

# Audio-Visual Hallucinations in a Patient Poststem Cell Transplant

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## Abstract

Tramadol is the most common weak opioid used today. It has unique pharmacology and is notorious for numerous side effects as well as drug interactions. Patients undergoing stem cell transplant are susceptible to polypharmacy as a result of the generous use of antibiotics and symptom management drugs. Here, we describe a case where concurrent use of tramadol and fluconazole can cause hallucinations as a result of drug interaction.

**Keywords:** Fluconazole, polypharmacy, tramadol

## INTRODUCTION

Oral mucositis is a common complication after stem cell transplantation (SCT) in a patient with hematological malignancy. These patients are usually subject to polypharmacy regimens to treat primary disease as well as prevent therapy-related side effects. Weak opioids such as tramadol are commonly employed for the pain associated with mucositis in these patients. Here, we describe an interesting and relatively uncommon drug interaction between commonly used drugs post-SCT, tramadol, and fluconazole.

## CLINICAL VIGNETTE

A 46-year-old male with multiple myeloma was admitted in the medical oncology ward for receiving SCT. He had achieved partial remission after six cycles of bortezomib, dexamethasone, and vincristine since his diagnosis 4 months prior and was currently on bortezomib maintenance.

Conditioning was performed with high-dose melphalan regime, and he underwent a successful and uncomplicated transplantation.

He developed expected post-SCT oral mucositis with a severity Grade III as per the WHO criteria and associated gastrointestinal mucositis with diarrhea. This was being managed with tramadol 50 mg and ondansetron 50 mg thrice daily.

On day 11 posttransplant, he developed febrile neutropenia. He was investigated with blood cultures and was started on a comprehensive regimen of broad-spectrum antibiotics which included ceftriaxone, amikacin, metronidazole, teicoplanin, piperacillin-tazobactam, and fluconazole, given his immunocompromised status. Fluconazole was administered by intravenous infusion, dosed at 200 mg once daily for candidiasis prophylaxis.

After 2 days of initiating fluconazole, the patient developed audio-visual hallucinations – somewhat predictably prior to sleep (hypnagogic) and occurring randomly during the day. He reported that he visualized two people talking to each other and at times could recognize their faces. He reported that he was very anxious about these incidents and he was scared of falling asleep. His son said that he witnessed him mumbling during the early sleep and also mentioned certain instances when his father would get up from his sleep and recite what he saw. The family members did not notice any episodes of confusion/incoherence or inappropriate talk.

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After suspecting a potential drug interaction in this case, the patient was switched to low-dose morphine for pain and tramadol was discontinued. The patient's symptoms improved greatly in the next 2 days and he was able to sleep better and without any further incidents.

The patient overall recovered from his fevers and was discharged home after 3 weeks of inpatient stay with prescriptions for mouthwash, antiemetics, fluconazole prophylaxis 200 mg once daily, acyclovir 400 mg once daily, paracetamol 500 mg thrice daily, Vitamin D capsules, and calcium tablets.

## DISCUSSION

The acute onset of hallucinations in this patient was correlated with other symptoms to consider the possibility of delirium and the causes of it. This patient did not manifest any acute/fluctuating confusional state or incoherence. There seemed a possibility of isolated audio-visual hallucinations in this patient with an obscure cause.

Oral and gastrointestinal mucositis is very common after SCT and can impair patient's quality of life significantly. It is the result of depletion of rapidly regenerating oral epithelium due to myelosuppressive toxicity. A recent prospective observational study from Germany in 45 SCT patients found the incidence of oral mucositis up to two-thirds of the recipients (42%–72%) with associated significantly lower physical functioning and oral health-related quality of life.<sup>[1]</sup> The pain also correlated with the severity of oral mucositis.

Tramadol is a weak opioid analgesic (acting at the mu opioid receptors) and a serotonin and norepinephrine reuptake inhibitor. Its active metabolite is O-desmethyltramadol. The drug undergoes bioconversion through two cytochrome P450 (CYP450) enzymes, CYP2D6 and CYP3A4.<sup>[2]</sup> Eighty percent of tramadol is metabolized by CYP2D6 and the rest by CYP3A4. The latter enzyme is an easily saturable enzyme, therefore, vulnerable to drug interactions. In addition, certain rarer genetic polymorphisms associated with CYP2D6 can affect its metabolism and vulnerability to drug interactions.<sup>[3]</sup> Decrease in the seizure threshold and development of serotonin syndrome are certain complications specific to tramadol.

Antifungals such as fluconazole are frequently administered for either preventing or treating fungi such as *Candida* which is a relatively common infection in the immunosuppressed. Importantly, these drugs are the inhibitors of CYP3A4 enzyme.

During scrutiny for potential drug–drug interactions in our case, we found a single case report published in 2010, describing similar complex audio-visual hallucinations from coadministration of clarithromycin and tramadol.<sup>[4]</sup> Fluconazole may have increased the substrate levels of tramadol in this case, and the hallucinations might have resulted from elevated tramadol levels. The drug levels were not performed due to

technical reasons and also their limited utility in this case. However, elevated level of tramadol remains the most probable reason after ruling out the other causes of hallucinations.

Multiple case reports have otherwise described interactions between opioids and azole drugs. Hallberg *et al.* described a case of fluconazole-induced higher blood fentanyl levels in a patient on fentanyl patch, leading to mortality as a result of opioid toxicity.<sup>[5]</sup> Another case report by Mercadante *et al.* describes a similar itraconazole – fentanyl interaction in a cancer patient.<sup>[6]</sup>

Our case demonstrates how a timely scrutiny of polypharmacy patients for drug–drug interactions can identify the cause for symptoms and prevent further investigations and potential harm. Our patient's hallucinations disappeared in 2 days after discontinuing tramadol, without requiring antipsychotics.

## CONCLUSION

We describe an example of uncommon and less published interaction between the opioid tramadol and antifungal azole fluconazole presenting with audio-visual hallucinations. Our case highlights the important role of carefully evaluating for drug interactions in high-risk palliative care and oncology patients who are commonly subject to polypharmacy regimens.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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