

## REVIEW ARTICLE

### USEFULNESS OF ANTI-EMETICS IN THE TREATMENT OF CANCER: A REVIEW

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**ABSTRACT:** In the treatment of cancer, nausea and vomiting are two of the most important and common toxic effects of chemotherapy and adversely affects the patient's quality of life and worse withdrawal from treatment. Physiologically, emesis is controlled by the vomiting centre in the medulla, that integrates afferent input from the vestibular system, the chemoreceptor trigger zone (CTZ), the cortex and the gut. Mechanistically, antiemetic mediate their action by blocking various type of receptors involved in inducing emesis and located in different regions and various organ of the body. Some of the most important anti-emetics used in prevention of nausea and vomiting are ondansetron, granisetron, metochlopramide, aprepitant and palonosetron. In addition to this, aprepitant also combined with dexamethasone and the 5-HT<sub>3</sub> antagonists to enhance prevention of acute emesis. In this comprehensive review an attempt is made at summarizing on the various antiemetic agents and their usefulness in the treatment of cancer. Also emphasis is placed on the recent research on combination of antiemetic and elucidating the role of various agents used in the combinations of to mediate optimal effects.

**KEYWORD:** chemotherapy-induced nausea and vomiting (CINV), anti-emetics, olanzapine

### INTRODUCTION:

Chemotherapy, an important modality in the control and cure of cancer is hampered by the intense nausea and vomiting induced by cytotoxic agents. Radiation therapy used for cancer patients is also strongly emetogenic. This distressing symptom would hamper the continuation of the therapy and worsen the quality of life, making it hard to function normally from day to day, causing anxiety and depression. Uncontrolled nausea and vomiting may even make the patient consider stopping the treatment.

This will invariably affect the cancer cure and survival. Most of the anticancer drugs show severe nausea and vomiting as an integral adverse effect. Chemotherapy induced nausea and vomiting (CINV) is divided into acute, delayed, anticipatory, breakthrough and refractory phases and the right choice of antiemetic could circumvent this problem. The knowledge of the pathophysiology of CINV has advanced in the recent years. It has been noted that various neurotransmitters play an important role in the pathogenesis of CINV<sup>[1]</sup>.

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The important neurotransmitters said to be involved in CINV are serotonin, substance P and dopamine, and their receptors are located in the gastrointestinal tract and the central nervous system. In CINV, these neurotransmitters are released into the gastrointestinal tract and central nervous system in response to chemotherapeutic agents, and impulses thus produced are relayed into the vomiting centre resulting in nausea and vomiting. The other neurotransmitters involved in nausea and vomiting are cannabinoids, histamine, GABA and acetylcholine. It is postulated that there are a total of twenty neurotransmitters and receptor systems involved in the vomiting reflex.

Thus, agents which block the receptors of these neurotransmitters can be used to pharmacologically treat nausea and vomiting. The presently available arrays of antiemetics have to be used judiciously and in rational combinations to achieve the required effect. It has been observed that combination of metoclopramide, dexamethasone and lorazepam in cisplatin-induced emesis was controlled in only 60% of the patients<sup>[2]</sup>. The newer class of antiemetic agents, 5HT<sub>3</sub> antagonists (such as ondansetron or granisetron) is highly effective in continuing acute phase of cisplatin induced emesis in around 70-90% of patients.

Chemotherapy induced nausea and vomiting adversely affects the quality of life of cancer patients, often leading to poor compliance with the treatment regimen and serious metabolic complications. In a recent study, out of 400 patients receiving cisplatin as a part of their chemotherapeutic regimen, 26.5 % of patients did not complete their cycles because of the intense nausea and vomiting that had occurred due to cisplatin<sup>[3]</sup>.

The recent introduction of more effective antiemetic agents has improved the quality of life significantly. However, CINV still remains a significant complication of cancer chemotherapy and requires constant medical attention. A comparative study was conducted by Muller et al. for cisplatin administration to compare ondansetron with

metoclopramide. In acute phase, complete/major response was seen in 72% ondansetron patients compared to 41% of the metoclopramide group.

In the delayed phase, metoclopramide was stronger than ondansetron to prevent nausea and vomiting<sup>[4]</sup>. A phase III, double blind randomized trial evaluated the efficacy and safety of palonosetron in preventing acute and delayed chemotherapy induced nausea and vomiting following highly emetogenic chemotherapy. Clinical response (CR – no nausea, no emesis) rates were higher with palonosetron than ondansetron during the delayed phase. Patients pre-treated with palonosetron plus dexamethasone had higher CR rates than those receiving ondansetron plus dexamethasone during the delayed phase (42% vs. 28.6%)<sup>[5]</sup>.

