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Review Article

Does an Antipsychotic Hold the Key to Nausea Treatment in Cancer Patients? A Review on the Anti-Nausea Effects of Olanzapine in Oncology

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ABSTRACT

Olanzapine is an antipsychotic and has increasingly become a reliable option in treating cancer-associated nausea and vomiting, especially in cases involving use of high-emetic risk chemotherapy agents. How nausea and vomiting occur in this context is explored, along with the mechanism of action of olanzapine and its beneficial as well as adverse effects. Analyzing sources implicated in understanding olanzapine's role in cancer treatment, this review notes the harms associated with nausea and vomiting induced by chemotherapy and radiation therapy (CINV and RINV, respectively), as well as evidence to support the use of olanzapine over options such as dexamethasone and aprepitant. How nausea is caused by anticancer therapy via stimulation of the chemoreceptor trigger zone is explained. To familiarize readers with recommendations from various guidelines, levels of emetic risk are defined, and examples are given to identify which chemotherapy agents fit into these levels. The mechanism of action of olanzapine is explained, in terms of its effects on receptors, its targeted areas in the brain, and suggestions for administration times to avoid sedation. Olanzapine's beneficial effects in terms of quality of life, mental health benefits, and cost-effectiveness are suggested, along with adverse effects such as somnolence, weight gain, and QT prolongation.

Keywords: Olanzapine, guidelines, CINV, RINV, Nausea, Dosage, Administration

1. Introduction

Cancer-associated nausea and vomiting, particularly chemotherapy and radiation therapy (RT) induced nausea and vomiting (CINV and RINV, respectively), pose unique challenges for patients and healthcare workers alike. Due to its distressing nature, many patients living with CINV experience poor quality of life[1-7]. Chemotherapy dramatically alters the gastrointestinal (GI) system's microbiome, leading to not only widespread negative GI impacts such as abdominal pain and nausea, but also poor mental health[8]. Poor mental health, chronic pain, and nausea all appear intertwined in the life of an oncology patient[8,9]. In fact, having the lived experience of cancer and all the complex nuances that accompany it increase one's risk of having a psychiatric disorder[9]. Because of its background as an antipsychotic, olanzapine's propensity for aiding in mental health-related symptoms in patients living with cancer is an added benefit[6]. This discovery allows for the unification of two branches of medicine: psychiatry and oncology, where patients living through the adversities of cancer may find solace from CINV and the mental health implications that arise from having a cancer diagnosis, all by using an unlikely hero such as olanzapine.

Difficulties arise from the perspective of those working in healthcare. It has been widely researched that following guidelines to control CINV results in better resulting care of this treacherous adverse effect[1-3,7], but some researchers note that there are still yet inconsistencies in enacting these guidelines into practice[1,3]. One study suggests that difficulties in following guidelines is often multifaceted, with oncology nurses sometimes being unfamiliar with guidelines and physician preference

seemingly overriding recommendations from these guidelines[3]. It is in this context that one can see the need to improve treatment on cancer-associated nausea and vomiting, not only with raising awareness of the need to follow guidelines, but to also highlight the use of medication options that may be previously thought to be unconventional, such as olanzapine. This review utilized information from 30 different sources, which were located using the search engine located on the Northern Ontario School of Medicine University's Health Sciences Library website with search entries such as "antinausea guidelines oncology" and "history of olanzapine and antiemesis". To assess olanzapine's role in CINV and RINV treatment, this review first analyzes how nausea occurs because of anticancer therapy, and then reviews emetic risk as well as recommendations put forth by guidelines. To support the use of olanzapine, the harms associated with CINV and RINV are discussed, and there are arguments put forward that suggest olanzapine's advantages over alternative options such as aprepitant and dexamethasone. Next, olanzapine's mechanism of action is explored as well as recommendations on how to administer this medication. Finally, beneficial, and adverse effects of olanzapine are assessed.

