

Serotonin syndrome

What is serotonin syndrome?

Serotonin syndrome (SS) – also called serotonin toxicity – is a potentially life-threatening drug-induced condition caused by too much serotonin in the synapses of the brain.

The condition presents with a combination of neuromuscular, autonomic and mental state symptoms. Most cases involve two drugs that increase serotonin in different ways or an overdose of one serotonin-elevating drug.

The most common implicated drugs are monoamine-oxidase inhibitors (MAOIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs); the list of potential causes includes certain herbal remedies and illicit drugs.^[1]

SS can occur as a consequence of normal therapeutic drug use, self-poisoning or drug interactions.^[2] There is a wide spectrum of illness ranging from barely noticeable minor symptoms such as tremor, through to life-threatening acute illness.^[3]

The syndrome is not widely recognised amongst clinicians. A failure to appreciate the syndrome means that mild cases may be overlooked; continuing or increasing the offending drug can cause progression to severe illness.^[3]

It is underdiagnosed due to the heterogeneity of its presentation, because there are evolving diagnostic criteria, a lack of awareness amongst prescribers and mistaking of the symptoms for features of a pre-existing psychiatric illness. It should not be confused with the neuroleptic malignant syndrome.^[4]

There is some controversy about the pharmacology of SS.^[5] There is evidence that it is activation of the 5-HT_{2A} receptor that is required for serious SS rather than 5-HT_{1A} receptors.^[6] Accordingly, there has been much scientific criticism of government agency warnings of a serotonin syndrome risk from co-prescriptions of triptans and SSRIs; while cases of SS have been reported, the risk seems to be very low.^[7]

How common is serotonin syndrome? (Epidemiology)

- Incidence is unclear due to the extent of underdiagnosis.
- Post-marketing surveillance studies on nefazodone (no longer licensed but unlicensed preparations are still available) suggest an incidence of 0.4 cases per 1,000 patient-months of treatment.^[3]
- It is estimated that 14-16% of those who take overdoses of SSRIs display features of the syndrome.^[8]
- Deaths with SSRI overdose are associated with combinations of other medications or illicit substances.

Risk factors

Use of serotonergic agents is the risk factor for SS. SS may be produced by large doses/overdose of a single drug or by combinations of drugs. The most common causative combinations include an MAOI.^[6]

Drugs implicated in SS include:

- Antidepressants: SSRI, SNRI, TCA, MAOI, St John's wort, lithium.
- Analgesics: tramadol, pethidine, fentanyl, dextromethorphan (in OTC cough remedies).
- Antiemetics: ondansetron, metoclopramide.
- Recreational: cocaine, MDMA, amphetamine, LSD.
- Others: eg, linezolid, tryptophan, buspirone, methylthioninium chloride (methylene blue).

It is worth checking with a reputable formulary or toxicologist whether there are any known drug interactions causing the syndrome, where it is suspected in an individual taking serotonergic agents.^[9]

Although the epidemiology of SS has yet to be extensively studied, the combination of age and comorbidities may increase the risk.^[10]

Serotonin syndrome symptoms (presentation)

SS is characterised by the presence of a triad of:^[1]

- Autonomic hyperactivity
- Neuromuscular abnormality
- Mental status changes

Not all of these features are present in all cases.

The diagnosis is likely only in the setting of starting or increasing the dose (or, indeed overdose) of a potent serotonergic drug, or shortly after a second serotonergic drug is added leading to a drug interaction.^[6]

Symptoms usually occur within six hours of taking the provoking drug. Mild cases may go unrecognised. Tremor, akathisia and diarrhoea are early features. Agitation, hypervigilance and pressured speech may occur. Acute delirium is a feature of severe cases.

Examination

Examination should seek signs of:

1. Autonomic disturbance – namely:

- Hypertension.
- Tachycardia.
- Hyperthermia.
- Hyperactive bowel sounds.
- Mydriasis.
- Excessive sweating.

2. Neuromuscular dysfunction – namely:

- Tremor.
- Clonus - inducible or spontaneous.
- Ocular clonus.
- Hypertonicity.
- Hyperreflexia (this symptom can be masked if there is severe muscle rigidity).

3. Altered mental state - namely:

- Anxiety.
- Agitation.
- Confusion.
- Coma.

