

# Antiemetics/Antivertigo Agents Review

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## Antiemetics/Antivertigo Agents Review

### FDA-Approved Indications

Antiemetic Drugs	Manufacturer	Indication(s)
<b>NK<sub>1</sub> receptor antagonist</b>		
aprepitant (Emend®) <sup>1</sup>	Merck	In combination with other antiemetic agents for: <ul style="list-style-type: none"> <li>◆ Prevention of acute and delayed nausea and vomiting (N/V) associated with highly emetogenic cancer chemotherapy, including high-dose cisplatin</li> <li>◆ Prevention of N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy</li> </ul> Prevention of post-operative N/V
fosaprepitant dimeglumine (Emend® for injection) <sup>2</sup>	Merck	In combination with other antiemetic agents for: <ul style="list-style-type: none"> <li>◆ Prevention of acute and delayed nausea and vomiting (N/V) associated with highly emetogenic cancer chemotherapy, including high-dose cisplatin</li> <li>◆ Prevention of N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy</li> </ul>
<b>5-HT<sub>3</sub> antagonists</b>		
dolasetron (Anzemet®) <sup>3</sup>	Sanofi-Aventis	Prevention of N/V associated with moderately emetogenic cancer chemotherapy; including initial and repeat courses  Prevention of postoperative N/V
granisetron (Granisol™, Kytril®) <sup>4,5</sup>	generic	Prevention of N/V associated with initial and repeat courses of emetogenic cancer therapy including high-dose cisplatin  Prevention of N/V associated with radiation, including total body irradiation and fractionated abdominal radiation
granisetron transdermal (Sancuso®) <sup>6</sup>	ProStrakan	Prevention of N/V in patients receiving moderately or highly emetogenic chemotherapy regimens of up to five consecutive days duration
ondansetron (Zofran®, Zuplenz®) <sup>7,8</sup>	generic, Strativa	Prevention of N/V associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m <sup>2</sup>  Prevention of N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.  Prevention of N/V associated with radiotherapy in patients receiving total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen  Prevention of post-operative N/V
palonosetron (Aloxi® IV) <sup>9</sup>	Helsinn Healthcare/ MGI Pharma	Prevention of acute and delayed N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy  Prevention of acute N/V associated with initial and repeat courses of highly emetogenic cancer chemotherapy  Prevention of post-operative N/V for up to 24 hours following surgery.

**FDA-Approved Indications (continued)**

Antiemetic Drugs	Manufacturer	Indication(s)
<b>Cannabinoids</b>		
dronabinol (Marinol <sup>®</sup> ) <sup>10</sup>	generic	Treatment of N/V associated with cancer chemotherapy who have failed to respond adequately to conventional antiemetic treatments Anorexia associated with weight loss in patients with AIDS
nabilone (Cesamet <sup>®</sup> ) <sup>11</sup>	Meda Pharmaceuticals	Treatment of N/V associated with cancer chemotherapy who have failed to respond adequately to conventional antiemetic treatments
<b>Antidopaminergic Agents</b>		
metoclopramide (Reglan <sup>®</sup> ) <sup>12,13</sup>	Alaven Pharm	Treatment of N/V secondary to delayed gastric emptying
metoclopramide (Metozolv ODT) <sup>14</sup>	Salix Pharmaceuticals	Relief of heartburn symptoms of refractory gastroesophageal reflux disease (GERD) when other treatments do not work Relief of symptoms of slow stomach emptying in patients with diabetes (diabetic gastroparesis)
<b>Others</b> <sup>15,16</sup>		
phosphorated carbohydrate solution (Emetrol <sup>®</sup> OTC)	WellSpring	Relief of nausea due to upset stomach from intestinal flu, stomach flu, and food or drink indiscretions.
trimethobenzamide (Tebamide, Tigan <sup>®</sup> )	King Pharm	Treatment of N/V associated with gastroenteritis, medication-induced nausea, and other illnesses

Antivertigo Drugs <sup>17,18</sup>	Manufacturer	Indication(s)
<b>Antihistamines</b>		
cyclizine (Bonine <sup>®</sup> for Kids OTC)	McNeil	Treatment and prevention of N/V and dizziness associated with motion sickness
dimenhydrinate (Dramamine <sup>®</sup> OTC)	McNeil	Treatment and prevention of motion sickness Prevention of post-operative N/V
diphenhydramine (Benadryl)	McNeil	Treatment and prevention of N/V associated with motion sickness
meclizine (Antivert, Univert)	generic, Pfizer	Treatment and prevention of motion sickness Treatment and prevention of radiation induced nausea and vomiting
<b>Phenothiazines</b>		
promethazine (Phenergan)	generic, Wyeth	Treatment and prevention of N/V associated with motion sickness
prochlorperazine (Compazine <sup>®</sup> )	generic, GlaxoSmithKline	Treatment of N/V associated with cancer chemotherapy, radiation, and post-op N/V To alleviate the symptoms of vertigo
<b>Anticholinergics</b>		
scopolamine (Transderm-Scop <sup>®</sup> )	Novartis	Treatment and prevention of motion sickness Prevention of post-operative N/V

## Overview

Chemotherapy-induced vomiting (emesis) and nausea can significantly affect a patient's quality of life, leading to poor compliance with further chemotherapy treatment. In addition, nausea and vomiting can result in metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of the patient's performance status and mental status, wound dehiscence, esophageal tears, and withdrawal from potentially useful or curative anticancer treatment. Approximately 70 to 80 percent of all cancer patients receiving chemotherapy experience nausea and/or vomiting, whereas 10 to 44 percent experience anticipatory nausea and/or vomiting.<sup>19</sup>

The goal of antiemetic therapy is to prevent nausea and vomiting (N/V) completely. As a result of research over the last 20 years, this goal is achieved for many patients receiving chemotherapy or radiation therapy. Research has increased understanding of the pathophysiology of these symptoms and has resulted in therapy that is more effective and safer than in the past. With currently available agents, complete control of emesis (e.g., no vomiting) is achievable in the majority of patients in the first 24 hours and in approximately 45 percent of patients during the first week of chemotherapy.<sup>20,21</sup> Complete control correlates highly with patient perception of emesis and with patient satisfaction with their emetic control.

Nausea, the perception that emesis may occur, can be judged only by the patient. Nausea is quantified by the use of various questionnaires, such as visual analog scales (VAS).<sup>22,23,24</sup> The incidence of nausea correlates well with the incidence of vomiting, although chemotherapy-induced nausea occurs at a greater frequency.<sup>25,26</sup> Total control (no nausea or vomiting) is ideal, but lesser control rates such as major control (fewer than three emetic episodes) or minor control (three to five emetic episodes) may still have some value in difficult emetic situations. The American Society of Clinical Oncologists (ASCO) advises the use of complete control rates for the evaluation of emetic situations.

