SEROTONIN SYNDROME

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Serotonin: A History Still in the Making

A monamine neurotransmitter with multiple receptor-based functions
• Serotonin cannot cross the BBB: peripheral & CNS synthesis
• Produced from dietary L-tryptophan: decarboxylation & hydroxylation
• Multiple Family receptors (n=7) with many subtype receptors

Physiologic Actions are Tightly Regulated: Combination of Factors
• Stored presynaptically or rapidly metabolized by MAO
• Binds to post-synaptic receptors: mood, personality, sleep, N&V, pain, cognition, temp regulation, appetite, other
• Peripherally involved with vascular tone & GI motility
• Effect cessation: reuptake pumps or metabolism
Table 1. Effects of 5-HT receptor subtypes in relation to serotonin toxicity

<table>
<thead>
<tr>
<th>5-HT RECEPTOR</th>
<th>MAIN ACTION RELATED TO SEROTONIN TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>Neuronal inhibition, regulation of sleep, feeding, thermoregulation, hyperactivity associated with anxiety, hyperactivity associated with depression</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1B&lt;/sub&gt;</td>
<td>Locomotion, muscle tone</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1C&lt;/sub&gt;</td>
<td>Neuronal excitation, learning, peripheral vasoconstriction, platelet aggregation</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt;</td>
<td>Stomach contraction</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;2B&lt;/sub&gt;</td>
<td>Nausea and vomiting, anxiety</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Gastrointestinal motility</td>
</tr>
</tbody>
</table>

5-HT = serotonin.
Data from Bayer and Shannon,*

Syndrome: A Definition

Derived from Greek word meaning concurrence; is a collection of signs and symptoms that are observed in, and characteristic of, a single condition.

Wikipedia, April 2014

Serotonin Syndrome (Serotonin Toxicity)

Classically characterized by the triad of neuroexcitatory effects, including mental status changes; neuromuscular hyperactivity; autonomic instability
Serotonin and Our National Consciousness

1984 death of Libby Zion: NEJM 1988;318:771-75
- Father: a lawyer & New York Times writer
- ED presentation of fever, agitation & confusion unrecognized
- Patient died within 8 hours
- Internist: meperidine for “agitation” but pt on MAOI for depressive Sxs

Serotonin Syndrome: Introduction

- Develops soon after starting or increasing dose of a serotonin-active agent
- Usually a result of overdose or drug-drug interaction
- Resulting symptom complex: mild, moderate or severe effects
- Morbidity directly linked to severity, including death
- A distinct symptom complex from NMS, MH, others
Five Probable Perturbations for Drug-Induced Serotonin Syndrome

1. Decreasing serotonin metabolism, e.g., MAOIs, linezolid
2. Decreased serotonin reuptake, e.g., SSRIs, SNRIs, TCAs, tramadol, cocaine
3. Increasing serotonin neuro-release, e.g., amphetamine, Ritalin, cocaine, reserpine
4. Increasing serotonin precursors/agonists, e.g., l-tryptophan, LSD, buspirone
5. Direct serotonin receptor stimulation: sumatriptan, buspirone

Table 3. Medications causing serotonin syndrome

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>DRUGS CAUSING SEROTONIN SYNDROME</th>
<th>DRUG COMBINATIONS CAUSING SEROTONIN SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased production of serotonin</td>
<td>L-tryptophan</td>
<td>L-tryptophan with MAOI</td>
</tr>
<tr>
<td>Increased serotonin release from neurons</td>
<td>Amphetamines, MDMA</td>
<td>Amphetamines and MAOI</td>
</tr>
<tr>
<td>5-HT3 antagonist</td>
<td>Buspirone</td>
<td>Buspirone</td>
</tr>
<tr>
<td>Decreased serotonin reuptake</td>
<td>SSRIs, Venlafaxine, Clomipramine, Imipramine, Tramadol, meprobamate, methadone, fenfluramine, Brotizolam, St. John’s wort</td>
<td>Analgesics with MAOI or SSRI</td>
</tr>
<tr>
<td>MAO inhibition</td>
<td>MAOIs, Lithium</td>
<td>MAOIs with all serotonin drugs</td>
</tr>
<tr>
<td>Uncertain</td>
<td>-</td>
<td>Macrolactams and SSRIs or venlafaxine</td>
</tr>
</tbody>
</table>

Serotonin Syndrome: Incidence

Incidence rate complicated by symptom spectrum

- First described in 1959 (TB pt: meperidine & iproniazid): Pt died
- First recognized in 1960 and defined as indoleamine syndrome
- Serotonin Syndrome: term first coined in 1982 pt >2 pro-serotonergic meds
- First comprehensive review Sternbach’s: Am J Psych 1991;48:705

Exact incidence is unknown

- Mild/moderate cases often unrecognized by gen practitioners
- Most commonly considered in Over Dose: ~ 14-18%
- TESS data:
- Poor Dx recognition underscores importance for understanding Sx complex
Serotonin Syndrome: Clinical Features

