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Current Pharmacotherapy for Chemotherapy-Induced Nausea and Vomiting in Cancer Patients

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Abstract

Introduction—Nausea and vomiting are two of the most frequent and troubling side effects patients experience during chemotherapy, interfering with compliance with cancer therapies and quality of life. While newly available treatments have improved our ability to manage nausea and vomiting, anticipatory and delayed nausea and vomiting are still major problems for patients receiving chemotherapy. Many cancer patients consider delaying future chemotherapy cycles and some contemplate stopping chemotherapy altogether because of their fear of experiencing further nausea and vomiting.

Areas Covered—The purpose of this article is to provide an overview of the pathophysiology of chemotherapy-induced nausea and vomiting, the recommended guidelines for treatment, current agents in late-stage clinical trials, and future research needs to address the continued challenges of treatment-related nausea and vomiting.

Expert Opinion—Despite advances in pharmaceutical and behavioral therapies, and the provision of standard clinical guidelines for effectively managing chemotherapy-induced nausea and vomiting (CINV), patients continue to experience CINV. Moreover, control of nausea, acute and delayed, and anticipatory nausea and vomiting (ANV) remains an important, unmet need among cancer patients. It is critical to focus attention on better understanding the mechanisms underlying nausea, anticipatory symptoms, and delayed symptoms.

Keywords

cancer treatments; chemotherapy; nausea; vomiting; chemotherapy-induced; nausea and vomiting; anticipatory nausea and vomiting; emesis

I. Introduction

Cancer treatments often cause a host of side effects in a majority of cancer patients; these side effects are quite challenging for patients and providers to manage and often have a negative impact on quality of life. Chemotherapy-induced nausea and vomiting (CINV) are two of the most common and troublesome side effects experienced by cancer patients.^{1,2} These side effects can interfere with compliance with treatment; patients sometimes delay chemotherapy cycles and contemplate refusing future treatments because of fear of further CINV.¹ While significant advances have been made in the treatment of acute chemotherapy-induced vomiting (CIV), chemotherapy-induced nausea (CIN), anticipatory nausea and vomiting (ANV), and delayed nausea and vomiting (DNV) remain substantial challenges for

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cancer patients and their providers.^{1,34} Anticipatory nausea is reported by 30% of patients who experienced nausea during earlier chemotherapy cycles. Anticipatory vomiting is reported by 20% who experienced vomiting during earlier chemotherapy treatment cycles.^{5,6} Anticipatory, acute, and delayed CINV lead to poorer chemotherapy adherence, impaired function, increased anxiety and depression, and diminished quality of life (QOL) among patients.^{7–10} Physicians and patients consequently increase utilization of healthcare resources to manage these side effects, substantially increasing the public health burden of cancer and its treatment.^{7–10} The purpose of this review is to provide an overview of the patho-psychophysiology of CINV, the recommended guidelines for treatment of CINV, current agents in Phase III clinical trials, and areas for further research.

II. Pathophysiology of Chemotherapy-Induced Nausea and Vomiting

Chemotherapy-induced debilitating side effects of nausea, vomiting, and retching, though related, are actually three distinct symptoms and often go hand-in-hand.^{11,12} Nausea is an unpleasant sensation experienced in the back of the throat and epigastrium that may or may not result in the expulsion of contents from the stomach, while vomiting is the motor reflex resulting in forceful upward expulsion of contents from the stomach.^{12,13} Retching involves the attempt to expel contents from the stomach without actually expelling them.^{12,14}

