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Review Article

Exploring Nausea and Vomiting: Pathophysiology, Mechanisms and Future Research Directions

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ABSTRACT

Nausea and Vomiting are among the major health burdens affecting nearly 90-95% of the worldwide population. Nausea and vomiting, commonly called emesis, are prevalent symptoms associated with various medical conditions and treatments. This review paper systematically examines the pathophysiology of emesis and the current landscape of antiemetic therapies, focusing on their mechanisms of action, efficacy, and adverse effects. The paper provides a comprehensive overview of the classes of antiemetic drugs consisting of antagonists of the dopamine, serotonin, and neurokinin-1 receptors among others. It offers insights into the comparative effectiveness of different antiemetic agents in diverse clinical settings, such as Nausea and Vomiting caused by Chemotherapy (CINV) and Nausea and Vomiting associated with Pregnancy (NVP). In conclusion, this review paper provides an extensive and current analysis of antiemetic therapies, offering clinicians and researchers valuable insights into the current state of antiemetic pharmacology.

Keywords: Nausea, Vomiting, Antiemetics, Herbal drugs.

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INTRODUCTION

Nausea and Vomiting are among the major health burdens affecting nearly 90-95% of the worldwide population.[1,2] Nausea causes pain in the stomach which causes the urge to vomit. Multiple factors result in vomiting including drug overdose, due to traveling, and overeating.[3] Nausea and Vomiting are common symptoms found during 3rd to 8th week of pregnancy. During nausea and vomiting, the body feels weak due to weight loss, dehydration, and electrolyte imbalance.[4] In general, but not always, nausea occurs before vomiting; that is, nausea can occur without vomiting. Emesis is a complex process that requires central neurologic coordination while nausea does not require activation of vomiting reflux. They are caused due to various reasons such as traveling, food poisoning, overdose, and unpleasant odor.[5,6] Various stimuli responsible for emesis are such as Cancer chemotherapy, Cardiac glycosides, Uremia, Ketoacidosis, Hypoxia, Motion sickness, Meniere's disease, Radiotherapy, Gastroenteritis, Smell, Thought, and Anticipatory emesis.[7] Antiemetics plays a major role in cancer treatment for chemo- and radiotherapy patients. They also have some side effects and reactions similar to anticancer drugs. Ideal Antiemetic are those that have complete antiemetic control, fewer side effects, are easy to apply, and are cost-effective. Constipation, diarrhea, and headache are rare symptoms of antiemetics and these are dose-dependent symptoms.[8,9]

Commercially used antiemetics drugs which are commonly employed, have several side effects such as headaches, hypertension, and several other problems. The movement towards non-chemical and non-industrial therapies has risen because of the medication's limited effectiveness and potentially harmful side effects.

PATHOPHYSIOLOGY OF EMESIS

When vomiting reflux starts due to activation of the vomiting centre, emesis occurs. There are three processes involved in vomiting reflux (Figure 1).[27,28]

The pre-ejection phase, is characterized by both stomach relaxation and nausea with retroperistalsis.

The vomiting phase, is characterized by difficult breathing and gastrointestinal muscle action before vomiting.

The Ejection Phase

This is characterized by a sharp contraction of the abdominal muscles after the upper oesophagal sphincter relaxes, allowing the contents of the stomach to pass out.

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Classifications, Mechanism of Action, Medical Interactions of Antiemetic Drugs

Antagonists for 5-HT3 Receptors

By inhibiting serotonin from attaching to the 5-HT3 receptors, 5-HT3 receptor blockers such as ondansetron (Zofran) and palonosetron (Aloxi) can stop nausea and vomiting. Danasetron was the first-generation 5-HT3 receptor blocker used to treat and prevent acute nausea and vomiting related to cancer therapy as well as Postoperative Nausea and Vomiting (PONV). Chemotherapy-Induced Nausea and Vomiting (CINV) and Postoperative Nausea and Vomiting (PONV) are currently patients having laparoscopic surgery are treated and prevented using palonosetron. Comparing it to other 5-HT3 receptor antagonists, it is safer and more effective.[29,30]

D2 Receptor Antagonists

D2 receptors in the CTZ are blocked by medications such as olanzapine, butyrophenones, and phenothiazines. Phenothiazine, including Prochlorperazine (Compro) is a drug with antipsychotic properties that is frequently employed to treat motion sickness, migraines, postoperative nausea and vomiting, chemotherapy, radiation therapy, and severe morning sickness in pregnant women. Because they inhibit The CTZ's D2 dopaminergic receptors and butyrophenones, like droperidol (Inapsine), which is used to treat schizophrenia and other psychiatric illnesses, additionally act as potent antiemetic medications.[31,32]

