



# Antiemetic use of olanzapine in patients with advanced cancer: results from an open-label multicenter study

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## Abstract

**Introduction** The antipsychotic drug olanzapine is effective against chemotherapy-induced nausea and targets multiple receptors known to be involved in the emetic reflex arch. The drug has a mean half-life of 30 h, which allows for a single daily administration and is therefore of interest in patients with advanced cancer suffering from nausea.

**Objectives** To investigate the antiemetic effect and tolerability of olanzapine in patients with advanced cancer not receiving chemotherapy or irradiation.

**Methods** Patients with advanced cancer (no curable treatment options) with at least “moderate” nausea and/or one emetic episode within the last 24 h were included if they had not received chemotherapy or irradiation (last 2 weeks) and had no reversible causes of nausea/vomiting. Patients were administered 10 mg olanzapine daily for 5 days (the first day subcutaneously and the following 4 days orally). Nausea, vomiting, and adverse effects were assessed daily for 7 days. The primary efficacy parameter was nausea after 24 h.

**Results** Forty patients from four centers were included and all evaluable after 24 h. Thirty-six patients experienced some degree of improvement. The mean two-item N/V score (0–100) at baseline was 66 and improved to 21 and 24 after 24 h and 7 days, respectively. During the course of the study, the dose of olanzapine was reduced in three patients due to adverse events. Five patients were withdrawn from the study primarily due to progression of malignant disease or per patient’s request.

**Conclusions** Olanzapine appears effective and tolerable as an antiemetic in patients with advanced cancer. Future research should examine a lower dose (5 or 2.5 mg), preferably in a randomized controlled trial.

**Keywords** Nausea · Vomiting · Advanced cancer · Olanzapine · N/V

## Introduction

Patients with advanced cancer often have multiple (or unknown) causes of nausea and vomiting (N/V) [1], and it is therefore of interest to focus on antiemetic

drugs with binding affinity for multiple receptors known to affect the emetic reflex arch. An example of this is the antipsychotic agent olanzapine with significant binding affinity for dopaminergic (D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>), serotonergic (5-HT<sub>2a</sub>, 5-HT<sub>2c</sub>, 5-HT<sub>3</sub>, 5-HT<sub>6</sub>), adrenergic

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( $\alpha_1$ ), histaminergic ( $H_1$ ), and muscarinic cholinergic ( $M_1$ ,  $M_2$ ,  $M_3$ ,  $M_4$ ) receptors [2]. In recent years, olanzapine has been recommended by evidence-based guidelines as part of an antiemetic regimen for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV) [3–5].

In N/V not related to chemotherapy (non-CINV), the recommendations for prophylaxis and treatment are based on a lower level of evidence. Current consensus-based guidelines for advanced cancer conclude that the antiemetic of choice is metoclopramide with alternatives being haloperidol, levomepromazine, and olanzapine [6]. A number of retrospective studies, case reports, and a small randomized trial have indicated an antiemetic effect of olanzapine in patients with advanced cancer, but the level of evidence is low [7–19].

In patients with advanced cancer, the knowledge of adverse events regarding olanzapine is sparse. Since most of the above-mentioned studies are retrospective, almost no systematic recordings of adverse events have been published. A Cochrane review compared olanzapine to other atypical antipsychotics in more than 9000 patients with a psychiatric diagnosis. Olanzapine induced a high level of weight gain [20], but the doses used in the psychiatric setting are usually higher and the duration of therapy longer compared to olanzapine used as an antiemetic. In a mixed group of cancer patients with delirium, olanzapine seemed to induce more sedation than haloperidol, risperidone, and aripiprazole but lower rates of extrapyramidal symptoms than haloperidol [21]. A recent Cochrane review suggests that olanzapine probably increases the risk of fatigue and somnolence in patients with cancer receiving chemotherapy [22].

The above-mentioned studies on olanzapine in cancer patients used a tablet-based treatment, but the use of oral treatments in patients suffering from N/V is suboptimal [23]. Olanzapine is available in different administration forms. The orodispersible tablet has the same pharmacokinetic properties as the oral tablet [24], and is therefore to be preferred in patients with nausea and/or vomiting. The powder for injection of olanzapine has the same adverse event profile as the oral formulation [25], and is widely used in Danish palliative care departments as a subcutaneous injection.

The objective of this trial (DANSAC-OPEN) is to investigate the antiemetic use of olanzapine in patients with advanced cancer not receiving chemotherapy or irradiation. Specifically, we want to investigate the following:

1. Can olanzapine 10 mg as a single daily dose reduce patient-reported nausea and/or emesis (a) over 24 h and (b) over 7 days?
2. The tolerability of olanzapine 10 mg daily for 5 days.