2. Mechanisms Behind the Causation of Nausea Associated with Anticancer Therapy

Two options for treating cancer are chemotherapy and radiation therapy (RT), and they induce nausea and vomiting via different mechanisms. Chemotherapy has the astonishing ability to stunt the growth of a tumour or even kill it, but not without killing nearby normal cells, causing a wide array of adverse effects[10]. Chemotherapy induced nausea and vomiting (CINV) occurs when serotonin (5HT-3) receptors located in the upper gastrointestinal region become stimulated, thus causing stimulation of the vomiting center located in the medulla oblongata, along with the stimulation of neurokinin-1 (NK-1) and dopamine (D2) receptors found in the chemoreceptor trigger zone[6,11]. Other stimulated areas include the area postrema, cerebral cortex, and the limbic system[6]. Knowing the causative agents behind CINV means that treatment can target these receptors via blockade of serotonin, dopamine, and substance P[11]. It is of significance to note that CINV can be classified as either acute (which occurs up to 24 hours after chemotherapy is administered) or delayed (which occurs on the second day of treatment and can last up to seven days)[1,10]. Nausea and vomiting involve three phases, including pre-ejection, retching, and ejection of vomitus[12]. RT induces vomiting via the stimulation of release of serotonin from enterochromaffin cells within the intestines and stomach, along with the release of substance P from the brain and dopamine which is proposed to also increase changes in gastrointestinal motility. This allows for the activation of NK-1 receptors, D2 receptors, and 5HT3 receptors[6], which makes treatment of RINV apparently like CINV in the blockade of these receptors.

Because olanzapine has a background in psychiatry[10,12-14], it is prudent to also comment on the possible relationship between mental health and cancer-related nausea and vomiting. Pain and anxiety commonly interplay between each other, with pain being a common feature in cancer, whether it be caused by physical causes such as metastasis, RT, or chemotherapy[1,6], or psychosocial causes such as social exclusion, existential fears, or reduced quality of life[9]. Anxiety and depression may also arise surrounding concerns of recurrence of cancer and metastasis[15]. Anxiety and depression can be noted as a potential cause of nausea and vomiting in these cases, as well as gastrointestinal (GI) causes including bowel obstruction and gastroparesis[6]. Recent developments have noted a relationship between the GI tract and mental health, with this being highlighted in a study involving cancer survivors, a significant number of which experienced poorer scores of mental health, and higher rates of diarrhea, constipation, abdominal pain, and bloating[9]. Opioids, which are used in controlling pain, may also cause nausea and vomiting in oncology patients[6], and addictions issues that may arise in cancer survivors due to opioid use adds another convoluted layer to understanding the relationship between cancer, pain, and mental health[15]. Potential future studies may choose to elaborate on olanzapine's role in treating patients living with both CINV and significant mental health issues exacerbated by the psychosocial aspects of being a cancer patient.

3. Understanding Emetic Risk and Associated Guidelines with Anticancer Therapies

To best understand olanzapine's role in the treatment of CINV and RINV, it is helpful to become aware of what guidelines recommend and how these staples in oncology define levels of emetic risk. Various guidelines, including those from the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) report that chemotherapy agents with high emetic risk produce a greater than 90% risk of vomiting and include any regimens that include cyclophosphamide and an anthracycline (AC combination), as well as cisplatin, dacarbazine, mechlorethamine, and streptozocin, among others[2,5,16,17]. Moderate risk agents carry a 30-90% risk of emesis and include agents such as bendamustine, busulfan, carboplatin, daunorubicin, and irinotecan[2,16,17]. Low risk chemotherapy agents as well as immunotherapy agents carry a risk of emesis of 10-30% and include agents like docetaxel, eribulin, necitumumab, and paclitaxel[2,16,17]. Finally, minimal emetic risk agents carry a less than 10% risk of emesis and include both chemotherapy and immunotherapy agents such as pembrolizumab, trastuzumab, vinorelbine, nivolumab, and bevacizumab[2,5,16,17].

In cases where high emetic risk agents are used, a four-drug combination is recommended by ASCO and MASCC/ESMO for the treatment of delayed CINV, and these agents include a NK-1 receptor inhibitor (such as aprepitant), a 5HT-3 receptor antagonist (such as ondansetron or palonosetron), dexamethasone, and olanzapine, with some of these drugs being implemented dependent on what day of chemotherapy the patient is on. Specifically, these organizations have recommended that if agents such as cisplatin and other high emetic risk chemotherapies are used, then to administer all four options on the first day, and then on days two to four, olanzapine and dexamethasone are to be administered. In cases where chemotherapy involves an AC combination, then the same would be true with the use of all four medications on day one but on days two to four, dexamethasone is excluded[5,16,17]. However, NCCN presents 3 different treatment options, with option A being favoured and aligning with the recommendations from ASCO and MASCC/ESMO in cases where an AC combination is involved[2,5,16,17]. Option B involves the use of olanzapine, palonosetron, and dexamethasone on day one and olanzapine on days two to four, whereas option C involves a NK1-receptor antagonist, a 5HT-3 receptor antagonist, and dexamethasone on day 1, with aprepitant and dexamethasone recommended for use on days two to four[2,5].

