Serotonin Syndrome in COVID-19: Polypharmacy with Paxlovid and Kratom

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INTRODUCTION

- With the spread of COVID-19, the Food and Drug Administration granted emergency use authorization to Paxlovid **(nirmatrelvir/ritonavir)** for treatment of mild to moderate COVID-19 infection
- Paxlovid, while overall safe, is a potent cytochrome P450 (CYP) 3A4 inhibitor
- The increasing use of multiple treatment modalities, including complementary and alternative medicine, raises the risk of interactions and toxicity
- Kratom, derived from the tropical evergreen Mitragyna speciosa, has bioactive alkaloids mitragynine (MG) and 7-hydroxymitragynine (7-HG) that act as partial opioid receptor agonists

PRESENTATION

A 55-year-old female, with a history of bipolar disorder, presented to the emergency department for altered mental status after a positive COVID-19 PCR test.

- Reported adherence to home medication regimen of quetiapine 600 mg and metoprolol 50 mg
- Initiated Paxlovid for mild COVID-19 infection on day 2 of symptom presentation
- Her PCP appropriately reviewed interaction between Paxlovid and quetiapine, and recommended she discuss a temporary dose adjustment with her psychiatrist
- The patient did not adjust the dose, and later reported reported headaches, vertigo-like symptoms, and weakness
- Her husband noticed that she became confused and diaphoretic, and he became concerned when she became agitated

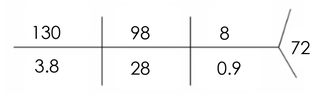
On ED Presentation

T: 36.3 °C BP: 189/86 HR: 121 O2 %: 96% on RA

- Examination demonstrated confusion (alert and oriented to name only), marked facial flushing, and mild hypertonia
- Differential for the constellation of symptoms included hyperactive delirium, atypical migraine, hypertensive emergency from ingestion, and dehydration
- Psychiatry was consulted for management of agitation in the ED

LABS

Hospital Day 1:



Urine toxicology: negative
Acetaminophen: <1 Aspirin: <1
LFTS: wnl
ABG: 7.34 / 32 / 100 / 28

EKG: Normal sinus rhythm
CT Head: no abnormalities

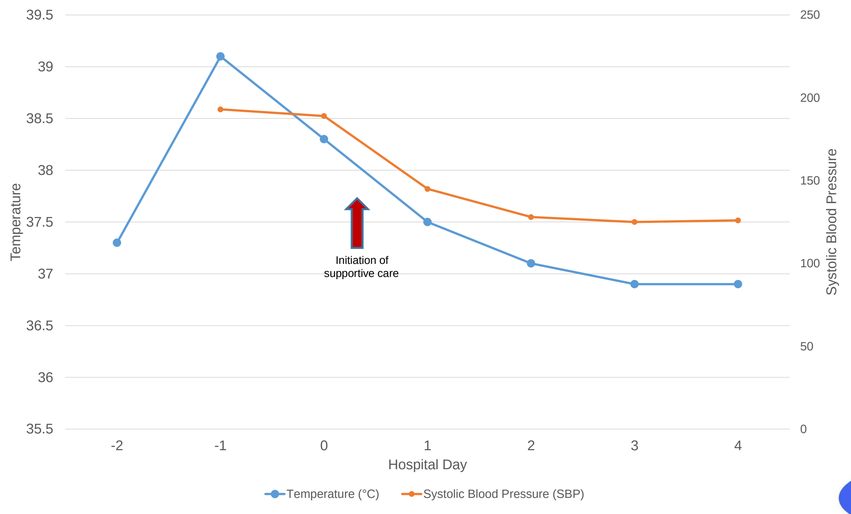


Figure 1: Fever curve and systolic blood pressure charted through hospital course

HOSPITAL COURSE

- Patient received intravenous 0.9% normal saline at 100 mL/h for 10 h daily
- IV Lorazepam was administered twice to target anxiety
- On further exam, inducible lower extremity clonus was elicited
- Collateral information was obtained: the patient's sister revealed that the patient had concurrently taken kratom, which she had used with effect for peri-menopausal symptoms, at a reported dose of 5 mg twice a day.
- Kratom use, given its known action as a CYP3A4 inhibitor, suggested serotonin syndrome as the diagnosis
- Team recommended discontinuation of quetiapine, Paxlovid, and kratom
- Standard strength acetaminophen was used on a parenteral basis to treat the headache
- With close monitoring and supportive care, the autonomic instability, confusion, and musculoskeletal exam findings resolved rapidly

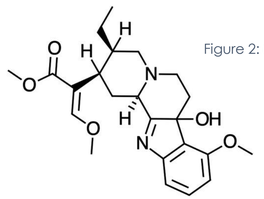


Figure 2: Molecular structure of mitragynine, one of the psychoactive alkaloids in kratom

DISCUSSION

- Serotonin syndrome may be caused by individual or combined administration of serotonergic agents
- The US product label for quetiapine recommends reduction to one sixth of the original dose if co-administered with a potent CYP3A4 inhibitor
- Limited evidence exists of serotonin syndrome with quetiapine monotherapy
- Given presenting symptoms of inducible clonus, confusion, autonomic instability, and hypertonia, the patient met Hunter Serotonin Toxicity Criteria

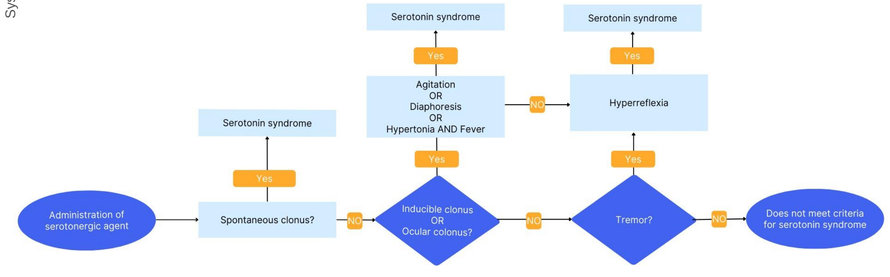


Figure 3: Hunter Serotonin Toxicity Criteria

- Evidence exists for drug toxicity in instances concomitant administration of Paxlovid and tacrolimus, which is also metabolized by CYP3A4 enzyme
- No cases have yet been reported of serotonin toxicity in the setting of Paxlovid usage
- Discontinuation of Paxlovid reduces CYP3A4 inhibition by up to 60% in the first 24 hours and up to 90% by Day 5
- Co-administration of multiple CYP3A4 inhibitors can cause serotonin syndrome, even when the dose of the serotonergic agent is stable
- Use of nirmatrelvir/ritonavir in patients treated with serotonergic agents can be considered with a proactive plan to minimize toxicity risk by empirically modifying the dosing during use

SELECTED REFERENCES

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