



## THE SPECTRUM OF SEROTONIN SYNDROME

### Definition

The spectrum of symptoms exhibited by patients with serotonin syndrome ranges from barely discernable to life-threatening. Serotonin syndrome is caused by overstimulation of central and peripheral serotonin receptors. It is defined as an adverse drug reaction which results from drug therapy, poisoning or drug-drug interactions which can be fatal. The symptoms of this syndrome include neuromuscular hyperactivity, autonomic hyperactivity and cognitive-behavioral changes which can be identified as mild, early or subacute. The symptoms of serotonin syndrome may be observed after a dose increase, drug overdose or addition of a drug with serotonergic effects.<sup>1,2</sup> Symptoms often occur within minutes of a change in dose or overdose. Approximately 67 percent of patients with serotonin syndrome present within 6 hours of initial start of medication, a dose change or overdose.<sup>3</sup> See Table 1 for a list of symptoms.

### History

Reports of fatalities from serotonin syndrome date back to 1959, when a tuberculosis patient received meperidine and then suffered from "fatal toxic encephalitis".<sup>2</sup> Perhaps the most widely recognized case of serotonin syndrome was

reported in 1984 at New York Hospital, where 18 year-old Libby Zion died from a combination of phenelzine, a monoamine oxidase inhibitor, and meperidine.<sup>4,5</sup>

### Effects of Serotonin

Although the effects of serotonin are most commonly associated with depression, over 90 percent of the serotonin in the body is found in the GI tract. Over 10 known serotonin receptor subtypes can be found throughout the body. Serotonergic neurons are involved with the regulation of blood pressure and body temperature, vomiting, sleep, appetite, anxiety and the perception of pain.<sup>4</sup> Although serotonin syndrome is most often associated with monoamine oxidase inhibitors, the incidence is increasing with the proliferation of drugs which enhance serotonin.<sup>1</sup> It is not uncommon for patients to receive multiple serotonergic medications. Treatment of patients with chronic pain and its comorbid condition, depression often involves one or more drugs which increase serotonin. Patients with migraine headaches may receive a drug in the triptan class as well as tramadol for pain, a tricyclic antidepressant or trazodone for sleep and an SSRI for depression. The over-the-counter cough suppressant, dextromethorphan adds to the risk of increased serotonin levels as well.<sup>6</sup>

Table 1 Symptoms of Serotonin Syndrome<sup>1,4</sup>

Neuromuscular	Autonomic	Cognitive-Behavioral
ataxia/lack of coordination	dilated or non-reactive pupils	agitation/irritability
Babinski's sign (bilateral)	diaphoresis	anxiety
hyperreflexia	diarrhea/hyperactive bowel sounds	coma/unresponsive
muscle rigidity	flushed skin	confusion/disorientation
myoclonus	hypertension/hypotension	dizziness
nystagmus	hyperthermia	hallucinations
shivering/chills	sinus tachycardia	hypomania
tremor	tachypnea	lethargy
		seizures

Table 2 Drugs which increase serotonin levels<sup>8</sup>

Increases serotonin production	Inhibits serotonin reuptake	Inhibits serotonin metabolism	Increases release of serotonin	Stimulates serotonin receptors
l-tryptophan	chlorpheniramine	isocarboxazid	dextromethorphan	buspirone
	cyclobenzaprine	linezolid	meperidine	dihydroergotamine
	dextromethorphan	methylene blue	methadone	lithium
	meperidine	phenelzine	MDMA (Ecstasy)	lysergic acid (LSD)
	methadone	selegiline	mirtazapine	meperidine
	pentazocine	tranylcypromine		metoclopramide
	SSRIs			Triptans
	tramadol			
	trazodone			
	tricyclic antidepressants			
	venlafaxine			

Drugs boost serotonin levels by increasing the production, inhibiting the uptake, increasing the release, inhibiting the metabolism or directly stimulating the serotonin receptors. See Table 2 for a list of drugs and their mechanism of increasing serotonin. It is important to note that serotonin is affected by not only prescription medications, but over-the-counter medicines as well as illegal drugs. Serotonin syndrome has been caused by a single therapeutic dose of an SSRI.<sup>7</sup>

### Treatment

Treatment of serotonin syndrome generally entails discontinuation of the suspected drug(s) and supportive care. After discontinuation of the causative agent(s), mild cases of the syndrome typically resolve within 24 hours. Hyperthermia is treated with aggressive external cooling. Seizures, agitation and rigidity have been treated with benzodiazepines. The serotonin antagonist, cyproheptadine can be used to treat severe symptoms with a dose of 4 to 8 mg every 1 to 4 hours with a maximum daily dose of 32mg.<sup>4,8</sup>

### References

<sup>1</sup>Boyer WE, Shannon M. The serotonin syndrome. *N Engl J Med* 2005;352:1112-20.  
<sup>2</sup>Dvir Y, Smallwood P. Serotonin syndrome: a complex but easily avoidable condition. *General Hospital Psychiatry* 2007; 30:284-287.  
<sup>3</sup>Mason PJ, Morris VA, Balcezak TJ. Serotonin syndrome: presentation of 2 cases and review of the literature.  
<sup>4</sup>Utox Update, 2002 Volume 4, Issue 4.  
<sup>5</sup>Maganti R, White BD. Resident Work Hours, Fatigue and Impairment.  
<sup>6</sup>Ener RA, Meglathery SA, Van Decker WA, Gallagher RM. Serotonin Syndrome and Other Serotonergic Disorders. *Pain Medicine* 2003:63-74  
<sup>7</sup>Gill M, LoVecchio F, Selden B. Serotonin syndrome in a child after a single dose of fluvoxamine. *Ann Emerg Med* 1999;33:457-9.  
<sup>8</sup>*Pharmacists Letter*. October 2009, Volume 25, Number 251002.

### Nebraska Medicaid Profile Review

Two hundred profiles of patients taking multiple serotonergic agents were reviewed. Many patients were receiving serotonergic medications from multiple providers. Numerous patients were taking medications which increase serotonin levels through different mechanisms. A significant number of patients receiving multiple serotonergic medications were also being treated for anxiety, sleep disorder, diarrhea and hypertension. While only a small percentage of patients may reach excessive serotonin levels requiring emergent care, there is a potential for many patients to exhibit mild symptoms.

### Conclusion

The management of each patient's drug therapy depends upon an assessment of the patient's entire clinical situation of which only the providers caring for the patient are aware. A complete medication history is the key to evaluating a patient's clinical manifestation of serotonin syndrome. Patients taking multiple serotonergic medications should be evaluated for symptoms of serotonin syndrome and modify drug therapy if determined appropriate.

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