Nausea and vomiting are among the top 4 most feared side effects of chemotherapy. They commonly occur together; however, nausea, a subjective symptom, probably occurs more frequently than vomiting. Chemotherapy-induced nausea and vomiting (CINV) can be extremely debilitating and adversely affect the quality of life of the patient.

**Mechanisms of CINV**

There are several pathways through which chemotherapeutic agents may stimulate nausea and vomiting. Central and peripheral neurologic pathways are capable of stimulating the emetic center. The chemoreceptor trigger zone (CTZ) is located on the floor of the fourth ventricle of the cerebellum. Chemotherapeutic agents and their metabolites stimulate the CTZ, which in turn stimulates the vomiting center. The vomiting center is stimulated by a number of neurotransmitters (Table 1). The peripheral pathway is mediated by the vagal and splanchnic afferent nerve fibers. Chemotherapy can damage the mucosa of the small intestine and subsequent release of serotonin from the enteral chromaffin cells. The vagal and greater splanchnic nerve fibers are then stimulated, which leads to the stimulation of the vomiting center and CTZ.

Another receptor important in the regulation of the vomiting reflex is substance P. Substance P is an 11-amino acid neuropeptide that is located primarily in the gastrointestinal tract and central nervous system. Biologic effects of substance P are exerted when the substance binds to the tachykinin neurokinin receptor.

**Potential for Causing CINV**

Some antineoplastic medications are more likely to cause nausea and vomiting than others. Chemotherapeutic agents are divided into 5 levels based on their likelihood of causing nausea and vomiting when no antiemetic agent is used (Table 2). The dosing and schedule of the antineoplastic agents are also important. An agent with a low emetogenic potential given in high doses may have the potential to dramatically increase nausea and vomiting. Antineoplastic drugs are commonly used in combination—this is another factor to consider when evaluating the emetogenic potential of these agents. The emetogenic potential of all the antineoplastic drugs combined and the individual drug doses used need to be considered when selecting the antiemetics to be used in any given patient.

- Level 1 agents are associated with the lowest frequency of nausea and vomiting. Examples of agents in this level include hydroxyurea, low-dose methotrexate, and vinblastine.
- Level 2 agents are associated with a low frequency of nausea and vomiting and include etoposide, 5-fluorouracil, moderate-dose methotrexate, and paclitaxel.
- Level 3 agents are associated with moderate frequency of nausea and vomiting and include cyclophosphamide, doxorubicin, idarubicin, and moderate-to-high dose methotrexate.
- Level 4 agents are associated with high frequency of nausea and vomiting and include cyclophosphamide, doxorubicin, idarubicin, and moderate-to-high dose methotrexate.
- Level 5 agents are associated with the highest frequency of nausea and vomiting and include cisplatin, high-dose cyclophosphamide, dacarbazine, mechlorethamine, and streptozocin.

**Pharmacologic Antiemetic Treatment**

Neurochemical control of vomiting is the basis for pharmacologic antiemetic treatment. Several different
classes of antiemetic agents are used in the management of CINV, some of which are approved by the US Food and Drug Administration (FDA) for this indication, as outlined in Table 3.7,9

DOPAMINERGIC ANTAGONISTS

Dopaminergic antagonists exert their antiemetic activity via dopaminergic receptors at the CTZ, other central nervous system centers, and peripherally.7

Phenothiazines. Phenothiazines are generally used with Level 2 antineoplastic agents and are valuable in treating delayed nausea and vomiting.6 Chlorpromazine is associated with greater sedation and anticholinergic effects, whereas prochlorperazine and perphenazine are associated with less sedation and greater incidence of extrapyramidal reactions.7

Substituted Benzamides. Prior to the development of 5-HT3 receptor antagonists (which will be discussed in the following section), metoclopramide was considered the most effective single antiemetic agent against highly emetogenic agents, such as cisplatin.7 Metoclopramide is associated with akathisia and dystonic extrapyramidal effects. Dystonia is more common in patients younger than 30 years of age, and akathisia is more common in patients older than 30 years of age. The antihistamine diphenhydramine is commonly used prophylactically or as treatment to antagonize extrapyramidal reactions, such as cogwheeling rigidity and acute dystonia and tremor. Akathisia is best treated by lowering the dose of metoclopramide, switching to a lower potency antiemetic if possible, or adding a benzodiazepine.

