

# Update on the Management of Postoperative Nausea and Vomiting and Postdischarge Nausea and Vomiting in Ambulatory Surgery

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## KEYWORDS

- Ambulatory surgery • Antiemetic • Multimodal prevention
- Postoperative nausea and vomiting
- Postdischarge nausea and vomiting • Prophylaxis

Over the past several decades, as the risk of major mortality due to surgery has decreased, attention has shifted to addressing factors that negatively influence patient morbidity and patient satisfaction, such as postoperative nausea and vomiting (PONV). Since the previous article on PONV in this publication,<sup>1</sup> several developments have aided in the prevention and management of this complication of surgical anesthesia. The 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) receptor antagonists continue to be the mainstay of antiemetic therapy, but newer approaches, such as neurokinin-1 antagonists, a longer-acting serotonin receptor antagonist, multimodal management, and novel techniques for managing high-risk patients, are gaining prominence.

PONV continues to be one of the most common complaints following surgery, occurring in more than 30% of surgeries, or as high as 70% to 80% in certain high-risk populations without prophylaxis.<sup>2</sup> Though generally nonfatal and self-limited, PONV may lead to rare but serious medical consequences, including dehydration and electrolyte imbalance, venous hypertension, bleeding, hematoma formation, suture dehiscence, esophageal rupture,<sup>3,4,5</sup> blindness,<sup>6</sup> and aspiration.<sup>7</sup> PONV also has a profound impact on patient satisfaction, quality of life, and estimated health

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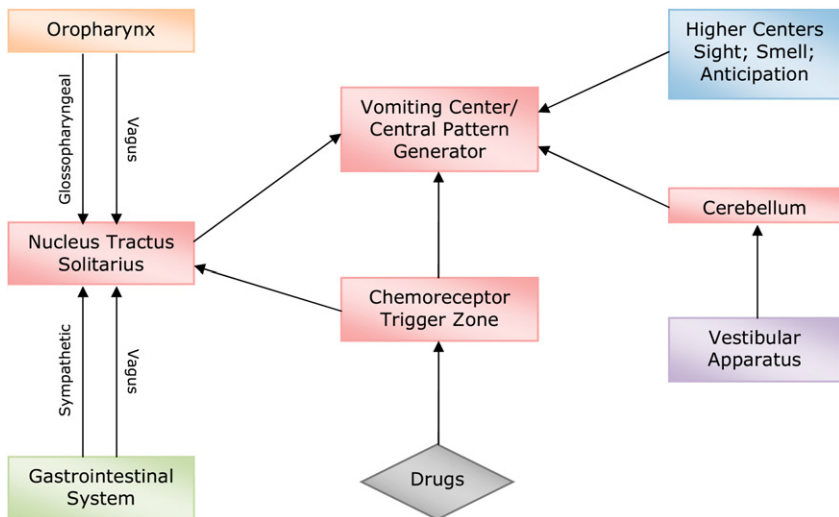
care costs as a result of delayed discharge, prolonged nursing care, and unanticipated hospital admissions.<sup>8,9</sup> PONV is often cited as one of the postsurgical complications patients would most like to avoid, and patients have reported being willing to pay between \$56 and \$100 out of pocket for an effective antiemetic.<sup>10</sup>

Nausea and vomiting due to surgery may also occur beyond the immediate postoperative period. Although not as well studied as PONV, the related problem of postdischarge nausea and vomiting (PDNV) has received increasing attention from health care providers, especially because patients who experience no PONV immediately after surgery may develop PDNV after discharge. In one study, approximately 36% of patients who experience PDNV had not experienced any nausea or vomiting before discharge.<sup>11</sup> Surveys of patients following ambulatory surgery have found PDNV to range between approximately 20% and 50%, resulting in increased difficulty in performing activities of daily living and longer recovery times before resuming normal activity.<sup>11–14</sup>

The issues of PONV and PDNV are especially significant in the context of ambulatory surgeries, which comprise more than 60% of the combined 56.4 million ambulatory and inpatient surgery visits in the United States.<sup>15</sup> Although the incidence of PONV and PDNV in ambulatory surgeries may be slightly lower than that of inpatient surgeries, it is believed to be underreported, given the limited amount of time that ambulatory surgery patients spend under direct medical care.<sup>16</sup> Yet because of this relatively brief period that ambulatory patients spend in health care facilities, it is particularly important to prevent and treat PONV and PDNV swiftly and effectively.

## MECHANISM OF EMESIS

Much of our current understanding of the basic neuroanatomy and physiology of emesis comes from the work of Wang and Borison in the 1950s.<sup>17,18</sup> The central coordinating site for nausea and vomiting is located in an ill-defined area of the lateral reticular formation in the brainstem (**Fig. 1**).<sup>18</sup> This “vomiting center,” as it is traditionally called, is not so much a discrete center of emetic activity as it is a “central pattern generator” (CPG) that sets off a specific sequence of neuronal activities throughout the medulla to result in vomiting.<sup>19</sup> Multiple inputs may arrive from areas such as



**Fig. 1.** Mechanism of nausea and vomiting.

the higher cortical centers, cerebellum, vestibular apparatus, vagal, and glossopharyngeal nerve afferents to trigger the complex motor response of emesis; direct electrical stimulation of the CPG also causes emesis.<sup>20</sup> A particularly important afferent is the chemoreceptor trigger zone (CTZ), located at the base of the fourth ventricle in the area postrema and outside the blood-brain barrier, which plays a role in detecting emetogenic agents in the blood and cerebrospinal fluid (CSF).<sup>21</sup> Although direct electrical stimulation of the CTZ does not cause vomiting, the CTZ communicates with the adjacent nucleus tractus solitarius (NTS), which in turn projects into the CPG.<sup>22</sup> Signals between these anatomic areas are mediated through a variety of neurotransmitter receptor systems, including serotonergic, dopaminergic, histaminergic, cholinergic, and neurokininergic; antiemetic prophylaxis or therapies block one or more of the associated receptors, including serotonin 5-HT<sub>3</sub>, dopamine D<sub>2</sub>, histamine H<sub>1</sub>, muscarinic cholinergic, and neurokinin NK<sub>1</sub>.<sup>23</sup>