In cases where carboplatin area under the curve (AUC) equal to or less than 4 mg/mL per minute (which is associated

with a moderate emetic risk), ASCO and MASCC/ESMO recommend using a three-drug antiemetic combination of the same medications excluding olanzapine. For patients receiving all other moderate emetic risk agents, these organizations recommend offering patients a serotonin receptor antagonist and dexamethasone on day one[5,16,17]. NCCN again suggests three different treatment options, but in this case without a suggested preference outlined. Option D involves a 5-HT3 receptor antagonist and dexamethasone on day 1, with either dexamethasone being recommended on days two to three or a monotherapy of a 5-HT3 receptor antagonist. Option E involves olanzapine, palonosetron, and dexamethasone on day one, and then olanzapine alone on days two and three. Finally, option F involves a NK-1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone on day 1, with aprepitant with or without dexamethasone (both to be administered on days two and three)[2,5].

As for cases involving low emetic risk anticancer therapies, different organizations recommend different algorithms. NCCN recommends either starting a 5HT-3 receptor antagonist, metoclopramide, prochlorperazine, or dexamethasone before initiating anticancer therapy[2,5]. MASC/ESMO similarly recommends use of either a 5HT-3 receptor antagonist, a dopamine receptor antagonist, or dexamethasone[5]. ASCO guidelines suggest either a single dose of a 5HT-3 receptor antagonist or a single dose of dexamethasone before starting anticancer therapy[5,16,17]. All the above organizations recommend that antiemetic therapies should not be offered in cases of use of minimal emetic risk agents[2,5,16,17]. Just as there is a range of emetogenicity with chemotherapy, there is also a range of risk associated with RINV depending on which body part is treated with RT. For example, RT that involves the whole body has a risk of RINV of 90%, while RT administered to the head or upper region of the abdomen has a risk of RINV of 3-90%[16,17].

4. Harms Associated with CINV, RINV, and other Antiemetic Candidates

CINV can be detrimental to oncology patients as it may discourage patients from continuing their treatment regimens, also adversely impeding on quality of life and one's ability to complete activities of daily life[1]. Without antiemetics, this dampening on the quality of life of patients living with cancer is exacerbated as vomiting incidence could increase to 70-80% in patients living with lung cancer[18], and to more than 90% in patients being treated with highly emetogenic chemotherapy[19]. Vomiting can cause dehydration, imbalances in electrolytes, and therefore extended hospitalizations that impede on one's quality of life[4]. Vomiting associated with radiation therapy is exceedingly common, with rates of 40-80% dependent on the body systems being treated with radiation, and because of this, these patients additionally face potential malnourishment and patient declination of further radiotherapy[6].

Before the use of anti-serotonergic therapies, CINV was treated using high-dose metoclopramide along with a corticosteroid as well as either diphenhydramine or lorazepam. Corticosteroids in general may lead to abnormalities to metabolism especially in relation to its potential to cause hypothalamic-pituitary-adrenal axis suppression, as well as adverse effects related to the central nervous system, eye pathologies such as cataracts and glaucoma, poor wound healing, elevated risk of infection, hypertension, and myopathy. Corticosteroids can also increase the risk of osteoporosis and osteonecrosis with long-term use[13]. In assessing the possible harms associated with dexamethasone use, various sources report abdominal symptoms, weight gain, and insomnia[4,15,20-22], as well as agitation[4,15,21,22], increased appetite[4,15,20,22], skin rash[20,21], and acne[4,15,22] (Table 1). All these adverse effects suggest a possible hinderance on quality of life[20]. Also of note is the notion that dexamethasone use as an antiemetic may impact the efficacy of immune checkpoint inhibitors, which are often prescribed in cases of gynecologic cancers[23]. Additionally, it has been suggested that dexamethasone use can be decreased without sacrificing a reduction in control of CINV[20,21], with its use possibly being limited to the first day of chemotherapy as noted by different guidelines[2,5,16,17,20].

