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OLANZAPINE FOR NAUSEA AND VOMITING IN VARIOUS ETIOLOGIES: A REVIEW

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A B S T R A C T

Nausea is an unpleasant response followed by the risk of vomiting that results rapid forced ejection of gastric substance from the stomach upwards and out of the mouth. The Gastrointestinal tract, vestibular system, and thalamus are the sites that cause this event. Serotonin type 3 (5-HT3), Mu, neurokinin-1 (NK-1), kappa opioids, dopamine type 2 (D2) are CTZ receptors that cause emesis. 5-HT3 antagonists, antihistamines, and phenothiazines are common antiemetic agents. Olanzapine is an atypical antipsychotic second-generation medication with antiemetic properties. This article review used a classical method to identify studies related to the mechanism and efficacy of olanzapine as an antiemetic. The journal article related to olanzapine in nausea and vomiting that published on 2002 until 2022 for critical appraisal. The purpose of this literature review is to provide a review of antiemetics, especially olanzapine as a therapy option, as well as to evaluate the mechanism and efficacy of olanzapine. The activity of olanzapine with several receptors associated with nausea and vomiting suggests that it may have antiemetic activity. Olanzapine inhibits the 5-HT2C receptor, which is located near small intestine enterochromaffin cells and is required for the emetic response. In CINV therapy, research suggests combining olanzapine 10 mg with a 5-HT3 antagonist, NK-1 antagonist, dexamethasone. There is a lack of data in literature on the use of olanzapine in hyperemesis gravidarum. From the review we concluded that olanzapine can be considered for use as a therapy for the treatment of nausea and vomiting.

Keywords: Olanzapine 1, Antiemetics 2, Nausea 3, Vomiting 4, CINV 5

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1. Introduction

Nausea and vomiting have many etiologies. Nausea is an unpleasant feeling that can lead to emesis. Vomiting is a physical condition that occurs when gastric contents are forced upwards and out of the mouth from the stomach. Vomiting is induced by noxious activation of the vomiting center, either directly or indirectly through one or more of four additional sites: the GI tract, the vestibular system, the chemoreceptor trigger zone, and higher centers in the cortex and thalamus. When receptors are triggered, neuronal pathways are formed that go to the vomiting center, where emesis occurs. Neural traffic from the GI tract goes along cranial nerves IX (glossopharyngeal) and X (vagal) afferent fibers. The capacity to block the indicated receptor sites makes antiemetic candidates for pharmacological interventions (Becker, 2010). The chemoreceptor trigger zone (CTZ) is located in the medulla near the floor of the fourth ventricle and the vomiting center and gets signals from the nucleus tractus solitarius and the vagus nerve. The CTZ in the postrema area is one of the four major areas associated in emesis. In addition to the CTZ, the GI tract, vestibular system, and higher centers in the cortex and thalamus contribute to the process in inducing emesis by transmitting information to the vomiting center. Opioids, kappa Mu, serotonin type 3 (5-HT3), neurokinin-1 (NK-1) and dopamine type 2 (D2) are CTZ receptors that cause emesis. Dog studies revealed that enkephalin, histamine receptors (H1, H2) are involved in the CTZ gag reflex (MacDougall & Sharma, 2020). Two types of drugs are used to control acute nausea and vomiting: which act centrally to stop nausea and vomiting, and peripherally by controlling gastrointestinal motility as a prokinetic. Antiemetic therapies include antihistamines, phenothiazines and 5-HT3 antagonists (Cangemi & Kuo, 2019).

The antiemetic efficacy of olanzapine, a medicine traditionally used as an antipsychotic, has been proposed since the early 2000s. Olanzapine is an antagonist of several neurotransmitter receptors including serotonin receptors (5-HT2a, 5-HT2c, 5-HT3, 5-HT6), histamine receptors (H1, H2), catecholamines (alpha1 adrenergic receptors) and dopaminergic at brain receptors (D1, D2, D3, D4), and acetylcholine at muscarinic receptors. Olanzapine binds to D2 receptors and 5-HT2 with a five-fold affinity (Saudemont et al., 2020). Current studies have discovered multiple receptors that cause nausea and vomiting, making it difficult to treat with a single drug. Olanzapine has been reported in studies to be effective as antiemetic (Licup & Baumrucker, 2010). As a result, the purpose of this literature review is to provide a review of antiemetics, especially olanzapine as a therapy option, as well as to evaluate the mechanism and efficacy of olanzapine.

2. Material and Methods

This article review used a classical method to identify studies related to the mechanism and efficacy of olanzapine as an antiemetic. We search and identified various research articles via the MeSH PubMed database, and ScienceDirect, as well as Google Scholar with the keywords "Olanzapine", "Antiemetics", "Nausea", "Vomiting", "Hyperemesis" and "Efficacy" as relevant references. We obtained 15 relevant articles and reviewed the mechanism and effectiveness of olanzapine as an antiemetic, which represented as the primary source for this review article. We use the journal article related to olanzapine in nausea and vomiting that published on 2002 until 2022 for critical appraisal.

