Chemotherapy-Induced Nausea and Vomiting: Identifying and Addressing Unmet Needs

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ABSTRACT

Objective: To review current issues in chemotherapy-induced nausea and vomiting (CINV) management and consider practical options to optimize antiemetic use and improve outcomes.

Methods: Practical review of current evidence and examination of management strategies.

Results: Management of CINV is primarily guided by evidence-based recommendations from the American Society of Clinical Oncology (ASCO), the Multinational Association of Supportive Care in Cancer (MASCC), and the National Comprehensive Cancer Network (NCCN), which recommend selection of antiemetics based on the emetogenicity of the chemotherapy regimen. 5-HT₃ antagonists, often heralded as one of the most significant advances in the treatment of CINV, and newer NK-1 antagonists play a predominant role for moderately and highly emetogenic chemotherapy. However, limited adherence to guidelines is a concern. Strategies to improve outcomes therefore initially focus on ensuring optimal selection and use of antiemetic agents. Beyond antiemetic selection, more sophisticated approaches can be proposed to improve outcomes across the breadth of supportive care by involving multidisciplinary expertise in integrated care strategies.

Conclusion: Despite significant advances with antiemetics, CINV remains an important problem for many cancer patients. Developing integrated approaches to improve the care of at-risk patients represents a crucial step towards improving outcomes.

Nausea and vomiting have long been acknowledged to be among the most feared and distressing side effects of chemotherapy. Chemotherapy-induced nausea and vomiting (CINV) can have significant effects on both quality of life and physical functioning [1,2]; in severe cases, CINV can lead to serious complications or a clinical decision to delay, reduce, or even stop chemotherapy [1–4]. As a consequence, control of CINV is a high priority for improving clinical outcomes in patients with cancer.

Antiemetic prophylaxis has been improving continuously over the past decades; at the same time, chemotherapy agents have themselves changed, affecting the side effect profile that patients experience. The introduction of 5-HT₃ antagonists in the 1990s represents one of the most significant advances in the treatment of CINV to date [5], followed by more recent developments with NK-1 receptor antagonists and evidence-based treatment strategies.

Nevertheless, there remain considerable unmet needs in CINV. Crucially, observational studies indicate that around one-third to one-half of patients at risk experience CINV despite prophylaxis, with concomitant detrimental effects on quality of life [6–9]. This article reviews the current evidence and treatment options for CINV and considers integrated strategies to improve outcomes for patients.

OVERVIEW OF CINV

Incidence and Impact

The overall incidence of CINV is challenging to estimate, as risks vary greatly depending on the emetogenicity of chemotherapy and a number of risk factors. Nevertheless, it is generally accepted that without appropriate prophylaxis, 70% to 80% of all cancer patients receiving chemotherapy experience nausea and/or vomiting [10]. Even with prophylaxis, observational studies indicate that as many as half of patients may experience uncontrolled nausea or vomiting [6–9]; for example, Grunberg et al reported that greater than 35% of patients experienced nausea within 24 hours of chemotherapy, with 54% experiencing nausea and 32% experiencing vomiting in the following 4 days [7].

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While improvements in antiemetic therapy have enabled improvements in quality of life for patients undergoing emetogenic chemotherapy, unmet needs remain [11]. The burden that uncontrolled CINV places on patients and their families and carers can be substantial, impacting both physical well-being and quality of life. The direct physiological effects of nausea and vomiting include metabolic imbalances (hypokalemia, hyponatremia, hypochloremic alkalosis), degeneration of functional ability and performance status, nutrient depletion, anorexia, and esophageal tears [1,2]. Moreover, if the symptoms of severe emesis are not recognized and treated, a number of potentially serious complications could arise. These may include dehydration, weight loss, metabolic disorders, dental erosion, wound dehiscence, and aspiration pneumonia [1,2].

Beyond its direct physiological effects, CINV can affect diverse aspects of patients’ quality of life, such as daily functioning, leisure activities, and the enjoyment of food and drink [6,9]. Interestingly, there is some evidence to suggest that nausea often has a greater impact on quality of life than vomiting in patients receiving chemotherapy [6].