Two other antiemetics of interest in guidelines are aprepitant and palonosetron[2,5,12,16]. Aprepitant, which is a neurokinin-1 (NK-1) receptor antagonist, works via the blockade of NK-1 central receptors found in areas of the brainstem that are integral in the reflex of vomiting, including the area postrema, nucleus tractus solitarius (NTS), and the central pattern generator. Aprepitant thereby reduces the launch of the vomiting reflex. Blockade of peripheral NK-1 receptors also occurs, allowing for the decreasing of vagal afferent signaling. Aprepitant use is associated with the following adverse effects: headache, fatigue, loss of appetite, constipation, nausea, diarrhea, and hiccups[24]. Interestingly, aprepitant can also interfere with dexamethasone metabolism[4], which is oftentimes a mainstay in the treatment of CINV[2,5,16,17]. Palonosetron is a 5-HT3 receptor antagonist, known to be in the same class of antiemetics as ondansetron, which has commonly been used for the treatment of CINV[2]. Palonosetron works via its blockade of serotonin receptors located in the peripheral vagus nerve terminals and the central CTZ of the area postrema. Blockade of these receptors attenuate the release of serotonin from enterochromaffin cells usually caused by anticancer therapy, thereby decreasing CINV due to the decrease in serotonin activation of 5-HT3 receptors found in vagal afferents that induce the reflex of vomiting. Common adverse effects include headache, constipation, diarrhea, and dizziness. It is also worth noting that in combination with other serotonergic medications, whether these additional medications be for the treatment of psychiatric illness or further treatment of CINV, the risk of serotonin syndrome is something clinicians should be aware of[25]. Comparing and contrasting adverse effect profiles and mechanisms of actions between different antiemetic options may be of great benefit, as it will warrant further research into modifying future CINV treatment guidelines, taking into considerations other adverse effects that may accompany unique anticancer therapy regimens, such as emetogenicity and possible increased potential of antiemetics to hamper or increase quality of life.

Table 1. Comparison of adverse effects of common CINV antiemetics.

Drugs	Mechanism of Action Against CINV	Adverse Effects	Other Notes
Corticosteroid *-Dexamethasone*	-Active in the central nervous system during acute and de-layed phases of emesis related to cisplatin therapy -May activate glucocorticoid receptors in the nucleus of the medulla's solitary tract -Antagonizes 5-HT receptors involved in emesis production	- Abdominal symptoms - Weight gain - Insomnia - Agitation - Increased appetite - Skin rash - Acne	-Decreases efficacy of immune checkpoint inhibitors

NK-1 Receptor Antagonist *-Aprepitant*	-Binds to central NK-1 receptors located in the NTS, central pattern generator, and area postrema (all crucial to the vomiting reflex). -Binds to peripheral NK-1 receptors found throughout the GI tract, thereby decreasing vagal afferent signaling.	- Headache - Fatigue - Loss of appetite - Diarrhea - Constipation - Nausea - Hiccups	-Interferes with dexamethasone metabolism, causing the need for decreased doses of dexamethasone
5-HT3 Receptor Antagonist *-Palonosetron*	-Binds to central and peripheral 5-HT3 receptors indicated in the production of the vomiting reflex, causing attenuation of serotonin release from enterochromaffin cells that activate vomit-inducing vagal afferents -Causes blockade of centrally located serotonin receptors in the CTZ of the area postrema, a key factor in the vomiting reflex	- Constipation - Headache - Diarrhea - Dizziness	-Be aware of potential for serotonin syndrome in patients who are using additional serotonergic medications.
Atypical Antipsychotic *-Olanzapine*	-Blocks dopamine (D1, D2, D3, D4), which attenuates the vomiting reflex triggered by the area postrema, and blocks serotonin (5-H2a, 5-HT2c, 5-HT3, 5-HT6). Blockade of dopamine and serotonin dampen the effects of the CTZ -Blocks catecholamines (a1-adrenergic receptors), and acetylcholine at muscarinic receptors (M1, M2, M3, M4). -Blockade of histamine at H1 receptors, together with blockade of serotonin at 5-HT2b and 5-HT2c receptors, cause a bolstering of appetite via the dimerization with ghrelin receptors and increasing the production of ghrelin.	- Sedation/somnolence - Dizziness - Weight gain - QT prolongation - Increased risk of extrapyramidal symptoms - Increased risk of loss of control of diabetes mellitus	-One important consideration for physicians is that female gender is a risk factor for CINV, increased blood concentrations of olanzapine, and EPS.

5. Mechanism of Action and Administration of Olanzapine

Olanzapine works via a variety of mechanisms, and is known to be an atypical second-generation thienobenzodiazepine antipsychotic[10,12] with blockade of dopamine (D1, D2, D3, D4 receptors) and serotonin (5-HT2a, 5-HT2c, 5-HT3, 5-HT6)[12-14], the former of which (specifically the D2 and D3 receptors) exerts its antinausea properties in the postrema region[6], and together purported to work on the chemoreceptor trigger zone (CTZ) and vomiting center of the brain[24]. Olanzapine also works via the blockade of catecholamines at alpha1 adrenergic receptors (α1), acetylcholine at muscarinic receptors, (M1, M2, M3, M4) and histamine at H1 receptors[12-14]. Overall, in its action against the centers of vomiting in the brain and entero-chromaffin cells, olanzapine has antinausea effects which in turn allow for beneficial action against anorexia. This is via its ability to boost appetite via its action on histaminergic receptors and serotonergic receptors (specifically, 5HT2B and 5HT2C) by dimerizing with ghrelin receptors, thereby antagonizing them and increasing the production of ghrelin (Figure 1; Table 1). Hepatic metabolism occurs via the mechanisms of glucuronidation and oxidative metabolism[6]. Olanzapine has a bioavailability of 85%, with a half-life of between 21 hours and 60 hours and a peak plasma concentration of approximately four to six hours[6,10].