A randomized double blind study demonstrated the beneficial role of NK-1 antagonists in the prevention of delayed emesis. These agents also provide additional benefits in the prevention of acute nausea and vomiting when combined with a 5HT-3 antagonist and dexamethasone. The addition of the NK-1 antagonist, aprepitant, to standard antiemetics resulted in superior protection against cisplatin induced nausea and vomiting in 72.7% of 260 patients compared to 52.3% in a standard therapy group of 260 patients<sup>[6]</sup>. Despite the availability of various antiemetic agents for prevention and treatment of CINV, nausea and vomiting still occurs as a major adverse effect, affecting the outcome of chemotherapeutic treatment and patient's quality of life.

### **Physiological and pathological aspects of Nausea and vomiting:**

#### **The Vomiting Reflex**

The vomiting reflex is mediated neurologically by the activation of the bilateral nucleus tractus solitarius, or emetic center, situated in the parvocellular reticular formation in the lateral region of the medulla oblongata. This area plays a key role in initiating, controlling, regulating, and organizing the

vomiting reflex. Both neural and humoral pathways are involved in triggering vomiting [7].

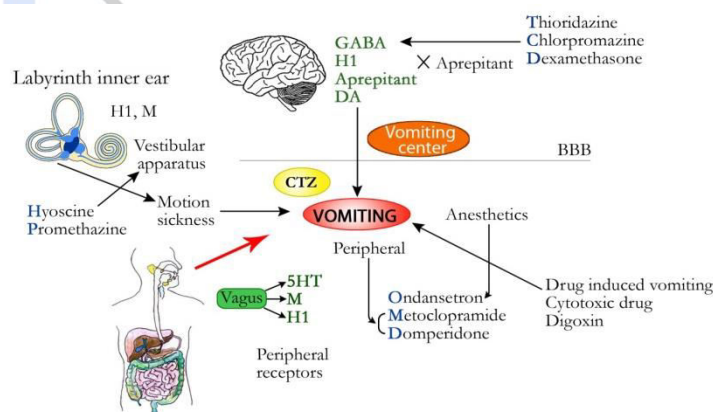
### Neural pathway

There are six important components in this pathway. The vomiting center (i) receives impulses from the gastrointestinal tract (ii) (afferent neurons); the higher centers of the brain (iii) (cerebral cortex and limbic system), the vestibular apparatus (iv), and the chemoreceptor trigger zone (CTZ)(v). Finally, the vomiting center sends signals through the efferent motoneurons (vi) to complete the vomiting reflex. Stimulation of the vagal and sympathetic afferent neurons initiates the impulse that travels directly to the emetic center. These afferent neurons originate from the gastrointestinal tract, particularly the duodenum, as well as other areas, including the urinary and reproductive system, liver, pancreas, peritoneum, and cardiac vessels. The higher centers of the brain (the cerebral cortex and the limbic system), initiate emesis via three mechanisms: The psychogenic stimulation caused by fear, stress, excitement, or pain; traumatic stimulation related to head injuries and increased intracranial pressure and direct stimulation of the vomiting center by inflammatory diseases, hydrocephalus, orneoplasia<sup>[8, 9]</sup>.

The chemoreceptor trigger zone (CTZ) situated close to the area postrema on the base of the fourth ventricle, lies outside the blood brain barrier and has numerous dopamine D<sub>2</sub> receptors, serotonin 5-HT<sub>3</sub> receptors, opioid receptors, acetylcholine receptors, and receptors for substance P. Stimulation of different receptors are involved in different pathways leading to emesis. It possesses free nerve endings that maintain direct contact with the cerebrospinal fluid via ependymal pores or the sheath surrounding fenestrated capillaries <sup>[9, 10]</sup>. These free nerve endings are activated by the vestibular system or through the humoral pathway by conditions affecting the blood or cerebrospinal fluid (e.g., drug administration, infection, osmolar and acid-base disorders, electrolyte derangements, metabolic diseases<sup>[11]</sup>). Finally, to initiate the

vomiting reflex, efferent motor signals are transmitted to the upper gastrointestinal tract through the sensory aspect of cranial nerves V, VII, IX, X, and XII and to the diaphragm and abdominal muscles via the spinal nerves.

Nausea and vomiting are not diseases but symptoms that accompany various kinds of underlying diseases. It is basically a defense mechanism and is self-limiting if the precipitating cause/ disease is treated. There are many causes of nausea and vomiting, the most common being gastroenteritis, motion sickness, head injuries and side effects of some medications. Though usually harmless, vomiting can still be a symptom of more serious conditions like myocardial infarction, encephalitis, meningitis, intestinal obstruction, appendicitis, migraine headaches, and brain tumors, which when left untreated, may lead to life threatening complications.



