



UW PACC

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

SEROTONIN SYNDROME: WHAT DO I DO?

JAMES LEE, MD

UNIVERSITY OF WASHINGTON

CONSULTATION-LIAISON PSYCHIATRY FELLOWSHIP



SPEAKER DISCLOSURES

✓ No conflicts of interest

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

Mark Duncan MD
Rick Ries MD
Kari Stephens PhD
Barb McCann PhD

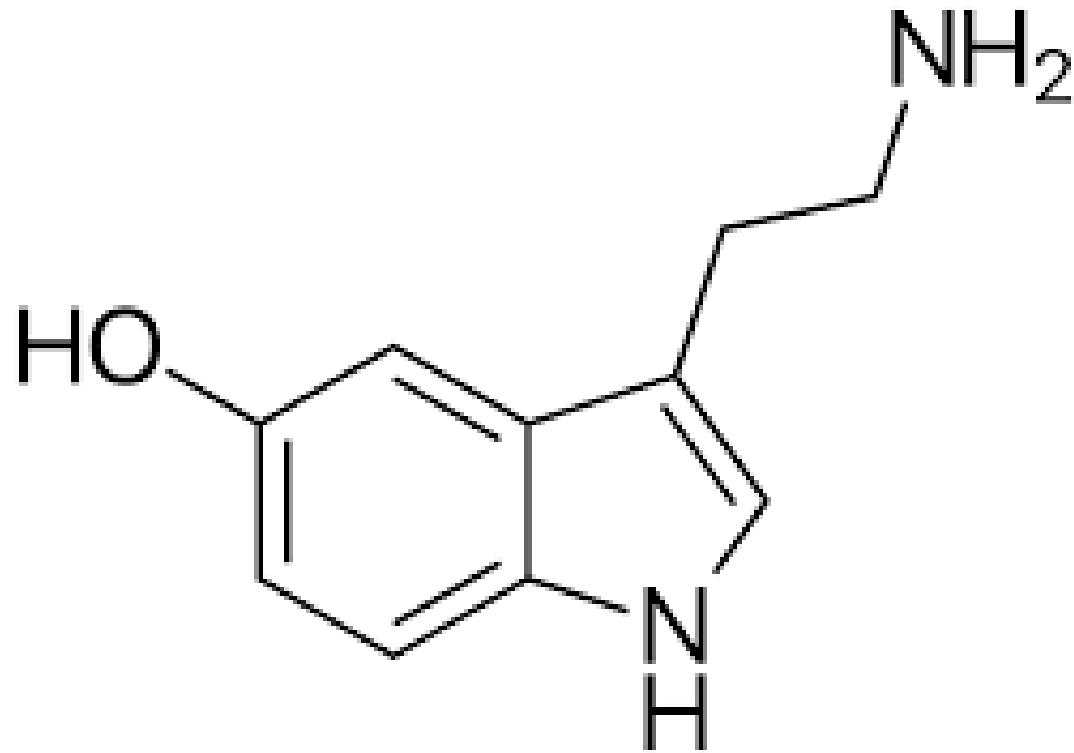
Anna Ratzliff MD PhD
Betsy Payn MA PMP
Esther Solano
Cara Towle MSN RN

OBJECTIVES

By the end of this presentation, participants should be able to:

1. Identify common presentations of serotonin syndrome
2. Name at least three (3) non-psychiatric medications that can cause/worsen serotonin syndrome
3. List the next steps for treatment of serotonin syndrome in the outpatient setting

FREE ASSOCIATE WITH ME



Serotonin

- Neurotransmitter
- Happiness
- 5-HT
- Antidepressants

SEROTONIN: A HISTORY

- Quest for the mysterious substance behind vasoconstriction substance in platelets (1910s through 1940s)
- Smooth muscle contraction in GI tract (1940s)
- Later found in brain, lung, kidney (alongside platelets and GI tract)
- Third neurotransmitter to have been discovered
 - Linked to mood, behavior, sleep cycles, appetite
- Also linked to hypertension, enteric movement, pulmonary hypertension, platelet aggregation

SEROTONIN: THE RECEPTORS

Table 1. Location of 5-HT receptor subtypes, function and clinically relevant receptor agonists and antagonists. Receptor agonists and antagonists that are used experimentally to manipulate many of these receptors are not of clinical use, and therefore not mentioned here. Modified from Katzung *Basic Clinical Pharmacology*