Because of this peak occurring within this window of four to six hours, it is suggested that olanzapine may be administered about 5 hours before bedtime, as olanzapine is known for causing sedation[10,19]. One study suggests that risks of adverse effects are comparable between intramuscular (IM) and intravenous (IV), but that IV administration may potentially decrease the risk of drug-associated arrhythmias. IV olanzapine may be appropriate in patients with acute CINV as it may also shorten the amount of time spent by a patient in an emergency department as compared to onset of effects post-IM administration. However, IV administration of olanzapine has not yet been approved[10]. Some studies note that risk factors exist for the development of CINV, including female gender and younger age[20,23], as well as exposure to multiple cycles of highly emetogenic chemotherapy[20], therefore it is proposed that olanzapine use may be useful in these target populations. It has also been noted that olanzapine use in the treatment of CINV associated with moderate-emetogenic agents is not generally recommended as a first-line option. One can deduct from this reasoning that another possible target population for the use of olanzapine is that of oncology patients receiving highly emetogenic chemotherapy, as supported by guidelines in an above paragraph[2,5,16,17].

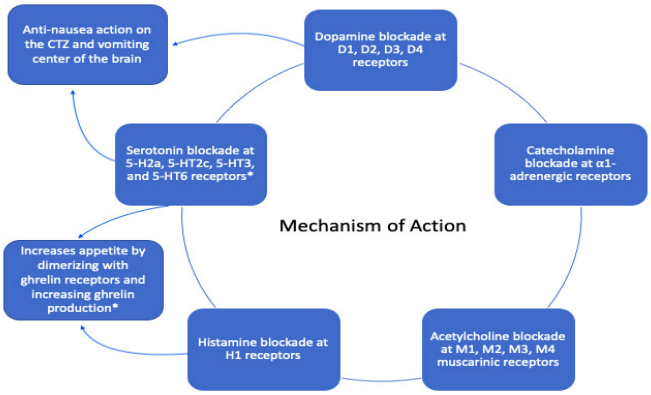

Figure 1: Diagram of the mechanism of action of olanzapine.

*Serotonin blockade at the 5-HT2b and 5-HT2c receptors increase appetite via its interaction with ghrelin.

6. Beneficial Effects of Olanzapine

Despite a background as an antipsychotic, olanzapine has the potential to have immense improvement of the quality of life of patients facing cancer. In 2009, olanzapine was approved for the treatment of schizophrenia by the Food and Drug Administration of the United States[27]. Originally used as a psychotropic in the treatment of schizophrenia[10,11] and bipolar disorder[10], olanzapine is a highly potent agent in the realm of antipsychotics with a 40 times more potent inhibition of α_2-adrenergic receptors in comparison to clozapine[28]. Although one source suggests that olanzapine is usually used by patients living with pathologies

that psychiatric and acute in nature[10], its natural home in the world of the treatment of psychosis assists in the mental health repercussions that can accompany a cancer diagnosis. It has been noted that oncology patients may go on to develop depression, anxiety, as well as sleep or adjustment disorders[11], and that olanzapine can play a role in decreasing anxiety and depression[6], in addition to its role in antiemesis[2,4,17,29]. Olanzapine fortunately has a lower incidence of extrapyramidal symptoms as compared to clozapine, specifically parkinsonism, dystonia, and akathisia. It was back in 2003 when olanzapine was first found to be effective in the treatment and prevention of nausea in patients who are palliating and being treated with opioids[28], with its antiemetic effects confirmed in the early 2000s[7,10]. As for quality of life, some sources have noted that olanzapine has an influence on improvement of symptoms and functional outcomes[14], along with a propensity to increase appetite[18] and boost well-being[6]. Although this review focuses on the antiemetic effects of olanzapine, one study suggests that quality of life studies is essential in oncology, as they may serve as a possible replacement to studies centered on survival in patients with advanced cancer[14].