The severity of symptoms ranges from mild to life-threatening. Progression from restlessness, diaphoresis, and neuromuscular dysfunction to confusion, convulsions and death has been described.

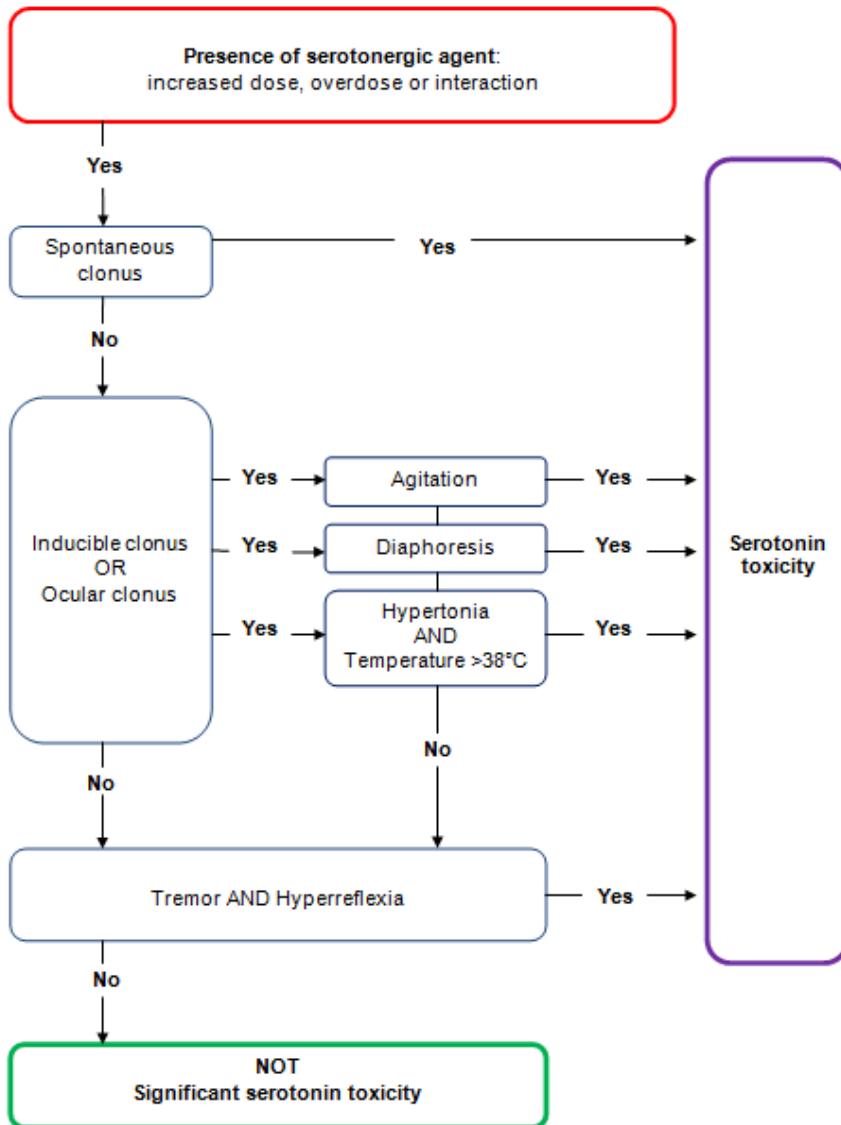
Skin appearance should be normal in SS, a fact that helps to differentiate it from two similar diagnoses (see below). The presence of muscular hypertonicity, sustained clonus and hyperthermia (which may rise as high as 41°C) indicate severe disease.

A neonatal behavioural syndrome - also called poor neonatal adaptation syndrome - can also occur as a result of maternal SSRI use during late pregnancy.^[11]

The Hunter serotonin toxicity criteria

These criteria have been developed (following a review of a large series of patients with serotogenic drug overdose) to confirm the diagnosis of moderate or severe toxicity.^[4]

Decision Rules Hunter Serotonin Toxicity Criteria



Differential diagnosis

- Anticholinergic poisoning (normal reflexes, dry mouth, hot and dry skin, absent bowel sounds).
- **Malignant hyperthermia** (caused by inhalational anaesthetics; mottled and patchily cyanotic skin, severe rigidity and hyporeflexia).
- **Neuroleptic malignant syndrome** (slow-onset idiopathic reaction to dopamine antagonists, with bradykinesia and 'lead-pipe' muscular rigidity).
- Other **poisoning**.
- **Catatonia**.