Moreover, consideration should be given to the knock-on effects of CINV. Haiderali et al estimated the total costs associated with CINV at $779 per patient following the first chemotherapy cycle, with more severe CINV attracting higher costs [8]. Perhaps more worrisome, severe CINV may lead to a clinical decision to delay, reduce, or even stop chemotherapy [2,4,12]. Although continued chemotherapy can substantially improve life expectancy and quality of life, many patients fear that side effects will reduce their overall quality of life, particularly during the palliative care phase [13]; discontinuation of chemotherapy may therefore be a particular challenge in the palliative stages of treatment.

**Classification**

CINV is typically classified based on the timing (or phase) of the nausea and/or vomiting in relation to chemotherapy. Anticipatory nausea and vomiting occurs prior to administration, and is thought to be a conditioned response to a negative chemotherapy experience, occurring in up to 20% of patients by the fourth treatment cycle [14,15]. Anticipatory nausea and vomiting is difficult to treat once developed [14]. Therefore, current guidelines emphasize the importance of effectively preventing acute or delayed CINV (the negative experience) from the first time chemotherapy is administered, thereby avoiding the subsequent development of a conditioned response. However, if anticipatory nausea does occur, behavioral therapy with systematic desensitization is the primary treatment recommended [16].

Acute CINV typically occurs within 24 hours after chemotherapy administration, while delayed CINV usually develops 24 to 120 hours after administration [2,17]. Delayed CINV has a higher incidence than acute CINV and also has a pronounced impact on patient quality of life [6,8,9,12]. Evidence suggests, however, that delayed CINV is underreported by patients, and its incidence is underestimated by most oncology physicians and nurses [7]; while uncontrolled acute CINV is correlated with escalation of antiemetic treatment, the same cannot be said for delayed CINV [9].

Chemotherapy agents and regimens are classified based on the risk of nausea and vomiting they carry. Such classification of emetogenicity provides a valuable framework for guiding antiemetic treatment decisions in practice [14]. In the mid-1990s, Hesketh and colleagues developed a classification scheme in which individual chemotherapy agents were assigned to 1 of 5 emetogenic levels [18]. An algorithm was then devised to determine the emetogenicity of multiple-agent regimens by identifying the most emetogenic agent in the combination and assessing the relative contribution of the other agents [18]. More recently, a 4-level classification for single antineoplastic agents has been agreed by the major expert bodies in cancer care, with new agents being added as they are developed (Table 1) [2,14,16]. Low, moderate and high emetogenic risk chemotherapy are commonly abbreviated as LEC, MEC and HEC, respectively.

The above classifications are primarily applicable to single-day chemotherapy cycles. However, the assessment of emetogenicity has become complicated by the increasing use of multi-day chemotherapy regimens—in part triggered by a rise in the use of oral chemotherapy agents, which tend to be used in extended regimens [14]. Antiemetic treatment decisions for multi-day regimens are complicated by the overlap of acute and delayed emesis after the first day of chemotherapy [2]. In addition, some agents only become consistently emetogenic after a week or more of continuous administration [14]. This area is relatively underrepresented in the literature and, crucially, the established emetogenicity scales have not been validated against multi-day regimens. A practical method for assessing the emetogenic risk of multi-day regimens was proposed as part of a recent evaluation of multi-day antiemetic therapy [19]. This study adopted...
an emetogenicity classification for 3- to 5-day chemotherapy regimens based on a modification of the Hesketh scale [19]. Although not formally validated, this approach offers a pragmatic option for use in routine practice.

**Risk Factors**

Beyond the inherent emetogenic risk of each chemotherapy regimen, a number of factors affect the risk of CINV in individual patients. In particular, women have an elevated risk of experiencing CINV as do younger patients and those who don’t drink much alcohol. A history of morning sickness or previous CINV can also increase a patient’s individual risk of CINV [2,5,14]. These risk factors are well established, and there have been relatively few further studies in recent years. Leading treatment guidelines recommend that the choice of antiemetic prophylaxis is primarily guided by the emetogenicity of the chemotherapy regimen, rather than patient-related risk factors [5]. However, some guidelines recommend that these factors should be taken into account in individual treatment decisions [2,20], although more research is necessary to establish the effect of such an approach on overall treatment outcomes [5].

