PRACTICE NEWS

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Serotonin Syndrome: Fentanyl and Selective Serotonin Reuptake Inhibitor Interactions

Serotonin syndrome is a rare but potentially fatal adverse drug reaction associated with increased serotonergic activity in the central nervous system. It is characterized by a triad of symptoms, which include altered mental status, neuromuscular hyperactivity, and autonomic instability or hyperactivity. Due to the potential of rapid onset, it is important for clinicians to recognize the signs and symptoms of serotonin syndrome. Serotonin syndrome symptoms may resemble other conditions. Although this article focuses on serotonin syndrome as a result of an adverse interaction of selective serotonin reuptake inhibitors (SSRI) and fentanyl, it is important for not only anesthesia professionals, but all clinicians—such as those in emergency medicine and critical care—to be aware of this syndrome and its management. This article discusses the clinical manifestations of the serotonin syndrome and highlights reported cases of serotonin syndrome specifically related to an interaction between SSRIs and fentanyl, a commonly used opioid in anesthesia practice.

Keywords: Fentanyl, serotonin syndrome, serotonin toxicity, SSRI.

What Is Serotonin Syndrome?

Serotonin syndrome is a potentially fatal condition associated with increased serotonergic activity in the central nervous system that can be attributed to certain drugs, interactions between drugs, or intentional overdose.[1] The terms *serotonin toxicity* and *serotonin syndrome* are often used interchangeably. Gillman reasons that the term *serotonin toxicity* is more accurate, as it reflects "the broad spectrum of serotonin-related side effects progressing to toxicity."[2,3] As *serotonin syndrome* is used predominantly in the literature and anesthesia-related texts, we will use the term *serotonin syndrome* throughout this article.

Serotonin syndrome is often characterized by a triad of symptoms, which include altered mental status, neuromuscular hyperactivity, and autonomic instability or hyperactivity.[4] The symptoms can range from mild to severe and can be fatal if left untreated.[5] Table 1 provides a summary of mild, moderate, and severe symptoms associated with serotonin syndrome. Patients may be discharged following anesthesia with unrecognized symptoms of serotonin syndrome. After cessation of the drugs responsible for this syndrome, symptoms usually abate within 24 hours. However, in severe cases, it can take up to several days for symptoms to abate.[6]

What Causes Serotonin Syndrome?

A large number of drugs with serotonergic activity have been implicated in serotonin syndrome (see Table 2). Antidepressants known as *serotonin reuptake inhibitors* (SSRIs) are most commonly responsible for this condition.[7] SSRIs work by increasing the levels of serotonin in the brain, which can be effective for treating depression. However, when used in combination with other serotonergic drugs, SSRIs can significantly increase the levels of serotonin in the central nervous system, which may result in subsequent serotonin syndrome.[5]

Incidence

According to the 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data, 47,115 people reported toxicity related to SSRIs, resulting in 1,723 moderate adverse events, 152 major adverse events, and 7 deaths.[8] However, these numbers are likely to be underestimated as serotonin syndrome may be confused with other medical conditions, especially if symptoms are mild.[9] Furthermore,

Mild	Akathisia
	Anxiety
	Diaphoresis
	Hyperreflexia
	Mild hypertension
	Mydriasis
	Myoclonus
	Restlessness
	Shivering
	Tachycardia
	Tremor
Moderate	*Symptoms as above, and*
	Agitation
	Easily startled
	Hyperactive bowel sounds
	Hypervigilance
	Increased confusion
	Inducible clonus
	Myoclonus
	Ocular clonus
	Pressured speech
	Temperature of at least 40° C
Severe	*Symptoms as above, and*
	Acute respiratory distress syndrome
	Coma
	Delirium
	Diffuse intravascular clotting
	Disseminated intravascular coagulopathy
	Dramatic swings in pulse rate and blood pressure
	Elevation of serum aminotransaminases and creatinine
	Hypertension (can deteriorate to shock)
	Hypotonicity
	Metabolic acidosis
	Muscle rigidity
	Myoglobinuria
	Renal failure
	Respiratory failure
	Rhabdomyolysis
	Seizures
	Spontaneous clonus
	Tachycardia
	Temperature greater than 41.1° C

Table 1. Signs, Symptoms, and Complications of Serotonin Syndrome[10,13,16,19]

