Review article

Usefulness of antiemetics in clinical cancer treatment: An understudied topic in pharmacy

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ABSTRACT

The administration of cytotoxic substances in cancer therapy leads to profound nausea and vomiting, hence impeding the progress of cancer treatment. Cancer radiation therapy is also known to induce nausea and vomiting. An inconvenient symptom would impede therapy and diminish the overall quality of life, causing anxiety and hopelessness and rendering everyday activities challenging When used together with dexamethasone, 5-HT3 receptor antagonists are highly efficient in reducing acute vomiting caused by cisplatin and mildly emetogenic therapy. Further research is required to gain a deeper understanding of the occurrence of CINV (Chemotherapy induced nausea and vomiting) in relation to new chemotherapies, particularly those taken orally on a daily basis. Determining the best combinations and timing of their administration in situations where chemotherapy is given over multiple days is important and the findings will greatly benefit patients by reducing treatment dropout rates and facilitating adherence to their chemotherapy regimens.

Keywords: Chemotherapy induced nausea and vomiting; neurotransmitters; nausea; vomiting.

INTRODUCTION

The administration of cytotoxic substances in cancer therapy leads to profound nausea and vomiting, hence impeding the progress of cancer treatment. Cancer radiation therapy is also known to induce nausea and vomiting. An inconvenient symptom would impede therapy and diminish the overall quality of life, causing anxiety and hopelessness and rendering everyday activities challenging. The patient may discontinue treatment due to uncontrollable nausea and vomiting. This will have a significant influence on the treatment and overall survival rates of cancer patients. Most anticancer drugs commonly cause severe nausea and vomiting as side effects. An appropriate antiemetic can effectively mitigate CINV (Chemotherapy induced nausea and vomiting), which encompasses acute, delayed, anticipatory, breakthrough, and refractory phases.

Recent breakthroughs have enhanced our understanding of the pathogenesis of CINV. Neurotransmitters play a role in the development of CINV (1). CINV is associated with serotonin, substance P, and dopamine, all of which have receptors in both the gastrointestinal tract and central neurological system. Chemotherapeutic treatments elicit the release of these neurotransmitters in the gastrointestinal tract and central nervous system, which then transfer signals to the vomiting center, resulting in the occurrence of nausea and vomiting. Nausea and vomiting can also be induced by cannabinoids, histamine, GABA, and acetylcholine. Vomiting may include the activation of up to twenty neurotransmitters and receptor systems.

Pharmaceutical substances that hinder the activity of these specific receptors for chemical messengers in the brain can relieve the symptoms of nausea and vomiting. Prudent utilization of different antiemetics in appropriate combinations is necessary to achieve the intended outcome. Metoclopramide, dexamethasone, and lorazepam were used to handle only 60% of patients who experienced emesis because of cisplatin treatment, according to Kris *et al.* 1985(2). Among 70-90% of patients, the administration of 5HT3 antagonists such as ondansetron or granisetron effectively prevents acute cisplatin-induced vomiting. CINV adversely impacts the quality of life of cancer patients by leading to noncompliance with treatment and metabolic complications. According to a recent study conducted by de Jongh et al. in 2003, out of 400 patients who were treated with cisplatin, 26.5% were unable to complete their treatment cycles due to experiencing severe nausea and vomiting (3).

The efficacy of antiemetics has experienced substantial advancements in recent years, resulting in a remarkable enhancement of quality of life. CINV remains a significant adverse effect of cancer therapy that requires careful medical monitoring. Muller et al. investigated the efficacy of ondansetron in combination with metoclopramide for the delivery of cisplatin. The incidence of acute complete/major response was greater (72%) in patients who received ondansetron compared to those who received metoclopramide (41%). Metoclopramide is more efficacious than ondansetron in preventing delayed-phase vomiting and nausea (4). The efficacy and safety of Palonosetron in preventing immediate and delayed CINV following highly emetogenic treatment

were evaluated in a phase III, double-blind, randomized trial. Palonosetron exhibited a superior clinical response rate (complete absence of nausea and emesis) during the delayed period in comparison to ondansetron. The complete response (CR) rate during the delayed phase was higher in patients who had prior treatment with palonosetron, and dexamethasone (42%) compared to those who received prior treatment with ondansetron and dexamethasone (28.6%).

A study discovered that NK-1 antagonists effectively reduced delayed emesis. The concurrent use of these medications with a 5HT-3 antagonist and dexamethasone aids in the mitigation of acute nausea and vomiting. In their study, Abhay *et al.,* (5) found that the use of the NK-1 antagonist aprepitant, together with standard antiemetics, resulted in a 72.7% protection rate against cisplatin-induced nausea and vomiting in a group of 260 patients. Chemotherapy frequently causes nausea and vomiting, which can have a negative impact on the effectiveness of treatment and overall well-being. However, there are several antiemetic medications available that can effectively prevent and manage CINV.

Physiological mechanism for nausea and vomiting

The emetic center (bilateral nucleus *tractus solitarii*) in the parvocellular reticular formation of the lateral medulla oblongata is the brainstem structure responsible for mediating the vomiting response. This region is critical for the initiation, regulation, and organization of the vomiting reflex. Nausea and vomiting have been linked to both neurological and humoral mechanisms (6).