Olanzapine as part of a treatment regimen also has efficacy benefits as compared to aprepitant[6,18,30]. For example, in patients receiving a combination of palonosetron and dexamethasone along with RT for treatment of locally advanced cancer of the esophagus, patients noted a substantial improvement in nausea after receiving 10 mg of olanzapine per day compared with IV aprepitant[6]. Olanzapine has a high safety profile and high CR rate against nausea and vomiting induced by carboplatin[30]. In one randomized, double-blind, phase III study, it was noted that there was a higher percentage of patients who had no experiences with CINV in the first 24 hours following chemotherapy, as well as within 25 to 120 hours, and the general 120-hour duration post-chemotherapy in patients who had received olanzapine along with dexamethasone, aprepitant, and a 5HT-3 receptor antagonist than those who received a placebo along with the aforementioned medications[31] (Table 2). There is also significant cost-effectiveness in comparison to this same agent. One study has suggested that four days use of oral olanzapine at a dose of 10 mg per day is considerably less expensive than a one-time IV dose of aprepitant[6]. In a study examining patients experiencing CINV and being treated with cisplatin, treatment with 5 mg of olanzapine (as opposed to the previous dosage of 10 mg) when given with ondansetron and dexamethasone was found to be a potential replacement for aprepitant in the same treatment regimen. This discovery suggests an even more significant potential for cost-benefit effectiveness in using olanzapine instead of aprepitant[18]. It should be also noted that in patients with advanced cancer who are not receiving chemotherapy or RT, olanzapine (at a dose of 10 mg) is an effective option for the treatment of nausea and vomiting[13].

Table 2: Clinical Trials with Olanzapine for Treatment of CINV.

Citation	n	Type of Study	Intervention(s)	Duration	Outcomes
Navari, et al. 2016[31]	380	Randomized, double-blind, phase 3 trial	Compared olanzapine with placebo in combination with dexamethasone, aprepitant or fosaprepitant, and a 5-HT3 receptor antagonist in patients with no previous chemotherapy treatment receiving cisplatin or cyclophosphamide-doxorubicin.	120 hours, evaluated in three separate periods (first 24 hours after chemotherapy, period of 25 to 120 hours after chemotherapy, and the 120- hour period overall).	-Greater proportion of patients without CINV in olanzapine group in all three periods as compared to placebo group (first 24-hour period [74% vs. 45%, P=0.002], 25-120 hours period [42% vs. 25%, P=0.002], and overall 120-hour period [67% vs. 52%, P=0.007]).
Wang, et al. 2018[18]	40	Observational study	Olanzapine 5 mg administered at bedtime 1 day before cisplatin therapy as well as on days 1 to 5. Complete response (CR) rate, rates of lack of nausea and vomiting, Self-Rating Anxiety Scale (SAS), Self-rating Depression Scale (SDS), and The Functional Living Index-Emesis (FLIE) were assessed over three phases (acute, delayed, and overall). Patients utilized a symptom diary to record nausea, vomiting, retching, use of rescue therapy, and adverse effects every 24 hours for 120 hours.	5 days separated into three phases (acute phase was defined as the first 24 hours after chemotherapy, the delayed phase was defined as the period of 25 hours to 120 hours, and the overall phase was the entire 120 hours after cisplatin was administered).	-CR for the acute, delayed, and overall phases were 82.5%, 75.0%, and 70.0%, respectively. No nausea rates were 70.0% in the acute phase and 62.5% in the delayed phase, while no vomiting rates were 85.0% phase in the acute phase and 77.5% in the delayed phase. In the overall phase, the no nausea rate was 57.5%, while the no vomiting rate was 75.0%.
Iihara, et al. 2020[23]	57	Single-arm, multi-institution, phase 2 study	5 mg of olanzapine was administered once daily at bedtime over 4 days to gynecological oncology patients in combination with NK1-RA antagonist, 5-HT3 receptor antagonist, and dexamethasone to prevent CINV in patients receiving carboplatin (BCDCA) combination therapy. Patients recorded symptoms of nausea, lack of appetite, sedation, and lack of concentration over 7 days from the initiation of CBDCA therapy, along with a five-item vomiting scale, a four-item scale evaluating the use of rescue medication, and a four-item scale evaluating lack of appetite. Patient Reported Outcome (PRO) Common Terminology Criteria for Adverse Events (CTCAE) version 1.0 was use on day 7 of the study, with evaluation of the following symptoms: nausea, vomiting, concentration, decreased appetite, changes to taste, xerostomia, hiccups, constipation, diarrhea, dizziness, and insomnia.	7 days, with evaluation of the following phases: acute (0-24 hours), delayed phase (24-120 hours), overall assessment period (120 hours; 5 days after initiation of CBDCA therapy) and extended-overall period (0-168 hours; 7 days).	-Complete response (CR; meaning no emesis and rescue therapy) rate was 78.9% for the overall phase, while the CR for the acute and delayed phases were 96.5% and 80.7% respectively. -Sedation was noted in 73.7% of patients, but sedation of grade 2 or above was only noted in 3.5% of patients.