Serotonin reuptake inhibitors	Selective serotonin reuptake inhibitors: fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline, escitalopram
	Other antidepressants: venlafaxine, clomipramine, imipramine
	Opioid analgesics: pethidine, tramadol, fentanyl, dextromethorphan
	Herbal products: St. John's wort
Monoamine oxidase inhibitors	Irreversible monoamine oxidase A inhibitors: phenelzine, tranylcypromine
	Reversible monoamine oxidase A inhibitors: moclobemide
	Others: linezolid
Serotonin-releasing agents	Fenfluramine
	Amphetamines
	Methylenedioxymethamphetamine (MDMA; ecstasy)
Miscellaneous	Lithium
	Tryptophan

Table 2. Drugs Associated With Serotonin Syndrome (adapted from Isbister et al, 2007)[5]

healthcare providers may not be aware of this condition and/or the interactions among prescribed drugs.[10] Given the common prescription of SSRIs for treating depression and other conditions, the incidence of serotonin syndrome will likely increase in the future.

Fentanyl and SSRI Interaction

Case reports suggest that serotonin syndrome may be caused by an interaction between fentanyl and SSRIs. The exact mechanisms through which this reaction occurs are not fully understood.[6] Fentanyl is commonly used in most anesthesia techniques as an analgesic. Its short half-life makes it an appealing drug choice in anesthesia.[6,11] In patients already taking other SSRIs, the administration of fentanyl may precipitate serotonin syndrome. Fentanyl and other phenylpiperidine opioids (eg, meperidine, tramadol, sufentanil, alfentanil, and remifentanil) seem to be weak SSRIs and may also enhance serotonin release.

Current research regarding the interaction between fentanyl, SSRIs, and serotonin syndrome is based on case studies, several of which have been summarized in Table 3. Case studies are prone to research bias and limited generalizability. Nevertheless, case studies can help identify the important areas for further investigations involving systematically collected data. The cases described here suggest that patients taking SSRIs are at an increased risk for serotonin syndrome following fentanyl administration. Most of these patients developed severe symptoms and required emergency care.

Clinical Findings of Serotonin Syndrome

Serotonin syndrome can manifest in a variety of ways, including mental status changes, autonomic hyperactivity, and neuromuscular abnormalities.[12] Mild symptoms may include mild hypertension, tachycardia, and tremor that can rapidly progress to more severe symptoms, such as delirium, neuromuscular rigidity, and hyperthermia.[7,10,13] People of all age groups, including newborns and older adults, can develop this condition.[1] Clinicians need to pay close attention to warning signs in cases of suspected serotonin syndrome. The most important signs include clonus and generalized hyperreflexia that can be accompanied by rigidity, especially in the lower extremities.[1] Changes in mental state and autonomic functions can also be observed in patients with moderate to severe serotonin syndrome.[5]

