
| Cold remedies | Dextromethorphan + SSRIs or TCAs or atypical antipsychotics |
| Atypical antipsychotics | Olanzapine + citalopram and lithium Risperidone + paroxetine or fluoxetine |
| Antibiotics/antifungals | Linezolid + SSRIs or tapentadol Fluconazole + citalopram Ciprofloxacin + methadone + venlafaxine |

Abbreviations: MAOIs, monoamine oxidase inhibitors; SNRIs, selective norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; ST, serotonin toxicity; TCAs, tricyclic antidepressants.

Pathophysiology

Tryptophan is a precursor of serotonin and must be ingested from foods, including meats, dairy, fruits, and seeds. About 90% of all serotonin is made in the gastrointestinal epithelium and is the major component of the brain-gut axis.²⁶ Serotonin cannot cross the blood-brain barrier; therefore, it is synthesized and stored in presynaptic terminals around the midline of the brainstem.^{1,26} Transport of serotonin is provided by serotonin transporter (SERT).^{1,26,27} Once released, serotonin can either stimulate postsynaptic neuron receptors or is taken up into the presynaptic terminals for reuse. SSRI antidepressants, such as citalopram and paroxetine inhibit the reuptake of serotonin by binding to 2 different sites on the SERT thus allowing more available serotonin to be accessible to other neurons.²⁷ There are 7 families of serotonin receptors, 5-HT₁ to 5-HT₇ and at least 15 mammalian subtypes.^{28,29} The majority of these receptors have been implicated in depression or depressive-like behavior as evidenced by the efficacy of increasing extracellular serotonin for the treatment of

depression with SSRIs, SNRIs, TCAs, and MAOIs.²⁹ Three of the most studied receptors include 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A}.

Etiology

Most serotonin-induced drug fatalities occur when combining serotonergic drugs that work through different pathways (Table 2).³⁰ The most toxic combination of serotonin-enhancing drugs includes MAOIs taken with SSRIs or SNRIs, or a combination of 2 MAOIs.⁵⁻⁹

Other potentially lethal combinations may include polypharmacy with antidepressants, pain medications, OTC medications, and illicit drugs. Linezolid, a new synthetic antimicrobial, is considered to be a weak MAOI. Therefore, prescribing it with other serotonin-elevating agents has been reported to precipitate ST.¹⁸

Most cases of ST do not require hospitalization and can be managed by stopping the medication or decreasing the dose. Therapeutic doses of a single drug are highly unlikely to cause toxicity, although there have been reported cases of patients who are sensitive or more susceptible and develop symptoms after administration of a single agent and/or a dosage increase.

Delayed ST reactions have occurred because of a prolonged half-life of a drug, iron deficiency anemia, and coingestion of shorter acting serotonin antagonists.³¹ Most antidepressants have a short half-life (< 24 hours) except for fluoxetine. A decrease in iron may contribute to ST because iron is needed to process serotonin from tryptophan. An example of 2 shorter-acting serotonin antagonists include cyproheptadine and olanzapine. Cyproheptadine is used in the treatment of ST, and olanzapine is an antipsychotic.

SYMPTOMS

Symptoms of ST range from mild to severe and include a combination of neuromuscular, autonomic, and mental status changes (Table 3).^{5,10} Mild symptoms of ST can start within 1 to 2 hours after ingesting a medication that increases serotonin to a toxic state unless the drug has a long half-life (eg, fluoxetine). Sometimes mild symptoms of ST can be difficult to distinguish from common drug AEs, flu symptoms, or viruses. Patients taking therapeutic doses of SSRIs

can experience serotonin symptoms, such as lower limb hyperreflexia or a few beats of ankle clonus without being toxic. One thing to remember is that not all patients will start with mild symptoms and may present in moderate or severe distress.

Moderate-to-severe ST symptoms require hospitalization, usually in the intensive care unit (ICU). At this stage, clonus progresses from the lower extremities to the upper body and becomes more generalized. Ocular clonus can be continuous, intermittent, or have a ping pong effect (short cycle, periodic, alternating lateral gaze).

Severe ST is life threatening and leads to multiorgan failure within hours if not treated. The patient is intubated to assist with breathing and sedated because excess agitation and muscular tremors can increase temperature, which is already elevated by the time the symptoms reach the severe state. Of note, hyperthermia is due to a noninfectious elevation of body temperature from hypertonicity, agitation, and muscle rigidity. A true core temperature $> 105.8^{\circ}\text{F}$ causes irreversible cell damage, cerebral injury, and death.^{32,33} The patient can develop seizures and a coma. Multiorgan failure occurs, including rhabdomyolysis, myoglobinuria, renal failure, metabolic acidosis, acute respiratory distress, and disseminated intravascular coagulation.

DIAGNOSIS

The diagnosis of ST is clinical and based on a history of ingesting serotonin-elevating medications and physical findings as per Hunter Serotonin Toxicity Criteria³⁴ (Table 4). An in-depth history needs to include previous and current prescriptions, indications of the prescriptions (eg, therapeutic, increase in dosage, suicide intent), OTC medications, and illicit drug use. Early recognition of symptoms, identification of serotonergic medications, and appropriate resuscitative measures lead to more successful outcomes. A serotonin drug level is ineffective and does not correlate with the dosage since serotonin does not cross the blood-brain barrier.

