Serotonin Syndrome

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Serotonin Syndrome

Serotonin Syndrome is

• A potentially life-threatening condition
• Caused by serotonin toxicity in the central nervous system (CNS)
  • Serotonin toxicity is a term used to describe the expected and problematic effects of excess serotonergic activity
• Most often results from an overdose or when a combination of medications increase serotonin activity
• It can occur with a single therapeutic dose of one medication

What is serotonin?

What does serotonin do?

• CNS roles
  • Attention
  • Behavior
  • Thermoregulation
• Peripheral nervous system roles
  • Gastrointestinal motility
  • Vasconstriction
  • Uterine contraction
  • Bronchoconstriction
  • Platelet aggregation

Demographics and Incidence

• SS has been documented in every age group
• Poison center and post-marketing surveillance data report
  • Tens of thousand of SSRI exposures are reported every year
  • ~15% of those cases lead to SS
  • ~2-12% of severe SS cases lead to death
• Susceptibility to serotonergic excess seems to vary between individuals
Serotonin syndrome

- Classic clinical triad
  - Mental status changes
  - Neuromuscular abnormalities
  - Autonomic hyperactivity

Mental status changes

Symptoms may include

- Agitation
- Anxiety
- Disorientation
- Restlessness
- Excitement

Neuromuscular abnormalities

Symptoms may include

- Tremors
- Clonus
- Hyperreflexia
- Muscle rigidity
- Bilateral Babinski Signs
- Akathisia

Autonomic Hyperactivity

Symptoms may include

- Hypertension
- Tachypnea
- Tachycardia
- Hyperthermia
- Mydriasis
- Diaphoresis
- Dry mucous membranes
- Flushed skin
- Shivering
- Vomiting
- Diarrhea
- Hyperactive bowel sounds
- Arrhythmias

What is serotonin syndrome?

Serotonergic excess causes toxicity on a spectrum

Diagnosis

This is a clinical diagnosis based on

- Medication history
- Physical exam
- Neurological exam
- Timing of symptoms
Medication History

- Should include all medications and recent changes
  - Prescription meds
  - Illicit drugs
  - Over-the-counters
  - Alternative medications/herbals
  - Dietary supplements
- Dose or dosing interval changes
- Formulation changes
  - Immediate release, extended release, etc

Causative Medications

- Medications with the following serotonergic effects
  - Impairs reuptake from the synaptic cleft
  - Direct serotonin receptor agonism
  - Inhibit serotonin metabolism
  - Increase release of serotonin
  - Increase sensitivity of serotonin receptor
  - Increase serotonin synthesis
- Medication combinations can increase serotonin activity by
  - Additive effects
  - Altering the metabolism of serotonergic drugs

Meds that impair reuptake from the synaptic cleft

- Selective serotonin reuptake inhibitors (SSRIs)
  - Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
  - Desvenlafaxine, duloxetine, milnacipran, and venlafaxine
- Dopamine-norepinephrine reuptake inhibitors
  - Bupropion
- Serotonin modulators
  - Nefazodone, trazodone, and vilazodone

Meds that impair reuptake from the synaptic cleft

- Tricyclic antidepressants (TCAs)
  - Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nor-tripryline, protriptyline, trimipramine
- 5-HT3 receptor antagonists
  - Dolasetron, granisetron, ondansetron, palonosetron
- Certain opioids
  - Fentanyl, meperidine, tapentadol, methadone, and tramadol
- Pentazocine

Meds that impair reuptake from the synaptic cleft

- St. John’s wort (Hypericum perforatum)
- Metoclopramide
- Valproate
- Carbamazepine
- Sibutramine
- Dextromethorphan
- Cyclobenzaprine
- MDMA (Ecstasy)
- Cocaine

Meds with direct serotonin receptor agonism

- Buspirone
- Triptans
  - Sumatriptan, rizatriptan, others
- Ergot derivatives
  - Dihydroergotamine, methylergonovine
- Fentanyl
- Lysergic acid diethylamide (LSD)
Meds that inhibit serotonin metabolism

- Monoamine oxidase inhibitors (MAOIs)
  - Phenelzine, tranylcypromine, isocarboxazid, moclobemide, selegiline, rasagline, procarbazine, Syrian rue (Peganum harmala/harmine)
  - Linezolid
  - Tedizolid
  - Methylene blue

Source: UpToDate

Meds that increase release of serotonin

- Amphetamines
  - Dextroamphetamine, methamphetamine, and others
- Amphetamine derivatives
  - Fenfluramine, dexfenfluramine, phenetermine
- Cocaine
- MDMA (Ecstasy)
- Levodopa

