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Pharmacy & Therapeutics Update: Drug Information for Health Care Professionals

Medical University of South Carolina

Heather Kokko
Medical University of South Carolina

Kelli Garrison
Medical University of South Carolina

Jason Cooper
Medical University of South Carolina

Chris Wisniewski
Medical University of South Carolina

See next page for additional authors

Authors

Medical University of South Carolina, Heather Kokko, Kelli Garrison, Jason Cooper, Chris Wisniewski, and James New

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Drug Information Center
Department of Pharmacy Services
RT Annex, Room 604
Phone: 792-3896
E-mail: druginfo@musc.edu

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In This Issue

Serotonin Syndrome

By Roxana Dumitru, PharmD
PGY1 Pharmacy Resident

Serotonin syndrome is an iatrogenic disorder that was originally reported in the 1950s with the first patient presentation occurring in 1982.[1-3] This serotonergic toxicity is a state of excess serotonin activity or overstimulation of serotonin receptors caused by the therapeutic use, overdose, or withdrawal of serotonergic agents. It may also result from a drug interaction of one or more serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), or others.[1,4] The severity of symptoms spans a spectrum of toxicity that correlates with the intrasynaptic serotonin concentration.[1] Toxicity may be seen in approximately 15% of patients who overdose on SSRIs.[5]

Serotonin, or 5-hydroxytryptamine (5-HT), is a neurotransmitter that is synthesized both peripherally and centrally from the dietary amino acid L-tryptophan.[1] While the majority of this neurotransmitter (90%) is synthesized peripherally, its concentration in the brain is the main factor in the development of serotonin toxicity.[2] Its quantity and actions are tightly regulated by a combination of reuptake mechanisms, feedback loops, and metabolizing enzymes.[6] Within the central nervous system (CNS), serotonin regulates emotion, personality, sleep, appetite, temperature, and pain, as well as sexual and cardiopulmonary functions.[1,6] Outside of the CNS, it acts to regulate smooth muscle tone, specifically of the blood vessels and gastrointestinal tract.[1,5,6]

There are seven main types of serotonin receptors (5-HT_1 through 5-HT_7). It is hypothesized that the 5-HT_{2A} subtype mediates the most important consequences of serotonin toxicity and is also a key player in receptor treatment targets.[5,6] 5-HT_{1A} receptors were also historically thought to play a role in the pathogenesis of the syndrome, but drug targets at this receptor subtype have either shown a lack of benefit or proved to be detrimental.[5] With respect to disease pathophysiology, a classic negative feedback system occurs with serotonin release and utilization.[3] Once serotonin is me-

Figure 1. Diagnosis of Serotonin Syndrome[1]

(Inclusion + Inclusion – Exclusion = Diagnosis)

Inclusion
Use of serotonergic agent within prior 5 weeks

PLUS

Inclusion
Altered mental status
Muscle rigidity
Hyperreflexia
Tremors
Clonus
Diaphoresis
Hyperthermia

MINUS

Exclusion
Infection
Intoxication
Neuroleptic malignant syndrome
Delirium tremens
Malignant hyperthermia

EQUALS

DIAGNOSIS OF SEROTONIN SYNDROME

tabolized in the presynaptic neuron from L-tryptophan, it is released into the synaptic cleft during axonal stimulation and acts upon the 5-HT receptors (specifically 5-HT_{1A} and $5HT_{2A}$).[3] Serotonin that is not taken up by the post-synaptic neuron is then either degraded by monoamine oxidase or taken up by the presynaptic neuron receptors and stored in vesicles until the next axonal stimulation occurs.[2,3] The mechanisms that result in a hyperserotonergic state include an increase in serotonin production or decrease in serotonin metabolism.[1]

