Special Article

Society for Ambulatory Anesthesia Guidelines for the Management of Postoperative Nausea and Vomiting

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The present guidelines were compiled by a multidisciplinary international panel of individuals with interest and expertise in postoperative nausea and vomiting (PONV) under the auspices of The Society of Ambulatory Anesthesia. The panel critically evaluated the current medical literature on PONV to provide an evidence-based reference tool for the management of adults and children who are undergoing surgery and are at increased risk for PONV. In brief, these guidelines identify risk factors for PONV in adults and children; recommend approaches for reducing baseline risks for PONV; identify the most effective antiemetic monotherapy and combination therapy regimens for PONV prophylaxis; recommend approaches for treatment of PONV when it occurs; and provide an algorithm for the management of individuals at increased risk for PONV.
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Postoperative nausea and vomiting (PONV) is a continuing concern in surgical patients and the management of this problem is still confusing. In the United States, more than 71 million inpatient and outpatient operative procedures are performed each year (1). Untreated, PONV occurs in 20%–30% of the

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general surgical population and in up to 70%–80% of high-risk surgical patients (2–4). The adverse effects of PONV range from patient-related distress to postoperative morbidity. PONV associated with ambulatory surgery increases health care costs due to hospital admission and accounts for 0.1%–0.2% of these unanticipated admissions, which is significant in the United States where more than 31 million patients undergo ambulatory surgery each year (1,5–7).

The present guidelines were developed under the auspices of the Society of Ambulatory Anesthesia (SAMBA). The panel reviewed new literature since a previous consensus guideline on PONV was published in 2003 (8). A Medline search revealed that an additional 250 comparative antiemetic trials were published since February 2002, when the medical literature was last reviewed. These guidelines provide up-to-date information to practicing physicians and other health care providers about strategies to prevent and treat PONV.

Establishment of Expert Guidelines

To produce the SAMBA guidelines for the management of PONV, an unrestricted educational grant was provided by Baxter (transdermal scopolamine), GSK (ondansetron), Merck (aprepitant), MGI Pharma (palonosetron) and Roche, Inc. (granisetron). The primary author was requested to form a multidisciplinary international panel of individuals (anesthesiologists, surgeon, pharmacist, nurse anesthetist, perianesthesia nurse, and a biostatistician). Members from the first PONV consensus panel (8) were contacted. Additional experts were sought from Europe, Australasia, and from other health care disciplines. The panel selections were based on significant expertise in this area of research and representation in professional societies with an interest in the management of PONV. Sponsoring pharmaceutical companies did not play any role in the selection of the panel or topics. Panel members were asked to review the medical literature on PONV (from November 2005). Members, working in pairs, undertook a topic to research and presented the evidence-based data to the group, who discussed the evidence and reached consensus on its inclusion in the guidelines. When full agreement could not be obtained, the majority view was presented and the lack of full agreement was stated. Members of SAMBA also had an opportunity to review and comment on the consensus statements prior to publication. A draft of the consensus guidelines was presented to an audience at the 2006 SAMBA midyear meeting and was subsequently posted on the website for 4 wk from November 1 to November 29, 2006, for SAMBA member comments. The members' comments were sent by e-mail to the Chair of the SAMBA Scientific Committee, who anonymized them and sent them to the guidelines panel for review and discussion. A consensus was reached on each item submitted to either incorporate it in the guidelines or reject it based on the presence of adequate published data.

Goals of Guidelines

The panel defined the following goals for the guidelines: 1) Identify the primary risk factors for PONV in adults and postoperative vomiting (POV) in children; 2) Establish factors that reduce the baseline risks for PONV; 3) Determine the most effective antiemetic monotherapies and combination therapy regimens for PONV/POV prophylaxis, including pharmacologic and nonpharmacologic approaches; 4) Ascertain the optimal approach to treatment of PONV with or without PONV prophylaxis; 5) Determine the optimal dosing and timing of antiemetic prophylaxis; 6) Evaluate the cost-effectiveness (C/E) of various PONV management strategies using incremental C/E ratio (cost of treatment A − cost of treatment B)/(success of treatment A − success of treatment B); 7) Create an algorithm to identify individuals at increased risk for PONV and to suggest effective treatment strategies.

Strength of Evidence

A variety of grading systems has been proposed to document the strength of evidence of randomized and observational studies supporting a treatment. The panel decided not to grade the included literature but to base its recommendations exclusively on valid studies with a minimal risk of bias. Thus, recommendations were made only if they were supported by randomized trials and systematic reviews of randomized trials that documented efficacy and harm of antiemetic interventions, and by nonrandomized studies that used logistic regression to identify risk factors of PONV.

Guideline 1: Identify Patients' Risk for PONV

Risk factors for PONV in adults are shown in Table 1 and Figure 1.

Risk factors for POV in children are shown in Figure 2.

