



Agitation in the Overdose Patient: Is it Serotonin Syndrome?



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Cindy's case

A 15-year-old female presented to the ED with an intentional ingestion of hydromorphone, amitriptyline and venlafaxine. On arrival, patient was mildly drowsy, but oriented.

Vitals

- Temperature: 36.9°C
- Heart rate: 112 bpm
- Respiratory rate: 16
- BP: 118/66 mmHg
- Oxygen saturation: 98% on room air

ECG showed sinus tachycardia with a QRS interval of 90. Routine blood work was unremarkable and acetaminophen, ethanol and salicylate levels were negative.

Past medical history

Depression, occasional ethanol, marijuana and ecstasy use.

Two hours after arrival, the patient became restless and agitated. Vital signs were now:

- Heart rate: 144 bpm
- BP: 140/80 mmHg
- Core temperature: 38.2°C

The patient was also diaphoretic with mydriasis, marked clonus and hyperreflexia.

Read on for more on Cindy...

Questions & Answers

1. *What is going on?*

The patient is showing features of serotonin syndrome (SS). This is a disorder that can be caused by use of drugs or combinations of drugs which increase serotonin availability. It most often occurs when two or more serotonergic drugs are used simultaneously. The most severe cases tend to result from drug interactions, especially when a monoamine oxidase inhibitor is involved. It may develop after therapeutic use or overdose. 5-Hydroxytryptamine (HT) 1A and 5-HT_{2A} receptors are primarily responsible for the serotonin syndrome, with 5-HT_{2A} receptors playing an important role in inducing hyperthermia.

2. *How do I diagnose SS?*

There is no test that confirms the diagnosis of SS. Medication and drug history in a patient with clinical features suggestive of SS (Table 1) are key to diagnosing this condition. SS may occur at therapeutic doses or in overdose and can occur with a single culprit medication. Often, however, more than one concomitantly ingested serotonergic medication is involved. Patients must not have recently started or increased the dose of a neuroleptic prior to the onset of effects. See Table 2 for a list of drugs implicated in SS.

3. *How is SS differentiated from neuroleptic malignant syndrome (NMS)?*

The condition most often confused with SS is NMS. Both conditions have autonomic hyperactivity and altered mental

Table 1

The clinical features of serotonin syndrome (SS)

Physiological category	Symptoms
Autonomic hyperactivity	Tachycardia, hypertension, hyperthermia, mydriasis, diaphoresis, flushing
Mental status changes	Anxiety, decreased level of consciousness, agitation, hallucinations, coma
Neuromuscular hyperactivity	Hyperreflexia, shivering, tremor, clonus, myoclonus, muscular rigidity (late finding, mainly lower limbs), opisthotonus, trismus, nystagmus

Cindy's case cont'd

Cindy received benzodiazepines and cyproheptadine 4 mg in the ED. She was admitted to the ICU with a diagnosis of SS and was treated with cyproheptadine 4 mg q.4.h. for 54 hours. Her stay was complicated by rhabdomyolysis which was treated with IV fluids and sodium bicarbonate. Renal function and urine output remained normal. Symptoms gradually resolved and patient was transferred to the medical floor on day 3 for further medical and psychiatric management.

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status, but NMS has neuromuscular hypoactivity as opposed to the neuromuscular hyperactivity seen in SS. These two conditions have very different etiologies (serotonin excess vs. dopamine blockade) and can usually be distinguished by physical examination, although more complex cases may have significant clinical overlap.

In addition, other medical conditions, such as infection, trauma, metabolic causes and alcohol/sedative withdrawal must be considered.

4. What are the complications of SS?

Untreated SS may result in severe hyperthermia, rhabdomyolysis and agitation resulting in physical harm to patient or staff. Seizures may also occur. Clinical interventions, such as sedation, may also result in respiratory depression requiring endotracheal intubation.

5. How do I manage SS in the ED?

General treatment

Supportive care: For patients with mild to moderate serotonin-related symptoms, cessation of suspected drug treatment(s) is indicated. Maintain IV access and infuse isotonic fluids as needed.

Agitation

Nonpharmacologic management: explanation and reorientation strategies by staff, appropriate lighting, avoid provoking stimuli.

Benzodiazepines are the most common drugs used for treating agitation (e.g., diazepam, lorazepam, midazolam). Large doses may be required in the first hour of treatment, but may result in need for intubation. Monitor for respiratory depression.

Physical restraints may be initially necessary, but should only be a temporizing measure until chemical restraints take effect. Prolonged use of physical restraints may exacerbate rhabdomyolysis and cause other injuries.

Table 2

Selected drugs associated with SS

Drug class	Specific drugs
Antidepressants	
SSRI	Paroxetine, sertraline, fluoxetine, citalopram
Atypical antidepressants	Venlafaxine, trazodone, nefazodone
TCA	Clomipramine, amitriptyline, imipramine
MAOI	Tranylcypromine, phenelzine, clorgyline, moclobemide, selegiline
Lithium	
Opiates	Tramadol, meperidine, dextromethorphan, methadone, pentazocine
Stimulant street drugs	Cocaine, MDMA, other amphetamines
Hallucinogens	Lysergic acid diethylamide (LSD)
Antibiotics	Linezolid

SSRI: Selective serotonin reuptake inhibitor

TCA: Tricyclic antidepressant

MAOI: Monoamine oxidase inhibitor

MDMA: Methylenedioxymethamphetamine

Neuromuscular hyperactivity (muscle rigidity)

Cyproheptadine is a serotonin antagonist. It is well tolerated, although is available only in oral formulation. For intubated patients, it may be administered by nasogastric tube. The correct dose has not been well established, but the following doses are generally accepted:


- **Adult dosing:** 4 mg to 8 mg initially p.o. or via nasogastric tube, then 4 mg every two to four hours, up to a maximum of 32 mg in 24 hours.
- **Pediatric dosing:** 0.25 mg/kg/day divided every six hours, maximum 12 mg/day.

Hyperthermia

Ongoing agitation and muscle hyperactivity can exacerbate hyperthermia. Aggressive treatment must be instituted with benzodiazepines, propofol and possibly neuromuscular paralysis with non-depolarizing agents such as rocuronium or vecuronium. Consider external cooling measures such as cooling fans and ice packs. A patient with a core temperature > 38.5°C or severe muscle rigidity should also be treated with cyproheptadine.

6. What is the usual outcome of patients with SS?

Most patients exhibit a self-limiting course with the supportive therapy described above. Symptoms typically resolve in 24 to 48 hours.

More severe cases may require prolonged hospitalization and may develop disseminated intravascular coagulation, adult respiratory distress syndrome, acidosis, severe rhabdomyolysis and renal failure. 

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