Hashimoto, et al. 2020[19]	710	Randomized, double-blind, placebo-controlled, phase 3 study	5 mg of olanzapine was administered with standard antiemetic therapy (including aprepitant, palonosetron, and dexamethasone) and compared to placebo with the above standard therapy in patients with malignant tumours and who were receiving cisplatin therapy. Either placebo or olanzapine was administered after dinner for 4 days following administration of cisplatin. Diary entries were made by patients every 24 hours recording the number of vomiting episodes, time of first vomiting, nausea severity using a Likert scale, number of times rescue medications were used and the time it was first administered, severity of anorexia, severity of daytime somnolence and impaired concentration related to this, and frequency of sleepiness.	4 days duration, with the acute phase defined as 0-24 hours after starting cisplatin therapy, he delayed phase defined as 24-120 hours, and the overall phase defined as 0-120 hours following initiating cisplatin therapy.	-Complete response was defined as lack of vomiting, retching, and use of other antiemetics in the delayed phase. The number of patients who achieved this in the acute and overall phases were measured as well, along with measurement of nausea on a 4-grade scale and recording of any adverse events. Complete response in the delayed phase was noted in 79% of patients in the olanzapine group [95% CI 75-83; 280 of 354 patients], as compared to 66% of patients in the placebo group [p<0.0001; 231 of 351 patients]. 2 patients in the olanzapine group had adverse effects, with one reporting grade 3 constipation and the other reporting grade 3 somnolence.
Yamamoto, et al. 2021[30]	140	Three multicenter, prospective, single-arm, open-label phase 2 studies	5 mg of olanzapine was administered to oncology patients facing either lung cancer, gynecological cancer, or thoracic malignancies and being treated with CBDCA. Adverse effects were recorded in patient diaries using the CTCAE version 4.0, Eastern Cooperative Oncology Group (ECOG) performance status, and use of rescue medication was also recorded. Different antiemetic regimens were used in the three studies, with the first one involving a 5-HT receptor antagonist, aprepitant, dexamethasone, and olanzapine, the last of which was administered every day for 4 days. The second study involved administration of granisetron, aprepitant, dexamethasone (in either PO or IV formulations), and olanzapine again given over 4 days every day. Finally, the third study involved administration of granisetron, dexamethasone (either IV or PO), and olanzapine administered everyday over 4 days.	Studies 1 and 3 had a duration of 5 days, while the second study occurred over 7 days from the initiation of CBDCA therapy. CINV was assessed in the overall phase (0-120 hours after initiating cisplatin), acute phase (0-24 hours after initiating cisplatin), and in the delayed phase (24-120 hours after cisplatin initiation).	-Complete response was defined as no emetic episodes and no use of CINV rescue medication, while complete control (CC) rate while was defined as lack of emetic episodes, no use of CINV rescue medications, and lack of nausea higher than mild, and total control (TC) was defined as lack of emetic episodes, no nausea, and no CINV rescue medication administration. As compared to the placebo group, complete response was noted in 87.9% of the olanzapine group, complete control 86.4%, and total control 72.9%, all of which were noted in the overall phase.
Gao, et al. 2022[32]	132	Prospective randomized controlled trial	5 mg of olanzapine was administered in two groups, one with triple therapy consisting of aprepitant, tropisetron, and dexamethasone, and the other with the same above agents excluding aprepitant. Both groups were receiving cisplatin therapy. Cisplatin regimens occurred in combination with one other chemotherapy agent, of which included: gemcitabine, docetaxel, etoposide, pemetrexed, paclitaxel, capecitabin and irinotecan, sometimes with bevacizumab or Herceptin additionally. Olanzapine was administered every day for 3 days in both groups following initiation of cisplatin, with the aprepitant group being given aprepitant 125 mg PO on the first day and 80 mg on the following 2 days. Times and dates of vomiting and retching episodes were recorded, along with the use of rescue therapy. FLIE questionnaire scoring was recorded by patients on day 5, post-treatment exams were completed on days 6-8, and follow-up on days 19-21, whereby adverse effects were recorded for aprepitant and olanzapine.	Administration of antiemetics occurred over 3 days, while post-treatment examinations occurred on days 6-8, and follow-up sessions on days 19-21.	-Complete response was defined as the absence of vomiting episodes, lack of use of rescue medications, both in the overall phase. These markers were also assessed in the acute and delayed phases. TC rate was defined as the lack of nausea and vomiting episodes, lack of rescue medication use, again both measured in the overall phase. Complete response was 76.0% in the aprepitant group, and 67.0% in the triple group, while complete response in the acute phase was noted to be 100.0% in the aprepitant group and 93% in the triple therapy group. FLIE questionnaire scoring demonstrating no impact of CINV on daily living in both groups.

