Peer Review File

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Reviewer A

Comment 1: Overall, the case series appears original and is clinically significant.
However, the approval status of olanzapine differs among countries. For example, in Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has approved 5-mg olanzapine for the treatment of nausea and vomiting due to chemotherapy. This difference in approval status among countries should be considered.

Reply: We thank the reviewer for their comments and added the comments in italics:

Changes in Text: (172) late stage emesis (25 to 120h) after receiving chemotherapy and studies report sedation as the main adverse event.[12-15] ***Of note, one randomized placebo controlled trial reported the 5 mg dose of olanzapine was just as effective as the higher dose of 10 mg [12] and, in Japan, is the approved dose for the prevention of CINV.***

Reviewer B

Comment 2: The purpose of this study was to highlight the benefits and risks of olanzapine for cancer-related symptom management. The manuscript is well written, but, before considering it for publication, I have the following recommendations for the authors to consider when preparing a revised version of their article.
1. Background: what is different it compared to other anti-psychotic drugs (ex. quetiapine, clozapine)?

Response: Agree with the reviewer, although quetiapine and clozapine are atypical antipsychotics which may have similar benefits, but at least in the USA, olanzapine is being embraced in the palliative setting. the following edits have been made.

Changes in text: (70)In the palliative care setting, 15-35% of all drugs are used off label due to a lack of funding for clinical trials and widespread use in the community.[4] ***Unlike other atypical anti-psychotics such as quetiapine and clozapine, olanzapine is increasingly used as the antiemetic of choice, at least in the USA, and has been increasingly incorporated*** for the symptomatic treatment of anxiety, anorexia, insomnia, ***and potentially reduce craving for opioids***.[5] *[5.5]* The following case series will highlight the potential benefits and risks of off-label use of olanzapine for symptom

management in cancer patients.

Comment 3: 2. Results: please show the table with a summary of participants' characteristics and prescribed medication, side effects, etc.

Response: Unfortunately, the submitted article is a case series and not a clinical study but future research is needed regarding benefits of olanzapine for symptom management.

Comment 4: 3. Discussion: to draw a conclusion, the characteristics of the three patients in this study are heterogeneous. please report the strength and limitations of the study.

Response: Unfortunately, submitted article is a case series and future clinical trials are needed.

Reviewer C

Comment 5: The authors report 3 cases of patients with advanced cancer who were given olanzapine for varying reasons.
There are multiple grammatic errors in this report, some of which are as follows (the full extend or the errors are more evident by reading the whole sentences in the manuscript):
59 breast, status post right-sided mastectomy, has noted

Response: Agree with reviewer, removed medical jargon and attempted to improve grammer.

Changes in Text: (78) A female patient in her 70s with stage IV infiltrating ductal carcinoma of the right breast ***with a history of*** right-sided mastectomy ***and*** metastatic disease involving her left breast, sternum and left proximal femur ***presents with*** difficulty tolerating treatment with letrozole, palbociclib, and denosumab due to symptoms.

Comment 6: 73 In the past, an extensive workup was conducted at an outside facility included a

Response: Agree with reviewer, edits have been made.

Changes in Text: In *an outside facility*, an extensive workup was conducted and included a normal gastro-motility study, an unremarkable upper and lower endoscopy, and a negative *computerized tomography scan of the abdomen*.

Comment 7: 75 negative abdominal computed tomography. Question of migraines mimicking nausea

Response: Agree with reviewer, edits have been made.
Changes in Text: (94) *Patient's primary care physician was concerned about* migraines mimicking nausea *and referred to a* local neurologist. *Neurological evaluation included* a negative magnetic resonance imaging (MRI) of the brain, but a possible abnormal electroencephalogram (EEG).

Comment 8: 86 A man in his 50s with renal cell carcinoma with rhabdoid features status post
87 nephrectomy and metastatic involvement of the lungs and bone.