The neural route triggers NIV through the vomiting center (i) is stimulated by the vestibular apparatus (ii), the cerebral cortex (iii), the limbic system (iv), and the chemoreceptor trigger zone (CTZ) (v), among other areas of the brain. The last step in the vomiting reflex is for the vomiting center to send signals along the efferent motor neurons (vi). The emetic center receives its impulse after being stimulated by the vagal and sympathetic afferent neurons. These afferent neurons travel from the gut, particularly the duodenum, to various organs and tissues such as the bladder, ovaries, pancreas, peritoneum, and heart. Emesis is triggered in three ways by the higher brain regions (the cortex and the limbic system): fear, stress, excitement, or pain (psychogenic stimulation); traumatic stimulation associated with head injuries and elevated intracranial pressure (traumatic stimulation) and Inflammatory disorders, hydrocephalus, and neoplasia have all been shown to directly stimulate the vomiting center (6,7).

The chemoreceptor trigger zone (CTZ) has much dopamine D2 receptors, serotonin 5-HT3 receptors, opioid receptors, acetylcholine receptors, and substance P receptors and is located outside the blood brain barrier near the region postrema at the base of the fourth ventricle. Emesis can be triggered in a few different ways, each involving the stimulation of a unique set of receptors. It has axons that are not attached to anything, so their ends can freely communicate with the CSF through ependymal pores or the sheath enclosing fenestrated capillaries (8). Conditions affecting blood or cerebrospinal fluid (such as drug administration, infection, osmolar and acid-base disorders, electrolyte derangements, metabolic illnesses) might activate these free nerve terminals via the humoral pathway (9). Finally, the vomiting reflex is triggered when efferent motor impulses are sent to the diaphragm and stomach muscles via the spinal neurons and the sensory aspect of cranial nerves V, VII, IX, X, and XII.

Nausea and vomiting are not diseases in and of themselves, but rather indications of other, more serious conditions. Self-limiting if the triggering factor or condition is cured, it is essentially a defense mechanism. Nausea and vomiting can have a variety of reasons, the most common of which include gastroenteritis, motion sickness, head traumas, and drug reactions. The symptoms of myocardial infarction, encephalitis, meningitis, intestinal blockage, appendicitis, migraine headaches, and brain tumors, many of which are treatable but can be fatal if left untreated, include vomiting (10).

Chemotherapy induced nausea and vomiting (CINV)

While chemotherapy provides advantages for those with cancer, its detrimental side effects significantly diminish their quality of life. The introduction of emetogenic cisplatin occurred in the 1970s. Patients typically experienced 10 episodes of vomiting within a 24-hour period after receiving cisplatin. Metoclopramide effectively alleviated CINV during the 1980s. The antiemetic efficacy was diminished due to the reduction of extrapyramidal side effects. In the 1990s, the use of 5HT3 antagonists resulted in a decrease in CINV. The introduction of NK1 antagonists, specifically aprepitant and fosaprepitant, brought about a significant change in the prevention of CINV in 2006. CINV can be intense. Most cancer patients undergoing chemotherapy have CINV. Unmanaged CINV can lead to severe malnutrition, excessive loss of body fluids, disturbances in electrolyte levels, and deterioration in both mental and physical health. Despite the progress in medical treatments, people opt for experiencing nausea and vomiting rather than extending their lifespan, so forsaking potentially life-saving chemotherapy treatments. There are numerous efficacious and well-tolerated antiemetic medications available to mitigate CINV.

Classification of CINV

A basic understanding of the forms of CINV is required for the specific treatment of each type, which

is based on the underlying pathophysiological process for each type.

Acute emesis: emesis occurring during the first 24 hours after chemotherapy.

Delayed emesis: Emesis occurring more than 24 hours and lasting for up to five days after chemotherapy is classified as delayed.

Refractory emesis: Emesis that can occur anytime, due to inadequate prophylaxis, inadequate treatment, or highly emetogenic regimens.

Anticipatory emesis (ANV): Anticipatory emesis is a conditioned response in patients who have had poorly controlled CINV during previous cycles of chemotherapy.

Breakthrough CINV: Nausea and vomiting that occurs despite antiemetic therapy and requires rescue medication.

Risk factors in CINV

The likelihood of CINV is influenced by various patient-specific factors and the specific chemotherapeutic treatment employed, both of which contribute to an increased susceptibility to CINV. The emetogenic potential of chemotherapeutic medicines has been classified and rated in the table provided by the American Society for Clinical Oncology recommendation in 2006. The precise mechanism by which chemotherapy induces nausea and vomiting remains poorly comprehended. Nausea and vomiting are intricate physiological responses. The vomiting center (VC) is responsible for coordinating the afferent and efferent circuits involved in the process of vomiting. The emetic center is situated within the medulla oblongata of the brainstem. The ventral tegmental area (VC) consists of three components that collaborate in the regulation of vomiting: the area postrema (AP), the nucleus *tractus solitarius* (NTS), and the dorsal motor vagal nucleus (DMVN) (6). The following mechanisms have been proposed: The method that is most commonly used is likely to be:

1. Chemotherapeutic drugs can stimulate the chemoreceptor trigger zone (CTZ) in two ways: directly and indirectly.
2. When the gastrointestinal (GI) tract is aroused, signals are sent to the nucleus tractus solitaries by the vagal sensory fibers. As a result of this stimulation, the enterochromaffin cells (EC) lining the gastrointestinal mucosa produce serotonin and substance P.
3. Due to unclear vestibular processes, CINV are more likely to occur in individuals with a history of motion sickness.
4. Changes to the senses of smell and taste, such as chemotherapy-induced changes to flavor (such as a metallic aftertaste, a loss of flavor altogether, or the bitter aftertaste with 5FU),
5. Psychological factors, not the chemotherapy drugs, are thought to be the primary cause of adverse nausea and vomiting (ANV).
6. There are multiple pathways contributing to CINV, including the emetogenic potential of different chemotherapy medicines, making it unlikely that a single antiemetic will be effective in all cases.

