The serotonin syndrome is a potentially life-threatening adverse drug reaction that results from:

* therapeutic drug use
* intentional self-poisoning
* inadvertent interactions between drugs

Three features of the serotonin syndrome are critical to an understanding of the disorder:

First, the serotonin syndrome is NOT an idiopathic drug reaction; it is a predictable consequence of excess serotonergic agonism of central nervous system and peripheral serotonergic receptors.

Second, excess serotonin produces a spectrum of clinical findings.

Third, clinical manifestations of the serotonin syndrome range from minimal to lethal.
The death of an 18-year-old patient named Libby Zion in New York City in NY in 1984, which resulted from coadministration of meperidine and phenelzine, remains the most widely recognized and dramatic example of this preventable condition.

**Definition and Epidemiology**

The serotonin syndrome is described as a **clinical triad** of:

* mental-status changes
* autonomic hyperactivity
* neuromuscular abnormalities

(but not all of these findings are consistently present in all patients with the disorder)

Mild symptoms may be easily overlooked, and increasing the dose of the causative agent or the addition of a drug with proserotonergic effects may provoke a dramatic deterioration.
The incidence of the serotonin syndrome is thought to mirror the increasing number of proserotonergic agents being used in clinical practice.

In 2002, the Toxic Exposure Surveillance System, which receives case descriptions from office-based practices, inpatient settings, and ED, reported 26,733 incidences of exposure to SSRIs that caused significant toxic effects in 7349 persons and resulted in 93 deaths.

Performing a rigorous epidemiologic assessment of the serotonin syndrome remains difficult, since more than 85% of physicians are unaware of the serotonin syndrome as a clinical diagnosis.

The syndrome occurs in approximately 14 to 16% of persons who overdose on SSRIs.

Several barriers limit the ability of clinicians to diagnose the condition.

First, the syndrome may be missed because of its vague manifestations.

Second, a strict application of the diagnostic criteria proposed by Sternbach potentially rules out what are now recognized as mild, or subacute cases of the disorder.

Third, clinicians cannot diagnose a condition of which they are unaware.
A striking number of drugs and drug combinations have been associated with the serotonin syndrome.

Table 1: Drugs Implicated in Severe Serotonin Syndrome

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Tryptophan</td>
<td>Serotonin precursor</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Inhibit serotonin reuptake</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Inhibit serotonin reuptake</td>
</tr>
<tr>
<td>MAOIs and selective serotonin reuptake inhibitors</td>
<td>Inhibit metabolism of 5-HT</td>
</tr>
<tr>
<td>Methotrione</td>
<td>Serotonin agonist</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Inhibit serotonin reuptake</td>
</tr>
<tr>
<td>L-DOPA</td>
<td>Partial serotonin agonist</td>
</tr>
<tr>
<td>Amphetamines and anorexiantics</td>
<td>5-HT release &amp; 5-HT reuptake</td>
</tr>
<tr>
<td>Monoamine reuptake inhibitors</td>
<td>Various</td>
</tr>
<tr>
<td>SSRI, St John’s wort, all of the above?</td>
<td>Unknown</td>
</tr>
<tr>
<td>Lithium</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Note: Interactions are more common between drugs with different mechanisms of increasing serotonin.

A single therapeutic dose of an SSRI has caused the serotonin syndrome.

Administration of serotonergic agents within 5 weeks after the discontinuation of fluoxetine therapy has produced a drug interaction culminating in the serotonin syndrome.

Moreover, the addition of drugs that inhibit cytochrome isoforms CYP2D6 and CYP3A4 to therapeutic SSRI regimens has been associated with the serotonin syndrome.
Specific drugs, such as MAOIs that are irreversible or nonselective or that inhibit monoamine oxidase subtype A, are strongly associated with severe cases of the syndrome, especially when these agents are used in combination with meperidine, dextromethorphan, SSRIs, MDMA, or “ecstasy”.

**Diagnostic criteria**

The most accurate are the Hunter Toxicity Criteria Decision Rules which is 84% sensitive and 97% specific when compared with the gold standard of diagnosis by a medical toxicologist.

In a comparison with the original Sternbach Criteria, the Hunter Criteria performed with greater accuracy and were less likely to miss early, mild, or subacute forms of serotonin syndrome.