In general, CINV can be further classified as acute, delayed, or anticipatory,^{15,16} depending on the time of onset: a) acute CINV occurs in the first 24 hours after chemotherapy administration, with a maximal intensity after 5–6 hours;^{17–20} b) DNV usually occurs 24 hours post-treatment and can persist for as long as 5–7 days, with maximal intensity occurring 48–72 hours after drug administration;^{17–19,21,22} and c) ANV is an expected or conditioned response that usually occurs prior to the actual administration of chemotherapy based on previous experiences of NV and expectations of experiencing NV in the context of chemotherapy administration.^{23–26} It may be triggered by factors such as tastes, odors, sights, thoughts, or anxiety associated with the treatment.^{27–32} ANV is usually more difficult to control than acute or delayed CINV. Also, there is no clear distinction for when acute CINV ends and DNV begins and thus, both are considered approximations. Further, these different forms and time intervals of CINV, ANV and DNV, indicate the existence of differences in pathological and physiological pathways involved.^{27,33–35}

The CINV process, triggered by chemotherapeutic agents, involves a complex network of neuroanatomical and peripheral centers, neurotransmitters, and receptors. The central and peripheral regions include a) the emetic or vomiting center (VC), which is the primary structure for coordinating nausea and vomiting and includes a collection of neurons within the medulla oblongata; b) the chemoreceptor trigger zone (CTZ) in the area postrema located at the floor of the fourth ventricle of the brain; c) the vagal nerve afferents that project from the gastrointestinal (GI) tract to the nucleus of the solitary tract (NTS) and the dorsal motor nucleus of the vagus (DMV); and d) the enterochromaffin cells (EC) in the GI tract (see Figure 1).^{33,36–38} The central nervous system plays a critical role in the pathophysiology of CINV, by receiving and processing a variety of emetic stimuli and then generating and sending efferent signals to a number of organs and tissues, which result in nausea and vomiting.¹³ Each individual may require a different degree of stimulation to the VC in order to reach the threshold of nausea or vomiting, thereby resulting in differing individual responses to the same stimuli.³⁹

Multiple neurotransmitters and their cognate receptors are involved in CINV, and these neurotransmitters/receptors operate via different signaling mechanisms. The three main neurotransmitters are serotonin (5-HT), substance P (SP), and dopamine.⁴⁰ The receptors associated with 5-HT and SP are 5-hydroxytryptamine (5-HT₃) and neurokinin-1 (NK-1),

respectively. 5-HT is the primary mediator of neural signals from the gut to the NTS, activating 5-HT₃ receptors in the gut and NTS. SP primarily transmits signals from the vagus nerve to NK-1 receptors in the CTZ. The role of dopamine is less clear but dopamine receptor antagonists are effective and likely have anti-dyspeptic effects.⁴¹ It is known that inhibition of some of these pathways results in a reduction in CIV and to a lesser extent CIN. This suggests that the induction of nausea and vomiting may not involve same pathways but, rather, different biological mediators in distinct pathways.

Chemotherapeutic agents are toxic to the ECs lining the GI mucosa causing the generation of free radicals which in turn cause ECs to release excessive amounts of serotonin.^{35,42} The released serotonin, at elevated levels, then binds to 5-HT₃ receptors present on the terminal side of vagal nerve afferents which lie in close proximity to ECs.^{43–45} The binding at the 5-HT₃ receptors conducts information regarding chemical stimuli to the brain, which may then either initiate emesis directly (acute CINV) or sensitize the vagus nerve to other substances (such as SP) released from ECs or generated by cell death, thereby, resulting in prolonged forms of nausea and vomiting (DNV).^{46,47} Findings from clinical studies have led to the hypothesis that in the presence of chemotherapy, 5-HT/5-HT₃ receptor signaling plays a major role in the mechanism of acute CINV but a lesser role for DNV.^{27,48–50}

The neurotransmitter SP is widely distributed in the central and peripheral nervous systems and is the preferred ligand for NK-1 receptors.⁵¹ These receptors are located in the gut, the area postrema, and the NTS regions.⁵² Like serotonin, SP release is mediated by chemotherapy but it appears to bind largely to NK-1 receptors that are centrally located (namely NTS) which then pass the signal via the vagal afferent nerves to the CTZ and then to the VC,^{53–55} thereby, mediating the induction of vomiting. It is likely that the centrally located signaling is most important for CINV.⁵⁶ Also, SP binding to NK-1 receptors in the gut may play an auxiliary role in nausea and vomiting.⁵³