The prevention of delayed emesis and anticipatory emesis is equal in importance to the need to prevent acute (within first 24 hours) chemotherapy- and radiation-induced emesis. Risk factors for emesis include patient characteristics (age, sex, history of N/V, etc.) and emetogenicity of chemotherapy or radiotherapy. The 2009 National Comprehensive Cancer Network (NCCN) states that the choice of antiemetic should be based on emetic risk of the chemotherapy, prior experience with antiemetics, as well as patient factors.<sup>27</sup> The 2010 update to the NCCN Antiemesis guidelines states that antiemetic therapy should be initiated prior to start of chemotherapy to provide maximal protection against chemotherapy-induced emesis. In addition, the antiemetic therapy should be continued for the same timeframe as the duration of the emetic activity of the chemotherapeutic agent being used.<sup>28</sup>

Newer antiemetic regimens are more convenient for patients to receive and for healthcare professionals to administer. As antiemetic usage has grown, the classes of agents for treatment, the agents available, and their indications have increased in number, as well. The prevention and treatment of cancer chemotherapy- and radiotherapy-related N/V have come to be based largely on the use of type-3 serotonin (5-HT<sub>3</sub>) receptor antagonists.<sup>29</sup> Aprepitant (Emend), a neurokinin-1 (NK<sub>1</sub>) receptor antagonist, is used in combination with a corticosteroid and a 5-HT<sub>3</sub> receptor antagonist when treating chemotherapy-induced N/V. The cannabinoids are synthetic delta-9 tetrahydrocannabinol (THC) products and include two products, dronabinol (Marinol) and nabilone (Cesamet).

The 2006 ASCO guidelines state that "at equivalent doses, serotonin receptor antagonists have

equivalent safety and efficacy and can be used interchangeably.”<sup>30</sup> The 2008 Multinational Association of Supportive Care in Cancer (MASCC) guidelines, the American Society of Health-System Pharmacists (ASHP), and the NCCN agree with this position.<sup>31,32,33</sup> In addition, nabilone (Cesamet) was added to the 2007 NCCN Antiemesis guidelines update of recommended breakthrough treatments for CINV (chemotherapy induced nausea and vomiting). The 2010 NCCN Antiemesis guidelines confirm the various routes of administration for antiemetics including oral, rectal, intravenous (IV), intramuscular (IM), and transdermal. Oral antiemetics remain equally effective, safe, more convenient and often less costly than other routes of administration. Although studies may show these agents to be equally effective on a population basis, individual patients may respond differently to them.

The 2006 ASCO and 2008 MASCC guidelines have incorporated aprepitant (Emend) into first-line therapy for patients on chemotherapy of high emetic risk (with a 5-HT<sub>3</sub> antagonist and dexamethasone), patients receiving an anthracycline and cyclophosphamide (with a 5-HT<sub>3</sub> antagonist and dexamethasone), and the prevention of delayed emesis with agents of high emetic risk (with dexamethasone). For patients receiving other chemotherapy of moderate emetic risk or radiation therapy of high emetic risk, a two-drug regimen of a 5-HT<sub>3</sub> receptor serotonin antagonist and dexamethasone is recommended. Patients receiving moderately emetic radiation therapy should receive a 5-HT<sub>3</sub> antagonist.<sup>34,35</sup>

The 2010 NCCN Antiemesis guidelines identify emesis prevention treatment options for high, moderate, low, and minimal emetic risk IV chemotherapy, oral chemotherapy, as well as breakthrough treatment for chemotherapy-induced N/V. For patients receiving IV chemotherapy with high emetic risk, an oral or IV formulation of a serotonin antagonist, corticosteroid, and neurokinin-1 antagonist should be initiated prior to the chemotherapy. For patients receiving IV chemotherapy with moderate emetic risk, an oral or IV regimen of a serotonin antagonist and a corticosteroid with or without a neurokinin-1 antagonist should be initiated one day prior to the start of chemotherapy. On days two to three of this regimen, three options are possible: serotonin antagonist monotherapy, corticosteroid monotherapy, or a neurokinin-1 antagonist. For patients who receive low emetic risk IV chemotherapy, alternative options may include oral or IV formulations of dexamethasone, prochlorperazine, or metoclopramide. There is no routine prophylaxis for patients who receive minimal emetic risk IV chemotherapy. For patients who receive oral chemotherapy where prophylaxis is recommended, an oral serotonin antagonist should be initiated prior to chemotherapy. Conversely, for patients who receive oral chemotherapy where no prophylaxis or as needed prophylaxis is recommended, patients may receive alternative agents like metoclopramide or prochlorperazine. If N/V persist, then an oral serotonin antagonist could be initiated. Finally, for breakthrough treatment of chemotherapy-induced N/V, the general principle is to add one agent from a different class as needed to the existing regimen (e.g., antipsychotic, benzodiazepine, cannabinoid, dopamine receptor antagonist, phenothiazine, serotonin antagonist, or corticosteroid). Based on response to the breakthrough treatment, the antiemetic therapy is adjusted and/or modified.

Motion sickness is the result of a conflict between the various senses in regard to motion. The semicircular canals and otoliths in the inner ear sense angular and vertical motion, while the eyes and the proprioceptors determine the body's position in space. When signals received by the eyes or the proprioceptors do not match those being transmitted by the inner ear, motion sickness occurs. It can occur in either the presence or absence of actual motion, such as when viewing a slide through a microscope. Symptoms include nausea, vomiting, pallor, sweating, and often a sense of impending doom. There are both non-pharmacologic and pharmacologic

interventions for the prevention or management of motion sickness. None are ideal, and the medications typically cause drowsiness or similar adverse effects.<sup>36</sup>

### **Pharmacology**

NK<sub>1</sub> receptor antagonist – aprepitant (Emend)<sup>37</sup>, fosaprepitant (Emend for Injection)<sup>38</sup>

Aprepitant exerts its main antiemetic action by occupying brain substance P-NK<sub>1</sub> receptors. This receptor pathway regulates the behavioral responses to a range of noxious and stressful stimuli. Expression in the brainstem emetic nuclei has implicated substance P in the control of vomiting.<sup>39</sup> Aprepitant has little or no affinity for 5-HT<sub>3</sub>, D<sub>2</sub>, or corticosteroid receptors.

5-HT<sub>3</sub> antagonists [dolasetron (Anzemet), granisetron (Granisol, Kytril), granisetron transdermal (Sancuso), ondansetron (Zofran, Zuplenz), palonosetron (Aloxi IV)]<sup>40,41,42,43,44</sup>

Dolasetron, granisetron, ondansetron and palonosetron selectively block 5-HT<sub>3</sub> receptors. While the mechanism of action of these drugs has not been fully elucidated, they are not D<sub>2</sub> receptor antagonists. Serotonin receptors of the 5-HT<sub>3</sub> type are found centrally in the chemoreceptor trigger zone and peripherally at vagal nerve terminals in the intestines. It has not been determined whether the antiemetic action of the 5-HT<sub>3</sub> antagonists is mediated centrally, peripherally, or a combination of both sites. N/V during chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. The released serotonin may stimulate vagal afferents through the 5-HT<sub>3</sub> receptors and initiate the vomiting reflex.

Cannabinoids [dronabinol (Marinol), nabilone (Cesamet)]<sup>45,46,47</sup>

Dronabinol and nabilone act on the cannabinoid receptors (CB1 and CB2) in the brain. These receptors are believed to regulate nausea and vomiting. Like most cannabinoids, these agents have complex effects on the central nervous system (CNS) and may even exert central sympathomimetic activity.