## Methods

### Patients

Patients were recruited from participating Danish Departments of Oncology or Palliative Care Units and could be recruited from the hospital, hospice, or at home.

Inclusion criteria were as follows: age  $\geq 18$  years old, a diagnosis of advanced cancer defined as a solid tumor without curable treatment options, life expectancy exceeding 2 weeks, and one or both of the following: (1) nausea at least “moderate” within the last 24 h, scored on a 4-graded scale (none, mild, moderate, or severe) or (2) at least one emetic episode within the last 24 h.

Exclusion criteria were as follows: contraindications for olanzapine, cardiovascular disease (other than hypertension), Parkinson’s disease, dementia, epilepsy, symptoms of increased intracranial pressure, malignant bowel obstruction, cognitive impairment or language barrier that makes the patient unable to complete the questionnaires, surgery to the brain or abdomen within the last 2 weeks, exposure to general anesthesia within the last 4 days, chemotherapy or radiation therapy towards the brain or abdomen within the last 2 weeks, pregnancy, and reversible causes of nausea/vomiting as judged by the treating physician (e.g., hypercalcemia, uremia, hypomagnesemia, newly commenced/changed opioid-therapy, other medication with emetic potential).

### Study design and management

This was an open-label multicenter study to investigate the efficacy and tolerability of olanzapine in patients with advanced cancer not receiving chemotherapy or irradiation.

Data were collected on paper. All data were centrally entered into the online database REDcap, an approved and secure database.

Procedures, data entering, and data processing were reviewed according to GCP regulations by an independent monitoring unit, paid with funds outside of this study. The monitoring plan included full monitoring of inclusion criteria and vital parameters for all patients and full monitoring of all data in one third of the records. This reflects the standard procedure, where the sponsor and GCP unit agree on which variable needs full monitoring while the remaining variables are randomly checked to avoid systematic errors.

Permissions from the Danish Medicines Agency and the Local Ethics Committee were obtained before initiation of the study. No study procedures were initiated before a written informed consent had been signed by the patient.

## Treatment

Immediately following completion of baseline procedures, the patients received 10 mg olanzapine as a subcutaneous injection. All other prophylactic antiemetics were stopped, but the patient could receive rescue antiemetics. Twenty-four hours following the injection of olanzapine, the patient was evaluated by study staff either by phone or in person and continued on an oral dose of 10 mg olanzapine before bedtime for the following 4 days. However, in case of adverse events, a dose reduction to 5 mg was allowed. If the patient required a dose reduction, olanzapine could be administered as a tablet or an orodispersible tablet at night for the remaining of the 4 days.

## Clinical assessment

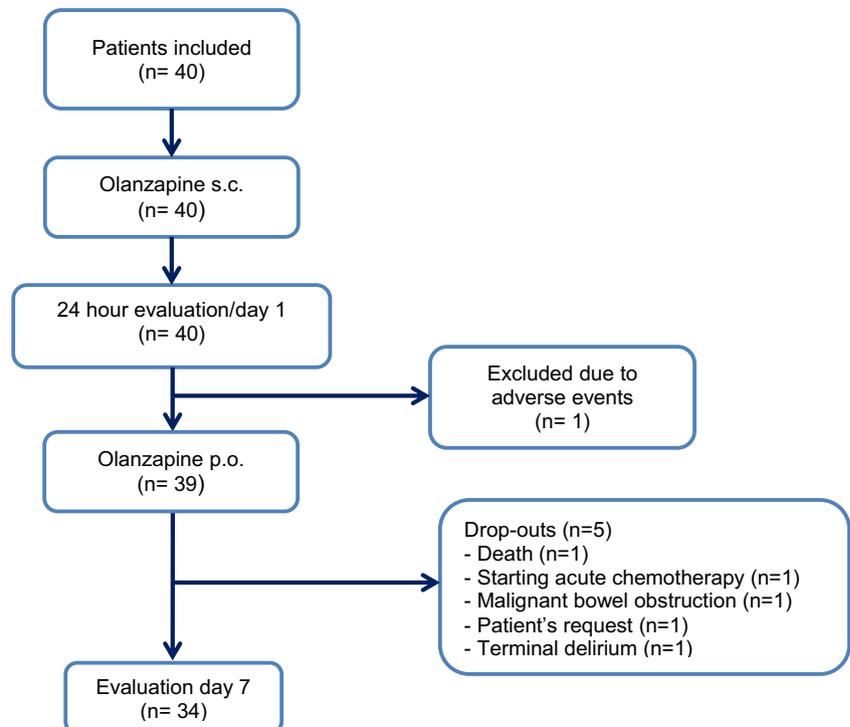
Follow-up time was 7 days, and efficacy parameters included a daily patient diary and an extended version of the EORTC QLQ-C15-PAL questionnaire [26] completed at baseline, 24 h following the injection (selected items only), and after 7 days (Fig. 1).