3. Result and Discussion

Olanzapine indication and mechanism

Olanzapine is an atypical antipsychotic drug that works on serotonin and dopamine receptors. The drug acts as a dopamin receptor antagonist in the mesolimbic pathway, preventing dopamine from activating post-synaptic receptors. Olanzapine works by binding to the receptor and rapidly dissociates, allowing normal dopamine neurotransmission to occurred. Patients experience delusions, hallucinations, disorganized speech, behaviors, and thoughts as a result of D2 receptor effects. Olanzapine inhibits serotonin receptors in the frontal cortex (Thomas K & Saadabadi A, 2022). Olanzapine's effect on serotonin reduces in a reduction in negative symptoms which include poor attention, avolition, flat affect, alogia, and anhedonia (Tollens et al., 2018). The activity of olanzapine in humans with 5-HT3 receptors has not been established but olamzapine has an antagonistic response at guinea-pig GIT receptors (Davis & Sanger, 2021).

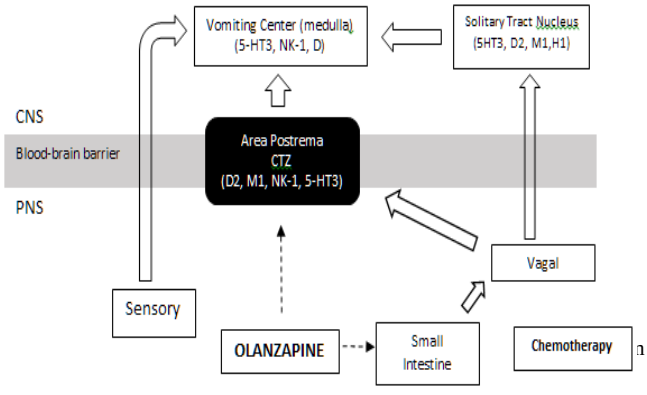
Olanzapine was administered orally and intramuscularly to treat chronic schizophrenia in patients over the age of 13, as well as other psychiatric disorders. Olanzapine is also used in the short-term management of adults with bipolar disorder who are experiencing acute or mixed manic episodes, in conjunction with lithium or valproate. Furthermore, in patients over the age of ten, olanzapine is approved for the management of depressive episodes related with type 1 bipolar disorder and treatment-resistant depression. Olanzapine is also approved to treat psychomotor agitation caused by schizophrenia and bipolar mania (Thomas K & Saadabadi A, 2022). Schizophrenia is a psychotic disorder have such symptoms hallucinations, delusions, and disruptions in perception, thought, and behavior. Schizophrenia has traditionally been associated with both positive and negative symptoms, such as delusions, hallucinations, and impaired formal thinking, as well as a lack of speech, anhedonia, and a lack of motivation (Hany M et al., 2022). Type 1 bipolar disorder identifies with at least one manic episode in one's lifetime, though depressive episodes are frequent (Jain A & Mitra P, 2021).

Oanzapine and samidorphan are prescribed together for type I bipolar disorder, either in addition to lithium or valproate, as monotherapy for the acute management of manic or mixed episodes, or as maintenance therapy. Olanzapine is also prescribed for the management of adults schizophrenia. Olanzapine is offered in a disintegrating tablet formulation, which benefits patient compliance by

making it easier to take the medication orally. The dosages of the tablet preparation are 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg. This formulation is highly helpful for individuals who struggle taking pills but want to take them orally, patients who are resistant to taking medication by not swallowing tablets, and those who are agitated. Olanzapine in injection form is available at a dose of 5 mg/mL. This is the most appropriate dosage form for agitated patients who are noncompliant with their medications and refuse or are unable to swallow oral drug formulations. However, because tablets have a longer half-life than injections, they cannot be used as a replacement therapy for long-acting injectable antipsychotic drugs (Thomas K & Saadabadi A, 2022).

Olanzapine as antiemetics

Olanzapine is used for two purposes in antiemetic therapy: prophylaxis and rescue. The following day or the following chemotherapy block, olanzapine is added to the prophylactic therapy indication. Olanzapine is given orally 1 hour before chemotherapy, with or without other antiemetics, for prophylaxis. In salvage indications, olanzapine is combined with aprepitant, 5-HT3 receptor antagonists, and dexamethasone to treat uncontrolled vomiting. When olanzapine fails to control vomiting, other antiemetics such as diazepam, metoclopramide, palonosetron, ondansetron, or may be used (Lee et al., 2020). Olanzapine has a strong affinity for several CNS receptors. The recommended initial dose for adults is 5 mg per day, preferably at night due to the risk of drowsiness, or 2.5 mg per day for geriatric (Saudemont et al., 2020). Olanzapine binds to a variety of dopaminergic (D1, D2, D3, D4, D5) and serotoninergic (5HT2A, 2C, 5HT3, 5HT6, and 5HT7) receptors, but its affinity for 5HT2 receptors, particularly 5HT2A, is greater than that for dopaminergic receptors. Olanzapine also inhibits the muscarinic M1, M2, M3, M4, M5 receptors (supporting decrease the possibility of extrapyramidal effects), as well as the a1-adrenergic and histamine H1 receptors. It has a reduced affinity for 5HT1, GABA (Gamma-AminoButyric Acid), ß-adrenergic, and benzodiazepine receptors. Olanzapine has a mild antagonistic impact on N-Methyl-D-Aspartate (NMDA) receptors additionally. Because olanzapine interacts with several receptors associated in nausea and vomiting, it may have antiemetic activity (Passik et al., 2002) (Eric Prommer, 2013).



