



The Bulletin of Medicaid Drug Utilization Review in Iowa

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SEROTONIN SYNDROME

Serotonin syndrome is an adverse drug reaction of serotonin excess that can result from therapeutic drug use, interaction with serotonergic drugs, or overdose of serotonergic drugs.² This condition most often occurs when two or more serotonergic agents with different mechanisms of action are taken concurrently.⁷ With the vast number of serotonergic medications available on the market, it is important that health care providers recognize the signs, symptoms and causes of serotonin syndrome in order to prevent or detect this condition. Although this drug-induced condition is somewhat rare, it can be fatal if not properly diagnosed and treated.

Serotonin is a neurotransmitter that is responsible for mood, emotion, emesis, sexual behavior, food intake, thermoregulation, and sleep-wake cycles.² Serotonin also plays a role in regulating vascular tone, platelet aggregation, and gastrointestinal motility in the periphery.⁶ The serotonin receptors that are most likely to be involved in serotonin syndrome are the 5-HT_{1A} and 5-HT_{2A}.¹ Other neurotransmitter receptors have been hypothesized to contribute to this syndrome, such as N-methyl-D-aspartate (NMDA), γ -aminobutyric acid (GABA), and dopamine.²

Serotonin syndrome is thought to be an uncommon adverse drug reaction. However, with the increase in the number of prescriptions for selective-serotonin reuptake inhibitors (SSRIs) and other serotonergic drugs it appears that the incidence of serotonin syndrome may be increasing in a similar fashion.⁵ The Toxic Exposure Surveillance System reported in 2002 that of 26,733 patients exposed to SSRIs, 7349 (27.5%) had toxic side effects, and 93 of the cases were fatal.² 14-16% of patients who overdose on SSRIs subsequently experience serotonin syndrome.^{3,4} The actual incidence of serotonin syndrome is unknown due to the misdiagnosis, unrecognized or unreported cases, especially those with mild symptoms.⁶

Cases of serotonin syndrome have been reported in infants, children, adolescents, adults and elderly.² Some patients present with serotonin syndrome with the use of a single serotonergic medication, while others can take many of these types of drugs with no adverse effects.² The variability of doses and combinations at which patients present with serotonin syndrome suggests that individual susceptibility is a factor.⁷ However, there is no evidence that age or any other patient specific factors increase the risk of serotonin syndrome. The only known factor that increases the likelihood of developing serotonin syndrome is the use of serotonergic drugs.

Five different mechanisms for increased serotonin stimulation exist, including: 1) blockade of serotonin reuptake; 2) inhibition of serotonin metabolism; 3) increased production of serotonin; 4) increased serotonin release; and 5) direct serotonin receptor stimulation.⁶ It is also important to note that medications that inhibit the metabolism of serotonergic medication can lead to serotonin syndrome if used concurrently. For example, case reports of serotonin syndrome have been reported during initiation of a new medication that inhibits CYP3A4 and/or CYP2D6 in patients who were already taking a SSRI.²

Symptoms

The signs and symptoms associated with serotonin syndrome can vary greatly from case to case making it difficult to recognize and diagnose. However, three clinical features are usually involved in describing this condition: 1) autonomic hyperactivity; 2) altered mental status; and 3) increased neuromuscular tone.⁵

Symptoms associated with pediatric cases seem to be similar to those of adults.⁶ Onset of symptoms are generally rapid and usually occur within 2 hours of event that lead to increased serotonergic activity (i.e. dose increase of a SSRI).⁷ A reported 60 percent of patients have symptoms at 6 hours of medication initiation or increase.² However, in some cases, it may take 24 hours or more before symptoms present.⁶

The symptoms associated with serotonin syndrome (Table 2) may be indicative of the severity of the case. Mild cases of serotonin syndrome may present with akathisia, tremor, tachycardia, diaphoresis, or mydriasis. In moderate cases, the patient may also experience altered mental status, hypertension, and hyperactive bowel sounds. Eventually hyperthermia and clonus, especially in the lower extremities may develop. Muscle rigidity and hypertonicity, severe hypertension and tachycardia, and agitated delirium are associated with severe serotonin toxicity.² Secondary complications associated with serotonin syndrome include disseminated intravascular coagulation, kidney failure, metabolic acidosis, rhabdomyolysis and acute respiratory distress syndrome.^{5,7}

Diagnosis

Diagnosis of serotonin syndrome is based solely on symptomatology. A patient's medication history of prescription drugs, over-the-counter medications, and herbals or natural products is also very important in identifying the underlying cause of serotonin syndrome.² Diagnosis criteria have been developed by several researchers. The first researcher to develop criteria for serotonin syndrome was Sternbach in 1991, after reviewing 38 cases reported in the literature.⁴ One of the downfalls of Sternbach's criteria was the requirement for no recent addition or increase of a neuroleptic agent.⁴ Considering the commonality of a patient taking both a neuroleptic and serotonergic medication, this criterion made it very difficult to meet all specifications for diagnosis. The Hunter Serotonin Toxicity Criteria for diagnosing serotonin syndrome was established in 2003 and appears to have more sensitivity and specificity than Sternbach's criteria.^{4,6}

The diagnosis of serotonin syndrome should be differentiated from other conditions that present with similar symptoms, including anticholinergic poisoning, malignant hyperthermia, and neuroleptic malignant syndrome (NMS).² Anticholinergic syndrome can be distinguished from serotonin syndrome by the absence of bowel sounds and presence of dry, erythematous skin.² Patients with malignant hyperthermia will often present with skin that is cyanotic in areas with patches of bright red flushing, rigor mortis-like rigidity, and hyporeflexia.² The literature suggests that serotonin syndrome is most often misdiagnosed as NMS, a condition associated with dopamine antagonists. However, in patients taking both serotonin agonists and dopamine antagonists, the offending drug may be difficult to distinguish.² The condition of NMS can be differentiated from serotonin syndrome by its slow onset (1-3 days), bradykinesia, and "lead pipe" muscular rigidity in both upper and lower extremities.⁶