**PROPHYLAXIS AND TREATMENT OPTIONS**

**Neurophysiology**

Evidence accumulating in recent years has shown that the activation of neurotransmitters via peripheral and central pathways highly influences the development of CINV [21]. As a result, treatment of CINV focuses on the modulation of neurotransmitter and receptor systems [21]. While numerous neurotransmitters may contribute to the vomiting response, two of the most clinically important are 5-HT and substance P. The activation of these influences the development of CINV at different phases (acute and delayed, respectively) and may therefore be used to guide treatment decisions or influence drug selection (Table 2) [3].

**Historical Perspectives**

Antiemetic prophylaxis has been improving continuously over the past decades. In the past, patients receiving cisplatin would frequently be admitted and heavily sedated with lorazepam; in contrast, with modern antiemetics and a shift towards less highly emetogenic chemotherapies (eg, carboplatin rather than cisplatin), many fewer patients require admission and antiemetic outcomes have improved dramatically.

Corticosteroids were first found to have antiemetic properties more than 30 years ago [22]. As research gradually revealed more about the mechanisms and signaling systems involved in CINV, a growing number of therapeutic targets were identified. An initial focus on the dopamine system pointed to the use of phenothiazines and butyrophenones.

Subsequently, studies of the 5-HT
3 receptor in particular proved to be a key advance, and the introduction of 5-HT
3 antagonists in the 1990s is often heralded as one of the most significant advances in the treatment of CINV [5]. The emergence of the NK-1 receptor antagonist aprepitant in 2003, followed by development of novel delivery mechanisms and combination regimens for 5-HT
3 antagonists, represent key recent developments in this field.

**Agents and Evidence**

Given the involvement of several neural systems in the pathophysiology of CINV, it is logical to consider target-
ing any or all of these systems for prevention of nausea and vomiting. Consequently, a wide array of antiemetic agents from several different classes are in common use (Table 3).

Consistent with the unmet needs in this area, CINV remains an active subject of research. There is a plethora of published and ongoing studies examining the efficacy of the key agents, and numerous comprehensive reviews are available [3,10,23]. Treatment guidelines (see below) are based on thorough and up-to-date systematic reviews and so provide an ideal starting point for understanding the evidence in this area. Moreover, a 2010 Cochrane review examined the comparative evidence between 5-HT₃ antagonists for highly emetogenic chemotherapy, reviewing 16 randomized controlled trials involving a total of 7808 participants [24]. The authors found little evidence for efficacy differences between first-generation 5-HT₃ antagonists. Interestingly, the authors highlighted the results of a head-to-head comparison between palonosetron and oral granisetron, which suggested that the second-generation agent shows superior efficacy in the delayed phase [24]. Further Cochrane reviews focusing on NK-1 antagonists and cannabinoids are currently in progress [25,26], and the results are awaited with interest.

Beyond specific agents, consideration may be given to alternative delivery formulations. More drugs are becoming available in forms other than IV, including more oral forms and a broadening array of transmucosal and transdermal delivery methods. In the case of antiemetics, the growing choice of delivery options offers improved flexibility to meet the needs of each individual patient. For example, the transdermal formulation of granisetron adds an extra option for sustaining therapeu-

tic drug levels over many days in patients receiving multi-day chemotherapy, and as an alternative to IV therapy for patients unable to swallow [2,19].

**Guidelines**

Current treatment approaches to CINV are predominantly guided by recommendations from the American Society of Clinical Oncology (ASCO), the Multinational Association of Supportive Care in Cancer (MASCC), and the National Comprehensive Cancer Network (NCCN) [2,14,16], providing robust and evidence-based guidance drawn from systematic reviews and expert consensus. The recommendations advocate approaching CINV based primarily on the emetogenic risk of chemotherapy. For MEC and HEC regimens, 5-HT₃ antagonists and NK-1 antagonists represent the core treatments, while other agents such as phenothiazines, metoclopramide, cannabinoids and steroids offer effective options for LEC and as adjuncts in more emetogenic regimens [2,14,16].

Research has shown that following treatment guidelines results in significantly improved emetic control, compared to antiemetic regimens inconsistent with guidelines: approximately 60% of patients experienced complete control of CINV when following guidelines, compared to 50% of those patients using other regimens ($P = 0.008$) [27]. However, there are numerous anecdotal concerns about both the awareness and implementation of these guidelines by clinical staff [4,23]. If this is indeed the case—that there is a lag in understanding or use of the latest agents and protocols—this could potentially lead to inequalities of care and suboptimal treatment outcomes, and hence provide some explanation of the lingering unmet need.

