abstract

*Nausea and emesis are distressing symptoms that can contribute to malnutrition, dehydration, and decreased quality of life in older patients. Dopaminergic, cholinergic, histaminergic, serotonergic, and neurokinin receptor mechanisms play roles in the causation of nausea. Pharmacologic therapy targeted at these and other mechanisms is necessary to effectively treat the symptoms of nausea and vomiting. Multidrug regimens that target multiple mechanisms are often needed to control persistent symptoms. However, caution is advised when prescribing these medications in older patients, as many of the effective medications can cause sedation, confusion, or delirium. This article describes the mechanisms of nausea and vomiting and reviews effective treatment regimens.*

***Key words:*** *nausea, vomiting, emesis, antiemetics, older adults*

# Nausea and Vomiting: An Overview of Mechanisms and Treatment in Older Patients

***Esmé Finlay, MD,*** *Fellow, Division of Hematology/Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA.*

***Joseph B. Straton, MD, MSCE,*** *Chief Medical Director, Wissahickon Hospice; Assistant Professor, Family Medicine and Community Health; Assistant Professor, Anesthesiology and Critical Care, Hospital of the University of Pennsylvania, Philadelphia, PA, USA.*

***Jonathan R. Gavrin, MD,*** *Director, Symptom Management and Palliative Care; Clinical Associate Professor, Anesthesiology and Critical Care; Clinical Associate Professor, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA.*

## Introduction

Nausea and vomiting are frequent sources of distress for patients with life-threatening illness. Often these symptoms are so severe that they prevent socialization, including the ability to eat, thus depriving people of important human interactions during medical therapy or near the end of life. Symptoms can be iatrogenic or secondary to the disease process, be that process visceral, in the central nervous system, the vestibular apparatus, or simply due to extensive, generalized wasting. Nausea is common during cancer therapy and during the course of AIDS but also can emerge secondary to palliative medications, particularly opioid analgesics, thereby limiting the acceptance of palliative therapy and the titration of drugs to achieve acceptable relief of aversive symptoms. Vomiting may promote dehydration, electrolyte imbalance, aspiration pneumonia, and malnutrition.

## Mechanisms

Nausea and vomiting, although distinct phenomena, are related closely. Nausea is a subjective feeling mediated in the cerebral cortex. Vomiting, or emesis, is a physiological event, integrated in the medulla, characterized by a coordinated series of muscular relaxations and contractions that result in the expulsion of gastric and upper small bowel contents through the esophagus and out through the mouth. Nausea often results in vomiting; vomiting, although not necessarily associated with nausea, typically accompanies it. Successful treatments target the cortical, brain stem, and peripheral triggers.

The mechanisms and mediators of nausea and vomiting are complex and remain incompletely defined. However, research over the last two decades has shed substantial light on physiologic mechanisms of nausea and emesis. An understanding of these mechanisms can guide clinicians in tailoring therapy for individual patients. The "vomiting centre" lies in the dorsal motor nucleus (DMN) complex consisting of the dorsal motor nucleus of the vagus, the nucleus tractus solitarius (NTS), and the area postrema in the brainstem. The chemoreceptor trigger zone (CTZ) is in the highly vascular area postrema (AP), located at the caudal end of the fourth ventricle on the dorsal surface of the medulla. The AP is devoid of an effective blood-brain barrier, and is thereby bathed in both blood and cerebrospinal fluid (CSF).[1–3] It is rich with opioid, cannabinoid, dopaminergic, cholinergic, histaminergic, serotonergic, and neurokinin (NK-1/substance P) receptors.[4–8] Inputs to these regions are varied and come from gustatory, gastrointestinal, neuroendocrine,

vestibular, and cerebrocortical sources. Activation of these receptors stimulates the vomiting centre, which in turn produces nausea and can initiate vomiting (Figure 1). A vestibular component is particularly prevalent with opioid-induced nausea and can severely limit ambulation. Impaired gastrointestinal motility, associated with aging, diabetes mellitus, chemotherapy-induced autonomic neuropathies, opioid therapy, inactivity, and primary gastrointestinal pathology, is an important cause of nausea or emesis. Endocrine and electrolyte imbalances can stimulate the vomiting centre. Sights and smells, presumably after cortical processing, can produce direct or anticipatory nausea, often followed by vomiting.