Recent studies have suggested that there is receptor cross-talk between 5-HT₃ and NK-1 receptor signaling pathways.^{57,58} Receptor cross-talk is defined as the activation of one receptor by its ligand which then affects the cellular responses of another receptor system. Animal studies suggest that the cross-talk may allow synergistic action between 5-HT₃ and NK-1 receptor antagonists in controlling acute CINV and DNV^{59,60} and present the possibility of improved CINV treatment. However, the mechanistic details of the 5-HT₃/NK-1 receptor crosstalk have not been elucidated.^{57–59}

In addition, clinical trials involving the use of 5-HT₃ receptor antagonists and aprepitant (NK-1 receptor antagonist) have further confirmed the hypothesis that acute and delayed CINV having different pathophysiologies.³⁴ Accumulating evidence suggests that delayed CINV is largely associated with the activation of NK-1 receptors by SP.^{27,40,61} However, multiple overlapping neurotransmitters (e.g., dopamine), acting in the peripheral and central nervous systems, may also be involved in acute and delayed CINV.⁶²

Other pathways, besides 5-HT/5-HT₃ and SP/NK-1, are also involved in the induction of CINV but very little is known about the mechanism by which they regulate the emetic response. For instance, dopamine release may also play a role in triggering nausea and vomiting; dopamine receptor antagonists (e.g., promethazine, metoclopramide) have been shown to be effective in treating CINV,³⁵ although their mechanism of action is less clear. Additional research has also investigated agents that may affect gamma-aminobutyric acid (GABA) and histaminic and muscarinic receptors.⁶³ Better understanding of the role of these mediators and their CINV-related mechanisms may help in the development of additional effective antiemetic drugs.

III. Pathopsychology of CINV

In addition to the physiological factors reviewed above, psychological factors may affect both the frequency and severity of CINV. The specific subset of CINV, ANV, appears particularly linked to psychological processes. The three predominant factors related to acute and delayed CINV and ANV in specific are classical conditioning, which may lead to anticipatory nausea; demographic and treatment-related factors; and anxiety or negative expectancies, which may engender and increase sensitivity to nausea.

The National Cancer Institute has cited classical conditioning as the theoretical mechanism best able to explain the genesis of ANV.⁶⁴ In the classical conditioning of ANV, an unconditioned stimulus (chemotherapy) that naturally produces an unconditioned response (nausea) is paired with a conditioned stimulus. Potential conditioned stimuli in the context of ANV can include the sights and smells of the clinic, the nurses, the treatment room, etc. After repeated pairings of the unconditioned stimulus with this conditioned stimulus, exposure to the conditioned stimulus alone is sufficient to elicit the conditioned response (nausea).^{65–67} The cancer patient's nausea is anticipatory, as it may begin even before administration of the chemotherapeutic agent.

The conditioned nature of ANV is supported by the finding that rates and severity of ANV tend to increase after repeated chemotherapy cycles;⁶⁶ that is, repeated pairings of the unconditioned and conditioned stimuli. Due to the psychobehavioral underpinning of this symptom, behavioral interventions have proven particularly efficacious in treating ANV. Specifically, progressive muscle relaxation (PMR), either alone or in combination with systematic desensitization, has been shown to reduce patient reports of ANV.⁶⁸ In PMR, patients are trained to tense and then relax various groups of muscles in order to produce an overall relaxation response. This technique may be paired with systematic desensitization, wherein patients are exposed to conditioned stimuli and prompted to practice PMR, thus breaking the association between the conditioned stimulus and response. While these behavioral interventions have proven efficacious, it remains unclear how best to integrate such treatments into cancer centers, and whether other ancillary treatments such as psychopharmacological agents or acupuncture might also be beneficial in addressing ANV. Future research in ANV should include combined assessment of behavioral and pharmacological approaches to determine whether these may improve CIN and ANV.