Antiemetics for CINV

There are various types of antiemetic medications available, each designed to target certain neurotransmitter receptors involved in the physiological mechanisms that cause nausea and vomiting. Hernstedt *et al.,* (11) offer corroborating evidence for this claim. Every antiemetic is specifically formulated to reduce or eradicate the symptoms of nausea and vomiting, which are two of the most incapacitating adverse effects of cancer chemotherapy. These side effects are responsible for causing up to 20% of patients to postpone or decline potentially life-saving treatment (12). Antiemetic drugs are classified based on their specific mechanism of action in preventing nausea and vomiting. Given that CINV involves multiple pathways in its underlying mechanisms, it is not unexpected that a combination medicine would be more efficacious in its treatment. Treatment protocols for the prevention of nausea and vomiting that adhere to the guidelines set forth by the American Society for Clinical Oncology.

Serotonin antagonists

Enterochromaffin cells, also known as EC cells, are responsible for storing more than 90% of the serotonin, a kind of monoamine neurotransmitter, found in the human body's digestive tract. The central nervous system comprises the remaining serotonergic neurons. A study conducted in 2009 by Berger et al. (13) the body employs a concise biochemical process using two enzymes, tryptophan hydroxylase (TPH) and aromatic amino acid decarboxylase (AAAD), to convert the amino acid tryptophan into serotonin. The TPH-mediated response is the stage of the process that limits the rate. TPH1 is expressed in several organs, but TPH2 is specifically expressed in the brain. Serotonin undergoes metabolism to form 5-hydroxyindoleacetic acid (5-HIAA), which is then excreted in the urine. Testing urine can reveal the presence of abnormally high levels of serotonin and 5-hydroxyindoleacetic acid (5-HIAA) secretion.

The many enterochromaffin cells in the gastrointestinal tract react to food intake by releasing serotonin into the intestinal lumen. Vomiting occurs when 5-HT3 receptors in the chemoreceptor trigger zone (CTZ) are activated, because of the high sensitivity of enterochromaffin (EC) cells to radiation and cancer chemotherapy. This leads to an excessive release of serotonin by EC cells, which exceeds the absorption capacity of platelets. Compounds that block the 5-hydroxytryptamine 3 (5-HT3) receptor are highly effective in preventing nausea and vomiting

(14). The 5-HT3 receptor is an ion channel that is regulated by ligands. The 5-HT3 receptor consists of five subunits arranged in a pseudo-symmetrical manner around a pore that conducts ions. Certain individuals have a higher propensity to encounter feelings of nausea and vomiting as a result of a genetic variation in one of the subunits. The 5-HT3 receptor exhibits a broad distribution across the brain and the peripheral nervous system. It serves as a mediator in various physiological processes. When serotonin activates the ion channel, the following events ensue. Neuronal activation in autonomic and nociceptive neurons leads to vomiting in the peripheral nervous system (15). On the other hand, the vomiting center, anxiety, and susceptibility to seizures are all located in the central nervous system.

5-HT3 receptor antagonists

The introduction of 5-HT3 receptor antagonists has significantly improved the treatment of patients undergoing highly emetogenic chemotherapy, representing a significant advancement in the prevention of CINV. Carbazole-, indazole-, indole-, and imidazole-main-chained ondansetron, granisetron, dolasetron, and alosetron are examples of competitive antagonists that target the 5-HT3 receptor. Palonosetron differs from the previous substance by having a fused tricyclic ring and a quinuclidine side chain. This structural arrangement allows it to act as a non-competitive antagonist of the 5-HT3 receptor. Ondansetron, a 5-HT3 antagonist developed by Glaxo in the early 1980s, blocks both peripheral and central signals that cause vomiting and has a modest inhibitory effect on 5-HT4 receptors. The metabolism of this substance is carried out by the liver enzymes CYP2D6, 1A2, and 3A. Thus far, there have been no documented instances of significant drug interactions. The half-life of the substance ranges from 3 to 4 hours, while its duration of action spans from 4 to 12 hours. They exhibit a favorable safety profile, with the predominant side impact being a headache. Adverse responses, including allergies and skin irritations, have been documented following intravenous administration. Additionally, certain people may experience minor symptoms of both constipation and diarrhea.