Antidopaminergics [metoclopramide (Reglan, Metozolv ODT)]<sup>48,49,50</sup>

Metoclopramide aids in gastric motility increasing emptying and intestinal transit. Antiemetic properties are due to its effects on central and peripheral dopamine receptors. It blocks dopaminergic activity to the medullary chemoreceptor trigger zone.

Phenothiazines [promethazine (Phenergan), prochlorperazine (Compazine, Compro)]<sup>51,52</sup>

The phenothiazines block postsynaptic dopaminergic receptors in the brain including the chemoreceptor trigger zone (CTZ). This mechanism contributes to depression of the reticular activating system and affects basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis. Promethazine also has both antihistaminic and anticholinergic properties.

Antihistamines [cyclizine (Bonine for Kids OTC), dimenhydrinate (Dramamine OTC), diphenhydramine (Benadryl), meclizine (Antivert, Univert)]<sup>53,54</sup>

Histaminergic (H1) antagonists act on the vomiting center and vestibular pathways making them effective in the prevention and treatment of motion sickness induced N/V.

Anticholinergics [(scopolamine (Scopace, Transderm-Scop)]<sup>55,56</sup>

Scopolamine exerts its activity in the central nervous system by blocking activity to the vomiting center and vestibular nuclei.

**Pharmacokinetics**

<b>Antiemetics</b>				
<b>Drug</b>	<b>Bioavailability (%)</b>	<b>Half life (t<sub>1/2</sub>) (h)</b>	<b>Metabolites</b>	<b>Excretion (%)</b>
<b>NK<sub>1</sub> receptor antagonist</b>				
aprepitant (Emend) <sup>57</sup>	60-65	9-13	7, activity questionable	urine: 57 feces: 45
fosaprepitant (Emend for Inj) <sup>58</sup>	--	9-13	prodrug converted to aprepitant	urine: 57 feces: 45
<b>5-HT<sub>3</sub> antagonists</b>				
dolasetron (Anzemet) <sup>59</sup>	75	8.1	hydrodolasetron, active	urine: 61 feces: 39
granisetron (Granisol, Kytril) <sup>60,61</sup>	--	6.2	yes, activity questionable	urine: 49 feces: 34
granisetron transdermal (Sancuso) <sup>62</sup>	--	N/A; drug is released from patch continuously	yes	urine: 61 feces: 34
ondansetron (Zofran, Zuplenz) <sup>63,64</sup>	56	3.1-6.2	yes, none significant	urine: 5
palonosetron IV (Aloxi IV) <sup>65</sup>	97	40	--	urine: 80 feces: 5 to 8
<b>Cannabinoids</b>				
dronabinol (Marinol) <sup>66</sup>	10-20	25-36	yes, one active	urine: 15 feces: 50
nabilone (Cesamet) <sup>67</sup>	5-20	2-35	yes, active and inactive	urine: 22 feces: 67
<b>Antidopaminergics</b> <sup>68,69</sup>				
metoclopramide (Reglan)	65-95	5-6	None	urine: 85 feces: 2
metoclopramide (Metozolv ODT) <sup>70</sup>				
<b>Others</b> <sup>71,72</sup>				
phosphorated carbohydrate solution (Emetrol OTC)	--	--	--	--
trimethobenzamide (Tebamide, Tigan)	60-100	7-9	yes, one active	urine: 30-50

Granisetron transdermal patch (Sancuso) delivers 66 percent of active ingredient following application for seven days.

**Pharmacokinetics (continued)**

<b>Antivertigo Agents</b> <sup>73,74</sup>				
<b>Drug</b>	<b>Bioavailability (%)</b>	<b>Half life (t<sub>1/2</sub>) (h)</b>	<b>Metabolites</b>	<b>Excretion (%)</b>
<b>Antihistamines</b>				
cyclizine (Bonine for Kids OTC)	--	7	yes, one active	--
dimenhydrinate (Dramamine OTC)	--	--	--	--
diphenhydramine (Benadryl)	65-100	4-8	yes, five active	urine: 50-65
meclizine (Antivert, Univert)	--	6	yes, one active	--
<b>Phenothiazines</b>				
promethazine (Phenergan)	Low	9-16	yes, one active	--
prochlorperazine (Compazine, Compro)	12.5	6-10 (single dose) 14-22 (repeat dosing)	yes; one active	--
<b>Anticholinergics</b>				
scopolamine (Transderm-Scop)	--	--	yes	Urine: 34

**Contraindications/Warnings**<sup>75,76,77,78,79,80,81,82,83,84,85</sup>

5-HT<sub>3</sub> receptor antagonists are contraindicated in patients with known hypersensitivity to the drug or any of its components. Cross hypersensitivity reactions have been reported in patients who received other selective 5HT<sub>3</sub> receptor antagonists. These reactions have not been seen with dolasetron.

Granisetron and ondansetron do not stimulate gastric or intestinal peristalsis. They should not be used instead of nasogastric suction. Their use in patients following abdominal surgery or in chemotherapy-induced N/V may mask a progressive ileus and/or gastric distention.

5-HT<sub>3</sub> receptor antagonists should be administered with caution in patients who have or may develop arrhythmias or prolongation of cardiac conduction intervals, particularly QT<sub>c</sub>.

Patients with phenylketonuria should be informed that ondansetron orally disintegrating tablets contain < 0.03 mg phenylalanine in both the 4 mg and 8 mg tablets.

The concomitant use of apomorphine with ondansetron (Zofran, Zofran ODT, Zuplenz) is contraindicated based on reports of profound hypotension and loss of consciousness with coadministration.

Adverse psychiatric effects can persist for 48 to 72 hours following discontinuation of nabilone (Cesamet). Cautious use of both cannabinoids [dronabinol (Marinol) and nabilone] in patients

with current or previous psychiatric disorders (e.g., manic depression, depression, and schizophrenia) is recommended.

Cautious use of the cannabinoids (dronabinol and nabilone) is recommended also in patients with a history of substance abuse and dependence.

Although, a causal relationship has not been established, dronabinol may lower the seizure threshold, therefore it should be used with caution in patients with a history of seizure disorder.

Dronabinol and nabilone should be used with caution in patients with cardiac disorders due to occasional hypotension, possible hypertension, syncope, or tachycardia.

Proteinuria has been reported in 6.8 percent of patients receiving aprepitant (Emend) in clinical trials.

Metoclopramide (Reglan, Metozolv ODT) has a black box warning for chronic long-term or high-dose use which can lead to increased risk of tardive dyskinesia, involuntary and repetitive movements of the body, even after the drug had been discontinued.

#### *REMS (Risk Evaluation and Mitigation Strategy)*

Metoclopramide has a REMS associated with discussing the risk of tardive dyskinesia with chronic use. Treatment for longer than 12 weeks should be avoided in all but rare cases where therapeutic benefit is thought to outweigh the risk of developing this condition.