- Dystonia.
- Recreational drug toxicity, especially [amphetamines/cocaine](#) (many features of their toxicity are due to serotonergic effects).
- [Hyperthyroidism](#).
- [Tetanus](#).
- [Delirium tremens](#).
- [Encephalitis](#).
- [Rhabdomyolysis](#).
- [Meningitis](#).
- Withdrawal syndromes.
- Wernicke's encephalopathy.

Investigations

- There are no specific confirmatory investigations - the diagnosis is clinical.
- Check U&Es and creatine kinase to look for evidence of rhabdomyolysis and consequent renal impairment.
- Toxicology screen, particularly for agents likely to be responsible.
- FBC and blood culture/microbiological samples can suggest alternative causes of fever.
- LFTs.
- CXR if respiratory complications.
- CT scanning of the head for patients with trauma, seizures, hypertension or focal neurology.
- Lumbar puncture for patients with fever and altered mental state.

Serotonin syndrome treatment

If SS is suspected then the likely causative drug(s) should be stopped. Refer patients with severe symptoms or patients who have ingested an MAOI and an SSRI to the hospital, as their condition can worsen quickly.

Once SS has resolved, try other drugs or restart low doses slowly, and rule out other contributing drugs such as OTC medications or illicit drugs. For most patients who experience serotonin-mediated side-effects, appropriate changes to their medications will manage symptoms and prevent toxicity.^[1]

- In all cases the most important step is to remove the offending agent or interacting drugs. In cases of recent ingestion/large overdose, activated charcoal may help to prevent absorption. Supportive measures such as IV fluids and control of agitation with benzodiazepines are also used.
- Mild cases usually resolve within 24 hours of discontinuation and may need supportive measures only. Beware of drugs with long half-lives or active metabolic breakdown products (for example, fluoxetine), where it may take longer.
- Moderately severe cases should have cardiovascular and thermal disturbances corrected and receive 5-HT_{2A} antagonists such as cyproheptadine (as yet there is no definitive evidence for its efficacy).
- Severe cases need aggressive treatment and intensive care with early sedation, neuromuscular paralysis and ventilatory support.
- In the UK, advice for health professionals is available from the [Toxbase® website](#).

Complications

- Hyperthermia can lead to metabolic acidosis, rhabdomyolysis, acute kidney injury and disseminated intravascular coagulation. Thermal disturbance should be aggressively managed. Any patient with a temperature over 40.5°C should be managed with:
 - Paralysis and ventilation.
 - Ice bath immersion/ice packs if not responsive (to prevent disseminated intravascular coagulation and organ failure).

Antipyretic agents have no role, as hyperthermia is due to muscular activity rather than hypothalamic mechanisms. Chlorpromazine may be used to treat agitation and hyperthermia.

- Seizures.
- Aspiration pneumonia.
- Respiratory failure.

Prognosis

If patients recover from an acute episode and avoid provoking agents then the outlook is good. Most deaths occur within the first 24 hours.

Preventing serotonin syndrome

- Caution in the prescription of serotonergic agents. All patients starting SSRIs should be counselled about:
 - Potential interactions (including OTC and 'herbal' medication).
 - The symptoms of serotonin toxicity and SS.
- Improved knowledge amongst the medical community. Do not prescribe an SSRI together with an MAOI. Particular care should be taken when changing SSRIs or prescribing more than one antidepressant.

- Improved pharmacogenetic understanding to identify those at increased risk.
- Adequate post-marketing surveillance of new serotonergic therapies.

Disclaimer: This article is for information only and should not be used for the diagnosis or treatment of medical conditions. Egton Medical Information Systems Limited has used all reasonable care in compiling the information but makes no warranty as to its accuracy. Consult a doctor or other healthcare professional for diagnosis and treatment of medical conditions. For details see our [conditions](#).

Authored by:	Peer Reviewed by: Dr Toni Hazell	
Originally Published: 24/02/2024	Next review date: 25/01/2024	Document ID: doc_2768

View this article online at: patient.info/doctor/serotonin-syndrome

Discuss Serotonin syndrome and find more trusted resources at [Patient](#).



To find out more visit www.patientaccess.com
or download the app



Follow us