## Treatment

In general, it is clinically difficult and unnecessary to distinguish treatment of nausea from treatment of vomiting. Based upon an understanding of the nausea-related receptors, clinicians can apply a targeted approach to the use of antinausea medications. Persistent nausea responds best to around-the-clock, scheduled dosing of medications (Figure 2). By targeting several of the known receptors, a multidrug regimen can be employed, titrating doses according to efficacy and side effects to effectively manage symptoms.

## Dopamine-Blocking Agents

There are three major groups of antidopaminergic agents: metoclopramide, the butyrophenones, and most phenothiazines, the notable exception being the antihistamine promethazine (see below). The effects of antidopaminergic drugs are idiosyncratic and difficult to predict. If an agent does not work or causes undesirable side effects, a trial of another drug within the dopamine-blocking family is appropriate. The two clinically available and useful butyrophenones are haloperidol and droperidol, the former available orally and parenterally, the latter only by injection. Droperidol is the more effective antiemetic but can cause dysphoria in many patients. Droperidol also has been associated with fatal cardiac arrhythmias at high doses (greater than 25 mg) due to

**Table 1:** Biochemistry of Antiemetics

| Agent | Side Effects/Cautionary Notes |
|---|---|
| *Dopamine Blockers* | |
| metoclopramide (Reglan®) | EPS |
| CNS effect | sedation |
| gastric effect | dysphoria |
| butyrophenones | confusion |
| droperidol | |
| haloperidol | |
| phenothiazines | |
| prochlorperazine (Compazine®) | |
| *Histamine (H1) Blockers* | |
| diphenhydramine (Benadryl®) | sedation |
| hydroxyzine (Atarax®, Vistaril®) | confusion |
| dimenhydrinate (Dramamine®) | dry mouth/dry skin |
| Promethazine (Phenergan®) | urinary retention |
| | blurred vision |
| *Acetylcholine Blockers* | |
| scopolamine | dry mouth |
| transdermal | confusion |
| intravenous | sedation |
| belladonna | |
| dimenhydrinate (Dramamine®) | |
| *Serotonin Receptor Blockers* | |
| ondansetron (Zofran®) | headache |
| palonosetron (Aloxi®) | |
| granisetron (Kytril®) | |
| dolasetron (Anzemet®) | |
| *Substance P Antagonists* | |
| aprepitant (Emend®) | fatigue, diarrhea, constipation |
| *Nonspecific Antiemetics* | |
| Benzodiazepines | sedation |
| | confusion |
| | amnesia |
| | suppression of REM sleep |
| *Nonpharmacologic antiemesis* | |
| Relaxation | Rarely work alone |
| Imagery | Excellent adjunctive therapy |
| Reframing | |
| Biofeedback | |
| Acupuncture | |
| *Cannabinoids* (Marinol®) | sedation, dysphoria |
| *Corticosteroids* | Multiple, including hypertension, psychosis/delirium, medication-induced hyperglycemia |

prolongation of the QT interval, which can lead to *torsades de pointes*. At the low doses (0.625 mg–2.5 mg) necessary for treatment of nausea or emesis, dysphoria is uncommon and arrhythmias are exceedingly rare.[9] A baseline ECG is recommended for patients who are to receive the drug; predisposition to cardiac arrhythmias, a common issue among older adults, or prolonged QT at baseline are relative contraindications to the use of droperidol. Haloperidol is not associated with cardiac arrhythmias but can be quite sedating, especially among older adults. It is worth noting that butyrophenones are not respiratory depressants. Phenothiazines can have a pronounced sedating effect and are associated with acute confusional states; they should be used with caution for older adults. Metoclopramide enhances gastric emptying and can be effective in patients with decreased motility but should be avoided in patients with bowel obstruction. All dopamine-blocking agents can cause extrapyramidal symptoms (EPS). These are treated effectively with either diphenhydramine or benztropine.

## Antihistamines

Activation of histamine-1 (H1) receptors in the brain will cause nausea and emesis. Histamine-2 (H2) receptors appear to have no direct relationship to nausea and vomiting. The H1 receptor-blocking agents, diphenhydramine, hydroxyzine, meclizine, dimenhydrinate, and promethazine effectively inhibit the emetic response. These agents are sedating but they, like the butyrophenones, are not respiratory depressants. The H1 blockers have varying degrees of anticholinergic properties, most pronounced with dimenhydrinate, which contribute to their side effect profile, including dry mouth, confusion, and urinary retention, the last being a particular concern in men with benign prostatic hypertrophy (BPH). With older adults, caution is needed and dose reductions should be considered when initiating antihistamines or titrating doses. On a positive note, these drugs also counteract EPS; thus, combining H1 blockers and antidopaminergic agents can be effective in many patients.