Diagnosis of serotonin syndrome is based on the clinical presentation of a patient that has used a serotonergic medication prior to presentation (Figure 1).[1] Symptoms usually present within 6 to 8 hours of initiating or increasing serotonergic medications.[2] No laboratory or radiologic test is available to confirm the diagnosis, as it is mainly one of exclusion.[1] It is important to clinically differentiate serotonin syndrome from other similarly presenting conditions, specifically neuroleptic malignant syndrome (NMS), which may also display muscle rigidity and autonomic abnormalities.[1,3] A primary difference lies in treatment modalities between these two conditions.[1] Dopamine agonists are commonly used to treat NMS, but these agents may exacerbate the symptoms of serotonin syndrome.[1] Other diseases that should be excluded are infectious causes, herpetic encephalopathy, heat stroke, myocardial necrosis, delirium tremens, and intoxication by adrenergic or anticholinergic agents (Figure 1).[4] Symptomatically, mild cases may present with restlessness or diarrhea; severe cases may display profound muscle rigidity and hyperthermia (Table 1).[3,6] Given the heterogeneity of symptoms, mild symptoms can be easily overlooked or presumed to be caused by sub-

Table 1. Signs and Symptoms of Serotonin Syndrome[2,6]

Severity	Autonomic signs	Neurological Signs	Mental Status	Other
Mild	- afebrile or low grade fever - tachycardia - mydriasis - diaphoresis or shivering	- intermittent tremor - akathisia - myoclonus - mild hyperreflexia	- restlessness - anxiety	
Moderate	- increased tachycardia - fever (up to 41°C) - diarrhea with hyperreactive bowel sounds - diaphoresis	- hyperreflexia - inducible clonus - ocular clonus - myoclonus	- easily startled - increased confusion - agitation	- rhabdomyolysis - metabolic acidosis - renal failure - DIC
Severe	- temperature often greater than 41°C	- increased muscle tone (lower limbs > upper) - myoclonus or hyperreflexia	- delirium - coma	- rhabdomyolysis - metabolic acidosis - renal failure - DIC

Abbreviations: DIC - disseminated intravascular coagulopathy

therapeutic dosing.[3,6] This would incorrectly lead to a possible medication dosage increase secondary to presumed ineffectiveness of therapy.[3,6]

Currently, the two main diagnostic criteria published are the Sternbach triad and the Hunter Serotonin Toxicity Criteria. The former is a triad of cognitive-behavioral, neuromuscular, and autonomic derangements, which may present abruptly and progress rapidly.[1,5] Not all patients will manifest signs and symptoms of all three features.[5,6] Physical presentation includes confusion, agitation, reduced level of consciousness, seizures, myoclonus/clonus, hyperreflexia, tremors, muscle rigidity, ataxia, akathisia, hyperthermia, hypertension, tachycardia, diaphoresis, lacrimation, mydriasis, shivering and diarrhea. Hunter's criteria were developed based on the results of an observational study assessing 2222 patients who presented with serotonergic agent overdose. Based on a pattern of similar presentations, the syndrome was described as a spectrum of 7 signs and symptoms including clonus, hyperreflexia, tremors, agitation, diaphoresis, hypertonicity, and hyperthermia.[1] These characteristics have been noted to be more specific than Sternbach's criteria.[3] Patients that present with more severe toxicity may show elevations in total creatine kinase, leukocyte counts, and transaminases, along with lower bicarbonate concentrations.[4] Disseminated intravascular coagulation (DIC), kidney failure, acidosis, or acute respiratory distress syndrome (ARDS) are secondary complications of these presentations.[4] Overall, serotonin toxicity is widely under-recognized because of variability in clinical manifestations, lack of awareness of the syndrome and limitations of available diagnostic criteria.[5]

Early diagnosis and prompt treatment initiation are vital in the management of serotonin syndrome.[1] Fatal complications such as seizures, coma, hypotension, ventricular arrhythmias, DIC, rhabdomyolysis, metabolic acidosis, and renal failure may occur.[1] Most patients improve completely within 24 hours; however, symptoms may persist longer in 40% of patients. Life-threatening toxicity may occur in 50% of patients who have ingested a combination of an MAOI and an SSRI with an estimated mortality of 2 to 12% in severe cases (Table 2).[2]