To fulfill the Hunter Criteria, a patient must have taken a serotonergic agent and have ONE of the following:

* Spontaneous clonus
* Inducible clonus plus agitation or diaphoresis
* Ocular clonus plus agitation or diaphoresis
* Tremor and hyperreflexia
* Hypertonia
* Temperature above 38°C plus ocular clonus or inducible clonus

**Table 1: Symptoms Associated with Serotonin Syndrome**

<table>
<thead>
<tr>
<th>Mental status changes</th>
<th>Motor Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety (4%)</td>
<td>Myokymia (39%)</td>
</tr>
<tr>
<td>Hypertension (27%)</td>
<td>Hyperreflexia (12%)</td>
</tr>
<tr>
<td>Acidity (15%)</td>
<td>Muscle rigidity (12%)</td>
</tr>
<tr>
<td>Cess (29%)</td>
<td>Rigidity (40%)</td>
</tr>
<tr>
<td>Cardiac acceleration</td>
<td>Tremor (5%)</td>
</tr>
<tr>
<td>Minor hypotension (47%)</td>
<td>Ataxia/coordination (48%)</td>
</tr>
<tr>
<td>Hypertension (13%)</td>
<td>Somnolence (47%)</td>
</tr>
<tr>
<td>Hypertension (13%)</td>
<td>Nystagmus (37%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Seizures (12%)</td>
</tr>
<tr>
<td>Nausea (37%)</td>
<td>Other</td>
</tr>
<tr>
<td>Diarrhea (5%)</td>
<td>Diaphoresis (4%)</td>
</tr>
<tr>
<td>Abdominal pain (4%)</td>
<td>Uncoordinated pupil (20%)</td>
</tr>
<tr>
<td>Fatigue (2%)</td>
<td>Tachypnea (30%)</td>
</tr>
<tr>
<td></td>
<td>Hypothermia (15%)</td>
</tr>
</tbody>
</table>

Patients with **mild cases** may be afebrile but have tachycardia, with a physical examination that is notable for autonomic findings such as shivering, diaphoresis, or mydriasis.

The neurologic examination may reveal intermittent tremor or myoclonus, as well as hyperreflexia.

A **moderate case** of the serotonin syndrome involves vital-sign abnormalities as tachycardia, hypertension, and hyperthermia. A core temperature as high as 40°C is common.

Physical examination: mydriasis, hyperactive bowel sounds, diaphoresis, and normal skin color. The hyperreflexia and clonus may be considerably greater in the lower extremities than in the upper extremities.

Patients may exhibit horizontal ocular clonus.

Changes in mental status include mild agitation or hypervigilance and pressured speech.

Patients may easily startle.

**Severe cases** may have severe hypertension and tachycardia and may deteriorate into frank shock. Such patients may have agitated delirium, muscular rigidity and hypertonicity. Again, the increase in muscle tone is considerably greater in the lower extremities. The muscle hyperactivity may produce a core temperature of more than 41.1°C in life-threatening cases.
Laboratory abnormalities (moderate to severe)
* metabolic acidosis,
* rhabdomyolysis,
* elevated serum aminotransferase
* elevated creatinine,
* renal failure,
* disseminated intravascular coagulopathy.

Many of these abnormalities arise, however, as a consequence of poorly treated hyperthermia.

Statistically significant association with the diagnosis were primarily neuromuscular sx (hyperreflexia, clonus, myoclonus, ocular clonus, peripheral hypertonicity, and shivering).

Autonomic derangements:
tachycardia, mydriasis, diaphoresis, increased BS, diarrhea.

The onset of symptoms is usually rapid, with approximately 60% of patients with the serotonin syndrome present within six hours after initial use of medication, an overdose, or a change in dosing.

Patients with mild manifestations may present with subacute or chronic symptoms, whereas severe cases may progress rapidly to death. The serotonin syndrome is not believed to resolve as long as precipitating agents continue to be administered.

Pathophysiology and Molecular Mechanisms
Serotonin is produced by the decarboxylation and hydroxylation of L-tryptophan.

Its quantity is regulated by a combination of reuptake mechanisms, feedback loops, and metabolizing enzymes.

Serotonin receptors are divided into seven 5-hydroxytryptamine (5-HT) families (5-HT₁ to 5-HT₇), several of which have multiple members (e.g., 5-HT₁A, 5-HT₁B, 5-HT₁C, 5-HT₁D, 5-HT₁E, and 5-HT₁F).

Serotonergic neurons in the CNS are found primarily in the midline raphe nuclei, from the midbrain to the medulla.

