

# Serotonin Syndrome With Fluoxetine: Two Case Reports

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**Background:** Serotonin syndrome is a rare but serious complication of treatment with serotonergic agents. In its severe manifestations, death can ensue. Early recognition and aggressive management are crucial to mitigating the syndrome. Often the presentation can be subtle and easy to miss.

**Case Reports:** We present 2 cases of serotonin syndrome seen in the psychiatric consultation service of a busy academic hospital. Both patients had favorable outcomes because of early recognition and aggressive management.

**Conclusion:** Physicians should carefully consider and rule out the clinical diagnosis of serotonin syndrome when presented with an agitated or confused patient who is taking serotonergic agents.

**Keywords:** Antidepressive agents–tricyclic, fluoxetine, monoamine oxidase inhibitors, serotonin, serotonin syndrome, serotonin uptake inhibitors

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## INTRODUCTION

Serotonin syndrome is a rare but serious complication of treatment with certain psychotropic drugs, such as serotonin reuptake inhibitors (SSRIs). The actual risk of serotonin syndrome is difficult to estimate; however, the American Association of Poison Control Centers reported 46,587 exposures to SSRIs in 2011, of which 11 resulted in death, and 1,757 had serious outcomes.<sup>1</sup> This report is likely an underrepresentation, and the number of actual cases is assumed to exceed the number of reported cases. Serotonin syndrome is often undiagnosed for the following reasons: a presentation characterized by mild symptoms that are misattributed to other common side effects of treatment, varying diagnostic criteria, and misdiagnosis of the syndrome. However, the number of reported cases of serotonin syndrome has increased, likely secondary to the widespread use of serotonin-modifying drugs and increasing awareness of the syndrome.<sup>2</sup>

Multiple pharmacologic agents are known to cause serotonin syndrome. Most frequently implicated are 3 classes of psychotropic drugs that boost serotonin in the synaptic cleft: SSRIs, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs).<sup>2</sup> Other common psychotropic drugs include certain amphetamines such as phentermine and select opiate receptor-binding agents such as oxycodone, meperidine, and tramadol. The antiemetic ondansetron, the antihistamine chlorpheniramine, and the mood stabilizer lithium have also been associated with increased serotonin levels.<sup>2</sup> Illegal recreational drugs such as lysergic acid diethylamide, methylenedioxymphetamine, and cocaine have been implicated

in causing serotonin syndrome. Historically, the most frequent cause of the syndrome has been the use of MAOIs in combination with other agents. However, because MAOIs are currently being prescribed at decreased rates, SSRIs such as fluoxetine are now more commonly implicated with serotonin syndrome.<sup>1</sup>

Since the advent of SSRIs, a significant number of serotonergic antidepressants are being prescribed by general practitioners and specialists, in addition to psychiatrists. Consequently, all physicians must be well versed in the syndrome. The syndrome typically occurs when 2 or more serotonergic drugs are prescribed in combination, but it can also occur in cases of single-drug overdose. We present 2 cases that occurred in proximity in a busy psychiatric consultation service. The first patient had taken an excessive amount of a single agent (fluoxetine), and the second patient had been prescribed 2 agents simultaneously (fluoxetine and ondansetron). Our purpose is to emphasize the need for increased vigilance with serotonin-modifying medications and to stress the importance of having a decreased threshold of diagnosis for serotonin syndrome.

## CASE REPORT 1

A 15-year-old female with a 2-year psychiatric history of major depressive disorder treated with 20 mg daily of fluoxetine presented to the emergency department (ED) with altered mental status, seizure, tremors, and emesis. Approximately 3 hours prior to presentation, the patient took 45-60 pills of 20-mg fluoxetine after an argument with her father regarding an ex-boyfriend. Shortly after the overdose, she called her father and told him about the pills she had

taken. The patient's father found her actively seizing and lying next to vomit containing approximately 10 partially digested pills. It was later determined that this was the second incidence of vomiting she experienced after ingesting the pills (the first being into the toilet), making the actual pill intake difficult to determine with certainty.