Granisetron

Unlike other 5-HT antagonists, granisetron has very low affinity for dopaminergic, adrenergic, benzodiazepine, histaminic, and opioid receptors (16). Granisetron is administered orally in a single dose of 2mg. Alternatively, granisetron can be administered intravenously to people who are unable to take it orally. This can be done with either a 30-second injection or a 5-minute infusion. In 2008, the Food and Drug Administration (FDA) of the United States granted authorization for the utilization of a transdermal granisetron patch. Granisetron exhibits 10-15 times greater potency than ondansetron and demonstrates superior efficacy in the management of CINV. The oral dosage results in a bioavailability of 60%. The half-life of the substance is between 3 and 14 hours, and it binds to proteins in plasma at a rate of 65%. The indications are as follows:

1. Drugs that inhibit the 5-HT3 receptor are the primary treatment and prevention for CINV. Prior to the therapy, a standard practice is to administer an intravenous dosage of 10 mcg/kg around 30 minutes in advance.
2. Acute or chronic medical conditions, particularly acute gastroenteritis, can induce feelings of nausea and result in vomiting.
3. Nausea and vomiting caused suddenly or by ongoing medical conditions or acute inflammation of the stomach and intestines, and management of cyclic vomiting syndrome.
4. It is well tolerated. The common side effects are headache, dizziness, and constipation.

Dolasetron

Dolasetron mesylate and hydro dolasetron serve as antagonists on the serotonin type 5HT3 receptor. Because dolasetron has significant cardiovascular side effects, specifically dose dependent QTc prolongation, it is no longer indicated for the treatment of CINV. The maximal safe dose for CINV was 100 mg administered intravenously. The use of this medicine for post-operative nausea and vomiting has not been stopped, despite the reduced effective dose of 12. 5mg I. V. in these patients, as stated by the FDA in 2012.

Palonosetron

This 5-HT3 antagonist has recently been incorporated into therapeutic practice. It functions as an antagonist specifically targeting the serotonin receptor known as 5HT3. An intravenous dose of palonosetron, measuring 0. 25 milligrams is given 30 minutes prior to the initial chemotherapy treatment. The enzymes CYP2D6, and to a lesser extent, CYP3A and CYP1A2, are accountable for the metabolic breakdown of palonosetron. The half-life of palonosetron is 40 hours, and its binding affinity to the 5-HT3 receptor surpasses that of other medicines in its category (17). Palonosetron should be administered with caution to patients who have or are at risk of QTc prolongation. It is generally well accepted, with the most significant side effects being headache and constipation.

Palonosetron exerts a negligible impact on the cytochrome P450 pathway. No pharmaceutical interactions linked to enzyme induction or inhibition have been documented. However, it is important to note that apomorphine is prohibited due to its potential to produce substantial hypotension and altered consciousness when administered concurrently.

Palonosetron is authorized for the management of nausea and vomiting induced by cancer chemotherapy

that is mildly to very emetogenic, both during and after the treatment. The suggested dosage is 0. 25 milligrams, administered intravenously within a 30-second timeframe on cycle day 1, approximately 30 minutes prior to the administration of chemotherapy. Nevertheless, palonosetron has a significantly higher price compared to alternative medications. Consequently, it is imperative to consider cost-effectiveness as a crucial factor when choosing a 5-HT3 receptor antagonist.

Corticosteroids

The precise mechanism by which corticosteroids exert their effects in CINV remains mostly unclear. Research conducted on pigeons indicates that steroids may have an antiemetic effect, which is likely due in part to their impact on the central nervous system (18). Additional research indicates that the impact could potentially be attributed to the stimulation of glucocorticoid receptors in the nucleus of the solitary tract in the medulla. The drugs dexamethasone and methylprednisolone have been found to counteract the effects of 5-HT3A receptors in Xenopus oocytes. This helps to explain why corticosteroids are effective in preventing and treating CINV (19).

Role in management of CINV and acute CINV

Corticosteroids are taken alongside a neurokinin (NK1) antagonist to effectively manage CINV. The most effective therapies for mild emetogenic circumstances are a 5-HT3 antagonist and 8 mg of intravenous dexamethasone. Dexamethasone is suggested for managing delayed CINV in regimens that cause mild or substantial nausea and vomiting. The suggested dose is typically 8 mg once or twice daily; however, it may vary depending on factors such as the use of other antiemetics and the level of emetogenicity.

Research suggests that the use of corticosteroids may not be necessary for the treatment of delayed CINV. Patient tolerance of corticosteroids in the treatment of CINV is high, and their effectiveness is increased when used in combination with other medications. The most reported side effects include constipation, anxiety, temporary increases in blood sugar levels, and gastrointestinal discomfort. Utilizing corticosteroids for short durations is deemed advantageous when they result in minimal adverse effects (20). Despite the introduction of newer 5-HT3 antagonists and NK1 receptor antagonists, corticosteroids remain the primary component of most preventive treatment plans and are essential for their effectiveness.

Neurokinin antagonists

The actions of substance P (SP) are facilitated by the G-protein receptor neurokinin-1 (NK1), which is associated with the inositol phosphate signal transduction pathway. Von Euler and Gaddum identified Substance P, a substance that causes low blood pressure and muscle spasms, in the digestive system and brain of horses in 1931. In 1973, Erspamer and Melchiorri introduced the term "tachykinin" to describe the rapid initiation of contractile action in smooth muscle by substance P. Tachykinins are a group of natural substances that attach to tachykinin receptors, which are a type of G protein-coupled receptors (GPCRs).