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**Table 2. Roles of 5-HT and Substance P in CINV**

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Role in CINV</th>
<th>Phase of CINV Affected</th>
</tr>
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<tbody>
<tr>
<td>5-HT</td>
<td>5-HT (serotonin) is released from enterocromaffin cells following gastrointestinal damage</td>
<td>Acute phase</td>
</tr>
<tr>
<td></td>
<td>5-HT activates the peripheral pathway and binds to 5-HT₃ receptors on the vagus nerve of the GI tract, stimulating emesis</td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td>Release of substance P (present in large amounts in the CTZ and area postrema of the brain) causes activation of the central pathway</td>
<td>Delayed phase</td>
</tr>
<tr>
<td></td>
<td>Substance P binds to NK-1 receptors in the brain and induces vomiting</td>
<td></td>
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</tbody>
</table>

CTZ = chemoreceptor trigger zone. Content from references 3 and 30.
Despite the availability of a wide range of effective treatment options, CINV remains an important clinical problem. Given that a variety of effective antiemetics with different modes of action are available, the emphasis must be on the appropriate use of these drugs. First and foremost, this means appropriate selection of agents. Nonetheless, following published guidance does not represent a panacea, as evidence indicates that nausea and vomiting remains problematic in some patients, even when guidelines are being followed [28]. Consequently, more sophisticated strategies are needed.

### Table 3. Agents Used for Prophylaxis and Treatment of CINV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>Glucocorticoids</strong></td>
<td></td>
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<tr>
<td>Dexamethasone</td>
<td>Oral, IV</td>
<td>May be used alone for LEC regimens; most commonly used in combination regimens for MEC and HEC, where it increases the complete response rate by approximately 15–20% [31]</td>
</tr>
<tr>
<td><strong>First-generation 5-HT&lt;sub&gt;3&lt;/sub&gt; antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolasetron</td>
<td>Oral, IV</td>
<td>IV formulation no longer indicated for CINV due to risk of torsade de pointes; risk lower with oral formulation, but caution is needed [32]</td>
</tr>
<tr>
<td>Granisetron</td>
<td>Oral, IV, transdermal</td>
<td>Transdermal formulation offers alternative for patients who cannot swallow [19]</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Oral, IV, oro-dispersible</td>
<td>Oro-dispersible formulation may be helpful for patients with dysphagia or anorexia; risk of QT prolongation [33]</td>
</tr>
<tr>
<td><strong>Second-generation 5-HT&lt;sub&gt;3&lt;/sub&gt; antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palonosetron</td>
<td>Oral, IV</td>
<td>High affinity for 5-HT&lt;sub&gt;3&lt;/sub&gt; receptor and 40 hour half-life [2]; superior to other 5-HT&lt;sub&gt;3&lt;/sub&gt; antagonists for MEC and HEC [24]</td>
</tr>
<tr>
<td>Ramosetron</td>
<td>Oral, IV</td>
<td>Similar efficacy to granisetron with longer duration of action (half-life 5.78 ± 1.18 hours) [34]</td>
</tr>
<tr>
<td><strong>Cannabinoids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronabinol</td>
<td>Oral</td>
<td>May be useful adjunctive therapy in refractory CINV; clinical utility may be limited by side effects [10]</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Oral</td>
<td>Semi-synthetic cannabinoid; no clear advantage over dronabinol [35]</td>
</tr>
<tr>
<td><strong>NK-1 receptor antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aprepitant</td>
<td>Oral</td>
<td>Administered in combination with 5-HT&lt;sub&gt;3&lt;/sub&gt; antagonists and dexamethasone to prevent both acute and delayed cisplatin-induced emesis [2]</td>
</tr>
<tr>
<td>Fosaprepitant</td>
<td>IV</td>
<td>Single-day IV regimen bioequivalent to the 3-day aprepitant (oral) regimen [36]</td>
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<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Oral</td>
<td>NCCN guidelines: not recommended as single agent but a useful adjunct to reduce anxiety [2]</td>
</tr>
<tr>
<td><strong>Dopamine receptor antagonists and phenothiazines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Oral, solution, IV</td>
<td>Typically used for LEC, as adjunct in MEC and HEC, and for breakthrough nausea and vomiting; patients should be monitored for dystonic reactions [2]</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>Oral, IV, suppository</td>
<td>Typically used for LEC, as adjunct in MEC and HEC, and for breakthrough nausea and vomiting; patients should be monitored for dystonic reactions [2]</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Oral, syrup, suppository, IV</td>
<td>Typically used for LEC, as adjunct in MEC and HEC, and for breakthrough nausea and vomiting [2]</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Oral</td>
<td>Evidence for efficacy when given in combination with dexamethasone and palonosetron [37]</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Oral</td>
<td>Addition to ondansetron + dexamethasone regimen significantly increases complete response in patients receiving MEC or HEC [38]</td>
</tr>
</tbody>
</table>