Initially, the patient was able to drink charcoal, but she eventually was unable to follow commands, so charcoal was administered via nasogastric tube. She was also given a 1-time dose of lorazepam (2-mg injection) and intravenous (IV) fluids (1,000 mg of 0.9% sodium chloride [NaCl]).

The patient was transferred to the pediatric intensive care unit (PICU). Her vital signs were notable for sustained tachycardia (150-170 bpm), although her heart rate had been decreasing since reaching the floor. She had no significant fever. During subsequent examination, she stared blankly at the wall, did not track well, and was confused. Her pupils were dilated but reactive to light. She was tremulous and was noted to have inducible clonus of the left foot as well as mild hyperreflexia. No ocular clonus or rigidity was noted. Her presentation was consistent with serotonin syndrome that can have prolonged duration with fluoxetine ingestion secondary to the medication's extended half-life. She was managed in the PICU with IV fluids (5% dextrose and 0.9% NaCl at 100 mL/h) and lorazepam (3-mg dose every 4 hours). Cyproheptadine was considered to treat the patient's serotonin syndrome but was not administered at that time. The patient was monitored closely for rigidity, spontaneous clonus, autonomic instability, and hyperthermia.

On day 2 of her admission, the patient had bilateral clonus in the morning and was therefore administered cyproheptadine (loading dose of 12 mg and PRN 4 mg every 6 hours). The benzodiazepines had improved her heart rate, blood pressure, and tremors, but she remained tachycardic. The patient was still not oriented to person, place, or time. She reported hallucinations and was disorganized and agitated. She had occasional lucid periods when she was able to answer questions. Her IV fluids were reduced to 50 mL/h (5% dextrose and 0.9% NaCl). We were concerned that the patient may have taken multiple doses of melatonin and Midol, but a repeat acetaminophen level test 18 hours postoverdose remained low.

On day 3, the patient's symptoms had improved significantly. She was stabilized, and her mental status returned to baseline, with normal vitals and normal physical examination results. A plan for transfer to an inpatient psychiatric unit was arranged and discussed with the patient and her parents. She was medically cleared and transferred to an outside facility the following morning.

## CASE REPORT 2

A 17-year-old male with a 1-month history of major depressive disorder presented to the ED with ataxia, slurred speech, and myoclonic jerking movements.

The patient was initially started on a dose of 10 mg per day of fluoxetine at the time of diagnosis. Approximately 3 weeks prior to presentation, he was admitted to an outside hospital for suicidal ideation. While there, he was treated with fluoxetine 20 mg per day, and the dose was subsequently increased to 30 mg per day 9 days prior to presentation at our facility. Approximately 5 days prior to

admission, the patient reported generalized weakness, dizziness, lethargy, and difficulty walking. He also reported nausea unaccompanied by vomiting. He saw his primary care physician for these symptoms and was prescribed ondansetron to use as needed for nausea. The patient's symptoms continued, and he took two 4-mg doses of ondansetron 2 days prior to presentation and a third 4-mg dose the morning of admission in addition to his fluoxetine dose. At this point, the patient's mother noted that her son's weakness had worsened. She stated that his eyes were rolling around in his head, and he was having difficulty speaking and walking. He had an episode of brief unconsciousness that she described as fainting. He also had frequent twitching and jerking with unusual positions of his hands and feet.

In the ED, the patient was treated with 1-time doses of lorazepam (1 mg) and cyproheptadine (12 mg), with relief of symptoms. He was admitted to the PICU with a diagnosis of serotonin syndrome and was continued on lorazepam (1 mg twice daily) and cyproheptadine (8 mg four times daily). The patient had whole-body myoclonic jerks every 20 seconds. His vital signs were stable. During physical examination, he had myoclonic jerks in response to movements of his extremities, and his strength was decreased globally. He did not have any confusion, hyperreflexia, sustained clonus, muscle rigidity, or abnormality of tone.