Receptor subtype	Location/function	Agonist	Antagonist
5-HT _{1A}	CNS: neuronal inhibition, behavioral effects (sleep, feeding, thermoregulation, and anxiety)	Buspirone*	Yohimbine*
5-HT _{1B}	CNS: presynaptic inhibition, behavioral effects Vascular: pulmonary vasoconstriction		Yohimbine*
5-HT _m	CNS: locomotion Vascular: cerebral vasoconstriction	Sumatriptan	Yohimbine*
5-HT _{2A}	CNS: neuronal excitation, behavioral effects, and learning; Smooth muscle: contraction, vasoconstriction/dilatation Platelets: aggregation		Ketanserin Cyprohepatdine* Chlorpromazine* LSD
5-HT _{2B}	Stomach fundus		Chlorpromazine* Yohimbine*
5-HT _{2C}	CNS: choroid plexus, CSF secretion		Metoclopramide*
5-HT ₃	Sensory and enteric nerves, emesis		Ondasetron* Dolasetron*
5-HT ₄	CNS and myenteric neurons, GI motility	Metoclopramide* Cisapride*	
5-HT _{5A}	CNS: function unknown		
5-HT ₆	CNS: function unknown		
5-HT ₇	CNS, blood vessels, GI tract: function unknown		

SEROTONIN: THE PATHWAYS

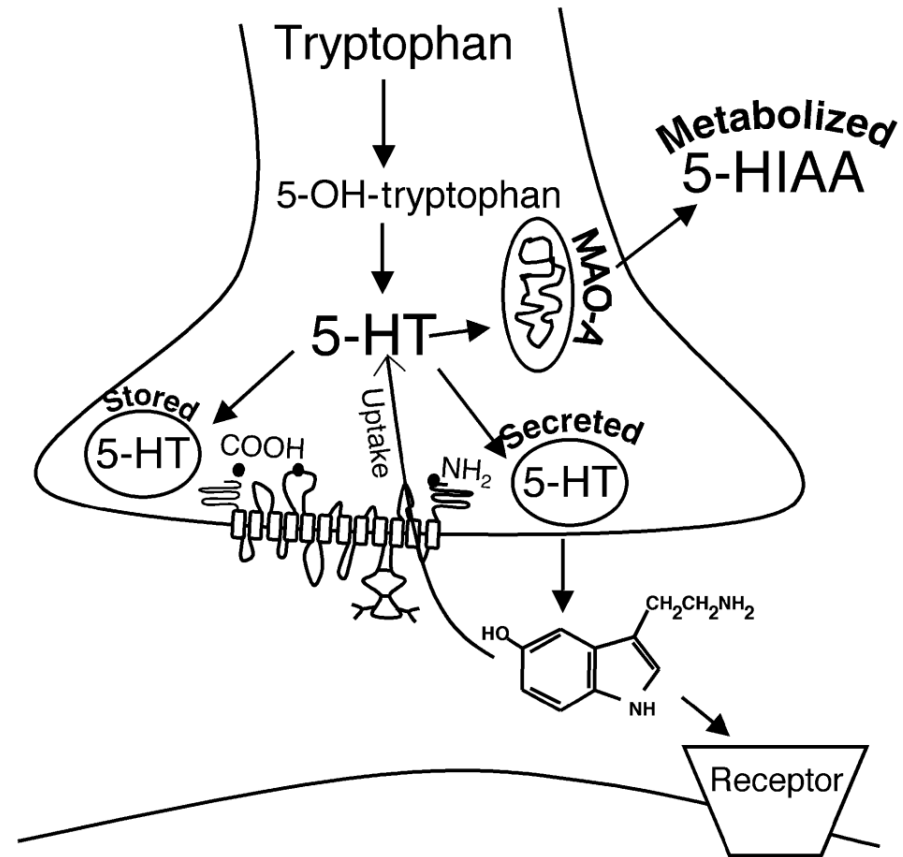
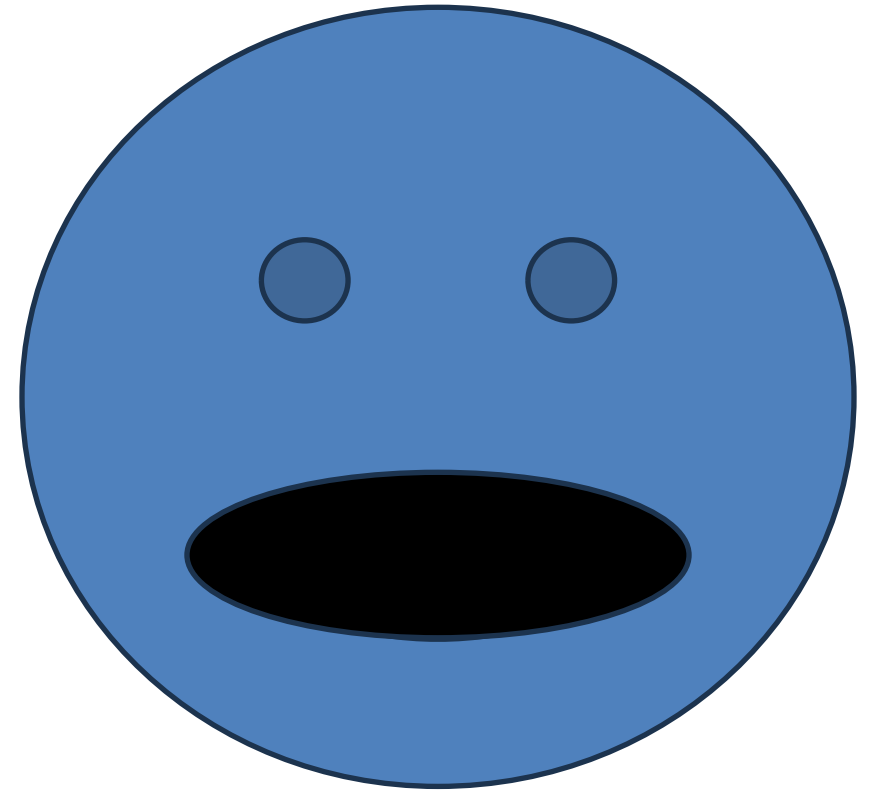
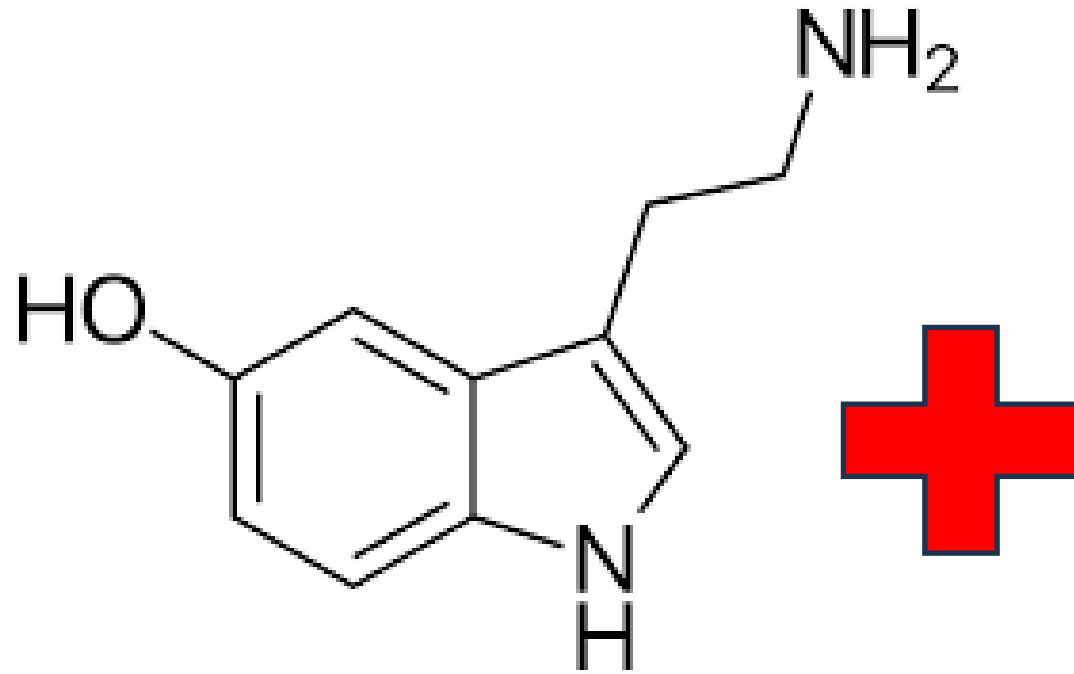