Treatment

Once serotonin syndrome is suspected or diagnosed, the first and most important step to therapy is discontinuing the offending drug(s). Symptoms usually cease within 24 hours of removal of excess serotonin, with the exception of drugs with long elimination half-lives.⁵ Supportive care, including intravenous fluids and stabilization of vital signs, should also be implemented immediately.² Cooling measures should be initiated if hyperthermia is present.⁶ In severe cases where body temperature is greater than 41.1°C, immediate paralysis with nondepolarizing agents and orotracheal intubation should be initiated.²

A serotonin antagonist may be administered to reverse serotonin stimulation. The 5-HT_{2A} antagonist cyproheptadine has been used with anecdotal success, but its efficacy has not been established.⁶ The suggested doses of cyproheptadine for adults is 4-8 mg every 1-4 hours with a maximum of 32 mg in 24 hours, and 0.25 mg/kg/day in divided doses of every six hours for children with a maximum of 12 mg per day.¹ Other 5-HT_{2A} antagonist reported in the literature are 50 to 100 mg of chlorpromazine and 10 mg of olanzapine.² However, chlorpromazine has been said to be an outdated therapy, and atypical antipsychotics, including olanzapine, have been reported as causing serotonin syndrome.⁶ Also, propranolol, bromocriptine, and dantrolene are not recommended for use in serotonin syndrome.²

Benzodiazepines, such as diazepam, may be indicated even in mild cases to control agitation or seizures, and has been shown to improve survival in animal models.² Other drug therapies that have been indicated to control symptoms include low dose direct-acting sympathomimetic amines for hypotension, and nitroprusside or esmolol for hypertension and tachycardia.² Antipyretics are not indicated in serotonin syndrome as the increase in body temperature associated with this condition is a result of increased muscular activity, not hypothalamic control.⁶

There is still much to learn about how to better prevent, diagnose, and treat serotonin syndrome. Pharmacists can play an important role in preventing and recognizing serotonin syndrome by monitoring patient medication profiles for possible

excess serotonin stimulation. Much care must be taken when new medications are added or dosages are increased that may lead to excess serotonin stimulation.

Table 1. Drugs Associated with Serotonin Syndrome^{1,5}

Reduced Serotonin Reuptake	Decreased Serotonin Metabolism	Direct Serotonin Agonist	Increased Serotonin Release	Increased Serotonin Production	Other Drugs Associated with Serotonin Syndrome
SSRI TCA Trazodone Nefazadone Venlafaxine	MAOI Selegiline	Buspirone LSD Trazodone Meperidine	Mirtazapine Amphetamines Phentermine Cocaine	L-tryptophan	Atypical Antipsychotics Lithium Carbamazepine

Table 2. Symptoms Associated with Serotonin Syndrome⁶

Cognitive	Autonomic	Neuromuscular
Anxiety	Diaphoresis	Myoclonus
Confusion	Hyperthermia	Clonus
Delirium	Tachycardia	Nystagmus
Agitation	Hyper/hypotension	Hyperreflexia
Hypomania	Tachypnea	Tremor
Euphoria	Mydriasis	Seizures
Headache	Nausea/vomiting	Ataxia
Hallucinations	Diarrhea	Akathisia
Insomnia	Shivering	Restlessness
Coma	Arrhythmias	Incoordination

(Endnotes)

¹ Birnes P, Coppin D, Schmitt L, Lauque D. Serotonin Syndrome: A Brief Review. CMAJ. 2003 May 27; 168(11): 1439-42.

² Boyer EW, Shannon M. The Serotonin Syndrome. N Engl J Med 2005; 352(11):1112-20.

³ Isbister GK, Bowe SJ, Dawson A, Whyte IM. Relative Toxicity of Selective Serotonin Reuptake Inhibitors (SSRIs) in Overdose. J Toxicol Clin Toxicol 2004; 42:277-85.

⁴ Dunkley EJC, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: Simple and Accurate Diagnostic Decision Rules for Serotonin Toxicity. Q J Med 2003; 96:635-642.

⁵ Ganetsky M, Brush D. Serotonin Syndrome – What Have We Learned? CPEM 2005 Jun; 6(2): 103-8.



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ANNUAL CALL FOR NEW COMMISSION MEMBERS

Physicians and Pharmacists: Are you looking for a new professional opportunity?

According to CMS regulations, each state's medical assistance program shall assemble a group of actively practicing health care professionals to perform drug use review, as well as educational interventions, in an effort to improve medication use. In Iowa, this group is named the Iowa Medicaid Drug Utilization Review Commission. The Commission is composed of four physicians, three pharmacists, and a representative from one of the two Colleges of Pharmacy in Iowa who serve four-year staggered terms, as well as a representative from the Department of Human Services.

The Medicaid DUR Commission is an excellent opportunity to share your professional expertise and to learn from your colleagues. Most importantly, you will have an opportunity to improve the quality of care provided to this patient population. Past participants have expressed great admiration for work of the Commission and have described being a Commissioner as their most professionally rewarding experience. Please consider if this opportunity would fit your skills and expertise.

The Department of Human Services is particularly interested in physicians and pharmacists that serve all age ranges in their practice setting. Any physician or pharmacist interested in serving in this capacity should send a resumé or curriculum vitae, as well as a letter indicating their interest, to Shelly Larson as shown below. Candidates that would like more information about the Commission or who would like to speak to a present Commissioner are also encouraged to call.

The deadline for applications is May 6, 2007.

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