The classification of tachykinin receptors consists of three groups: NK1, NK2, and NK3. Tachykinins comprise Neurokinin A, Neurokinin B, and Substance P. They attach to and interact with the NK1, NK2, and NK3 (21). Substance P, a peptide consisting of eleven amino acids, exhibits a high affinity for the NK 1 receptor. According to Patel et al**.,** 2003 (22), NK 2 and NK 3 receptors exhibited a strong binding affinity towards neurokinin A and neurokinin B. The involvement of substance P and its receptor Neurokinin 1 (NK1) in CINV is becoming increasingly evident via further research (23).

Substance P is extensively distributed throughout the body, encompassing the brain and spinal cord. The protagonist P is the cause of the vomiting. The brainstem contains nuclei that have NK1 receptors, which are specifically localized in the dorsal vagal complex. Animal studies demonstrated that inhibiting NK-1 receptors decreased the emetic response to cisplatin and other emetic medications such as apomorphine and ipecac. Therefore, out of all the antiemetics that are NK-1 receptor blockers, these antagonists provide the most extensive range of effectiveness (24).

Aprepitant

Aprepitant is a potent antagonist that specifically binds to and blocks human substance P/neurokinin 1 (NK1) receptors with a high affinity. The nonlinear pharmacokinetics of this substance are characterized by saturation of metabolism and decreasing clearance as the dose increases. An oral dose of 125 mg of Aprepitant is administered on days 1 and 3. The bioavailability of aprepitant is 60-65% when taken orally, and its absorption is not influenced by the consumption of food. It has been proven to successfully cross the placental barrier in animals and can breach the blood-brain barrier in humans. 53Aprepitant undergoes significant hepatic metabolism, primarily through CYP3A4 mediated pathways, with some involvement of CYP1A2 and CYP2C19 enzymes.

After oral administration, the plasma concentrations of aprepitant are comparable between males and females after a single dose of 125 mg. According to the product description for APREPITANT, there is no need to adjust the dosage for senior individuals, even if they are at a higher risk of dehydration owing to severe nausea and vomiting. Patients experiencing mild hepatic insufficiency can safely consume

aprepitant without the need to decrease their dosage. Insufficient attention has been given to conducting adequate research on patients suffering from severe hepatic insufficiency.

Potentially harmful responses with the use aprepitant include dizziness; increased liver function tests, gastritis, diarrhea, hiccups, and asthenia are among the most reported side effects. Few individuals showed signs of both dehydration and thrombocytopenia, according to studies by Hesketh *et al.*,(25). Apriptant may interact with drugs metabolized by CYP3A4 because it inhibits the 3A4 isoenzyme at therapeutic dosages. The area under the curve (AUC) can increase fivefold and the half-life threefold when azoles are administered with aprepitant, hence caution is required when providing the two drugs together. Some drugs, such ritonavir, nefazodone, nelfinavir, paroxetine, and imatinib, necessitate close monitoring for possible harm. For the time being, aprepitant has little effect on CYP2C9 activity. Therefore, it is possible for warfarin and phenytoin to interact with each other. Aprepitant should be given to chemotherapy patients who are likely to experience nausea to a significant or moderate degree.

Fosaprepitant

The US Food and Drug Administration has granted approval for the clinical application of the aprepitant prodrug, fosaprepitant. The intravenous administration of a 115 mg dose should only occur on the first day of chemotherapy, precisely 30 minutes prior to the commencement of treatment. An oral precipitant should be administered (80 mg once day in the morning on days 2 and 3). The liver and other tissues outside the liver, such as the kidney, lung, and ileum, quickly metabolize fosaprepitant into aprepitant. Aprepitant exhibits a significantly high level of plasma protein binding, exceeding 95%. The morpholine ring and its side chains are primary locations for metabolic oxidation. No metabolic activity was seen for CYP2D6, CYP2C9, or CYP2E1. The half-life of a precipitant is 9-13 hours. Fosaprepitant, when combined with other antiemetics, can effectively decrease the occurrence of nausea and vomiting induced by highly emetogenic chemotherapy, such as high-dose cisplatin, throughout both the immediate and delayed stages of treatment. The efficacy of fosaprepitant in the treatment of chronic emesis and nausea has not been investigated. Prolonged administration of medication is not recommended). Fosaprepitant is biologically equivalent to aprepitant. Patients experiencing severe nausea and/or vomiting due to their treatment may be unable to orally consume antiemetics (26).

Cannabinoids

Cannabis is one of the earliest psychoactive substances used in human society. The cannabis genus comprises three main species: sativa, indica, and ruderalis. Cannabis, also known as marijuana, is derived from the dried leaves and flowers of the Cannabis sativa plant. In 1839, William O'Shaughnessy, a British physician and surgeon working in India, discovered the pain-relieving, appetite-boosting, nausea-reducing, muscle-relaxing, and seizure-preventing properties of cannabis. The dissemination of his discoveries resulted in the adoption of medical cannabis. Queen Victoria was prescribed it to alleviate dysmenorrhea. Nevertheless, American authorities vehemently denounced the utilization of cannabis due to its association with mental instability, moral and intellectual deterioration, aggression, and numerous criminal activities. It was removed from the United States Pharmacopeia in 1942.