Fig. 2. Depiction of serotonergic synapse and handling of 5-HT from synthesis, storage, release, uptake via SERT and metabolism. With permission from Ni & Watts, 2003.

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Serotonin Syndrome

Scary?

Life-threatening?

Vital Instability

SEROTONIN SYNDROME - EPIDEMIOLOGY

- All age groups!
 - Consider specifically the pediatric population
- Incidence?
 - ...We don't really know 😞
 - Likely underdiagnosed, especially in outpatient settings
- In Toxic Exposure Surveillance Syndrome, an estimate of...
 - 54,410 cases of SSRI poisoning in 2016, resulting in 102 deaths
 - ~15% of these poisonings met criteria for serotonin syndrome
- Another large US dataset estimating incidence from 0.07-0.19%

SEROTONIN SYNDROME – CLINICAL FEATURES

- Clinical Triad
 - Neuromuscular Abnormalities
 - Autonomic Hyperactivity
 - Altered Mental Status
- Neuromuscular: Clonus, tremor, hyperreflexia, hypertonia
- Autonomic: Hyperthermia, tachycardia, hypertension, diarrhea
- Mental Status: Agitation, confusion, anxiety, delirium, coma

SCREENING FOR SEROTONIN SYNDROME

TABLE 3 Symptoms of serotonin syndrome by severity.

