Background: Serotonin syndrome (SS) is a life-threatening but preventable condition marked by dangerously elevated serotonin (5-hydroxytryptamine, 5-HT) levels. Patients typically present with a combination of mental status changes, autonomic instability, and neuromuscular hyperactivity that begins within hours of serotonergic medication ingestion (1-3). Without appropriate intervention, a patient’s condition can rapidly deteriorate. If these symptoms are incorrectly attributed to other causes, the medications given to treat the assumed cause could inadvertently worsen a patient’s condition (4). This Fast Fact will offer guidance on how to recognize SS and manage it among seriously ill patients.

Diagnosis: SS is typically diagnosed using either the Hunter Serotonin Toxicity Criteria or Sternbach Criteria. The Hunter criteria require at least one of the following features to be present: spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor with hyperreflexia; or hypertonia with temperature above 100.4°F/38°C and ocular or inducible clonus (5). The Sternbach criteria require three of ten clinical features – agitation, diaphoresis, ataxia, diarrhea, mental status change, hyperreflexia, myoclonus, tremor, shivering, hyperthermia – to be coincident with the addition or recent increase of a known serotonergic drug therapy (6). The Hunter criteria is more widely accepted due to its higher sensitivity and specificity (7). Timely diagnosis is essential in the management of SS. Without laboratory tests to assist with diagnosis, a thorough medication history including timing of new medications or dose changes plus a thorough physical exam is critical.

Differential Diagnosis: Neuroleptic malignant syndrome (NMS), anticholinergic syndrome, sepsis, and malignant hyperthermia may mimic SS (8-10). SS differs from NMS not just by the precipitating medication, but by onset time (within hours of serotonergic medication ingestion, compared to days/weeks for NMS) and by clinical presentation (neuromuscular hyperactivity such as tremor, hyperreflexia and myoclonus with SS, rather than rigidity and bradycardia with NMS) (11).

Culprit Medications: Though severe cases have been described with supra-therapeutic doses of a single drug, SS usually results from a combination of serotonergic drugs and can occur even when each medication is within therapeutic range (12). SS appears to be a dose-dependent phenomenon (12). Selective serotonin reuptake inhibitors (SSRIs) are the most associated medication class with SS. The following medications have been associated with SS as well (see below) (13-28).
- Analgesics: fentanyl, methadone, meperidine, tramadol, tricyclic antidepressants (TCAs), carbamazepine, valproic acid, and cyclobenzaprine.
- Antidepressants: SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and selegiline
- Antiemetics: olanzapine
- Antitussives: dextromethorphan
- Others: linezolid, methylene blue, St. John’s Wart, peganum harmala
- Although triptans, mirtazapine, trazodone, ondansetron, and metoclopramide are commonly listed as culprit medications, they appear to be less likely to cause SS.

Awareness and Prevention: The prevalence of SS among seriously ill patients is not known. In the palliative care or end-of-life setting, the potential for symptomatic benefit of culprit medications often outweighs the risk of adverse events related to SS, since it is felt to be a rare complication. So rather than avoiding all culprit medications in the seriously ill, clinicians should have increased awareness of SS among those on culprit medications, as doing so should improve prevention and early detection (1). Even mild cases of SS may exacerbate pre-existing symptoms caused by the underlying disease, with potential worsening of quality of life. Therefore, collaboration with a clinical pharmacist and/or a careful medication reconciliation also is recommended when prescribing multiple serotonergic agents (13).

Treatment: If SS is identified, serotonergic medications should be carefully reviewed and then tapered or discontinued based on the patient’s symptom burden and goals of care. Mild cases often improve within 24 hours after stopping the causative agent(s) and usually do not require hospital admission or
additional intervention (8). For moderate to severe cases which usually involve hypertonicity, hyperthermia, autonomic instability, or progressive cognitive changes, hospitalization or close clinical supervision is suggested (4). Benzodiazepines and cyproheptadine (a 5-HT2A receptor antagonist) may control agitation and tremor (1,29). For severe cases, external cooling, neuromuscular paralysis, sedation, and mechanical ventilation may be pursued if in line with the patient’s goals of care (1). Even in severe cases, symptoms usually resolve within days (1).

References


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