



PALLIATIVE CARE CASE OF THE MONTH

“Serotonin Syndrome”

by

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Case: Palliative Care was consulted by the surgical service to see a 51-year-old male with a history of decompensated cirrhosis from alcohol use for goals of care after multiple intra-abdominal surgeries due to small bowel obstruction and volvulus with limited additional treatments. Within two days of our meeting with the patient, he developed new agitation and confusion. He had been without mental status issues and was getting lactulose multiple times a day with multiple bowel movements daily. On exam, he had stable vital signs were only notable for a temperature of 37.4° C (99.3° F), disorganized thinking and inattention with a new spontaneous myoclonus, and hyperreflexia. Labs were without elevation in white count or left shift, electrolyte abnormalities, or other obvious explanation for his encephalopathy. His medications included venlafaxine ER, buspirone, and oxycodone. He had been started on dextromethorphan four hours prior to the increase in agitation, for which olanzapine was given overnight. Concern for serotonin syndrome rose to top of the differential diagnosis, and medication adjustments were recommended with help from the palliative pharmacist.

Background: Serotonin syndrome is defined as a set of symptoms that occur related to excessive iatrogenic serotonergic activity in the nervous system and can be potentially life-threatening.¹⁻³ Serotonin syndrome can occur in all age groups, from infants to older adults, and it is increasing in incidence as more serotonergic medications are used each decade.² The true incidence is difficult to assess since serotonin syndrome can go unrecognized and can be falsely attributed to alternate explanations. Fewer than 300 deaths per year are credited to serotonergic medications.⁴ Classically, patients experience changes in mental status, autonomic instability, and neuromuscular hyperactivity as a spectrum in the setting of serotonergic medications.^{2,5} Most cases occur when patients receive multiple medications with serotonergic activity or have significant exposure to a single serotonergic drug, such as in an overdose.⁶ The primary key for treatment is recognition of serotonin syndrome, withdrawal or tapering of any suspected agents, and supportive care. Since many medications that treat symptoms are associated with serotonin syndrome, thoughtful prescribing and early identification of serotonin syndrome is an important skill for any palliative care clinician.

Pathophysiology: Serotonin syndrome occurs when there is excessive serotonin (5-hydroxytryptamine or 5-HT) at both peripheral and central 5-HT receptors.⁷ In the central nervous system (CNS), serotonin helps with many functions including attention, aggression, motor control, and thermoregulation. In the peripheral nervous system (PNS), serotonin can impact GI peristalsis, vasoconstriction, and bronchoconstriction.^{1,8}

Serotonin is naturally found in the gastric and intestinal mucosa and is also stored in platelets.⁸ Of the neurotransmitters, serotonin has the largest amount of receptors and different subtypes.⁸ This likely explains the variability and extent of symptoms associated with serotonin syndrome. The condition does seem to be dose-related with predisposing factors, such as dysfunction of vascular or pulmonary endothelium, atherosclerosis, or hypertension.⁸

Any combination of medications that increase serotonergic neurotransmission have the risk of leading to serotonin syndrome, which include serotonin precursors, serotonin agonists, medications leading to serotonin release, serotonin reuptake inhibitors, and monoamine oxidase inhibitors (MAO-I).³ MAO-Is increase serotonin by inhibiting its breakdown. See Table 1 for more examples.

| Table 1: Medications That Can Contribute to Serotonin Syndrome ^{3,8,9} |
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| Amphetamines and illicit drugs: Dextroamphetamine, methamphetamine, MDMA (ecstasy), cocaine, LSD |
| Analgesics: Codeine, fentanyl, methadone, meperidine, tramadol |
| Antidepressants and mood stabilizers: |
| <ul style="list-style-type: none"> • SSRIs: Citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline • SNRIs: Duloxetine, venlafaxine • TCAs: Amitriptyline, clomipramine, desipramine, imipramine, nortriptyline • MAO-Is: Isocarboxazid, phenelzine, tranylcypromine, selegiline (used for Parkinson’s) • Miscellaneous: Bupropion, Buspirone, Lithium, Trazodone |
| Antiemetics: Metoclopramide, ondansetron, olanzapine |
| Nutritional or Herbal Supplements: St John’s wort, Ginseng, L-tryptophan |
| Miscellaneous: Dextromethorphan, Linezolid, methylene blue |

