

An insidious onset of symptoms

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Ms. S's depression and anxiety have been well controlled by medication, but after several months, she develops tremors, poor concentration, and confusion. What is causing her symptoms?



How would you handle this case?

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CASE Tremors, increasing anxiety

Ms. S, age 56, has a history of depression and anxiety. Previously, she tried several selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), which failed to treat her symptoms. Ms. S is switched from duloxetine, 120 mg/d, to fluoxetine, 20 mg/d, while continuing bupropion, 150 mg/d, and gabapentin, 600 mg/d. She tolerates fluoxetine well, but 5 months later, she requests a dosage increase because her depressive and anxious symptoms re-emerge.

Ms. S states that for weeks she had been feeling "off." She describes tremors in her upper extremities, trembling voice, poor concentration, confusion, short-term memory deficits, and anxiety. She states that the symptoms were bothersome enough that she noticed them, but not so significant that she attributed them to a medical problem. She says she believed her anxiety was just becoming worse, which was why she asked to increase the fluoxetine dose. Fluoxetine is increased to 40 mg/d.

What could be the cause of Ms. S's symptoms?

- worsening anxiety
- serotonin syndrome
- drug of abuse
- neuroleptic malignant syndrome (NMS)

The authors' observations

The incidence of serotonin syndrome has increased because of increasing use of serotonergic agents.¹⁻³ Although the severity could range from benign to life-threatening, the potential lethality combined with difficulty of diagnosis makes this condition of continued interest. Stimulation of the 5-hydroxytryptamine (5-HT) receptor subtypes, specifically 5-HT_{1A} and 5-HT₂, are implicated in this syndrome.^{4,5}

Serotonin syndrome is a clinical diagnosis with a triad of symptoms that includes mental status changes, autonomic hyperactivity, and neuromuscular abnormalities.^{1,2} However, because of the varied presentation and similarity to other syndromes such as NMS, serotonin syndrome often is undiagnosed.⁵

TREATMENT Discontinue fluoxetine

Several months after the fluoxetine increase, Ms. S's symptoms worsen, and she notices

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Table 1

Hunter Serotonin Toxicity Criteria: Decision tree for predicting serotonin toxicity

In the presence of a serotonergic agent:
1. IF (spontaneous clonus = yes) THEN serotonin toxicity = YES
2. ELSE IF (inducible clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
3. ELSE IF (ocular clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
4. ELSE IF (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES
5. ELSE IF (hypertonic = yes) AND (temperature >38°C) AND [(ocular clonus = yes) OR (inducible clonus = yes)] then serotonin toxicity = YES
6. ELSE serotonin toxicity = NO
Source: Reference 6

Clinical Point

The diagnosis of serotonin syndrome is most accurately made using Hunter Serotonin Toxicity Criteria

significant hypertension of 162/102 mm Hg by checking her blood pressure at home. She had no history of hypertension before taking fluoxetine. She tells her psychiatrist she has been experiencing confusion, shakiness, loss of balance, forgetfulness, joint pain, sweating, and fatigue, along with worsening anxiety. The treatment team makes a diagnosis of serotonin syndrome and recommends discontinuing fluoxetine and starting cyproheptadine, 4 mg initially, and then repeating the cyproheptadine dose in several hours if her symptoms do not resolve. Approximately, 2.5 months after the serotonin syndrome reaction, Ms. S receives hydroxyzine, 10 mg every 8 hours, as needed for anxiety.

The authors' observations

The diagnosis of serotonin syndrome is most accurately made using Hunter Serotonin Toxicity Criteria (*Table 1*⁶). Because Ms. S had an insidious onset of symptoms, and treatment was initiated before full evaluation, it is unknown if she met Hunter criteria. To meet these criteria, a patient must have ≥1 of the following⁶:

- spontaneous clonus
- inducible clonus plus agitation or diaphoresis
- ocular clonus plus agitation or diaphoresis

- tremor plus hyperreflexia
- hypertonia plus temperature >38°C plus ocular or inducible clonus.

The Sternbach diagnostic criteria for serotonin syndrome (*Table 2*,³ *page e3*) is another commonly used tool.³ These criteria include the addition or increase of a serotonin agent and absence of substances or metabolic derangements that could account for symptoms and at least 3 of the following 10 symptoms³:

- mental status changes (confusion, hypomania)
- agitation
- myoclonus
- hyperreflexia
- diaphoresis
- shivering
- tremor
- diarrhea
- incoordination
- fever.

Ms. S met the Sternbach diagnostic criteria for serotonin syndrome.

Ms. S was taking a single serotonin agent and initially had mild symptoms. More commonly, a patient who presents with serotonin syndrome has been receiving ≥2 serotonergic agents or toxic levels of a single agent, and these agents usually include a psychotropic medication such as a monoamine oxidase



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inhibitor, tricyclic antidepressant, or SSRI, as well as a medication from a different class, such as dextromethorphan, linezolid, tramadol, methylene blue, and/or St. John's wort.^{1,7-13} However, in this case, Ms. S also was taking bupropion, a known inhibitor of cytochrome P450 2D6. Bupropion might have increased Ms. S's fluoxetine levels.