**Figure.1 Schematic representation of etiopathology of vomiting and site of action of Antiemetics**

### Complications of nausea and vomiting<sup>[12]</sup>.

**Aspiration of vomitus:** Vomiting can be dangerous if the gastric content enters the respiratory tract as the individual may choke and asphyxiate or suffer aspiration pneumonia.

**Dehydration and electrolyte imbalance:** Prolonged and excessive vomiting can cause dehydration and may alter the electrolyte status in the individual.

**Mallory-Weiss tear:** Repeated or profuse vomiting may cause intramural esophageal lesions or small tears in the esophageal mucosa (Mallory-Weiss tear) resulting in fresh red blood mixed with vomit after several episodes.

**Dentistry:** Recurrent vomiting observed in bulimia nervosa, may lead to destruction of the tooth enamel due to acidity of vomitus.

**Malnutrition:** With the loss of intake of food, the individual may eventually become cachectic.

**Discontinuation of therapy:** If nausea and vomiting is induced by medications, it may drive the patient to stop taking those medications resulting in therapeutic failure. e.g.: chemotherapy induced nausea and vomiting. Thus, prolonged vomiting has dire consequences and requires careful medical management.

### Chemotherapy induced nausea & vomiting (CINV)

Although chemotherapy is a boon to patients with cancer, it still has varied adverse effects affecting patient's quality of life. Cisplatin, which is a highly emetogenic chemotherapeutic agent, was introduced in the 1970's. Within 24 hours of administration of cisplatin, the patient would vomit on an average of 10 times. The introduction of metoclopramide in the 1980s provided some relief in CINV. However, the risk of extrapyramidal side effects made it a less perfect antiemetic. With the advent of 5HT<sub>3</sub> antagonists in 1990s, the incidence

of CINV reduced to a certain extent. The use of NK1 antagonists following the approval of aprepitant in 2006 and fosaprepitant in 2008 was a big milestone achieved in combating CINV.

Chemotherapy-induced nausea and vomiting (CINV) is potentially the most severe and most distressing of all the adverse effects of cancer treatment. Most people receiving cancer chemotherapy experience at least some CINV. Uncontrolled CINV can give rise to medical complications, including poor nutrition, dehydration, electrolyte imbalances, and physical and mental deterioration. In spite of advances in treatment, the most important concern for patients is thenausea and vomiting associated with the cancer treatment rather than their life expectancy, leading to discontinuation of an otherwise lifesaving chemotherapeutic regimen<sup>[13]</sup>. Significant progress has been made with the development of a number of effective and well-tolerated antiemetic treatments. Still CINV remains an important adverse effect of treatment.

### 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. In the absence of effective prophylaxis, it most commonly begins within one to two hours of chemotherapy and usually peaks in the first four to six hours.

**Delayed emesis** — Emesis occurring more than 24 hours after chemotherapy is classified as delayed. It can last for up to five days.

**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. It can be elicited by a variety of stimuli and cognitive activities in

association with subsequent cycles of chemotherapy<sup>[14]</sup>. The occurrence of ANV increases with each cycle. By the fourth cycle, at least 20-50 % patients experience ANV.

**Breakthrough CINV**—is nausea and vomiting that occurs despite antiemetic therapy and requires rescue medication.

### Risk factors in CINV

The risk of CINV depends on various patient related factors and the chemotherapeutic regimen administered, and they increase the chances of CINV.

**Emetogenic drugs in cancer:** According to The American Society of Clinical Oncology (ASCO), chemotherapeutic agents have been classified based on their emetogenic potential. The following table gives a classification of the cancer chemotherapy agents according to their emetogenicity<sup>[15]</sup>.

**Pathophysiology of CINV:** The exact mechanism by which chemotherapy induces nausea and vomiting has not been clearly understood. Vomiting is a complex reflex mechanism. It involves afferent and efferent pathways and a vomiting center (VC). Within the medulla oblongata of the brain stem is the vomiting center. VC has three components, a) area postrema (AP), b) nucleus tractus solitarius (NTS) and c) dorsal motor vagal nucleus (DMVN), which integrate the emetic response<sup>[16]</sup>. The following mechanisms have been postulated:

- 1) Stimulation of the chemoreceptor trigger zone (CTZ) directly or indirectly by the chemotherapeutic agent – thought to be the most common mechanism
- 2) Stimulation of the gastrointestinal (GI) tract resulting in release of serotonin and substance P from the enterochromaffin cells (EC) of the GI mucosa, which send signals via the vagal sensory fibers to the nucleus tractus solitarius.
- 3) Vestibular mechanisms (patients with history of motion sickness are more likely to

experience CINV, the exact mechanism being unclear).

- 4) Alterations in taste and smell – alterations in taste following chemotherapy (Cisplatin or gallium nitrate cause loss of taste or metallic taste, 5FU – bitter taste)
- 5) ANV – is not caused by the chemotherapeutic agents, but involves a psychological mechanism<sup>[6]</sup>.