Severity	Symptoms
Mild	Anxiety, hypertension, tachycardia, hyperreflexia, diarrhoea
Moderate	Agitation, clonus, tremor, hyperthermia
Severe	Life-threatening hyperthermia, confusion, hypertonicity, respiratory failure, coma, death

Source: The Maudsley Prescribing Guidelines in Psychiatry.²²

SCREENING FOR SEROTONIN SYNDROME

Hunter Criteria

- **Replaced the Sternbach Criteria**
- 1) One serotonergic agent
- 2) One of the following conditions:
 - Spontaneous clonus
 - Inducible clonus PLUS agitation or diaphoresis
 - Ocular clonus PLUS agitation or diaphoresis
 - Tremor PLUS hyperreflexia
 - Hypertonia PLUS temperature above 38C PLUS ocular clonus or inducible clonus

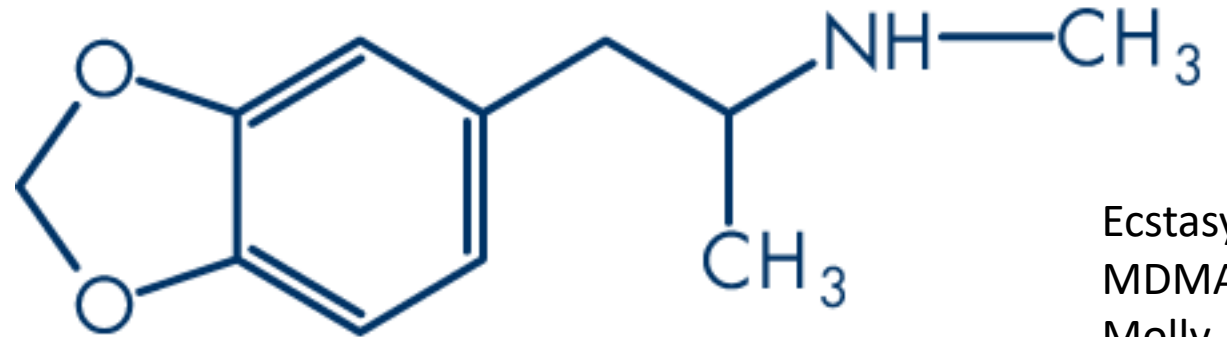
AN EXCITING CASE!

A 23yo trans male mechanic with a history of depression and cannabis use appears to your urgent care clinic with feeling tremulous and having a racing heart rate after going to a festival last night. You see that the top of his tongue is bright blue.

What are your next steps?

- History
- Physical Exam
- Labs/Workup

AN EXCITING CASE (CONT.)



Ecstasy
MDMA
Molly
Disco Biscuit



AN EXCITING CASE!

A 23yo trans male mechanic with a history of depression and cannabis use appears to your urgent care clinic with feeling tremulous and having a racing heart rate after going to a festival last night. You see that the top of his tongue is bright blue.

Dx: A combination of patient's ongoing sertraline alongside having had MDMA the prior night, causing a mild serotonin syndrome.