The patient diary included the following assessments: (a) number of emetic episodes, (b) time to the first emetic episode, (c) degree of nausea (recorded on a 4-graded scale (“none,” “mild,” “moderate,” or “severe”)), (d) use of rescue antiemetics, and (e) compliance regarding study medication. An emetic episode was defined as a vomit or dry retch.

The EORTC QLQ-C15-PAL questionnaire was extended with the addition of five items regarding nausea/vomiting from the validated EORTC item bank [27]. The added items were as follows (during the past week): (1) Have you vomited? (2) Has nausea or vomiting interfered with your ability to enjoy life? (3) Have you eaten less because of nausea or vomiting? (4) Has nausea or vomiting interfered with your physical activities like taking a walk? (5) Has nausea or vomiting interfered with your sleep? When reporting on the selected N/V items 24 h following the injection, all items were initiated with “During the past 24 hours (following the injection): Have you ...” The items were selected to measure both a higher and lower degree of nausea/vomiting than the original nausea item, allowing a more precise measurement of N/V using the derived “two-item N/V score” (as in EORTC QLQ-C30) or the “multi-item N/V score.” The two-item N/V score has a range of 0–100, where 100 = worst outcome. The items selected from the item bank for this study were scored using a *T* score where the European Norm is 50 and SD = 10, and yielded a range of 48–103 for the multi-item N/V score, where 48 = a patient responding “none” to all N/V items and 103 = a patient responding “very much” to all N/V items.

Adverse events were recorded in accordance with the CTC-AE version 4.0 guidelines. Primary adverse events recorded were (a) fatigue, (b) sedation, (c) dizziness, (d) extrapyramidal symptoms, (e) constipation, (f) hypotension, and (g) seizures.

**Fig. 1** The patient flow



## Objectives and statistical analysis

Primary objective:

- Change in nausea score recorded on the diary at baseline and 24 h following injection of 10 mg olanzapine. Presented in a contingency table and tested for symmetry using an exact marginal homogeneity test.

Secondary objectives:

- The two-item N/V score and multi-item N/V score from the extended EORTC questionnaire recorded at baseline, 24 h after injection, and after 7 days, tested for significant differences using a Wilcoxon signed-rank test.
- The number of emetic episodes tested for significant differences between baseline and 24 h following injection using Wilcoxon's signed-rank test.
- Adverse events recorded at baseline, 24 h after injection, and at 7 days tested for significant changes using an exact marginal homogeneity test.

The threshold for a significant  $p$  value is 0.05 in all analyses.

## Results

From August 2016 to August 2018, 40 patients from four centers were included.

No patients were lost to follow-up within the first 24 h, meaning that all 40 patients are included in the analysis of the primary parameter (effect on nausea and/or vomiting within the first 24 h). Patient baseline characteristics are shown in Table 1 and patient flow is shown in Fig. 1.

## Efficacy

**Nausea** Thirty-five of 40 patients experienced an improvement in nausea and five patients reported the same degree of nausea after 24 h ( $p < 0.001$ ) (Table 2).

**Emesis** Nineteen patients reported one or more emetic episodes at baseline with seven patients reporting a single emetic episode and 12 reporting more than one at baseline (Fig. 2). Twenty-four hours following injection of olanzapine, 29 patients had not experienced any emetic episodes while three patients reported a single episode and five patients reported more than one emetic episode ( $p = 0.003$ ). In three patients, there were no records on emetic episodes after 24 h.

The two-item N/V score had a mean of 66 at baseline, 21 at 24 h, and 24 at 7 days respectively (Fig. 3). This is statistically

**Table 1** Patient characteristics at baseline

	<i>n</i> (%)
Number of patients	40
Female	22 (55)
Male	18 (45)
Age (median, range)	67 (37–88)
Cancer diagnosis	
Gastrointestinal	9 (23)
Pancreatic	8 (21)
Lung	6 (15)
Breast	6 (15)
Prostate	2 (5)
Stomach	2 (5)
Urinary	2 (5)
Gynecologic	2 (5)
Other	3 (8)
Antiemetics*	
Metoclopramide	13 (33)
Ondansetron	11 (28)
Domperidone	10 (26)
Haloperidol	6 (15)
Corticosteroids	4 (10)
Cannabinoids	1 (3)
None	5 (13)

\*Antiemetics used within the last 24 h before inclusion in the study. Some patients used more than one drug

significant comparing baseline to day 1 ( $p < 0.001$ ) and day 7 ( $p < 0.001$ ).