### RISK FACTORS AND PROTECTIVE FACTORS FOR PONV AND PDNV

Assessment of patient risk factors is a key component in guiding antiemetic prevention and management strategies. A variety of surgical, anesthetic, and patient factors have been investigated as predictors of patient risk for PONV, the most significant of which are listed in **Table 1**. However, according to the 2007 Society for Ambulatory Anesthesia (SAMBA) Guidelines for the Management of PONV, only a few baseline risk factors occur with enough consistency to be validated as independent predictors for PONV.<sup>24</sup> Several predictive models have been developed to stratify risk for PONV, but a simplified scoring system by Apfel and colleagues<sup>25,26</sup> continues to be one of the most popular and compares favorably against other scoring systems. In a 2-center inpatient study, Apfel and colleagues<sup>27</sup> identified 4 highly predictive risk factors for PONV: female gender, history of motion sickness or PONV, nonsmoker, and use of perioperative opioids. The presence of 0, 1, 2, 3, or 4 of these factors corresponded to a PONV incidence of 10%, 21%, 39%, 61%, and 79%, respectively. The Apfel score may be used to guide antiemetic strategies for high-risk patients, and in at least 2 studies, prophylaxis based on Apfel scores has led to a significant decrease the incidence of PONV.<sup>28,29</sup>

The use of risk scores in predicting postoperative vomiting (POV) has also been extended to the pediatric population with the P<sub>O</sub>stoperative V<sub>O</sub>miting in Children score (POVOC score).<sup>30</sup> The incidence of POV in pediatric patients is estimated to

**Table 1**  
Risk factors for PONV and PDNV

Patient Factors	Anesthetic Factors	Surgical Factors
Female	Use of perioperative opioids	Duration of surgery
Nonsmoker	Use of volatile anesthetics	Type of surgery, including:
History of motion sickness or previous PONV	Nitrous oxide	Abdominal
Family history of motion sickness or PONV (pediatric)		Ear, nose, and throat
Age $\geq 3$ y (pediatric)		Gynecologic
		Laparoscopic
		Ophthalmologic
		Orthopedic
		Plastic
		Strabismus (pediatric)

be about between 9% and 42% overall, and as high as 80% for specific types of surgery.<sup>31</sup> However, it should be noted that nausea is often not recorded, as it is often difficult to assess in this younger patient population. To develop the POVOC score, Eberhart and colleagues<sup>30</sup> compiled data from 1257 pediatric surgeries at 4 institutions and identified 4 independent risk factors for POV: duration of surgery 30 minutes or longer, age 3 years or older, strabismus surgery, and a positive history of POV in the child or POV/PONV in relatives (mother, father, or siblings). Similar to the Apfel score, the incidence of POV was 9%, 10%, 30%, 55%, and 70% for 0, 1, 2, 3, and 4 risk factors present, respectively. To date, there has only been one external validation study, which found that a modified POVOC score (excluding strabismus surgery) accurately predicted POV in pediatric patients, at a level comparable to the Apfel score for adults.<sup>32</sup>

The 1999 study by Sinclair and colleagues,<sup>33</sup> spanning 3 years and involving more than 17,000 patients, continues to be the most comprehensive examination of PONV risk factors specifically in ambulatory surgery patients. In addition to the 4 factors identified by Apfel and colleagues, duration of anesthesia longer than 30 minutes, general anesthesia, and type of surgery were also cited as independent predictors of PONV. However, it should be noted that while certain types of surgeries (particularly plastic, ophthalmologic, and orthopedic surgeries) appear to be correlated with higher rates of PONV, there is conflicting evidence as to whether other independent risk factors associated with type of surgery are actually responsible for the increased rates of PONV.<sup>24</sup> Other studies, not confined specifically to ambulatory surgery patients, have also pointed to the use of volatile anesthetics, use of nitrous oxide, and administration of intraoperative and postoperative opioids as significant risk factors for PONV.<sup>24,34–37</sup>

Risk factors for PDNV have mainly been studied in the context of risk factors for PONV. However, a recent study by White and colleagues<sup>38</sup> suggests that while higher Apfel scores correlate to a greater incidence of PONV symptoms in the early (0–24 hours) postoperative period, it appears to have little predictive value for emetic symptoms occurring in the late (24–72 hours) postoperative/postdischarge period. Nevertheless, the few studies attempting to identify specific PDNV risk factors have found them to be similar to those typically associated with PONV. Mattila and colleagues<sup>14</sup> evaluated postdischarge symptoms in 2754 adult and pediatric ambulatory surgery patients, and found that the odds ratios (ORs) of postdischarge vomiting were 0.23 and 0.26 for local and spinal anesthesia, respectively, when compared with general anesthesia. Female gender was also a risk factor for PDNV, with ORs of 2.74 and 2.79 for nausea and vomiting, respectively. Duration of surgery longer than 30 minutes increased the risk for nausea only, with a 56% increase in incidence of postdischarge nausea for surgeries 30 to 59 minutes' duration, and a 64% increase for surgeries 60 minutes or longer. However, type of surgical procedure had no impact.

In the same study, no specific risk factors for postdischarge vomiting could be identified in the pediatric population, although use of general anesthesia, age 3 years or older, and duration of surgery 30 minutes or longer correlated with an increased risk of postdischarge nausea.<sup>14</sup> Other studies have suggested that PDNV in children may be correlated to factors such as emetic symptoms prior to discharge, increased age, duration of journey home after discharge, pain at home, and use of postoperative opioids, but these associations need further study.<sup>24,39,40</sup>

## ANTIEMETICS IN CLINICAL PRACTICE

Most antiemetic agents act on one or more of the neurotransmitter receptor types found in the anatomic sites responsible for emesis. To date, no single agent has

been found to block all receptor types, nor is there any single drug that is completely effective against PONV in all cases. Thus, appropriate prevention and management of PONV and PDNV require familiarity with a broad range of drug classes. In comparing various antiemetics and the evidence for or against them, it is helpful to determine the number needed to treat (NNT), or the number of patients that must be exposed to a particular intervention in order for one patient to benefit over receiving placebo or no treatment. The number needed to harm (NNH) is an estimate of the frequency of drug-related adverse effects. A list of common antiemetics, typical dosages, and NNT are listed in **Table 2**.

### Serotonin Antagonists

Since their introduction in the early 1990s to treat chemotherapy-induced nausea and vomiting,<sup>41</sup> serotonin antagonists have become one of the cornerstones of modern antiemetic prophylaxis and therapy, particularly in the setting of PONV. Serotonin is found in high levels in the enterochromaffin cells of the gastrointestinal tract, as well as in the central nervous system, and may be released to stimulate either the vagal afferent neurons or the CTZ to activate the vomiting center.<sup>42</sup> Although there are multiple serotonin receptor types, the 5-HT<sub>3</sub> subtype appears in its greatest concentration in the NTS, area postrema, and the dorsal motor nucleus of the vagus nerve, which all play a significant role in coordinating the vomiting reflex.<sup>43</sup> The 5-HT<sub>3</sub> receptor antagonists (5-HT<sub>3</sub> RAs), which include ondansetron, granisetron, dolasetron, ramosetron, tropisetron, and most recently palonosetron, act by inhibiting the action of serotonin in 5-HT<sub>3</sub> receptor-rich areas of the brain.

