Serotonin Toxicity Precipitated by Tramadol in the Setting of Polypharmacy: Case report and literature review of Serotonin Syndrome

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Introduction

Serotonin Syndrome (SS) - characterized by the triad of altered mentation, neuromuscular excitation and autonomic dysfunction - is caused by overstimulation of the central and peripheral serotonin receptors. Often seen in the setting of polypharmacy with multiple serotonergic agents [1, 2] and not as an idiopathic drug reaction[4]. The incidence is unknown, though the true number of cases is very likely to be much higher than the number reported, considering over 85% of physicians are unaware of it being a clinical diagnosis [4, 5].

This case provides a unique opportunity to observe an opiate -Tramadol- precipitating the Serotonin Syndrome in the setting of polypharmacy, instead of the classic serotonergic agents.

Objective

To present a case of Serotonin Syndrome precipitated by the addition of Tramadol to a concomitant regimen of Oxycodone, Citalopram, and Trazodone.

To raise awareness about patients' safety and the dangers of multiple providers writing prescriptions without first considering the medication reconciliation and possible adverse interactions.

Case

The patient is a 79-year-old Caucasian female with a non-exclusive past medical history of Non-Ischemic Cardiomyopathy, Major Depressive Disorder, Diabetes Mellitus type 2 with associated neuropathy and Chronic Pain secondary to malignancy who presented to the emergency department with generalized weakness and worsening tremors involving upper and lower extremities. She reported that the tremors intensified when standing from a sitting position, causing a non-traumatic fall. As per the patient's husband, she had episodic visual and auditory hallucinations. On physical examination she had altered mentation, tremors, diaphoresis, fever, tachypnea with labored breathing, and 3+ pitting edema of the extremities. She was admitted with a presumptive diagnosis of Heart Failure exacerbation triggered by Community Acquired Pneumonia. On medication review, an extensive regimen including several cardiovascular, anti-hypertensive, antidepressants and pain control agents were noted.

-Lisinopril- -Cholecalciferol- -Levothyroxine- -Gabapentin-

-Metformin- -Ubidecarenone- -Magnesium oxide-

-Propranolol- -Aspirin- -Carvedilol- -Furosemide-

-Oxycodone- -Tramadol- -Trazodone- -Citalopram-

Of note, a week prior to admission, patient had been started on Tramadol. She was started on empiric Ceftriaxone and Doxycycline. Her WBC trended down from 13.2 to 10.8. Her blood cultures were negative, and her antibiotics were discontinued. SS was suspected upon review of medications by the Hospitalist team. Her Tramadol was immediately discontinued, and her symptoms ceased within 24 hours. Patient was discharged after an additional day of observation with a new regimen of medications and instructions to follow up with her PCP.

Discussion

Serotonin Syndrome is a threatening and potentially lethal complication of serotonergic polypharmacy. It is typically the result of the initiation of a new pharmacologic agent or dose escalation of the culprit agent to a medical regimen including other serotonergic agents. All drugs and supplements that directly or indirectly increase central serotonin neurotransmission can produce this toxicity. The specific drug mechanisms involve:

Decrease serotonin breakdown
Decrease serotonin reuptake
Increased serotonin precursors or agonists
Increased serotonin release
CYP2D6 and CYP3A4 inhibitors

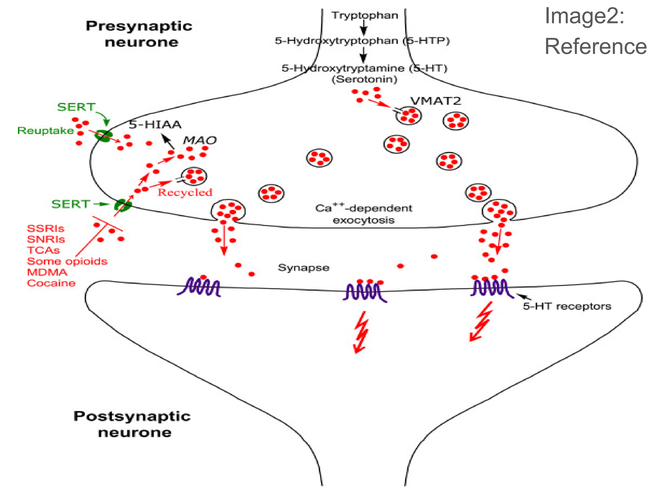
The diagnosis is made purely upon clinical suspicion since there is no specific diagnostic test [2]. Additionally, patients can have a wide range of presentation from mild symptoms to a life-threatening [5]. The clinical triad that characterizes serotonin syndrome includes altered mentation, neuromuscular excitation and autonomic dysfunction. The timing and severity of the SS is dependent upon medication concentration and patient genetic factors [5].

Image1:
Reference # 6.

The syndrome was likely induced in our patient due to the compiled effect of reuptake inhibition of Serotonin by Oxycodone, selective reuptake inhibition of the same by Citalopram, and antagonization of receptors and inhibition of specific serotonergic reuptake by Trazodone, aggravated by the addition of Tramadol, triggering the acute toxicity in our patient. Most patients typically come to the hospital within 6 hours of medication adjustment, but this patient was not hospitalized until 11 days after treatment initiation. Patients with a mild presentation are typically afebrile [5]. Even though this patient had a milder form of the syndrome she still had a fever, which may have been influenced by her history of inflammatory illnesses, making her body more prone to fevers to fight off adverse reactions. Of note, serum serotonin concentrations have no correlation with the severity of the syndrome [5]. Additionally, even a single therapeutic dose of an SSRI agent can induce the syndrome [4]. Cessation of serotonergic agents is the mainstay of treatment [2].

Receptor Effects

Image2:
Reference # 3.



Conclusion

It is important to recognize Serotonin Toxicity in our patients because many healthcare providers will encounter this iatrogenic diagnosis during their careers. Clinical diagnosis of SS is challenging due to the syndrome having a wide range of presentations. This patient had a mild course but was still febrile. She had multiple factors in her history that may have influenced her presentation, including inflammatory illnesses as well as being on a SSRI and a SARI, concomitantly with an Opiate. The addition of Tramadol was the "tipping of the scale". This is unique because as healthcare providers we don't often associate Opioids with Serotonin.

Patient's Safety: On a detailed history collection. Our team found that since mid-year-2019 our patient had been prescribed controlled substances by 5 different physicians(2 General Practitioners, 2 Pain Control Specialists, and 1 PMNR). Additionally, had been hospitalized 3 times. With this number of interactions with healthcare providers how come it took for our patient to have a potentially fatal adverse event for a provider to reconcile her medications? Furthermore, take ownership and configure her home regimen for the least number of adverse interactions and avoid polypharmacy.

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