Source: UpToDate

Meds that increase sensitivity of serotonin receptor

- Lithium

Source: UpToDate

Meds that increase serotonin formation

- Tryptophan

Source: UpToDate and Google Images

Drug Interactions

- Combining multiple serotonergic agents increases risk
  - Be aware of long acting meds, like fluoxetine, which may exhibit serotonergic effects for weeks after the last dose
- Always consider how medications may alter the metabolism of serotonergic agents
  - Most interactions involve the cytochrome P450 enzyme system
    - More than 50 different isoforms responsible for the metabolism of many medications
    - Ex) CPY3A4, CPY2C9, CY2D9 and so forth

Cytochrome P450 enzymes

- Substrate – a drug that is metabolized by a particular enzyme
  - Ex) Venlafaxine is substrate of CPY3A4
- Inducer – a drug that increases the activity of a particular enzyme
  - Ex) Carbamazepine is an inducer of CPY1A2, 2C9, and 3A4
- Inhibitor – a drug that decreases the activity of a particular enzyme
  - Ex) Ciprofloxacin inhibits CPY1A2
Physical exam findings

- Agitation
- Akathisia
- Anxiety
- Diaphoresis
- Dry mucus membranes
- Flushed skin
- Hypertension
- Hyperthermia
- Increased bowel sounds
- Mydriasis
- Shivering
- Tachycardia

Neurological exam findings

Neuromuscular findings may be more pronounced in the lower extremities

- Bilateral Babinski Signs
- Deep tendon hyperreflexia
- Inducible or spontaneous clonus
- Muscle rigidity
- Ocular clonus
- Tremor

Diagnostic criteria

- Two criteria exist for aiding SS diagnosis
  - Sternbach’s criteria - older
    - 75% sensitive and 96% specific for diagnosing SS
  - Hunter criteria - newer and most commonly used
    - 84% sensitive and 97% specific for diagnosing SS
  - Gold standard is the diagnosis by a medical toxicologist

Hunter Criteria

Must be exposed to a serotonergic agent and have at least one below

- Spontaneous clonus
- Inducible clonus with agitation or diaphoresis
- Ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia
- Temperature above 38°C with ocular clonus or inducible clonus

Differential Diagnosis

- Neuroleptic Malignant Syndrome (NMS)
- Malignant Hyperthermia
- Sympathomimetic toxicity
- Anticholinergic toxicity
- Encephalitis

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What is serotonin syndrome?

**Serotoninergic excess causes toxicity on a spectrum**


**Management**

- Mild cases to moderate cases
  - Discontinue serotoninergic agents
  - Provide supportive cares
  - Sedation with benzodiazepines
  - Treat autonomic instability and abnormal vital signs
  - Consider giving a serotonin antagonist if abnormalities persist

- Severe cases – including hyperthermic patients (>41°C)
  - Endotracheal intubation
  - Paralysis

**Management**

- Discontinue serotoninergic agents
  - Signs and symptoms generally start to resolve within 24 hours for short acting agents
    - Some drugs have longer half lives and/or duration of effect and thus toxicity may persist for days

- Provide supportive cares
  - Supplemental O2 to keep sats above 94 %
  - Crystalloid fluids for volume depletion
  - Cardiac monitoring

- Treat autonomic instability and abnormal vital signs
  - Hypertension
    - Use short acting agents like esmolol or nitroprusside
    - Avoid long acting agents like propranolol
  - Hypotension – most often seen with MAOI induced SS
    - Use direct acting agents like norepinephrine, epinephrine, or phenylephrine
    - Avoid dopamine

- Consider giving a serotonin antagonist
  - Cyproheptadine is a 5-HT1A and 5-HT2A receptor antagonist
    - Initial dose is 12 mg followed by 2 mg Q2H until response
    - Optimal dosing is not established
    - Available as 4 mg tablets and 2mg/5mL oral syrup
    - Tablets can be crushed and given via nasogastric tube
    - It is not known if cyproheptadine affects patient outcomes

- Chlorpromazine and olanzapine are not recommended for use a serotonin antagonists
  - Undesirable side effect profiles
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<th>Management</th>
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<tbody>
<tr>
<td>• Patients with temperatures greater than 41.1°C</td>
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<tr>
<td>• Endotracheal intubation</td>
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<td>• Sedation</td>
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<tr>
<td>• Paralysis</td>
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<tr>
<td>• Reduce temperature with external cooling</td>
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<tr>
<td>• Do not use acetaminophen or dantrolene</td>
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