#### **Drug Interactions**

aprepitant (Emend)<sup>86</sup> and fosaprepitant dimeglumine (Emend for Injection)<sup>87</sup>

Aprepitant should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents, which are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant 80 or 125 mg could result in elevated plasma concentrations of these concomitant medicinal products. The effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than its effect on the pharmacokinetics of intravenous (IV) CYP3A4 substrates. Coadministration of aprepitant with drugs that inhibit CYP3A4 activity (e.g., ketoconazole, itraconazole, diltiazem, clarithromycin) may result in increased plasma concentrations of aprepitant. In addition, coadministration with aprepitant could elevate plasma concentrations of pimozone, terfenadine, astemizole, or cisapride, potentially causing serious or life-threatening reactions. CYP2C9 metabolism may be induced by aprepitant. Weak inhibition of CYP enzymes by 40 mg doses of aprepitant is not expected to affect concentration of other drugs to a significant degree.

Coadministration of aprepitant with warfarin may result in a clinically significant (14 percent) decrease in INR. In patients on warfarin, INR should be closely monitored at seven to 10 days following initiation of the three-day regimen of aprepitant with each chemotherapy cycle.

The efficacy of oral contraceptives during administration of aprepitant may be reduced.

Because administration of aprepitant with dexamethasone or methylprednisolone approximately doubles the area-under-the-curve (AUC) of the corticosteroid, doses of the coadministered corticosteroid should be reduced by 50 percent when coadministered with aprepitant.<sup>88</sup>

5-HT<sub>3</sub> receptor antagonists<sup>89,90,91,92,93,94</sup>

Dolasetron (Anzemet), granisetron (Granisol, Kytril, Sancuso), palonosetron (Aloxi IV) and ondansetron (Zofran, Zuplenz) are metabolized by various CYP450 enzymes; however, due to the variety of enzymes involved, no clinically significant drug interactions have been identified at this time.

Blood levels of hydrodolasetron increased 24 percent when dolasetron was coadministered with cimetidine (nonselective inhibitor of CYP450) for seven days and decreased 28 percent with coadministration of rifampin (potent inducer of CYP450) for seven days.

In patients treated with potent inducers of CYP3A4 (e.g., phenytoin, carbamazepine, and rifampin), the clearance of ondansetron was significantly increased, and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.

QT prolongation has been reported with granisetron. Use of granisetron in patients concurrently treated with drugs known to prolong the QT interval and/or are arrhythmogenic, may result in clinical consequences.

Cannabinoids<sup>95,96</sup>

Both of the cannabinoids, dronabinol (Marinol) and nabilone (Cesamet), are highly protein bound and may displace other highly protein bound drugs. Examples include tricyclic antidepressants, amphetamines, barbiturates, benzodiazepines, fluoxetine, theophylline, and others. A change in dosage of the concomitant drug may be necessary. Consult prescribing information for dosages recommendations.

Nabilone should not be taken with alcohol, sedatives, hypnotics, or other psychoactive substances because these substances can potentiate its central nervous system effects.

Antidopaminergics<sup>97,98,99</sup>

Metoclopramide is a weak inhibitor of CYP2D6. It may enhance the toxic effects of antipsychotics, selective serotonin reuptake inhibitors, tricyclic antidepressants, promethazine, and droperidol. Avoid alcohol intake as it may increase CNS depression.

Phenothiazines<sup>100,101</sup>

Prochlorperazine: may diminish the effect of dopamine agonists (antiparkinson's agents). Prochlorperazine may enhance the toxic effects of antipsychotics and enhance CNS depressant effects of opioids, barbiturates and other CNS agents. Promethazine is a major substrate of CYP2D6; therefore, monitor therapy with CYP2D6 inhibitors or inducers. Avoid combination with metoclopramide or serotonin modulators.

Antihistamines<sup>102,103</sup>

Cyclizine, dimenhydrinate, diphenhydramine, and meclizine may enhance the toxic effects of CNS depressants and anticholinergics. Diphenhydramine moderately inhibits CYP2D6 so therapy with tramadol, codeine, tamoxifen, and nebivolol should be monitored.

**Adverse Effects**

Antiemetic Drug	Hepatic function abnormalities	Tachycardia	Headache	Euphoria	Hypotension	Diarrhea	Fatigue	Nausea
<b>NK1 receptor antagonist</b>								
aprepitant (Emend) <sup>104</sup>	6	nr	5-16.4	nr	0.5-3	5.5-10.3	17.8-21.9	7.1-12.7
fosaprepitant dimeglumine (Emend for injection) <sup>105</sup>	≥1	nr	2.2	nr	nr	1.1	2.9	nr
<b>5-HT3 antagonists</b>								
dolasetron (Anzemet) <sup>106</sup>	<1	2.2-3	7-22.9	nr	5.3	2.1-5.3	2.6-5.7	nr
granisetron (Granisol, Kytril) <sup>107,108</sup>	5-6	nr	14-21	nr	≤1	4-9	nr	nr
granisetron transdermal (Sancuso) <sup>109</sup>	nr	nr	<1	nr	nr	nr*	nr	nr
ondansetron (Zofran, Zuplenz) <sup>110,111</sup>	1-2	reported	11-27	nr	5	3-7	9-13	nr
palonosetron (Aloxi IV) <sup>112</sup>	nr	1	9	<1	nr	1	<1	nr
<b>Cannabinoids</b>								
dronabinol (Marinol) <sup>113</sup>	<1	>1	<1	3-10	0.3-1	0.3-1	nr	3-10
nabilone (Cesamet) <sup>114</sup>	nr	reported	6	11	8	reported	nr	4

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

\*Constipation is the predominant adverse effect associated with granisetron transdermal (Sancuso), occurring at a rate of 5.4 percent.

**Adverse Effects (continued)**

Antiemetic Drug	Hepatic function abnormalities	Tachycardia	Headache	Euphoria	Hypotension	Diarrhea	Fatigue	Nausea
<b>Antidopaminergics</b> <sup>115,116</sup>								
metoclopramide (Reglan)	nr	nr	4.2	nr	reported	nr	2.8	5.6
metoclopramide (Metozolv ODT)	nr	nr	5.2	nr	nr	nr	2.1	4.2
<b>Other</b> <sup>117,118</sup>								
trimethobenzamide (Tebamide, Tigan)	nr	nr	reported	nr	nr	reported	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Antivertigo Agents <sup>119,120</sup>	Drowsiness	Xerostomia	Tachycardia	Rash	Blurred Vision	Urinary Retention
<b>Antihistamines</b>						
cyclizine (Bonine for Kids OTC)	>10	>10	nr	1-10	nr	1-10
dimenhydrinate (Dramamine OTC)	reported	reported	reported	nr	reported	reported
diphenhydramine (Benadryl)	reported	reported	reported	nr	reported	reported
meclizine (Antivert, Univert)	>10	1-10	<1	<1	<1	<1

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

**Adverse Effects (continued)**

<b>Antivertigo Agents<sup>121,122</sup></b>	<b>Drowsiness</b>	<b>Xerostomia</b>	<b>Tachycardia</b>	<b>Rash</b>	<b>Blurred Vision</b>	<b>Urinary Retention</b>
<b>Phenothiazines</b>						
promethazine (Phenergan)	reported	reported	nr	nr	nr	nr
prochlorperazine (Compazine)	reported	nr	nr	nr	reported	nr
<b>Anticholinergics</b>						
scopolamine (Transderm-Scop)	16	60	nr	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

## **Special Populations**

### Pediatrics

Prescribing information states that ondansetron (Zofran) can be used for patients older than four years old. However, little information is available about ondansetron dosage in pediatric patients four years of age or younger. There is no experience with the use of ondansetron 24 mg dosage in pediatric patients. There is no experience with the use of oral ondansetron in the prevention of radiation-induced or postoperative nausea and vomiting in pediatric patients.<sup>123</sup> Although not FDA-approved, there are data that also support using ondansetron in patients six months and older for post-operative N/V.

