

## REVIEWER'S REPORT

Manuscript No.: IJAR-51601

Date: 14/05/2025

**Title: Olanzapine-Associated Oral Candidiasis in an Immunocompetent Patient: A Case for Further Investigation**

### Recommendation:

Accept as it is .....

**Accept after minor revision.....Yes.....**

Accept after major revision .....

Do not accept (*Reasons below*) .....

Rating	Excel.	Good	Fair	Poor
Originality	•			
Techn. Quality	•			
Clarity		•		
Significance	•			

Reviewer Name: Dr. Sireesha Kuruganti

**Date:** 14/05/2025

### Reviewer's Comment for Publication.

*(To be published with the manuscript in the journal)*

*The reviewer is requested to provide a brief comment (3-4 lines) highlighting the significance, strengths, or key insights of the manuscript. This comment will be Displayed in the journal publication alongside with the reviewers name.*

The manuscript presents an interesting and potentially underrecognized adverse effect of olanzapine. The case of an immunocompetent patient developing oral candidiasis following olanzapine administration is clinically relevant. The paper is generally well-structured, moving logically from introduction to case presentation, discussion, and conclusion.

### Detailed Reviewer's Report

Manuscript Review: Olanzapine-Associated Oral Candidiasis in an Immunocompetent Patient

This report provides a detailed review of the manuscript "Olanzapine-Associated Oral Candidiasis in an Immunocompetent Patient: A Case for Further Investigation." The review assesses various sections of the paper, highlighting strengths and areas for potential improvement, with references to specific line numbers from the provided document.

#### Overall Assessment

The manuscript presents an interesting and potentially underrecognized adverse effect of olanzapine. The case of an immunocompetent patient developing oral candidiasis following olanzapine administration is clinically relevant. The paper is generally well-structured, moving logically from introduction to case presentation, discussion, and conclusion. However, certain areas could benefit from further clarification and detail to strengthen the arguments and enhance the manuscript's impact.

Specific Comments by Section:

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### 1. Title (Lines 1-3)

\* The title "Olanzapine-Associated Oral Candidiasis in an Immunocompetent Patient: A Case for Further Investigation" is clear, concise, and accurately reflects the core subject of the manuscript. It immediately informs the reader about the drug involved, the adverse effect, the patient's immune status, and the nature of the report.

### 2. Introduction (Lines 7-35)

#### \* Strengths:

\* Lines 7-10 effectively define oral candidiasis and its common cause (*Candida albicans*) and typical patient population (secondary immunosuppression).

\* Lines 10-13 clearly describe the clinical presentation of oral candidiasis.

\* Lines 13-18 appropriately list conditions and treatments that increase the risk of oral candidiasis, emphasizing the role of immune function.

\* Lines 19-25 successfully introduce the uniqueness of the case: an immunocompetent adult developing oral candidiasis after olanzapine treatment, with no prior history or known risk factors for immunosuppression.

\* Lines 25-32 appropriately raise the possibility of olanzapine having an underrecognized adverse effect and potentially immunomodulatory or immunosuppressive mechanisms, citing emerging reports.

#### \* Areas for Consideration:

\* While the introduction sets the stage well, it could briefly mention if any atypical antipsychotics other than olanzapine have been linked to oral candidiasis to provide broader context, if such literature exists.

### 3. Case Presentation (Lines 36-67)

#### \* Strengths:

\* Lines 37-42 provide a clear history of the patient, including age, diagnosis (paranoid schizophrenia), reason for current admission (exacerbation of psychotic symptoms), and precipitating factors (non-compliance with medication due to work-related stress, leading to insomnia, appetite loss, and weight loss). The previous stable medication (paliperidone) is also mentioned.

\* Lines 42-43 state the rationale for initiating olanzapine (severity of symptoms, need for rapid stabilization) and the starting dose (10 mg).

\* Lines 44-49 clearly describe the timeline of symptom onset: alleviation of psychotic symptoms but development of tongue pruritus and discoloration within 24 hours, progressing to impaired mastication, phonation, and halitosis within 48 hours.

\* Lines 49-50 mention the admission to the emergency department due to concerns about airway compromise.

\* Lines 50-54 detail the examination findings (white curd-like plaques), initial diagnosis (oral candidiasis), and investigations that ruled out common causes of immunodeficiency (normal granulocyte, agranulocyte, leukocyte levels; negative HIV test).

\* Lines 54-56 clarify the patient's diabetic status (well-managed with Metformin and Dapagliflozin, HbA1C within reference range).

\* Lines 56-58 present a crucial piece of information: a similar episode 10 years prior with the same dose of olanzapine. This significantly strengthens the association.

\* Lines 58-61 describe the management (discontinuation of olanzapine, increased fluid intake) and outcome (resolution of oral candidiasis within 48 hours), strongly suggesting olanzapine as the causal factor.

#### \* Areas for Consideration:

\* Line 42: While the patient was previously stable on paliperidone for 3 years, it might be useful to explicitly state why a switch was made to olanzapine rather than re-initiating or adjusting paliperidone, especially if paliperidone has a different risk profile for such side effects. The text does state "need for rapid stabilization," implying olanzapine was chosen for this property, but a bit more direct reasoning on the choice over paliperidone could be beneficial.

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\* It would be helpful to know if any oral swabs or cultures were taken to confirm *Candida albicans* specifically, or if the diagnosis was purely clinical.