Certain personal characteristics and events related to cancer treatment appear to increase the likelihood that a patient will experience ANV. Variables cited by the National Cancer Institute as being correlated with ANV are listed in Table 1. In addition to the emetogenic potential of the chemotherapeutic agent, an age under 50 and female gender are the most common indicators of CINV and ANV.^{64,67,69} Screening patients for these variables and for the cognitive/emotional factors below may help providers to identify patients likely to develop ANV. At present, there remains a need to develop a succinct and comprehensive screening process for risk factors related to ANV and to integrate such a process into cancer center treatment evaluations.

Two final psychological factors related to nausea and vomiting are patients' levels of anxiety and negative thoughts and expectation about the treatment. In the population at large, nausea can be characterized as a symptom of anxiety and anxiety disorders.⁷⁰ In cancer patients, high levels of anxiety are associated with experiencing ANV,¹⁹ likely both due to the emetogenic effect of anxiety itself and the increased sensitivity to somatic cues experienced by highly anxious individuals. Given the link between anxiety and ANV in cancer patients, use of benzodiazepines is indicated as an ancillary treatment to reduce rates of ANV.⁷¹ Several studies have indicated a link between pre-treatment expectancies about

nausea and rates of CINV.^{72,73} Perhaps unsurprisingly, those who report a greater expectancy of experiencing nausea and vomiting post-cancer treatment are more likely to experience CINV. These expectancies represent a potential target for intervention. At present, few studies have tested interventions aimed at cognitively restructuring negative expectancies related to cancer treatment as a means to reduce both anticipatory and post-treatment nausea.

IV. Antiemetics for CINV

Advances in 5HT₃ antagonists and NK-1 antagonists have dramatically improved control of CINV. Palonosetron and aprepitant, as the newer superior antiemetics, are now incorporated as standard of care. Palonosetron is superior to earlier 5HT₃ antagonists due predominately to a significantly longer half-life (approximately 40h, 10x longer than first generation antagonists). Palonosetron also has a very high binding affinity, a high selectivity to the 5HT₃ receptors (with little effect on other receptors); and an exceptional safety profile.⁷⁴ A single dose (0.25 mg IV) of palonosetron can prevent acute CINV resulting from moderately to highly emetogenic chemotherapy.^{8–10} Recent studies comparing palonosetron to ondansetron and granisetron suggest the superiority of palonosetron on all days, but particularly between 24 and 120 hours after chemotherapy. Complete response rates (i.e. no emetic responses and no rescue medication usage) range from 48% to 57% using 0.75 mg of palonosetron and only 39% to 45% when not using it.^{75–77} Saito and colleagues conducted a comparative effectiveness non-inferiority randomized clinical trial between palonosetron and granisetron for both acute and chronic CINV in 1019 patients. This study showed non-inferiority of palonosetron compared to a first generation 5HT₃ antagonist in the acute CINV (0–24 hours) and superiority of palonosetron in DNV (24hrs to 120h).⁷⁶ Therefore, current evidence supports the use of the second generation 5HT₃ receptor antagonist in the control of acute and delayed CINV over first generation 5HT₃ receptor antagonists (e.g., ondansetron, granisetron, dolasetron) for moderately emetogenic chemotherapy agents.⁷⁶

