Delayed Nausea/Emesis

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9.1 Introduction

Chemotherapy-induced nausea and vomiting is a source of substantial physical and psychological distress among cancer patients. From a list of chemotherapy-associated effects, patients continue to rank nausea and vomiting as 2 of their top 3 most feared effects of therapy [1]. Without suitable prophylaxis, 70–80 % of all chemotherapy patients will suffer these symptoms [2]. Severe or prolonged effects can interfere with a patient's ability to receive proper treatment, and as many as 20 % of patients have even postponed or refused potentially curative chemotherapy due to fear of further episodes [3].

Aside from compromising adherence to therapy and diminishing physical health, nausea and vomiting contributes to emotional distress and embarrassment, increased anxiety and depression, and a decreased quality of life [4, 5]. The impact on daily living can be substantial. The importance of controlling these symptoms is evidenced by results of a recent study on ovarian cancer, in which patients chose "complete to almost complete control of nausea and vomiting" among their most favorable health states, just below "perfect health" and "clinical remission" [6].

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9.1.1 Types of Chemotherapy-Induced Nausea and Vomiting

Underlying mechanisms of chemotherapy-induced nausea and vomiting appear to differ based on when symptoms occur. One of the most commonly accepted classification systems describes five distinct subtypes:

- *Acute-Onset Nausea and Vomiting.* Acute nausea and vomiting occurs within the first 24 h of therapy. Symptoms begin within a few minutes to hours and are usually worst at 5–6 h following therapy. Patients with acute symptoms are significantly more likely to experience delayed symptoms; therefore, all parameters predicative of acute emesis are also considered risk factors for delayed symptoms [7].
- *Delayed Nausea and Vomiting.* Delayed symptoms begin >24 h to several days after the administration of chemotherapy. They reach maximum intensity in 48–72 h and can last 6–7 days [7]. Delayed symptoms, at least in part, are related to the actions of substance P, whereas acute symptoms are most often associated with serotonin. The exact mechanisms are discussed in subsequent sections.
- *Anticipatory Nausea or Vomiting.* Anticipatory nausea or vomiting occurs *before* a patient's next chemotherapy cycle, as preparations begin for the next treatment. It is most often a learned or classically conditioned response and typically occurs after a prior negative experience. Episodes can be triggered by tastes, odors, sounds, sights of the clinic, or simply thoughts and anxiety related to symptoms [8, 9]. Incidence among chemotherapy patients ranges from 18–57 %, with symptom rate and severity tending to increase in subsequent cycles [4, 8].
- *Breakthrough Nausea or Vomiting*. Nausea and vomiting occurring within 5 days of therapy, despite adequate prophylaxis, is termed breakthrough nausea and vomiting. These symptoms are challenging to reverse, and multiple "rescue" antiemetics are often required [4].
- *Refractory Nausea or Vomiting.* Refractory nausea or vomiting occurs in subsequent cycles after antiemetic prophylaxis and/or rescue treatments have failed in prior cycles, usually after several courses of therapy [10, 11]. Patients with ongoing symptoms require a change in prophylactic antiemetic regimen, as their symptoms are no longer responding to their current therapy.

9.2 Mechanism of Disease

The signaling pathways responsible for nausea and vomiting are activated by noxious stimuli such as inflammation, ischemia, or irritation [7]. The vomiting process involves a pre-ejection phase, a retching phase, and an ejection phase, and the physical act results from rhythmic muscle contractions of the abdominal wall and respiratory system [12]. Nausea is more of a subjective feeling of discomfort. The intricate motor reflex required for vomiting involves a complex network of central and peripheral signaling centers, which include the enterochromaffin cells of the

gastrointestinal (GI) tract, the vagal afferent pathways projecting from the gut to the nucleus tractus solitarii and dorsal motor nucleus of the vagus nerve, and the chemoreceptor trigger zone and vomiting center of the brain [13, 14].

The chemoreceptor trigger zone (CTZ) is located in the area postrema on the dorsal surface of the brainstem, along the floor of the fourth ventricle [13, 14]. Unlike other parts of the blood–brain barrier, this highly vascularized area has fenestrated blood vessels lacking tight gap junctions between cells. This makes the area anatomically specialized to sample elements circulating in the blood or cerebrospinal fluid and allows agents such as opioids and dopaminergic agonists to enter and bind local receptors to induce vomiting [15].

The vomiting center is not a distinct place, but a collection of neurons, thought to be located in the dorsolateral reticular formation near the medullary respiratory centers of the brainstem, that contain receptors for opiates and the neurotransmitters choline, histamine, dopamine, serotonin, and substance P [16]. This is the primary area responsible for integrating the afferent stimuli received from activated receptors via the vagal and spinal sympathetic nerves. It then coordinates the efferent signals sent out to the parts of the body involved in vomiting to produce the emetic response. End organs include the cranial nerves, salivation and respiratory centers, and abdominal muscles [17]. Individual patients require different degrees of stimulation to overcome the response threshold of their vomiting centers, which likely contributes to the range of symptoms observed [7, 13].

9.2.1 Chemotherapy-Induced Nausea and Vomiting

Instigators of chemotherapy-induced nausea and vomiting include gut-derived peptides and breakdown products from cytotoxic chemotherapeutic agents. Neurotransmitters released from the enterochromaffin cells of the gut in response to these emetogenic stimuli bind receptors at the end of afferent sympathetic nerves to initiate the process [17]. Activating signals also emanate from the cerebral cortex and limbic system in response to sensory stimuli (i.e., smell, taste, and physiologic stress or pain), from the chemoreceptor trigger zone and from the vestibular-labyrinthine apparatus of the inner ear in response to body motion. These signals combine with the converging inputs from the GI tract to produce the emetic response.

The three primary neurotransmitters implicated in chemotherapy-induced nausea and vomiting include serotonin (5-hydroxytryptamine), substance P (binds neurokinin-1 [NK-1] receptors), and dopamine [5, 12, 17]. *Serotonin*, which seems to be the main neurotransmitter in *acute* pathways, is released from area postrema cells of the chemoreceptor trigger zone and enterochromaffin cells of the GI tract, to initiate the afferent stimuli that ultimately converge on the vomiting center [4].