Serotonergic (5-HT), Dopaminergic (D), muscarinic (M), and receptor histaminergic (H pathways are all inhibited by olanzapine. for central nervous system (CNS); neurokinin-1 (NK-1); and peripheral nervous system (PNS).

Olanzapine in Chemotherapy induced Nausea and Vomiting (CINV)

A common adverse drug reaction from chemotherapy is chemotherapy-induced nausea and vomiting (CINV). If nausea and vomiting cases are not controlled, they will reduce and worsen clinical conditions such as dehydration, electrolyte imbalance, and malnutrition and quality of life (X. F. Wang et al., 2014). It also increase hospital costs due to the therapeutic management of fluid and nutrient depletion, electrolyte disturbances, and other related reaction (Babu et al., 2016). Patients who suffer from nausea and vomiting as a side effect of chemotherapy will be concerned for the duration of their treatment. Primary cancer treatment may be refused if nausea and vomiting are not controlled. Patients may be so afraid of side effects that they refuse pain medication (Passik et al., 2002). Individuals who are susceptible to CINV must be identified so that clinicians can use more stringent and effective prophylactic regimens to prevent its progression. For CINV, many antiemetic agents with various mechanisms of action have been evolved, the majority of which are usually given as prophylactic drugs. NK1 receptor antagonist, corticosteroids, 5-HT3 antagonists are currently the most common used antiemetic (Gupta et al., 2021). Patients getting chemotherapy who experience severe nausea and vomiting may need to reduce their dose, postpone their treatment, or perhaps permanently stop it. CINV can be categorized as acute emesis (occurring <24 hours following chemotherapy), and delayed emesis (occurring between 24-120 hours following chemotherapy), and anticipatory emesis (hours to days before chemotherapy) (Fonte et al., 2015). The central nervous system (CNS) and gastrointestinal tract (GIT) communicate with various neurotransmitters and receptors as part of the multifactorial complicated pathophysiology of CINV. Defective small intestine enterochromaffin cells release serotonin after chemotherapy treatment and bind to 5-HT3 receptors on neighboring vagal afferents (Navari & Navari, 2016). Through afferent nerve fibers, the emetic area of the brain receives sensory signals from the gastrointestinal system. The brainstem's emetic center is made up of a loosely connected network of neurons that receive signals from the digestive system as well as the chemotherapeutic trigger zone in the postrema region (Bayo et al., 2012). The emetic center, where the direction of efferent signal production to the abdominal muscles, diaphragm, and then vomiting happens, consolidates these sensory impulses. Chemotherapeutic drugs could directly activate chemoreceptors in the postrema region, which are situated beyond the blood-brain barrier. The pathophysiology of CINV is described in Fugure 1 (Aapro, 2018).

The main target of antiemetic therapy is dopamine, serotonin (5-HT3), substance P, and neurokinin-1 (NK-1) receptor stimulatory effects. Chemotherapy induces emesis via two major mechanisms: peripheral and central. The

peripheral mechanism is associated to 5-HT3, which is found in the GI tract and is stimulated within the first 24 hours after chemotherapy. This mechanism is related to acute vomiting. The central NK-1 receptor mechanism predominantly associated with the delayed type of vomiting occurs in the brain and is acute vomiting stimulus can often occur via the central pathway (Athavale et al., 2020). Olanzapine works by blocking many neurotransmitter receptors, it can be administered as a single broad-spectrum antiemetic for nausea and vomiting induced by multiple or non-specific reasons in patients with advanced cancer, as well as for comfort care at the end of life (Tanaka et al., 2019). Olanzapine is associated to various neurotransmitters that can be suppressed by olanzapine to exert antiemetic efficacy, including 5-HT2c and 5-HT3 and dopaminergic D2 (Saudemont et al., 2020). Olanzapine shows a high affinity for the 5HT2A receptor, which is up to 5 times stronger than the dopamine receptor, which means it is less likely to cause extrapyramidal side effects. Because of its affinity for numerous receptors, olanzapine has been identified as an important drug in the treatment of delirium, nausea, and vomiting(Eric Prommer, 2013).