Aprepitant and fosaprepitant are potent, CNS-penetrant, selective NK-1 receptor antagonists of substance P, and are an essential component in triggering the emetic reflex, as mentioned above.⁷⁸ Aprepitant is a three day regimen, with a recommended dosing of 125 mg orally 1 hour prior to chemotherapy administration (Day 1) and 80 mg orally once daily in the morning on Days 2 and 3. Fosaprepitant is a pro-drug of aprepitant for injection (150 mg over 15 minutes) and can be substituted for aprepitant 30 minutes prior to chemotherapy on Day 1 only. Hesketh et al., in 2003, published a randomized, double blind, parallel-group, placebo-controlled trial of 530 patients receiving cisplatin (highly emetogenic) to receive the current standard therapy (ondansetron and dexamethasone on Day 1 and dexamethasone on Days 2–4 or the same regimen with aprepitant added on Days 1–3. The aprepitant group response was superior to the standard therapy group in acute and delayed phases as well as overall.⁷⁸ A second Phase III randomized study conducted by Poli-Bigelli and colleagues also revealed these same findings.⁷⁹ Subsequently, Herrstedt and colleagues conducted a prospective, randomized, double blind, parallel study of 866 patients receiving moderately emetogenic chemotherapy over multiple cycles demonstrated the efficacy of aprepitant in prevention of nausea and emesis over all four cycles of treatment.⁸⁰ Another randomized, placebo-controlled trial subsequently evaluated daily aprepitant (over 3 days) versus a single daily dose of aprepitant (Day 1 plus 2 days of placebo) for effect on acute and delayed CINV.⁸¹ All participants received palonosetron and dexamethasone on Days 1–4 in this study. The study demonstrated no statistically significance between groups, suggesting that one dose of aprepitant with a standard antiemetic regimen has similar effectiveness to a traditional three-day aprepitant regimen for CINV.⁸¹ The use of aprepitant may also provide an advantage because patients only have to take one dose on day 1 with moderately

emetogenic chemotherapy regimens.⁸² Fosaprepitant may offer an option for patients who cannot tolerate oral administration of antiemetics.⁸³

V. Phase II/III Clinical Trials of Novel Agents for CINV Control

Several drugs are currently in late stages of randomized clinical trial testing for CINV including netupitant, carbamazepine, gapapentin, and olanzapine. Netupitant is a selective NK-1 receptor antagonist with potential long-lasting antiemetic activity even with one dose. Netupitant competitively and strongly binds to and blocks the activity of NK-1 receptors in the central nervous system, thereby inhibiting NK-1-receptor binding of substance P, which results in the prevention or alleviation of CINV. Because of these characteristics, Netupitant may have superior effects on delayed CINV and better control nausea compared to aprepitant. This agent may also enhance the effects of other antiemetics when given in combination. NETU-08-18 is an ongoing randomized Phase III study assessing efficacy and safety of a single oral dose of netupitant and palonosetron (300 mg/0.50 mg respectively), versus oral palonosetron (0.50 mg), both given with oral dexamethasone ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01339260) Identifier: NCT01339260). Planned accrual in this study is 1460 patients receiving moderately emetogenic chemotherapy, and it will determine if netupitant and palonosetron combined are more effective (i.e. complete emetic response) than palonosetron alone. Another ongoing study, NETU-10-29 is a Phase III study of 400 patients (3:1 randomization) looking at the safety of netupitant and palonosetron, both given with oral dexamethasone, when compared to aprepitant and palonosetron among patients receiving highly and moderately emetogenic chemotherapy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01376297) Identifier: NCT01376297). This second study is not designed to address whether netupitant is superior to aprepitant in reducing nausea and vomiting but rather the adverse event profile after repeated chemotherapy cycles.

Carbamazepine is an anticonvulsant and mood-stabilizing drug used primarily in the treatment of epilepsy, bipolar disorder, and trigeminal neuralgia. It is also used off-label for other indications, including complex regional pain syndrome and phantom limb syndrome. Carbamazepine stabilizes the inactivated state of voltage-gated sodium channels, making fewer of these channels available to open and leaving affected cells less excitable. Carbamazepine has also been shown to potentiate GABA receptors. Based on case reports describing improvement in refractory nausea and vomiting with carbamazepine,⁸⁴ a small study is ongoing in Brazil that is evaluating the safety and efficacy of carbamazepine in preventing CINV among 43 participants ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01581918) Identifier: NCT 01581918). In this Phase II study, carbamazepine is given orally (200 mg) beginning three days before a moderately or highly emetogenic chemotherapy dose and continued for five days after chemotherapy infusion. The primary goal is to assess complete CINV response.