## Anticholinergics

The most useful anticholinergic for nausea is scopolamine, a belladonna alkaloid available in a convenient transdermal delivery system. Scopolamine is indicated for motion sickness and postoperative nausea, but is also effective for the vestibular nausea ("spinning sensation") often associated with opioid use. The transdermal patch takes 4 hours to achieve detectable plasma levels with peak effects at about 24 hours.[10] For patients over age 65 years, the recommended starting dose is one-half patch. To prevent postoperative nausea and vomiting (PONV), it is recommended to apply the patch the night before surgery. Alternatively, an intravenous loading dose of 0.1 mg scopolamine normally achieves rapid relief. The most common side effect of anticholinergics is dry mouth, but they are known to cause confusion and, rarely, urinary retention in older adults.

## Serotonin-Blocking Agents

The serotonin (5-HT3) receptor-blocking agents ondansetron, granisetron, dolasetron , and palonosetron (currently available in the U.S. but not in Canada) are commonly used for chemotherapy induced nausea and vomiting (CINV), especially in combination with other antiemetics.[13] They also are effective for PONV and may be used for treatment of chronic nausea although they have not been validated in this setting. Headache is a common side effect and caution is advised in patients with migraines. 5-HT3 blockers vary in degree of drug-drug interaction, dosing schedule, and cardiovascular risk (prolongation of QTc); these factors should be considered when choosing an agent for older adults.[12] Ondansetron can cause or exacerbate constipation, a consideration in older adults. Granisetron may be used for older adults with increased cardiovascular risk, given low incidence of cardiovascular side effects.[12–14] Palonosetron is unique in its high receptor binding affinity and long half-life.[11] Both granisetron (oral and intravenous) and palonosetron (intravenous only) offer once-daily dosing, which is convenient for older individuals assigned to multiple medications.[11–14]

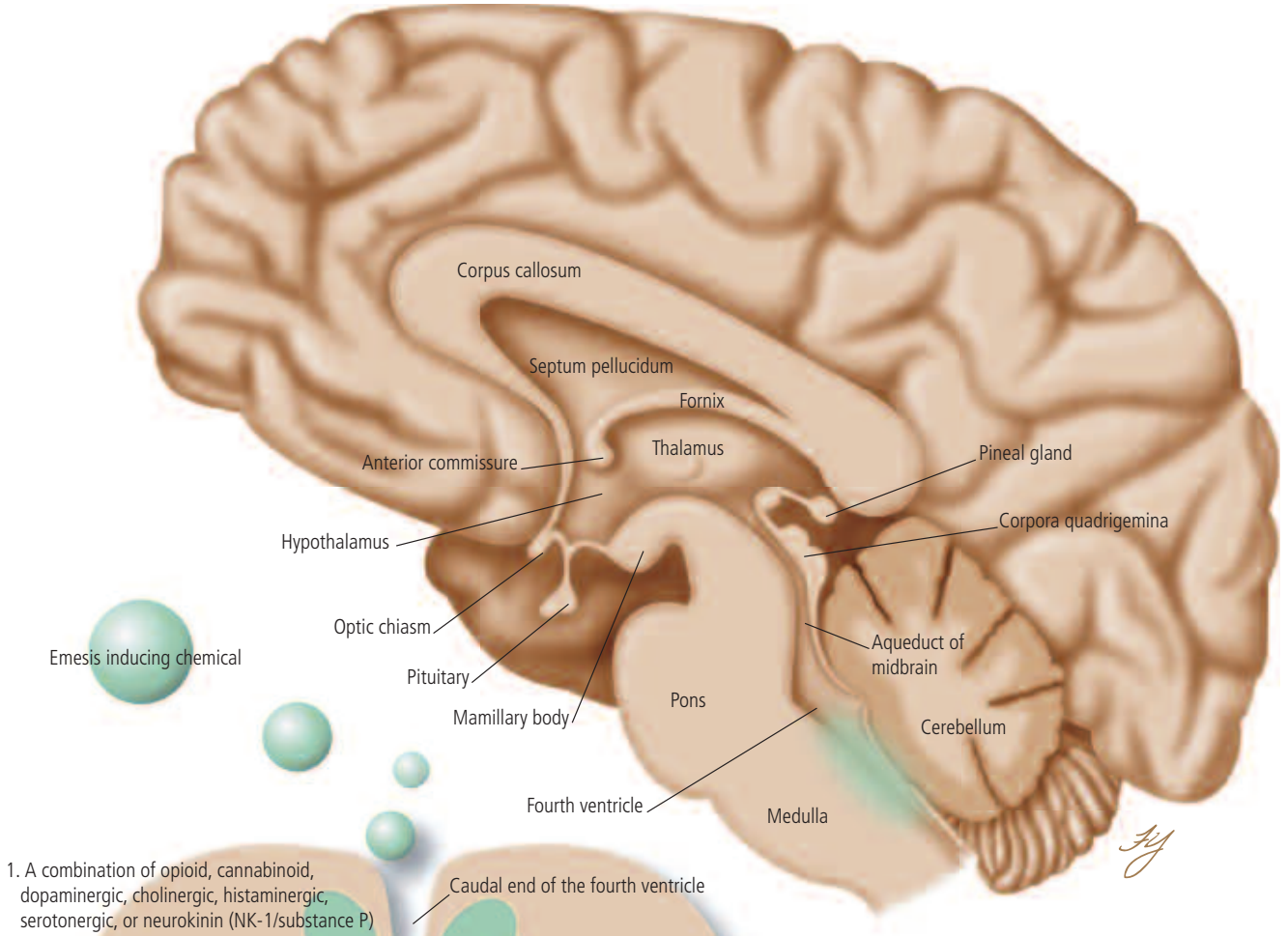
## Substance P/neurokinin 1 (NK-1) Receptor Antagonists