SEROTONIN: THE PATHWAYS

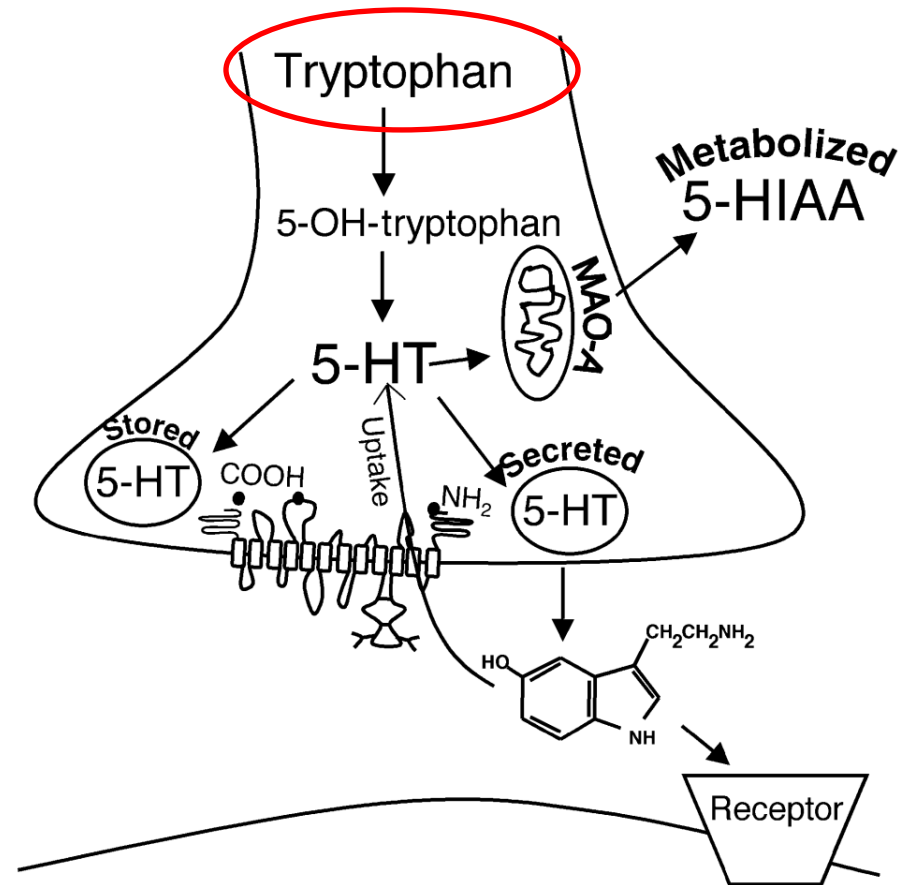
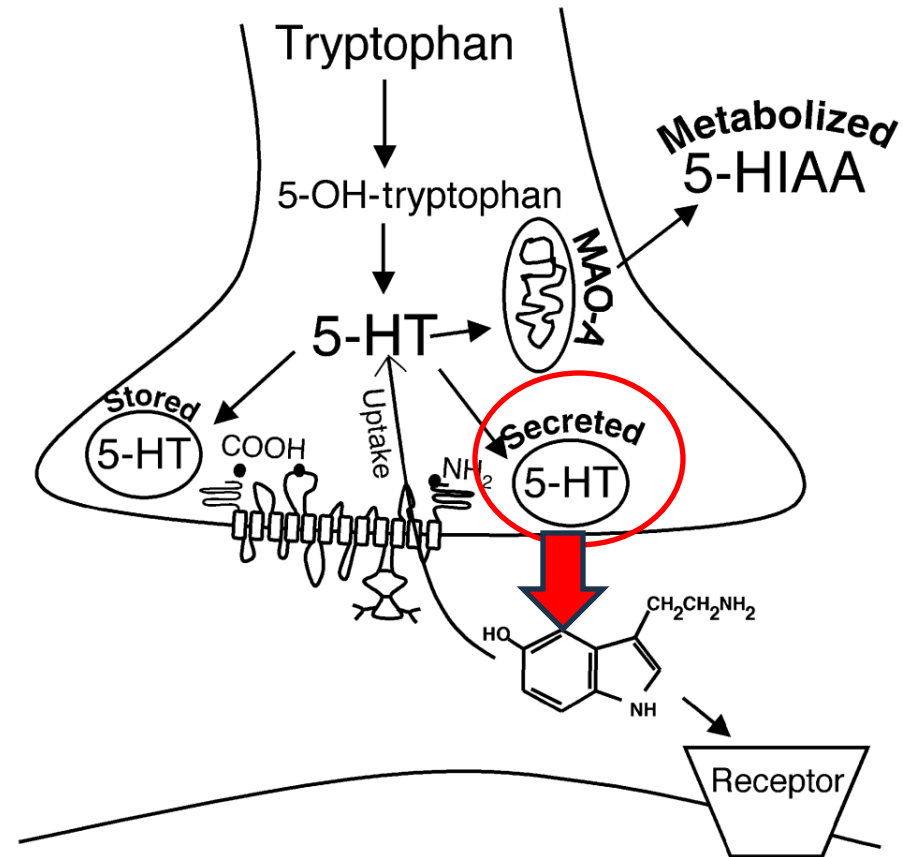


Fig. 2. Depiction of serotonergic synapse and handling of 5-HT from synthesis, storage, release, uptake via SERT and metabolism. With permission from Ni & Watts, 2003.