Clinical presentation and diagnosis: Serotonin syndrome is a clinical diagnosis made in the setting of thorough symptom history, physical exam, and medication review. Mental status changes (confusion and hypomania) can happen within hours of medication administration and are the most frequent signs and symptoms followed by neuromuscular hyperactivity (myoclonus and hyperreflexia).¹ Clonus can be inducible, spontaneous, or ocular.³ Severe cases that can necessitate supportive care in the intensive care unit and even be fatal causing rhabdomyolysis, disseminated intravascular coagulation (DIC), and multiorgan failure, which are more often associated with significant overdoses of SSRIs or MAOIs.⁹

Personal details in the case published have been altered to protect patient privacy.

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Clinical presentation and diagnosis (Continued)

Two main criteria exist to help with diagnosis: Hunter Serotonin Toxicity Criteria and Sternbach's Criteria for Serotonin Syndrome, the former being more sensitive and specific than the latter.¹⁰ For Hunter Serotonin Toxicity Criteria, in the presence of a serotonergic agent, the patient must have one of the following:

- Spontaneous clonus
- Inducible clonus plus agitation or diaphoresis
- Ocular clonus plus agitation or diaphoresis
- Tremor plus hyperreflexia
- Hypertonia plus temperature 39°C (100.4°F) plus ocular or inducible clonus

Differential Diagnosis: Etiologies to consider and rule out are sepsis, metabolic derangements, such as hyperthyroidism, electrolyte abnormalities, and hypoglycemia, and intoxication or withdrawal from other substances.

Neuroleptic malignant syndrome (NMS) is important to consider in the differential diagnosis whenever evaluating for serotonin syndrome. The primary trigger is dopamine blockade from neuroleptic antipsychotic agents, such as haloperidol or chlorpromazine, leading to "lead pipe rigidity" rather than myoclonus.⁹ More commonly, NMS includes rhabdomyolysis, leukocytosis, and metabolic acidemia and less so agitation, confusion, and hyperreflexia. Resolution happens over days to weeks instead of within 24 hours.⁹ The antidote for NMS, dantrolene, is contraindicated in serotonin syndrome.⁹

Prevention and Management: Many serotonergic medications can be helpful for patients with serious illness, and they therefore may not be possible to avoid altogether. Rather, it is important to be carefully aware of all serotonergic medications prescribed. Prescribing an MAOI with an SSRI should be avoided, and adhering to washout periods when switching off an MAOI, which can have persistent activity, or SSRI with a long half-life, such as fluoxetine, is necessary.³

The mainstay of treatment is to discontinue any recently added serotonergic agent and provide supportive measures.^{1,9} As most cases involve multiple serotonergic medications, any unnecessary agents should be deprescribed. If immediate discontinuation of these medications is not possible, they should be tapered to avoid abrupt withdrawal. Typically, in mild cases with symptoms of fatigue, "jitteriness", or headache, the symptoms resolve within 24 hours after cessation of the offending serotonergic agent, and hospital admission is not usually indicated.^{8,9} However, if a patient has more severe symptoms including cognitive changes, neuromuscular changes, or fever, this patient should be admitted to the hospital, and if the fever is difficult to control and autonomic instability occurs, would consider admission to for the intensive care unit might be necessary.⁹

Supportive measures can include cooling blankets for hyperthermia, as acetaminophen is ineffective.⁹ When more serious, some instances require vasopressor support for hemodynamic instability and benzodiazepines or even paralysis for neuromuscular excitability and prevention of rhabdomyolysis.^{1,2,9} Cyproheptadine is a 5-HT receptor antagonist available enterally with rapid results; it should be scheduled frequently since there will be a recurrence of symptoms until serotonin syndrome resolved.¹¹

Case Conclusion: The primary team made the recommended adjustments to discontinue the patient's dextromethorphan ER and olanzapine and decrease his venlafaxine and buspirone. He was using less oxycodone at this time, and that was continued as needed. Benzodiazepines were recommended instead of olanzapine for agitation. Within 24 hours of medication changes, his mentation significantly improved, he had fewer myoclonic jerks, and he was able to ambulate unassisted. The quick resolution of symptoms with medication changes helps support the diagnosis of serotonin syndrome.

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