On day 2 of admission, the patient's vital signs remained stable, and no hyperthermia was noted. The patient continued to have occasional twitches, principally in his legs, but no other symptoms. Psychiatry staff were consulted, and the patient expressed anhedonia, depressed mood, and sleep and appetite disturbances but denied suicidal ideation. He was administered mirtazapine (7.5 mg nightly). The patient stepped down to the floor in stable condition.

On day 3 of admission, the patient continued to improve and had no further myoclonic jerking or twitching. However, on days 4 and 5, he reported a severe bilateral frontal headache with photosensitivity and noise sensitivity. Neurology staff were consulted and determined that the headache was likely connected to his psychiatric presentation. The patient was treated with naproxen (250 mg twice daily as needed) and ketorolac (30 mg) on various occasions with relief. We considered the patient's initial presentation, as well as his subsequent headache, a result of his predisposition for a high-amplitude response to SSRIs. He had described a history of minor reactions to other over-the-counter medications. The patient is possibly a rapid metabolizer of certain cytochrome P450 enzymes that are involved in the catabolic pathway of many drugs, including fluoxetine. Pharmacogenomics testing of the patient's cytochrome P450 enzyme system was conducted, but the results are unknown. His headache eventually abated, and he was discharged home.

## DISCUSSION

Serotonin is a neurotransmitter found primarily within neurons located in the raphe nuclei. It plays a major role in sleep-wake cycles, mood, emotions, and thermoregulation. Serotonin receptors have been known to have a role in multiple psychiatric and medical conditions, including de-

pression and anxiety. Modification of serotonin levels in the brain has been associated with treatment of these conditions. However, supratherapeutic doses of medications intended to increase the levels of serotonin can overstimulate serotonin receptors and cause serotonin syndrome.<sup>3</sup>

Serotonin is a monoamine composed of a carboxyl amide side chain attached to an indole ring. Serotonin is synthesized from the essential amino acid tryptophan in a 2-step process, with tryptophan hydroxylase functioning as the rate-limiting enzyme in its production. There are 2 different isoforms of tryptophan hydroxylase.<sup>4</sup> Tryptophan hydroxylase 1 is predominantly found in peripheral tissue, while tryptophan hydroxylase 2 is the predominant isoform in the brain.<sup>3</sup> After synthesis, serotonin is stored in synaptic vesicles and is released into the synaptic cleft by exocytosis where it may bind to presynaptic and postsynaptic serotonin receptors. Reuptake of the extracellular serotonin by the presynaptic neuron is also possible. Serotonin regulates its own synthesis via inhibitory autoreceptors. Serotonin is metabolized in 2 steps: oxidative deamination by monoamine oxidase that yields 5-hydroxyindole-3-acetaldehyde and further oxidization by aldehyde dehydrogenase to 5-hydroxyindoleacetic acid.<sup>4</sup>

Neurons that synthesize serotonin form 9 distinct areas in the raphe nuclei located in the brainstem. These populations are termed B1-B9. These serotonin neurons project widely, innervating many regions within the neuraxis. The caudal cell groups, B1-B4, provide the primary descending serotonin projections that project to the spinal cord, medulla, pons, midbrain, and cerebellum. The rostral cell groups, B5-B9, give rise to the primary ascending projections. These projections lead to the forebrain, amygdala, thalamus, hypothalamus, and striatal and cortical projections.<sup>3,5</sup>

