SEROTONIN SYNDROME

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Serotonin: A History Still in the Making

A monamine nurotrasmitter 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

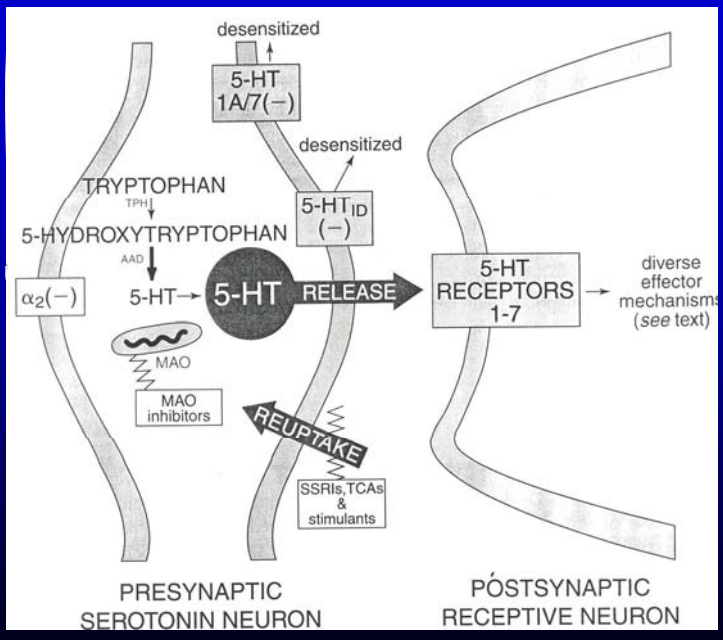
- Stored presynapticaly or rapidly metabolized by MAO
- Binds to post-synaptic receptors: mood, personality, sleep, N&V, pain, cognition, temp regulation, appetite, other
- Peripherally involved with vascular tone & GI motility
- Effect cessation: reuptake pumps or metabolism

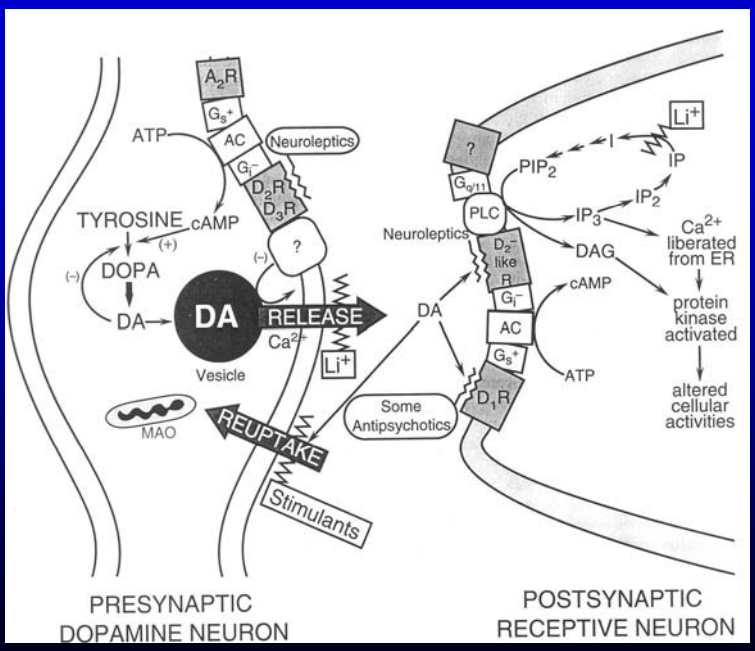
Table 1. Effects of 5-HT receptor subtypes in relation to serotonin toxicity

5-HT RECEPTOR	MAIN ACTION RELATED TO SEROTONIN TOXICITY
5-HT_{1A}	Neuronal inhibition, regulation of sleep, feeding, thermoregulation, hyperactivity associated with anxiety, hypoactivity associated with depression
5-HT_{1D}	Locomotion, muscle tone
5-HT_{2A}	Neuronal excitation, learning, peripheral vasoconstriction, platelet aggregation
5-HT_{2B}	Stomach contraction
5-HT_{3}	Nausea and vomiting, anxiety
5-HT_{4}	Gastrointestinal motility

5-HT—serotonin.
Data from Boyer and Shannon.[4]

Frank C. Can Fam Physician 2008; 54:988-92.