The type of drug determines the length and response of the episode. The drug(s) elimination half-lives need to be calculated along with the pharmacokinetic or pharmacodynamics; agonist, antagonist, reuptake inhibitor, etc. Many drugs have half-lives of

TABLE 3 Serotonin Toxicity Signs/Symptoms^{5,10}

| Mild | Moderate | Severe |
|-----------------------------|--|--|
| Tremors | Hyperreflexia | Hyperthermia ($> 101.3^{\circ}\text{F}$) |
| Incoordination | Clonus: lower extremities with generalized progression | Hyper/hypotension |
| Restlessness | Myoclonus (muscle jerks) | Sustained clonus or rigidity |
| Headaches | Ocular clonus | Confusion |
| Insomnia | Shivering with teeth chattering | Delirium |
| Nausea | Agitation | Tonic-clonic seizures |
| Diarrhea | Diaphoresis | Respiratory depression |
| Clonus of lower extremities | Tachycardia | Rhabdomyolysis |
| | Dyspnea | |
| | Dilated pupils | |

< 24 hours; therefore, reducing or eliminating the offending drug(s) will result in a steady reduction of symptoms. Exceptions include medications with a longer activity, such as the irreversible MAOIs (eg, phenelzine, isocarboxazid) and drugs with a longer half-life, such as fluoxetine. These types of medications may have been stopped weeks earlier and may prolong reduction of symptoms.

When initiating or increasing SSRIs or SNRIs, there are common nontoxic AEs that are not consistent with ST, including anxiety, restlessness, and irritability that may last for 2 weeks. The difference in toxic vs nontoxic reactions are the timing and rapid progression of symptoms. The toxic symptoms will start within hours of ingesting the offending agents(s) and progress rapidly to severe symptoms within 24 hours. Therefore, it is imperative to review AEs with the patient and or caregiver, so they may act as their own advocate and seek immediate assistance.

Differentials

There are symptoms specific to ST that can be used to differentiate it from other conditions. These include hyperthermia, bilateral symmetric clonus (inducible, spontaneous, ocular), and hyperreflexia. These criteria form the basis for Hunter criteria.

Differential diagnoses to consider include neuroleptic malignant syndrome; antidepressant initiation AEs; antidepressant discontinuation syndrome; malignant hyperthermia; anticholinergic toxicity;

TABLE 4 Hunter Criteria (Need 3 to Diagnose)²⁷

| Criteria | Descriptions |
|----------|--|
| 1 | Spontaneous clonus |
| 2 | Inducible clonus AND agitation OR diaphoresis |
| 3 | Ocular clonus AND agitation OR diaphoresis |
| 4 | Tremor AND hyperreflexia |
| 5 | Hypertonic AND temperature > 100.4°F AND ocular clonus OR inducible clonus |

meningitis/encephalitis; sepsis; drug overdose; alcohol/benzodiazepine withdrawal; and preeclampsia. Neuroleptic malignant syndrome (NMS) is the disorder most often misdiagnosed as ST. Key elements that distinguish ST from NMS include the timing of the clinical course (NMS develops over days to weeks); the medications ingested (NMS from dopaminergic drugs); and the symptoms of NMS (bradyreflexia, bradykinesia, bradyphrenia, and no clonus). According to Gillman, serotonin toxicity is a manifestation of toxicity that is predictable and common with specific drug combinations, while NMS is a “rare idiosyncratic reaction to essentially normal doses and very rarely occurs after overdoses.”³⁵ Preeclampsia is a pregnancy complication that can mimic ST with symptoms of hypertension, clonus, and hyperreflexia. It has been estimated to complicate 2% to 8% of pregnancies and remains a principle cause of maternal and fetal morbidity and mortality.^{36,37}

TREATMENT

Mild-to-moderate symptoms usually resolve on their own 1 to 3 days after decreasing or stopping the offending drug. The timing will depend on the half-life or active metabolites of the drug. Treatment is largely supportive and may require treatment for control of agitation with benzodiazepines and IV fluids for dehydration/hypotension.¹⁴ In cases not responding to supportive care, treatment with oral cyproheptadine is recommended.¹⁴

There are other medications that have been used in treatment such as olanzapine, chlorpromazine, propranolol, bromocriptine, dantrolene, droperidol, and haloperidol, but their efficacy is unproven and not recommended.¹⁰ Chlorpromazine can cause hypotension and increase hyperthermia. Propranolol has a long duration of action, may cause a prolonged hypotension, and can

mask tachycardia that can be used to monitor the effectiveness of treatment.¹⁰ Bromocriptine is a serotonin agonist and may exacerbate symptoms. Dantrolene has no effect on survival in animal models.¹⁰ Droperidol and haloperidol can worsen hyperthermia by inhibiting sweating.³⁸

Mechanical ventilation should be considered especially if muscle rigidity progresses and depressed respiratory function occurs. If the temperature starts to rise, immediate sedation, paralysis, mechanical ventilation, and cyproheptadine are administered. The overall goal is prevention of hyperthermia, which leads to multiorgan failure. A core temperature of $\geq 104^{\circ}\text{F}$ is associated with neurologic cell death, and recovery is minimal.³² Consultation with an experienced toxicologist is strongly recommended. Antipyretics should not be used, because elevated temperature is centrally mediated from muscle rigidity. If presentation occurs within 1 hour, activated charcoal can be used for detoxification of potentially lethal amounts.

