CAUTIONARY REMINDER OF SEROTONIN SYNDROME RISKS IN PATIENTS RECEIVING MAT

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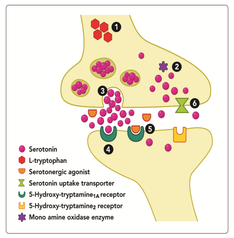
Introduction

Serotonin Syndrome (SS) is a life-threatening condition associated with increased serotonergic activity in the CNS. This can result from therapeutic medication use, drug interactions, and intentional self-poisoning.

Etiology:



1 Increased synthesis
i.e. increase substrate: L-tryptophan

2 Decreased metabolism
Monoamine oxidase inhibitors (MAOIs):
Phenelzine, Tranylcypromine, Moclobemide, Selegiline, Isocarboxazid, Linezolid, Methylene blue

3 Increased release:
Amphetamines, Cocaine, Fenfluramine, Sibutramine, Ecstasy, Phenantherene Opioids (Oxycodone, buprenorphine), Tramadol

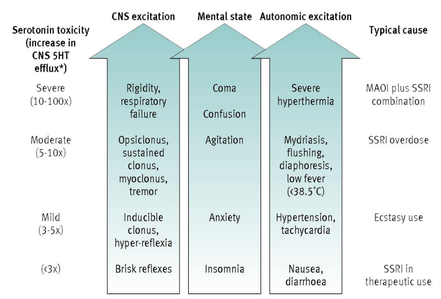
4 Serotonin (5-hydroxy-tryptamine) receptor agonism:
Buspirone, Lysergic acid diethylamide (LSD), Di-hydro ergotamine (DHE), Triptans, Mirtazapine

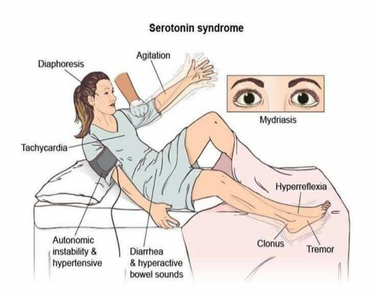
5 Increased serotonin (5-hydroxy-tryptamine) receptor sensitivity:
Lithium

6 Decreased reuptake:
Tricyclic Antidepressants (TCAs):
Amitriptyline, Imipramine, Clomipramine, Desipramine, Doxepin
Selective serotonin reuptake inhibitors (SSRIs):
Paroxetine, Sertraline, Fluoxetine, Fluvoxamine, Citalopram, Escitalopram
Serotonin noradrenaline reuptake inhibitors (SNRIs):
Venlafaxine, Duloxetine, Milnacipran
Other Antidepressants:
Trazodone, Nefazodone
Opioids:
Fentanyl, Methadone, Meperidine, Dextromethorphan, Tramadol
Miscellaneous:
Ondansetron,Granisetron, St. John's Wort

Classically associated with simultaneous administration of 2 serotonergic agents, but it can occur after initiation of a single serotonergic drug or increasing the dose of a serotonergic drug in individuals with serotonin sensitivity.

Clinical Features:



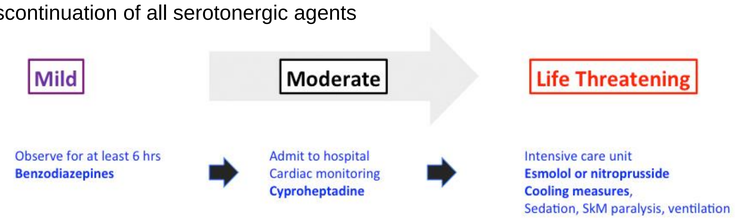


Diagnosis:

Hunter Serotonin Toxicity Criteria	Labs
Patient has taken serotonergic agent AND meets one of the following criteria: - Spontaneous clonus - Inducible clonus + [agitation or diaphoresis] - Ocular clonus + [agitation or diaphoresis] - Tremor + hyperreflexia - Hypertonia + temperature > 38 C + [ocular clonus or inducible clonus]	**Solely clinical diagnosis.** **No confirmatory labs.** **Monitor for complications:** **- Elevated WBC** **- Elevated creatine phosphokinase** **- Decreased serum bicarb**

Treatment:

Discontinuation of all serotonergic agents



Case Presentation

26yo male presents to the clinic with complaints of new onset motor tics, tremors, and hyperactivity. He has a PMH of anxiety and depression. Four days ago, he was started on SSRI, sertraline 50mg qd. Patient also is on Medication Assisted Treatment (MAT) for the past 2 years, for a prior opioid abuse history. He receives monthly Sublocade injections.

Clinic Course:

Physical Exam:
- General: diaphoretic, flushed, tremulous
- Cardiac: tachycardiac
- Neuro: AAOx3, CN 2-12 grossly intact, No focal numbness or weakness, Negative Babinski, Negative Clonus, Positive hyperreflexia (patellar reflex +4 bilaterally)
- Psych: anxious mood, agitated behavior, normal thought process

Point of Care EKG:
- Sinus tachycardia, with no other acute abnormalities

Clinical suspicion:
- Positive Hunter Serotonin Toxicity Criteria.
- Urgently transferred patient to ED for further care.

ED Course:

Labs:
- CBC, CMP, urinalysis, urine drug screen, serum alcohol were all unremarkable

Management:
- For mild Serotonin Syndrome
- Received IV fluids hydration
- Received low dose Ativan 0.5mg
- Monitored for 6 hours
- Symptoms normalized
- Discharge to home, with SSRI on hold

Clinic Follow-up:

- Culprit SSRI, sertraline was held for one week, before restarting another SSRI at low dose, escitalopram 5mg, and gradually titrated up as needed, while watching for repeat SS signs.

Discussion

- This case illustrates a patient who was started on sertraline for depression & anxiety and soon developed SS, due to medication interactions with Sublocade, which he was receiving for MAT.
- Sublocade is buprenorphine (an opiate) in an extended-release monthly injection, indicated for the treatment of opioid use disorder.
- The proposed mechanism for buprenorphine's serotonergic action is an inhibition of GABA-ergic neurons that are known to decrease serotonin release. This disinhibition results in increased serotonin release.
- Opioid use disorder is often associated with mental health comorbidities. These patients receiving MAT are likely also on psychiatric medications. And this polypharmacy combination poses risks for serotonin toxicity.
- As more serotonergic drugs become available, the incidence of adverse drug reports increase. The true incidence of SS is unknown, as it's underdiagnosed. Reasons include that SSRIs are not the sole culprits for SS, symptoms are nonspecific, and more than 85% of physicians are unaware of which drug combinations may cause SS.

Considerations:

- SS is easier to prevent than treat. Clear and frequent communication is crucial amongst prescribing providers for their at-risk patients, regarding new medication changes.
- When choosing/switching serotonergic agents, attention should be given to their half-life, watching what drugs with longer bioavailability can pose higher serotonergic risks (i.e. fluoxetine).
- Further research also warranted to explore SS risks in different MAT options comparatively. Sublocade, Suboxone (buprenorphine with naloxone), and Vivitrol (naltrexone) all are options for opioid use disorder. All three can precipitate SS, but future studies may help understand which poses higher risk

Conclusion:

- Patients on MAT and receiving psychiatric medications need to be carefully managed for medication changes, to avoid increased serotonergic activity as a side effect, which may lead to serotonin toxicity.

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