Serotonin Syndrome

Characteristics: A rare but potentially life-threatening drug reaction that can range from mild to severe. Presents with muscle rigidity (typically hypertonicity, hyperreflexia, clonus), hyperthermia, and altered mental status. While very similar to neuroleptic malignant syndrome (NMS) in presentation, serotonin syndrome typically has a much more acute onset (drastic change from baseline within three to four hours).

Meds That Cause It: Any drugs that can increase serotonin activity either with increased serotonin release, inhibition of serotonin metabolism, inhibition of serotonin reuptake, or activation of serotonin receptors. Most common culprits include MAOIs, SSRIs, SNRIs, buspirone, lithium. Consider nonpsychiatric medications that can have serotonergic effects (eg, fentanyl, meperidine, tramadol, linezolid, dextromethorphan).

Mechanism: Excess serotonergic activity.

General Management:

- Discontinue any serotonergic medications.
- Consider differential diagnoses, including NMS.
- Monitor vital signs and creatinine kinase levels to assess severity and guide supportive care, including stabilizing vital signs and providing intravenous fluids if necessary.

First-Line Medications:

Benzodiazepines. Any of them will work (eg, lorazepam [Ativan] 0.5–1 mg BID or diazepam [Valium] 10 mg BID).

Second-Line Medications:

Cyproheptadine (Periactin) 12 mg followed by 2 mg Q2 hours until improvement, then 8 mg Q8 hours until resolution.

Clinical Pearls:

- The combination of triptans (eg, sumatriptan) and other serotonergic medications like SSRIs will often trigger an alert in your EMR or at the pharmacy. While triptans are serotonergic, they are fairly weakly serotonergic and typically taken sporadically. Hence, this combination is less likely to result in serotonin syndrome.
- Caution with CYP450 inhibitors, which can raise levels of serotonergic medications and thereby increase risk of serotonin syndrome.
- The most severe cases of serotonin syndrome often involve MAOIs combined with other serotonergic agents or overdose situations involving serotonergic drugs.
- Clonus is more specific to serotonin syndrome (vs "lead pipe" rigidity seen in NMS) and presents as involuntary, rhythmic muscle contractions. Clonus tends to happen more in the lower rather than upper extremities, so be sure to check the patient's legs (flex the patient's foot upward and look for a rhythmic beating of the foot and ankle).
- Avoid using cyproheptadine if anticholinergic syndrome cannot be ruled out as it may exacerbate.
- Patient may be restarted on serotonergic medication 24–48 hours after complete resolution, but limit number of serotonergic agents and use minimally effective dose.

Not-So-Fun Fact:

MDMA (ecstasy) in combination with SSRI can lead to serotonin syndrome. This has been a factor in a number of deaths, particularly in adolescents and young adults, at popular music festivals.