Managing CINV with a single antiemetic will not work always, due to the several mechanisms involved in CINV and difference in the emetogenic potential of the chemotherapeutic drugs.

### Antiemetics in CINV

Several classes of antiemetic drugs are available that antagonize the neurotransmitter receptors known to be involved in the physiology of nausea and vomiting<sup>[17]</sup>. The goal of each antiemetic is to reduce/abolish nausea and vomiting, the major adverse events of cancer chemotherapy which forces up to 20% of patients to postpone or refuse potentially curative treatment<sup>[18]</sup>. The antiemetic drugs are classified according to their primary action (some agents affect multiple receptors). It is not surprising that a combination therapy is more effective in the treatment taking into consideration that multiple pathways are involved in the pathophysiology of CINV. The antiemetic regimens according to the ASCO guidelines<sup>[15]</sup>.

**Serotonin antagonists:** Approximately 90% of the human body's total serotonin - a monoamine neurotransmitter, is located in the enterochromaffin cells (EC cells) in the alimentary canal. The rest is present in the serotonergic neurons in the CNS<sup>[19]</sup>. In the body, serotonin is synthesized from the amino acid tryptophan by a short metabolic pathway consisting of two enzymes: tryptophan hydroxylase (TPH) and aromatic amino acid decarboxylase (AADC). The TPH-mediated reaction is the rate-limiting step in the pathway. TPH exists in two forms: TPH1, found in several tissues, and TPH2,

which is a brain-specific isoform. 5-Hydroxyindoleacetic acid (5-HIAA), a breakdown product of serotonin is excreted in urine. Measurement of serotonin and 5-HIAA in urine is done to determine their excess secretion in certain tumors. Enterochromaffin cells, which are abundant in the gut, release serotonin in response to food in the gut lumen. EC cells are very sensitive to irradiation and cancer chemotherapy, releasing more serotonin in response to them, than the platelets can absorb, leading to very high levels of free serotonin in the blood, causing activation of 5-HT<sub>3</sub> receptors in the CTZ, leading to vomiting. 5-HT<sub>3</sub> receptor antagonists are effective anti-emetics<sup>[20, 21]</sup>. 5-HT<sub>3</sub> receptor is a ligand gated ion channel. The 5-HT<sub>3</sub> receptor is composed of five subunits pseudo symmetrically arranged about a central ion conducting pore. Polymorphisms in the subunits can lead to increased susceptibility to nausea and vomiting. The 5-HT<sub>3</sub> receptor is present throughout the central and peripheral nervous systems. It mediates a variety of physiological functions. When the ion channel is activated by serotonin, the following effects occur. In the CNS nausea and vomiting center in brain stem, anxiety, seizure propensity while in the PNS neuronal excitation (in autonomic, nociceptive neurons), emesis<sup>[22]</sup>.

**5-HT<sub>3</sub> receptor antagonists:** The introduction of the 5-HT<sub>3</sub> receptor antagonists has represented a significant clinical advance in the prevention of CINV, especially in patients receiving highly emetogenic chemotherapy. Ondansetron, granisetron, dolasetron, and alosetron are competitive antagonists of the 5-HT<sub>3</sub> receptor, with structural similarity to 5-HT, and with carbazole, indazole, indole, and imidazole main-chains, respectively. In contrast, palonosetron is a non-competitive antagonist of the 5-HT<sub>3</sub> receptor, with a fused tricyclic ring and a quinuclidine side chain. Ondansetron the prototype 5-HT<sub>3</sub> antagonist, developed by Glaxo around 1984, blocks emetogenic impulses both at their peripheral and

central origin, and also has a weak 5-HT<sub>4</sub> antagonistic action. It is metabolized in the liver by CYP2D6, 1A2 and 3A. No significant drug interactions have been noted. It has a t<sub>1/2</sub> of 3-4 hrs, and duration of action of 4 -12 hrs. They are well tolerated, although the most common side effect seen is headache. Following I.V administration, rashes and allergic reactions have been noticed. Mild constipation and diarrhea also can be seen in a few patients.

**Granisetron:** Granisetron is a potent and highly selective 5-HT<sub>3</sub>-receptor antagonist that has little or no affinity for other 5-HT receptors, or dopaminergic, adrenergic, benzodiazepine, histaminic, or opioid receptors<sup>[23]</sup>. Oral granisetron is administered as a 2mg dose once. However, for patients in whom oral administration is not suitable, granisetron can also be administered intravenously via a 30 second injection or as a 5-minute infusion. A granisetron transdermal patch was approved by the US FDA on September 12, 2008<sup>[24]</sup>. Granisetron is 10-15 times more potent than ondansetron, and more effective in treating CINV. Following oral administration, the bioavailability is 60%. It is 65 % plasma protein bound, T<sub>1/2</sub> is 3-14 hrs.