Aprepitant is the sole drug in this class currently available commercially in the United States (but not in Canada), and only as an oral preparation. Clinical trials of this medication have demonstrated efficacy for preventing both acute and delayed CINV in combination with 5-HT3 blockers and dexamethasone.[5,8,11,16] Additional studies are needed to better define drug-drug interactions due to its CYP3A4 metabolism and side effects in older adults.[13] Fatigue, diarrhea, and constipation are commonly reported side effects. In the future, it is likely that data will support use of 5-HT3 receptor antagonists and aprepitant for chronic nausea from other causes, especially in the palliative care setting. 5-HT3 and NK-1 receptor antagonists have not been associated with significant cognitive disorders[13,15] making them an appealing therapeutic choice in older at-risk populations and in the palliative setting in which patients and families desire to preserve alertness for quality of life.

## Nonspecific Antiemetics

Nonspecific antiemetic therapies include benzodiazepines, cannabinoids, and corticosteroids. Benzodiazepines bind to the inhibitory gamma aminobutyric acid (GABA) receptors.[17] Investigators have shown their utility for anticipatory nausea in chemotherapy and nausea associated with anxiety, presumably by targeting the cortical mechanisms that result from stimulation of the limbic system, and especially when used in combination with other antiemetics.[18] Benzodiazepines are potent amnestic drugs, can cause confusion or disinhibition, and should not be considered as first-line antiemetics for older adults. Cannabinoids also influence the limbic system and sometimes can relieve nausea refractory to other agents, but they frequently cause cognitive and sedating side effects.[19] The use of corticosteroids,