Authors	Patient	SSRI(s) and concomitant drug(s)	Description of adverse event	Outcome
Rastogi et al[9]	58-year-old male receiving treatment for chronic back pain and depression.	• 75 µg/hr fentanyl patch replaced every 3 days; • 5/325 mg oral oxycodone/acetaminophen 2x/day; • 200 mg celecoxib 2x/day; • 40 mg citalopram 1x/day; • 50 mg mirtazapine at bedtime for depression; • 4 mg doxazosin for benign prostatic hypertrophy; • 12.5 mg zolpidem at bedtime for insomnia.	Patient developed anxiety, tremulousness, fever, and sweating after increasing frequency for replacement of fentanyl patch from 2 to 3 days. The symptoms worsened after he discontinued the patch. Patient was admitted to emergency care with hypertension, tachycardia, tachypnea, anxiety, inability to stand still, and mild confusion.	The symptoms resolved after 1 day following discontinuation of suspicious agents.
Altman et al[20]	44-year-old female receiving hysterectomy/ bilateral salpingo-oorphorectomy and other related procedures.	• Benzodiazepine (clonazepam); • SSRI (duloxetine); • Anticonvulsants (lamotrigine and topiramate); • Serotonin secretagogue (lithium); • Serotonin receptor blocker (quetiapine). • Anesthetized with IV fentanyl 100 µg, propofol 120 mg, and rocuronium 50 mg.	Patient developed hypertonia and spontaneous clonus in upper and lower extremities towards the end of surgery.	The symptoms resolved over 4 days after treatment with hydromorphone IV (for controlling pain), followed by oral acetaminophen-hydrocodone.
Kirschner & Donovan[6]	46-year-old female receiving treatment for carpal tunnel at an outpatient surgery center.	• 50 mg sertraline daily and 10 mg cetirizine as needed for seasonal allergy. • Medical history revealed depression and alcohol abuse. Patient suspected of having a substance abuse problem. • Anesthetized with IV fentanyl 50 µg, midazolam 2 mg, and propofol 60 mg (she was not intubated). Additional 40 mg propofol was given later in the procedure.	Patient developed tachycardia, agitation, confusion, low extremity rigidity, hyperreflexia, and sustained ankle clonus.	All symptoms resolved within 3 days after receiving treatment with airway intubation and propofol infusion.
	59-year-old female with recurrent ovarian cancer and prior abdominal hysterectomy/ bilateral salpingo-oorphorectomy.	• Insulin; • Trazodone; • Escitalopram; • Gabapentin; • Lansoprazole; • Lorazepam; • Oxycodone; • Cetrizine. • Anesthetized with IV fentanyl 250 µg, etomidate, vecuronium, morphine, and cefazolin.	On the first postoperative day, patient experienced tachycardia, agitation, diaphoresis, hyperreflexia, and ankle clonus.	Patient made full recovery within 3 days following treatment with lorazepam and cyproheptadine via orogastric tube.
Alkhatib et al[11]	39-year-old female with alcoholic cirrhosis presented with hematemesis.	• 100 mg sertraline (Zoloft) daily. • Anesthetized with 50 µg fentanyl and 2 mg midazolam.	Patient experienced clonus and hyperthermia.	After being treated with propofol sedation, cooling blanket, and cyproheptadine, patient's symptoms resolved within 3 days.

Table 3. Summary of Cases Involving Fentanyl and SSRI Interaction Resulting in Serotonin Syndrome

Sternbach	Hunter
Must exhibit at least 3 of the 10 following features, with the addition of or increase in a known serotonergic agent: • Mental status changes • Agitation • Myoclonus • Hyperreflexia • Diaphoresis • Shivering • Tremor • Diarrhea • Incoordination • Fever	Must use serotonergic drug, in addition to 1 or more of the following: • Spontaneous clonus • Inducible clonus with agitation or diaphoresis • Ocular clonus with agitation or diaphoresis • Tremor and hyperreflexia • Hypertonia, temperature above 100.4° F (38° C) with ocular or inducible clonus

Table 4. Diagnostic Criteria for Serotonin Syndrome

Diagnosis

Currently, there are two main diagnostic criteria to establish serotonin syndrome: the Sternbach's criteria and the Hunter Serotonin Toxicity criteria. Developed in 1991, the Sternbach's criteria include 10 clinical features, and require three of these 10 features to be present to establish the diagnosis clinically (see Table 4). While the Sternbach's criteria can be useful in recognizing early signs of serotonin syndrome, it has been criticized for its lack of specificity of symptoms, which can also be found in other medical conditions.[12,14] More recently, the Hunter Serotonin Toxicity Criteria was developed and consists of simple but accurate decision rules.[14] The Hunter's criteria, with its emphasis on clonus as the most important feature of serotonin syndrome, appear more sensitive (84% vs 75%) and more specific (97% vs 96%) than Sternbach's criteria. Not surprisingly, the Hunter's criteria are considered to be the preferred diagnostic tool.

The onset of symptoms is typically rapid, with symptoms often occurring within minutes of drug administration, dosage change, or overdose.[10] Approximately 60% of serotonin syndrome cases present within 6 hours of drug therapy.[10] There are no laboratory tests available for diagnosis of serotonin syndrome.[7,15] Laboratory and diagnostic testing is used to rule out alternative explanations for the observed signs and symptoms.[7] Serotonin syndrome may initially resemble other conditions, such as adverse drug reactions, meningoencephalitis, severe sepsis, delirium tremens, heat stroke, neuroleptic malignant syndrome, sympathomimetic toxicity, anticholinergic poisoning, or malignant hyperthermia.[5,7,15] Examination of specific neurological symptoms and ruling out other conditions will aid the clinician in making the differential diagnosis.[5]