Butyrophenones. Although these agents are not indicated for CINV by the FDA, these neuroleptic agents are used as antiemetics in clinical practice.7,10 Both droperidol and haloperidol are associated with extrapyramidal reactions, akathisia, hypotension, and sedation. Diphenhydramine is commonly given to antagonize the extrapyramidal reactions. The droperidol labeling carries a warning of QT prolongation or torsade de pointes.

5-HT3 ANTAGONISTS

The 5-HT3 antagonist antiemetic agents work through antagonism of serotonin 5-HT3 receptors in the gastrointestinal tract, CTZ, and other central nervous system structures.7 These agents are commonly combined with corticosteroids and are the antiemetics of choice for Level 3, 4, and 5 antineoplastic agents.4 No significant differences in response rates have been demonstrated among the available agents (dolasetron, granisetron, and ondansetron), and their side-effect profiles appear to be similar. Palonosetron is a new 5-HT3 antagonist that was recently approved for acute and delayed CINV.11 Two additional agents in this class are under investigation for use in the United States: batanopride and tropisetron.12,13

SUBSTANCE P ANTAGONISTS

Substance P antagonists represent a relatively new class of antiemetic therapy. Aprepitant has been approved for use with other antiemetics for acute and delayed CINV due to highly emetogenic chemotherapy (including cisplatin regimens) and in clinical studies, was combined with dexamethasone on days 1 through 4 and with ondansetron on day 1.9 However, aprepitant has not been evaluated for the treatment of established CINV. Because aprepitant is
a CYP3A4 inhibitor, a potential drug interaction exists between aprepitant and agents that are primarily metabolized by the CYP3A4 system. Some agents are specifically contraindicated (pimozide, terfenadine, astemizole, cisapride). Caution is advised against the use of aprepitant and some chemotherapeutic agents metabolized via CYP3A4. In clinical studies, aprepitant was commonly used with etoposide, vinorelbine, or paclitaxel with no dose adjustment. However, only a small number of patients received docetaxel, vinblastine, vincristine, or ifosfamide with aprepitant. Therefore, particular caution is required when these agents are used in combination.

**Corticosteroids**

Corticosteroids are commonly combined with 5-HT\textsubscript{3} antagonists for the treatment of CINV induced by Level 3, 4, and 5 agents and are sometimes used as monotherapy for Level 2 and 3 agents.\textsuperscript{4} Steroids have been found to decrease or eliminate episodes of nausea and vomiting and may also improve a patient’s mood, producing a subjective sense of well-being or euphoria.\textsuperscript{7} However, steroids may also cause depression and anxiety in some patients. When combined with high-dose metoclopramide, steroids help to control the frequency of adverse events, such as diarrhea. Clinical studies have demonstrated that dexamethasone potentiates the antiemetic properties of 5-HT\textsubscript{3} antagonists. Some side effects are associated with significant morbidity; thus, long-term use of corticosteroids is not appropriate.

**Cannabinoids**

Dronabinol has demonstrated efficacy and safety in the management of CINV and is indicated in patients who have failed previous antiemetic therapy.\textsuperscript{8}

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### Table 3. Antiemetic Agents Used in the Management of Chemotherapy-Induced Nausea and Vomiting