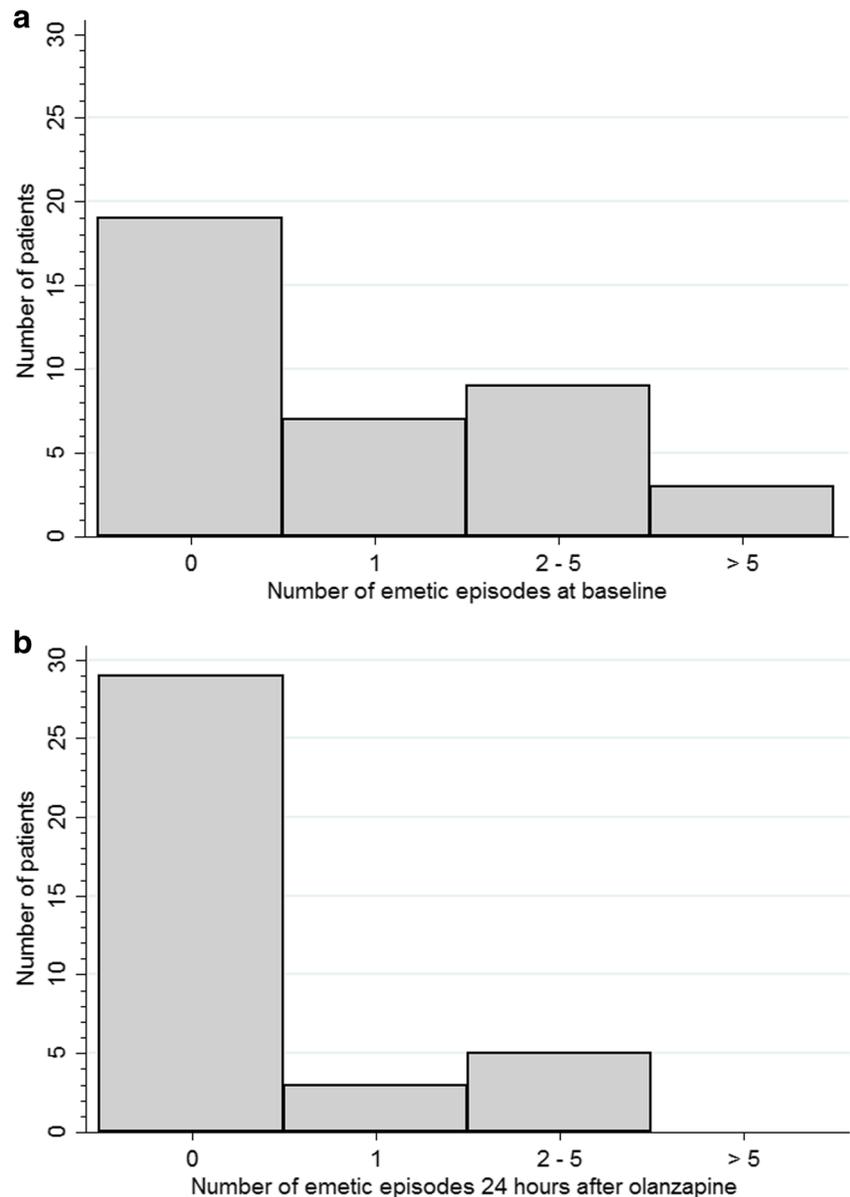
The multi-item N/V score had a mean of 85 at baseline and 61 at 24 h and 64 at 7 days respectively. This is statistically significant comparing baseline to day 1 ( $p < 0.001$ ) and day 7 ( $p < 0.001$ ).

**Antiemetics** At baseline, 35 of 40 patients had received antiemetic treatment within the previous 24 h, some with more than one drug. The most commonly used treatments included metoclopramide, ondansetron, and domperidone (Table 1). In

**Table 2** The degree of nausea recorded at baseline and 24 h after the injection of olanzapine (italic, improvement; bold, worsening)

At baseline	After 24 h				Total
	None	Mild	Moderate	Severe	
None	0	<b>0</b>	<b>0</b>	<b>0</b>	0
Mild	<i>1</i>	1	<b>0</b>	<b>0</b>	2
Moderate	<i>10</i>	<i>11</i>	3	<b>0</b>	24
Severe	<i>6</i>	3	4	1	14
Total	17	15	7	1	40

**Fig. 2** The number of emetic episodes at baseline (a) and 24 h after the first dose of olanzapine (b)



the 24 h following the first dose of olanzapine, 10 patients needed rescue antiemetics.