General management strategies include elimination of the precipitating agent(s), supportive measures to control agitation, hyperthermia (ie, use of active cooling measures), autonomic dysfunction, which are commonly manifested as fluctuations in blood pressure and heart rate.[1] In severe cases, cardiopulmonary support is necessary with endotracheal intubation, mechanical ventilation, sedation, and neuromuscular paralysis, along with the use of intravenous (IV) fluids and vasoactive drugs.[1]

Benzodiazepines are commonly used to achieve sedation, reduce muscle rigidity, and dampen the hyperadrenergic response seen with serotonergic toxicity.[1,5] In severe cases, neuromuscular blockers, specifically non-depolarizing types such as vecuronium, may be necessary as second-line therapy.[1] Succinylcholine should be avoided due to its risk of arrhythmias from hyperkalemia resulting from rhabdomyolysis.[5] Dantrolene, a skeletal muscle relaxant, and bromocriptine, a dopamine agonist, have been reported to improve symptoms in case reports, but they have also been implicated in the development of serotonin toxicity and are generally not recommended.[2,6] In the treatment of hyperthermia, there is a lack of benefit with using antipyretics such as acetaminophen, as this elevated temperature is not caused by an

Table 2. Drug Combinations that May Result in Serotonin Syndrome[3]

All SSRIs in combination	Clomipramine & MAOI
Venlafaxine & lithium	Clomipramine & trazodone
Venlafaxine & fluoxetine	Dextromethorphan & paroxetine
Venlafaxine & mirtazapine	Linezolid & citalopram
Fluoxetine & sertraline	SSRI & St. John's wort
Fluoxetine & tramadol	SSRI & MAOI
Trazodone & buspirone	Meperidine & MAOI

Table 3. Drugs with Serotonergic Activity that May Cause Serotonin Syndrome[1,3,5,6]

Drug Class	Examples
Monoamine Oxidase Inhibitors	isocarboxazid, phenelzine, tranylcypromine, pargyline, moclobemide
Selective Norepinephrine Reuptake Inhibitors	venlafaxine, duloxetine, sibutramine, milnacipran
Selective Serotonin Reuptake inhibitors	citalopram, fluvoxamine, fluoxetine, paroxetine, sertraline
Tricyclic Antidepressants	amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, protriptyline, doxepin
Other Antidepressants	bupropion, nefazodone, trazodone, mirtazepine
Analgesics	codeine, fentanyl, meperidine, tramadol, pentazocine, methadone
Antibiotics	linezolid, ritonavir, furazolidone
Anticonvulsants	valproate, lithium
Antiemetics	ondansetron, metoclopramide
Antihistamines	chlorpheniramine, brompheniramine
Antimigraines	sumatriptan, zolmitriptan, rizatriptan, naratriptan, almotriptan, frovatriptan, eletriptan
Dopamine Agonists	amantadine, bromocriptine, levodopa
Herbals or Dietary Supplements	*Hypericum perforatum* (St. John's wort), *Panax ginseng*, tryptophan
Other Over-the-counter Medications	dextromethorphan
Illicit Drugs	amphetamines, cocaine, lysergic acid diethylamide (LSD), MDMA (ecstasy)
Others	buspirone, procarbazine, selegiline

alteration in the hypothalamic regulation.[1,5] Rather, hyperthermia is due to increased muscular activity, underscoring the need for paralysis in severe cases.[1,5] Neuromuscular paralysis with intubation should be considered in all patients with temperatures greater than 41°C.[2] Physical restraints should be avoided as they can increase the muscle contractions associated with hyperthermia, lactic acidosis and rhabdomyolysis.[2,5] Aggressive fluid hydration is necessary to avoid the risk of myoglobinuria.