#### 4. Discussion (Lines 68-114)

##### \* Strengths:

\* Lines 68-72 effectively reiterate the infrequency of oral candidiasis with olanzapine in immunocompetent patients and the typical associations of thrush with impaired mucosal immunity.

\* Lines 72-75 highlight that the patient was thoroughly evaluated for common predisposing factors, which were found to be normal, thereby strengthening the link to olanzapine.

\* Lines 77-83 present a plausible mechanism: olanzapine's antagonism of muscarinic receptors leading to xerostomia, which in turn compromises oral defense mechanisms (reduced salivary flow, antimicrobial proteins). This is well-explained and referenced. (Table 1 is referenced here).

\* Lines 84-88 further elaborate on how xerostomia can facilitate fungal colonization by altering oral pH and reducing mechanical clearance.

\* Lines 92-97 discuss another relevant mechanism: olanzapine's documented metabolic side effects (weight gain, insulin resistance, hyperglycemia) potentially creating an enriched environment for *Candida* growth due to elevated salivary glucose levels. (Table 1 is referenced here).

\* Lines 98-105 introduce the immunomodulatory properties of antipsychotics, including olanzapine, referencing studies on cytokine alterations in schizophrenia and modulation of leukocyte function by some antipsychotics.

\* Lines 106-109 strongly conclude that oral candidiasis can be an adverse drug reaction to olanzapine even in immunocompetent individuals, emphasizing the recurrence on re-exposure and rapid resolution on discontinuation.

\* Lines 110-114 provide practical clinical implications, suggesting preventive strategies and considerations for alternative agents.

##### \* Areas for Consideration:

\* Line 96: "Table 1: Mechanism of Oral Candidiasis in patient taking olanzapine" is mentioned. The table itself (page 4) is a helpful visual summary of the discussed mechanisms (Immunomodulatory effects, Altered oral flora, Dry mouth, Metabolic S/E, Behavioral factors).

\* The discussion on immunomodulatory properties (Lines 98-105) is relevant. It could be slightly expanded to discuss how these immunomodulatory effects might specifically predispose to fungal infections in the oral mucosa, if literature supports a more direct link beyond general immune parameter changes.

#### 5. Summary (Lines 115-130)

##### \* Strengths:

\* Lines 116-117 briefly reintroduce olanzapine and its uses.

\* Lines 117-122 succinctly summarize the key proposed mechanisms: anticholinergic properties leading to reduced salivary secretion and metabolic side effects creating a favorable environment for *Candida* growth.

\* Lines 122-124 also rightly include exacerbating factors like poor oral hygiene and high sugar diets.

\* Lines 124-130 effectively conclude by emphasizing the multifactorial relationship and the importance of early recognition and intervention.

##### \* Areas for Consideration:

\* The summary is concise and covers the main points well. No major additions seem necessary.

#### 6. References (Lines 131-175)

\* The references appear to be relevant to the topics discussed (oral candidiasis, HIV, cancer therapy side effects, diabetes, olanzapine pharmacology, saliva, xerostomia, metabolic effects of antipsychotics, cytokine alterations in schizophrenia).

\* The formatting seems generally consistent, though a journal-specific style guide would determine exact adherence.

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\* DOI links are provided for many references, which is good practice.

### 7. Figures and Tables

\* Figure 1 (Page 7, Line 177): "Case presenting with oral candidiasis". The image clearly shows white plaques on the tongue, consistent with the clinical description of oral candidiasis. It adds visual evidence to the case report.

\* Table 1 (Page 4, referenced in text e.g., Line 83, Line 97): "Mechanism of oral candidiasis". This flowchart is a very useful and clear summary of the potential multifactorial mechanisms by which olanzapine might contribute to oral candidiasis. It covers immunomodulatory effects, altered oral flora, dry mouth (xerostomia), metabolic side effects, and behavioral factors.

### 8. Language and Clarity

\* The language used is scientific and appropriate for a case report.

\* The manuscript is generally well-written and easy to understand.

\* The term "immunocompetent" is consistently used and is central to the case's significance.

### Concluding Remarks and Recommendations

This manuscript reports a valuable clinical observation that contributes to the understanding of olanzapine's potential adverse effect profile. The recurrence of oral candidiasis upon re-exposure to olanzapine in an otherwise immunocompetent individual, with resolution upon discontinuation, provides a strong basis for the authors' conclusions.

### Key Strengths:

\* Clear presentation of a rare but important adverse drug reaction.

\* Thorough exclusion of common causes of immunosuppression.

\* Strong temporal relationship between drug administration, symptom onset, and symptom resolution.

\* Plausible mechanisms for the adverse reaction are discussed with supporting literature.

\* Good use of a figure and a table to support the text.

### Suggestions for Minor Improvement:

\* Consider briefly addressing the choice of olanzapine over paliperidone in the Case Presentation (Line 42).

\* Specify if mycological confirmation (e.g., swab, culture) of *Candida* species was performed.

\* If possible, slightly elaborate on how olanzapine's immunomodulatory effects might specifically link to increased susceptibility to oral fungal infections in the Discussion (Lines 98-105).

The manuscript is a useful addition to the literature and highlights the need for clinicians to be aware of this potential side effect, even in patients without typical risk factors for oral candidiasis. The call for "Further Investigation" in the title is well justified.