Serotonin Syndrome
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I. Introduction
- Serotonin Syndrome (SS) is an idiosyncratic drug reaction and is a direct result of psychopharmacologic drug therapy. The underlying cause of the syndrome is an overall increase in CNS (mainly lower brainstem and/or spinal cord) serotonin neurotransmission which is typically associated with initiation of use or an increase in dose of a seritomimetic agent or if these agents are used in conjunction with a monoamine oxidase inhibitor (MAOI). With the latter it is often secondary to initiating therapy with a seritomimetic agent before an adequate wash out period has taken place after stopping MAOI use. It is not dose dependent and in fact the vast majority of cases demonstrate therapeutic drug levels at the time the disorder is diagnosed.

II. Serotonin Pharmacology
- Serotonin is synthesized from the amino acid l-tryptophan. L-tryptophan is hydroxylated and then decarboxylated to give 5-hydroxytryptamine (5-HT or serotonin). Serotonin is a neurotransmitter that is believed to help regulate a variety of functions including motor function, temperature regulation, mood, sexual function, pain perception and personality. Serotonin also acts peripherally to stimulate smooth muscle.
- Serotonin activity is terminated mainly by reuptake into the presynaptic nerve terminal. Once inside it is either stored or metabolized by MAO and eliminated. There are seven different classes of receptors associated with serotonin. Only 2 are thought to be intimately involved in development of the syndrome; 5-HT1a and 5-HT2.

III. Pathophysiology
- Any drug or drug combination which can result in increased serotonin neurotransmission at the 5-HT1a and 5-HT2 receptors can lead to SS.
- **Serotonin syndrome occurs most commonly when two serotonergic agents that increase serotonergic activity by different mechanisms are taken in combination.**
- The onset of the syndrome is typically within minutes to hours of the addition of a second drug or an increase in the dose of the initial drug.
- Mechanisms of serotonin syndrome include:
  1. Increased dosing of l-tryptophan leading to increased serotonin production
  2. Any drug which causes the release of serotonin (e.g. amphetamines)
  3. Use of MAOIs which can lead to increased presynaptic serotonin concentrations
  4. Use of serotonin reuptake inhibitors which can increase synaptic serotonin concentrations
  5. Use of serotonin agonists
  6. Use of lithium which can increase the postsynaptic serotonin receptor response.
## SEROTONERGIC AGENTS

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| Selegeline (LSD)                            | 5-HT

| Amphetamines, especially MDMA (Ecstasy)     | Causes serotonin release                                                  |
| Cocaine                                    | Causes serotonin release                                                  |
| Lithium                                    | Enhances serotonin release, potentiates the effect of 5-HT

| Levodopa, Bromocriptine, Amantadine         | Increased dopaminergic activity with secondary stimulation or serotonin release |
| Buproprion (Wellbutrin)                     | Increased dopaminergic activity with secondary stimulation or serotonin release |
| MAOIs (phenylzine, tranylcypromine, selegiline) | Inhibit breakdown of serotonin                                          |
| Clomipramine                                | Inhibit serotonin reuptake                                               |
| Selective serotonin reuptake inhibitors (SSRIs) (eg. Fluoxetine, sertraline, paroxetine) | Inhibit serotonin reuptake                                               |
| Meperidine (Dermerol)                       | Inhibit serotonin reuptake                                               |
| Dextromethorphan                            | Inhibit serotonin reuptake                                               |
| Trazodone, Nefazodone, fluvoxamine          | Inhibit serotonin reuptake                                               |
| Venlafaxine (Effexor)                       | Inhibit serotonin reuptake                                               |
| TCAs such as Amitriptyline/imipramine      | Inhibit serotonin reuptake                                               |
| Tryptophan                                  | Metabolized to serotonin                                                 |
| Sumatriptan                                 | Serotonin receptor agonist                                                |
| Buspirone (Buspar)                          | Serotonin receptor agonist                                                |

### IV. Clinical Effects

**A. Altered mental status**

- Agitation, confusion, disorientation, anxiety, coma

**B. Neuromuscular dysfunction**

- Myoclonus, rigidity, incoordination, hyperreflexia, seizures (rare, usually tonic-clonic)

**C. Autonomic dysfunction**

- Hyperthermia (reported in half of all cases), nausea, diarrhea, headache, mydriasis, nystagmus (rare), diaphoresis (reported in half of all cases), tachycardia, ventricular arrhythmias (rare) tachypnea, hypertension/hypotension

**D. Other**

- Rhabdomyolysis, acute renal failure, DIC

### V. Laboratory Monitoring

- No confirmatory tests available
- Diagnosis is one based more on exclusion of other causes and history of drug use
- Labs that should be monitored include: EKG, electrolytes, CPK (if muscle activity exaggerated), ABGs (if symptoms warrant)
VI. Differential Diagnosis
- The most common disease state for which SS may be confused is neuroleptic malignant syndrome. Please see the table on page 777 in the Mills article referenced below for a comparison of the two syndromes.

VII. Treatment
- Mainstay of therapy is supportive care
- Discontinue suspected agents
  A. Seizures
    - Diazepam: 0.1-0.2 mg/kg IV, can repeat every 10-15 minutes up to 30 mg
    - Phenobarbital: 10-20 mg/kg IV at a rate < 50 mg/min
  B. Hyperthermia
    - Ice, cooling blankets, misting patient and evaporating with fans, control of agitation (see below)
    - If above methods fail, paralysis should be considered
  C. Agitation
    - Diazepam: 0.1-0.2 mg/kg IV, can repeat every 1-4 hours as needed
    - Lorazepam: 2-4 mg IV prn may also be used
    - Note: Rhabdomyolysis can occur in severe case of agitation/muscle hyperactivity.
    - Treatment includes:
      ✓ Alkalization of urine to pH 7.5 and diurese with mannitol 1g/kg IV over 30 minutes
      ✓ Maintain urine output of 2 ml/kg/hr
      ✓ Catheterization may be required
  D. Sinus tachycardia
    - If patient is hemodynamically stable this typically does not need to be treated.
    - If potentially serious ventricular arrhythmias develop:
      ✓ Supraventricular tachyarrhythmias: Propranolol- 1 mg IV q 2-5 minutes up to 5 mg
      ✓ Ventricular arrhythmias: Lidocaine - 1mg/kg bolus followed by 1-4 mg/min
  E. Cyproheptadine
    - Serotonergic antagonist (blocks 5-HT1a and 5-HT2)
      ✓ Has been used in the past with some benefit noted
      ✓ Dose: 0.5 mg/kg/day PO only (tablet or syrup) up to max daily dose of 32 mg
    - Other drugs that have been used with mixed results include propranolol, methysergide, nitroglycerin

References