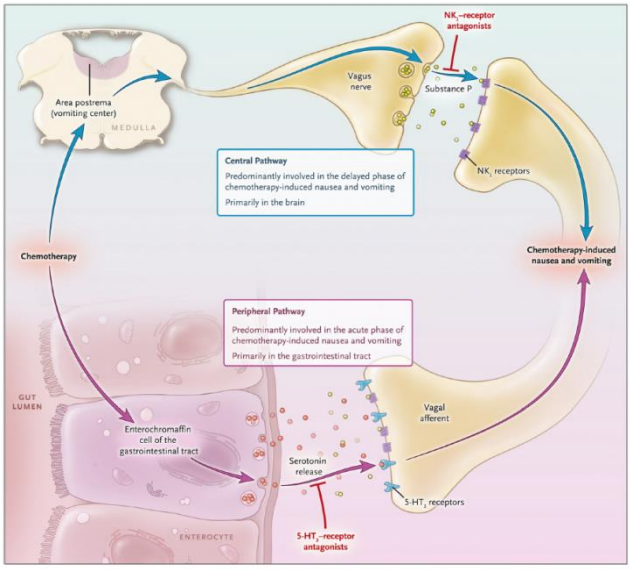


Fig. 1 Pathophysiology of chemotherapy-induced nausea and vomiting[1]. From N Engl J Med, Navari RM, Aapro M, Antiemetic Prophylaxis for Chemotherapy-Induced Nausea and Vomiting, Volume No. 374, Page No. 1357, Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

Figure 1. CINV Pathophysiology. Adopted from reference (Aapro, 2018). Open access under CC BY-NC.

Olanzapine in Hiperemesis Gravidarum

Pregnancy-related nausea and vomiting are very common conditions with estimated prevalence rates ranging from 50% to 85%, but most self-management is sufficient. This popular term morning sickness can be minimized by obstetricians or other midwifery providers. This is because vomiting in pregnant women has a high likelihood of hospitalization (Yeh et al., 2018). Morning sickness as symptom in pregnancy start in the first trimester, at around 6-8 weeks of pregnancy, usually peaking around 9 weeks gestation and resolving around 12 weeks. Only a small proportion of women experience it after 20 weeks gestation. Avoidance of trigger foods and adequate oral hydration are often sufficient, women who experience severe and prolonged symptoms will require antiemetic medication (Jarvis & Nelson-Piercy, 2011). Although most health professionals are familiar with hyperemesis gravidarum as a serious condition with a genetic cause, some may need to be made aware that the patient's quality of life can improve significantly with adequate medication and care. Neglected patient symptoms can have serious long-term consequences for the mother, fetus, and child. Continued efforts to establish an international consensus on the definition of hyperemesis gravidarum will improve the standardization of future studies (Fejzo et al., 2019). Concerning a Norwegian study published in 2017, the research showed a relation between depression and hyperemesis gravidarum, with a track record of depression relatedd with a higher risk of hyperemesis gravidarum (OR 1.49, 95% CI 1.23-1.79).(Kjeldgaard et al., 2017). Then, the hormonal aspect relates to the level of human chorionic gonadotropin (hCG). Increasing hCG levels during the first trimester, coinciding with the onset of hyperemesis symptoms. Some studies have shown a correlation between higher hCG levels and hyperemesis. However, more research is required in this area.. However, this research needs more studies (Jennings LK, 2022).

Olanzapine acts by blocking many neurotransmitter receptors to exert antiemetic efficacy, including 5-HT2c and 5-HT3 and dopaminergic D2 (Saudemont et al., 2020). Olanzapine has a pregnancy safety profile, antiemetic effectiveness in various situations, and 5-HT3 antagonism (Sharma et al., 2022). There is a lack of data in literature on the use of olanzapine in hyperemesis gravidarum. Improving nutritional status, promoting weight gain, and decreasing the need for invasive treatments are all part of the treatment of HG. Furthermore, extending the pregnancy allows the fetus to grow weight. The obstetric outcomes of olanzapine and mirtazapine are comparable, although mirtazapine had better symptom control. Mirtazapine improves in treating refractory HG while having no negative effects on the developing fetus (Galletta et al., 2022).