Substance P, the most well-known mammalian tachykinin peptide, is found in high concentrations in the vomiting center and vagal afferent neurons of the brain stem and spinal cord. As a neurotransmitter, it is released from the terminal of sensory nerves in response to pain or inflammation and acts as the preferred ligand for NK-1 receptors of the gut, area postrema (or chemoreceptor trigger zone), and nucleus

tractus solitarius [12]. Substance P can induce vomiting by activating neurons that cause vasodilation and rapid contraction of smooth muscles in the gut [18]. When substance P release is mediated by chemotherapy, it does this by binding to various NK receptors, primarily located centrally in the nucleus tractus solitarius, as NK-1 receptors in the gut are thought to play only a small, ancillary role [19]. These activated receptors then transmit signals to the chemoreceptor trigger zone and finally to the vomiting center of the brain, to induce vomiting [19].

The role of *dopamine* is less clear, but inhibition of dopaminergic pathways has been shown to reduce symptoms of nausea and vomiting [4]. Antiemetic agents that act at the dopamine receptor include phenothiazines, benzamides, and butyrophenones. Drugs such as metoclopramide, a benzamide, can affect both dopamine *and* serotonin receptors [17].

9.2.2 Acute and Delayed Pathways

Acute and delayed nausea and vomiting should be regarded as two distinct entities, mediated by different biologic mechanisms or, at the very least, divergent signaling pathways [2, 20]. This is supported by the wide range of symptom severity and duration seen with each, as well as multiple findings of clinical trials involving serotonin and NK-1 antagonists, which suggest distinct underlying mechanisms. Acute and delayed symptoms also respond differently to antiemetic agents, with acute symptoms often more easily controlled than others [20].

The *acute phase* of chemotherapy-induced nausea and vomiting is initiated when cytotoxic substances damage the enterochromaffin cells that line the mucosa of the gastrointestinal tract. This promotes the formation of free radicals and leads to the release of serotonin (5-HT_3), substance P, and cholecystokinin from the damaged cells [20]. Serotonin then binds 5-HT_3 receptors on the terminal side of vagal afferent nerves, which lie in close proximity [21]. The chemical stimuli are then propagated as nerve impulses via afferent sensory pathways to the dorsal vagal complex of the central nervous system, which consists of the vomiting center, the area postrema (or chemoreceptor trigger zone), and the nucleus tractus solitarius.

The sensory inputs are integrated and processed by the vomiting center to either initiate an immediate emetic response, as seen with acute symptoms, or to sensitize the vagus nerve to other transmitters subsequently released [22]. Evidence suggests the latter circumstance is what results in the extended or postponed response seen with delayed nausea and vomiting [22]. It is likely, however, that serotonin signaling pathways play a much larger role in the development of acute symptoms and only a minor role in delayed symptoms.

The *delayed phase* of chemotherapy-induced nausea and vomiting is most often activated by the [substance P → NK-1 receptor] interaction. However, in reality, delayed symptoms are likely multifactorial, with overlapping mediators and signaling pathways that are still not fully understood [2, 5]. Putative mechanisms include disruption of the blood–brain barrier by antineoplastic agents, leading to a mild and reversible cerebral edema and increased intracranial pressure that could

potentiate emetic inputs, as well as disruption of intestinal motility by chemotherapeutic agents, leading to gastroparesis and/or protracted symptoms of nausea and vomiting [9, 23].

Some speculate that delayed symptoms result from the accumulation of emetogenic metabolites from chemotherapeutic agents in the gut. Adrenal hormones may also play a role, as urinary cortisol excretion appears to be inversely related, and noradrenaline excretion directly related, to the intensity of delayed chemotherapy-induced nausea and vomiting [24, 25]. This may be partly due to the anti-inflammatory properties of cortisol, which may promote an antiemetic effect by preventing the release of serotonin in the gut [24]. In contrast, noradrenaline may *cause* an emetogenic effect by increasing the sensitivity of serotonin receptors or promoting serotonin release [25].

9.3 Delayed Nausea and Vomiting

Delayed nausea and vomiting most commonly occurs after the administration of highly or moderately emetogenic chemotherapy such as cisplatin or cyclophosphamide [8, 7], but it can also occur with others (i.e., doxorubicin) given at high doses, or for 2 or more consecutive days [7]. In 1985, the pattern of delayed emesis was described in 86 patients receiving cisplatin therapy [26], and only acute antiemetic prophylaxis on day 1. During the first 24 h, 38 % of patients vomited. Over the next 4 days, 93 % experienced some form of delayed symptom, with 61 % experiencing emesis and 78 % reporting nausea. Symptom intensity peaked at 48–72 h following therapy [26].

This pattern appears to differ based on the type of chemotherapy administered. Cisplatin-related delayed emesis, for example, occurs in a *biphasic* pattern [9]. Studies by Gralla et al. showed patients without antiemetic prophylaxis experienced nausea or vomiting within the first 24 h following cisplatin therapy (120 mg/m^2) [27]. Symptoms began with a short latency of 2–3 h and peaked at 6–8 h after therapy. This acute phase lasts for 10–18 h before subsiding, followed by a distinct delayed phase occurring > 24 h later.

In contrast, symptoms following moderately emetogenic chemotherapy usually occur in a *monophasic* pattern. Described by Martin in 1996, initial symptoms have a longer latency of 6–12 h, and in these cases, nausea and vomiting can persist over 24–36 h without relief [28]. In a study involving 31 breast cancer patients receiving 5-fluorouracil, doxorubicin, and cyclophosphamide, patients were observed for 4 consecutive days without antiemetic prophylaxis, and most had vomiting for ≥ 2 days [28]. A study involving carboplatin showed emesis intensity peaks between 8 and 12 h after chemotherapy. Although symptoms subsided significantly by 24 h, 11 % of patients continued to have emesis for another 48 h. Based on his findings, Martin suggested that two patterns of delayed emesis exist. He recommended reserving the term "delayed emesis" for the biphasic pattern of symptoms following cisplatin therapy and the term "prolonged emesis" for the late or sustained emesis following non-cisplatin therapy [28].

9.3.1 Incidence of Disease

Data regarding the incidence of delayed nausea and vomiting has been sparse. A 2004 study, conducted among patients from 14 oncology practices in six countries, showed 60 % of patients receiving highly emetogenic chemotherapy experience delayed nausea and 50 % delayed emesis. With moderately emetogenic chemotherapy, 52 % experienced delayed nausea and 28 % delayed emesis [29]. A subsequent study in 2007 investigating acute and delayed nausea and vomiting in ten community oncology clinics showed similar results, with 36 % of patients experiencing acute symptoms and 59 % experiencing delayed [30].