Cannabis produces more than 460 chemical components, with 60 of them being cannabinoids. THC, also referred to as dronabinol, is the primary psychoactive compound found in cannabis. Following reports from young patients that smoking marijuana before chemotherapy reduced nausea and vomiting, clinical trials were done to investigate the effects of THC. Extensive study has been conducted for many years on the medicinal properties of Δ9-THC and four other cannabinoids (Δ8-THC, nabilone, levonantradol, and nonabine) in alleviating CINV. The recently discovered CB1 and CB2 receptors have revealed the molecular processes via which cannabis effectively reduces vomiting (27).

Endocannabinoids are arachidonic acid-like substances that act as endogenous ligands for cannabinoid receptors. Five endocannabinoids have been discovered, with anandamide and 2-arachidonoylglycerol being the most extensively studied. Cannabinoids have potential therapeutic effects in various areas such as pain relief, muscular relaxation, immune system suppression, inflammation reduction, allergy prevention, sedation, mood enhancement, hunger stimulation, prevention of vomiting, reduction of intraocular pressure, widening of bronchial tubes, protection of nerve cells, and inhibition of tumor growth.

Cannabinoid receptors

The two G protein-coupled receptors (GPCRs) responsible for cannabinoid signaling are CB1 and CB2. The central nervous system predominantly possesses CB1 receptors. They manipulate neurons. CB2 receptors are present in both the spleen and mast cells. Both dronabinol and nabilone are authorized for the prevention and treatment of CINV. Omni neuromodulation refers to the direct modification or inhibition of neurotransmitters through CB1 receptor agonism by cannabis. Cannabinoids exert an influence on CB receptors, as well as on the dopaminergic, serotonergic, noradrenergic, and opioid systems (28**)**.

The presence of CB1 receptors is few in the brainstem

but numerous in the central nervous system (CNS), which accounts for the absence of respiratory depression effects caused by cannabis. The process of CB1 ligands acting as retrograde synaptic messengers to induce antiemetic effects in the endocannabinoid system involves multiple phases. This stimulates the release of neurotransmitters from neurons located before the synapse. Endocannabinoids are released by the activated postsynaptic receptors and then diffuse back to connect with the presynaptic CB1 receptor. This connection activates a G-protein that decreases the release of neurotransmitters, which is known as depolarization-induced suppression of inhibition (29**)**.

Dronabinol

Dronabinol, classified as a Schedule III prohibited narcotic, contains delta-9-tetrahydrocannabinol (THC), which is the primary psychoactive component found in marijuana. Aside from its approved indications, this medication can also be employed for the treatment of CINV in patients who have not experienced alleviation from 5-HT3 receptor antagonists, corticosteroids, or neurokinin 1 antagonists. Dronabinol is available in pill form with dosages of 2. 5mg, 5mg, and 10mg. The recommended dosage for treating nausea and vomiting caused by cancer chemotherapy is 5-15 mg/m2/dose. This should be taken 1-3 hours before treatment and can be repeated up to 4-6 times per day as needed.

The bioavailability ranges from 5% to 20%. The proteins in the plasma exhibit a high affinity for binding it, ranging from 90% to 99%. The liver is responsible for metabolizing it through the enzyme CYP2C9, and it also acts as an inhibitor of the enzyme CYP3A4. Dronabinol exhibits a diverse array of effects that primarily affects the central nervous system and peripheral autonomic system, encompassing psychomimetic and depressive characteristics. Individuals often report experiencing unpleasant effects such as drowsiness, anxiety, confusion, hallucinations, tiredness, and exhilaration. It aids individuals who have not experienced relief from conventional antiemetic medications.

Nabilone

Nabilone is a synthetic cannabinoid that has a somewhat extended duration of action, with a half-life ranging from 8 to 12 hours. The suggested starting dosage is 1-2 mg BD, administered once to three hours prior to chemotherapy, twice daily. The maximum permissible daily dosage is 6mg, which ensures safety. The adverse consequences encompass somnolence, vertigo, xerostomia, elation, ataxia, cephalalgia, and difficulty concentrating. Caution should be exercised when using nabilone in individuals who now or previously have had psychiatric illnesses and substance abuse, as it may potentially amplify central nervous system effects. Additionally, it is advised to avoid combining nabilone with alcohol, sedatives, hypnotics, or other psychoactive substances.

Nabilone does not significantly inhibit or activate CYP3A4 isoenzymes. If multiple antiemetics have proven ineffective in managing CINV, physicians may opt to give nabilone. Additionally, it may contribute to the prevention of nausea and vomiting in pregnant individuals. One advantage of it over dronabinol is that it has a lower dosing frequency, requiring only two doses per day, while dronabinol can be taken up to six times a day.

Dopamine receptor antagonists

The chemoreceptor trigger zone is involved in the regulation of nausea and vomiting through interactions between dopamine and other neurotransmitters. During the 1960s to the late 1980s, the primary treatment for CINV involved the administration of dopamine antagonists, such as prochlorperazine and metoclopramide.