Olanzapine in Digestive Disorder

Vomiting induced by the digestive system has a wide-ranging impact on the body. The GIT, musculoskeletal system, oropharynx and vestibular system all send afferent signals. Signals from the CTZ, synapse on the vagus nucleus, cerebral cortex, afferent pathways which stimulates the vomiting center on its own. According to one theory, mild stimulation of this pathway causes nausea, whereas more intense stimulation causes vomiting. The GIT, abdominal wall muscles, diaphragm, and oropharynx all play roles in the sequence of processes that results in vomiting. In short, the stomach relaxes as the antral contractions stop the lower esophageal sphincter relaxes, the pyloric tone rises, diaphragm contract, the abdominal wall muscles and the contents of the stomach are pushed upwards to the mouth for expulsion. Then, to prevent

aspiration, respiration blocks, vocal cords and the glottis close, and the soft palate rises. Histamine, dopamine, norepinephrine, serotonin, vasopressin, substance P, acetylcholine, beta-endorphins, and cortisol are the main neurotransmitters and hormones involved in this process (Andrews & Sanger, 2014). Olanzapine works by inhibiting the 5-HT2C receptor, which is located near small intestine enterochromaffin cells and is required for the emetic reaction after chemotherapy. Vagal afferent fibers transmit signals to the nucleus tractus solitarius and the area postrema on the dorsal surface of the fourth ventricle's caudal end. Because it lacks a blood-brain diffusion barrier for large molecules, the CTZ, also known as the area postrema, is exposed to chemotherapy-like stimuli in blood or cerebrospinal fluid. Through binding to dopamine D2, D3, and D4 receptors, dopamine agonists and opioids have induced emesis in the postrema area (Deremer et al., 2016).

Olanzapine for Pediatrics

Olanzapine is frequently prescribed to pediatric patients suffering from psychiatric disorders. Olanzapine is also a treatment option CINV in children (Flank et al., 2014). Olanzapine is an effective therapy for children and adolescents with schizophrenia, bipolar disorder, anorexia nervosa with delusions, pervasive developmental disorders, and other disorders at doses from 2.5-20 mg/day. Increased body weight is the most frequently occurring side effect of olanzapine use, and the risk is higher in pediatric than in adult. When compared to risperidone or haloperidol, olanzapine has the potential to increase body weight in both children and adolescents (Frémaux et al., 2007). The efficacy of olanzapine in children over the age of 13 years with doses at 2.5-20 mg and titrated according to individual tolerance is considered a relatively safe antiemetic. However, the side effects of olanzapine use in children are of little clinical significance (Flank et al., 2014). Combination of Olanzapine with standard antiemetics, proved promising results in the therapy of CINV in children (Lee et al., 2020).

Olanzapine for Pregnancy and Lactation

Although the use of olanzapine has been observed during pregnancy and lactation, no controlled clinical trials have been investigated to asses the risk of olanzapine exposure to babies and fetuses. There have been no studies on the therapeutic use of olanzapine in pregnancy and lactation (Brunner et al., 2013). Psychotropic medications are frequently prescribed for postpartum women suffering from psychiatric disorders, especially psychotic disorders, major depression, and bipolar mood episodes. Based on the literature and the outcomes, there is proof that using olanzapine during pregnancy is safe, particularly in the Indian setting (Manoj K Sahoo et al., 2022). Doses of olanzapine prescribed to breastfeeding mothers of up to 20 mg daily resulted in low levels of breast milk and undetectable levels in breastfed infants' serum. In the majority of cases, no short-term side effects have been found, but sedation has occurred. Long-term olanzapine use in infants has revealed that the infants develop normally (Uguz, 2019). However, studies show that olanzapine use during pregnancy is related to neonatal hyperinsulinemia in the absence of gestational diabetes. This is related to the mechanism, either directly or indirectly through the mother's glucose metabolism (Rowe et al., 2012).