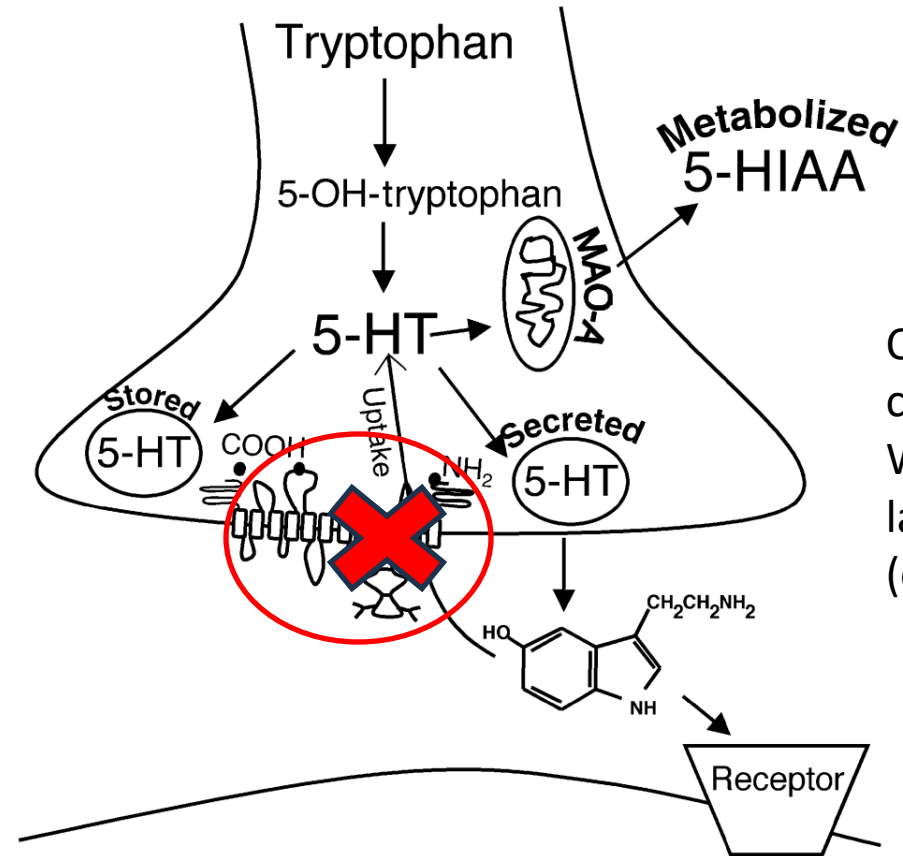
SEROTONIN: THE PATHWAYS



Amphetamines, MDMA,
cocaine, mirtazapine

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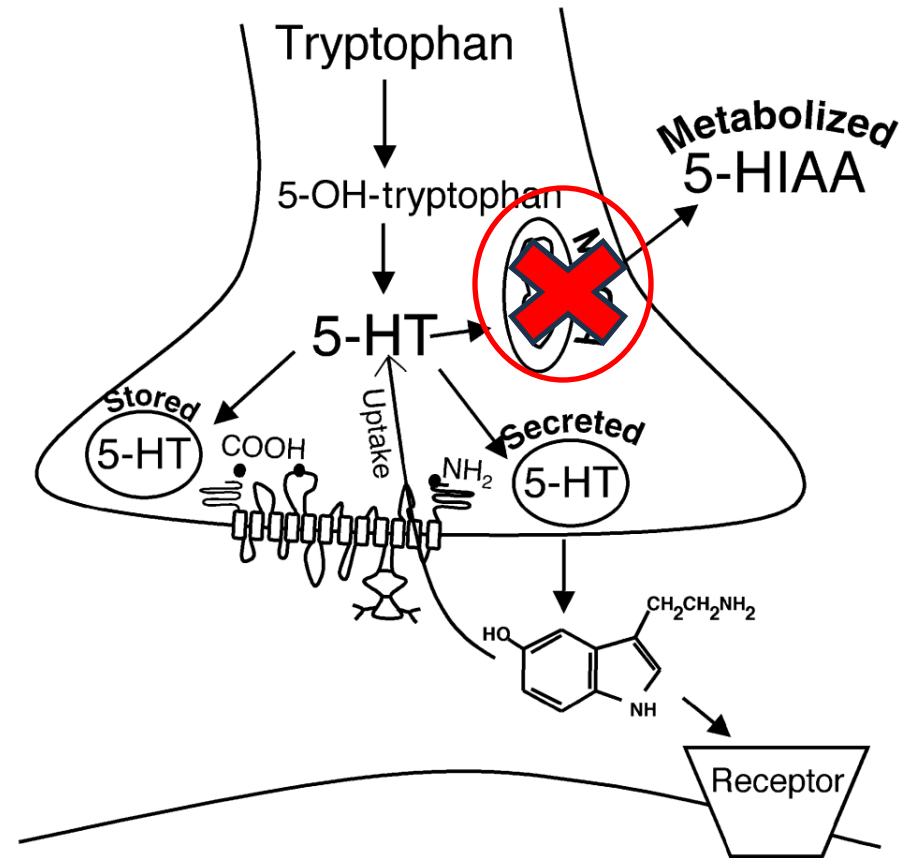
SEROTONIN: THE PATHWAYS



Cocaine, MDMA, SSRIs, SNRIs, bupropion, cyclic antidepressants (TCAs), St. John's Wort, dextromethorphan, tramadol, lamotrigine, 5-HT₃ receptor antagonists (ondansetron)