A study by the Anti-Nausea Chemotherapy Registry (ANCHOR) found that delayed symptoms occurred more often than acute and that their impact on quality of life was greater (more often from delayed nausea than vomiting) almost twice as many patients experienced *delayed* versus *acute* emesis, with delayed symptoms occurring even in patients who did not suffer acute episodes. Overall, nearly one-half of patients experienced a negative impact on daily life, even with only moderately emetogenic regimens [11].

9.3.2 Risk Factors

Treatment-specific risk factors predictive for acute or delayed nausea and vomiting include (1) the medication dose, (2) the schedule and route of administration, and (3) the specific chemotherapeutic agents used [8]. Patient characteristics associated with increased risk include female gender, age <50 years, history of low or no prior alcohol intake (<1 oz/day), those with poor quality of life, or those with a history of previous chemotherapy-induced emesis [31]. Minor risk factors include any history of poor emesis control, including motion sickness or hyperemesis in pregnancy [8]. At present, there remains a need for a comprehensive risk screening process, as well as a way to assimilate such a process into current cancer care.

A number of predictive factors specific to *delayed* nausea and vomiting have been identified. The most important of which is the presence or absence of acute symptoms in the first 24 h [9]. Approximately twice as many patients who experience acute emesis go on to develop delayed symptoms, compared to those without [32, 33]. In later cycles, the incidence of delayed symptoms is not only dependent on the control of acute symptoms during *that* cycle, but also on the incidence of *delayed* symptoms in *prior* cycles [34]. Other factors predictive of delayed symptoms include higher cisplatin dose, female gender, and younger age [5, 9, 33].

9.3.3 Classification of Emetogenicity

The risk of nausea and vomiting specific to the chemotherapeutic agent is based on its inherent emetogenic potential, the dose intensity and frequency, and its combination with other drugs or radiation therapy [35]. Intravenous medications tend to

cause more nausea than oral medicines [8], and treatment to the brain or GI tract is also more emetogenic, as nerve impulses responsible for nausea and vomiting are concentrated in these locations. Chemotherapy agents are classified into categories according to their potential for nausea and vomiting, in the setting of no prophylaxis. The following classification system, from which national consensus guidelines are developed, is widely accepted as the standard [8]:

1. *Highly Emetogenic Chemotherapy (HEC)*: At least 90 % of patients experience nausea and vomiting when no prophylactic protection is provided.
2. *Moderately Emetogenic Chemotherapy (MEC):* 30–90 % of patients experience nausea and vomiting if adequate prophylaxis not provided. This includes anthracycline- and cyclophosphamide [AC]-containing regimens.
3. *Low Emetogenic Potential:* 10–30 % of patients experience nausea and vomiting without appropriate prophylaxis.
4. *Minimal Emetogenic Potential:* <10 % of patients experience nausea and vomiting without prophylaxis.

9.3.4 Challenges Specific to Delayed Symptoms

Trials have indicated that 60–90 % of patients receiving cisplatin chemotherapy will experience nausea and vomiting if not given adequate prophylaxis [2]. Even with the best antiemetics, however, 40–60 % of patients still go on to develop delayed cisplatin-induced emesis [9]. Although chemotherapy-induced nausea and vomiting is generally well managed in the first 24 h, there is still a lack of optimal management strategies for delayed, anticipatory, or refractory symptoms. Antiemetics are far less efficacious for delayed symptoms, making it even more difficult to provide adequate protection for these patients [36, 37].

This difficulty may stem from the fact that treatment guidelines are based largely on chemotherapy emetogenicity, and currently accepted emetogenicity classification systems are based on *acute* symptoms [11]. Complicating matters further is the multifactorial pathophysiology of delayed nausea and vomiting, which is still not fully understood. Resultant diversity among treatment recommendations has made management a challenge [4, 5].

Studies have also suggested that healthcare professionals severely underestimate the intensity and impact of chemotherapy-induced nausea and vomiting. A study in 2004 concluded that physicians and nurses correctly predicted the incidence of *acute* symptoms, but significantly underestimate the incidence of *delayed* symptoms, regardless of the specific chemotherapy agent used [29]. This likely results from the subjective and frequently unobservable nature of delayed nausea and vomiting, which usually occurs at home and out of view of the provider, making it difficult to appreciate symptom severity or provide adequate relief [29]. Furthermore, the intensity of delayed symptoms may be less severe than that of acute, causing some to underestimate the need for intervention. These factors can lead to delays in diagnosis, undertreatment, and underreporting [30].

9.4 Primary Antiemetic Therapy

Most antiemetics competitively block neurotransmitter receptor sites, thereby inhibiting stimulation of peripheral nerves [7]. Without antiemetics, >90 % of patients receiving highly emetogenic chemotherapy will vomit. With appropriate prophylaxis, this number falls to approximately 30 % [8, 38]. Preventing symptoms is generally more successful than treating them; therefore, scheduled, around-the-clock antiemetic administration is preferred over "as needed" dosing [8]. The most effective regimen should be implemented *prior to* the first course of chemotherapy, as opposed to assessing emetic response after less-than-optimal treatment [8, 39, 40]. This is especially true with anticipatory or conditioned responses. For best results, antiemetics should start 30 min prior to chemotherapy, be continued throughout infusion, and then for the entire time the chemotherapy agents exert emetic activity. The entire period of risk can last *at least* 3 days following the last dose of highly emetogenic chemotherapy and 2 days following the last dose of moderately emetogenic therapy, so prophylaxis should continue for *at least* 2–4 days after completion of therapy [8]. In multiday regimens, delayed symptoms can still occur several days after the final dose, even if symptoms did not appear previously.

Experience has shown that antiemetic efficacy decreases during subsequent cycles, making frequent reassessment critical. Adequate hydration and correction of electrolytes should be maintained [8]. If symptoms are refractory to treatment, despite adequate prophylactic dose and continuous 24 h administration, a trial of combined therapies can be used to block multiple emetic pathways at once. Updated guidelines recommend antiemetics with the highest therapeutic index, and this includes serotonin (5-HT_3) receptor antagonists, corticosteroids, and NK-1 receptor antagonists [8, 39]. These agents are effective, have good safety profiles, and can be administered safely in combination [41]. For those patients with persistent emesis, or inability to swallow pills, possible routes of administration include sublingual, nasal, rectal, intramuscular, intravenous, or transdermal. Suppositories, dissolvable tablets, dermal patches, and nasal sprays can also be of value [8].