The safety and effectiveness of ondansetron soluble film (Zuplenz) has been established for the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy in patients ages four years and older.<sup>124</sup> Otherwise, the safety and effectiveness of this product in children have not been evaluated.

Dolasetron (Anzemet) is indicated for use in patients over two years old in the prevention of post-operative N/V and the prevention of chemotherapy-induced N/V.

Safety and efficacy of granisetron (Granisol, Kytril) and granisetron transdermal (Sancuso) have not been established for pediatric patients.<sup>125,126</sup> Granisetron may be effective in patients older than four years old, according to limited randomized, controlled trials for post-operative N/V.<sup>127,128,129</sup> There is no experience with oral granisetron in the prevention of radiation-induced nausea and vomiting in pediatric patients.

Safety and effectiveness of use of palonosetron (Aloxi) for injection in patients below the age of 18 years have not been established.<sup>130</sup>

Aprepitant (Emend) has not been studied in patients under 18 years old. Neither dronabinol (Marinol) nor nabilone (Cesamet) have been studied in children. Caution is recommended in prescribing dronabinol or nabilone for children because of the psychoactive effects.

Cyclizine (Bonine for Kids OTC), dimenhydrinate (Dramamine OTC), and diphenhydramine (Benadryl) have been used to prevent and treat N/V associated with motion sickness in pediatric populations.

### dolasetron (Anzemet) and ondansetron (Zofran)

In a randomized, placebo-controlled, double-blind trial, oral dolasetron and ondansetron were compared in preventing post-operative N/V in 150 children after various surgical operations.<sup>131</sup> Children were assigned randomly to one of three groups to receive dolasetron 1.8 mg/kg, ondansetron 0.15 mg/kg, or a placebo. All children received methylene blue capsules orally as an indicator before the induction of anesthesia. Post-operative contamination of the mouth and the endotracheal tube by methylene blue, and post-operative N/V were recorded for 24 hours. In the one-hour period after the operation, there were no differences between the groups. During the period one to 24 hours after surgery, dolasetron was significantly better than placebo (16 versus 48 percent for nausea and vomiting, respectively). Over the entire 24 hours, both dolasetron and ondansetron were significantly better than placebo (32 versus 48 versus 78 percent, respectively, for nausea and vomiting). There were no significant differences between dolasetron and ondansetron, and no important adverse events were reported.

Pregnancy<sup>132,133,134,135,136,137,138,139,140</sup>

The NK-1 receptor antagonist, aprepitant, is Pregnancy Category B. The 5-HT<sub>3</sub> antagonists, ondansetron, granisetron, dolasetron, and palonosetron are Pregnancy Category B. The cannabinoids, dronabinol and nabilone, are Pregnancy Category C.

Metoclopramide (Reglan, Metozolv ODT) is Pregnancy Category B.

Trimethobenzamide (Tigan, Tebamide) is Pregnancy Category C.

Geriatrics<sup>141</sup>

Dronabinol should be used with caution in elderly patients because they may be more sensitive to its neurological, psychoactive, and postural hypotensive effects.

**Dosages**

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
<b>NK<sub>1</sub> receptor antagonist</b>						
aprepitant (Emend) <sup>142</sup>	125 mg one hour prior to chemotherapy, then 80 mg once daily for two days as part of regimen including corticosteroid and a 5-HT <sub>3</sub> antagonist	--	--	40 mg up to three hours prior to induction of anesthesia	--	capsules: 40, 80, 125 mg tri-fold pack: one 125 mg capsule and two 80 mg capsules
fosaprepitant dimeglumine (Emend) <sup>143</sup>	<p>Single Dose regimen for Highly Emetogenic Chemotherapy (HEC) – 150 mg on Day 1 as an infusion over 20 to 30 minutes approximately 30 minutes prior to chemo in combination with a corticosteroid and a 5-HT<sub>3</sub> antagonist</p> <p>3-Day Dosing regimen for HEC – 115 mg on Day 1 as an infusion over 20 to 30 minutes approximately 30 minutes prior to chemo. Oral Emend 80 mg capsules are administered daily on Days 2 and 3.</p>	--	--	--	--	injection: 115 mg per vial 150 mg per vial
<b>5-HT<sub>3</sub> antagonists</b>						
dolasetron (Anzemet) <sup>144</sup>	100 mg orally within one hour before chemotherapy	2-16 years: 1.8 mg/kg (up to 100 mg) orally within one hour before chemotherapy	--	100 mg within two hours before surgery	2-16 years: 1.2 mg/kg (up to 100 mg) given within two hours before surgery	tablets: 50, 100 mg injection: 12.5 mg per 0.625 mL 100 mg per 5 mL 500 mg per 25 mL

**Dosages (continued)**

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
granisetron (Granisol, Kytril) <sup>145,146</sup>	2 mg up to 1 hour before chemotherapy for one dose OR 1 mg up to 1 hour before chemotherapy followed by 1 mg 12 hours after the first dose	--	2 mg once daily taken within 1 hour of radiation	--	--	tablets: 1 mg oral solution: 1 mg/5 mL  injection: 0.1 mg per mL 1 mg per mL
granisetron transdermal (Sancuso) <sup>147</sup>	Apply single patch to upper outer arm 24 hours prior to chemotherapy. Remove 24 hours after completion of chemotherapy. The patch can be worn for up to seven days.	--	--	--	--	transdermal patch containing 34.3 mg granisetron that releases 3.1 mg over 24 hours for seven days
ondansetron (Zofran, Zuplenz) <sup>148,149</sup>	<b>High emetogenicity:</b> 24 mg given 30 minutes before start of chemotherapy;  <b>Moderate emetogenicity:</b> 8 mg given 30 minutes before start with a subsequent dose 8 hours after the first dose. , 8 mg should then be given every 12 hours for 1-2 days following completion of chemotherapy.	<b>High emetogenicity:</b> No experience with 24 mg dosage  <b>Moderate emetogenicity:</b> 4-11 years: 4 mg given 30 minutes before chemotherapy with subsequent doses 4 and 8 hours after the 1 <sup>st</sup> dose. 4 mg should be given every 8 hours for 1-2 days after completion of chemotherapy. ≥12 years: same as adult.	8 mg up to two hours before radiation and up to three times daily for one to two days	16 mg one hour before induction of anesthesia	--	tablets: 4, 8, 24 mg  oral soluble film (Zuplenz): 4, 8 mg  oral solution: 4 mg/5 mL  tablets, orally disintegrating (ODT): 4, 8 mg  injection: 2 mg per mL
palonosetron (Aloxi IV) <sup>150</sup>	A single 0.25 mg IV dose administered over 30 seconds. Dosing should occur approximately 30 minutes prior to start of chemotherapy	--	--	A single 0.075 mg IV dose administered over 10 seconds immediately prior to the induction of anesthesia	--	Injection (single use vial): 0.25 mg per 5 mL 0.075 mg per 1.5 mL

