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Serotonin Syndrome

Description: Serotonin Syndrome can be a life-threatening event. It is due to excess serotonergic activity in the CNS. It can be precipitated by medication interactions, accidental overdoses, or after self-poisoning.

Meds Involved: Look for it in patients on multiple Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Reuptake Inhibitors (SRIs), recent changes to a single SSRI, or drugs that increase serotonergic neurotransmission in some way. For example, the MAOI's inhibit serotonin breakdown. LSD and L-tryptophan serve as precursors of serotonin. Finally, some drugs, like cocaine, the amphetamines, and lithium, can enhance serotonin release. The following are commonly associated with serotonergic excess — **Tryptophans, MDMA (Ecstasy), Meperidine, Tramadol, SSRIs, SNRIs, DNRI, Serotonin Modulators, Tricyclic antidepressants (TCADs), St. John's wort, ondansetron (Zofran), Reglan, Valproate, Carbamazepine, Dextromethorphan, Cyclobenzaprine, Buspirone, the Triptans, Ergots, Fentanyl, LSD, and Lithium.**

Serotonin's Actions in the Body: Serotonin is a neurotransmitter that is involved in mood, attention, behavior, heat regulation, gut motility, vasoconstriction, uterine contraction, platelet aggregation, and bronchoconstriction.

Pathophysiology: Multiple postsynaptic serotonin receptors are thought to be involved in the development of SS— specifically 5-HT1A and 5-HT2A.

How to diagnose: This is a clinical diagnosis based on patient's history and symptoms. No test can definitively prove it. Pay close attention to patient's history, medication history, and psychiatric history. Also, there are 3 types of clinical manifestations: **think "CAN" => CNS dysfunction, autonomic dysfunction, and neuromuscular dysfunction.** In general, the diagnosis is one of exclusion, and should be considered in patients taking combinations of serotonergic drugs; in those where doses have been recently changed; and in acute ingestions of serotonergic agents.

Pertinent History: As above and be sure to ask exact dose and formula of medications, recent medication changes, and recent dosing changes. The time of onset of symptoms is relevant, as SS can progress rather rapidly.

Physical Examination: **Tachycardia**, hypertension, **fluctuations in blood pressure**, **hyperthermia**, ocular clonus, **hyperreflexia and myoclonus that are more pronounced in the legs than in the arms**, muscle rigidity, dry mucous membranes, bilateral babinski, flushed skin, increased bowel sounds, dilated pupils.

Pearls and Pitfalls: Serum Serotonin levels don't correlate with extent of syndrome and take too long to return usually. Don't give tylenol for the fever as it is more so due to metabolic activity vs re-setting temperature set-point in brain (cooling works best).

The worst pitfall for me: not doing aggressive medical care: fluids, cooling, intake/output, management of rigidity/myoclonus with BDZ, etc

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Duration: Symptoms usually resolve within 24 hours of stopping serotonergic med; can be longer when drugs have active metabolites or after overdoses.

DDx:

1. **Anticholinergic Toxicity** (muscle reflexes are normal in Anticholinergic Tox)
2. **Malignant Hyperthermia** (exposure to halogenated anesthetics and succinylcholine during intubation; ask about family hx)
3. **NMS** (NMS is a longer course, bradyreflexia, usually no myoclonus, nine-day course of syndrome vs 24-hr seen in Serotonin Syndrome; high mortality)
4. **Encephalopathies** (but tremors, hyperreflexia and clonus that are greater in the lower extremities, ocular clonus, and increased tone are typically NOT seen w/ an infectious cause of delirium)

Diagnostic Studies: Again, these are more for monitoring than anything else; let clinical judgement be the guide for which to order but it is important to consider:

CBC, CMP, CPK, Coags, Blood Cx, UA (blood, myoglobin presence), CXR, CT Brain, LP

Diagnostic Criteria: Hunter Toxicity Criteria Decision Rule (84% Sens/97% Spec): Pt has taken a Serotonergic agent and at least **ONE** of the following:

1. Spontaneous Clonus
2. Tremor PLUS Hyperreflexia
3. Hypertonia PLUS temp above 38 + ocular clonus or inducible clonus
4. Inducible clonus PLUS agitation or diaphoresis
5. Ocular Clonus PLUS agitation or diaphoresis

Therapy:

1. D/c serotonergic agents (see above)
2. Supportive care (IV Fluids),
3. Sedate w/ benzos (specifically **5-10 mg of IV Diazepam**)
4. If unresponsive to supportive measures consider **Cyproheptadine** (non-selective serotonin antagonist) as **4 mg tabs or 2mg/5 mL syrup**. No IV formulation so patient may need OG or NG tube
5. GCS <12, pt should probably be intubated as at increased risk for aspiration
6. If significantly hyperthermic pt may require paralysis and intubation. The syndrome usually resolves within 24 hours.

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