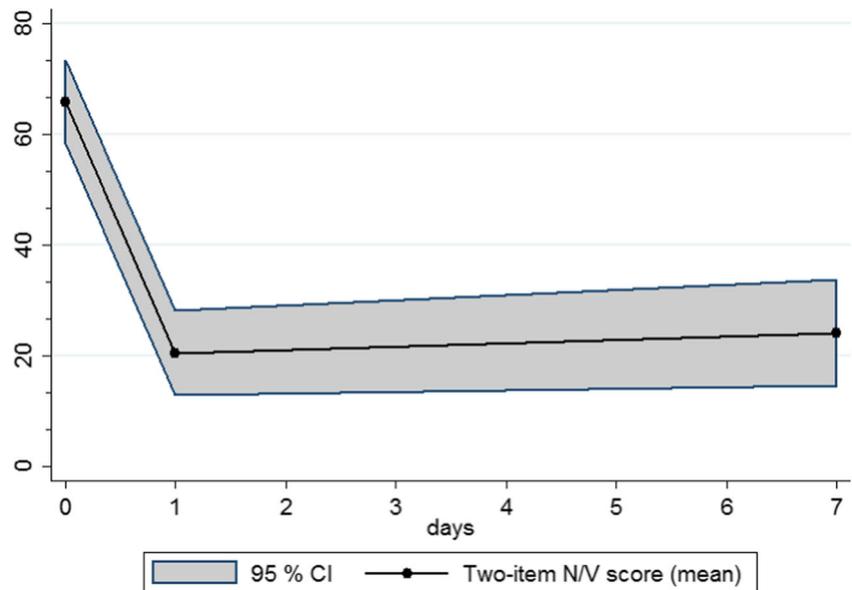
### Tolerability

A total of 15 patients had some degree of worsening in regard to fatigue, dizziness, and/or sedation when comparing baseline and 24 h after the injection of olanzapine (Table 3). Three patients had a worse degree of all three adverse events, one of whom was withdrawn from the study due to these symptoms. Two patients had both fatigue and sedation while the remaining 10 patients reported a single symptom. No adverse events were statistically significant different at baseline and after 24 h. No patients reported hypotension, constipation, or seizures. One patient, who had suffered from episodes of tremor in one

hand during the last 6 months, developed such an episode day 6, subsiding without any intervention. During the course of the study, three patients were reduced in dose of olanzapine due to adverse events, one after 24 h and two during day 2. Five patients were discontinued in the study. One patient was discontinued due to malignant bowel obstruction possibly aggravated by the use of olanzapine. One died during the study due to progression in the malignant disease, and the remaining three patients were discontinued due to progression in the malignant disease or by patient's request (Fig. 1).

At 7 days, eight, two, and six patients reported a lower degree of fatigue, dizziness, and sedation respectively while zero, four, and two reported a higher degree. The occurrence of these symptoms was not significantly different at baseline and day 7.

**Fig. 3** The two-item N/V score recorded at baseline, 24 h, and 7 days after the first dose of olanzapine



## Discussion

This open study appears to be the first prospective study to investigate the efficacy and tolerability of olanzapine within this patient group since the pilot study by Passik et al. in 2002 [28]. Our results indicate that olanzapine is an effective and tolerable antiemetic in patients with advanced cancer not

receiving chemotherapy or irradiation. This finding seems to be in agreement with the limited number of case reports and retrospective studies previously published [8–18].

Though adverse events did not meet statistically significant levels, we noticed a pattern with some patients experiencing fatigue, sedation, and dizziness following the subcutaneous injection of olanzapine 10 mg. This mode of administration has been tested in patients with advanced cancer once before [25] and four of 24 included patients experienced some degree of systematic adverse events (hypotension, paradoxical agitation, seizure, and diabetes insipidus). Since our patients did not report the same levels of adverse events after changing to the oral formulation, we speculate that this could be due to the following: (a) the injection is the first dose of olanzapine and the tolerability might improve with subsequent doses, (b) the subcutaneous injection causes on average a 5 times higher peak concentration than the equivalent oral dose [29] possibly resulting in more adverse events, and (c) the injection is administered during the day while the oral tablet is administered before bedtime, which may decrease the severity and frequency of some adverse events. Further investigation into the difference between modes of administration is needed since no further conclusions can be drawn from our results.

The dose of olanzapine chosen for this study is in the higher end when comparing to former publications in this patient group [8–18]. When looking at CINV studies, small-dose effect studies of questionable quality have demonstrated no dose effect on neither efficacy nor tolerability of olanzapine in doses ranging from 2.5–10 mg [30, 31]. In a review of studies of olanzapine in CINV, 811 patients were included, all received 10 mg olanzapine daily for up to 5 days. The authors concluded that the use of olanzapine was associated with significant improvements in CINV prevention and no significant safety concerns could be found following this

**Table 3** The degree of adverse events recorded at baseline and 24 h after the injection of olanzapine (*italic*, improvement; **bold**, worsening)