**Dosages (continued)**

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
<b>Cannabinoids</b>						
dronabinol (Marinol) <sup>151</sup>	Initial dose of 5 mg/m <sup>2</sup> given one to three hours prior to chemotherapy, then every two to four hours after for a total of four to six doses per day. The initial starting dose may be adjusted in increments of 2.5 mg/m <sup>2</sup> if necessary up to a maximum of 15 mg/m <sup>2</sup> .	--	--	--	--	capsules: 2.5, 5, 10 mg
nabilone (Cesamet) <sup>152</sup>	Usual adult dose is 1 to 2 mg twice daily. 1 or 2 mg may be given the night prior to chemotherapy or one to three hours before initial chemotherapy. Maximum daily dose of 6 mg in divided doses.	--	--	--	--	capsules: 1 mg
<b>Antidopaminergic Agents</b> <sup>153, 154</sup>						
metoclopramide (Reglan)	1 to 2 mg/kg 30 minutes before chemotherapy and repeated every two hours for two doses, then every three hours for three doses	1 to 2 mg/kg/dose every two to four hours (maximum of five doses per day); pretreatment with diphenhydramine decreases risk of extrapyramidal reactions.	--	--	--	Tablets: 5, 10 mg Solution: 5 mg/5 mL Injection: 5 mg per mL

Antiemetics/Antivertigo Agents

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
metoclopramide (Metozolv ODT) <sup>155</sup>	--	--	Relief of symptomatic GERD – 10 to 15 mg four times daily at least 30 minutes prior to eating and at bedtime up to 12 weeks  Relief of symptoms associated with diabetic gastroparesis – 10 mg four times daily at least 30 minutes prior to eating and at bedtime for two to eight weeks.	--	--	Orally disintegrating tablets: 5, 10 mg
<b>Others</b> <sup>156,157</sup>						
trimethobenzamide (Tebamide, Tigan)	--	--	--	N/V of known etiology in adults: 300 mg three to four times daily as needed	--	suppositories: 200 mg injection: 100 mg per mL capsules: 300 mg

**Dosages (continued)**

Antivertigo Agents <sup>158,159</sup>	Adult	Pediatric	Availability
<b>Antihistamines</b>			
cyclizine (Bonine for Kids)	--	Ages six years and older: Chew one tablet thoroughly every six to eight hours (Do not exceed three tablets in 24 hours)	Chewable Tablets: 25 mg
dimenhydrinate (Dramamine OTC, Motion Sickness OTC)	Adults and children 12 years and older: one to two tablets every four to six hours (Do not exceed eight tablets in 24 hours)	Children ages six to 12 years: ½ to one tablet every six to eight hours (Do not exceed three tablets in 24 hours) Children ages two to six years: ½ tablet every six to eight hours (Do not exceed more than one and one-half tablets in 24 hours)	Tablets: 50 mg Chewable tablets: 50 mg
diphenhydramine (Benadryl)	Injection: 10 to 50 mg IV or IM as needed for motion sickness. May increase dose to 100 mg if required. Maximum daily dose of 400 mg.  Oral: 25 to 50 mg every six to eight hours in adults and children ages 12 years and older. Administer first dose 30 minutes prior to motion exposure and repeat before meals and before bedtime for the duration of the journey.	Ages six to twelve years: 12.5 mg to 25 mg every four to six hours (Do not exceed 150 mg in 24 hours)  Ages two to six years: 6.25 mg every four to six hours (Do not exceed 37.5 mg in 24 hours)	Tablets: 25, 50 mg Capsules: 25, 50 mg Injection: 50 mg per mL Oral dissolving film: 25 mg Oral solution: 12.5 mg per 5 mL
meclizine (Antivert, Dramamine Less Drowsy OTC, Univert)	Adults and children 12 years and older (OTC Dramamine Less Drowsy): one to two tablets once daily Adults: 25 to 50 mg every 24 hours (Do not exceed two tablets in 24 hours)	--	Chewable Tablets: 25 mg Tablets: 12.5, 25, 50 mg

**Dosages (continued)**

Antivertigo Agents <sup>160,161</sup>	Adult	Pediatric	Availability
<b>Phenothiazines</b>			
promethazine (Phenergan)	<p><b>Motion Sickness</b> Adults: 25 mg (oral or rectal) 30 to 60 minutes prior to departure, then every 12 hours as needed</p> <p><b>N/V</b> Adults: 12.5 to 25 mg every four to six hours as needed</p>	<p><b>Motion Sickness</b> Children over two years of age: 12.5 mg to 25 mg (oral or rectal) twice daily as needed</p> <p><b>N/V</b> Children over two years of age: 0.5 mg per pound (max 25 mg) every four to six hours as needed</p>	<p>Tablets: 12.5, 25, 50 mg Oral solution: 6.25 mg per 5 mL Suppositories: 12.5, 25, 50 mg Injection: 25 mg per mL 50 mg per mL</p>
prochlorperazine (Compazine, Compro)	<p>Immediate release tablets: 5 to 10 mg three to four times daily</p> <p>Rectal suppositories: 25 mg twice daily</p> <p>IV or IM: 5 to 10 mg repeated every 3 to 4 hours as needed (Max dose is 40 mg/day)</p>	<p>Oral or rectal: Children 2 to 12 years (weight 18 to 39 kg): 2.5 mg three times per day or 5 mg twice per day (max: 15 mg/day). Children 2 to 12 years (weight 14 to 17 kg): 2.5 mg two to three times per day (max: 10 mg/day). Children 2 to 12 years (weight 9 to 13 kg): 2.5 mg once or twice per day (max: 7.5 mg/day). Children &lt; 2 years of age and infants (weight &lt; 9 kg): Dosage not established.</p>	<p>Tablets, immediate-release: 5, 10 mg Suppositories: 25 mg Injection: 5 mg per mL</p>
<b>Anticholinergics</b>			
scopolamine (Maldemar, Scopace, Transderm-Scop)	<p><b>N/V-</b> SC injection: 0.6 to 1 mg Motion sickness- Transdermal: one disc applied behind the ear four hours prior to antiemetic need (Disc may stay in place for up to three days. If repeat dose needed, then apply to skin behind opposite ear. Oral: 250 to 800 mcg one hour prior to need for antiemetic</p>	<p><b>N/V-</b> SC injection: 0.006 mg per kg</p>	<p>Tablets: 0.4 mg Injection: 0.4 mg per mL Transdermal: 1.5 mg per 72 hours</p>

## ***Clinical Trials***

### Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

A number of clinical trials have evaluated ondansetron compared to other antiemetic agents. None of these trials have involved the use of the oral film used as the delivery mechanism in Zuplenz. While no clinical trials have been undertaken to evaluate Zuplenz, this product has demonstrated bioavailability similar to that of the orally disintegrating dosage form of ondansetron.