Metoclopramide

Metoclopramide shares a comparable chemical composition with procainamide, and, akin to procainamide, it activates serotonin and dopamine receptors. It inhibits activity at 5-HT3 receptors and acts as a stimulator at 5-HT4 receptors, while also inhibiting activity at D2 receptors. Dopamine production suppression: Dopamine is a neurotransmitter that exerts an inhibitory influence on the digestive system. Decreases the probability of vomiting by inducing relaxation in the lower esophageal sphincter (LES) and reducing the speed at which the stomach releases its contents. The anti-nausea and anti-vomiting actions of metoclopramide are caused by its ability to act as an agonist at D2 receptors in the chemoreceptor trigger zone (CTZ) of the central nervous system. Myenteric plexus 5HT 4 agonism, characterized by the stimulation of serotonin receptors leads to an increase in acetylcholine release, resulting in prokinetic effects (30). Metoclopramide is quickly absorbed by the oral route. It has successfully traversed the placental and blood-brain barriers and is currently detectable in human milk. Conjugation occurs in the liver. The predicted half-life is between three and six hours. The onset of action following oral administration ranges from 30 to 60 minutes, while intramuscular treatment results in an onset of action within around 10 minutes. Intravenous administration, on the other hand, leads to an onset of action within approximately 2 minutes. Urination expels it from the body during a 24-hour period. The blocking of the D2 receptor leads to drowsiness, muscle dystonia, and, at sufficiently large doses, extrapyramidal symptoms. Additional potential adverse effects include galactorrhea in females and gynecomastia in males. It has been effective in both the prevention and treatment of chemotherapy-induced nausea and vomiting. Metoclopramide is no longer advised as a

treatment for delayed CINV in the latest ASCO antiemetic guidelines, as there are more efficacious alternatives now available. It should only be utilized as a last resort after exhausting all other potential treatments.

Domperidone

Domperidone, like metoclopramide, functions as a D2 receptor antagonist. Although it has a weaker ability to prevent nausea and vomiting compared to metoclopramide, it is considered safer because it does not pass through the blood-brain barrier and does not result in extrapyramidal side effects. To optimize its effectiveness in CINV, it is enhanced by mixing it with prochlorperazine (which blocks D2 receptors and muscarinic receptors), diphenhydramine (an H1 blocker), and dexamethasone. It exerts antiemetic actions by activating D2 receptors in the central tegmental region (CTZ). The bioavailability of orally administered drugs is restricted (15%) due to the process of first-pass metabolism. Common symptoms encompass diarrhea, xerostomia, cutaneous eruption, cephalalgia, and arrhythmia. Not effective as a standalone treatment for CINV.

Benzodiazepines

Benzodiazepines (BZDs) are utilized for the treatment of anxiety and have demonstrated efficacy in alleviating ANV (anticipatory nausea and vomiting) in specific individuals. They are also utilized in the treatment of refractory and breakthrough CINV. Anti-nausea and anti-vomiting medications, sedatives, and memory-loss drugs such as benzodiazepines (BZDs) can effectively prevent the occurrence of nausea and vomiting. Lorazepam and clonazepam are commonly prescribed medications.

CONCLUSION

The review provides a summary of whether antiemetics should be used individually or in combination, based on the total emetic potential of the chemotherapeutic treatment regimen. When used together with dexamethasone, 5-HT3 receptor antagonists are highly efficient in reducing acute vomiting caused by cisplatin and mildly emetogenic therapy. Further research is required to gain a deeper understanding of the occurrence of CINV in relation to new chemotherapies, particularly those taken orally on a daily basis. Determining the best combinations and timing of their administration in situations where chemotherapy is given over multiple days is important and the findings will greatly benefit patients by reducing treatment dropout rates and facilitating adherence to their chemotherapy regimens.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