9.4.1 Serotonin Receptor Antagonists

First-generation 5-HT_3 receptor antagonists have a well-established role in preventing acute nausea and vomiting, but are far less effective for delayed symptoms [32, 37]. Randomized controlled trials in which 5-HT_3 receptor antagonists were combined with dexamethasone for the prevention of *delayed nausea*, or compared with prochlorperazine in the prevention of *delayed emesis*, failed to show a significant increase in efficacy [37, 42]. Subsequent analyses in 2005 found there was neither clinical evidence nor adequate deliberation of cost-effectiveness to justify the use of first-generation antagonists for > 24 h following chemotherapy [43]. Based on these findings, *first-generation* 5-HT_3 antagonists are *not* recommended as standard prophylaxis for delayed nausea and vomiting.

Introduced in 2003, *palonosetron* is a second-generation 5-HT_3 receptor antagonist which now offers a good alternative for preventing delayed symptoms. Compared with first-generation agents, palonosetron similarly binds 5-HT_3 receptors in the central nervous system and gut, but differs in its significantly prolonged half-life of about 40 h (~10 times longer than earlier agents), and its high binding affinity, which is 30–100-fold greater than first-generation agents [44]. Palonosetron also exhibits positive cooperativity at its binding site, likely triggering 5-HT_3 receptor internalization and causing prolonged inhibition [14, 44]. The resultant high selectivity for 5-HT_3 receptors likely contributes to palonosetron's excellent safety profile and the increased efficacy for delayed symptoms.

Studies comparing palonosetron to ondansetron, dolasetron, and granisetron report superiority of palonosetron for both acute and delayed symptoms, but particularly between 24 and 120 h after chemotherapy, supporting its specific role in delayed prophylaxis. Complete response rates (no emesis, no rescue) with palonosetron were 48–57 % [45, 46]. A randomized non-inferiority trial in 2009 comparing palonosetron and granisetron for acute and chronic chemotherapy-induced nausea and vomiting in 1019 patients showed non-inferiority of palonosetron for acute symptoms and *superiority* of palonosetron for delayed symptoms [47]. These findings led to palonosetron becoming the *preferred* 5-HT_3 receptor antagonist (over first-generation agents) by international guidelines and the US FDA for the prevention of acute symptoms with highly or moderately emetogenic chemotherapy and *delayed* symptoms with moderately emetogenic agents [8, 33, 39]. It is important to note that neither regimen provided effective control of nausea symptoms, with only 31.9 % of patients in the palonosetron group and 25.0 % in the granisetron group experiencing "no nausea" [47].

9.4.2 Neurokinin 1 Receptor Antagonists

Neurokinin 1 (NK-1) receptor antagonists inhibit the action of substance P at its receptor site, both in the vomiting center and in the gut [19, 48]. Although there are several emetic pathways, the [substance P → NK-1 receptor] interaction appears to play a role in the final common pathway regulating vomiting [13]. NK-1 receptor antagonists easily cross the blood–brain barrier and work primarily on centrally located NK-1 receptors [19]. *Aprepitant* was the first commercially available NK-1 receptor antagonist [12]. It is given orally usually with a 5-HT_3 receptor antagonist and dexamethasone on day 1 and with dexamethasone alone for delayed symptoms on days 2–3 [8, 33, 39]. A dose of 125 mg is given day 1, followed by 80 mg on days 2–3.

Multiple phase III clinical trials involving *highly emetogenic* agents have confirmed an approximate 20 % improvement in overall and complete response rates with the addition of aprepitant to a 5-HT_3 receptor antagonist and dexamethasone [49–51], leading international guidelines to consistently recommend aprepitant as part of the prophylactic regimen for initial and repeat courses of highly emetogenic

therapy [8, 39, 40]. In all studies, the comparative benefit was more pronounced in the delayed phase compared to the acute.

A subsequent trial by Warr et al. utilizing *moderately emetogenic* chemotherapy also found that the addition of aprepitant was superior to ondansetron and dexamethasone alone, over the entire 5-day study period (51 % vs. 42 %) [52]. When isolated to the delayed phase, complete response improved with aprepitant (55 % vs. 49 %); however, the difference was not statistically significant. This study helped support the addition of aprepitant for select agents of moderate emetogenic risk, as well.

Aprepitant is metabolized primarily by the CYP3A4 isoenzyme, leading to altered plasma levels when coadministered with other substrates, and dose adjustments may be necessary [53]. Although a number of chemotherapeutic agents are also metabolized through the CYP3A4 system (e.g., taxanes, etoposide, ifosfamide, imatinib, and vinca alkaloids), the theoretical concern that NK-1 antagonists interact with these agents has not been demonstrated [54]. Aprepitant is only for oral use, but a newer NK-1 receptor antagonist, *fosaprepitant*, is an IV alternative, which could be helpful in patients with severe mucositis, impaired swallowing, or GI disturbances. Fosaprepitant is given on day 1 of a 3-day regimen (with a 5-HT_3 receptor antagonist and dexamethasone), followed by oral aprepitant 80 mg on days 2 and 3 [10, 55]. Fosaprepitant also is a moderate inhibitor of CYP3A4, so the same precautions apply.

9.4.3 Corticosteroids

Although not approved by the FDA as antiemetics, corticosteroids represent an integral part of antiemetic prophylaxis, exhibiting considerable efficacy as single agents in both acute and delayed nausea and vomiting [36]. Their mechanism is not fully understood, but it is speculated that agents such as *dexamethasone* and *methylprednisolone* suppress symptoms by limiting inflammation and prostaglandin production and possibly by preventing serotonin release in the gut. They may also modify the blood–brain barrier and inhibit cortical input to the vomiting center, thereby raising the emetic threshold [14, 56] and allowing corticosteroids to exert a "booster-like effect" when coadministered with other antiemetic agents [48].

Serotonin receptor antagonists combined with dexamethasone for acute prophylaxis achieve complete response rates of 80–90 % with moderately emetogenic chemotherapy and 60–70 % with highly emetogenic chemotherapy [57, 58]. Addition of aprepitant further improves control of delayed symptoms, with both highly and moderately emetogenic regimens [33, 49, 51]. Guidelines now unanimously recommend dexamethasone (with a 5-HT_3 receptor antagonist and/or aprepitant) as the preferred agent for acute prophylaxis with agents of high, moderate, and low emetogenicity, as well as for the prevention of delayed symptoms (usually with aprepitant) with highly or moderately emetogenic therapy [8, 33, 39].

Current guidelines support a 20 mg dose of dexamethasone (12 mg when coadministered with aprepitant) for highly emetogenic regimens, and a single 8 mg dose

for moderate regimens [8, 33, 39]. The optimal duration for delayed prophylaxis is not well established, but some recommend 8 mg daily on days 2–4 (with aprepitant on days 2–3) for highly emetogenic regimens and 4 mg twice daily on days 2–3 for moderate regimens [8, 33, 39].