Fatigue	After 24 h				
At baseline	None	Mild	Moderate	Severe	Total
None	0	<b>1</b>	<b>1</b>	<b>0</b>	2
Mild	<i>1</i>	8	<b>4</b>	<b>0</b>	13
Moderate	<i>0</i>	<i>0</i>	11	<b>2</b>	13
Severe	<i>0</i>	<i>0</i>	<i>4</i>	8	12
Total	1	9	20	10	40
Sedation	After 24 h				
At baseline	None	Mild	Moderate	Severe	Total
None	17	<b>3</b>	<b>1</b>	<b>1</b>	22
Mild	3	9	<b>2</b>	<b>0</b>	14
Moderate	<i>1</i>	<i>1</i>	2	<b>0</b>	4
Severe	<i>0</i>	<i>0</i>	<i>0</i>	0	0
Total	21	13	5	1	40
Dizziness	After 24 h				
At baseline	None	Mild	Moderate	Severe	Total
None	13	<b>3</b>	<b>2</b>	<b>0</b>	18
Mild	2	15	<b>3</b>	<b>0</b>	20
Moderate	<i>0</i>	<i>0</i>	2	<b>0</b>	2
Severe	<i>0</i>	<i>0</i>	<i>0</i>	0	0
Total	15	18	7	0	40

Fatigue  $p = 0.18$ , sedation  $p = 0.74$ , dizziness  $p = 0.08$

short-term administration [32]. Another review questioned this conclusion, claiming that evidence is too low to conclude anything [23]. Two patients in our study were reduced in dose to 5 mg with continuous and unaltered effect, but no conclusions can be drawn from this and further research into the most appropriate dose of olanzapine is needed.

Thirty-five of 40 patients had received antiemetic treatment within the last 24 h before inclusion but still reported at least moderate nausea and/or at least one emetic episode. All of the five patients without previous antiemetic treatment reported an effect of olanzapine 24 h after the first dose, and 31 of 35 patients (89%) with no or insufficient effect of previous antiemetic treatment experienced an effect of olanzapine.

### Strengths and limitations of the study

The inclusion of 40 patients is an improvement in sample size compared to other studies within this field. The use of both a validated diary and a validated quality-of-life questionnaire makes comparisons to other studies possible. The nausea question and addition of five N/V items from the EORTC item bank along with the nausea score from the diary leave us with a fine-tuned and clinically relevant measurement tool. We included patients from multiple study sites and from hospital, hospices, or at home, representing the clinical everyday life of this patient group.

The open and uncontrolled design of this trial imposes some limitations in concluding on our objectives. We know that the lack of a control group includes a risk of overestimation both in regard to effect and level of adverse events. Even considering this, we find that the results are so convincing (all in favor of an effect of olanzapine) that we conclude that short-term use of olanzapine is effective in this patient group.

We used inclusion and exclusion criteria yielding a highly selected patient population and some difficulty in recruitment. Danish patients are generally undergoing active oncologic treatment very close to end of life and it was difficult finding patients both being 2 weeks from the last active treatment and still with a life expectancy exceeding 2 weeks. Also the fact that patients had to report at least moderate nausea and/or at least one emetic episode within the last 24 h with no reversible causes (no bowel obstruction, no increased brain pressure, no hepatic or renal failure, no newly commenced or changed opioid treatment, or other emetic drugs) limited the number of eligible patients. Finally, some patients were unable to fill in the study forms.

### Conclusions/perspectives

The aim of this open-label study was to expand our knowledge regarding treatment of nausea and/or vomiting in patients with advanced cancer by investigating the efficacy and

tolerability of olanzapine. Our results indicate that short-term use of olanzapine is both effective and tolerable.

Based on the findings of this study, olanzapine can be considered a reasonable option for the short-term management of nausea and/or vomiting in patients with advanced cancer. The use of olanzapine for a longer duration needs further investigation. Future research should also include a randomized controlled trial with olanzapine 5 mg and olanzapine 10 mg compared to placebo and a trial comparing the lowest effective dose of olanzapine with metoclopramide or haloperidol.

### Compliance with ethical standards

Permissions from the Danish Medicines Agency and the Local Ethics Committee were obtained before initiation of the study. No study procedures were initiated before a written informed consent had been signed by the patient.

**Conflict of interest** This study received funding from the Danish Cancer Society, the IMK Foundation, and Odense University Hospital. The funding sources had no influence on design, conduction, analyses of results, or manuscript writing. The authors declare no conflicts of interest.