## Figure 1: The Mechanisms of Nausea and Vomiting

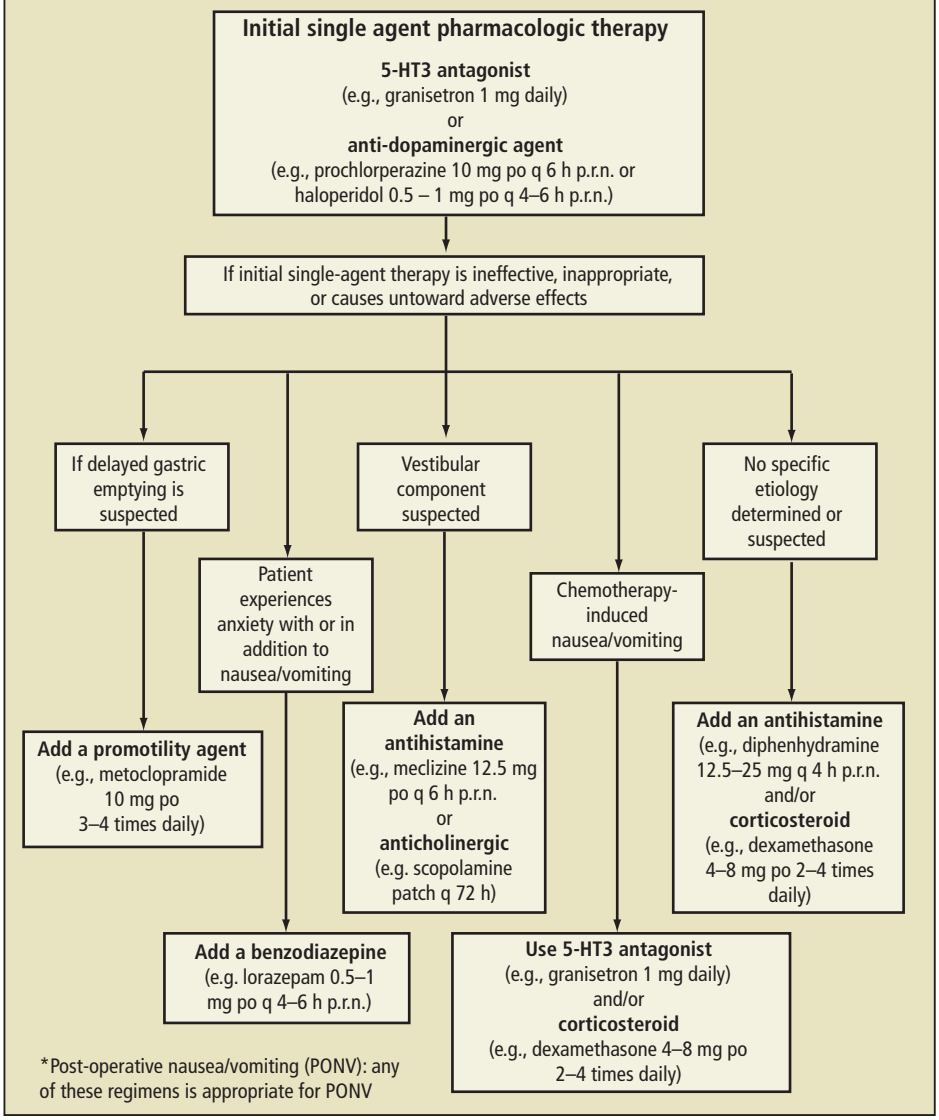



Nausea and vomiting can be considered separately. However, in most situations they are linked. Nausea is induced by activation of the central nervous system or organs of the gastrointestinal tract. Vomiting, or emesis, is a response to nausea. Just as nausea warns an individual not to continue a particular action or expose him- or herself to harmful agents, emesis is a response to agents the body considers toxic.

The vomiting centre acts as the control centre and will determine whether or not emesis will occur. It lies in the dorsal motor nucleus complex, which also consists the dorsal motor nucleus of the vagus, the nucleus tractus solitarius, and the area postrema in the brainstem. The vomiting centre receives messages from numerous sources. For example, the chemoreceptor trigger zone (CTZ) in the highly vascular area postrema (AP), located at the caudal end of the fourth ventricle on the dorsal surface of the medulla. Since the AP lacks an effective blood-brain barrier, the area is exposed to both blood and cerebrospinal fluid. Depending on which receptors are activated the CTZ will determine whether or not a signal will be sent to the vomiting centre.

Once the vomiting centre receives enough input from its surrounding sources, it will initiate nausea and potentially emesis.

**Figure 2:** Stepwise Treatment of Nausea and Vomiting




particularly dexamethasone, is effective for both PONV and CINV.[20–22] Except in those instances where nausea is mediated centrally due to increased intracranial pressure (ICP), in which case steroids decrease ICP, the mechanism by which corticosteroids work is undefined. As noted previously, corticosteroids are often used in combination with other antiemetics such as 5-HT3 blockers.[22,23] They should be used cautiously in older patients with comorbidities such as hypertension and diabetes,[11,24] as well as in patients with a history of delirium.[25]

