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Drugs Induced Nausea and Vomiting: an Overview

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I. Introduction

Every drug can produce untoward consequences and side effects, even when used according to standard or recommended methods for administration. Adverse drug reactions can involve every organ and system of the body and are frequently mistaken for signs of underlying disease. Similarly, gastrointestinal tract can be affected by many drugs or chemicals.

Among the drug-induced gastrointestinal adverse effects, nausea and vomiting are common side effects of drugs; usually occur early in the course of pharmacologic therapy [1]. Often, the symptoms will disappear with continued use. In some instances, concurrent administration of anti-emetics may be needed to prevent dehydration and electrolyte imbalances [2,3]. Nausea and vomiting are not always simple adverse effects; in some instances, the nausea and vomiting is a sign of a more serious situation. For example, nausea and vomiting associated with digoxin or theophylline may be a sign of drug toxicity [3].

Vomiting is forceful oral expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature [4] Nausea is the unpleasant sensation of the imminent need to vomit, usually referred to the throat or epigastrium; a sensation that may or may not ultimately lead to the act of vomiting [4].

The significant causes of nausea and vomiting include iatrogenic causes, toxicity, infectious causes, gastrointestinal disorders, and central nervous system or psychiatric conditions.Among iatrogenic causes, chemotherapeutic agents are the most well known. Infectious and toxic causes are usually self-limiting and include viral gastroenteritis as well as bacteria and their toxins. Gastrointestinal disorders are often caused by an inflammatory process, such as appendicitis, cholecystitis, or pancreatitis, or may be caused by obstruction or motility problems. Central nervous system or psychiatric causes include increases in intracranial pressure, migraine, and emotional or physical stressors.

In general, medications are associated with an increasing incidence of drug-induced (iatrogenic) complications. According to one study, the gastrointestinal tract was associated with 20% to 40% of the drug-induced adverse effects [5] Many gastrointestinal side effects, such as nausea, vomiting, dyspepsia, abdominal cramps, diarrhea, or constipation, occur without any identifiable lesion or cause [6, 7]. Usually, these effects are transient and resolve shortly after the drug is discontinued. However, there are some widely prescribed drugs that cause serious and lasting adverse effects (mucosal ulceration, stricture, or increased susceptibility to pseudomembranous colitis) [7]. In some situations, the adverse effects are worse than the illness for which the drug was prescribed [7]. Over time, these adverse effects may impact a patient's nutritional status. The elderly are most susceptible to these effects.

Pathophysiology of nausea and vomiting

The sensation of nausea and act of vomiting are protective reflexes that rid the intestine and stomach of toxic substances. The experience of nausea is subjective, and nausea may be considered a prodromal phase to the act of vomiting [8].

Vomiting consists of a pre-ejection phase, retching, and ejection and is accompanied by shivering and salivation. Vomiting is triggered when afferent impulses from the cerebral cortex, chemoreceptor trigger zone (CTZ), pharynx, and vagal afferent fibers of the gastrointestinal (GI) tract travel to the vomiting center, located in the medulla.

Efferent impulses then travel from the vomiting center to the abdominal muscles, salivation center, cranial nerves, and respiratory center, causing vomiting. It is thought that chemotherapeutic agents cause vomiting by activating neurotransmitter receptors located in the CTZ, GI tract, and vomiting center. Serotonin (5-hydroxytryptamine [5-HT3]) and dopamine receptors are the primary neuroreceptors involved in the emetic response, particularly the 5-HT3 receptor.1 [8]. Both the vomiting center (VC) and the chemoreceptor trigger zone (CTZ) in the brain play an important role in inducing vomiting[8].The vomiting center receives neural impulses from different sites in the body such as the CTZ and GI tract. Drugs like chemotherapy administration appear to induce vomiting by directly damaging cells in the GI tract[8]. This is followed by the release of significant amounts of serotonin, a neurotransmitter, from enterochromaffin cells in the GI tract. When the serotonin binds to serotonin ($5\text{-}HT_3$) receptors in the wall of the GI tract, neural impulses are sent to the VC [9].

Medication-induced Nausea

When a patient who is not receiving chemotherapy presents with nausea, it is often difficult to determine the cause. In addition to medications, other causes (eg, migraine, emotional response, pregnancy, and gastrointestinal disorders) must be considered. Nausea caused by medications is typically acute rather than chronic and usually is seen shortly after starting a medication[9]. Medications can cause nausea via several mechanisms. Dopaminergic agonists, nicotine, digoxin, and opiates have been shown to act on the area postrema. Some agents (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] and erythromycin) activate peripheral afferent pathways, stimulating the brainstem nuclei [9]. Nausea also can be induced through stimulation and activation of the chemoreceptor trigger zone (CTZ). Stimuli cause the CTZ to recognize a substance as foreign and activate the vomiting center.

The most common substances to cause stimulation are chemotherapy drugs, opiates, and ipecac syrup. Many other drugs (eg, antibiotics, NSAIDs, selective serotonin reuptake inhibitors [SSRIs], and digoxin) also can cause the activation of the CTZ[9]. The mechanism associated with a number of medication classes known to cause nausea remains unclear. Some of these include anti-arrhythmics, antihypertensives, diuretics, oral hypoglycemics, and oral contraceptives [9]. See in table 1.

