Delirium due to Concurrent Serotonin Syndrome and Naltrexone-Induced Withdrawal: A Case Study

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Introduction

- Naltrexone, an opioid antagonist at the Mu receptor used in the treatment of opioid use disorder and alcohol use disorder, also acts as an antagonist at the 5-HT3 serotonin receptor, increasing levels of serotonin in the brain (1).
- Naltrexone's synergistic effect with multiple serotonergic agents leads to serotonin syndrome, a syndrome of excessive serotonergic activation leading to symptoms such as clonus, autonomic instability, and delirium (2).
- Naltrexone can also increase the propensity for delirium by rapidly unbinding opioids from receptors if opioids have been used recently, precipitating severe withdrawal (6).
- This case is a presentation of concurrent severe opioid withdrawal and serotonin syndrome after first-time use of naltrexone in the setting of recent opioid use.

Patient History

- Patient is a 49-year-old female with a past psychiatric history of bipolar disorder, PTSD, schizoaffective disorder, and opiate use disorder, who presented to the emergency department via EMS with a chief complaint of full body spams for approximately 4 hours after taking naltrexone for the first time for opioid use disorder.
- Other symptoms included diaphoresis, muscle spasms, autonomic instability, and restlessness.
- She reports she had recently stopped buprenorphine after 1 month, with last use approximately 8 days prior to arrival. She voluntarily discontinued this due to perceived lack of benefit.

Physical Exam

- In the ED, patient's vital signs were temperature 97.6F, heart rate 108, respiratory rate 17, blood pressure 138/65 and SpO2 97% on room air. Records indicate the patient was alert and oriented.
- Physical exam was notable for diaphoresis and tachycardia as well as occasional 2-3 second periods of stiffening of upper and lower extremities with no loss of consciousness and self-resolution.
- HENT, eyes, pulmonary, abdominal, musculoskeletal and psychiatric portions of the exam were unremarkable.

Laboratory/Imaging Results

- Labs were significant for: CPK elevation.
- CMP, CBC, TSH, TP were within normal limits.
- β-hCG, salicylate, acetaminophen, COVID-19 testing were negative.
- QTc was prolonged at 627.

Table 1. Patient's Home Psychiatric Medication Use	
Citalopram 40mg PO QAM	Naltrexone 50mg PO Daily
Clonidine 0.3mg PO Q6H	Quetiapine 400mg PO QHS
Gabapentin 800mg PO TID	Vyvanse 70mg Daily
Buprenorphine/Naloxone Daily (not prescribed)	

Differential Diagnoses

- Naltrexone-induced opioid withdrawal
- Serotonin syndrome
- Drug intoxication
- Primary neurological disorder

Hospital Course

- In the ED, she was treated with a total of 4mg Lorazepam which was ineffective.
- Given continued uncontrolled spasms and autonomic instability with prolonged QTc interval, she was admitted to the hospital for further evaluation and treatment.
- Overnight, she became confused, disorganized, and agitated with visual hallucinations and attending to internal stimuli.
- Patient was initially treated with phenobarbital with concern for alcohol withdrawal resulting in delirium. This was quickly discontinued due to sedation.
- Further symptoms of inducible clonus with agitation, hyperreflexia, and hypertonia were found, and serotonin syndrome was diagnosed based on Hunter Criteria (2).

Serotonin Syndrome	Shared Signs & Symptoms[6]	Opioid Withdrawal
Spontaneous Clonus	Diaphoresis	Nausea and Vomiting
Inducible Clonus	Autonomic Disturbance	Abdominal Pain
Ocular Clonus	Fever	Diarrhea
Agitation	Muscle Aches	Rhinorrhea and Tearing
Hyperreflexia	Restlessness	Chills
Hypertonia	Insomnia	Joint Pain
	Dilated Pupils	Yawning
	Tremor	Anxiety/Irritability
		Piloerection

Table 2. Signs and symptoms of serotonin syndrome and opioid withdrawal

Pathophysiology

- Serotonin syndrome is a potentially life-threatening syndrome that is often caused by the use of multiple serotonergic agents from numerous drug classes, resulting in increased levels of serotonin in the body, leading to overactivation of 5-HT receptors, particularly 1A and 2A (3).
- As a result of this increase in serotonin leading to overactivation, patients often present with mental status changes and neuromuscular and autonomic hyperactivity leading to spontaneous or inducible clonus, ocular clonus, agitation, diaphoresis, hyperreflexia, hypertonia, tremors or fever (4).

Treatment

- After determining that patient was suffering from serotonin syndrome, she was started on cyproheptadine 12mg loading dose, with as needed dosing.
- Her home medications of quetiapine, citalopram, gabapentin, Vyvanse, topiramate, buprenorphine, promethazine, and naltrexone were held.
- Delirium resolved the following day, her mentation returned to baseline.
- She was then discharged from the hospital.

Discussion

- As the patient used several serotonergic agents (including buprenorphine) and exhibited symptoms of serotonin syndrome, it is a compatible etiology for the cause of her rapid decline.
- The administration of naltrexone could have also potentiated serotonergic activation in the central nervous system, exacerbating or causing the serotonin syndrome (5).
- This case was further complicated with the likely presence of naltrexone-induced opioid withdrawal, which is also known to cause delirium, and other overlapping symptoms of serotonin syndrome including diaphoresis, autonomic disturbance, fever, myalgias, restlessness, insomnia, and mydriasis (6).

Conclusion

This case demonstrates the continued need for diligent and cautious medication monitoring and prescribing given the broad breadth of serotonergic action in medications and substances. This case also highlights the recognition of overlapping pathology. Serotonin syndrome and opioid withdrawal are two syndromes with overlapping symptomology and agent etiology but with separate prognosis, severity, and treatment. Effective treatment of this patient relied on identification of the two different pathologies and concurrent treatments.

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