Antivertigo agents used in the prevention and treatment of N/V associated with motion sickness are included in this review. There is a paucity of clinical trial data available related to motion sickness, and the primary treatment option for this condition involves the use of older medications including the more sedating antihistamines. No clinical trials are included at this time related to vertigo and motion sickness prophylaxis and treatment.

### aprepitant (Emend) versus ondansetron (Zofran)

Patients receiving cisplatin were blindly assigned to receive one of the following three regimens: (1) aprepitant 375 mg one hour before cisplatin on Day 1 and aprepitant 250 mg on Days 2-5 (n=35); (2) aprepitant 125 mg before cisplatin and aprepitant 80 mg on Days 2-5 (n=81); or (3) placebo before cisplatin on Days 2-5 (n=86).<sup>162</sup> All groups received ondansetron 32 mg and dexamethasone 20 mg before cisplatin, and dexamethasone 8 mg on Days 2-5. The primary endpoint was complete response (no emesis and no rescue therapy) over five days following cisplatin in up to six cycles. The aprepitant 375/250 mg regimen was discontinued early in light of new pharmacokinetic data. In the first cycle, 64 percent of patients in the aprepitant group and 49 percent in the standard therapy group had a complete response (p<0.05). Thereafter, complete response rates for the aprepitant group were still 59 percent by Cycle 6, but decreased to 34 percent by Cycle 6 for the standard therapy group (p<0.05).

### dolasetron (Anzemet) versus ondansetron (Zofran)

A multicenter, randomized, double-blind study was designed to compare the antiemetic efficacy and safety of single oral doses of dolasetron with a multiple-dose regimen of oral ondansetron in 399 cancer patients receiving moderately emetogenic chemotherapy.<sup>163</sup> Single oral doses of 25, 50, 100, or 200 mg of dolasetron were administered one hour prior to the initiation of chemotherapy. Ondansetron 8 mg, or matching placebo for patients randomized to dolasetron, was given 1.5 hours before and 6.5, 14.5, and 22.5 hours after the start of chemotherapy. A

statistically significant ( $p < 0.001$ ) linear dose-response relationship was observed over the entire dolasetron dosage range for all efficacy parameters. Complete response rates were 45, 49.4, 60.5, and 76.3 percent for 25, 50, 100, and 200 mg dolasetron, respectively, and 72.3 percent for ondansetron patients. Overall, there were no significant differences in the incidence of adverse events between any of the dolasetron doses, or between dolasetron and ondansetron; headache was most frequently reported (approximately 15 percent for each drug). In the study, a single oral 200 mg dolasetron dose was therapeutically equivalent to multiple-dose ondansetron in the prevention of N/V following moderately emetogenic chemotherapy.

#### granisetron (Kytril) versus ondansetron (Zofran)

A double-blind study was conducted to determine the efficacy of oral ondansetron, oral granisetron, and IV ondansetron for the prevention/control of N/V associated with high-dose chemotherapy or radiotherapy prior to hematopoietic stem cell transplantation.<sup>164</sup> In addition to dexamethasone 10 mg IV, 102 patients were randomized to receive either ondansetron 8 mg orally every eight hours, granisetron 1 mg orally every 12 hours, or ondansetron 32 mg IV every 24 hours, each given on days one and two. Overall complete response rates were 48 percent for oral ondansetron, 47 percent for oral granisetron, and 49 percent for IV ondansetron; this difference is not statistically significant ( $p = \text{NS}$ ). Overall major efficacy rates were 82 percent for oral ondansetron, 84 percent for oral granisetron, and 81 percent for IV ondansetron ( $p = \text{NS}$ ). Mean VAS nausea scores were 32 for oral ondansetron, 32 for oral granisetron, and 27 for IV ondansetron ( $p = \text{NS}$ ).

A double-blind, randomized, crossover study comparing granisetron 3 mg/day and ondansetron 24 mg/day enrolled 309 patients receiving two cycles of identical chemotherapy over five days.<sup>165</sup> Primary efficacy variables were prospectively defined as complete response (no vomiting and mild or absent nausea) over five days and patient preference. Both agents achieved good control of emetic symptoms with five-day complete response rates of 44 percent on granisetron and 39.8 percent on ondansetron ( $p = \text{NS}$ ). Complete response rates were very similar in patients receiving either cisplatin or ifosfamide. There was a statistically significant difference in patient preference in favor of granisetron ( $p = 0.048$ ).

A randomized, cross-over pilot study of post-operative nausea and vomiting (PONV) was conducted in 250 female patients who received prophylactic ondansetron 4 mg at the end of a surgical procedure requiring general anesthesia.<sup>166</sup> Women were then followed post-operatively for four hours. Eighty-eight of the women developed PONV and were randomly assigned to receive one of the following: a repeat dose of ondansetron 4 mg ( $n = 30$ ), granisetron 1 mg ( $n = 30$ ), or granisetron 0.1 mg ( $n = 28$ ). They were followed for 24 hours. Patients who received the repeat dose of ondansetron had a complete response of 57 percent, those receiving granisetron 1 mg or 0.1 mg had complete responses of 60 percent and 68 percent, respectively. This difference was not statistically significant ( $p = 0.773$ ).

The efficacy of oral granisetron and oral ondansetron was compared for preemptive antiemesis in women undergoing modified radical mastectomy.<sup>167</sup> A randomized, double-blind, controlled study assigned 90 women, aged 18 to 65 years old, scheduled to receive radical mastectomies to receive orally granisetron 2 mg, ondansetron 4 mg, or placebo (30 women in each group) one hour before induction of anesthesia. Post-operative N/V was assessed until 24 hours post surgery. A complete response in zero to two hours after anesthesia was found in 43 percent, 63 percent, and 90 percent of patients who had received placebo, granisetron, or ondansetron, respectively; and of these, the percentages of patients requiring rescue antiemetics were 40 percent, 17 percent, and seven percent. The presence of N/V was less than 23 percent after

two hours in all three groups. Also, after two hours, N/V scores and need for antiemetics were similar in all three groups. Oral ondansetron 4 mg provided better preemptive antiemesis than oral granisetron 2 mg and placebo in the two hours following surgery with general anesthesia.

#### granisetron (Kytril) versus granisetron transdermal (Sancuso)

A Phase III, randomized, parallel-group, double-dummy, double-blind trial was conducted in 641 patients who receive multi-day chemotherapy to compare the efficacy, tolerability, and safety of granisetron transdermal to oral granisetron 2 mg once daily in the prevention of N/V.<sup>168</sup> The primary endpoint was proportion of patients achieving no vomiting and/or retching, no more than mild nausea, and without use of a rescue medication from the first administration until 24 hours after start of the last day's administration of multi-day chemotherapy. The effect of granisetron transdermal was established in 60.2 percent of patients and in 64.8 percent of the patient taking granisetron orally (p=NS).