Serotonin functions via multiple receptors. These serotonin receptors can be divided into 7 distinct families based on sequence homology and intracellular effect, and the families are designated 5-HT<sub>1R</sub> to 5-HT<sub>7R</sub>. These receptor families may contain a single member, such as 5-HT<sub>4R</sub>, 5-HT<sub>6R</sub>, and 5-HT<sub>7R</sub>, or they may contain multiple members. In addition to genetically encoded receptor subtypes, some receptor transcripts may undergo secondary modification by differential splicing that results in multiple variants. Further differentiation occurs secondary to ribonucleic acid (RNA) editing events such as when adenosine residues at specific positions are converted by RNA adenosine deaminases. This editing process leads to significant changes to receptor function. The majority of serotonin receptors are G protein coupled with the key exception of 5-HT<sub>3R</sub>, which is an ionotropic receptor. These G protein-coupled metabotropic receptors consist of an extracellular N-terminus, 7 transmembrane domains with 3 extracellular loops and 3 intracellular loops, and an intracellular C-terminus. They may be further divided into G<sub>s</sub> receptors, G<sub>i</sub> receptors, or G<sub>q</sub> receptors based on their method of activity. The G<sub>s</sub> receptors have stimulatory effects on adenylyl cyclase that lead to depolarization of the 5-HTR-bearing neuron. Receptors coupled to G<sub>i</sub> have inhibitory effects on adenylyl cyclase, resulting in hyperpolarization of neurons. G<sub>q</sub>-coupled 5-HTRs function via activation of phospholipase C that leads to depolarization of the neuron.<sup>5,6</sup>

Serotonin syndrome is the result of overstimulation of 5-HT<sub>1A</sub> receptors. The triad of sudden-onset cognitive

changes, autonomic instability, and neuromuscular changes characterizes the syndrome. Symptoms can include any combination of hyperthermia, tachycardia, diaphoresis, confusion, hyperreflexia, rigidity, shivering, agitation, restlessness, coma, nausea, diarrhea, flushing, and myoclonus.<sup>7</sup> The onset of these symptoms can vary, although they typically occur within 24 hours of an increased dosage of serotonin-increasing medications. Fluoxetine and its metabolite norfluoxetine have longer half-lives (1 week and 2.5 weeks, respectively) than other SSRIs and can precipitate serotonin syndrome even if discontinued as early as 5 weeks prior to beginning another serotonergic agent. Fluoxetine can cause symptoms that persist for days to weeks—even with treatment.<sup>8,9</sup>

The diagnostic criteria for serotonin syndrome are the Hunter Serotonin Toxicity Criteria. This diagnosis requires the use of a serotonergic agent plus 1 of the 5 following criteria: (1) spontaneous clonus, (2) inducible clonus plus agitation or diaphoresis, (3) ocular clonus plus agitation or diaphoresis, (4) tremor and hyperreflexia, and (5) hypertonia and a temperature >38°C with ocular or inducible clonus. The most important criteria for diagnosis are clonus and hyperreflexia. Severe muscle rigidity may possibly mask these symptoms.<sup>2,8</sup> In the most severe form of serotonin syndrome, respiratory failure and death can ensue. In addition to the clinical symptoms enumerated above, a number of laboratory abnormalities can be indicative of serotonin syndrome, including leukocytosis, low bicarbonate level, elevated creatinine level, and elevated transaminases. No correlation exists between serum serotonin concentrations and the severity of the syndrome.<sup>9</sup>

Management of the syndrome varies depending on severity. For mild symptoms, discontinuing the offending agents and providing supportive care are typically enough. The goal is to stabilize vital signs and provide cooling measures. For cases of mild agitation, fever, or hypertension, a low-dose benzodiazepine such as diazepam can be used along with observation for at least 6 hours. For moderate serotonin syndrome, such as if a patient's temperature is >40°C or there is evidence of ocular clonus, agitation, or hyperactive bowel sounds, benzodiazepines can be used and cyproheptadine can be added. Admission to the hospital for cardiac monitoring is also advised. For severe cases with dramatic swings in pulse and blood pressure or with muscle rigidity, esmolol or nitroprusside may be used along with sedation and paralysis with nondepolarizing agents. Intubation and intensive care unit admission should be considered.<sup>2,9</sup>

## CONCLUSION

These 2 cases illustrate common presentations of serotonin syndrome occurring with fluoxetine, either alone or in combination with another serotonergic agent. Both patients had favorable outcomes because of early recognition and aggressive management. Physicians should carefully consider and rule out the clinical diagnosis of serotonin syndrome when presented with an agitated or confused patient who is taking serotonergic drugs.

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