Table 1. Olanzapine as Antiemetics

Indication Therapy	***Study Design***	***Sample size***	***Main outcome measure***	***References***
Therapy *breakthrough* CINV in hematopoietic stem cell transplantation (HSCT).	RCT	There were 62 patients who were divided into three treatment groups at random. IV Ondansetron 32 mg in 250 mL NS continuous infusion for 24 hours in Group I (control) Group II: olanzapine 10 mg orally once per day, followed by IV ondansetron 3 x 8 mg Group III : IV Palonosetron 1 x 0.25 mg (no ondansetron for 3 days)	At 24 and 48 hours, the overall response rate indicated that olanzapine was considerably more effective than ondansetron. At 24 hours, olanzapine also more effective than palonosetron. Based on the nausea score, olanzapine was highly effective for breakthrough CINV in HSCT patients. Approximately 71% of patients were resolved within 48 hours. The positive response to olanzapine is associated with 5HT3 receptor blockage.	(Nakagaki et al., 2017)
Preventive therapy Cisplatin-INV chemotherapy in lung cancer	RCT	40 lung cancer patients received High Emetogenic Chemotherapy (HEC), namely 25 mg/day cisplatin for 3 days. Olanzapine (5 mg) was given the day before cisplatin administration and continued on 1-5 days	The results of our study, in lung patients receiving HEC, combination of olanzapine 5 mg with ondansetron and dexamethasone is effective in managing acute and delayed CINV, especially in multiday chemotherapy regimens.	(W. Wang et al., 2018)
CINV Preventive Therapy	RCT	There were 710 patients divided into two groups; 356 patients received olanzapine and 354 patients received a placebo. Patients received oral olanzapine 5 mg once daily on days 1-4 in combination based on standard antiemetic therapy in HEC (aprepitant, palonosetron, and dexamethasone)	When compared to some guidelines recommendations, combination of olanzapine 5 mg and four-drug combination therapy was sufficient to control nausea and vomiting. The olanzapine group experienced less insomnia and a significant decrease in appetite than the placebo group.	(Hashimoto H. , 2019)
Preventive therapy carboplatin induced nausea and vomiting	RCT	Olanzapine 5 mg will be given to the 33 patients receiving carboplatin-containing antiemetic therapy on days 1-4 after dinner.	The incidence of nausea in the delayed phase was 15.2% and 18.2% overall. The overall response rate for the administration was 93.3% (95% confidence interval, 80.4-98.3%). In patients receiving carboplatin-containing chemotherapy, olanzapine combination with antiemetic therapy with (5-HT3 receptor antagonists , aprepitant, dexamethasone) may improve CINV control.	(Tanaka et al., 2019)
Antiemetic therapy in palliative therapy	*Systematic review*	2 case studies, 2 literature reviews, 3 case series, 2 prospective studies, 3 retrospective studies and comprise the 13 articles.	Olanzapine has a good tolerance profile as an antiemetic in palliative therapy	(Saudemont et al., 2020)
CIV breakthrough antiemetic therapy in children	*RCT*	Children (5-18 years) who had experienced breakthrough CIV after receiving moderate-high emetogenic chemotherapy. 80 patients were evaluated (split into two groups, 39 receiving olanzapine and 41 receiving metoclopramide) Body Weight 10-20 kg: 2.5 mg/ 24 hours Body weight > 20 kg 5 mg/ 24 hours Metoclopramide oral syrup 1mg/mL and 10mg tablets BB 10-35 kg 0.15 mg/kg/BB / 8 hours, Patient >14 years BB> 35 kg: 10 mg / 8 hours	For nausea (59% vs 34%, P 0.026) and vomiting (72% vs 39%, P 0.003), the olanzapine group's CR levels were significantly higher than the metoclopramide group. After beginning rescue antiemetics, the mean nausea-reduced score was lower in the olanzapine group than metoclopramide group (P = 0.01). The olanzapine group experienced more hyperglycemia and drowsiness.	(Radhakrishnan et al., 2020)
Treatment of CINV in patient with Incomplete Malignant Bowel	RCT	16 patients received metoclopramide or olanzapine. Metoclopramide will be given 20–30 mg/day for 3 days and olanzapine 5 mg/day	Over the course of three days, the mean number of vomiting episodes per day in metoclopramide decreased from 1.50 to 0.65 (p = 0.83), while the olanzapine group decreased from 3.00 to 0.75. Olanzapine has an 87.5% patient satisfaction rate,	(Kaneishi et al., 2020)

Obstruction (iMBO)			while Metoclopramide has a 75% patient satisfaction rate.Olanzapine and metoclopramide induce side effects such as drowsiness and dizziness. The results demonstrated that olanzapine has efficacy towards CINV in advanced cancer patients with iMBO	
CINV therapy in breast cancer patients	RCT	120 patients (Chinese breast cancer) who have never received chemotherapy were assigned for (neo)adjuvant AC treatment. Antiemetic regimens include aprepitant, ondansetron and dexamethasone.	Studies have shown that combination of olanzapine in the standard antiemetic (ondansetron, dexamethasone , and aprepitant) significantly improves CINV control and improved patient quality of life. According to this study regimen, the benefits of other olanzapine combinations can reduce necessity dexamethasone on days 2-3 following chemotherapy.	(Yeo et al., 2020)
CINV therapy in breast cancer patients	*Brief Article*	This research collected data from a homogeneous group of Chinese breast cancer patients who were scheduled to receive HEC with AC as adjuvant chemotherapy. Subjects were randomly assigned to one of two antiemetic regimens at random: dexamethasone, aprepitant, and ondansetron with or without olanzapine.	Olanzapine has been shown to help relieve CINV in breast cancer patients.	(Yeo et al., 2020)
CINV prophylactic therapy	RCT	Individuals aged 18 and older with cancer who are not receiving chemotherapy (high-dose cisplatin (>70 mg/m^2) regimens) and being scheduled for adriamycin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 (AC)	In HEC patients who do not receive NK-1 antagonist therapy, olanzapine combined with ondansetron and dexamethasone improves CINV prevention and is safe.	(Vimolchalao et al., 2020)
CINV prophylactic therapy	*Systematic Review*	Systematic Reviews of Interventions: The Cochrane Handbook about nausea and vomiting CINV III : 3–5 times /day, affects eating and must be treated CINV IV : >5 times, uncontrollable	Olanzapine combined with 5HT3 can significantly reduce the incidence of CINV III, CINV IV and insomnia at high levels and chemotherapy moderate emetogenic compared to the combination of 5HT3 and Dexamethasone. Oral olanzapine 5 mg is more adequate for cancer patients.	(Zhou et al., 2020)
CINV Prophylactic Therapy in Paediatrics	RCT	During and two days after chemotherapy, all children aged 5-18 years received aprepitant, ondansetron, and dexamethasone. Oral olanzapine 0.14 mg/kg/day (2.5-10 mg) was given to participants in the cohort study during the chemotherapy and 3 days afterwards.	With an excellent safety profile, olanzapine significantly improves CIV (acute, delayed) in subjects who receive the first cycle of HEC.	(Naik et al., 2020)
CINV Prophylactic Therapy in Paediatrics	RCT	Data at Yeungnam University Hospital from January 2018 – March 2020 in children receiving moderate-high emetogenic chemotherapy using olanzapine as CIV control were retrospectively analyzed	Olanzapine, in combination with standard antiemetics, shows promise for prophylaxis and CINV therapy in children. Side effects that occur are related to sedation. Olanzapine is an important option to control CINV effectively which will increase the quality of life	(Lee et al., 2020)
CINV Preventive Therapy with HEC	RCT	Patients receiving doxorubicin + cyclophosphamide or cisplatin are given antiemetic therapy the day before chemotherapy, namely: APR Group (Group I) : PO APR 125 mg IV Ondansetron 8 mg IV Dexamethasone 12 mg PO OLN-matched placebo of 10 mg	In the acute, delayed, and overall periods, there was no significant difference in vomiting rates between groups. Depending on the type of chemotherapy, Group II provided better nausea control. Patients in the Group III group had nausea rates comparable to those in the Group I. During the delay, the Group II group experienced significantly less nausea than the Gruup I, as measured by the VAS. Studies show that patients in Groups I and II have better nausea control.	(Ithimakin et al., n.d.)