REFERENCES

1. Lorusso, V., Russo A, Giotta, F., Codega, P. Management of chemotherapy-induced nausea and vomiting (CINV): a short review on the role of netupitant-palonosetron (NEPA). Core Evidence. 2020;27:21-29.
2. Kris, M. G., Gralla, R. J., Clark RA. Incidence, course and severity of delayed nausea and vomiting following the administration of high dose cisplatin. J Clin Oncol. 1985;3: 1379-1384.
3. de Jongh, F. E., van Veen, R. N., Veltma, S. J., de Wit, R., van der Burg, M. E., van den Bent, M. J *et al.*, Weekly high-dose cisplatin is a feasible treatment option: analysis on prognostic factors for toxicity in 400 patients. Br J Cancer. 2003; 88(8):1199- 1206.
4. Herrstedt, J., Lindberg, S., Petersen, P. C. Prevention of chemotherapy-induced nausea and vomiting in the older patient: optimizing outcomes. Drugs and Aging. 2022; 39(1): 1-21.
5. Shelke, A.R., Mustian, K.M., Morrow, G.R. The pathophysiology of treatment- related nausea and vomiting in cancer patients: Current Models. Indian J Physiol Pharmacol. 2004; 48: 256-268.
6. Zhong, W., Shahbaz, O., Teskey, G., Beever, A., Kachour, N., Venketaraman, V., *et al.*, Mechanisms of nausea and vomiting: current knowledge and recent advances in intracellular emetic signaling systems. Int. J. Mol. Sci. 2021; 22(11):5797-5830.
7. Gelberg, H. Pathophysiological Mechanisms of Gastrointestinal Toxicity. Elsevier; Amsterdam, The Netherlands: 2018;139-178.
8. Heckroth, M., Luckett, R. T., Moser, C., Parajuli, D., Abell, T. L. Nausea and vomiting in 2021: a comprehensive update. J. Clin. Gastroenterol. 2021;55(4):279-299.
9. Miller, A. D., Leslie, R. A. The area postrema and vomiting. Front Neuroendocrinol. 1994;15(4):301-320.
10. Gupta, K., Walton, R., Kataria, S. P. Chemotherapy-induced nausea, and vomiting: pathogenesis, recommendations, and new trends. Cancer Treat. Res. Commun. 2021;26:100278-100285.
11. Herrstedt, J., Dombernowsky, P. Antiemetic therapy in cancer chemotherapy: current status. Basic Clin Pharmacol Toxicol. 2007;101:143-150.
12. Herrstedt, J. Nausea and emesis: Still an unsolved problem in cancer patients? Support Care Cancer, 2002;10: 85-87.
13. Berger, M., Gray, J. A., Roth, B. L. The expanded biology of serotonin. Annu. Rev. Med. 2009; 60: 355-366.
14. Irving, H., Turek, I., Kettle, C., Yaakob, N. Tapping into 5-HT3 receptors to modify metabolic and immune responses. Int. J. Mol. Sci. 2021; 22(21):11910-11915.
15. Gholipour, T., Ghasemi, M., Riazi, K., Ghaffarpour, M., Dehpour, A. R. Seizure susceptibility alteration through 5-HT 3 receptor: modulation by nitric oxide. Seizure.2010;19 (1): 17-22.
16. Blower, P. A pharmacologic profile of oral granisetron (Kytril tablets). Semin Oncol.,1995;22(10):3-5.
17. Wong, E. H., Clark, R., Leung, E., Loury, D., Bonhaus, D. W., Jakeman, L., *et al.*, The interaction of RS 25259-197, a potent and selective antagonist, with 5-HT_3 receptors, in vitro. Br J Pharmacol. 1995;114(4):851-859.
18. Tanihata, S., Oda, S., Nakai, S., Uchiyama, T. Antiemetic effect of dexamethasone on cisplatin-induced early and delayed emesis in the pigeon. Eur J Pharmacol. 2004;484: 311-321.
19. Czarnetzki, C., Albrecht, E., Desmeules, J., Kern, C., Corpataux, J. B., Gander, S., *et al*., Dexamethasone for the treatment of established postoperative nausea and vomiting: A randomized dose finding trial. Eur. J. Anaesthesiol. 2022; 39(6):549-557.
20. Herrstedt, J., Aapro, M. S., Smyth, J. F., Del Favero, A. Corticosteroids, dopamine antagonists and other drugs. Support Care Cancer. 1998; 6:204-214.
21. Nguyen. L. P., Cho, M., Nguyen, T. U., Park, H. K., Nguyen, H. T., Mykhailova, K., *et al.*, Neurokinin-2 receptor negatively modulates substance P responses by forming

complex with Neurokinin-1 receptor. Cell Biosci. 2023; 13(1):212.
22. Patel, L., Lindley, C. Aprepitant, A novel NK1-receptor antagonist. Expert Opin Pharmacother. 2003; 4:2279-2296.
23. Karthaus, M., Schiel, X., Ruhlmann, C. H., Celio, L. Neurokinin-1 receptor antagonists: review of their role for the prevention of chemotherapy-induced nausea and vomiting in adults. Expert Rev. Clin. Pharmacol. 2019;12(7):661-680.
24. Navari, R. M., Schwartzberg, L. S. Evolving role of neurokinin 1-receptor antagonists for chemotherapy-induced nausea and vomiting. Onco Targets Ther. 2018:6459-6478.
25. Hesketh, P. J., Grunberg, S. M., Gralla, R. J., Warr, D. G., Roila, F., de Wit, R., *et al.,* The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A multinational, randomized, double-blind, placebo- controlled trial in patients receiving high-dose cisplatin-the Aprepitant Protocol 052 Study Group. J Clin Oncol., 2003;21:4112-4119.
26. Weinstein, C., Jordan, K., Green, S., Khanani, S., Beckford-Brathwaite, E., Vallejos, W., *et al.,* Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy regimens: a subgroup analysis from a randomized clinical trial of response in subjects by cancer type. BMC cancer. 2020;20(1):1-10.
27. Millar, S. A., Maguire, R.F., Yates, A.S., O'sullivan, S.E. Towards Better Delivery of Cannabidiol (Cbd). Pharmaceuticals, 2020;13:219-225.
28. Behl, T., Makkar, R., Sehgal, A., Singh, S., Makeen, H. A., Albratty, M., *et al.,* Exploration of multiverse activities of endocannabinoids in biological systems. Int. J. Mol. Sci. 2022; 23(10):5734.
29. Della., P. A., Savinainen, J., Giniatullin, R. Inhibiting Endocannabinoid Hydrolysis as Emerging Analgesic Strategy Targeting a Spectrum of Ion Channels Implicated in Migraine Pain. Int. J. Mol. Sci., 2022;23(8):4407-4415.
30. Neumann, J., Seidler, T., Fehse, C., Marušáková, M., Hofmann, B., Gergs, U. Cardiovascular effects of metoclopramide and domperidone on human 5-HT4-serotonin-receptors in transgenic mice and in human atrial preparations. Eur. J. Pharmacol. 2021; 901:174074-174085.