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### References

- Glare P, Miller J, Nikolova T, Tickoo R (2011) Treating nausea and vomiting in palliative care: a review. *Clin Interv Aging* 6:243–259. <https://doi.org/10.2147/cia.s13109>
- Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC, Seeman P, Wong DT (1996) Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 14(2):87–96. [https://doi.org/10.1016/0893-133x\(94\)00129-n](https://doi.org/10.1016/0893-133x(94)00129-n)
- Berger MJ, Ettinger DS, Aston J, Barbour S, Bergsbaken J, Bierman PJ, Brandt D, Dolan DE, Ellis G, Kim EJ, Kirkegaard S, Kloth DD, Lagman R, Lim D, Loprinzi C, Ma CX, Maurer V, Michaud LB, Nabell LM, Noonan K, Roeland E, Rugo HS, Schwartzberg LS, Scullion B, Timoney J, Todaro B, Urba SG, Shead DA, Hughes M (2017) NCCN guidelines insights: antiemesis, version 2.2017. *J Natl Compr Cancer Netw* 15(7): 883–893. <https://doi.org/10.6004/jnccn.2017.0117>
- Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, Danso MA, Dennis K, Dupuis LL, Dusetzina SB, Eng C, Feyer PC, Jordan K, Noonan K, Sparacio D, Somerfield MR, Lyman GH (2017) Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 35(28): 3240–3261. <https://doi.org/10.1200/jco.2017.74.4789>
- Herrstedt J, Roila F, Warr D, Celio L, Navari RM, Hesketh PJ, Chan A, Aapro MS (2017) 2016 updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following high emetic risk chemotherapy. *Support Care Cancer* 25(1):277–288. <https://doi.org/10.1007/s00520-016-3313-0>
- Walsh D, Davis M, Ripamonti C, Bruera E, Davies A, Molassiotis A (2017) 2016 updated MASCC/ESMO consensus recommendations: management of nausea and vomiting in advanced cancer. *Support Care Cancer* 25(1):333–340. <https://doi.org/10.1007/s00520-016-3371-3>