7. Adverse Effects of Olanzapine Use

Olanzapine use is accompanied by potential adverse effects, with dizziness being the most common[1] and dose-dependent[1,32]. Somnolence and sedation may also occur[12,13,23]. In a mixed group of oncology patients experiencing delirium, patients taking olanzapine experienced increased sedation in comparison to patients taking haloperidol, risperidone, or aripiprazole. However, this same study noted that patients taking olanzapine also experienced lower rates of extrapyramidal symptoms as compared to patients taking haloperidol[13]. Another study notes that rates of somnolence may depend on how long olanzapine has been used, with somnolence and decreased concentration increasing to 82.5% on day three of the study but decreasing to 50.9% on day four. It should be noted that in this study, 64.9% of cases of somnolence and 47.4% of cases of decreased concentration were reported to be mild[23]. One study suggests decreasing the dose of olanzapine to five milligrams in patients 75-years of age and older, as well as in those who experience increased sedation when being administered a 10 mg dose[19] [19]. Another possible adverse effect to be aware of includes QT prolongation, which increases the risk of dangerous ventricular tachyarrhythmias. The QT interval is described as the space in between the Q and T waves on an electrocardiogram and is a measure of repolarization[12]. Finally, weight gain is also a potential adverse effect of olanzapine, and with its indelible

relationship with diabetes mellitus (DM), olanzapine can lead to loss of control of DM[12] (Table 1). DM also increases the risk of EPS[1]. One interesting factor to note is female gender, as females are inclined to increased olanzapine blood concentrations, and being a female increases risk of CINV[23] and EPS[11] (Table 1). Future studies may be devoted to how female gender increases the risk of CINV and which antiemetic options appear to be most effective in this population.

Extrapyramidal symptoms (EPS) are a potential adverse effect[11-13], with dyskinesia being a specific type of EPS related to olanzapine use[11,12]. EPS may range from acute to tardive. One source suggests that acute EPS happens within minutes to weeks post-administration, while tardive EPS occurs after a minimum of three months use, of which dosing may be continuous or intermittent. Tardive EPS is directly related to duration of use and is dose dependent, with these cases often becoming resistant to treatment. One potential drug interaction to be cognizant of is the combination of olanzapine and metoclopramide (which is a CYP2D6 inhibitor), as the latter may decrease the excretion of the former, potentially leading to prolonged EPS. EPS may also manifest as parkinsonism, where patients may experience rigidity, postural reflex disorder, mask-like facies, insomnia, and restlessness. One case study involved an oncology patient who was taking 5 mg of olanzapine on an intermittent basis for a seven-month duration along with metoclopramide and palonosetron. This patient was prescribed quetiapine and clonazepam as the patient was experiencing anxiety, insomnia, and restlessness, which in turn ended up causing prolonged EPS. This case study serves as a cautionary tale in understanding potential interactions between D2 receptor antagonists and antipsychotics[11].

8. Conclusions

In closing, olanzapine's continued presence on treatment regimens for cancer-therapy associated nausea and vomiting appears to have a bright future ahead. Olanzapine's effects on 5HT-3 receptors located in the GI tract and in vomiting centers in the brain allows for this medication to be effective particularly in the treatment of CINV induced by high emetic risk agents. These agents include AC combination and cisplatin. Because of its antipsychotic properties, beneficial effects are seen in the realm of treatment of depression and anxiety often seen in oncology patients, as well as in improving appetite. Olanzapine has proven to be a reliable option in cases where dexamethasone was previously used, as corticosteroids come with troublesome adverse effects such as insomnia, acne, agitation, and possible interaction with immune checkpoint inhibitors. Olanzapine may be administered at doses lower than 10 mg (such as 2.5 mg or 5 mg) to avoid common adverse effects including sedation or dizziness. Other adverse effects to be cognizant of include EPS, QT prolongation, and weight gain.

9. Author Contributions

E. M. was responsible for the design and writing of the manuscript. O. A. was responsible for the study conception, analysis, and revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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11. Conflicts of Interest

The authors have no relevant financial or non-financial interest to disclose.

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