Warning Label Controversies

In 2006, the US Food and Drug Administration (FDA) issued an advisory warning against concurrently using a tryptan antimigraine drug and serotonin-mediated medications.³⁹ In 2018, a research team conducted a 14-year retrospective analysis on 20,000 patients who were coprescribed a tryptan drug with SSRIs or SNRIs.⁴⁰ The study reported that the risk of ST was rare and suggested that the FDA reconsider their advisory. There are several other controversial medications with a ST FDA warning label due to their mechanisms of action and inaccurate case reports.⁴¹

Human Poisonings

Consistent with the 2017 American Association of Poison Control Centers Toxic Exposure report, antidepressants continue to be in the top 5 substance classes most frequently involved in human exposures.⁴² Most accidental ingestions of antidepressants occur in toddlers, whereas intentional ingestions are usually done by adolescents.⁴³ Over the past 10 years, antidepressants are the No. 1 fastest growing category of human exposures in all age groups.⁴²

ST in the Pediatric Population

ST in the pediatric population mirrors that in adults. Differences include the inability of the child to report symptoms, lack of clinician awareness, and reluctance of adolescents to disclose recreational drug use. Management is the same as for adults, including discontinuing the offending drug, supportive care, adequate sedation, oxygen, IV fluids, and continuous cardiac monitoring. Sedation is weight based for benzodiazepines. Mild-to-moderate reactions require admission for observation. Severe reactions require admission to the ICU.

There have been at least 4 published case reports of children aged < 6 years with moderate-to-severe ST secondary to acute vilazodone ingestion.⁴⁴ The dosages included 5.5 to 37 mg/kg. All 4 patients had altered mental status, seizures, hyperthermia, mild clonus, tachycardia, and hypertension. They all survived with intensive care treatment, including intubation, sedation, cyproheptadine in 2 cases, activated charcoal and IV lorazepam in the other cases.

Direk and colleagues reported a case of a 12-year-old girl who was brought to the emergency department by her stepmother for seizurelike activity and was diagnosed with epilepsy and status epilepticus.⁴⁵ In the pediatric ICU she developed tachycardia, fever, agitation, dilated pupils, tremors, increased deep tendon reflexes, spontaneous clonus, and horizontal ocular movements. A detailed clinical history was retaken and revealed that the child had been prescribed risperidone 1 week before by the psychiatric clinic due to behavioral problems, including stealing money, lying, and running away from home and school. On further investigation, the stepmother was taking clomipramine and discovered 9 missing pills.

Pregnancy and Lactation

The American College of Obstetricians and Gynecologists recommends that clinicians screen patients at least once during the perinatal period for depression and anxiety symptoms, using a standardized, validated tool and complete a full assessment of mood and emotional well-being during the postpartum, including screening for postpartum depression and anxiety with a validated in-

strument.⁴⁶ Treatment with antidepressants is controversial. “Current evidence is generally reassuring and indicates that the absolute risks of negative infant outcomes are small except for PNAS [poor neonatal adaptation syndrome], which largely appears to be self-limited.”⁴⁷ Antidepressants cross the human placenta and fetal blood-brain barrier.⁴⁸ Several cases of infant toxicity from SSRIs have been reported with citalopram and escitalopram.^{49,50} Symptoms included severe muscle rigidity, lethargy, tachycardia, QTc prolongation, altered consciousness, hypertonia, and seizures at birth. These mothers had taken an SSRI during pregnancy.

CONCLUSIONS

This article highlights some of the latest information on ST. Increased awareness of all clinicians and their patients may help decrease unnecessary comorbidities and death. Early identification of ST symptoms will increase the chances for survival, because of the rapid progression of symptoms within 24 hours. Most fatal reactions occur when combining MAOIs with SSRIs, SNRIs, or another MAOI. Overdose with an SSRI does not progress to the severe symptoms unless combined with another serotonin-elevating medication.

Education of all patients who are prescribed antidepressants must include awareness of the potential for serotonergic drug interactions, particularly from OTC medications, herbal medications, and illicit drugs. The diagnosis of ST is based on clinical findings and there must be a history of ingesting serotonin-elevating drug(s). Hunter Serotonin Toxicity Criteria is the gold standard for diagnosing symptoms along with consulting a toxicologist. Prevention of ST includes informed clinicians, patient education, careful prescribing and monitoring, and avoidance of multidrug regimens.

Author disclosures

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adverse effects—before administering pharmacologic therapy to patients.

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