#### granisetron (Kytril) versus palonosetron (Aloxi) for injection

A Phase III, multicenter, randomized, double-blind, double-dummy, stratified, parallel-group, active-comparator trial was conducted in 1,143 Japanese patients with cancer who received multi-day, highly emetogenic cancer chemotherapy (HEC) to compare the efficacy and safety of palonosetron versus granisetron for chemotherapy-induced N/V (CINV) with coadministration of dexamethasone.<sup>169</sup> HEC consisted of cisplatin or an anthracycline and cyclophosphamide combination (AC/EC). Patients were randomized to receive either single-dose palonosetron 0.75 mg or granisetron 40 mcg/kg on day one 30 minutes prior to the start of chemotherapy. Also, on day one, patients received dexamethasone 16 mg IV followed by an additional 8 mg IV for patients receiving IV cisplatin or 4 mg orally for patients receiving AC/EC on days two and three. The primary endpoints were the proportion of patients with a complete response (defined as no emetic episodes and no rescue medication) during the acute phase (zero to 24 hours after chemotherapy – considered a non-inferiority comparison with granisetron) and the proportion of patients with a complete response during the delayed phase (24 to 120 hours after chemotherapy – superiority comparison with granisetron). Approximately 1,114 patients were included in the efficacy analyses: 555 patients in the palonosetron group and 559 patients in the granisetron group. Of the 555 patients treated with palonosetron, 418 (75.3 percent) had a complete response during the acute phase compared with 410 of the 559 patients (73.3 percent) treated with granisetron [mean difference of 2.9 percent, 95% CI, -2.7 to 7.27]. During the delayed phase, 315 of 555 patients (56.8 percent) had a complete response in the palonosetron group compared with 249 of 559 patients (44.5 percent) in the granisetron group (p<0.0001). According to the authors, when administered with dexamethasone prior to HEC, palonosetron is non-inferior to granisetron in the acute phase and superior in the delayed phase. There is a comparable safety profile for both treatments.

#### dronabinol (Marinol), ondansetron (Zofran), combination therapy versus placebo

A five-day, double-blind, placebo-controlled study was conducted in 64 patients to compare the efficacy and tolerability of dronabinol, ondansetron, or the combination for delayed chemotherapy-induced nausea and vomiting (CINV).<sup>170</sup> Patients receiving moderately to highly emetogenic chemotherapy received dexamethasone 20 mg orally, ondansetron 16 mg IV, and either placebo or dronabinol 2.5 mg pre-chemotherapy on day one. Patients randomized to active treatment (dronabinol and/or ondansetron) also received dronabinol 2.5 mg after chemotherapy on day one. On day two, fixed doses of placebo, dronabinol 10 mg, ondansetron 16 mg, or combination therapy were administered. On days three to five, patients received

placebo, flexible doses of dronabinol 10 to 20 mg, ondansetron 8 to 16 mg, or dronabinol 10 to 20 mg and ondansetron 8 to 16 mg. The primary outcome was a total response (TR) of nausea intensity < 5 mm on visual analog scale, no vomiting/retching and no use of rescue antiemetic. The TR was similar for the active treatments: dronabinol (54 percent), ondansetron (58 percent), and combination (47 percent) versus placebo (20 percent). Nausea absence was significantly greater for the active treatment groups versus placebo (15 percent): dronabinol (71 percent), ondansetron (64 percent), and combination (53 percent,  $p < 0.05$  for all). Nausea intensity and vomiting/retching were lowest in patients treated with dronabinol. Dronabinol or ondansetron were similarly effective for the treatment of CINV. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone. All active treatments were well tolerated. The population size is the greatest limitation of these data.

#### orally disintegrating ondansetron (Zofran ODT) versus conventional tablet formulation of ondansetron (Zofran)

Due to a lack of other available data, this study has been included. The efficacy of ondansetron ODT was compared to the conventional oral tablet of ondansetron in controlling N/V among breast cancer patients receiving high-dose epirubicin.<sup>171</sup> In a randomized trial, 134 patients received ondansetron ODT 8 mg twice daily or ondansetron tablet 8 mg twice daily, both for three days. Ondansetron tablet was significantly better at controlling emesis (72 percent versus 52 percent, respectively,  $p = 0.020$ ) and statistically insignificant when attempting to control nausea (66 percent versus 48 percent, respectively,  $p = 0.054$ ) compared to ondansetron ODT. However, when looking at major control of emesis (as having zero to two emetic episodes during the three days) between the conventional ondansetron tablet versus ondansetron ODT, there was no real difference (76 percent versus 70 percent, respectively,  $p = 0.28$ ). For control of major emesis and nausea, there are no major differences between the formulations.

#### ondansetron (Zofran) versus transdermal scopolamine (Transderm-Scop)

A randomized, double blind, multicenter trial of 620 at-risk female patients undergoing outpatient laparoscopic or breast augmentation surgery was conducted to compare the impact of combination therapy versus monotherapy in the reduction of post-operative N/V.<sup>172</sup> Patients received either an active transdermal scopolamine patch or a placebo patch two hours before entering the operating room. Patients also received ondansetron 4 mg shortly before induction of anesthesia. Response to antiemetics, time to rescue antiemetics, number of doses of rescue antiemetics, severity and number of nausea and vomiting episodes were recorded. The combination of transdermal scopolamine and ondansetron statistically significantly reduced nausea and vomiting compared with ondansetron alone 24 hours after surgery. However, the same observations were not applicable at 48 hours post surgery. The proportion of patients who did not experience vomiting and did not use rescue medication was 48 percent for the combination group and 39 percent for the ondansetron group ( $p < 0.02$ ). Total response (no nausea, no vomiting/retching, and no use of rescue medication) was also statistically higher for the combination group compared with the ondansetron-only group (35 percent versus 25 percent,  $p < 0.01$ ). The time to first nausea, vomiting/retching, or rescue episode was statistically significantly longer for the combination group compared with the ondansetron-only group ( $p < 0.05$ ).

#### **Summary**

The 5-HT<sub>3</sub> antagonists offer significant advantages in the prevention of N/V due to chemotherapy and radiotherapy. Based on available data, there appears to be little significant difference among the drugs in this class. All of the available antiemesis guidelines reflect this

stance. Granisetron transdermal (Sancuso) may offer benefit to select patients undergoing moderate to highly emetogenic chemotherapy regimens who cannot tolerate other formulations. The transdermal formulation did demonstrate non-inferiority in efficacy to the oral formulation of granisetron. The ondansetron oral soluble film (Zuplenz) has demonstrated bioavailability similar to that of the orally disintegrating dosage form of ondansetron.

Aprepitant (Emend) can be used in combination with either dexamethasone or a 5-HT<sub>3</sub> receptor antagonist when treating chemotherapy-induced N/V or for use as monotherapy in prevention of post-operative N/V, but its effectiveness has not been compared to other agents for these uses.

The synthetic cannabinoids are recommended as second-line therapy for chemotherapy induced N/V when patients fail to respond adequately to conventional antiemetics. The significant risk for abuse and misuse, increased potential for drug interactions, and increased risk for psychotomimetic reactions that has not been observed with other oral antiemetics suggest the cannabinoids should be monitored closely and reserved for specific use only.

There are both non-pharmacologic and pharmacologic interventions for the prevention or management of motion sickness. None are ideal, and the medications used including antihistamines, phenothiazines and anticholinergics typically cause drowsiness or similar adverse effects.

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