Corticosteroids generally are well tolerated and safe. Trials utilizing dexamethasone prophylaxis for delayed emesis have reported moderate-to-severe insomnia (45 %), indigestion/epigastric discomfort (27 %), agitation (27 %), increased appetite/weight gain (16–19 %), and acne (15 %) [48, 59]. Previous concern that steroids may interfere with the antitumor effects of chemotherapy through immunosuppressive mechanisms has not been confirmed [60].

9.4.4 Dopaminergic Antagonists (Neuroleptics)

Dopamine provides a stimulatory effect in the medullary chemoreceptor trigger zone by binding to multiple local receptors (mostly the D2 subtype) [61]. Dopamine antagonists block these receptors, playing a major role in antiemetic therapy. Examples include phenothiazines, which directly target dopamine, and metoclopramide, a benzamide, which inhibits both the dopamine receptor and the serotonin receptor.

A high level of dopamine blockade results in extrapyramidal effects, disorientation, and sedation, limiting the usefulness of these agents to some degree. Currently, they are used primarily for established nausea and vomiting and not prophylaxis [8]. Cogwheel rigidity, acute dystonia, and tremor respond to anticholinergic medications, and akathisia is best treated by switching to a lower potency neuroleptic, decreasing the dose, or adding a benzodiazepine or beta-blocker such as propranolol [7].

9.4.4.1 Substituted Benzamides: Metoclopramide and Metopimazine

Metoclopramide works as a dopamine antagonist at low doses and a serotonin antagonist at high doses [42]. It has proven efficacy both in the prevention of delayed symptoms and the treatment of breakthrough symptoms [62]. Current Multinational Association of Supportive Care in Cancer (MASCC) and American Society of Clinical Oncology (ASCO) guidelines recommend metoclopramide be reserved for special circumstances, such as known intolerance to other agents, or symptoms refractory to 5-HT_3 receptor antagonists, dexamethasone and aprepitant, given the higher effectiveness of these agents [33, 39]. Serotonin receptor antagonists and metoclopramide are also alternatives to dexamethasone for preventing delayed symptoms with moderately emetogenic therapy. Metoclopramide appears most beneficial in the treatment of breakthrough symptoms occurring during the delayed period in spite of optimal prophylaxis [48, 63]. A relatively high dose (20 mg TID) may be more efficacious for delayed symptoms, but also leads to increased sedation and extrapyramidal effects [42].

9.4.4.2 Phenothiazines: Prochlorperazine and Promethazine

Phenothiazines and *butyrophenones* are not "first-line" agents for chemotherapy-induced nausea and vomiting, but they are still useful for managing breakthrough symptoms occurring during the acute or delayed periods [63]. *Prochlorperazine* is perhaps the most frequently (and empirically) used, and, in low doses, is generally effective in preventing nausea associated with radiation and acute or delayed symptoms induced by agents of very low to moderate emetic potential [7]. High IV doses (0.2–0.6 mg/kg/dose) may be required, especially in those with delayed nausea and vomiting on cisplatin regimens [64]. As with all dopamine-blocking agents, adverse effects are primarily extrapyramidal [7].

9.4.4.3 Atypical Neuroleptics

Olanzapine is an atypical antipsychotic medication of the thienobenzodiazepine class [65]. Although not approved by the FDA to treat nausea and vomiting, receptor-binding studies show olanzapine exhibits strong binding affinity for multiple receptors involved in emetic pathways, resulting in antagonism of dopamine at D1–D4 receptors; serotonin at 5HT2A, 5HT2C, 5HT3, and 5HT6 receptors; acetylcholine at muscarinic receptors; catecholamine at α1-adrenergic receptors; and histamine at H1 receptors [65].

Phase III clinical trials confirm the efficacy and safety of olanzapine, showing its addition to the 5-HT_3 receptor antagonist azasetron plus dexamethasone improved delayed nausea and vomiting in both highly and moderately emetogenic settings. Nausea was also significantly improved with the addition of olanzapine in highly emetogenic (no nausea: 70 % vs. 28 %) and moderately emetogenic regimens (86 % vs. 56 %) [66]. In 2011, a clinical trial randomized patients receiving highly emetogenic chemotherapy to either olanzapine or aprepitant on days 1–4, both combined with palonosetron and dexamethasone on day 1. Although complete response rates (no emesis, no rescue) were similar (acute: 100 % vs. 90 %; delayed: 77 % vs. 73 %), the frequency of patients reporting "no nausea" was significantly improved with olanzapine (60 % vs. 38 %), supporting its specific use for the control of acute and delayed nausea symptoms [67].

Currently, olanzapine is recommended by MASCC and the National Comprehensive Cancer Network (NCCN) for refractory and breakthrough symptoms [8, 33]. A dose of 5 mg daily beginning 2 days prior to chemotherapy, and then 10 mg daily from the start of therapy until 7 days after completion, is commonly prescribed. The most common side effects are typical of antipsychotic medications: fatigue, sedation, dizziness, weight gain, and dry mouth [8, 33, 66].

9.5 Other Agents

9.5.1 Benzodiazepines

Studies have indicated a link between pretreatment anxiety and rates of nausea and vomiting following therapy. Because of this, benzodiazepines are recommended by all three guidelines for refractory, breakthrough, and anticipatory symptoms [8, 39, 40].

Lorazepam is most commonly used, with side effects including sedation and short-term memory loss. A small phase II study showed that *midazolam*, a short-acting benzodiazepine, also resulted in reduced nausea and vomiting in 73 % of patients when added to granisetron plus dexamethasone for refractory symptoms [68].

9.5.2 Cannabinoids

Tetrahydrocannabinol (THC) is the active ingredient in marijuana responsible for its psychoactive properties. Synthetic derivatives such as delta-9-tetrahydrocannabinol (i.e., *dronabinol*) are known as endocannabinoids and they have weak antiemetic activity. In humans, two types of cannabinoid receptors exist (CB1 and CB2) [69]. Endocannabinoids bind CB1 receptors in the central nervous system, specifically the dorsal vagal complex, to produce an antiemetic effect by activating a G-protein-mediated reduction in neurotransmitter release [70]. Despite this, the usefulness of these agents is limited by their significant side effects of sedation, dizziness, hallucinations, and dysphoria [48].