		OLN10 group (Group II): PO OLN 10 mg IV Ondansetron 8 mg IV Dexamethasone 12 mg PO APR 125 mg equaled placebo OLN5 group (Grop III): PO OLN 5 mg IV Ondansetron 8 mg IV Dexamethasone 12 mg PO APR 125 mg equaled placebo		
Prophylactic Therapy of Carboplatin-INV in Patients with Thoracic Malignancies	RCT	Patients receiving AUC ≥5 mg/mL/min and never receiving moderate-high emetogenic chemotherapy. The patient received oral olanzapine 5 mg/day in combination with dexamethasone and granisetron after dinner for 4 days,	Prophylactic treatment with low-dose olanzapine, namely 5 mg plus dexamethasone and granisetron demonstrates long-lasting effectiveness with an acceptable safety profile. On days 3-4, the occurance of nausea and vomiting is higher than on other days.	(Sakai et al., 2021)
CINV prophylactic therapy	*Systematic Review*	Cochrane Central Register of Controlled Trials, Ovid, Embase, MEDLINE and were explored through April 23, 2020.	all HEC-related studies using Olanzapine 5-10 mg had statistically and clinically superior results in all emetic phases (acute and delayed)	(Chow et al., 2021)
CINV Theraphy in Breast Cancer Patients	*Systematic Review*	Cochrane Central databases, Web of Science, PubMed, and EMBASE	Breast cancer patients with HEC may benefit from antiemetic therapy containing olanzapine. In addition, because of its low cost, olanzapine is of value for clinical application and further research	(Xiao et al., 2021)
Postoperative Nausea Vomiting (PONV) preventive therapy	RCT	82 females scheduled for breast surgery were randomly divided into one of four groups: placebo, a single oral dose of olanzapine 5-10 mg or ondansetron 16 mg before anesthesia for 4 hours for olanzapine and 1 hour for ondansetron, or both. For 24 hours, all patients were observed.	Olanzapine can be used effectively and safely as a PONV prophylaxis, especially for high-risk surgery procedures performed under general anesthesia. The optimal oral dose for olanzapine as PONV has been described as a more effective use during the late postoperative period than ondansetron 16 mg	(Ibrahim et al., 2013)
Postoperative Nausea Vomiting (PONV) preventive therapy	RCT	For benign indications with a simplified risk = 2 factor, patients (20 to 65 years) are expected to undergo elective laparoscopic gynecological surgery for at least one hour. The patient received a placebo or oral olanzapine 5 mg in 2 hours before the anesthetic and dexamethasone. The results were seen from the occurance of PONV within 24 hours.	Olanzapine was only given once before surgery in this study. As a result, the risk of hyperglycemia is insignificant. Although there is the possibility of preoperative drowsiness, olanzapine is very effective to prevent PONV.	(Hiroyuki Seki et al., 2020)
hyperemesis gravidarum	clinical experience	women with serious symptoms who require multiple hospitalizations and are at risk of fetal restriction or are going to have a premature or low birth weight (LBW) birth	The effective low dose of olanzapine is 5 mg. Olanzapine has the potential for the management of hyperemesis gravidarum that is resistant to strander treatment	(Verinder Sharma, 2022)