7. Passik SD, Navari RM, Jung SH, Nagy C, Vinson J, Kirsh KL, Loehrer P (2004) A phase I trial of olanzapine (Zyprexa) for the prevention of delayed emesis in cancer patients: a Hoosier Oncology Group study. *Cancer Investig* 22(3):383–388
8. Jackson WC, Tavernier L (2003) Olanzapine for intractable nausea in palliative care patients. *J Palliat Med* 6(2):251–255. <https://doi.org/10.1089/109662103764978506>
9. Srivastava M, Brito-Dellan N, Davis MP, Leach M, Lagman R (2003) Olanzapine as an antiemetic in refractory nausea and vomiting in advanced cancer. *J Pain Symptom Manag* 25(6):578–582
10. Shinjo T, Okada M (2006) Olanzapine use in cancer patients for refractory vomiting. *Gan To Kagaku Ryoho* 33(3):349–352
11. Kitada T, Narimatsu T, Yamaguchi S (2009) Olanzapine as an antiemetic in intractable nausea and anorexia in patients with advanced hepatocellular carcinoma: three case series. [Japanese]. *Acta Hepatologica Japonica* 50(3):153–158
12. Navari RM, Brenner MC (2010) Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial. *Support Care Cancer* 18(8):951–956. <https://doi.org/10.1007/s00520-009-0739-7>
13. Kaneishi K, Kawabata M, Morita T (2012) Olanzapine for the relief of nausea in patients with advanced cancer and incomplete bowel obstruction. *J Pain Symptom Manag* 44(4):604–607. <https://doi.org/10.1016/j.jpainsymman.2011.10.023>
14. Murakami N, Tanabe K, Yamatani K, Kitazawa H, Fujikawa Y, Amemiya Y, Shimada M, Kadoya S (2012) Use of orally disintegrating olanzapine tablet for patients with cancerous peritonitis and postoperative gastric cancer receiving home palliative care. *Gan To Kagaku Ryoho* 39(4):649–652
15. Atkinson SR (2014) Olanzapine for intractable nausea and vomiting in palliative care patients not receiving chemotherapy. *J Palliat Med* 17(5):503–504. <https://doi.org/10.1089/jpm.2014.0030>
16. Suzuki M, Komuro K, Ohara K (2014) Olanzapine and betamethasone are effective for the treatment of nausea and vomiting due to metastatic brain tumors of rectal cancer. *Case Rep Gastroenterol* 8(1):13–17. <https://doi.org/10.1159/000358044>
17. Kaneishi K, Nishimura K, Sakurai N, Imai K, Matsuo N, Takahashi N, Okamoto K, Suga A, Sano H, Maeda I, Nishina H, Yamaguchi T, Morita T, Iwase S (2016) Use of olanzapine for the relief of nausea and vomiting in patients with advanced cancer: a multicenter survey in Japan. *Support Care Cancer* 24(6):2393–2395. <https://doi.org/10.1007/s00520-016-3101-x>
18. MacKintosh D (2016) Olanzapine in the management of difficult to control nausea and vomiting in a palliative care population: a case series. *J Palliat Med* 19(1):87–90. <https://doi.org/10.1089/jpm.2015.0224>
19. Dev R (2018) Intractable nausea and anorexia with weight loss in a patient with advanced breast cancer. *J Cachexia Sarcopenia Muscle* 9(1):203
20. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L, Kissling W, Leucht S (2010) Olanzapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev* (3):Cd006654. <https://doi.org/10.1002/14651858.CD006654.pub2>
21. Boettger S, Jenewein J, Breitbart W (2015) Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: a comparison of efficacy, safety, and side effects. *Palliat Support Care* 13(4):1079–1085. <https://doi.org/10.1017/s1478951514001059>
22. Sutherland A, Naessens K, Plugge E, Ware L, Head K, Burton MJ, Wee B (2018) Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults. *Cochrane Database Syst Rev* 9:CD012555. <https://doi.org/10.1002/14651858.CD012555.pub2>
23. Fonte C, Fatigoni S, Roila F (2015) A review of olanzapine as an antiemetic in chemotherapy-induced nausea and vomiting and in palliative care patients. *Crit Rev Oncol Hematol* 95(2):214–221. <https://doi.org/10.1016/j.critrevonc.2015.02.010>
24. Markowitz JS, DeVane CL, Malcolm RJ, Gefroh HA, Wang JS, Zhu HJ, Donovan JL (2006) Pharmacokinetics of olanzapine after single-dose oral administration of standard tablet versus normal and sublingual administration of an orally disintegrating tablet in normal volunteers. *J Clin Pharmacol* 46(2):164–171. <https://doi.org/10.1177/0091270005283839>
25. Elsayem A, Bush SH, Munsell MF, Curry E 3rd, Calderon BB, Paraskevopoulos T, Fadul N, Bruera E (2010) Subcutaneous olanzapine for hyperactive or mixed delirium in patients with advanced cancer: a preliminary study. *J Pain Symptom Manag* 40(5):774–782. <https://doi.org/10.1016/j.jpainsymman.2010.02.017>
26. Groenvold M, Petersen MA, Aaronson NK, Arraras JI, Blazeby JM, Bottomley A, Fayers PM, De Graeff A, Hammerlid E, Kaasa S, Sprangers MAG, Bjorner JB (2006) The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. *Eur J Cancer* 42(1):55–64
27. Petersen MA, Aaronson NK, Arraras JI, Chie WC, Conroy T, Costantini A, Dirven L, Fayers P, Gamper EM, Giesinger JM, Habets EJJ, Hammerlid E, Helbostad J, Hjermstad MJ, Holzner B, Johnson C, Kemmler G, King MT, Kaasa S, Loge JH, Reijneveld JC, Singer S, Taphoorn MJB, Thamsborg LH, Tomaszewski KA, Velikova G, Verdonck-de Leeuw IM, Young T, Groenvold M (2018) The EORTC CAT Core—the computer adaptive version of the EORTC QLQ-C30 questionnaire. *Eur J Cancer* 100:8–16. <https://doi.org/10.1016/j.ejca.2018.04.016>
28. Passik SD, Lundberg J, Kirsh KL, Theobald D, Donaghy K, Holtsclaw E, Cooper M, Dugan W (2002) A pilot exploration of the antiemetic activity of olanzapine for the relief of nausea in patients with advanced cancer and pain. *J Pain Symptom Manag* 23(6):526–532
29. EMA (2006) [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000115/WC500055207.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000115/WC500055207.pdf). Accessed July 2018
30. Bun S, Yonemori K, Akagi T, Noguchi E, Shimoi T, Shimomura A, Yunokawa M, Shimizu C, Fujiwara Y, Makino Y, Hayashi Y, Tamura K (2018) Feasibility of olanzapine, multi acting receptor targeted antipsychotic agent, for the prevention of emesis caused by continuous cisplatin- or ifosfamide-based chemotherapy. *Investig New Drugs* 36(1):151–155. <https://doi.org/10.1007/s10637-017-0487-3>
31. Yanai T, Iwasa S, Hashimoto H, Ohyanagi F, Takiguchi T, Takeda K, Nakao M, Sakai H, Nakayama T, Minato K, Arai T, Suzuki K, Shimada Y, Nagashima K, Terakado H, Yamamoto N (2018) A double-blind randomized phase II dose-finding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. *Int J Clin Oncol* 23(2):382–388. <https://doi.org/10.1007/s10147-017-1200-4>
32. Hocking CM, Kichenadasse G (2014) Olanzapine for chemotherapy-induced nausea and vomiting: a systematic review. *Support Care Cancer* 22(4):1143–1151. <https://doi.org/10.1007/s00520-014-2138-y>