Ondansetron (Zofran), granisetron (Kytril), dolasetron (Anzemet), and palonosetron (Aloxi) are all approved for use in PONV by the Food and Drug Administration (FDA) (ramosetron and tropisetron are not available in the United States). In general, all of the 5-HT<sub>3</sub> RAs are safe, effective, and have similar side effect profiles. Side effects are usually short term and of mild to moderate intensity, with the most common being headache, dizziness, constipation, and diarrhea.<sup>44–47</sup> However, the differing chemical

**Table 2**  
Number needed to treat (NNT) for common prophylactic antiemetic regimens

Agent or Strategies	NNT		
	Nausea	Vomiting	PONV
Ondansetron 4 mg IV <sup>53</sup>	4.6	6.4	4.4
Dexamethasone 8 mg IV or 10 mg PO (adults) <sup>75</sup>	Early 5.0 Late 4.3	Early 3.6 Late 4.3	
Dexamethasone 1–1.5 mg/kg IV (children) <sup>75</sup>		Early 10 Late 3.1	
Transdermal scopolamine 1.5 mg patch <sup>82</sup>	4.3	5.6	3.8
Droperidol 0.625–1.25 mg IV <sup>85</sup>	5	7	
Haloperidol 0.5–4 mg IM/IV <sup>92</sup>	3.2–4.5	3.9–5.1	
Metoclopramide 10 mg IV <sup>100</sup>	No significant effect	Early 9.1 Late 10	
Propofol infusion <sup>105</sup>	8.6 (Postdischarge 12.5)	11.2 (Postdischarge 10.3)	
Acupuncture <sup>123</sup>	30% baseline risk 11 70% baseline risk 5	30% baseline risk 11 70% baseline risk 5	

structures of each drug may explain slight differences in receptor binding affinity, dose response, and duration of action.<sup>23</sup> Most available data suggest that 5-HT<sub>3</sub> RAs are most effective when administered at the end of surgery,<sup>48–50</sup> but at least one study has suggested that dolasetron may be administered around the time of induction of anesthesia, with little effect on efficacy.<sup>51</sup>

All of the 5-HT<sub>3</sub> RAs are equally effective for the treatment of PONV.<sup>52</sup> Ondansetron, as the prototypical 5-HT<sub>3</sub> RA, has been the most studied. In a quantitative systematic review of placebo-controlled trials of ondansetron, Tramèr and colleagues<sup>53</sup> found that ondansetron, 4 mg had an NNT of about 4.6 for the prevention of vomiting, 6.4 for the prevention of nausea, and 4.4 for the prevention of both in the first 48 hours postoperatively. Risk of severe side effects was generally low, with an NNH of 36 for headache, 31 for elevated liver enzymes, and 23 for constipation. This study and others have also suggested that ondansetron is slightly more effective against vomiting than nausea.<sup>52,53</sup> However, a recent study by Jokela and colleagues<sup>54</sup> found that 4 mg ondansetron reduced the incidence of nausea by 26% over placebo, and vomiting by 33%, a difference that the investigators concluded was not of statistical significance. While not commenting on the anti-nausea versus anti-vomiting properties of ondansetron, a Cochrane systematic review found that ondansetron reduces the relative risk of nausea and vomiting by 32% and 45% over placebo, respectively.<sup>55</sup> The review also evaluated 5 studies of ondansetron and reported no evidence that the risk of PONV differed for groups based on timing of administration. Controversy also exists as to whether ondansetron offers greater benefit for PONV prophylaxis greater than 4 mg,<sup>56–59</sup> and a study in ferrets has found that the dose-response curve for ondansetron is unique in that it has better antiemetic efficacy at low (<50 µg/kg subcutaneously) and high (>100 µg/kg subcutaneously) doses.<sup>60</sup> However, for the purposes of clinical practice the usual recommended dose of ondansetron in humans is 4 mg intravenously (IV), administered at the end of surgery.<sup>24</sup>

Unlike ondansetron, the other 5-HT<sub>3</sub> RAs exhibit linear dose-response curves, with increasing doses achieving greater clinical effect until the maximal effective dose is reached.<sup>61</sup> The dose recommended for PONV prophylaxis with granisetron is 0.35 to 1.5 mg IV (5–20 µg/kg).<sup>24,62,63</sup> In a multicenter, dose-ranging study, Taylor and colleagues<sup>64</sup> found that intravenous doses as low as 0.1 mg given at the first symptoms of nausea or vomiting were effective in increasing the percentage of patients experiencing no vomiting in the first 24 hours to 38%, compared to 20% of patients with no vomiting on placebo. The recommended dose for dolasetron is 12.5 mg IV,<sup>24</sup> based on a trial demonstrating that single-dose dolasetron 12.5 mg administered before the end of surgery resulted in a greater than 50% increase in complete response (CR; no emesis and no rescue medication for 24 hours) over placebo, with no significant increase in CR at 25- or 50-mg doses.<sup>65</sup>

Palonosetron is the newest 5-HT<sub>3</sub> RA and has recently been approved in the United States for PONV. Unlike other drugs in its class, which exhibit simple bimolecular binding, palonosetron exhibits positive cooperativity in binding to its receptor; moreover, its molecular structure does not mimic that of serotonin and it therefore does not bind at the serotonin binding site of the 5-HT<sub>3</sub> receptor.<sup>66</sup> As a result, palonosetron may bind more tightly to the receptor, allow multiple palonosetron molecules to bind to a single receptor, and make it less likely to be displaced by serotonin molecules.<sup>67</sup> Furthermore, some data suggest that palonosetron may promote internalization of the 5-HT<sub>3</sub> receptor as an inverse agonist (similar to some G-protein coupled receptor antagonists), decreasing the function of the receptor in the absence of

agonist exposure.<sup>66</sup> Thus, receptor internalization may contribute to palonosetron's relatively long duration of action.

A large, randomized, placebo-controlled study by Candiotti and colleagues<sup>68</sup> found that 43% of patients given palonosetron 0.075 mg before induction exhibited CR in the 0 to 24 hours postoperatively, compared with 20% of patients who received placebo. Moreover, patients receiving palonosetron reported less severe nausea and decreased interference in postoperative function due to PONV. A separate study of European patients by Kovac and colleagues<sup>69</sup> found similar results for palonosetron, 0.075 mg in increasing CR rates, and the investigators also noted continued efficacy of palonosetron over placebo for 24 to 72 hours. It has been suggested that the long half-life of palonosetron may confer an antiemetic effect for several days after administration, which would be particularly useful in minimizing PDNV following ambulatory surgery; however, further studies are necessary to confirm any advantage over other serotonin antagonists.