The rostral end assists in the regulation of wakefulness, affective behavior, food intake, thermoregulation, migraine, emesis, and sexual behavior.
The neurons of the raphe in the lower pons and medulla participate in the regulation of nociception and motor tone.

In the periphery, the serotonin system assists in the regulation of vascular tone and gastrointestinal motility.

No single receptor appears to be responsible for the development of the serotonin syndrome, although several lines of evidence converge to suggest that agonism of 5-HT$_{2A}$ receptors contributes substantially to the condition.

Additional subtypes of serotonin receptors, such as 5-HT$_{1A}$, may also contribute.

Noradrenergic CNS hyperactivity may play a critical role, since the degree to which CNS norepinephrine concentrations are increased in the serotonin syndrome may correlate with the clinical outcome.
Other neurotransmitters, including N-methyl-D-aspartate (NMDA) receptor antagonists and GABA, may affect the development of the syndrome, but the role of these agents is less clear.

Dopaminergic receptors have also been implicated, but this association may arise from pharmacodynamic interactions, direct interactions between serotonin and dopamine receptors, other mechanisms, or a misdiagnosis of the serotonin syndrome as the neuroleptic malignant syndrome.

Diagnosis

No laboratory tests confirm the diagnosis of the serotonin syndrome. Instead, the presence of tremor, clonus, without additional extrapyramidal signs should lead clinicians to consider the diagnosis, which must be inferred from the patient's history and physical examination.
When obtaining the patient’s history:
* the use of prescribed drugs
* over-the-counter drugs
* illicit substances
* dietary supplements
* the evolution of symptoms and their rate of change

Physical examination should include assessment of deep-tendon reflexes, clonus, and muscle rigidity, an evaluation of the size and reactivity of the pupils, the dryness of the oral mucosa, the intensity of bowel sounds, skin color, and the presence or absence of diaphoresis.

Algorithm for Diagnosis.

These rules are simply, sensitive (84%), and highly specific (97%) for diagnosing the serotonin syndrome.
Clonus (inducible, spontaneous, and ocular) is the most important finding in establishing the diagnosis of the serotonin syndrome.

Hyperthermia and hypertonicity may mask the highly distinguishing findings of clonus and hyperreflexia and therefore cloud the diagnosis.

The differential diagnosis includes anticholinergic poisoning, malignant hyperthermia, and the neuroleptic malignant syndrome, each of which can be readily distinguished from the serotonin syndrome on clinical grounds and on the basis of the medication history.
**Management**

* The removal of the precipitating drugs  
* The provision of supportive care  
* The control of agitation  
* The administration of 5-HT\textsubscript{2A} antagonists  
* The control of autonomic instability  
* The control of hyperthermia

Many cases of the serotonin syndrome typically resolve within 24 hours after the initiation of therapy and the discontinuation of serotonergic drugs, but symptoms may persist in patients taking drugs with long elimination half-lives, active metabolites, or a protracted duration of action.

Supportive care, comprising the administration of intravenous fluids and correction of vital signs, remains a mainstay of therapy.

However, an abrupt deterioration in the condition of a patient indicates the need for an immediate, aggressive response.
Mild cases can usually be managed with supportive care, removal of the precipitating drugs, and treatment with benzodiazepines.

Moderately ill patients should have all cardiorespiratory and thermal abnormalities aggressively corrected and may benefit from the administration of 5-HT$_2$A antagonists.

Hyperthermic patients (those whose temperature is more than 41.1°C) are severely ill and should receive the above therapies as well as immediate sedation, neuromuscular paralysis, and orotracheal intubation.

Control of agitation with benzodiazepines is essential in the management of the serotonin syndrome, regardless of its severity.

Benzodiazepines such as diazepam improve survival in animal models and blunt the hyperadrenergic component of the syndrome.

Physical restraints are ill-advised and may contribute to mortality by enforcing isometric muscle contractions that are associated with severe lactic acidosis and hyperthermia. If physical restraints are used, they must be rapidly replaced with chemical sedation.
Pharmacologically directed therapy involves the administration of 5-HT$_{2A}$ antagonists.

Cyproheptadine is the recommended therapy for the serotonin syndrome, although its efficacy has not been rigorously established.

**Cyproheptadine**

Available only in oral form, but may be crushed and administered by NG tube.

- **Initial dose:** 12 mg and then 2 mg every two hours if symptoms continue.
- **Maintenance dose:** 8 mg every six hours.