Gabapentin was first developed as an anticonvulsant but is now generally used for painful neuropathy, post-herpetic neuralgia, and migraines. Gabapentin is an analog of GABA but does not bind to GABA-A or GABA-B receptors. Its mechanism of action is thought to be associated with certain voltage-dependent calcium channels which control the release of excitatory neurotransmitters. Small studies initially demonstrated substantial improvement in CINV when gabapentin was added to an antiemetic regimen of ondansetron and dexamethasone for patients receiving chemotherapy.^{85,86} The promising preliminary results of these small studies led to a recently completed Phase III randomized clinical trial. The North Central Cancer Treatment Group (NCCTG), using a multi-center placebo-controlled study design, randomized patients to gabapentin or placebo on days 1–5 of each (highly emetogenic) chemotherapy cycle along with a 5-HT₃ receptor antagonist and dexamethasone ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00880191) Identifier: NCT 00880191). The use of gabapentin may exploit additional neurotransmitters associated with nausea and vomiting; results of this

study are forthcoming with the primary outcome assessing complete response (i.e., no emetic episodes and no rescue medication) up to five days following receipt of chemotherapy.

Recent studies using olanzapine, the antipsychotic, suggest that this agent may also be important in the control of CIN since it is known to affect a wide variety of receptors including dopamine, 5-HT, and histaminic and muscarinic receptors. Early Phase II studies^{87,88} supported a recently completed Phase III randomized clinical trial of olanzapine compared to aprepitant for CINV. Although both regimens were similar in complete responses (i.e., no emetic episodes and no rescue medication), this study demonstrated that olanzapine was superior for control of nausea over aprepitant.⁸⁹

VI. Clinical Guidelines

The American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the Multinational Association of Supportive Care in Cancer (MASCC)^{90–93} have developed recommendations to guide clinical practice in the treatment of CINV.^{94,95} Adherence to these guidelines improves control of CINV by approximately 20%.⁹⁶ Chemotherapy regimens are classified into four categories according to potential for CINV—highly emetogenic (>90%), moderately emetogenic (both with and without anthracycline and cyclophosphamide [AC]; 30–90%), low emetogenic (10–30%), and minimally emetogenic (<10%). Patient expectations (risk of ANV), time of onset (acute and delayed CINV), and resistance to antiemetic treatment (breakthrough and refractory CINV) are also important to consider when treating CINV. Cisplatin, carboplatin, cyclophosphamide, and doxorubicin-based regimens are moderate/highly emetogenic agents leading to CINV.⁹⁷ Depending on the chemotherapeutic agents and sequence of administration, patients can develop both acute and delayed CINV. Recommendations of which antiemetics to use differ by the emetogenic potential of these agents. Additionally, the steroid dexamethasone, while not an antiemetic, is an integral agent of CINV control. Breakthrough CINV occurs when prophylactic antiemetic treatment fails and “rescue” antiemetics are required which often include combinations of older 5HT₃ receptor antagonists, along with other agents (e.g. benzodiazepine, cannabinoids, and olanzapine). Refractory CINV occurs when antiemetic regimens have failed in prior chemotherapy treatment cycles. See Figure 2 for a summary of the recommended treatment guidelines for acute and delayed CINV according to ASCO, NCCN, and MASCC.

VII. Expert Opinion and Future Research

The introduction of 5-HT₃ and NK-1 antagonists and establishment of standard guidelines, as reviewed in this article, have considerably reduced the incidence of CINV. Despite advances in pharmaceutical therapies, and the provision of standard clinical guidelines for effectively managing CINV, patients continue to experience CINV. Moreover, control of nausea, acute and delayed, and ANV remains an important, unmet need among cancer patients.