HEC = highly emetogenic chemotherapy; LEC = low emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy.

### IMPROVING OUTCOMES: TOWARDS INTEGRATED STRATEGIES

Despite the availability of a wide range of effective treatment options, CINV remains an important clinical problem. Given that a variety of effective antiemetics with different modes of action are available, the emphasis must be on the appropriate use of these drugs. First and foremost, this means appropriate selection of agents. Nonetheless, following published guidance does not represent a panacea, as evidence indicates that nausea and vomiting remains problematic in some patients, even when guidelines are being followed [28]. Consequently, more sophisticated strategies are needed.
With the increased availability and use of non-IV formulations of antiemetics, consideration may be given to whether patients are taking their medication correctly, and whether an alternative formulation may better meet their needs. Taking the patient perspective further, we can look for opportunities to encourage patient involvement in the treatment process. One such opportunity is with adjunctive antiemetics. Providing patients with supplemental antiemetics, along with careful education on how to use them, puts the patient in control and allows them to make the most of opportunities to improve symptom control. This strategy must include a strong educational aspect to ensure the adjuncs are used safely and effectively.

In fact, the broader benefits of patient education in this field could be substantial. This process will naturally begin with the treating physician but also opens up an important role for nurses and pharmacists. Oncology nurses and mid-level nurse practitioners are well placed to discuss diverse aspects of symptom and outcome management with patients, so expanding the educational side of this role could deliver important benefits in CINV control.

In addition to patient education, oncology nurses and oncology nurse practitioners are also ideally positioned to play a triage role for CINV. As established above, many cases of uncontrolled nausea and vomiting go unreported, particularly in the delayed phase. Hilarius and colleagues have suggested that clinic- and home-based symptom monitoring via recording emetic episodes and nausea assessments in a daily diary could help healthcare professionals monitor delayed CINV [9]. Other methods of monitoring, such as follow-up phone calls, may help to increase the accuracy of symptom records between clinic appointments [29]. By actively discussing and monitoring CINV and acting as an accessible contact for chemotherapy patients, oncology nurses and nurse practitioners may be able to increase the visibility of emerging issues for the treating physician and thereby assist in optimizing therapy.

Such expanding roles for nurses and nurse practitioners working alongside the oncologist throughout the treatment process highlight the potential for an integrated team approach to CINV, drawing on multiple disciplines in a holistic strategy to target supportive care. Such a “supportive care team” could incorporate oncologists and nursing staff alongside pharmacists, dietitians, social workers, and several other disciplines. Indeed, the team could almost incorporate any number of participants, depending on the needs of the patient and the resources available in a given setting. In this way, the team could work to address issues across the breadth of supportive care, and be individualized to the needs of each patient. Priority issues such as CINV can then receive the attention needed to ensure optimized patient outcomes, within a structure designed to understand and manage patients’ needs.

**CONCLUSION**

Despite dramatic improvements over recent decades, CINV remains a key challenge in caring for cancer patients, and control remains suboptimal. With a wide range of effective agents available, attention must shift to strategies that ensure optimal use of these agents. Evidence-based guidelines have been demonstrated to improve outcomes, yet concerns remain that these guidelines are not fully adopted.

Integrated approaches to supportive care and CINV represent promising options for improving chemotherapy outcomes. Building cross-disciplinary expertise in a supportive care team is one such approach. A simple, accessible system spanning the full breadth of supportive care offers an opportunity to individualize care to the needs of the patient, within the constraints of each care setting. For CINV, such teams would improve the visibility of uncontrolled nausea and vomiting while emphasizing and facilitating optimized, evidence-based use of antiemetics.

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