Few studies have examined 5-HT<sub>3</sub> RAs for the prevention of PDNV. A systematic review by Gupta and colleagues<sup>13</sup> found that ondansetron 4 mg resulted in a relative risk reduction of 23% and 37% for postdischarge nausea and vomiting, respectively. However, it should be noted that the NNT was 12.9 for nausea and 13.6 for vomiting. Ondansetron, granisetron, and dolasetron are available as intravenous medications or oral tablets; palonosetron is currently only available as an intravenous medication. Ondansetron is also available as an orally disintegrating tablet (ODT), which seems to be as effective as the intravenous form.<sup>70</sup> Some studies suggest that providing patients with the ODT before discharge may be particularly helpful in reducing the incidence of PDNV at home. In a study of pediatric patients, Davis and colleagues<sup>71</sup> found that only 14.5% of children who received 5 at-home doses of ondansetron ODT experienced postdischarge vomiting, compared with 32% of children receiving placebo. A small study by Gan and colleagues<sup>72</sup> found a decreased incidence of PDNV and PDNV severity in patients receiving ondansetron ODT following ambulatory surgery.

A relatively new but growing field in 5-HT<sub>3</sub> RA research is that of pharmacogenomics. The 5-HT<sub>3</sub> RAs are metabolized by cytochrome P450 in the liver, and differences in the activity or levels of the CYP2D6 isoform of the enzyme appear to have an effect on the pharmacokinetics and clinical efficacy of the drug in certain individuals.<sup>23</sup> Candiotti and colleagues<sup>73</sup> have reported that patients with 3 copies of the CYP2D6 gene or who have certain genetic polymorphisms in the CYP2D6 gene are ultrarapid metabolizers of ondansetron and are more likely to experience ondansetron failure for POV. Another recent study by Rueffert and colleagues<sup>74</sup> analyzed DNA from 95 patients who had suffered from POV and matched them with 94 controls. The researchers found that variations in the genes of the serotonin receptor subunits, HTR3A and HTR3B, were associated with increased individual risk of developing POV. Although pharmacogenomic research is still in its early stages and it is currently of limited use in actual clinical practice, it may provide greater insights into assessing individual patient risk for PONV in the future.

### **Steroids**

Dexamethasone has been shown to be useful in the management of PONV. The mechanism of its antiemetic activity has not been fully elucidated, but it is believed that corticosteroids act centrally to inhibit prostaglandin synthesis or to control endorphin release.<sup>75</sup> Dexamethasone may also be particularly effective when used in



combination with 5-HT<sub>3</sub> receptor antagonists, as it may (1) reduce levels of serotonin by depleting its precursor tryptophan, (2) prevent release of serotonin in the gut, and (3) sensitize the 5-HT<sub>3</sub> receptor to other antiemetics.<sup>75</sup>

According to a study by Wang and colleagues,<sup>76</sup> dexamethasone is most effective for PONV prophylaxis when administered at induction rather than at the end of surgery. A systematic review and meta-analysis of 17 trials by Karanicolas and colleagues<sup>77</sup> found that dexamethasone reduced the incidence of postoperative nausea (PON) by 41%, POV by 59%, and nausea or vomiting by 45% relative to placebo, with the incidences of headache and dizziness being similar between the 2 groups. These results are similar to an earlier quantitative systematic review, which reported an NNT of 7.1 for the prevention of early vomiting in adults and children, and 3.8 for the prevention of late vomiting.<sup>75</sup> Karanicolas and colleagues<sup>77</sup> also reported that doses of 8 to 16 mg were significantly more effective at reducing PONV than doses of 2 to 5 mg, consistent with an earlier study by Elhakim and colleagues concluding that a dose of 8 mg dexamethasone provided maximal PONV prophylaxis when combined with ondansetron.<sup>78</sup> However, the SAMBA guidelines recommend a prophylactic dose of dexamethasone 4 to 5 mg IV at induction, which seems to be as effective as ondansetron 4 mg IV in preventing PONV.<sup>24</sup>

### ***Cholinergic Antagonists***

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The anticholinergic agents are among the oldest antiemetics. Both scopolamine (hyoscine) and atropine block muscarinic cholinergic emetic receptors in the cerebral cortex and the pons.<sup>79</sup> However, atropine has weaker antiemetic effects than scopolamine<sup>80</sup> and is generally not used in the postoperative period because of its cardiovascular effects.<sup>1</sup>

Most studies of scopolamine for use in PONV have investigated transdermal scopolamine (TDS) patch, designed to release 1.5 mg of scopolamine over 3 days. In a double-blind sham and placebo-controlled study of 150 patients, White and colleagues<sup>81</sup> compared preoperative transdermal scopolamine (TDS) 1.5 mg patch to intravenous ondansetron 4 mg or droperidol 1.25 mg administered before the end of surgery. The investigators found that premedication with TDS was as effective as ondansetron or droperidol in the prevention of both early and late PONV/PDNU, but also noted that TDS was associated with a greater risk of dry mouth. These findings correlate with an earlier quantitative systematic review by Kranke and colleagues,<sup>82</sup> which found that although TDS is an effective antiemetic and has an NNT of 5.6 for the prevention of POV, the NNH is 5.6 for visual disturbances, 12.5 for dry mouth, and 50 for dizziness. Thus, the high rate of anticholinergic side effects of scopolamine may limit its use as a stand-alone antiemetic agent.

Scopolamine may be most useful as an adjunct to other antiemetics. In a trial of outpatient plastic surgery patients at high risk for PONV, Sah and colleagues<sup>83</sup> found that those who received a preoperative TDS patch in addition to intraoperative ondansetron had a statistically significant reduction in PON between 8 and 24 hours in comparison with those who received a placebo patch and ondansetron only. However, a similar, larger, multicenter trial found that a combination TDS and ondansetron reduced PONV as compared with ondansetron alone 24 hours after surgery, but not at 48 hours.<sup>84</sup> This study also noted that the incidence of adverse effects, including anticholinergic effects was not statistically different between the 2 groups, while patient satisfaction in the TDS group was significantly higher, suggesting that scopolamine might be a safe and effective adjunct in the management of PONV, especially when used in combination with ondansetron.



## **Dopamine Antagonists**

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The dopamine receptor antagonists act at the  $D_2$  receptors in the CTZ and area postrema to suppress nausea and vomiting. There are 3 types of dopamine antagonists commonly used as antiemetics: butyrophenones, benzamides, and phenothiazines.

### **Butyrophenones**

In addition to their strong  $D_2$  receptor antagonism, the butyrophenones are  $\alpha$ -blockers, contributing to their adverse effects of sedation and extrapyramidal symptoms, although the latter are rare at the low doses given for PONV.<sup>80</sup> The 2 primary antiemetic agents in this group are haloperidol and droperidol. The clinical efficacy of droperidol 0.625 to 1.25 mg IV before the end of surgery has been well established,<sup>85,86</sup> and until recently it had been widely used in the prevention and management of PONV as a cost-effective antiemetic. The IMPACT trial, a factorial trial of more than 5000 patients, found that droperidol is as effective as ondansetron and dexamethasone in reducing the risk of PONV.<sup>2</sup> A meta-analysis by Leslie and Gan<sup>87</sup> examining the safety of the 5-HT<sub>3</sub> antagonists with dexamethasone or droperidol found that all were generally well tolerated and had comparable safety profiles, even when used in combination.