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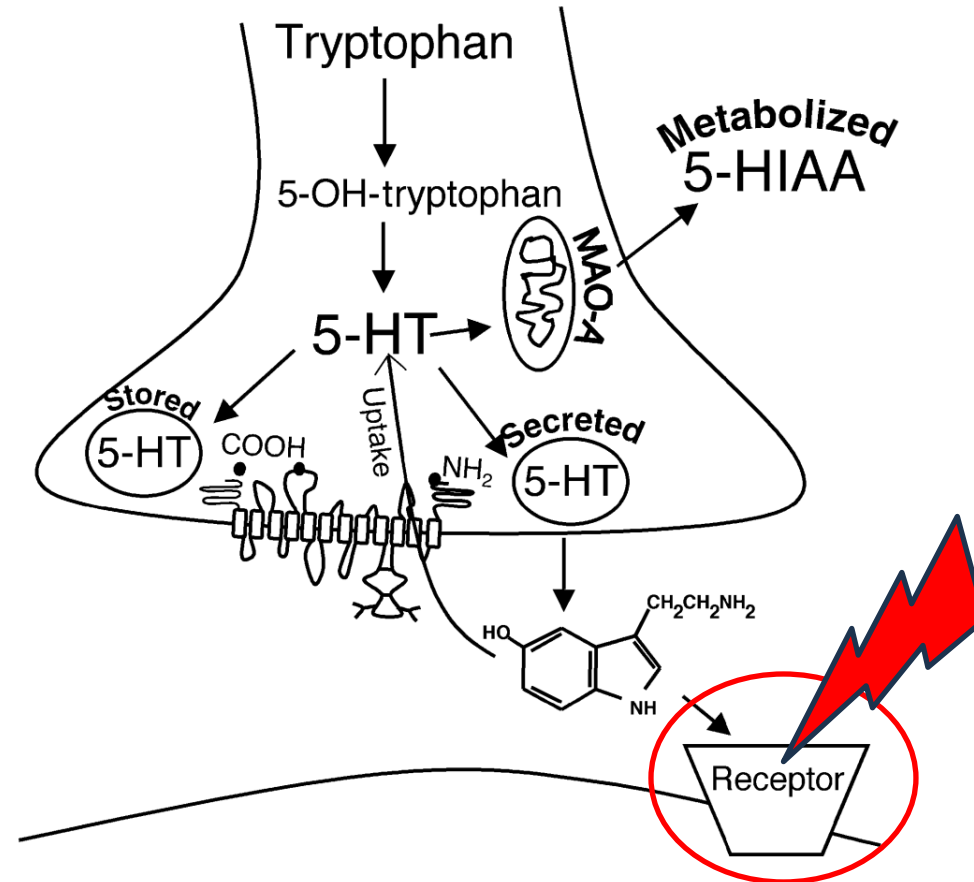
SEROTONIN: THE PATHWAYS