#### Indications

- Chemotherapy-induced nausea and vomiting (CINV) 5-HT<sub>3</sub> receptor antagonists are the primary drugs used to treat and prevent CINV. They are usually given 10mcg/kg intravenously about ½ hr before beginning therapy.
- Post-operative and post-radiation nausea and vomiting
- Nausea and vomiting due to acute or chronic medical illness or acute gastroenteritis Treatment of cyclic vomiting syndrome

#### Adverse effects

It is well tolerated. The common side effects are headache, dizziness and constipation.

**Dolasetron:** Dolasetronmesylate and its active metabolite hydrodolasetron are selective 5HT<sub>3</sub> receptor antagonists. The t<sub>1/2</sub> is 4-9 hrs. The use of dolasetron in CINV is no longer recommended, as it causes serious cardiovascular adverse effects (dose dependent QTc prolongation). The dose approved for CINV was 100mg I.V. However, its use in post-operative nausea and vomiting has not been removed as the dose required is lower in these patients (12.5mg I.V) (FDA drug 2012)<sup>[25]</sup>.

**Palonosetron:** It is the most recent 5-HT<sub>3</sub> antagonist to enter clinical use. It is a second generation 5HT<sub>3</sub> antagonist. Palonosetron is given as a single 0.25-mg intravenous dose 30 minutes before the initial dose of chemotherapy. Palonosetron is metabolized via the CYP2D6 enzyme pathway and to a lesser extent, CYP3A and CYP1A2 enzyme pathways. When compared with other agents in the class, palonosetron exhibits a longer half-life (40 hours) and has a greater 5-HT<sub>3</sub> receptor binding affinity<sup>[26]</sup>. Palonosetron should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc<sup>[27]</sup>. It is well tolerated, common side effects being headache and constipation. Palonosetron has only a minor effect on the cytochrome P450 pathway. No drug interactions have been reported related to enzyme induction or inhibition; however, concurrent use of apomorphine may result in profound hypotension and altered consciousness and is contraindicated<sup>[28]</sup>. Palonosetron is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderate to highly emetogenic cancer chemotherapy. Recommended dosage is 0.25 mg administered intravenously as a single dose over 30 seconds approximately 30 minutes prior to the administration of chemotherapy on day 1 of each cycle. Palonosetron, however, is substantially more expensive than the alternative agents, and cost-effectiveness should be taken into consideration when choosing among the available 5-HT<sub>3</sub> receptor antagonists.

**Corticosteroids:** The mechanism of action of corticosteroids in CINV is relatively unknown. Studies in pigeons suggest that the antiemetic effect of steroids may be partially from their activity in the central nervous system<sup>[29]</sup>. Few other studies also suggest that the effect may be due to activation of glucocorticoid receptors in the nucleus of the solitary tract in the medulla<sup>[30]</sup>. Dexamethasone and methylprednisolone have also been shown to antagonize 5-HT<sub>3A</sub> receptors in *Xenopus* oocytes; thus explaining the beneficial effects of corticosteroids in CINV prophylaxis and treatment<sup>[31]</sup>.

**Role in management of CINV Acute CINV:** The role of corticosteroids in acute CINV management is in combination with either a 5-HT<sub>3</sub> antagonist alone or as part of triple-drug therapy with a neurokinin (NK1) antagonist. In the moderately emetogenic setting, when used in combination with a 5-HT<sub>3</sub> antagonist, the recommended dose of dexamethasone is 8 mg I.V. Dexamethasone is also recommended for the management of delayed CINV in both high and moderately emetogenic chemotherapy regimens. Doses are generally 8 mg once or twice daily, depending on emetogenicity and concurrent antiemetics. Few recent data have suggested that corticosteroids could be eliminated from the delayed setting without decreased efficacy in CINV control. Corticosteroids used in CINV in combination with other agents are more effective than when used alone and are very well tolerated. The most common side effects are transient elevations in glucose, insomnia, anxiety, and gastrointestinal upset. However, in most settings the duration of therapy with a corticosteroid is short and side effects can be managed, and the benefits are thought to outweigh any adverse effects<sup>[32]</sup>. Corticosteroids continue to play a key role in the management of CINV, even with the development of NK1 receptor antagonists and second-generation 5-HT<sub>3</sub> antagonists and it remains the backbone of most CINV prophylactic regimens.