## Nonpharmacological Techniques

Nonpharmacological therapies for nausea and vomiting include hypnosis, cognitive behavioural training, progressive muscle relaxation, distraction, and reframing. To date they have produced mixed results.[26] Behavioural interventions are recommended as an adjunct to antiemetics for patients with mild to moderate nausea or vomiting but require highly motivated patients. When patients are ill, are being treated with sedatives or opioids that can impair concentration, have baseline cognitive impairment, or are approaching death, behavioural training is rarely appropriate.[26] The PONV literature suggests that acupuncture or acupressure at the P6 point on the wrist may provide relief to surgical patients, but further research is necessary to define utility in a broader palliative setting.[27] Palliative surgical intervention, including gastrostomy, bypass, or laparotomy, may be useful in patients with malignant bowel obstruction and intractable nausea and vomiting.[28] In a small study of patients with malignant intestinal obstruction, palliative venting gastrostomy was shown to significantly reduce nausea associated with vomiting, and enable small amounts of oral intake.[29]

## Nausea and Vomiting among Older Adults

Older adults may have age-related physiologic etiologies for nausea and vomiting such as delayed gastric emptying as well as disease-specific etiologies for nausea and vomiting. Often, physicians must balance multiple comorbidities and the challenge of polypharmacy[12] with the goal of symptomatic relief. Medications that have beneficial antiemetic properties, such as benzodiazepines and anticholinergics are associated with increased risk of delirium.[25,30,31] Hepatic dysfunction and decreased cytochrome P450 metabolism of medications, common in older adults, are concerns; problems may be compounded by polypharmacy in this population. Medications with limited drug-drug interactions and simple dosing regimens, such as granisetron, are attractive therapeutic options but have not specifically been validated in non-CINV clinical settings.[12] Future research should address utility of newer antiemetics in geriatric and palliative settings. Longer-acting medications and medications with alternative dosing routes, such as transdermal scopolamine, prochlorperazine suppositories, or subcutaneous metoclopramide or haloperidol, may provide patients, families, and physicians with adequate options to create effective antiemetic regimens.

## Conclusions

There is no fixed recipe for effective nausea and emesis management. Scientific elucidation of the key mechanisms involved in nausea and vomiting (summarized in Table 1) permits targeted therapy. If single drug therapy is ineffective,

## Key Points

Successful treatments for nausea and vomiting target the cortical, brain stem, and peripheral triggers.

Older adults may have age-related physiologic etiologies for nausea and vomiting such as delayed gastric emptying as well as disease-specific etiologies for nausea and vomiting.

Persistent nausea responds best to around-the-clock, scheduled dosing of medications; a multidrug regimen can be employed, titrating doses according to efficacy and side effects to effectively manage symptoms.

It is strongly recommended to use multiple drug regimens early, since the emesis-nausea cycle can be difficult to break after onset.

Behavioural therapies for nausea and vomiting have produced mixed results, and are appropriate only for highly motivated patients; they are not advised for those with compromised concentration, cognition, or who are approaching death.

it is strongly recommended to use multiple drug regimens early, since the emesis-nausea cycle can be difficult to break after onset. Titration of medications will depend on a balance between efficacy and side effects. Optimal symptom management remains an art, the critical element being the response of the patient. Clinicians must work with patients to achieve the best balance between relief and unacceptable side effects, basing medication modifications on receptor pharmacology and subjective patient report. A sensible algorithm for initial therapy has been provided (Figure 2). ga

No competing financial interests declared.