- No lab tests: purely a clinical diagnosis
- History extremely important: Rx/illicit drug use; new/dose change
- Drug-Drug interactions; possible CYP & receptor PGs
- Restarting serotonin drug & insufficient washout
- Rapid Sx onset – usually within 6 hours & resolves within 24 hours

Serotonin Syndrome: Symptom Triad

- Neuroexcitatory / altered mental status: ~ 40% of patients
  spectrum from: agitation, excitability, irritability, hyperactivity, restlessness, anxiety, hypomania, confusion lethargy, delirium, hallucinations, drowsiness to coma

- Neuromuscular hyperactivity: ~ 50% of patients
  rigidity, hyperreflexia & hypertonia (greatest in legs); teeth grinding; myoclonus; ataxia; tremor (mostly legs), nystagmus

- Autonomic Instability: ~ 40% of patients
  Dilated/non-reactive pupils, tachycardia, tachypnea, fever, diarrhea, abdominal pain, flushing, diaphoresis, hyper/hypotension.
**TABLE 2**

Sternbach's clinical criteria for SS diagnosis

- Recent addition or increase in dosage of agents that increases serotonin activity or are available in the central nervous system
- The presence of 2 of the following clinical signs or symptoms:
  - Agitation
  - Altered mental status (confusion, hypomania)
  - Ataxia/Incoordination
  - Diaphoresis
  - Diarrhea
  - Fever
  - Hyperreflexia
  - Myoclonus
  - Shivering
  - Tremor
- Absence of other possible etiologies (e.g., infection, metabolic disorder, endocrine disorder, substance abuse, withdrawal, etc.)
- No recent addition or increase in the dose of a neuroleptic drug

SS: serotonin syndrome.

Source: References 1, 52, 60, 65.

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**TABLE 3**

Hunter serotonin toxicity criteria

- In the presence of a serotonergic agent
- Any of following clinical signs and symptoms:
  - Hypertonia, temperature >38°C/100.4°F
  - Inducible clonus and agitation or diaphoresis
  - Ocular clonus and agitation or diaphoresis
  - Ocular or inducible clonus
  - Spontaneous clonus
  - Tremor and hyperreflexia

Source: References 3, 52, 60-67.

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Serotonin Syndrome: Differential Diagnosis

Anticholinergic Syndrome

• Normal reflexes, dry oral mucosa/MM, hot, red, blotchy dry skin, urinary retention, dilated pupils & photophobia, altered consciousness – agitation, auditory/sensory hallucinations, tachycardia, hyperthermia, decreased bowel sounds

Sympathomimetic Syndrome

• tachycardia, hypertension, diaphoresis, hyperthermia, altered consciousness
Neuroleptic Malignant Syndrome – NMS

Distinct in implicated medication (dopamine antagonists) & time course vs Serotonin Syndrome

• Usually days to weeks for NMS (vs < 24 hours)
• Usually bradykinesia & lead-pipe rigidity vs agitation, hyperreflexia, tremors, clonus, myoclonus
• Hyperthermia: very high up to 46C (114.8 F)
• Metabolic acidosis, rhabdomyolysis, dark urine
• No GI abnormalities, muscular rigidity or hyperreflexia

Malignant Hyperthermia – MH

• Usually occurs in minutes after exposure (halothane/succinylcholine)
• Skin: mottled with areas of cyanosis & areas of bright red flushing
• Hyporeflexia with rigor-mortis like muscular rigidity
Serotonin Syndrome: Treatment

Largely Supportive and Symptom Targeted

Define Symptom severity: Mild, Moderate or Severe

- Presentation severity dictates Rx: type & aggressiveness
- D/C all serotonin modulating drugs
- Recent, large OD consider oral activated charcoal
- IV fluids, benzos for agitation/hyperreflexia/muscle rigidity
- Monitor I/O, K, CPK, myoglobin, Cr/BUN, pH
- Fever – muscle relax; not acetaminophen, ibuprofen
- Cyproheptadine & Chlorpromazine: 5HT2A antagonists????

Serotonin Syndrome: Treatment Pearls

- Any CV instability begin IV fluids: monitor K, CPK, for rhabdomyolysis
- Hyperreflexia, serious myoclonus: benzos – no data
- High temp: cooling blanket, hydration, benzos: traditional agents ineffective (muscle)
- Severe temp: intubation and pharmacologic paralysis; dantrolene
- Cyproheptadine: possible use in moderate to severe toxicity; only oral CPZ IM/IV
- Estimated mortality with severe toxicity: 2 to 12%
Serotonin Syndrome: Conclusions

- Rare Occurrence – Missed Diagnosis
  - Consider in any patient on serotonin drug
  - Increasing incidence as serotonin Rx increasing
- Diagnosis of exclusion with serotonin history: DIs
- Remember the triad: altered MS, autonomic hyperactivity, neuromuscular abnormalities
- Rx dependent upon severity
- Prompt recognition most important prognostic factor

REFERENCES