**Neurokinin antagonists:** The actions of substance P (SP) are mediated through the neurokinin-1 (NK<sub>1</sub>) receptor, a G-protein receptor coupled to the inositol phosphate signal transduction pathway. Substance P was discovered by Von Euler and Gaddum in 1931 as a hypotensive and spasmogenic agent present in the equine gut and brain. The term “tachykinin” was coined by Erspamer and Melchiorri, in 1973, to describe the fast development of contractile action in smooth muscle by SP. Tachykinins comprise of endogenous ligands for tachykinin receptors, which belong to the G protein-coupled receptor family (GPCRs). There are three types of tachykinin receptors identified - NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub><sup>[33]</sup>. Members of the tachykinin family comprises of Substance P, Neurokinin A and Neurokinin B. They act on receptors NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub>. Substance P, a 11 amino acid peptide, has strong affinity to NK<sub>1</sub>. Neurokinin A and neurokinin B have strong affinity towards NK<sub>2</sub> and NK<sub>3</sub> respectively<sup>[34]</sup>. The significance of the interaction between substance P and its receptor Neurokinin 1 (NK<sub>1</sub>) in CINV is becoming clearer with more studies being done<sup>[35]</sup>. Substance P is widely distributed in the mammalian central nervous system and other tissues. Substance P itself induces emesis. NK<sub>1</sub> receptors are located in the brain stem nuclei of the dorsal vagal complex. Animal studies have shown that NK-1 receptor blocker agents prevent cisplatin- induced emesis and also, emesis caused by a variety of other known emetic stimuli (apomorphine, and ipecac), giving the NK-1 receptor antagonists the broadest range of activity of all antiemetics in preclinical studies<sup>[36]</sup>.

**Aprepitant:** Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK<sub>1</sub>) receptors. It exhibits nonlinear pharmacokinetics, i.e. there occurs saturation of metabolism and decreased clearance with increasing dose<sup>[37]</sup>. The oral administration of aprepitant is at doses 125 mg on day 1 and 80 mg once daily on days 2 and 3. The bioavailability of aprepitant is 60-65% after an oral dose and food does not interfere with the oral absorption. It crosses the blood brain barrier in humans and has been shown to cross the placental barrier in animals.<sup>[53]</sup> Aprepitant undergoes extensive metabolism in the liver, primarily by CYP3A4 mediated pathways with minor action by CYP1A2 and CYP2C19 enzymes<sup>[38]</sup>. No clinically significant difference exists in the plasma concentrations of aprepitant between males and females after a single 125 mg oral dose. No dose adjustment is needed in geriatric population even though they are at a higher physiologic risk of dehydration as a result of severe nausea and vomiting<sup>[38,14]</sup>. Aprepitant is well tolerated in patients with mild hepatic insufficiency, without the need for any dose reduction. Studies are lacking in patients with severe hepatic insufficiency.

#### Adverse effects

Most commonly observed side-effects are asthenia, hiccups, diarrhea, gastritis, elevation in liver function tests and dizziness. Few patients have reported thrombocytopenia and dehydration<sup>[35, 39]</sup>. Risk of drug interactions when co-administered with drugs metabolized by CYP3A4 is seen as at therapeutic doses, aprepitant inhibits CYP 3A4 isoenzyme. A five-fold increase in AUC and three-fold increase in half-life of aprepitant was noted when given along with ketoconazole, which warrants caution while administering along with azoles<sup>[38]</sup>. Other drugs, which need careful monitoring of toxicity are imatinib, irinotecan, nefazodone, nelfinavir, paroxetine and ritonavir<sup>[38]</sup>. Aprepitant can produce a transient, modest induction of CYP2C9 activity. This can result in clinically significant interaction with warfarin and

phenytoin.<sup>57</sup> Aprepitant is recommended for high and moderate emetogenic risk chemotherapy.

**Fosaprepitant:** Fosaprepitant is a prodrug of aprepitant and is a clinically approved drug by US FDA. The recommended dose is 115 mg IV 30 minutes prior to chemotherapy on day 1 only. Thereafter, oral doses of aprepitant (80 mg once daily in the morning on day 2 and 3) should be administered. Fosaprepitant is rapidly converted to aprepitant in the liver and multiple extrahepatic tissues, including kidney, lung and ileum. Aprepitant is highly plasma protein bound (>95%). Metabolism is largely via oxidation at the morpholine ring and its side chains. Metabolism by CYP2D6, CYP2C9, and CYP2E1 has not been detected. The  $t_{1/2}$  of aprepitant is between 9 and 13 hours. Fosaprepitant is indicated, in combination with other antiemetics, for the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy and for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy, including high-dose cisplatin. Fosaprepitant has not been evaluated for the treatment of established nausea and vomiting. Chronic continuous administration is not recommended<sup>[40]</sup>. Fosaprepitant is bioequivalent to aprepitant. However it offers benefits in patients who may be unable to tolerate oral administration of antiemetic due to nausea or vomiting during therapy<sup>[41]</sup>.