The American Society of Clinical Oncology (ASCO) and NCCN guidelines suggest cannabinoids for patients intolerant or refractory to 5-HT_3 receptor antagonists, corticosteroids, and aprepitant, or for consideration in the treatment of breakthrough symptoms [8, 39]. Available in oral form, *Dronabinol* is usually prescribed at a dose of 5–0 mg/m2 every 3–4 h. Sedation or psychiatric effects occur more often at higher doses.

9.6 Novel and Investigative Agents

Gabapentin is a gamma aminobutyric acid (GABA) analog and anticonvulsant, thought to control voltage-gated calcium channels responsible for the release of excitatory neurotransmitters [4]. When added to ondansetron and dexamethasone in preliminary studies, gabapentin significantly improved chemotherapy-induced emesis [71]. Recently, the North Central Cancer Treatment Group competed enrollment for a phase III randomized controlled trial investigating gabapentin in the prevention of acute and delayed symptoms with highly emetogenic chemotherapy [72].

Carbamazepine is an anti-seizure and mood-stabilizing drug with antiemetic activity thought to result from stabilization of inactivated voltage-gated sodium channels and potentiation of GABA receptors [4]. Case reports describe improved refractory symptoms with carbamazepine, and currently, an ongoing trial in Brazil is evaluating its safety and efficacy in chemotherapy patients [4].

Rolapitant and *netupitant* are NK-1 receptor antagonists with potent binding affinity for NK-1 receptor-binding sites, as demonstrated by positron emission tomography (PET) results following a single dose of netupitant [73]. This powerful selectivity suggests potential long-lasting effects, which could allow improved control of delayed symptoms [10, 73]. Ongoing studies include two randomized clinical trials, one assessing efficacy and safety of a single oral dose of netupitant for

moderately emetogenic chemotherapy [10] and a second evaluating the safety of netupitant (administered with palonosetron and dexamethasone), as compared to aprepitant [4].

9.7 Consensus Treatment Guidelines (Single-Day Chemotherapy)

Data suggests poor compliance with recommendation guidelines in clinical practice, despite studies showing guideline adherence can improve the control of nausea and vomiting by 20 % [74]. Current guidelines were published by the American Society of Clinical Oncology (ASCO) and the Multinational Association of Supportive Care in Cancer (MASCC) with the European Society for Medical Oncology (ESMO) in 2011 and by the National Comprehensive Cancer Network (NCCN) in 2012 [8, 39, 40].

Guideline recommendations are based on the emetogenic potential of chemotherapeutic agents (oral and intravenous), and newer guidelines provide recommendations for the entire period of risk, incorporating dosing schedules for both *acute* and *delayed* symptoms into a single algorithm [33]. As previously discussed, one of the most important prognostic factors for delayed nausea and vomiting is the control of acute symptoms. Therefore, any prophylactic regimen for delayed symptoms must include adequate protection against acute symptoms as well. Due to the involvement of multiple neurophysiologic pathways, combination antiemetic regimens have become the standard of care. Please refer to Table 9.1 for a detailed review.

I. *For highly emetogenic chemotherapy (HEC):*
   (a) A three-drug combination is unanimously recommended at least 30 min prior to chemotherapy to prevent *acute* symptoms:
      (i) 5-HT_3 receptor antagonist (palonosetron)
      (ii) NK-1 receptor antagonist (aprepitant)
      (iii) Corticosteroid (dexamethasone)
   (b) For *delayed* prophylaxis, dexamethasone should be continued on days 2–4, and oral aprepitant should be continued on days 2 and 3.
      (i) If aprepitant is replaced with fosaprepitant on day 1, then only dexamethasone is continued on day 2–4 post-therapy.

II. *For moderately emetogenic chemotherapy (MEC):*
   (a) A two-drug combination of a 5-HT_3 receptor antagonist (palonosetron preferred to first-generation agents) plus dexamethasone is recommended for *acute* prophylaxis.
   (b) For *delayed* prophylaxis, dexamethasone is continued on days 2–3 (ASCO guidelines) or days 2–4 (MASCC, NCCN recommendations).
   (c) NCCN guidelines recommend aprepitant (days 1–3) or IV fosaprepitant (day 1 only) be added to the 5-HT_3 receptor antagonist and dexamethasone for select agents of moderate risk which appear to have increased emetogenicity compared to other agents in their class.

Table 9.1 Antiemetic prophylaxis recommendations

Emetic risk category	Phase	Guideline recommendations		
		MASCC/EMSO	NCCN	ASCO
I. High (>90 %) risk	Acute	5-HT_3RA (palonosetron) + DMZ + APR *(or FOS)*	5-HT_3RA[a] + DMZ (12 mg) + APR (125 mg)	5-HT_3RA (palonosetron) + DMZ + APR
	Delayed	DMZ + APR	DMZ (8 mg, days 2–4) + APR (80 mg, day 2 and 3)	DMZ + APR
II. AC-based regimens[b]	Acute	5-HT_3RA (palonosetron) + DMZ + APR/FOS	5-HT_3RA[a] + DMZ (12 mg) + APR (125 mg)[c]	5-HT_3RA (palonosetron) + DMZ + APR
	Delayed	APR *(none, if Fos used day 1)*	DMZ (8 mg) *or* a 5-HT_3 RA (days 2–4) (*if used day 1, cont APR on days 2–3)*	APR *(days 2 and 3)*
III. Moderate (30–90 %) risk	Acute	5-HT_3RA (palonosetron) + DMZ	5-HT_3RA[a] + DMZ (12 mg)[c]	5-HT_3RA (palonosetron) + DMZ
	Delayed	DMZ	DMZ (8 mg) *or* a 5-HT_3RA (days 2–4)	DMZ
IV. Low (10–30 %) risk	Acute	DMZ *or* 5HT_3RA *or* dopamine antagonist	Metoclopramide, with or without diphenhydramine, DMZ *or* prochlorperazine	DMZ (8 mg)
	Delayed	[d]	[d]	[d]
V. Minimal (<10 %) risk	Acute	[d]	[d]	[d]
	Delayed	[d]	[d]	[d]

Abbreviations: *MASCC* The Multinational Association of Supportive Care in Cancer, *EMSO* European Society for Medical Oncology, *ASCO* American Society of Clinical Oncology, *NCCN* National Comprehensive Cancer Network (lists "with or without Lorazepam" with all prophylactic regimens), 5-HT_3 *RA* serotonin receptor antagonist, *DMZ* dexamethasone, *APR* aprepitant, *Fos* fosaprepitant (IV alternative to aprepitant)

[a]5-HT_3RA – Although palonosetron is preferred to first-generation agents in both MASCC and ASCO guidelines, NCCN guidelines do not specify palonosetron as the recommended 5-HT3 agent (ondansetron, granisetron, dolasetron, and palonosetron listed as acceptable choices)

[b]AC-based regimens, containing anthracyclines and cyclophosphamides, were initially categorized as "moderate risk", but are now routinely treated as highly emetic agents

[c]In the moderate-risk group, NCCN recommends the addition of aprepitant to AC-based regimens and other agents having increased emetic activity compared to others in their group (e.g., carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate)

[d]No prophylaxis recommended

(i) Includes carboplatin, doxorubicin, ifosfamide, and methotrexate, among others.
(ii) Evidence supporting aprepitant in moderately emetogenic settings is still evolving; ASCO and MASCC guidelines leave this to the discretion of the provider.