MAO-inhibitors

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SEROTONIN: THE PATHWAYS



Buspirone, triptans, ergot derivatives, fentanyl, LSD, metaxalone

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SEROTONIN: THE PATHWAYS

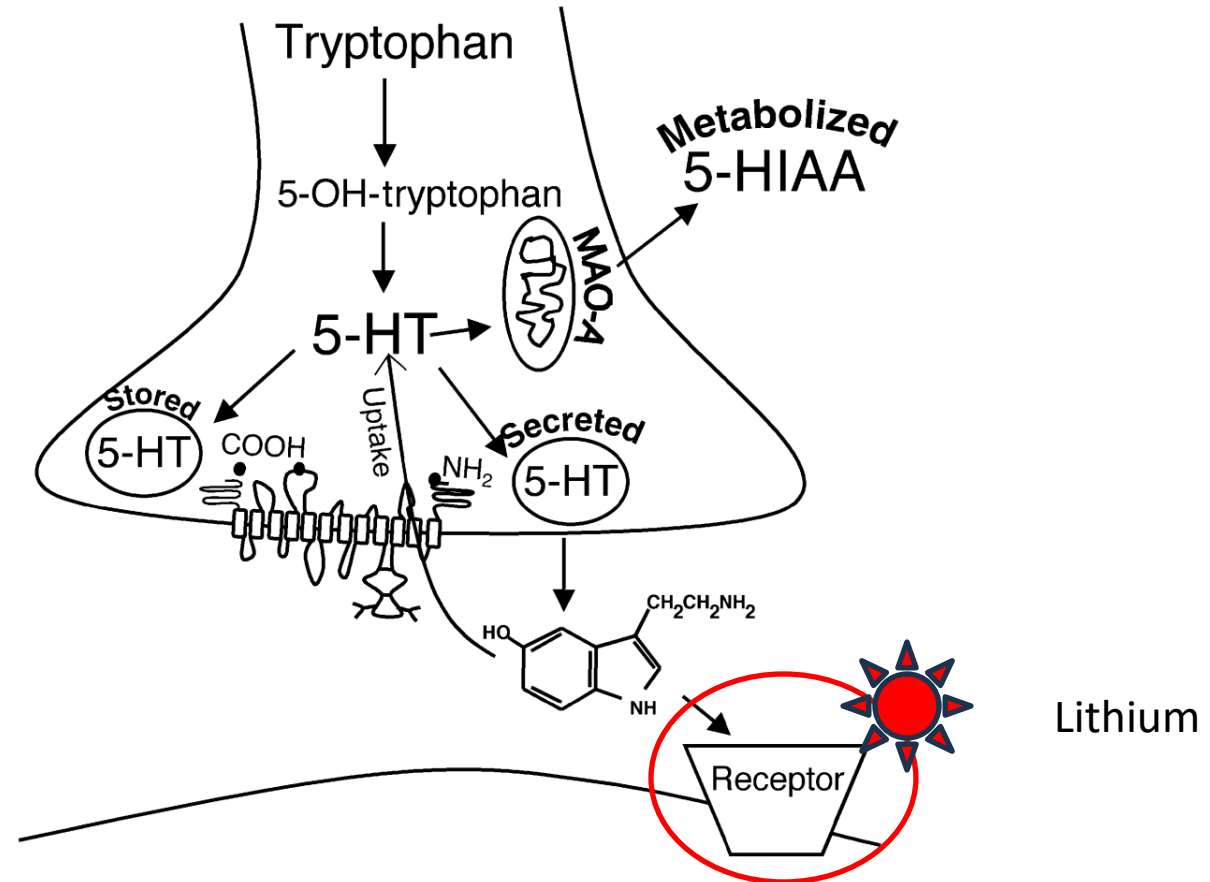


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SEROTONIN SYNDROME SUSPECTS

Mechanism	Potential Agents
Increases serotonin formation	Tryptophan, oxitriptan
Increases release of serotonin	Amphetamines, MDMA, cocaine, mirtazapine
Impairs serotonin reuptake	Cocaine, MDMA, SSRIs, SNRIs, bupropion, cyclic antidepressants (TCAs), St. John's Wort, dextromethorphan, tramadol, lamotrigine, 5-HT3 receptor antagonists (ondansetron)
Inhibits serotonin metabolism via inhibition of MAO	MAO-inhibitors
Direct serotonin receptor agonists	Buspirone, triptans, ergot derivatives, fentanyl, LSD, metaxalone
Increases sensitivity of postsynaptic serotonin receptor	Lithium

ANOTHER EXCITING CASE!

A 68yo man with a history of schizoaffective disorder appears to your clinic for a 4-day history of “muscle issues” and feeling like his heart is racing. His medication regimen is notable for recently starting a new prescription of risperidone, alongside his long-term antidepressant escitalopram.

What are the next steps?

DIFFERENTIAL

- What are other diagnoses that can resemble serotonin syndrome?

Neuroleptic Malignant Syndrome

Anticholinergic Poisoning

Acute Dystonia

Malignant Hyperthermia

Benzodiazepine Withdrawal

Thyroid Storm

The Flu

DIFFERENTIAL

Serotonin syndrome and neuroleptic malignant syndrome: Distinguishing features

	Serotonin syndrome (SS)	Neuroleptic malignant syndrome (NMS)
Onset	Within 24 hours	Days to weeks
Neuromuscular findings	Hyperreactivity (tremor, clonus, reflexes)	Bradyreflexia, severe muscular rigidity
Causative agents	Serotonin agonist	Dopamine antagonist
Treatment agents	Benzodiazepine, cyproheptadine	Bromocriptine
Resolution	Within 24 hours	Days to weeks

THE TREATMENT

- **Five Basic Principles**
- DISCONTINUE serotonergic medications!
- Supportive care targeted towards vital signs
- Benzos Benzos Benzos for sedation
- Consider serotonin antagonists
- Reevaluate serotonergic agents

REVIEW OF THE CASES – HOW TO TREAT

- 1st Case: Our patient with MDMA
 - Instructed to stop serotonin
 - Some education about MDMA and its risks of serotonin syndrome
 - Could give a short course of benzodiazepines OR sending the patient to the ED for close monitoring
 - When symptoms have abated, consider restarting antidepressant or switching to a different medication with lesser risks for SSRI
- 2nd Case: NMS Patient
 - Will take on the order of days to weeks to resolve
 - Consider referral to ED versus giving a short course of benzodiazepines
 - Risperidone likely not the best choice for the patient

PEARLS IN THE OUTPATIENT SETTING

- Avoid concurrent multiple serotonergic antidepressants
 - SSRIs, SNRIs, TCAs, MAO-Is
 - Fluoxetine (Prozac) with a lengthy half-life
 - MAO-Is needing to flush out of the system
 - Don't forget buspirone and triptans
- Always consider other substance use
- Severe SS is hard to miss, easy to differentiate from NMS
- Mild SS is easy to miss, easy to mistake for the flu
- Treatment is supportive care and discontinuing serotonin agents
 - Is it worth starting again?

THANKS SO MUCH!