Olanzapine Safety

Olanzapine had similar safety to comparator antiemetic therapy; the potential for serious adverse events with olanzapine was not statistically significant in comparison to other therapies (Chow et al., 2021). Olanzapine has the potential to be effective in preventing nausea and vomiting caused by a variety of factors. Because of its effects on neurotransmitters, once-daily dosing is used as monotherapy, and because of its long half-life, it can be administered to improve patient adherence. Olanzapine is available in oral, intravenous, and subcutaneous formulations, making it a promising antiemetic therapy (Licup & Baumrucker, 2010). Olanzapine has been used as an effective prevention drug in the management of nausea and vomiting. Furthermore, new researches indicate that olanzapine can control nausea and vomiting caused by advanced cancer. Furthermore, olanzapine has an additional benefit in that it increases appetite. Another advantage is that it can be used as an insomnia treatment, and the prevention of benzodiazepines must put olanzapine top list of drugs that are prescribed for insomnia patients (Davis & Sanger, 2021). Olanzapine is an atypical atypical antipsychotic drug. Because of their rapid dissociation from dopamine D2 receptors, these drugs may decrease the side effects of extrapyramidal syndrome (EPS). Rebinding models that consider the postsynaptic D2 receptor microenvironment as well as integrated association and dissociation rates to determine the net rate of receptor blockade reversal accurately predict EPS. APDs with improved therapeutic profiles could be developed as a result of optimizing D2 receptor binding kinetics (Sykes et al., 2017).

Olanzapine Side Effects

Tolerable and mild side effects of olanzapine are including fatigue, somnolence, weight gain, postural hypotension, dizziness, constipation, restlessness, and dyspepsia (Passik et al., 2002). Olanzapine is frequently correlated with increasing body weight and metabolic disorders including dyslipidemia. Olanzapine will have an acute metabolic response with side effects associated with obesity. Olanzapine increased both food intake and body weight in rats, according to studies. Biochemical analysis revealed that olanzapine elevated blood TG, liver TG, insulin, and leptin levels. The group receiving olanzapine has more abdominal fat and larger fat cells in their abdominal fat tissue. The increase in lipogenesis will trigger an increase in hepatic SCD-1 activity which has the possibility of inducing the peripheral mechanism of olanzapine-induced dyslipidemia (Hou et al., 2018). According to research, obesity-related metabolic dysfunction induces hyperglycemia, markers of hepatic glucose output, and resistance of insulin in response to Olanzapine (Townsend et al., 2018).

Olanzapine has the side effect of somnolence. This challenge was discovered when comparing research studies in which the occurrence of drowsiness was related to a lower dose of olanzapine (5-10 mg), as well as the timing of administration (after an evening meal). It requires 3-5 hours for olanzapine to reach its maximum blood concentration. As an outcome, when olanzapine is given after dinner, its blood concentration peaks while the patient is sleeping. On day 2, the occurrence of drowsiness significantly high than at baseline and then decreased (Yanai et al., 2018).

CONCLUSION

Olanzapine is now used as a prophylactic medication in the treatment of nausea and vomiting of various ethylogies. Chemotherapy patients are at a 90% risk of experiencing emetogenic side effects. A review of the literature found that an addition of olanzapine 10 mg to antiemetic standard (NK-1 receptor antagonist, 5-HT-3 receptor antagonist, and dexamethasone) was effective for CINV. Then, in the clinical experience, we found a low dose of 5mg to be effective for hyperemesis gravidarum. An additional benefit of olanzapine is that it also increases appetite and treats insomnia. Drowsiness is one of the side effects related to olanzapine use. However, the level of drowsiness does not interfere with the patient's daily life. Olanzapine is safe for use by pediatrics and adults as an antiemetic. More investigation on the efficacy of olanzapine is needed. and the comparison of olanzapine among other antiemetics needs to be done. In addition, the effect of using olanzapine in pregnancy and lactation needs further research.

4. Conclusion

Olanzapine is now used as a prophylactic medication in the treatment of nausea and vomiting of various ethylogies. Chemotherapy patients are at a 90% risk of experiencing emetogenic side effects. A review of the literature found that an addition of olanzapine 10 mg to antiemetic standard (NK-1 receptor antagonist, 5-HT-3 receptor antagonist, and dexamethasone) was effective for CINV. Then, in the clinical experience, we found a low dose of 5mg to be effective for hyperemesis gravidarum. An additional benefit of olanzapine is that it also increases appetite and treats insomnia. Drowsiness is one of the side effects related to olanzapine use. However, the level of drowsiness does not interfere with the patient's daily life. Olanzapine is safe for use by pediatrics and adults as an antiemetic. More investigation on the efficacy of olanzapine is needed. and the comparison of olanzapine among other antiemetics needs to be done. In addition, the effect of using olanzapine in pregnancy and lactation needs further research.

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