Agents known to have nonspecific antiserotonergic actions, such as cyproheptadine, chlorpromazine, methysergide, and propranolol have been advocated, but their efficacy has not been fully established.[1] Caution is warranted with the use of propranolol which has 5-HT_{1A} antagonist activity and a long half life.[2] It can potentiate hypotension and make improvement in rate control a less effective strategy for monitoring response to treatment.[2] However, if patients require support for hypotension arising from MAOI interactions, low doses of direct-acting sympathomimetic amines (eg, norepinephrine, epinephrine, phenylephrine) should be used.[6]

Cyproheptadine, a 5-HT_{2A} antagonist, has been shown to reduce the severity of signs and symptoms in case reports but does not alter the time required for syndrome resolution. However, it can be safely administered in cases where NMS has not been excluded, as it does not possess any dopamine antagonist properties.[1] Cyproheptadine should be considered in moderate cases and is recommended in severe cases, despite a lack of randomized controlled trial evidence.[2] It is available only as an oral agent (tablets or liquid) although the tablet formulation may be crushed and placed down a nasogastric tube. The dose binds 85 to 95% of serotonin receptors, and is administered as a one time dose of 12 mg, adjusted to 2 mg every 2 hours or 4 to 8 mg every 6 hours until symptoms improve.[2,5]

Activated charcoal may be beneficial in acute ingestion of serotonergic drugs.[3] However, if char-

coal is administered, IV chlorpromazine may need to be used in place of cyproheptadine.[5] Recommendations for the use of chlorpromazine are controversial as some reports indicate effectiveness while others conclude that further symptomatic progression may occur. At present, chlorpromazine, which shows some affinity for 5-HT_{2A} receptors, is the only IV 5-HT_{2A} antagonist effective in the treatment of serotonin syndrome.[5] Serious hypotension may be seen as a result of its α-2 adrenoreceptor antagonism; therefore, its use should be avoided in severe cases of shock.[2,5] Dosing may be preceded by a fluid bolus to decrease the likelihood of hypotension.[5] The initial dose of chlorpromazine is 12.5 to 25 mg IV followed by 25 mg orally or IV every 6 hours, although higher doses have been used with apparent safety and effectiveness.[5] Intramuscular injections at doses of 50 to 100 mg may also be considered.[2] Chlorpromazine should be avoided if the drugs that precipitated serotonin toxicity have pronounced cardiotoxic or epileptogenic properties (eg, venlafaxine), as it may aggravate those symptoms.[5]

Finally, antipsychotics have 5-HT_{2A} antagonistic effects and are sometimes used.[2] Caution must be undertaken with antipsychotics, as case reports have cited them as precipitants of serotonin syndrome.[2] Although the atypical antipsychotics olanzapine and ziprasidone are available in short-acting intramuscular formulations, their efficacy in the management of serotonin toxicity has not been established.[5] Olanzapine is also available as a sublingual tablet that has been used in acute cases, but its efficacy has also not yet been identified.[2,5]

In summary, serotonin syndrome has a predictable constellation of signs and symptoms based on excess serotonin present at the neuronal synapse. Major pathways by which serotonin syndrome may be caused include increased production of serotonin, increased serotonin release from neurons, serotonin receptor antagonism, increased serotonin reuptake blockade, and monoamine oxidase inhibition. Life-threatening cases are usually seen as a result of a drug interaction between MAOIs combined with either SRIs (selective or nonselective) or serotonin releasers.[5] The syndrome is based on a diagnosis of exclusion, along with a recent history of serotonergic drug use. Presenting signs and symptoms may include clonus, hyperreflexia, tremors, agitation, diaphoresis, hypertonicity, and hyperthermia. These are broadly classified as a triad of mental status changes, neuromuscular rigidity, and autonomic instability. Treatment strategies include discontinuation of the offending agents and supportive treatment with IV hydration, active cooling techniques, and benzodiazepines. Serious cases may require intubation, mechanical ventilation, and neuromuscular paralysis. Finally, use of cyproheptadine may be warranted, while administration of antipsychotics or chlorpromazine is still controversial. Generally, prognosis in these patients is good, as serotonin toxicity does not result in permanent or long-term neurological damage, unless secondary complications have occurred.[5] Pharmacists can play an important role in preventing these potentially lethal drug interactions and assisting with the supportive/pharmacological therapy in these patients. Nurses and physicians have a vital role in promptly and correctly identifying crucial signs and symptoms upon presentation that are necessary for the diagnosis and effective treatment of these patients.