However, in 2001 the FDA issued a “black box” warning for droperidol, citing reports of severe cardiac arrhythmias (eg, torsades de pointes) and rare cases of sudden cardiac death associated with the use of droperidol.<sup>88</sup> Although the use of droperidol has declined precipitously since then, many experts and anesthesia providers still believe that the warning was not justified, and that droperidol remains a safe, effective, and economical antiemetic.<sup>88–90</sup> Nevertheless, the warning, along with the FDA’s recommendation that all elective surgery patients receiving droperidol be placed on continuous electrocardiographic monitoring for 2 to 3 hours following administration, has limited its use in the ambulatory setting.

Accordingly, there has been an increased interest in haloperidol as an antiemetic. Haloperidol has been used primarily as a potent antipsychotic since the 1960s.<sup>91</sup> Haloperidol has a faster onset of antiemetic action and has a longer half-life than droperidol, but its effect does not last as long, most likely because it has a weaker binding affinity than droperidol for the  $D_2$  receptors in the CTZ and area postrema.<sup>80</sup> In a meta-analysis of published and unpublished trials from 1962 to 1988, Buttner and colleagues<sup>92</sup> found that haloperidol 0.5 to 4 mg was effective for established PONV over placebo, with an NNT of 3.2 to 5.1 over the first 24 hours postoperatively, although some of the trials included had flaws in design or data reporting. A small study of 90 nonsmoking, female patients in Taiwan found that haloperidol 2 mg IV was as effective as ondansetron 4 mg IV in preventing PONV for the first 24 hours, with no QTc prolongation observed.<sup>92</sup> A similar study also did not observe QTc prolongation and found that haloperidol 1 mg IV was similar to ondansetron 4 mg IV, but both medications were only effective antiemetics relative to placebo in the early postoperative phase (0–2 hours).<sup>93</sup> More recent studies by Rosow and colleagues<sup>94,95</sup> have demonstrated the antiemetic efficacy of haloperidol over placebo and increased efficacy of haloperidol with ondansetron over ondansetron alone. However, additional studies are necessary to determine optimal dosing, timing, and safety profile before haloperidol may be used in regular clinical practice, either as prophylaxis or treatment.

### **Phenothiazines**

The phenothiazines, which include promethazine, chlorpromazine, prochlorperazine, perphenazine, and thiethylperazine, are some of the most commonly used antiemetics in the world. However, their use has fallen out of favor due to their high incidence of

adverse effects, such as sedation, restlessness, diarrhea, agitation, and central nervous system depression, and more rarely, extrapyramidal effects, hypotension, neuroleptic syndrome, and supraventricular tachycardia.<sup>23</sup> Promethazine 12.5 to 25 mg IV given at the induction of surgery,<sup>96</sup> and prochlorperazine 5 to 10 mg IV given at the end of surgery<sup>97</sup> have both been shown to have antiemetic efficacy when combined with ondansetron. A retrospective review has also suggested that promethazine 6.25 mg, a dose low enough to limit most adverse effects, may be more effective than ondansetron for treating PONV in patients who have failed previous ondansetron prophylaxis.<sup>98</sup> However, strong data are lacking and phenothiazines are currently not recommended as first-line antiemetic agents.<sup>24</sup>

### ***Benzamides***

The most commonly used antiemetic in this group is metoclopramide, a procainimide derivative that blocks D<sub>2</sub> receptors both centrally at the CTZ and area postrema, and peripherally in the gastrointestinal tract.<sup>80</sup> Metoclopramide increases lower esophageal tone and promotes gastric motility, which may make it useful in preventing the delayed gastric emptying caused by opioids.<sup>99</sup> A quantitative systematic review of 66 studies using various regimens of metoclopramide found no significant anti-nausea effect, an NNT of 9.1 to prevent early vomiting in adults, and an NNT of 10 to prevent late vomiting in the same population.<sup>100</sup> In children, the NNT to prevent early vomiting was 5.8, with no significant late anti-vomiting effect. The review also noted that the best documented doses of metoclopramide were 10 mg IV for adults and 0.25 mg/kg IV for children. A more recent double-blind study in children undergoing tonsillectomy failed to show equivalence between metoclopramide 0.5 mg/kg and ondansetron 0.1 mg/kg, and in fact showed that ondansetron was superior for control of POV.<sup>101</sup> Given the lack of evidence showing antiemetic efficacy, metoclopramide is not recommended for PONV at this time.

### ***Antihistamines***

The antiemetic properties of antihistamines such as diphenhydramine, dimenhydrinate, cyclizine, doxylamine, and promethazine are derived from their blockade of the histamine H<sub>1</sub> receptor in the NTS, at the vomiting center, and vestibular system; they have little or no direct action at the CTZ.<sup>42</sup> However, their anticholinergic activity is responsible for their most common side effects of sedation, dry mouth, blurred vision, and urinary retention. Although generally inexpensive and readily available, the use of antihistamines in PONV has not been well studied. In a meta-analysis of 18 controlled trials, Kranke and colleagues<sup>102</sup> reported that prophylactic dimenhydrinate (classified there to include both dimenhydrinate and the related diphenhydramine) reduces PONV in adults and children up to 48 hours after surgery, with a recommended dose of 1 mg/kg IV. There have been few studies of dimenhydrinate that specifically compare it with other antiemetics, and dose, timing, and side effect profiles have not been fully established. Doxylamine in combination with pyridoxine (Diclectin) has been shown to reduce the incidence of POV in women undergoing laparoscopic tubal ligation. Although doxylamine is available in the United States, the combination with pyridoxine is only approved in Canada.<sup>103</sup>

### ***Propofol***

The mechanism of antiemetic activity using propofol is unclear, but it has been observed that patients who receive propofol for induction tend to have less PONV.<sup>104</sup> This observation has been supported by several meta-analyses, including one that examined postoperative outcomes under inhaled and intravenous anesthetic

techniques.<sup>105</sup> Gupta and colleagues found that maintenance with a propofol infusion resulted in a decreased incidence of PONV and PDNV over inhaled anesthetics, with an NNT of 8.6 and 11.2 for PON and POV, respectively, and an NNT of 12.5 and 10.3 for postdischarge nausea and vomiting, respectively. A clinical trial of 2010 surgical patients in the Netherlands found that propofol total intravenous anesthesia (TIVA) resulted in a significant reduction of PONV compared with isoflurane-nitrous oxide anesthesia, with an NNT of 6.<sup>106</sup>

Recent studies have suggested that TIVA alone may not be an optimal strategy for PONV prophylaxis. In a small randomized trial, White and colleagues<sup>107</sup> found that although there were no significant differences in early PONV outcomes between patients given dolasetron prophylaxis and those given propofol-based TIVA, PDNV was significantly more common for patients in the TIVA group. The investigators suggest that although TIVA may be similar in efficacy to dolasetron for early PONV, its effects may be too short-lived to offer protection against PDNV.