**Cannabinoids:** Cannabis is one of the oldest psychotropic drugs known to man in history. There are several species of cannabis, namely *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. While marijuana is the popular name for the *Cannabis sativa*, cannabis refers to the dried leaves and flowers of this plant. In 1839, a British physician and surgeon working in India, William O'Shaughnessy, discovered the analgesic, appetite

stimulant, antiemetic, musclerelaxant and anticonvulsant properties of cannabis. The publication of his observations led to the beginning of the medical use of cannabis. It was also prescribed to Queen Victoria for relief of dysmenorrhea. However, the use of cannabis was condemned by the American authorities, for being responsible for insanity, moral and intellectual deterioration, violence and various crimes. In 1942, it was removed from the United States Pharmacopoeia.

More than 460 known chemicals have been obtained from cannabis, around 60 of which are grouped under the name cannabinoids. The major psychoactive ingredient of cannabis is delta-9-tetrahydrocannabinol (THC), also called dronabinol. The discovery by young patients that smoking marijuana prior to undergoing chemotherapy relieved the ensuing nausea and vomiting led to clinical trials demonstrating the efficacy of THC<sup>[42]</sup>. The therapeutic effects of  $\Delta^9$ -THC {(-)-trans-delta-9 tetrahydrocannabinol} and four other cannabinoids ( $\Delta^8$ -THC, nabilone, levonantradol and nonabine) against chemotherapy-induced nausea and vomiting (CINV) has been being studied for several decades. The molecular mechanisms by which cannabinoids prevent vomiting were recently discovered after the discovery of cannabinoid CB1 and CB2 receptors.

Endocannabinoids, which are arachidonic acid-like substances, are the endoligands of the cannabinoid receptor system<sup>[43]</sup>. Five endocannabinoids have been detected so far, of whom anandamide and 2-arachidonylglycerol are best studied. Properties of cannabinoids that might be of therapeutic use include analgesia, muscle relaxation, immunosuppression, anti-inflammatory effects, anti-allergic effects, sedation, improvement of mood, stimulation of appetite, anti-emesis, lowering of intraocular pressure, bronchodilation, neuroprotective and antineoplastic effects.

### **Cannabinoid receptors**

Two cannabinoid receptors have been identified, CB1 and CB2, both of which are GPCRs. The CB1 receptors predominate within the central nervous system (CNS). They are neuromodulatory in action. CB2 receptors are found in immune cells, particularly in mast cells, and the spleen. Two pharmaceutical cannabinoids have been approved for the prevention and treatment of CINV—dronabinol and nabilone. Cannabinoids are thought to directly modulate, or inhibit neurotransmitters via agonism of the CB1 receptors and this is called 'omni-neuromodulation'. Cannabinoids not only interact with CB receptors but also with the dopaminergic, serotonin, noradrenergic, and opioid systems. Although widely distributed in the CNS, the CB1 receptors are sparse within the brainstem, thus explaining the lack of respiratory depressant effects of cannabinoids.

The antiemetic effects of the endocannabinoid system are produced by a multi-step process in which the CB1 ligands act as retrograde synaptic messengers. In this process, neurotransmitters are released from the pre-synaptic neuron. They activate the post-synaptic receptors and in turn, the activated post-synaptic neurons release endocannabinoids which then diffuse back and bind to the pre-synaptic CB1 receptor. This binding results in activation of a G-protein leading to a reduction of neurotransmitter release, a process known as depolarization-induced suppression of inhibition (DSI).

### **Dronabinol**

Dronabinol is a schedule III controlled substance that contains delta-9-tetrahydrocannabinol (THC), a major substance found in marijuana. It is approved for appetite stimulation in AIDS-related anorexia and treatment of chemotherapy-induced nausea and vomiting in patients who have failed to respond to conventional anti-emetic therapies including 5-HT<sub>3</sub> receptor antagonists, corticosteroids and neurokinin 1 antagonists. Dronabinol is available in the dosage forms of 2.5, 5 and 10mg capsules. The

recommended dosage as an antiemetic for nausea and vomiting induced by cancer chemotherapy is 5–15 mg/m<sup>2</sup>/dose, 1–3 hours before chemotherapy, up to 4–6 doses per day (CPA). It has a bioavailability of 5–20%. It is highly plasma protein bound (90–99%). It is metabolized in the liver (CYP2C9) and is a CYP3A4 inhibitor. Dronabinol produces a mixture of psychomimetic and depressant effects, together with various centrally mediated and peripherally autonomic effects. Adverse effects seen are drowsiness, anxiety, confusion, hallucinations; fatigue and euphoria. It is beneficial in patients not responding to the other conventional antiemetics.