Management

Initial management of serotonin syndrome consists of supportive care and cessation of serotonergic drugs.[5,15] Supportive management to address symptoms may prevent secondary complications. Early management includes stabilization of vital signs, administration of oxygen and IV fluids, and continuous cardiac monitoring.[13] The course of treatment can vary based on the severity of the case. Many cases tend to resolve within 24 hours after initiation of supportive care and discontinuation of serotonergic drugs.[10,13] Symptoms may persist longer if the patient is taking medications with longer half-lives, active metabolites, or a protracted duration of action.[10] Benzodiazepines, such as diazepam or midazolam, may be used to control agitation or tremor for cases of any severity level.[10,13,16]

Mild cases, which can be characterized by mild hypertension, tachycardia, mydriasis, diaphoresis, shivering, tremor, myoclonus, and hyperreflexia,[13] may not require hospitalization, as supportive care and drug cessation can be enough for symptoms to subside.[7,15] Supportive care can aid in the prevention of secondary complications such as rhabdomyolysis, renal failure, and disseminated intravascular coagulation.[15] Patient vital signs, kidney function, and electrolytes should be monitored.[15]

Progressively increased toxicity several hours after ingestion of serotonergic drugs can be noted in patients with moderate cases.[15] Moderate cases can be characterized by a temperature >40º C (104º F), hyperactive bowel sounds, ocular clonus, agitation, hypervigilance, and pressured speech.[13] Those with moderate serotonin syndrome should be observed for a period of 6-12 hours.[5,15] Patients with moderate cases should have cardiorespiratory and thermal abnormalities corrected and may benefit from 5-HT_{2A} antagonist administration.[10] Patients with moderate to severe cases are typically treated with cyproheptadine.[7] Additionally, olanzapine or chlorpromazine are other drug options, but are not routinely used due to their potential side effects and toxicity.[7] In par-

ticular, caution should be taken if chlorpromazine is being considered to treat symptoms for patients with hypotension or neuroleptic malignant syndrome.[10,16]

Rapid deterioration of a patient's condition signals the need for an immediate, aggressive treatment.[10] Severe cases can be characterized by a temperature >41.1° C (106° F), dramatic swings in blood pressure and pulse rate, delirium, and muscle rigidity.[13] For severe cases, the patient should be admitted to the intensive care unit with a focus on hemodynamic stability and management of symptoms.[5,15] The same 5-HT_{2A} antagonist drug regimen may be used for severe symptoms, although patients who become hyperthermic may also require immediate sedation and intubation using a nondepolarizing neuromuscular blocking agent.[10,13,16] Succinylcholine use is not advised due to the risk of arrhythmia from hyperkalemia associated with rhabdomyolysis.[10,13,16] Active cooling is recommended, as antipyretic agents will not be effective in these cases.[13,15-17] Hyperthermia due to serotonin syndrome is caused by muscle hypermetabolism and not by central nervous system effects.[13,16] Dantrolene, used to treat malignant hyperthermia, has not been shown to be an effective treatment option for serotonin syndrome in animal models.[13,18]

Management of a patient experiencing serotonin syndrome is a team effort. Once a case is identified, in addition to the interprofessional team, consultation with a medical toxicologist, clinical pharmacologist, or a poison control center can support clinicians in the decision-making process regarding drug-drug interactions, potential side effects, and ongoing patient management.[10]

Implications for Anesthesia Practice

The intent of this article is to raise awareness of serotonin syndrome: its causes, clinical manifestations, and treatment options. Because fentanyl is widely used in anesthesia practice and has the potential to result in serotonin syndrome if combined with other serotonergic drugs, we highlighted several examples of cases resulting from SSRI and fentanyl interaction. Through a thorough patient assessment and evaluation, an anesthesia provider should be aware of potentially problematic drugs, herbal supplements, or illicit drugs that patients are taking. Due to the prevalent use of serotonergic drugs, clinicians need to be aware of the signs and symptoms of serotonin syndrome and how to differentiate it from other conditions. Clinicians also need to remain vigilant for signs and symptoms, as serotonergic properties of certain drugs may not be well established.[4] If possible, multidrug regimens should be avoided, or one serotonergic drug be discontinued prior to the administration of another. In the case of drugs required for sedation or general anesthesia, communication is important among all clinicians in the patient care team about the patient's drugs, the planned anesthetic, the requirements of the planned procedure, and the overall course of treatment.