Over the past several years, particularly as experience with the technique has increased and costs have decreased, the use of TIVA with propofol has become more popular for ambulatory surgery. One of the greatest limiting factors for increased use of TIVA continues to be cost, as economic analyses have suggested that routine use of TIVA for PONV prophylaxis is generally not cost-effective.<sup>106,108,109</sup> Nevertheless, propofol-based TIVA is still a reasonable option for high-risk patients, especially as part of a multimodal management strategy (see *Combination Therapies and Multimodal Prevention*, below).

## NOVEL ANTIEMETIC THERAPIES

### **Neurokinin-1 Antagonists**

The neurokinin-1 receptor antagonists (NK<sub>1</sub> RAs) are a new class of antiemetic drugs that competitively inhibit the binding of substance P, a neuropeptide released from enterochromaffin cells.<sup>110</sup> Substance P plays an important role in emesis as a ligand for neurokinin-1 receptors, which are located in the gastrointestinal tract and the area postrema.<sup>23</sup> The NK<sub>1</sub> RAs are believed to suppress nausea and vomiting by acting centrally on the neurotransmission between the NTS and CPG.<sup>111</sup> These agents may also act peripherally to block NK<sub>1</sub> receptors in the vagal terminals of the gut to decrease the intensity of the emetogenic signals sent to the CPG.<sup>112</sup>

The first NK<sub>1</sub> RA to be approved by the FDA was aprepitant (Emend), for chemotherapy-induced nausea and vomiting.<sup>113</sup> The first clinical trial to study the efficacy of aprepitant in PONV was a multicenter, double-blind study of 805 patients conducted by Gan and colleagues,<sup>114</sup> who found that preoperative aprepitant, both 40 mg and 125 mg orally were equivalent to preoperative ondansetron 4 mg IV in terms of CR rates, nausea control, and use of rescue antiemetics. However, the study also found that aprepitant was superior for prevention of vomiting in the first 24 and 48 hours, with no vomiting in 90% of patients in the aprepitant 40 mg group, 95% of the aprepitant 125 mg group, and 74% of the ondansetron group in the first 24 hours. A follow-up study by the same group in an international population confirmed that aprepitant was superior to ondansetron for incidences of no vomiting in the first 24 and 48 hours, and also found that peak nausea scores were lower in patients receiving either dose of aprepitant.<sup>115</sup> A post hoc analysis of the pooled data from both studies found that in the 24 hours after surgery, aprepitant 40 mg was slightly more effective than ondansetron in terms of no significant nausea (56.4% vs 48.1%), no nausea (39.6% vs 33.1%), no vomiting (86.7% vs 72.4%), no nausea and no vomiting

(38.3% vs 31.4%), and no nausea, vomiting, and no use of rescue antiemetics (37.9% vs 31.2%).<sup>116</sup> The study group also noted that the 125-mg dose was similar or even slightly less effective than the lower dose, leading to the recommended and approved preoperative dose of 40 mg for PONV prophylaxis.

NK<sub>1</sub> RAs are safe and well tolerated, with the most common side effects being asthenia, diarrhea, dizziness, and hiccups.<sup>117</sup> Although further studies are needed to establish their place in clinical practice, the NK<sub>1</sub> RAs offer many potential benefits for the management of PONV, especially as an alternative to patients who have failed treatment or prophylaxis with antiemetics in other classes. Aprepitant may be particularly useful in the ambulatory setting, as it comes in both a convenient oral form and a recently approved intravenous form (fosaprepitant) that may be useful for established PONV,<sup>113</sup> although clinical trials with the intravenous formulation have not been conducted in the PONV setting.

### **Opioid Antagonists**

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Perioperative opioid use has long been known to increase the risk of PONV by decreasing gastric motility and delaying gastric emptying via the inhibition of central  $\mu$ -opioid receptors.<sup>118</sup> Thus, the use of centrally acting opioid receptor antagonists, such as naloxone, may have antiemetic efficacy. Preliminary studies have found that low-dose naloxone (0.25  $\mu$ g/kg/h) is effective in reducing the incidence of PONV compared with placebo in both adults<sup>119</sup> and children.<sup>120</sup> A recent small study of 50 patients undergoing knee replacement surgery found that epidural sufentanil containing low-dose naloxone was effective in reducing PONV compared with sufentanil without naloxone.<sup>121</sup> However, there is a paucity of clinical data about the use of opioid receptor antagonists in PONV, and further study is necessary.

### **NONPHARMACOLOGIC TECHNIQUES**

Given that no single pharmacologic therapy is completely effective for PONV prophylaxis, nonpharmacologic techniques have become a reasonable adjunct to antiemetic drugs. Of all the nonpharmacologic techniques, acupuncture is one of the most well studied and accepted forms of treatment of PONV. The mechanism of acupuncture in the prevention of nausea and vomiting is not entirely clear; it may activate A- $\beta$  and A- $\delta$  fibers to influence neurotransmission in the dorsal horn or other centers, influence the release of endogenous opioids, or inhibit gastric acid secretion and normalize gastric dysrhythmia.<sup>122</sup>

Most data about acupuncture in PONV have examined the use of the acupuncture point pericardium 6, or P6, located 4 cm proximal from the wrist crease between the tendons of the palmaris longus and flexor carpi radialis muscles. A recently revised Cochrane database review of 40 randomized controlled trials determined that acupoint stimulation of P6 is effective in the prevention of PONV, with few side effects.<sup>123</sup> The NNTs were reported based on the baseline risk of nausea. At a control event rate of 30% (the estimated overall incidence of PONV), the NNT was 11 for both nausea and vomiting. At a baseline risk of 70% (estimate for high-risk populations), the NNT was 5 for both nausea and vomiting.

There are several comparable variations on traditional acupuncture, including acupressure and acupressure wristbands, acustimulation using transcutaneous electrical stimulation, acupuncture injections, and electroacupuncture.<sup>122</sup> These techniques may be of particular benefit in the ambulatory setting, as many of them can be performed rapidly and do not require special training. Another benefit of acupuncture is its favorable side effect profile compared with pharmacologic techniques,

making it a reasonable adjunct to antiemetic drugs. In a large prospective survey of doctors and physiotherapists, there were no serious adverse events due to acupuncture and the risk of adverse events was 14 per 10,000 treatments, with the most common being mild, including fainting, exacerbation of symptoms, and lost or forgotten needle.<sup>124</sup>

## THERAPIES LACKING SUFFICIENT EVIDENCE

In addition to some of the antiemetic agents mentioned previously, several other therapies that have been previously explored lack sufficient evidence or fail to demonstrate significant effect to be recommended for routine use in the management of PONV and PDNV.