### **Nabilone**

Nabilone is a synthetic cannabinoid. It has a long duration of action (8–12 hrs) and thus is usually administered twice daily, with the usual starting dose of 1–2 mg BD, one to three hours before chemotherapy. The maximum dose recommended per day is 6 mg. Adverse effects seen are drowsiness, vertigo, dry mouth, euphoria, ataxia, headache, and concentration difficulties. Nabilone should cautiously be used in patients with current or past history of psychiatric disorders and substance abuse and should not be taken with alcohol, sedatives, hypnotics, or other psychoactive substances due to the potential for augmentation of CNS effects. Nabilone does not induce CYP3A4 isoenzymes and lacks significant CYP3A4 inhibitory effect<sup>[44]</sup>. Nabilone is approved for use in CINV refractory to other antiemetics. It is also said to have a role in preventing anticipatory nausea and vomiting. Advantage over dronabinol is that it is administered twice daily whereas dronabinol may have to be taken up to 6 times a day<sup>[45]</sup>.

### **Dopamine receptor antagonists**

Dopamine is one of the neurotransmitters implicated in the control of nausea and vomiting via interactions in the chemoreceptor trigger zone. In the 1960's and through in the late 1980's, treatment of CINV primarily involved the use of dopamine

antagonists, such as prochlorperazine and metoclopramide.

### Metoclopramide

Metoclopramide was first described by Dr. Louis Justin Besancon and C. Laville in 1964<sup>[46]</sup>. It is chemically related to procainamide. It acts on both serotonergic and dopaminergic receptors. It is a mixed 5-HT<sub>3</sub> receptor antagonist/ 5-HT<sub>4</sub> receptor agonist, and a D<sub>2</sub> receptor antagonist.

Dopamine antagonism: Dopamine is an inhibitory neurotransmitter in the gastrointestinal tract. It delays gastric emptying, and causes lower esophageal sphincter relaxation (LES), thus aiding in nausea and vomiting. The antiemetic action of metoclopramide is due to its antagonist activity at D<sub>2</sub> receptors in the chemoreceptor trigger zone (CTZ) in the central nervous system (CNS)—this action prevents nausea and vomiting triggered by most stimuli.

**Serotonergic activity:** 5HT<sub>4</sub> agonism-prokinetic effects due to increased release of Ach in the myenteric plexus

Metoclopramide is absorbed rapidly orally. It crossed the BBB, placenta, and is secreted in breast milk. It is partly conjugated in the liver. The t<sub>1/2</sub> is 3-6 hrs. Onset of action orally is ½ to 1 hr, following I.M administration – 10 mins, and I.V – 2 mins. It is excreted in the urine within 24 hrs<sup>[47]</sup>. It causes sedation, muscle dystonias, and in higher doses may induce extrapyramidal side effects, all due to D<sub>2</sub> receptor blocking activity. It can also produce galactorrhoea in females and gynaecomastia in males. It has been used in prophylaxis and treatment of delayed nausea and vomiting in highly emetogenic chemotherapy. The present ASCO antiemetic guidelines no longer recommend metoclopramide for use in delayed CINV as there are more effective drugs available. Its use is recommended only when the conventional therapies fail.

### Domperidone

Domperidone is a D<sub>2</sub> receptor antagonist with mechanism of action like metoclopramide. Even though its antiemetic efficacy is lower than that of metoclopramide, it is safer given the fact that it does not cross the BBB, there are no extrapyramidal side effects seen. Its efficacy in CINV is improved when combined with prochlorperazine (D<sub>2</sub> receptor and muscarinic receptor blocker), diphenhydramine (H<sub>1</sub> blocker) and dexamethasone. It acts on the D<sub>2</sub> receptors in the CTZ thus eliciting antiemetic actions. It is absorbed orally, bioavailability is low (~15%), due to first pass metabolism. Loose stools, dry mouth, rashes, headache, cardiac arrhythmias are seen. No status as monotherapy in CINV.

### Benzodiazepines

Benzodiazepines (**BZDs**) are used to treat anxiety and to reduce the risk of ANV (anticipatory nausea and vomiting). They are also used in refractory and breakthrough CINV. BZDs is used for their anxiolytic, sedative and amnestic properties which are beneficial in anticipatory nausea and vomiting. Lorazepam and clonazepam are commonly administered.

### CONCLUSION:

In short the review concludes that antiemetics can be used alone or in combination depending upon the total emetic potential of the chemotherapeutic drug regimen. 5-HT<sub>3</sub> receptor antagonists are highly effective antiemetic drug that when used in combination with dexamethasone represents the most efficacious regimens for the prevention of acute emesis induced by cisplatin and by moderately emetogenic chemotherapy. Future research should be aimed at optimizing combinations and timing of antiemetic administration in multiple day chemotherapy settings and to clarify the incidence of CINV related to new chemotherapies, including daily oral treatments. The outcome of such studies will be very beneficial to the patients, reduce withdrawal from treatment

and ease the adherence to chemotherapy schedules.

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