A2R
Gs+
AC
ATP
Gi–
Neuroleptics
D2R
D3R
TYROSINE
cAMP
(+)
?
(–)
DOPA
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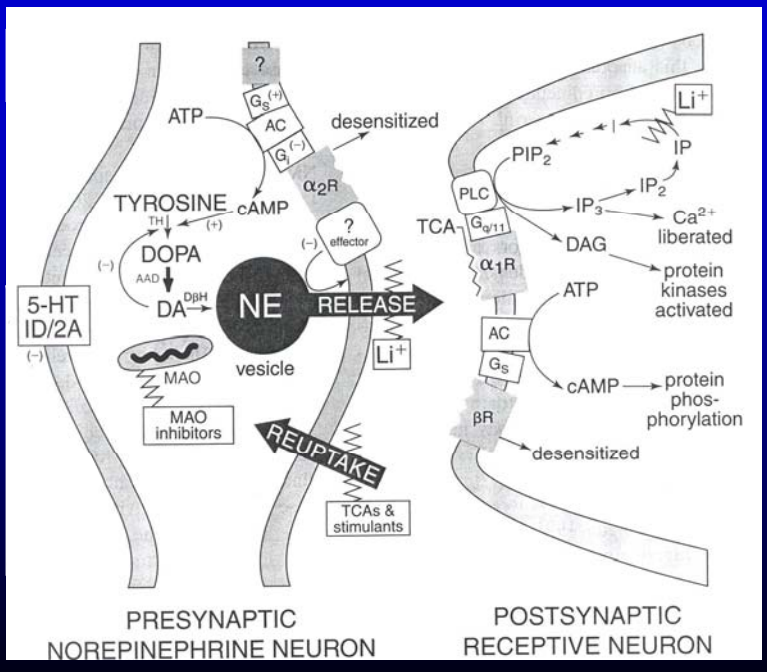
DA
DA
RELEASE
Ca2+
Vesicle
Li+
MAO
REUPTAKE
Stimulants
Some Antipsychotics
?
Gq/11
PLC
PIP2
I
IP
Li+
IP3
IP2
Ca2+ liberated from ER
Neuroleptics
DAG
D2-like R
Gi–
cAMP
protein kinase activated
AC
Gs+
ATP
D1R
altered cellular activities
PRESYNAPTIC DOPAMINE NEURON
POSTSYNAPTIC RECEPTIVE NEURON


?
Gs(+)
AC
Gi(–)
ATP
desensitized
α2R
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DOPA
AAD
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DβH
NE
RELEASE
5-HT ID/2A
(–)
MAO
vesicle
Li+
MAO inhibitors
REUPTAKE
TCAs & stimulants
PIP2
I
IP
Li+
PLC
IP3
IP2
TCA
Gq/11
Ca2+ liberated
DAG
α1R
protein kinases activated
ATP
AC
Gs
cAMP
protein phos-phorylation
βR
desensitized
PRESYNAPTIC NOREPINEPHRINE NEURON
POSTSYNAPTIC RECEPTIVE NEURON

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
1. Direct serotonin receptor stimulation: sumatriptan, buspirone

Table 3. Medications causing serotonin syndrome

MECHANISM	DRUGS CAUSING SEROTONIN TOXICITY WITHOUT DRUG INTERACTION	DRUG COMBINATIONS CAUSING MODERATE TO SEVERE TOXICITY
Increased production of serotonin	• L-tryptophan	• L-tryptophan with MAOI
Increased serotonin release from neurons[11]	• Amphetamines • NMDA	• Amphetamines and MAOI • NMDA and MAOI • NMDA and SSRI (lower risk)
5-HT_{1A} antagonism[11]	• Buspirone • LSD	• Paroxetine and buspirone
Decreased serotonin reuptake[9,11-13,15]	• SSRIs • Venlafaxine • Clomipramine, imipramine • Tramadol, meperidine, methadone, fentanyl • Dextromethorphan • St John's wort	• Analgesics with MAOI or SSRI • Clomipramine with MAOI • SSRIs, venlafaxine with MAOI • SSRIs, venlafaxine, buproprion
MAO inhibition[11,14]	• MAOIs • Selegiline • Linezolid	• Moclobemide and SSRIs or venlafaxine • Irreversible MAOIs with all serotonergic drugs • Linezolid and SSRIs
Uncertain	• Lithium[9]	

5-HT_{1A}—serotonin 1A receptor, LSD—lysergic acid diethylamide, MAO— monoamine oxidase, MAOI—monoamine oxidase inhibitor, NMDA—*N*-methyl-D-aspartate, SSRI—selective serotonin reuptake inhibitor.