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Example</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenothiazines</td>
<td>Dopaminergic antagonist</td>
<td>Prochlorperazine 10 mg (PO) to 25 mg (PR)</td>
<td>Drowsiness, Extrapyramidal reactions, Anticholinergic effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metoclopramide 1 to 3 mg/kg (PO or IV) every 3 hours for 3 to 5 doses</td>
<td>Extrapyramidal reactions, drowsiness, fatigue, diarrhea</td>
</tr>
<tr>
<td></td>
<td>Dopaminergic antagonist, weak 5-HT\textsubscript{3} receptor antagonist, enhances rate of gastric emptying</td>
<td>Droperidol 0.5 to 2 mg (IV, IM) every 3 to 4 hours (breakthrough) or prior to chemotherapy (acute)</td>
<td>QT prolongation or torsade de pointes, extrapyramidal reactions, drowsiness, dysphoria</td>
</tr>
<tr>
<td>Substituted benzamides</td>
<td></td>
<td>Dolasetron 100 mg (PO, IV)</td>
<td>PR and QTc prolongation, QRS widening, diarrhea, constipation, headache</td>
</tr>
<tr>
<td>Butyrophenones\textsuperscript{*}</td>
<td>Dopaminergic antagonist</td>
<td>Aprepitant 125 mg (PO) on day 1, 80 mg (PO) on days 2 and 3</td>
<td>Asthenia/fatigue, dizziness, diarrhea, hiccups, CYP3A4 inhibition in various products</td>
</tr>
<tr>
<td>5-HT\textsubscript{3} antagonists</td>
<td>5-HT\textsubscript{3} receptor antagonist</td>
<td>Dexamethasone 8 to 40 mg (PO, IM, IV)</td>
<td>Adrenal suppression, immunosuppression, hyperglycemia, psychosis, weight gain</td>
</tr>
<tr>
<td>Substance P antagonists</td>
<td>NK\textsubscript{1} receptor antagonists</td>
<td>Aprepitant 125 mg (PO) on day 1, 80 mg (PO) on days 2 and 3</td>
<td>Adrenal suppression, immunosuppression, hyperglycemia, psychosis, weight gain</td>
</tr>
<tr>
<td>Corticosteroids\textsuperscript{*}</td>
<td>Not fully understood</td>
<td>Dexamethasone 8 to 40 mg (PO, IM, IV)</td>
<td>PR and QTc prolongation, QRS widening, diarrhea, constipation, headache</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Complex effects on CNS with central sympathomimetic activity</td>
<td>Dronabinol 5 mg/m\textsuperscript{2} up to 15 mg/m\textsuperscript{2} 1-3 hours prior to chemotherapy and 2-4 hours after chemotherapy for a total of 4 to 6 doses/day</td>
<td>Dose-related ‘high,’ palpitations/tachycardia, sedation, dizziness/lightheadedness, weight gain</td>
</tr>
<tr>
<td>Benzodiazepines\textsuperscript{*}</td>
<td>Anxiolytic sedative</td>
<td>Lorazepam 0.5 to 2 mg (PO, IV, IM, SL) every 6 to 12 hours</td>
<td>Anterograde amnesia, ataxia, confusion, perceptual disturbances, psychological dependence, sedation</td>
</tr>
</tbody>
</table>

PO = by mouth; PR = rectally; IV = intravenously; IM = intramuscular; CNS = central nervous system; SL = sublingual.

\textsuperscript{*} Not approved by the US Food and Drug Administration for chemotherapy-induced nausea and vomiting.

\textsuperscript{†} Tolerance to subjective side effects generally occurs with chronic administration.

Data from National Cancer Institute Web site; Marinol\textsuperscript{®} [package insert]; Emend\textsuperscript{®} [package insert].
Dronabinol is available as an oral capsule; the recommended dose is 5 mg/m² given 1 to 3 hours before chemotherapy, then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses daily (orally). Because the side effects of dronabinol are dose related, lower doses have been found to be better tolerated. Often, patients are started at doses of 2.5 mg every 6 hours for nausea, and the dose is escalated. Dronabinol is associated with a low potential for abuse.

**BENZODIAZEPINES**

Although these agents do not have any intrinsic antiemetic activity as single agents, benzodiazepines are efficacious in anticipatory nausea. Therefore, their role in the management of CINV is usually as adjunctive therapy to other antiemetic agents. Benzodiazepines are able to decrease the severity of extrapyramidal symptoms—especially akathisia—associated with dopaminergic receptor antagonist antiemetics.

**COMBINATION THERAPY**

Combination antiemetic therapy utilizing agents with different mechanisms of action is standard of care. By combining several antiemetics, CINV can be addressed via several sites and mechanisms of action. A dopaminergic antagonist is commonly combined with agents that possess no dopamine-blocking effect. Patients who are receiving antineoplastic therapy at high dose with greater emetogenic potential should receive higher dosages of antiemetic therapy.

**NURSING INTERVENTIONS**

Numerous effective antiemetic agents are available for the management of CINV. Nurses need to be aware of the emetogenic potential of chemotherapeutic regimens. Making sure patients are premedicated for prevention of nausea and vomiting is important for the patient’s comfort and willingness to participate in further rounds of cancer treatment. In patients who are at high risk for delayed nausea, the antiemetic plan should include coverage of the period for which delayed nausea and vomiting is a threat.

Nurses should assess the level of nausea and vomiting patients experience after chemotherapy and modify interventions as appropriate.

Patients should be encouraged to contact the nursing staff with questions and concerns regarding CINV, and the continuation of antiemetic therapy through the time frame when risk of delayed nausea and vomiting is greatest should be stressed.

**REFERENCES**