(d) Aprepitant is unanimously recommended to prevent delayed symptoms with *AC-based* regimens, as most guidelines now consider these agents to be of high emetic risk.

III. *Agents of low or minimal emetogenic risk*
(a) *No* antiemetic prophylaxis is recommended for the prevention of *delayed* symptoms with agents of either low or minimal risk.

IV. *Additional recommendations:*
(a) The superiority of palonosetron over first-generation $5HT_3$ antagonists with both acute and delayed symptoms has been shown in randomized clinical trials, leading to recommendation for palonosetron (with dexamethasone) as the preferred 5-HT_3 receptor antagonist.
(b) If aprepitant *is* added in moderately emetogenic settings, any 5-HT_3 receptor antagonist is appropriate for coadministration (with dexamethasone) on day 1. Aprepitant 80 mg is then continued with dexamethasone alone on days 2 and 3.
(i) Day 1 doses of aprepitant (125 mg) and dexamethasone (8 mg) are decreased on days 2 and 3: aprepitant 80 mg with dexamethasone 4 mg.
(c) The NCCN recommends all regimens (high, moderate, and low emetic risk) be given with or without lorazepam, an H2 blocker, or proton pump inhibitor.

9.8 Non-pharmacologic Approach

A number of alternative therapies are available for patients whose nausea and vomiting is not well controlled. Herbal or natural remedies, such as ginger or peppermint, have been suggested for intractable symptoms of nausea and vomiting [48]. It has been suggested that they possess antiemetic properties stemming from calcium channel blocking activity that results in intestinal smooth muscle relaxation, but data is sparse among chemotherapy patients, and there are currently no studies underway [48].

Behavioral therapy techniques, acupuncture or acupressure, and even massage has shown promise in reducing severity and duration of symptoms [4]. The most frequently studied behavioral interventions include systematic desensitization with progressive muscle relaxation, guided imagery, and hypnosis. These interventions appear to be most effective with anticipatory symptoms [75]. Some studies have shown acupuncture may have a significant effect in reducing acute nausea and vomiting, but it does not appear to have any direct effect on delayed symptoms.

Lifestyle modification, including changes in diet and exercise, can also help alleviate symptoms. The NCCN recommends eating food that is "easy on the stomach" or "full-liquid" foods, eating small frequent meals, and eating food at room temperature [8]. Patients should avoid foods that induce nausea and control the overall amount consumed. A dietary consult may be helpful.

9.9 Symptoms That Occur Despite Prophylaxis

If *breakthrough symptoms* occur after appropriate prophylaxis, drugs from a different drug class should be given as rescue therapy. Patients with delayed breakthrough symptoms (days 2–5) should be considered for a 3-day regimen of a dopamine antagonist such as olanzapine or metoclopramide [10]. A recent phase III trial comparing oral olanzapine (10 mg/day x 3 days) to metoclopramide (10 mg TID x 3 days) found olanzapine to be significantly better at controlling breakthrough symptoms with highly emetogenic therapy [76]. Phenothiazine or dexamethasone may also be effective in this setting [8]. Aprepitant has been approved as an adjunct to $5HT_3$ antagonists and dexamethasone for the *prevention* of chemotherapy-induced nausea and vomiting, but has not been studied for breakthrough symptoms.

If *anticipatory symptoms* occur, behavioral therapy with systematic desensitization or other relaxation techniques and anti-anxiolytics, such as benzodiazepines, are most beneficial. Alternating routes, formulations, or schedules may be necessary if emesis is ongoing. For patients with *refractory symptoms* after prophylaxis failed in earlier cycles, a complete change in antiemetic regimen should be considered [10]. For patients receiving highly emetogenic therapy, olanzapine (days 1–3) can be substituted for the NK-1 antagonist aprepitant [67], and for those with moderately emetogenic regimens, aprepitant, or fosaprepitant, can be added [77]. One could also consider substituting high-dose metoclopramide, or other dopamine antagonists, for palonosetron [39]. Benzodiazepines like lorazepam or alprazolam can be given for anxiety with any cycle.

It is important to remember that antiemetic efficacy may decrease as chemotherapy cycles continue [40]. With refractory symptoms especially, it is also important to rule out nontreatment-related causes of nausea and vomiting. Frequent reassessment of emetic risk, disease status, concurrent illnesses, and medications can help ascertain that the best antiemetic regimen is being utilized [39].

9.10 Multidrug and Multiday Regimens

Multiday, high-dose, and combination chemotherapies pose unique challenges. When several different agents are required for *combination chemotherapy*, antiemetic therapy should be tailored to the chemotherapeutic drug with the highest emetic risk [39]. With *multiday regimens*, patients are at high risk for both acute and delayed symptoms. Recommending a specific antiemetic regimen is difficult in

these patients because acute and delayed symptoms begin to overlap after the first day of therapy. The duration of risk for delayed emesis is also difficult to predict, as it depends on the specific regimen used and the emetogenic potential of the drugs administered.

A combination of a first-generation 5-HT_3 receptor antagonist and dexamethasone +/− aprepitant for acute symptoms is recommended daily for each day of a *multiday* or *high-dose chemotherapy with stem cell transplant* [83]. Dexamethasone alone is standard for delayed symptoms, and this can be continued for 2–3 days following therapy completion [8, 33, 39]. If desired, IV palonosetron may be substituted for the oral 5-HT_3 receptor antagonist before a 3-day regimen, instead of using multiple daily doses. Unfortunately, these options are not very effective for delayed nausea and vomiting. Complete response rates for delayed symptoms with various high-dose regimens are 30–70 %, and most studies report ~50 % [78].