Frank C. Can Fam Physician 2008; 54:988-92.

TABLE 1
Drug combinations associated with SS

Antidepressants	**MAO-A irreversible:** Isocarboxazid, phenelzine, tranylcypromine **MAO-A reversible:** Moclobemide **MAO-B:** Selegiline **SNRIs:** Duloxetine, venlafaxine **SSRIs:** Citalopram, escitalopram, fluoxetine, paroxetine, sertraline **TCAs:** Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline **Other:** Bupropion, mirtazapine, nefazodone, trazodone
Opiate analgesics/pain medications	Buprenorphine, cyclobenzaprine, fentanyl, hydrocodone, meperidine, morphine, oxycodone, pentazocine, tramadol
OTC cough medication	Dextromethorphan
Antimigraine agents/triptans (5-HT1 agonists)	**Triptans:** Almotriptan, dihydroergotamine, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan **Others:** Carbamazepine, valproic acid
Psychedelics	Amphetamine, cocaine, LSD, MDA, MDMA ("ecstasy"), 5-MeO-DiPT ("foxy methoxy"), Syrian rue (*Peganum harmala*) seeds
Bariatric medications	Sibutramine, phenylpropanolamine
Herbal products	Ginseng, nutmeg, *Panax*, St John's wort, Syrian rue (*Peganum harmala*) seeds, yohimbe
Antibiotics	Linezolid
Antiemetics	Droperidol, granisetron, metoclopramide, ondansetron
Tryptophan (others)	5-HTP, buspirone, certain foods (eg, cheese, red wine), dextromethorphan, L-dopa, lithium, valproate
CNS stimulants	Amphetamine, cocaine, diethylpropion, methamphetamine, methylphenidate, phentermine, sibutramine
Anticonvulsants	Carbamazepine, valproic acid
Antiviral	Ritonavir
Others	Chlorpheniramine, olanzapine, reserpine

5-HTP: 5-hydroxytryptophan; 5-MeO-DiPT: 5-methoxy-diisopropyltryptamine; L-dopa: L-3,4-dihydroxyphenylalanine; LSD: lysergic acid diethylamide; MAO-A: monoamine oxidase A; MAO-B: monoamine oxidase B; MDA: methylenedioxyamphetamine; MDMA: 3,4-methylenedioxymethamphetamine; OTC: over the counter; SNRI: serotonin-norepinephrine reuptake inhibitor; SS: serotonin syndrome; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.

Source: References 1,3-12,14-17.

Iqbal MM, Basil MJ. Ann Clin Psych 2012;24(4):310-318

Serotonin Syndrome: Incidence

Incidence rate complicated by symptom spectrum

- First described in 1959 (TB pt: merperidine & 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
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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 all agents that increases serotonin activity or are available in the central nervous system
- The presence of ≥3 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 (eg, 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 1,52,64,65.

Iqbal MM, et al. Ann Clin Psych 2012;24(4):310-318

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 3,52,65-67.

Iqbal MM, et al. Ann Clin Psych. 2012;24(4):310-318

Table 2. Signs and symptoms of serotonin syndrome

SERIOUSNESS	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 hyperactive bowel sounds • Diaphoresis with normal skin colour	• Hyperreflexia • Inducible clonus • Ocular clonus (slow continuous lateral eye movements) • Myoclonus	• Easily startled • Increased confusion • Agitation and hypervigilance	• Rhabdomyolysis • Metabolic acidosis • Renal failure • Disseminated intravascular coagulopathy (secondary to hyperthermia)
Severe	• Temperature often more than 41°C (Secondary to increased tone)	• Increased muscle tone (lower limb > upper) • Spontaneous clonus • Substantial myoclonus or hyperreflexia	• Delirium • Coma	• As above

Data from Boyer and Shannon.[4]

Frank C. Can Fam Physician 2008; 54:988-92.

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

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