Anti-H1 Receptor Drugs

First-generation antihistamines with antiemetic properties include H1 receptor blockers, such as promethazine and diphenhydramine. Their activity is due to their H1 receptor's antagonistic activity in the vestibular nuclei. Due to its potent sedative properties, promethazine is the first medicine of choice for treating motion sickness-related nausea and vomiting, elevated acute morning sickness, and intracranial hypertension in pregnant women. Dimenhydramine is frequently employed to treat motion sickness-related nausea and vomiting. It is suitable for use as an antiemetic in the early stages of pregnancy, but it needs to be prevented in several stages of pregnancy due to its activity on the uterus.[33]

Acetylcholine (M) Receptor Antagonists

A tropane alkaloid drug called scopolamine blocks the vestibular apparatus's Ach emetic receptors. It is applied topically to prevent motion sickness and has antispasmodic effects. Furthermore, it functions extraordinarily well in modest doses (1 mg/24 hr intravenously) for the prevention and treatment of opioid-related PONV. Scopolamine is generally ineffective in managing CINV.[34]

Synthetic Cannabinoids

Although the Cannabis sativa plant, commonly referred to as Marijuana, contains over 80 distinct varieties of cannabinoids, Δ9-tetrahydrocannabinol (Δ9 –THC), is the most widely recognized variant. Synthetic Δ9-THCs like Dronabinol (Marinol) and Nabilone (Cesamet) inhibit emesis by acting on cannabinoid receptors, AP, and NTS. FDA has authorized Cesamet and Marinol in nausea and vomiting treatment due to radiation therapy and chemotherapy in individuals not reacting to existing antiemetic drugs. Additionally, Martinol has been used to increase appetite for individuals with anorexia and Acquired Immune Deficiency Syndrome (AIDS).[35,36]

Table 1: Natural Sources of Antiemetic Agents.

Plant	Pharmacological Roles	References
Ginger	Ginger root powder capsules, one gram each day, decrease the frequency of nausea and vomiting in pregnancy.	10
Chamomile	Lessens the intensity and frequency of nausea in pregnancy.	11
Mint and pomegranate	There was a reduction in nausea, but there was no discernible change in the severity of the frequency of nausea and vomiting.	12
Cardamom	The intensity of nausea and vomiting was reduced by inhaling cardamom aromatherapy, however, it failed to lower the quantity of vomiting and nausea.	13
Scutellaria baicalensis Georgi	The herb's antioxidant properties may be either entirely or partially in the role of reducing the nausea and vomiting induced by cisplatin.	14
American Ginseng Berry	Certain ginsenoside varieties might act antagonistically against the 5-HT3A receptor, which is linked to nausea and vomiting.	15
Korean Red Ginseng	It prevents cisplatin-induced nausea and vomiting.	16
Ganoderma lucidum (Fr.) Karst	In the rat pica model, Ganoderma lucidum extract reduced cisplatin-induced nausea and vomiting. The extract also had a positive impact on animals' general health and appetite.	17

Table 2: Antiemetic Agents with mechanism of action and use

Drug	Potential Indication	Receptors	References
Ondansetron	Postoperative, Chemotherapy-induced.	Serotonin	18
Domperidone	Gastroparesis, Postoperative, Chemotherapy induced.	Dopamine	19
Cyclizine	Motion induced, Vestibular.	Histamine, Muscarinic	20
Metoclopramide	Gastroparesis, Postoperative, Chemotherapy induced.	Dopamine, Serotonin	21
Prochlorperazine	Migraine-associated, Vestibular, acute generalised causes.	Dopamine, Serotonin, histamine	22
Levomepromazine	Palliative.	Dopamine, muscarinic, histamine	23
Hyoscine hydrobromide	Motion induced, Vestibular.	Muscarinic	24
Aprepitant	Chemotherapy-induced.	Neurokinin	25
Xonvea	Pregnancy induced.	Histamine	26

Table 3: Regions, receptor types, and stimuli that are implicated in vomiting.

Chemoreceptor Trigger zone	Vestibular Apparatus	Gastrointestinal Tract	Cerebral Cortex
Receptor: D2, 5HT-3, H1, ACh, Opioid, SP/NK 1. Circular glycosides, opiates, uremia, and cancer treatment are examples of stimuli.	M and H1 as receptors. Triggers: Menier illness, labyrinthitis, and motion sickness.	5-HT3 receptor. Chemotherapy for cancer, radiation, and gastroenteritis are stimuli.	Receptor: - Stimuli: Expectant emesis, smell, sight, and thinking.