Response: Agree with reviewer, edits have been made.
Changes in Text: (104) A man in his 50s with renal cell carcinoma with rhabdoid features *with a history of* nephrectomy and metastatic involvement of the lungs and bone *presents to SCC with abdominal pain*.

Comment 9: 97 escitalopram 10mg and alprazolam 2mg, averaging 2-3 tablets per day. Patient also noted profound fatigue (9/10).

Response: Agree with reviewer, edits have been made.
Changes in Text: In addition, *patient rated* anxiety (9/10) and depression (8/10) *high* despite being *treated with* escitalopram 10mg *daily* and *alprazolam 2mg as needed, averaging 2-3 pills per day*.

Comment 10: 113 A man in his 60s with pancreatic adenocarcinoma complicated by biopsy-proven

114 peritoneal disease, ascites, and portal vein thrombosis with associated portal
115 hypertension.

Response: Agree with reviewer, edits have been made.
Changes in Text: (129) A man in his 60s with pancreatic adenocarcinoma complicated by biopsy-proven peritoneal disease, ascites, and portal vein thrombosis *was referred to a Supportive Care Clinic for symptom management*. *His* chemotherapy, including gemcitabine plus cisplatin, was discontinued after a single cycle due to complications of melena and muscle weakness.

Comment 11: 151 Off-label use of olanzapine increasingly used for the treatment of anxiety, insomnia, and anorexia in cancer patients.

Response: Agree with reviewer, edits have been made.
Changes in Text: (163) *Olanzapine is* increasingly used *off-label* for the treatment of anxiety,

insomnia, and anorexia in cancer patients.

Comment 12: The table of potential side effects appear to be from a Physicians' Desk Reference (PDR) type of report, as opposed to a scientific report whereby cause and effect of each listed potential toxicity is substantiated. I don't think it is very helpful in this report of 3 cases.

Response: We appreciate the feedback from the reviewer. We have made edits and identified the source of information regarding adverse events of olanzapine and believe it to be useful for palliative care professional since olanzapine is increasingly used for symptom management.

Changes in Text: (226) Table 1 lists *potential* adverse events *associated with the use of* olanzapine *published by the Electronic Medicines Compendium based in the United Kingdom*.[33]

Comment 13: The first case notes how the patient did, with regards to nausea, 2 and 6 months following the time that she started it. While I suspect that the benefit was seen within the first day, and continued for months, this is not noted.

Response: we agree with the reviewer, edits have been made.
Changes in Text: (100) For her symptom burden, we recommended olanzapine 2.5mg PO every 12 hours for nausea. *Patient reported complete resolution of her symptoms with a singly nightly dose of olanzapine, and* she was tolerating treatment *without symptoms of nausea* on 2- and 6-month follow-up visits.

Comment 14: In the second case, no data are provided until one month later.

Response: we agree with the reviewer, edits have been made.
Changes in Text: (124) At 1 month follow up, with titration of ER morphine 30mg every 8hours, his pain improved to 4/10 and anxiety decreased to 3/10. The patient was able to taper off alprazolam without complications. At subsequent *monthly follow-up visits*, he continued escitalopram and olanzapine, decreased to 2.5mg prn during the daytime and scheduled 5mg at bedtime to help maintain sleep, without side effects and *good control of his symptoms. At 6-month follow-up visit, patient developed immunotherapy mediated pneumonitis with complications of dyspnea resulting in discontinuation of treatment and eventual referral to hospice care at home.*

Comment 15: In the third case, the discussion section notes that "Hepatic encephalopathy with elevated

ammonia levels were most likely due to portal vein thrombosis." Nonetheless, the authors spent substantial effort to blame the olanzapine for this toxicity.

Response: we agree with the reviewer. Neuro-oncology consultants felt that olanzapine contributed to confusion, we felt less likely and have made edits to clarify manuscript.

Changes in Text: (215) Hepatic encephalopathy with elevated ammonia levels *was* most likely due to portal vein thrombosis but *less likely* exacerbated by use of olanzapine, *which neuro-oncology consultants based on a single case report*.[7]