SEROTONIN SYNDROME PRECIPITATED BY COMBINATION OF FLUOXETINE AND ARIPIPRAZOLE

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INTRODUCTION

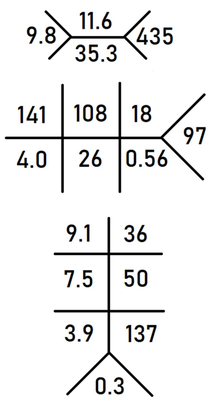
Serotonin syndrome is a neurological condition caused by excessive serotonergic activity in the central nervous system. Most commonly it is secondary to intentional or unintentional overdose of serotonergic medications. Less commonly it can be due to medication interactions. Patients will often exhibit mental status changes, autonomic instability, and neuromuscular changes. The diagnosis is clinical and often based on the Hunter Criteria, as it tends to have the best diagnostic accuracy in studies. Serotonin syndrome is possible at any age and prevalence has increased with increasing use of serotonin modulating medications. To fulfill the Hunter Criteria, patients must have taken a serotonergic agent and meet at least one of the following[1]:

- Spontaneous Clonus
- Inducible clonus + agitation or diaphoresis
- Ocular clonus + agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia
- Temperature above 38°C (100.4°F) + ocular clonus or inducible clonus

PATIENT PRESENTATION

10 year-old male with history of ADHD, MDD, and eczema presented for four days of tremors, bilateral arm posturing, restlessness, intermittent confusion, unsteady gait, trouble feeding himself. His parents denied facial flushing or diaphoresis. His parents reported he initially presented to outside ED 3 days prior and was diagnosed with serotonin syndrome at that visit. He was given a dose of lorazepam and discharged home with initial improvement, but he was instructed to keep taking fluoxetine. His symptoms recurred so he presented for further evaluation. Patient's other relevant medications included aripiprazole 5mg PO daily, dexmethylphenidate 20mg PO daily, and serdexmethylphenidate/dexmethylphenidate 53.2-10.4mg PO daily.

Temp 98.3F HR 112 RR 20
BP 120/87 O2 99% on room air



General: No distress, calm and cooperative with exam
Psych: Slow to respond on questioning, oriented to person, place, situation. Good eye contact but did have some intermittent ocular clonus
HEENT: PERRL with sluggish response and mild dilation 6mm at baseline to 4mm on light exposure
MSK: 5/5 strength noted to bilateral upper and lower extremities on push and pull when tested at shoulders, elbows, hips, knees, and ankles. Was able to ambulate in room without issues, and was able to stand on his toes and stand on his heels without issues.
Neuro: Hyperreflexic throughout, 3 beats of clonus per strike with reflex hammer on exam to patella and Achilles. Plantar reflex downgoing bilaterally.

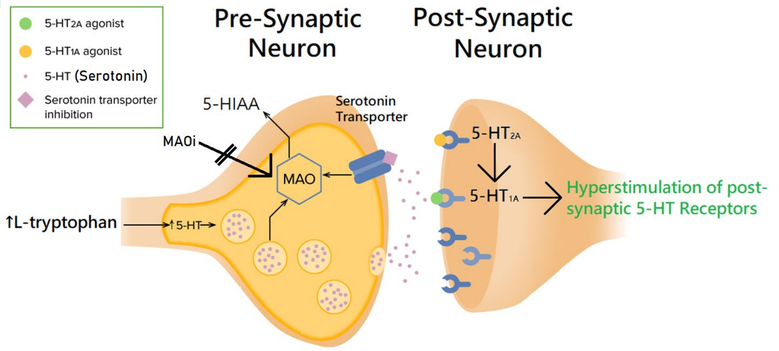
HOSPITAL COURSE

Patient was admitted to the hospital, all serotonergic medications were held. He was given lorazepam 1mg by mouth twice a day. Fluoxetine and aripiprazole, methylphenidate, and methylphenidate/serdexmethylphenidate were all held on discharge until follow-up with primary care physician. Patient was discharged on lorazepam 1mg by mouth twice a day for five additional days. On discharge symptoms improved significantly, but mild residual intention tremors persisted.