In 2011, palonosetron was given for 1, 2, or 3 days with dexamethasone in 73 patients receiving multiday high-dose chemotherapy before stem cell transplant. Although the study produced only a 20 % complete response rate (no emesis, no rescue), vomiting control was significantly improved, with 40–45 % of patients experiencing "no emesis" during the 7-day study period and having no serious adverse events [79]. In 2012, the subsequent addition of aprepitant to a 5-HT_3 receptor antagonist plus dexamethasone significantly improved complete response rates in patients receiving 5 days of cisplatin therapy [80].

In a study of 78 patients receiving multiday therapy, aprepitant was added to granisetron plus dexamethasone and continued for an additional 2 days following therapy. Complete response rates were 58 and 73 % for highly and moderately emetogenic chemotherapy, respectively [81]. Due to this, aprepitant is suggested for multiday regimens associated with a significant risk of delayed symptoms, with repeated dosing recommended over multiple cycles [39]. If well tolerated, aprepitant (80 mg) can be safely continued on days 4 and 5 following chemotherapy [82].

9.11 Other Considerations

9.11.1 Oral Chemotherapy Agents

An additional challenge in the prevention of delayed nausea and vomiting is the increasing use of oral chemotherapy, both cytotoxic and biologic. Oral agents often are given daily, as part of an extended therapeutic regimen, rather than a single IV dose. This chronic administration obscures the distinction between acute and delayed phases and has caused guideline committees to consider the emetogenic potential of oral chemotherapy separately. Oral agents warranting antiemetic prophylaxis include altretamine, busulfan, cyclophosphamide, etoposide, lomustine, procarbazine, and temozolomide [8].

An oral 5-HT_3 receptor antagonist (i.e., granisetron or ondansetron) is recommended daily for highly or moderately emetogenic oral agents. For low or minimal emetic risk, prophylaxis includes metoclopramide, prochlorperazine, or haloperidol [8].

9.11.2 Challenges of Delayed *Nausea*

Despite marked improvements in the control of emesis with newer antiemetics, the control of acute and delayed *nausea* remains an important, unmet need. In practice, 55–60 % of patients experience delayed nausea following chemotherapy, and only 25–38 % report delayed emesis [29, 83]. A recent study on the effects of delayed nausea and vomiting in cancer patients also showed patients report greater impairment of daily living and quality of life with delayed nausea, compared to vomiting [11]. Delayed nausea is more common than acute; it is often more severe and tends to be more resistant to antiemetic treatment [37].

Among antiemetics, olanzapine has shown excellent efficacy in phase II and III trials in the control of emesis *and* nausea in patients receiving highly or moderately emetogenic chemotherapy [66, 67]. In patients with severe, persistent, or delayed nausea despite standard prophylaxis, consideration should be given to include olanzapine in their antiemetic regimen, as it appears safe and effective for both the prevention and treatment of symptoms [76].

9.12 Summary and Conclusions

Over the past several decades, first generation 5-HT_3 receptor antagonists and dexamethasone have significantly improved the control of acute chemotherapy-induced nausea and vomiting. Unfortunately, these agents alone did not appear to adequately control delayed symptoms. Recent studies, however, have noted improvement in delayed symptoms with the use of three newer agents: palonosetron (a second-generation 5-HT_3 antagonist), aprepitant (an NK-1 receptor antagonist), and olanzapine (an antipsychotic) [10, 66]. The second-generation 5-HT_3 antagonist palonosetron has a longer half-life, higher binding capacity, and a different mechanism of action than first-generation agents and appears to be the most effective agent in its class. Although palonosetron improves complete response rates of both acute and delayed *emesis* in patients receiving moderately or highly emetogenic therapy, data suggest that *all* 5-HT_3 receptor antagonists exhibit poor control of nausea [52, 66, 84]. Clinical trials reporting significantly improved emesis have also reported "no nausea" in only 25 %, 32 %, and 33 % of chemotherapy patients with the use of granisetron, palonosetron, and ondansetron, respectively [47, 52, 85].

The combination of palonosetron, dexamethasone and the NK-1 receptor antagonist aprepitant has shown the most promise in clinical trials for improving acute and delayed emesis in patients receiving single-day chemotherapy over a 120-h period following administration. Many of these same studies have measured nausea as a secondary endpoint and have demonstrated that nausea is not well controlled. Olanzapine appears to be important in controlling nausea and has emerged in recent trials as a safe and effective preventative agent (with a 5-HT_3 receptor antagonist and dexamethasone) for emesis *or* nausea, as well as a very effective agent for the treatment of breakthrough symptoms. Clinical trials using gabapentin, cannabinoids, and ginger have not been definitive regarding efficacy in chemotherapy-induced nausea and vomiting to date. Additional studies are necessary in these

settings, as well as in the control of nausea, with multiday chemotherapy and with bone marrow transplantation.

Complications from chemotherapy-induced nausea and vomiting, particularly in patients who may already be debilitated, malnourished, or have recently undergone surgery or radiation therapy, can necessitate hospitalization and cause a wide range of poor health outcomes [11, 30]. Dehydration and electrolyte imbalance also increase the risk of serious medical complications. Poor control of symptoms in these settings can lead to increased healthcare utilization, patient costs, and level of anxiety [26].

In order to better control acute *and* delayed symptoms, we must first better understand the factors that contribute to susceptibility. We have identified a number of risk factors that may predict symptoms; however, this field needs further development and more comprehensive integration into mainstream cancer treatment. Understanding basic biologic, genetic, and clinical predictors of chemotherapy-induced nausea and vomiting may greatly enhance our ability to individualize treatment and tailor antiemetic prophylaxis to each patient.

Despite substantial progress with new antiemetics, and the establishment of standard clinical guidelines, a significant number of patients still experience symptoms. The ultimate goal of research and treatment should be to control all aspects of nausea and vomiting, so that chemotherapy is better tolerated and patients can receive their entire prescribed course of therapy without modification. For best control, antiemetic regimens should be determined prior to initiating therapy, based on the emetogenic potential of the chemotherapeutic agents and individual risk factors. Among currently available antiemetics, 5-HT_3 receptor antagonists, NK-1 receptor antagonists, and corticosteroids appear most effective, achieving complete protection in a majority of patients.

The management of delayed nausea and vomiting in cancer patients remains a challenge. Patients often experience more symptoms than perceived by practitioners. Many antiemetics are not as effective for delayed symptoms, especially delayed nausea. Treatment guidelines, in which rapidly evolving research is summarized into management recommendations by experts, can be a useful tool for practicing clinicians. At this time, chemotherapy-induced nausea and vomiting can be prevented in approximately 70–80 % of patients with appropriate intervention [49, 51].

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