Although earlier studies reported on the use of supplemental oxygen to reduce the incidence of PONV,<sup>125,126</sup> their findings have not been confirmed by subsequent studies. A systematic review of 10 trials by Orhan-Sungur and colleagues<sup>127</sup> reported that the relative risk of overall PONV in patients receiving 80% FiO<sub>2</sub> was 0.91, and concluded that supplemental oxygen did not reduce the incidence of PONV. Another recent randomized trial of 304 women receiving ambulatory gynecologic laparoscopy found that there were no significant differences in PONV or antiemetic use between women receiving 80% supplemental oxygen and those in the 30% oxygen control group.<sup>128</sup>

The use of cannabinoids, including dronabinol, tetrahydrocannabinol, and nabilone, in PONV has not been well studied, and clinical data are lacking. Tramèr and colleagues<sup>129</sup> conducted a systematic review of 30 trials evaluating cannabinoids in the setting of chemotherapy-induced nausea and vomiting, and found that dronabinol had superior antiemetic activity to phenothiazines. However, the analysis failed to demonstrate statistically significant improvement in antiemetic efficacy between dronabinol and placebo, and between nabilone and phenothiazines, although the investigators did cite a “clinically significant difference” in favor of the cannabinoids and urged further study. Nevertheless, given the common and often unpleasant side effects of most cannabinoids, which include dysphoria, depression, and hallucinations, they are unlikely to be used in regular clinical practice.<sup>129</sup>

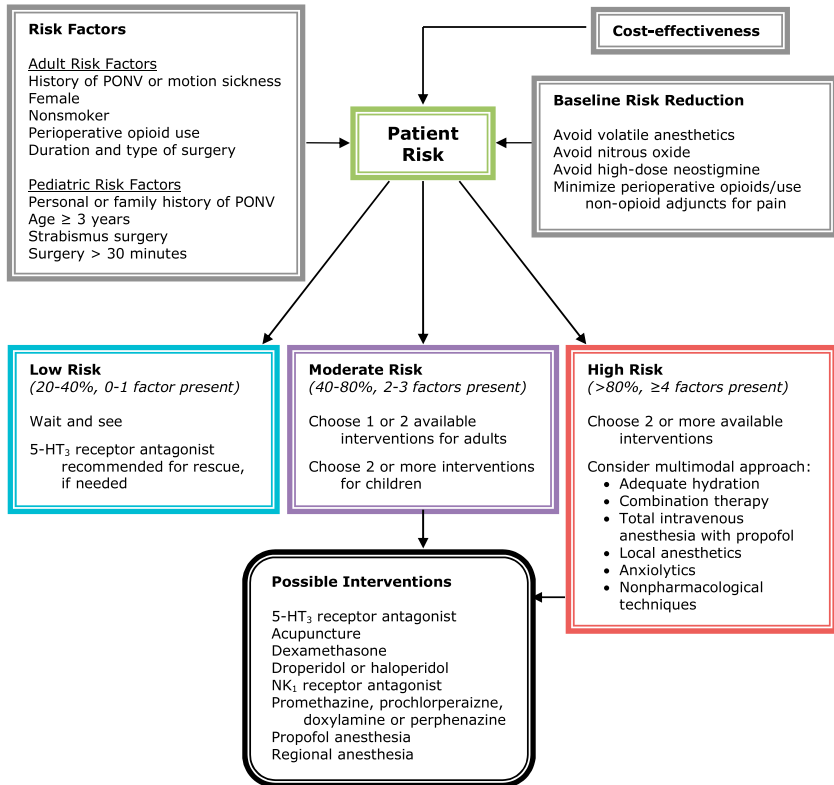
Despite its long history of use in traditional Chinese and Indian medicine, ginger (*Zingiber officinale*) does not appear to be effective for PONV. A systematic review of 6 randomized controlled trials by Ernst and Pittler was unable to draw a conclusion about the efficacy of ginger.<sup>130</sup> Since then, there have been few additional studies, with one placebo-controlled trial of 180 patients finding that ginger failed to reduce the incidence of PONV after gynecologic laparoscopy.<sup>131</sup>

## MANAGEMENT STRATEGY

As no single intervention can completely prevent or treat PONV, it is important to formulate multimodal approaches to maximize clinical efficacy while minimizing risks to the patient. While there is no clear formula for the prevention and management of PONV, an effective management strategy should consider (1) assessment of risk for developing PONV and baseline risk reduction, (2) prophylaxis and cost-effectiveness, (3) combination therapy, and (4) rescue treatment. **Fig. 2** shows a recommended management strategy based on patient risk.

### **Assessment of Risk and Baseline Risk Reduction**

As discussed earlier, the Apfel score may be a useful clinical tool in assessing patient risk. After taking these patient factors into consideration along with the surgical risk



**Fig. 2.** Antiemetic management strategies based on patient risk.

factors for PONV, the patient's overall risk for PONV should be determined, and the anesthesia technique should be tailored to minimize the patient's baseline risk.

When appropriate, the use of regional anesthesia over general anesthesia can significantly reduce a patient's risk of PONV.<sup>33</sup> In high-risk patients, avoidance of volatile anesthetics and nitrous oxide through the use of TIVA with propofol may be appropriate. Two meta-analyses by Tramèr and colleagues<sup>132,133</sup> have found that avoidance of nitrous oxide reduces the risk of PONV, with an NNT of 13 to prevent early and late vomiting. It should be noted, however, that in studies with higher than average baseline risks of PONV, the investigators found that the NNT was about 5, whereas in studies in which the risk was lower than average, omitting nitrous oxide had no effect on outcome. This observation emphasizes the importance of assessing a patient's individual risk factors before formulating an approach for the management of PONV. A separate systematic review by Tramèr and Fuchs-Buder<sup>134</sup> found that high-dose neostigmine (>2.5 mg) is associated with increased risk of PONV, suggesting reduction or avoidance of neostigmine as another strategy to decrease PONV risk. Baseline risk reduction may also be achieved by minimizing the use of intraoperative and postoperative opioids with nonopioid adjuncts, such as nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and local anesthetics.<sup>24</sup>