In order to better control CINV, we must better understand the factors that make individuals susceptible. As a field, we have identified a number of psychological and physiological factors that may predict CINV (Table 1); however, this is an area that must be further developed. For example, we know very little about basic biological and genetic predictors that might inform one's susceptibility to CINV. Understanding what these additional biological, genetic, and clinical factors are may greatly enhance our ability to individualize treatment for CINV.

It is critical to focus attention on better understanding the mechanisms underlying nausea, anticipatory symptoms, and delayed symptoms. Perhaps this area of research has been hampered due to lack of animal models for nausea, unlike that for emesis. However, a number of behavioral interventions and herbal supplements (e.g. PMR, acupuncture, exercise, ginger, and imagery) have shown promise in reducing the severity and duration of CINV, particularly ANV and delayed symptoms. Understanding the psychological and biological mechanisms by which these interventions improve CIN and ANV will further our understanding of the key components to nausea.

Future clinical trials assessing pharmaceutical agents should compare rational combinations of antiemetic drugs to continue to establish the ideal regimen. These studies need to further compare antiemetic doses, timing of administration, and various combinations of drugs to maximize beneficial effects. In addition to pharmacological control of CINV, further research should also investigate behavioral interventions and herbal supplements in combination with successful pharmacological interventions. Additional research findings will continue to improve control of anticipatory, and acute and delayed CINV above and beyond what is achieved by the current clinical guidelines. The ultimate goal of CINV research is to obtain complete control of all aspects of CINV so that chemotherapy can be better tolerated allowing for patients to receive their entire prescribed course of treatment without modification. Tailoring CINV treatments to the patient based on individual risk factors will greatly enhance the potential of antiemetics and behavioral approaches to eliminate CINV.

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Highlights

- Comprehensive review of physiological and psychological factors contributing to CINV
- Review of currently approved antiemetic agents
- Review of antiemetic agents in Phase II/III Trials
- Overview of clinical guidelines for CINV
- Expert Opinion focused on better treatment for nausea and individualized medicine to improve overall CINV

Figure 1. Emetic Pathways

Cytotoxic chemotherapies can damage the gastrointestinal (GI) tract and cause the Enterochromaffin cells (EC), distributed throughout the GI lining, to release neural signals via neurotransmitter release. These neurotransmitters activate the vagal afferents, by binding to the receptors, which then conduct the stimuli to the dorsal vagal complex consisting of emetic/vomiting center (VC), the area postrema (CTZ) and the nucleus tractus solitarius (NTS). These sensory inputs are then integrated resulting in the activation of the emetic response.

A. ACUTE NAUSEA AND VOMITING	
Emetic Risk	Antiemetics Recommended
High	5HT3 + DEX + APR
Moderate - AC	5HT3 + DEX + APR
Moderate - Other	PALO + DEX
Low	DEX or 5HT3 or DRA
Minimal	No routine prophylaxis
B. DELAYED NAUSEA AND VOMITING	
Emetic Risk	Antiemetics Recommended
High	DEX + APR
Moderate - AC	APR
Moderate - Other	DEX
Low	No routine prophylaxis
Minimal	No routine prophylaxis

5HT3 = serotonin receptor antagonist

DEX = dexamethasone

APR = aprepitant

PALO = palonosetron

DRA = dopamine receptor antagonist

Figure 2. Summary of Current Clinical Guidelines

Table 1

Demographic and treatment related factors correlated with ANV

1	Age younger than 50 years
2	Female gender
3	Susceptibility to motion sickness
4	Greater reactivity of the autonomic nervous system and slower reaction time
5	Morning sickness during pregnancy
6	Nausea and vomiting after last chemotherapy session
7	Feeling warm or hot all over after last chemotherapy session
8	Sweating after last chemotherapy session
9	Generalized weakness after last chemotherapy session
10	Percentage infusions of chemotherapy followed by nausea
11	Dizziness after last chemotherapy session
12	Lightheadedness.
13	Longer latency of posttreatment nausea and vomiting
14	Emetogenic potential of chemotherapeutic agents used