Predicting serotonin syndrome is difficult. Patient and caregiver education regarding the symptoms is also important for early recognition. Clinicians treating patients who are taking multiple drugs should educate their patients on the potential signs and symptoms of serotonin syndrome and appropriate steps to take should symptoms occur.[16] Patients should periodically review all of their prescribed and over-the-counter drugs and supplements with their clinician or pharmacist.

If a patient experiences serotonin syndrome, the clinician or facility may consider voluntary reporting of the case to the U.S. Food and Drug Administration (FDA) through the MedWatch program, found online at *www.fda.gov/Safety/MedWatch/*. MedWatch is a voluntary program that aids the FDA in identifying trends of side effects, adverse drug events, and other quality-related problems associated with medications or devices.

Early recognition of symptoms, discontinuation of serotonergic drugs, and immediate treatment can mitigate complications due to serotonin syndrome and yield a favorable prognosis for patients suffering from this condition. Through education and heightened awareness, safety can be increased for those patients who may be at an increased risk for experiencing serotonin syndrome.

REFERENCES

1. Boyer EW, Traub SJ, Grayzel J. Serotonin syndrome. *UpToDate*. 2014.
2. Gillman PK. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. *Br J Anaesth*. 2005;95(4):434-441.
3. Gillman PK. The spectrum concept of serotonin toxicity. *Pain Med*. 2004;5(2):231-232; author reply 233.
4. Thanacoody R. Serotonin syndrome. *Medicine*. 2011;40(2):63-64.
5. Isbister GK, Buckley NA, Whyte IM. Serotonin toxicity: a practical approach to diagnosis and treatment. *Med J Aust*. 2007;187(6):361-365.
6. Kirschner R, Donovan JW. Serotonin syndrome precipitated by fentanyl during procedural sedation. *J Emerg Med*. 2010;38(4):477-480.
7. Ables AZ, Nagubilli R. Prevention, recognition, and management of serotonin syndrome. *Am Fam Physician*. 2010;81(9):1139-1142.
8. Mowry JB, Spyker DA, Cantilena LR Jr, Bailey JE, Ford M. 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. *Clin Toxicol (Phila)*. 2013;51(10):949-1229.
9. Rastogi R, Swarm RA, Patel TA. Case scenario: opioid association with serotonin syndrome: implications to the practitioners. *Anesthesiology*. 2011;115(6):1291-1298.
10. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352(11):1112-1120.
11. Alkhatib AA, Peterson KA, Tuteja AK. Serotonin syndrome as a complication of fentanyl sedation during esophagogastroduodenoscopy. *Dig Dis Sci*. 2010;55(1):215-216.
12. Taylor JJ, Estes LL, Wilson JW. Linezolid and serotonergic drug interactions. *Clin Infect Dis*. 2006;43(10):1371.
13. Volpi-Abadie J, Kaye AM, Kaye AD.

Serotonin syndrome. *Ochsner J.* 2013;13(4):533-540.
14. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM.* 2003;96(9):635-642.
15. Iqbal MM, Basil MJ, Kaplan J, Iqbal MT. Overview of serotonin syndrome. *Ann Clin Psychiatry.* 2012;24(4):310-318.
16. Cooper BE, Sejnowski CA. Serotonin syndrome: recognition and treatment. *AACN Adv Crit Care.* 2013;24(1):15-20; quiz 21-12.
17. Isbister GK, Buckley NA. The pathophysiology of serotonin toxicity in animals and humans: implications for diagnosis and treatment. *Clin Neuropharmacol.* 2005;28(5):205-214.
18. Nisijima K, Yoshino T, Yui K, Katoh S. Potent serotonin (5-HT)(2A) receptor antagonists completely prevent the development of hyperthermia in an animal model of the 5-HT syndrome. *Brain Res.* 2001;890(1):23-31.
19. Frank C. Recognition and treatment of serotonin syndrome. *Can Fam Physician.* 2008;54(7):988-992.
20. Altman CS, Jahangiri MF. Serotonin syndrome in the perioperative period. *Anesth Analg.* 2010;110(2):526-528.

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