Many cases of serotonin syndrome resolve quickly and spontaneously. However, because Ms. S was taking a medication with a longer half-life (fluoxetine), her symptoms continued and progressively worsened over weeks to months. Primary care providers should be aware of this possible variation in the presentation of serotonin syndrome.^{1,14,15} Of note, Ms. S had taken other SSRIs and SNRIs with the same co-administered medications in the past without developing serotonin syndrome.

Ms. S was a healthy, middle-age patient who took no medications other than those listed, had no medical comorbidities, and had a straightforward psychiatric history, which makes the diagnosis of serotonin syndrome clearer. However, other potential differential diagnoses, such as NMS, delirium tremens, and anticholinergic toxicity, might cloud the clinical picture. When differentiating NMS and serotonin syndrome, it is helpful to note whether a patient shows tremor, diarrhea, and myoclonus present in the absence of muscular, "lead-pipe" rigidity, which suggests a diagnosis of serotonin syndrome.^{2,3,5,14}

How would you treat Ms. S?

- discontinue fluoxetine
- switch to a different antidepressant
- administer a serotonin antagonist
- begin an antihistamine

The authors' observations

Treating serotonin syndrome includes supportive care, discontinuing offending agents, administering benzodiazepines, and using a serotonin antagonist as an antidote for patients with moderate-to-severe cases.

Table 2

Sternbach diagnostic criteria for serotonin syndrome

1. Recent addition or increase of a known serotonergic agent
2. Absence of other possible etiologies (infection, substance abuse, withdrawal, etc.)
3. No recent addition or increase of a neuroleptic agent
4. ≥ 3 of the following symptoms: <ul style="list-style-type: none"> • mental status changes (confusion, hypomania) • agitation • myoclonus • hyperreflexia • diaphoresis • shivering • tremor • diarrhea • incoordination • fever

Source: Reference 3

Clinical Point

Serotonin syndrome symptoms can emerge with a single serotonergic agent, as was the case with Ms. S

Cyproheptadine is an antihistaminergic medication with non-specific 5-HT_{1A} and 5-HT₂ antagonism. It is FDA-approved for specific allergic reactions, urticaria, and anaphylaxis adjunctive therapy, but not for serotonin syndrome. Case series support the use of cyproheptadine for acute management of serotonin syndrome, with rapid symptom improvement.^{4,7,14,16-20} We observed a similar outcome with Ms. S. Her significant autonomic symptoms resolved rapidly, although she experienced some residual, mild symptoms that took weeks to resolve.

Because serotonergic agents are used frequently and readily by primary care clinicians as well as psychiatrists, the ability to properly diagnose this syndrome is vital, particularly because severe cases can rapidly deteriorate.^{1,9,18,19} This presentation of a single serotonergic agent causing significant symptoms that worsened over months is not typical, but important to recognize as a patient begins to experience autonomic instability. As was the case

Clinical Point

Cyproheptadine can be used safely and rapidly and should be considered a treatment option for serotonin syndrome

Related Resources

- Turner AH, Kim JJ, McCarron RM. Differentiating serotonin syndrome and neuroleptic malignant syndrome. *Current Psychiatry*. 2019;18(2):30-36.
- Iqbal MM, Basil MJ, Kaplan J, et al. Overview of serotonin syndrome. *Ann Clin Psychiatry*. 2012;24(4):310-318.

Drug Brand Names

Bupropion • Wellbutrin, Zyban	Gabapentin • Neurontin
Cyproheptadine • Periactin	Hydroxyzine • Atarax
Dextromethorphan • Benlylin	Linezolid • Zyvox
Duloxetine • Cymbalta	Tramadol • Ultram, Ryzolt
Fluoxetine • Prozac	

with Ms. S, it is important to remain vigilant when changing dosages or adding medications. Symptoms of serotonin syndrome might be vague and difficult to diagnose, especially if the clinician is not aware of the variability of presentation of this syndrome. Cyproheptadine can be used safely and rapidly and should be considered a treatment option for serotonin syndrome.

OUTCOME Hypertension resolves

After her first dose of cyproheptadine, Ms. S's blood pressure drops to 146/86 mm Hg. Three hours later, she repeats the cyproheptadine dose and her blood pressure drops to 106/60 mm Hg. She reports that her anxiety has lessened, although she is still tremulous. Overall, she says she feels better. She experiences improvement of her condition with a pharmacologic regimen of bupropion, gabapentin, and hydroxyzine.

Several weeks later, her health returns to baseline, with complete resolution of hypertension.

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Bottom Line

Although serotonin syndrome is most commonly associated with co-administered serotonergic medications, symptoms can emerge with a single, moderately dosed agent. Treatment includes withdrawing the offending agent, and administering serotonin agonists. Mild cases of serotonin syndrome usually resolve.