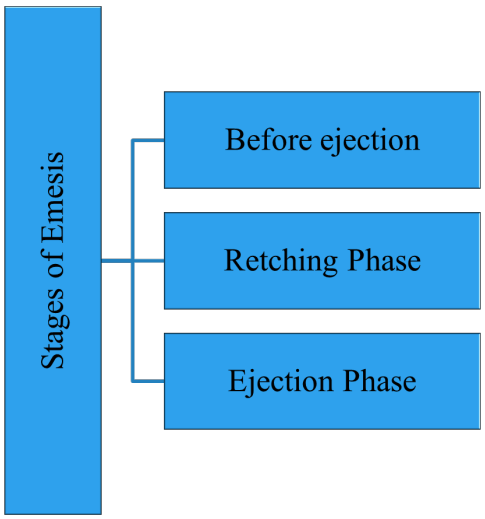

Figure 1: Stages of Emesis.

Corticosteroid Drugs

Corticosteroid drugs such as Maxidex, are employed in the management of intolerant hyperemesis gravidarum in pregnancy and to manage nausea and vomiting triggered by cancer chemotherapy treatments. In several studies, it was found that Dexamethasone is especially useful in treating Nausea and Vomiting in women undergoing Gynecological Laparoscopic Surgery. Very little (4–8 mg IV) is needed for this action, and it must be administered early in the anaesthetic cycle. According to Fero *et al.* Dexamethasone operates centrally through suppression of the nucleus tractus solitarius, according to investigations in animal models, even though its exact mode of action is undetermined.[27,37]

Table 4: Various Antiemetic Classes, Drugs, and Adverse Effects

Antiemetic class	Drugs	Adverse effects	References
5-HT3 Receptor Antagonists	Ondansetron and Palonosetron	Dry mouth, Constipation, Diarrhea, Abdominal pain, Renal insufficiency, Thrombocytopenia.	40
D2 Receptor Antagonists	Phenothiazines, Butyrophenones, Olanzapine	Sedation, tongue dryness, Disturbances in perception and vision, Hypotension, Depression, Urinary retention, and Malignant syndrome.	41,42
Anti-H1 Receptor Drugs	Promethazine, Dimenhydramine	Sedative, fatigue, parched mouth, blurry vision, impaired cognitive function, retention of urine, delusions, nightmares, Perplexity, sleeplessness, headache.	43
Acetylcholine (M) Receptor Antagonists	Scopolamine	Sedative, parched mouth, Bradycardia, retention of urine, Dyspnea, Seizures, Hypotension, Blurred vision, and Somnolence.	44
Synthetic Cannabinoids	Dronabinol, Nabilone	Dry mouth, Depression, Rapid and Irregular heartbeat, Postural hypotension, Euphoria, Hallucinations, and Visual disturbances.	45
Corticosteroid Drugs	Dexamethasone	Diabetes, Insomnia, Peptic ulcer, Anxiety, Hypertension, Osteoporosis, Muscle weakness, Sodium and water retention.	46
SP/NK1 Receptor Antagonists	Aprepitant	Dry mouth, Diarrhea, Dyspnea, Confusion, Light-headedness, Loss of appetite, Urinary retention, Tachycardia, Anorexia, and Weight loss.	47

Neurokinin-1 Receptor Antagonists

Emend (Aprepitant), is a brand-new antiemetic medication that is a member of the SP/NK1 receptor blocker pharmacological class. It penetrates through the Blood Brain Barrier (BBB) and inhibits Neurokinin receptors in the CNS. Emend, when combined with a 5-HT3 receptor blocker or dexamethasone, is helpful in the management of CINV. First-generation Antagonists for 5-HT3 Receptors and dexamethasone are particularly efficient in preventing acute emesis (first 24 hr after treatment).[38,39]

Chemotherapy-Induced Vomiting and Nausea

Chemotherapy-Induced Vomiting and Nausea (CINV) is an adverse effect of antineoplastic chemotherapy treatments that greatly impacts cancer patients' adherence to treatment and quality of life.[48] The primary mechanism of CINV comprises the modification of both central and peripheral neurotransmitters, including the substance SP, 5-Hydroxytryptamine (5-HT), and Dopamine (DA). By binding to the 5-HT3 receptor and NK-1 receptor, 5-HT3 and SP are strongly associated with the beginning of the CINV comprising two phases: the acute phase and the delayed phase.[48] The fundamental clinical prophylactic for the treatment of CINV is a 5-HT3R antagonist such as ondansetron with aprepitant, an NK-1R antagonist. While these antagonists appear to have a potential antiemetic effect, side symptoms such as fatigue, headaches, and constipation can frequently be reported.[49]