### **Prophylaxis and Cost-Effectiveness**

The cost-effectiveness of PONV prophylaxis is an important consideration in formulating a management strategy. Unfortunately, it is often difficult to gauge and compare

the cost-effectiveness of many antiemetic therapies, as cost-effectiveness analyses vary widely in terms of the antiemetic regimens they choose to evaluate, the costs they take into account, and the criteria they use in drawing a conclusion. A cost-effectiveness study by Hill and colleagues<sup>9</sup> compared ondansetron 4 mg, droperidol 0.625 mg, droperidol 1.25 mg, and placebo, and determined that the use of antiemetic prophylaxis was more cost-effective and achieved higher satisfaction rates compared with placebo in high-risk patients. Frighetto and colleagues<sup>135</sup> used a decision-analysis model to determine that prophylactic antiemetic therapy with dolasetron or droperidol was more cost-effective than no prophylaxis followed by subsequent rescue therapy. However, other studies have suggested that treatment of PONV may be more cost-effective than prophylaxis for patients at both low (30%) and high (60%) risk, due to the high efficacy of ondansetron for the treatment of established PONV.<sup>136</sup>

Despite these conflicting data, it seems that studies comparing antiemetic therapy with placebo tend to find that using an antiemetic is more effective than placebo and preferable to no prophylaxis.<sup>137</sup> Still, it remains unclear which antiemetic therapies are most cost-effective, what doses of medication are most cost-effective, and whether PONV prophylaxis is cost-effective for all patients or only for those at higher risk. Future studies have been encouraged to follow established guidelines for cost-effectiveness studies, such as reporting cost-effectiveness as a ratio of resource use to value of health consequences.<sup>138–140</sup>

### ***Combination Therapies and Multimodal Prevention***

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Because there are no single antiemetic agents that are completely effective in preventing or treating PONV, the concept of combination therapy using multiple agents has become particularly appealing. As noted earlier, the IMPACT trial found that ondansetron 4 mg IV, dexamethasone 4 mg IV, and droperidol 1.25 mg IV are equally effective as single agents for the prevention of PONV.<sup>2</sup> Due to their established efficacy and widespread use, these 3 agents are the most commonly studied antiemetics used in combination therapy. The IMPACT trial examined the effect of various combinations of the 3 therapies, and determined that each of the 3 antiemetics acted independently, such that combinations of any 2 or 3 of them would reduce the risk of PONV in an additive manner. These findings are similar to those of various meta-analyses and systematic reviews, which have reported that combinations of 5-HT<sub>3</sub> RAs and either droperidol or dexamethasone are equally safe and effective in reducing PONV.<sup>75,87,141</sup> A cost-effectiveness analysis by Pueyo and colleagues<sup>142</sup> compared each of the possible 2-drug combinations of ondansetron, droperidol, and dexamethasone. The investigators found that ondansetron and droperidol is less expensive than, and as effective as, ondansetron and dexamethasone, while being more effective than droperidol and dexamethasone—albeit at a slightly increased cost. Regardless, the evidence would suggest that combination therapy using any of these 3 drugs would be a reasonable strategy for decreasing PONV risk.<sup>24</sup>

In general, combination therapy is recommended for patients at moderate risk for PONV. For patients at high risk of PONV, combination antiemetic therapy can be used in conjunction with other pharmacologic and nonpharmacological techniques to further reduce the risk of PONV. This approach is often labeled “multimodal management” or “balanced antiemesis,” as it combines multiple therapeutic options to maximize antiemetic efficacy. Scuderi and colleagues<sup>143</sup> reported on the use of a multimodal approach that included preoperative anxiolysis, aggressive hydration, supplemental oxygen, droperidol and dexamethasone at induction, ondansetron at the end of surgery, TIVA with propofol and remifentanyl, and ketorolac, with no use of nitrous oxide or neuromuscular blockade. The multimodal approach achieved



a 98% CR rate, compared with 76% with antiemetic monotherapy using ondansetron 4 mg, and a 59% CR rate on placebo. However, the researchers did note that patient satisfaction scores were similar between the multimodal approach and monotherapy, although they were both higher than those for patients receiving placebo and rescue antiemetic therapy only.

Habib and colleagues<sup>144</sup> have compared 3 regimens: a multimodal management strategy, which included TIVA with propofol, ondansetron, and droperidol; a combination therapy with ondansetron and droperidol, and receiving isoflurane and nitrous oxide (no TIVA); and TIVA with propofol only. The CR rates at 24 hours were 80% for the multimodal approach, 63% for the combination therapy group, and 43% for the TIVA-only group. In slight contrast to the study by Scuderi and colleagues, patient satisfaction scores were found to be highest for the multimodal approach, over both combination therapy with inhaled anesthetics or TIVA only.

### ***Rescue Treatment and Management of PDNV***

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Even with baseline risk reduction and antiemetic prophylaxis, some patients will inevitably experience PONV or PDNV.<sup>16</sup> Before initiating rescue antiemetic drugs, other factors that may contribute to PONV should be considered and addressed, such as pain, concomitant use of opioids or other medications, or mechanical reasons (eg, blood in the throat, abdominal obstruction, and so forth). In general, patients who have not previously received antiemetic prophylaxis should be given a 5-HT<sub>3</sub> RA, while patients who have already received prophylaxis should be given a rescue antiemetic from a different treatment class than the prophylactic drug.<sup>24</sup> Unlike PONV prophylaxis, there are relatively few trials that have studied treatment options for established PONV. However, a systematic review by Kazemi-Kjellberg and colleagues<sup>52</sup> has evaluated several different antiemetic regimens and found that the NNT of 5-HT<sub>3</sub> RAs for established PONV is about 4 to 5. Treatment doses of 5-HT<sub>3</sub> RAs for established PONV are generally smaller than those needed for prophylaxis: ondansetron 1 mg, dolasetron 12.5 mg (similar to the recommended prophylactic dose), and granisetron 0.1 mg. Although ondansetron 1 mg has been shown to be as effective as ondansetron 4 mg for antiemetic rescue, most clinicians tend to use the 4-mg dose in practice. It should also be noted that in patients who received a 5-HT<sub>3</sub> RA for prophylaxis, no further benefit is achieved from repeat doses in the 6 hours after the initial dose.<sup>145</sup> In such cases, alternatives to 5-HT<sub>3</sub> RAs are recommended and include dexamethasone 2 to 4 mg, droperidol 0.625 mg, or promethazine 6.25 to 12.5 mg, although dexamethasone and transdermal scopolamine are not recommended for emetic episodes that occur more than 6 hours postoperatively, because of their longer duration of action.<sup>24</sup>

### **SUMMARY**

Although awareness has greatly increased over the past several decades and the number of available treatment options has also increased, PONV and PDNV remain a common problem of ambulatory surgery. Appropriate management of PONV begins with an assessment of risk and baseline risk reduction, followed by consideration of antiemetic prophylaxis and, if necessary, rescue treatment. In patients who are at increased risk, combination therapy or multimodal approaches is recommended in preventing PONV and PDNV. Given the brief period of time that ambulatory surgery patients are under direct medical care, it is particularly important to recognize these problems and appropriately administer longer-acting antiemetics to prevent negative medical consequences, maximize patient satisfaction and return to normal activity, and minimize health care costs.

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