TREATMENT[2]

Regardless of severity, the first step is to hold all potentially serotonergic medications. Antipsychotic medications should be avoided as well, especially atypical antipsychotics.
Mild and moderate cases can be treated with supportive care.
Severe cases can be treated with benzodiazepines and/or cyproheptadine.

Figure 1 Diagram of serotonin modulation at pre- and post-synaptic



PATHOPHYSIOLOGY

Serotonin syndrome is uncommon on single serotonin modulating agents at typical dosages, but risk increases with combining agents that are known to increase serotonin activity at the post-synaptic membrane[2].
As demonstrated in figure 1, the etiology of serotonin syndrome is over-stimulation of the two major post-synaptic serotonin receptors: 5-HT1A and 5-HT2A. However, the exact cause of the over-stimulation can occur through a multitude of mechanisms[2]. The most common reason is combining multiple serotonergic modulators. Potential culprits include agents like SSRIs and SNRIs that increase serotonin availability in the synaptic cleft, agents like buspirone that can act directly on post-synaptic receptors, agents with off-target serotonin activity like atypical antipsychotics, or even agents like MAOis that prevent pre-synaptic serotonin degradation[2] (see table 1). Drug-drug interactions are another potential issue, since inhibition of normal metabolism in the liver of one agent caused by another can result in a supratherapeutic response from a standard dose.

Table 1. An inexhaustive list of agents that can precipitate serotonin syndrome[1]

SSRIs & SNRIs	Cocaine	Methylene blue	5-HT3 antagonists	TCAs	Linezolid
Amphetamines	LSD	Tryptophan	St. John's Wort	Buspirone	Ergot Derivatives
Methylphenidates	Trazodone	MAO inhibitors	Cyclobenzaprine	Linezolid	Vortioxetine
Triptans	Buproprion	Lamotrogine	Mirtazapine	Merperidine	Selegeline
MDMA	Tramadol	Dextromethophan	Metaxolone	Lithium	Fentanyl

DIFFERENTIAL DIAGNOSIS[2]

Other Toxidromes:
- Malignant Hyperthermia
- Anticholinergic Toxicity
- Neuroleptic Malignant Syndrome
- Sympathomimetic Toxicity
- Alcohol or benzodiazepine withdrawal
- Acute dystonic reaction

Infectious Causes:
- Meningitis
- Encephalitis
- Gastroenteritis

Endocrine Causes:
- Thyroid Storm

DISCUSSION

The patient presented in this case had several distinct factors increasing his risk for serotonin syndrome including his specific combination of prescription medications as well as the concomitant administration of multiple serotonergic agents. It is also possible that his case was complicated by the prolonged half-life of fluoxetine[4]. Aripiprazole is an atypical antipsychotic, but it does have high affinity for both the 5-HT_{1A} and 5-HT_{2A} receptors[5]. Dexmethylphenidate has a known risk factor to increase the potency of serotonergic medications when administered in combination[6], and serdexmethylphenidate is simply a pro-drug that is metabolized into dexmethylphenidate[7].
Furthermore, and perhaps most importantly, there is also a reported interaction in the cytochrome P450 system when fluoxetine and aripiprazole are co-administered. Both medications undergo competitive metabolism via the CYP2D6 enzyme in the liver and cases of supratherapeutic levels of aripiprazole have been reported when co-administered. To complicate matters even further, some individuals have genetic mutations that can either upregulate or downregulate activity of the CYP2D6 enzyme[8].

CONCLUSIONS

In this poster, we have reviewed a case which demonstrates a potentially under-recognized cause of serotonin syndrome via competitive metabolism in the CYP450 system. Serotonin syndrome is a condition with varying severity and multiple potential etiologies. It is essential to understand the medications and conditions that can precipitate serotonin syndrome and perhaps even more important to understand some of the less intuitive causes, such as drug-drug interactions and medications that have serotonergic activity that one would not initially expect.

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