CLINICAL VIGNETTE

Serotonin Syndrome Caused by Mirtazapine and Quetiapine in a Patient with COVID-19

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Case Presentation

An 84-year-old male with a history of schizoaffective disorder, hypertension, hyperlipidemia, hypothyroidism, and atrial fibrillation presented to the emergency department after sustaining a ground-level fall at his home. The patient had been in his usual state of health when he "tripped and fell" while walking to the restroom at night. He could not identify a specific environmental hazard that led to the fall. He denied any new symptoms preceding the fall, including pre-syncopal symptoms, palpitations, or chest pain. There was no loss of consciousness, head trauma, or confusion were noted by the patient's niece, who drove him to the hospital. He is independent with all activities of daily living at baseline. Home medications include quetiapine (total daily dose: 625 mg), mirtazapine 30 mg nightly, levothyroxine 100 mg daily, metoprolol succinate 100 mg daily, and digoxin 0.25 mg daily. He denied recent changes to medications, herbal supplements, alcohol use, or other substance use.

In the emergency department, the patient had a temperature of 99.5 degrees F, blood pressure 111/71, pulse 82, and oxygen saturation 95% on room air. Examination by the admitting team was grossly unremarkable with the exception of an irregular heart rhythm. Initial laboratory testing was notable for WBC 3.8 x 10^3/µL, Hgb 13.4 g/dL, platelets 169 x 10^3/µL, creatinine 1.33 mg/dL (baseline creatinine 0.8 mg/dL), calcium 8.9 mg/dL, AST 37 U/L, ALT 24 U/L, alkaline phosphatase 53 U/L, high-sensitivity troponin 120 ng/L, and creatine kinase 805 U/L. COVID-19 nasopharyngeal PCR was positive. EKG showed atrial fibrillation without any new changes concerning for ischemia. Chest x-ray was unremarkable. CT head and x-ray studies of extremities did not reveal fracture or other pathology. Transthoracic echocardiogram showed severely dilated left atrium, normal left ventricular function, and no significant valvular abnormalities.

The patient was admitted to the Cardiology service for management of elevated troponin. The troponin level subsequently decreased to 114 ng/L and the patient remained without chest pain or anginal equivalents. The troponin elevation was attributed to a type II NSTEMI in setting of a COVID-19 infection and acute kidney injury. On hospital day #3, the patient developed fevers with maximum temperature 101.3 F, hypoxia requiring 2 liters/minute of oxygen and right-sided consolidation on chest x-ray. The patient was treated with dexamethasone, remdesivir, ceftriaxone, and azithromycin for COVID-19 versus bacterial, community-acquired pneumonia and the patient was transferred to the Geriatrics service for further management. On examination during hospital day #3, the patient appeared anxious. Cardiopulmonary exam demonstrated irregularly irregular rhythm, no murmurs, and clear lungs. Abdomen was soft and nontender. The patient was alert and oriented only to self and location, and exhibited poor insight and short-term recall. He was unable to state the days of week backwards. Cranial nerve exam was normal. Strength was full and sensation was grossly intact. Extremities were rigid and a resting tremor was present. Patellar reflexes were 3+ bilaterally and inducible ankle clonus was present. Plantar reflexes were flexor. Laboratories at this time were notable for increasing creatine kinase (2962 U/L) and liver transaminases (AST 130 U/L, ALT 69 U/L).

These clinical and laboratory findings raised concern for serotonin syndrome. Both quetiapine and mirtazapine were stopped, and lorazepam was given on an as needed basis for anxiety. Cyproheptadine was not administered. Subsequently, the patient's mental status, neuromuscular exam, creatine kinase level, and liver transaminases normalized. Quetiapine was resumed at a lower dose after a four-day washout period and the dose was gradually increased during the remainder of the admission. The patient was discharged on a total daily quetiapine dose of 425 mg. Mirtazapine was discontinued permanently.

Discussion

Serotonin syndrome is a classification of potentially life-threatening symptoms caused by excessive serotoninergic activity in the central nervous system. The condition of serotonin syndrome was first described in 1960 after observations of characteristic neurologic changes in patients receiving tryptophan and monoamine oxidase inhibitors (MAOI).[1] Serotonin syndrome can occur with any drug that increases 5-hydroxytroptophan, including MAOIs, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), lithium, amphetamines, meperidine, and many others (Table 1).[2,3] Quetiapine, a serotonin receptor antagonist, has also been

associated with serotonin syndrome, particularly when combined with other serotoninergic agents such as mirtazapine. The mechanism for quetiapine-associated serotonin syndrome is not fully understood. Proposed mechanisms include drug-drug effects on metabolism and selective activation of 5-HT1a receptors by 5-HT2a antagonism.[4]

