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Topic: Serotonin Syndrome

**Libby Zion and serotonin syndrome
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Case: An 18 year old college freshman in Vermont with a history of depression. She had been prescribed several medications including phenelzine, a MAOI inhibitor. She developed URI symptoms and febrile illness. She deteriorated and was admitted to a hospital in New York with a diagnosis of viral syndrome with hysterical features. She became increasingly agitated and febrile. She received injections of meperidine, haloperidol and was placed in physical restraints. She continued to worsen. Her last recorded temperature was 107F. She later suffered a cardiac arrest and died. The cause of death was thought due to **serotonin syndrome**.

Investigation of the case focused heavily on the administration of meperidine to sedate her as a potential

Why is this case so notorious? It led to a change in resident duty hours. The PGY1 and PGY2 residents involved in the case had been awake for many hours. This led to the creation of the Bell Commission which recommended strict new resident duty hours that were eventually adopted by the ACGME.

Serotonin syndrome

- Serotonin AKA 5-Hydroxytryptamine (5-HT) is a neurotransmitter active in the CNS and periphery involved with everything; mood, motor function, appetite, temperature, vomiting, pain, sleep, cognitive/sexual function, vascular tone
- Medications that utilize serotonin; SSRIs (selective serotonin reuptake inhibitors) affecting mood, triptans targeting pain perception and a serotonin antagonist, ondansetron, to treat vomiting.
- **Should we call it serotonin toxicity instead?** Unlike neuroleptic malignant syndrome which is an idiosyncratic reaction, serotonin syndrome stems from an excess of serotonin at the receptors. It is an anticipated effect when there is increased serotonin at the receptors.
- How do you get increased serotonin in your body?
 - Inhibition of serotonin metabolism. Example: Monoamine oxidase inhibitor such as linezolid (antibiotic utilized for MRSA and VRE).
 - Decreased re-uptake of serotonin. Example: SSRIs
 - Increased production. Example: taking dietary supplement such as 5-hydroxytryptophan (a precursor to serotonin).
 - Direct stimulation of serotonin receptors.
 - Some disease states such as hypertension, atherosclerosis and hyperlipidemia may decrease the amount of monoamine oxidase available.
 - Also medications are often metabolized through cytochrome p450 system. Patients with lower amounts of this enzyme due to phenotype or inhibition secondary to other medications may be at increased risk of serotonin syndrome.
- Wide spectrum of disease, very severe cases are rare. Many probably go undiagnosed and frequently resolve within 24 hours.
- **Discontinuing and starting a new drug?** Did the patient recently discontinue any medications? Need a period of time to washout the drug. For example, Prozac not only has a long half life but an active metabolite. Should wait at least 5 weeks prior to starting a new serotonergic medication.
- **The worst offenders?** Monoamine oxidase inhibitors: St. John's wort, linezolid.
- **Defining features of serotonin syndrome?** Clinical diagnosis, no lab tests available. Need to exclude other causes of symptoms such as infection.
 - **Three cardinal features:**
 - **Neuromuscular effects:** hyperreflexia, myoclonus, hypertonia, rigidity, characteristically more pronounced in lower extremities.
 - **Autonomic effects:** hyperthermia, tachycardic, diaphoretic, flushing, mydriasis.
 - **Mental status effects:** anxiety, agitation to confused/altered.
- **Differential diagnosis?** Several decision rules available.
 - Sternbach's Criteria.
 - Hunter Serotonin Toxicity Criteria; most accepted and easiest to use.Basically, if any patient has spontaneous clonus and has taken a serotonergic agent, it is serotonin syndrome.
- **Treatment?** Supportive care. Benzodiazepines. Although some suggest anti-psychotics (which are 5-HT receptor antagonists), if the diagnosis is unclear (for example: these patients may be on multiple agents including SSRIs, cocaine, antipsychotics) would advise against it as administration of haloperidol in neuroleptic malignant syndrome may make things much worse.
- **What about cyproheptadine?** Oral administration only (tablets, NGT/OGT). Initially marketed as anti-pyretic due to H1 antagonist. Now mostly used for suspected serotonin syndrome. However, literature supporting a benefit is limited and most of these cases will probably resolve naturally. Start with 8 or 12mg po. Serial doses, repeat 4 mg po q 4h.

Table 1

Drugs implicated in severe serotonin syndrome*

| <i>Drug</i> | <i>Mechanism</i> |
|---|-----------------------------|
| L-Tryptophan | Serotonin precursor |
| Selective serotonin reuptake inhibitors | Inhibit serotonin reuptake |
| Tricyclic antidepressants | Inhibit serotonin reuptake |
| Monoamine oxidase inhibitors (A>B) | Inhibit metabolism of 5-HT |
| Pethidine | Serotonin agonist |
| Tramadol | Inhibits serotonin reuptake |
| LSD | Partial serotonin agonist |
| Bupropion | Partial serotonin agonist |
| Amphetamines and anorectics | ↑5-HT release & ↓reuptake |
| Atypical antidepressants | Various |
| St John's wort | All of the above? |
| Lithium | Unknown |

* Note: Interactions are more severe between drugs with different mechanisms of increasing serotonin.