Five different kinds of Chemotherapy-Induced Vomiting and Nausea (CINV) have been identified based on when the signs and symptoms first emerge: breakthrough, refractory, acute, delayed, and anticipatory.[50] Acute CINV, which predominantly impacts the central and gastrointestinal tract and is most common minutes or hours after treatment, peaks at five or six hours.[51] Delayed CINV is primarily mediated by SP in central and typically manifests 24 hr after chemotherapy, peaking at 72 hr.[52] Because the preceding chemotherapy's poor control of sickness led to vomiting and nausea, anticipatory Chemotherapy-Induced Vomiting and Nausea (CINV) is defined as such. Refractory CINV occurs in the cycles of chemotherapy that follow breakthrough CINV. Breakthrough CINV is an illness that occurs despite appropriate prophylaxis following treatment. The most recent chemotherapy treatment triggers nausea and vomiting in patients with a breakthrough as well as refractory CINV.[53]

Antiemetic use in pregnancy

Pregnancy-related Nausea and Vomiting (NVP) is a common symptom. In North America and Europe, almost 60-80% of pregnancies are affected by Nausea and Vomiting which usually occur between three to eight weeks of pregnancy, symptoms peak between seven to twelve weeks.[54] Since NVP occurs during organogenesis, the period during which the fetus is most vulnerable to teratogens, exposure to some of the drugs used to treat NVP may increase the risk of unfavorable pregnancy-related consequences, such as congenital defects or spontaneous

abortion. The most frequently prescribed antiemetics are ondansetron (Zofran) and promethazine (Phenergan).[55] Promethazine is a neuroleptic drug that is a member of the phenothiazine family and has been used as an antiemetic during pregnancy. It produces strong antihistamines with antagonistic effects on Dopaminergic (D2) and serotonergic (5-HT2A, 5-HT2C) receptors. Ondansetron is a centrally-acting antagonist that binds to the 5-HT3 receptors 7 and was first prescribed to chemotherapy patients as an antiemetic.[56] Furthermore, it has been used as a psychotropic drug to treat psychotic symptoms in individuals with severe Parkinson's disease, and as an adjuvant to haloperidol in patients with schizophrenia. Antiemetics like ondansetron might affect the fetus during organogenesis due to its ability to cross the placental barrier.[57]

For the management of NVP, several pharmacotherapies are available. In Canada, the Antiemetic drug prescribed for use in Pregnancy is a combination of pyridoxine-hydrochloride which is an H1 blocker, and Doxylamine succinate. This combination is the recommended first-line treatment and provides a sustained release effect.[58]

CONCLUSION

In conclusion, this comprehensive review illuminates the current state of antiemetic therapies, focusing on their mechanisms of action, efficacy, and adverse effects with special emphasis on the pathophysiology of emesis, and the challenges that persist in effectively managing nausea and vomiting across various clinical scenarios

The review highlights the effectiveness of established antiemetic drug classes and their role in managing conditions such as CINV and NVP. This review paper provides a comprehensive and current overview of antiemetic therapies, offering clinicians and researchers valuable insights into the current state of antiemetic pharmacology. It serves as a foundation for future research directions.

FUTURE RESEARCH DIRECTIONS

Currently, antiemetics can control Vomiting in 90% of patients, but Nausea still causes difficulty during cancer treatment and is the adverse effect of many drugs like Antidepressants.

There is particular interest in clinical studies exploring therapeutics with potential anti-nausea characteristics because nausea isn't as well controlled as emesis. However, even if the focus is frequently on the development of novel treatments, will the use of existing medications in antiemetic therapy be the norm in the future?

More and more, medications that have historically served different purposes such as antipsychotics and neuropathic agents also have antiemetic characteristics.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CINV: Chemotherapy Induced Nausea and Vomiting; **NVP:** Nausea and Vomiting associated with Pregnancy; **PONV:** Postoperative nausea and vomiting; **CTZ:** Chemoreceptor Trigger Zone; **THC:** Tetrahydrocannabinol; **FDA:** Food and Drug Administration; **BBB:** Blood Brain Barrier; **CNS:** Central Nervous System; **AIDS:** Acquired Immune Deficiency Syndrome; **IV:** Intravenous; **DA:** Dopamine; **NK:** Neurokinin; **5-HT:** 5-Hydroxy tryptamine; **Ach:** Acetylcholine.

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