Manifestations of serotonin syndrome are often described as a triad of cognitive-behavioral changes (altered mental status, agitation), autonomic hyperactivity (fever, hypertension, tachycardia, mydriasis, diaphoresis), and neuromuscular abnormalities (tremor, hyperreflexia, clonus, rigidity).[2,5] No laboratory test exists for the diagnosis of serotonin syndrome, though nonspecific laboratory abnormalities have been reported, including leukocytosis, elevated creatine kinase, elevated liver transaminases, and decreased bicarbonate. The diagnosis of serotonin syndrome is clinical. One diagnostic tool is called the Hunter Serotonin Toxicity Criteria (Figure 1), which has a sensitivity and specificity of 84 and 97%, when compared to a gold standard of diagnosis by a medical toxicologist.[6]

The patient in this case exhibited multiple signs of serotonin syndrome, including changes in mental status, clonus, hypertonicity, hyperreflexia, and tremor, as well as elevated creatine kinase and liver transaminases. His presentation fulfills the Hunter Criteria for serotonin syndrome, and this diagnosis is supported by the fact that these symptoms resolved after discontinuation of the serotonergic medications. In this case, synergistic serotonergic effects from mirtazapine and high-dose quetiapine led to serotonin syndrome. This older adult patient was predisposed to serotonin toxicity by age-related changes in pharmacokinetics. Since this patient did not have recent dose adjustments to his psychiatric medication regimen prior to his presentation, it is possible that he had prior subacute or chronic serotonin syndrome that had not been detected. The onset of acute illness and inflammation related to his COVID-19 infection, as well as an acute kidney injury, may have led to changes in drug metabolism and clearance that caused increased serotonergic activity and led to the manifestations of serotonin syndrome described in this case.

In conclusion, physicians should be aware that serotonin syndrome is a predictable consequence of the usage of serotonergic drugs (frequently a combination of serotonergic drugs) and is preventable. While certain classes of psychiatric medications are classically associated with serotonin syndrome (MAOIs, SSRIs, TCAs), there is a remarkably long list of medications that have serotonergic activity including atypical antipsychotics, non-psychiatric medications, and recreational drugs. Physicians should have a high index of suspicion for serotonin syndrome when caring for a patient who is (1) receiving serotonergic agent(s) and (2) has at least one symptom of serotonin syndrome.

Figure 1: Hunter Serotonin Toxicity Criteria. Adapted from Dunkley et al.[6]

In the presence of a serotonergic agent, serotonin toxicity exists if any ONE of the following conditions is met:

1. Spontaneous clonus
2. Inducible clonus + agitation or diaphoresis
3. Ocular clonus + agitation or diaphoresis
4. Tremor + hyperreflexia
5. Hypertonia + temperature > 38°C + ocular or inducible clonus

Table 1: Drugs associated with serotonin syndrome, with associated mechanisms. Figure adapted from Jacqueline Volpi-Abadie et al.[3]

Mechanism	Associated drugs
Inhibit serotonin uptake	**Amphetamines/weight loss drugs**: phentermine **Antiemetics**: granisetron, ondansetron **Antihistamines**: chlorpheniramine **Certain opiates**: levomethorphan, levorphanol, meperidine, methadone, pentazocine, pethidine, tapentadol, tramadol **Cold remedies**: dextromethorphan **Drugs of abuse**: cocaine, MDMA **Herbal supplements**: St. John's wort **SNRIs/SSRIs**: desvenlafaxine, duloxetine, venlafaxine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline **TCAs**: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine **Other antidepressants**: bupropion, nefazodone, trazodone
Inhibit serotonin metabolism	**Anxiolytics**: buspirone **Herbal supplements**: St. John's wort **MAOIs**: furazolidone, isocarboxazid, linezolid, methylene blue, phenelzine, selegiline, Syrian rue, tranylcypromine **Triptans**: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan
Increase serotonin synthesis	**Amphetamines/weight loss drugs**: phentermine **Dietary supplements:** L-tryptophan **Drugs of abuse**: cocaine
Increase serotonin release	**Antidepressants:** mirtazapine **Amphetamines/weight loss drugs**: phentermine **Certain opiates**: meperidine, oxycodone, tramadol **Cold remedies**: dextromethorphan **Drugs of abuse**: MDMA **Parkinson disease treatment:** L-dopa
Activate serotonin receptors	**Anxiolytics**: buspirone **Antidepressants**: mirtazapine, trazodone **Antimigraines**: dihydroergotamine, triptans **Certain opiates**: fentanyl, meperidine **Drugs of abuse**: LSD **Mood stabilizers:** lithium **Prokinetic agents:** metoclopramide
Inhibit CYP450 microsomal oxidases	**CYP2D6** **Inhibitors**: fluoxetine, sertraline **Substrates**: dextromethorphan, oxycodone, phentermine, risperidone, tramadol **CYP3A4** **Inhibitors**: ciprofloxacin, ritonavir **Substrates**: methadone, oxycodone, venlafaxine **CYP2C19** **Inhibitors**: fluconazole **Substrates**: citalopram

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