References available upon request

INCOMPLETE ORDERS REMINDER

After a recent review, it was noted that MUSC prescribers are not following our guidelines on proper medication order writing. This is a significant safety issue for our patients. **As of January 4, 2010, orders not written correctly will not be accepted by nursing or pharmacy staff.** The prescriber will be contact regarding any incomplete so that the order can be re-written. Please refer to Policy C78: Medication Orders for the order writing guidelines https://www.musc.edu/medcenter/policy/Med/C078.pdf.

New Dosing Guidelines and Pocket Cards Available

New medication dosing guidelines/charts were created for the tackle boxes/code bags, while other guidelines have been updated. These documents are also available on the *Formulary and Drug Information Resources* at www.formweb.com.musc.

Dosing and Administration of Medications During Emergency Situations for Adult Patients: new dosing card that will be placed in all adult orange tackle boxes. This card contains dosing information for all medications found in the box. Available at: https://www.musc.edu/pharmacyservices/medusepol/EmergencyGuidelinesAdultTacklebox.pdf

Amiodarone Dosing (adult and pediatric): will be available where amiodarone dosing kits are located. Contains preparation, dosing and administration information for use in patients with or without a pulse for both adult and pediatric patients. Available at: https://www.musc.edu/pharmacyservices/medusepol/Amiodarone-AdultCard.pdf and https://www.musc.edu/pharmacyservices/medusepol/Amiodarone-PediatricCard_NoPulse.pdf.

Adult Continuous Infusions Guidelines: the guidelines were updated to include all continuous infusions used and developed to match the smart pump library. The updated guidelines have been available online but are now available as a pocket card. If you would like to request pocket cards for your area, please contact the Drug Information Center at 2-3896 or druginfo@musc.edu. Available at: https://www.musc.edu/pharmacyservices/medusepol/adultcontinfusion.pdf.

Opioid Comparison Chart: updated opioid comparison chart has been posted online. The updated chart contains new conversion calculation information, more detailed information regarding fentanyl and methadone dosing, and more details regarding use of naloxone. The updated guidelines have been available online but are now available as a pocket card. If you would like to request pocket cards for your area, please contact the Drug Information Center at 2-3896 or druginfo@musc.edu. Available at: http://www.musc.edu/pharmacyservices/medusepol/OpioidAnalgesicConversionChart.pdf.

Medical Center Policy Updates

C26: Sample Medication Policy

- Remove the following statement under reasons for giving a sample: "As a means of practical access to medications during the hours outside of the normal operating hours of community pharmacies.
- Remove: Physicians may receive samples for personal use" statement.

C60: Patient Care Unit Refrigerators

- Updated logs to remove 6 months of information. Increased information used on logs to more adequately document action steps taken.
- Records shall be kept for 3 years.

C61: Medication Administration

- The independent double check of high alert medications will still occur as part of our policy and practice.
- The documentation requirements have been removed from C61. This change will **NOT** affect the checking or documentation of chemotherapy.

C68: Standing Orders

- Delete 24 hour signature requirement; all standing/per protocol orders to be reviewed and approved via individual Service Line Administrator and Physician.

C78: Medication Orders

- Revisions to include use of CPOE
- Addition of discontinuation of protocol co-medications by pharmacy without contacting prescriber when the protocol medication is discontinued
- Addition of changes to oral formulations without contacting the prescriber
- Addition of IV-to-PO Conversion Program
- Addition of Pharmacy Order Entry Hard Stops
- Addition of appendix for essentials for medication orders
- Clarification that only medication orders require a weight.
- Clarification that medications that are NOT weight-based (eg, albuterol) do not require a mg/kg/interval.
- Addition that PRN orders for the same indication will be acted upon based on the clinical presentation of the patient, the patient's past history with the medication ordered and consultation with the prescriber if necessary

C82: Formulary Management

- Revisions to include use of CPOE
- Addition of IV-to-PO Conversion Program
- Addition of reference to the Drug Shortage and Recall Policy
- Addition of procedures for use of nonformulary medications

C159: Continuous Infusion Policy

- Addition of Bed Infusion Management Chart development and maintenance

These policy changes have been approved by the Medical Executive Committee and will be posted online soon.