Table 1.Vomiting as Adverse Effect at Therapeutic Dosage

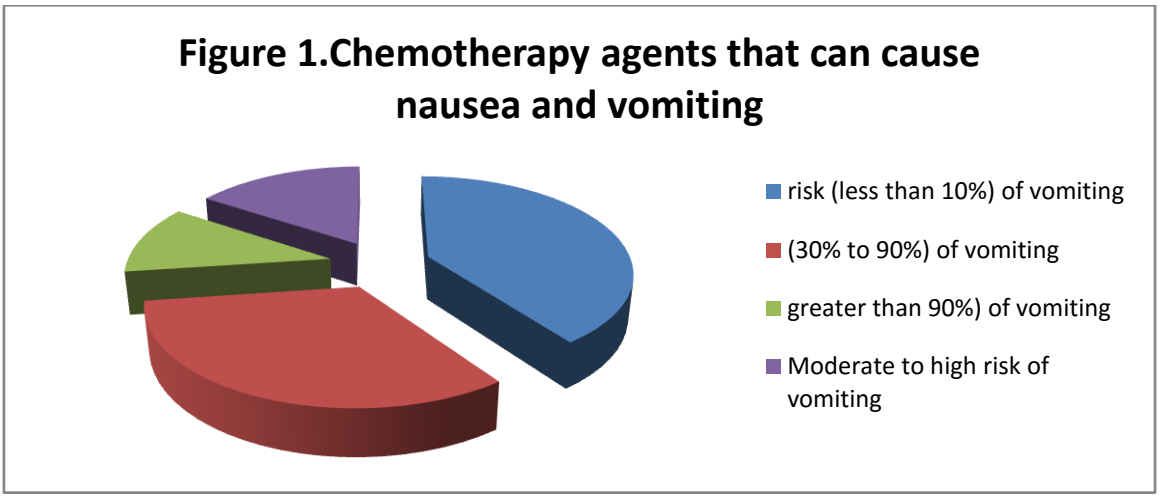
Classification	**Drugs**
A. Analgesics	1. Aspirin (local GI irritation) 2. NSAIDs (local GI irritation) 3. Morphine and other Opioids
B. Cardiovascular medications	1. Digoxin 2. Antiarrhythmics 3. Antihypertensives a. Beta Blockers b. Calcium Channel Blockers c. Diuretics
C. Dopamine antagonist	1. L-Dopa 2. Bromocriptine
D. Antibiotics	1. Erythromycin 2. Tetracycline 3. Sulfonamides 4. Antituberculous medications 5. Acyclovir
E. Chemotherapeutic medications	1. Severe: Cisplatinum, Dacarbazine, Nitrogen mustard 2. Moderate: Etoposide, Methotrexate, Cytarabine 3. Mild: Fluorouracil, Vinblastine, Tamoxifen
F. Miscellaneous medications and therapies	1. Estrogens (especially high dose) 2. Oral Contraceptives 3. Sulfasalazine 4. Azathioprine 5. Radiation Therapy 6. Oral Hypoglycemic medications
G. Neurologic medications	1. Antiparkinsonian medications 2. Anticonvulsants

Many factors contribute to the severity of chemotherapy-induced vomiting [10]. Each drug has a specific emetogenic potential (eg, minimal, moderate, high)[10]. For example, cisplatin has a high emetogenic potential and vinblastine has minimal emetogenic potential. Depending on the chemotherapeutic drug, the emetogenic potential can increase with escalating dose[11].The emetogenic potential of cyclophosphamide can be moderate or high depending upon the dose. When chemotherapeutic drugs such as cyclophosphamide and doxorubicin are co- administered, the emetogenic potential is greater than that of either drug alone[11,12]. Chemotherapy-induced vomiting is more common in females and younger patients [12]. See in table 2.

Table 2.Chemotherapy agents that can cause nausea and vomiting

Level	**Frequency of N/V**	**Drugs/agents**
Minimal	risk (less than 10%) of vomiting:	• Alemtuzumab • Asparaginase • Bevacizumab • Bleomycin • Cetuximab • Cladribine • Cytarabine (very low doses) • Decitabine • Denileukindiftitox

		• Dexrazoxane • Fludarabine • Gemtuzumab • Interferon alfa (low dose) • Ipilimumab • Methotrexate • Nelarabine • Ofatumumab • Panitumumab • Pegaspargase • Peginterferon • Pertuzumab • Rituximab • Temsirolimus • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vincristine, • Vinorelbine
Moderate risk	(30% to 90%) of vomiting:	• Aldesleukin (higher doses) • Amifostine (higher doses) • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan (high doses) • Carboplatin • Carmustine (lower doses) • Clofarabine • Cyclophosphamide (lower doses) • Cytarabine (high doses) • Dactinomycin • Daunorubicin • Doxorubicin • Epirubicin • Idarubicin • Ifosfamide • Interferon alfa (higher doses) • Irinotecan • Melphalan (higher doses) • Methotrexate (high doses) • Oxaliplatin • Temozolomide
High risk	(greater than 90%) of vomiting:	AC combination which is doxorubicin given with cyclophosphamide • Carmustine (high-dose) • Cisplatin (moderate to high doses) • Cyclophosphamide (high-dose) • Dacarbazine • Doxorubicin (high doses) • Epirubicin • Ifosfamide (high doses) • Streptozocin
Moderate to high risk of vomiting:		Altretamine • Busulfan (high doses) • Crizotinib • Cyclophosphamide (high doses) • Estramustine • Etoposide • Lomustine (single day) • Mitotane • Procarbazine • Temozolomide (high doses) • Vismodegib