## References


1. Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment, and prevention. Anesthesiology 1992;77:162–84.
2. Andrews, PLR. Physiology of nausea and vomiting. Br J Anaesth 1992;69(Suppl.1):2S–19S
3. Borison HL. Area postrema: chemoreceptor circumventricular organ of the medulla oblongata. Prog Neurobiol 1989;32:351–90
4. Stefanini E, Clement-Cormier Y. Detection of receptors in the area postrema. Eur J Pharmacol 1981;74:257–60
5. Peroutka SJ, Snyder SH. Antiemetics: neurotransmitter receptor binding predicts therapeutic action. Lancet 1982;1:658–9.
6. Palacios JM, Wamsley JK, Kuhar, MJ. The distribution of histamine H-1 receptors in the rat brain: an autoradiographic study. Neuroscience 1981;6:15–17.
7. Wamsley, JK, Lewis MS, Young WS III et al. Autoradiographic localization of muscarinic cholinergic receptors in rat brainstem. J Neurosci 1981;1:176–91.
8. Prommer E. Aprepitant (Emend): the role of substance P in nausea and vomiting. J Pain Palliat Care Pharmacother 2005;19:31–9.
9. Lischke V, Behne M, Doelken P, et al. Droperidol causes a dose-dependent prolongation of the QT interval. Anesthesia & Analgesia 1994;79:983–6.
10. Transdermal scopolamine. www.transdermscop.com/site2/prescribe.html. Accessed: 18 December, 2006
11. Aapro MS, Macciocchi A, Gridelli C. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting in elderly patients. J Support Oncol 2005;3:369–74.
12. Gridelli C. Same old story? Do we need to modify our supportive care treatment of elderly cancer patients? Focus on antiemetics. Drugs Aging 2004;21:825–32.
13. Aapro M, Johnson J. Chemotherapy-induced emesis in elderly cancer patients: The role of 5-HT3-receptor antagonists in the first 24 hours. Gerontology 2005; 51:287–96.
14. Aapro M. Granisetron: An update on its clinical use in the management of nausea and vomiting. Oncologist 2004;9:673–86.
15. Chawla SP, Grunberg SM, Gralla RJ, et al. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. Cancer 2003;97:2290–2300.
16. Warr, DG, Grunberg, SM, Gralla, RJ, et al. The oral NK1 antagonist aprepitant for the prevention of acute and delayed chemotherapy-induced nausea and vomiting: pooled data from 2 randomised, double-blind, placebo controlled trials Eur J Cancer 2005;41:1278–85.
17. Hobbs WR, Rall TW, Verdoom, TA. Hypnotics and sedatives: Ethanol. In: Hardman JG, Limbird LE, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed. McGraw Hill, New York, 1996.
18. Kris, MG, Gralla, RJ, Clark, RA, et al. Antiemetic control and prevention of side effects of anti-cancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone. A double-blind, randomized trial. Cancer 1987;60:2816–22.
19. de Jong FA, Engels FK, Mathijssen RHJ, et al. Medicinal cannabis in oncology practice: still a bridge too far? J Clin Oncol 2005;23:2886–91.
20. Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg 2000;90:186–94.
21. Feo CV, Sortini D, Ragazzi R, et al. Randomized clinical trial of the effect of preoperative dexamethasone on nausea and vomiting after laparoscopic cholecystectomy. Br J Surg 2006;93:295–9
22. Lindley C, Goodin S, McCune J, et al. Prevention of delayed chemotherapy-induced nausea and vomiting after moderately high to highly emetogenic chemotherapy: comparison of ondansetron, prochlorperazine, and dexamethasone. Am J Clin Oncol 2005;28:270.
23. Kris MG, Hesketh PJ, Somerfield, MR, et al. for the American Society of Clinical Oncology. Guideline for antiemetics in oncology: update 2006. 2006;24:2932–45.
24. Gridelli C, Maione P, Rossi A. Corticosteroids underemployment in delayed chemotherapy-induced nausea and emesis with poor adherence to American Society of Clinical Oncology Guidelines: is this a reasonable clinical choice for the elderly? J Clin Oncol 2003;21:4066–9.
25. Gaudreau JD, Gagnon P, Harel F, et al. Psychoactive medications and risk of delirium in hospitalized cancer patients. J Clin Oncol 2005;23:6712–18.
26. Syrjala KL, Cummings C, Donaldson GW. Hypnosis or cognitive behavioral training for the reduction of pain and nausea during cancer treatment: a controlled clinical trial. Pain 1992;48:137–46.
27. Rowbotham DJ. Recent advances in non-pharmacological management of postoperative nausea and vomiting. Br J Anaes 2005;95:77–81.
28. Dalal S, Del Fabbro E, Bruera E. Symptom control in palliative care – Part I: Oncology as a paradigmatic example. J Palliat Med 2006;9:391–408.
29. Brooksbank MA, Game PA, Ashby MA. Palliative venting gastrostomy in malignant intestinal obstruction. J Palliat Med 2002;16: 520–6.
30. Meier DE, Morrison SE, Ahronheim JC. Chapter 12 - Palliative Care. Duthie: Practice of Geriatrics. 1998. 3rd Edition. W. B. Saunders Company. St. Louis, MO.
31. Han L, McCusker J, Cole M, et al. Use of medications with anticholinergic effects predicts clinical severity of delirium in older medical inpatients. Arch Int Med 2001;16:1099–1105.