Treatment of the serotonin syndrome in adults may require 12 to 32 mg of the drug during a 24-hour period, a dose that binds 85 to 95% of serotonin receptors.

Atypical antipsychotic agents with 5-HT$_{2A}$–antagonist activity may be beneficial in treating the serotonin syndrome. The SL administration of 10 mg of olanzapine has been used successfully, but its efficacy has not been rigorously determined.

**Clinicians desiring a parenteral agent** should consider the IM administration of 50 to 100 mg of chlorpromazine.

Even though chlorpromazine is an outdated therapy that has been replaced in psychiatric practice by newer agents, its use may nonetheless be considered in severe cases.
Control of autonomic instability.

Hypotension arising from MAOI interactions should be treated with low doses of direct-acting sympathomimetic amines (e.g., norepinephrine, phenylephrine, and epinephrine).

When the MAO is inhibited, it cannot control the amount of epinephrine and norepinephrine produced, and an exaggerated hemodynamic response may ensue.

Patients with hypertension and tachycardia should be treated with nitroprusside and esmolol.

Control of hyperthermia.

It involves eliminating excessive muscle activity. Benzodiazepines have a beneficial effect in moderate cases.

In severely ill patients with a temperature >41.1°C, immediate paralysis with nondepolarizing agents such as vecuronium, followed by orotracheal intubation and ventilation.

Clinicians should avoid succinylcholine because of the risk of arrhythmia from hyperkalemia associated with rhabdomyolysis.

Recent case reports have shown that premature termination of neuromuscular paralysis was associated with a recrudescence of hyperthermia.
There is no role for antipyretic agents; the increase in body temperature is due to muscular activity, not an alteration in the hypothalamic temperature set point.

Potential pitfalls
* Misdiagnosis of the serotonin syndrome,
* Failure to comprehend its rapidity of progression
* Failure to identify adverse effects of pharmacologically directed therapy.

If the correct diagnosis is not obvious, a prudent course is to withhold antagonist therapy and provide aggressive supportive care, sedation with benzodiazepines, and, if necessary, intubation and paralysis.

Therapies such as propranolol, bromocriptine, and dantrolene are not recommended.

Propranolol may cause hypotension and shock in patients with autonomic instability. Furthermore, propranolol can abolish tachycardia that can be used to determine the duration and effectiveness of therapy.
Bromocriptine has been implicated in the development of the serotonin syndrome, and its use in patients in whom the neuroleptic malignant syndrome is misdiagnosed may worsen serotonergic signs.

**PEDIATRIC CONSIDERATIONS**

Similar pathophysiology and manifestations.

Any drug or drug combination that increases serotonergic neurotransmission can produce the syndrome.

The same diagnostic criteria, characterized by increased neuromuscular activity, are used in the pediatric population. Hyperreflexia, clonus, and hyperthermia remain important findings.

Several obstacles make the diagnosis of serotonin syndrome more difficult in pediatric patients.

Children may not be able to communicate vague symptoms; clinicians may not consider the syndrome a pediatric problem; and adolescents may be reluctant to disclose recreational drug use.

The fundamental principles of serotonin syndrome management remain unchanged in pediatrics.

In addition to cases in the general pediatric population, there are rare reports of neonates with symptoms resembling serotonin syndrome (small study showed that infants exposed to SSRIs late in pregnancy were at increased risk for adverse central nervous system effects).
Prevention

The serotonin syndrome can be avoided by a combination of pharmacogenomic research, the education of physicians, modifications in prescribing practices, and the use of technological advances.

Once toxicity occurs, consultation with a medical toxicologist, a clinical pharmacology service, or a poison-control center can identify proserotonergic agents and drug interactions, assist clinicians in anticipating adverse effects, and provide valuable clinical decision-making experience.

The avoidance of multidrug regimens is critical to the prevention of the serotonin syndrome.

If multiple agents are required, however, computer-based ordering systems and the use of PDAs can detect drug interactions and decrease reliance on memory in drug ordering.

Post-marketing surveillance linked to physician education has been proposed to improve awareness of the serotonin syndrome.
Eventually, the application of pharmacogenomic principles may help identify and protect patients at risk of serotonin syndrome before the administration of serotonergic agents.

Prognosis is generally favorable, as long as the entity is recognized and complications are treated appropriately.

References
2. Jonathan Grayzel, MD, FAAEM. Serotonin Syndrome. Up to date.
Thank You!

Questions or comments?