Management of Nausea and vomiting

General guideline

Firstly, review the 3-step process for evaluating nausea and vomiting recommended by the American Gastroenterological Association. The 3 recommended steps are as follows:

- Recognize and correct symptoms, such as dehydration or electrolyte abnormalities.
- Try to identify the underlying cause and provide specific therapy.

Use empiric therapy if no cause can be identified.The non-pharmacologic interventions are summarized in the Figure.

Therapies for known etiologies of nausea and vomiting include the following:

- ondansetron/dexamethasone for acute chemotherapy-induced nausea and vomiting and metoclopramide/dexamethasone for delayed chemotherapy-induced nausea and vomiting;
- tricyclic antidepressants for adults with cyclic vomiting syndrome;
- supportive treatment and possible gastric pacing for gastroparesis; and droperidol/dexamethasone or ondansetron for postoperative nausea and vomiting.

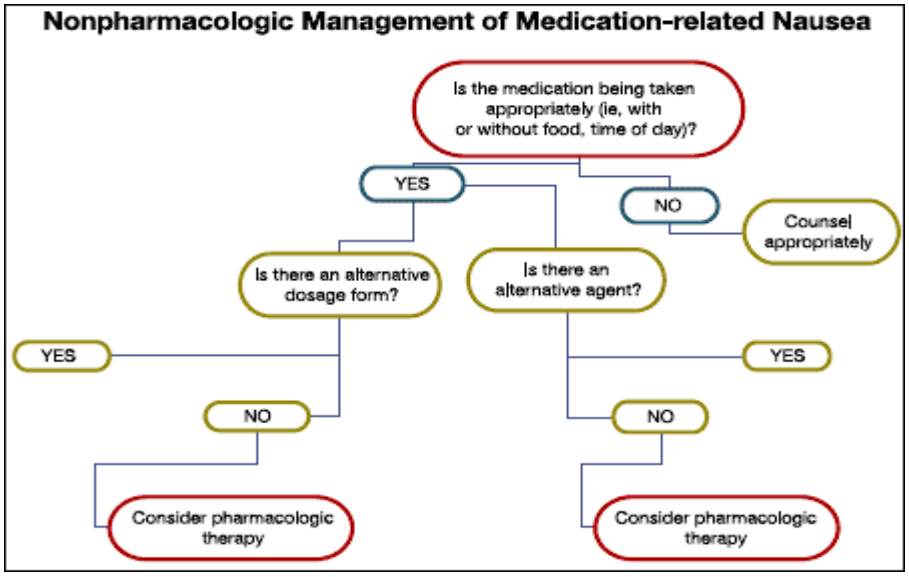


Figure 2 General guideline for management of nausea and vomiting[13]

Pharmacologic Agents

When non- pharmacologic recommendations do not work, patients can turn to pharmacologic agents to prevent and/or treat nausea caused by medication use. Dopamine antagonists, such as promethazine and prochlorperazine, are especially effective for opioid-induced nausea, but can be beneficial for nausea caused by other medications as well. They are a good choice for short-term offenders, such as antibiotics and NSAIDS.

Long-term use may be limited by extrapyrimidal side effects. The use of serotonin receptor antagonists (eg, ondansetron and granisetron) may be beneficial for long-term prevention of nausea.

II. Prevention

Preventing nausea caused by medication often can be achieved with a few simple reminders. Unless an agent is meant to be taken on an empty stomach, patients can be advised to take their medications with food. This is an easy way to prevent nausea, especially with notorious offenders, such as antibiotics, NSAIDS, and multivitamins. The time of day a medication is taken may be an important consideration when preventing nausea caused by dizziness. Taking medications such as Selective serotonin re-uptake inhibitors (SSRIs) at bedtime prevents the vomiting center from being activated by dizziness because the body is asleep [16]

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III. Conclusion

Many drugs can affect gastrointestinal injury including nausea and vomiting and that effect patient`s nutritional status. Elderly patients need extra attending because of their medical condition and concomitant drug therapy. Generally, most of the drugs reactions occur within 1 to 2 weeks following initiation of therapy, reaction seen after 2 weeks are less likely to be due to medication use. The majority of drug-induced gastrointestinal reactions are moderate in severity. Healthcare professionals can play an important role in reducing the incidence of drug-induced GI disorders by alerting the patient to the early warning signs and providing education to help patients prevent these effects.

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