Estimating an individual's risk for PONV can indicate who will most likely benefit from prophylactic antiemetic therapy. In adults, only a few baseline risk factors occur with enough consistency to be considered independent predictors for PONV (3,9–12,21–31). Female gender, nonsmoking, and the history of PONV or motion sickness are among the most important and prevalent patient-specific predictors. Some studies also reported migraine, young age, anxiety, and patients with a low ASA risk classification as independent predictors for PONV, although the strength of these factors varies from study to study (12,32). Anesthesia-related independent predictors are general anesthesia with volatile anesthetics, nitrous oxide, and

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Table 1. Risk Factors for Postoperative Nausea and Vomiting (PONV) in Adults

Patient-specific risk factors (3,9,10–14)
The most important being:
Female gender (RCT)
Nonsmoking status (RCT)
History of PONV/motion sickness (RCT)
Anesthetic risk factors (3,12–20)
The most important being:
Use of volatile anesthetics (RCT)
Nitrous oxide systematic review (SR)
Use of intraoperative (SR) and postoperative opioids (RCT)
Surgical risk factors (11,12,14)
Duration of surgery (each 30-min increase in duration increases PONV risk by 60%, so that a baseline risk of 10% is increased by 16% after 30 min) (Prospective observational study)
Type of surgery (laparoscopy, laparotomy, breast, strabismus, plastic surgery, maxillofacial, gynecological, abdominal, neurologic, ophthalmologic, urologic) (Prospective observational study)

RCT = randomized controlled trial; SR = systematic review.

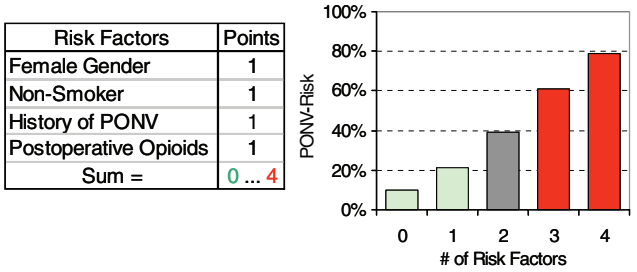

Figure 1. Simplified risk score for PONV in adults (3). Simplified risk score from Apfel et al. (3) to predict the patients risk for PONV. When 0, 1, 2, 3, or 4 of the depicted independent predictors are present, the corresponding risk for PONV is approximately 10%, 20%, 40%, 60%, or 80%.

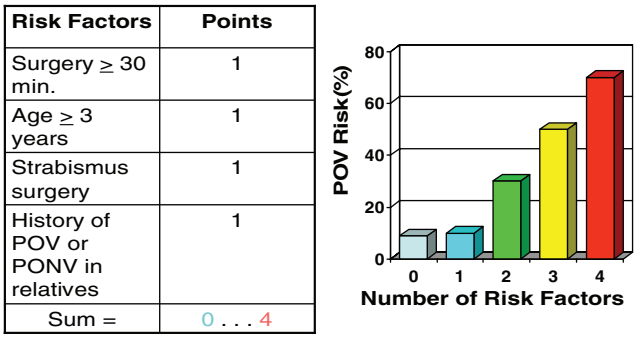

Figure 2. Simplified risk score for POV in children (39). Simplified risk score from Eberhart et al. (39) to predict the risk for POV in children. When 0, 1, 2, 3, or 4 of the depicted independent predictors are present, the corresponding risk for PONV is approximately 10%, 10%, 30%, 55%, or 70%.

the use of postoperative opioids. The emetogenic effect of the inhaled anesthetics and opioids appears to be dose related (13,15). Longer procedures under general volatile anesthetic with concomitantly longer exposure to the volatile anesthetics and increased postoperative opioid consumption are associated with an increased incidence of PONV (4,11).

It is appreciated that some types of surgery are associated with a higher incidence of PONV than others. However, no agreement could be reached about whether the association between type of surgery and increased PONV risk is causal. Numerous studies suggest that the higher incidences are due to other independent risk factors associated with the type of surgery (3,10,14,22,26,27,32), while other analyses suggest that certain types of surgery are independent risk factors (4,9,11,12,23,28,30) (Table 1).

Many factors commonly believed to augment risk are not actually independent factors. These include obesity, anxiety, antagonizing neuromuscular blockade (10,22,26,30,32–35). However, no single patient- or anesthetic-related risk factor is sufficiently sensitive or specific enough to provide a useful risk assessment for PONV. Several risk models have therefore been developed (30). The simplified models of Apfel et al. and Koivuranta et al. have shown some usefulness for the prediction of the PONV baseline risk in a variety of situations (Fig. 1) (10,24,27,28). It is important to note that no risk model can accurately predict the likelihood of an individual having PONV; risk models only allow clinicians to estimate the risk for PONV among patient groups (32).

In children, a number of papers have been published citing a variety of risk factors associated with POV (36–38). However, evidence is lacking to support these associations. More recently, Eberhart et al. (39) published a study of a large series of pediatric patients in which a multivariable analysis was applied to identify POV risk factors in children. Four independent predictors of POV were identified, including duration of surgery ≥30 min, age ≥3 yr, strabismus surgery, and a positive history of POV in the patient, parent or sibling (Fig. 2). They demonstrated that the risk for POV was 9%, 10%, 30%, 55%, and 70% when 0, 1, 2, 3, or 4 of those independent predictors were present.

Use of prophylactic antiemetics should be based on valid assessment of the patient's risk for POV or PONV. In other words, antiemetic prophylaxis should be used only when the patient's individual risk is sufficiently high. This can be estimated by multiplying the expected incidence (baseline risk) by the relative risk reduction resulting from prophylaxis. This approach produces a clinically meaningful decrease in the risk of PONV (2,40). However, more liberal prophylaxis is appropriate for patients in whom vomiting poses a particular medical risk, including those with wired jaws, increased intracranial pressure, gastric or esophageal surgery, and when the anesthesia care provider determines the need or the patient has a strong preference to avoid PONV.

Guideline 2: Reduce Baseline Risk Factors for PONV

Approaches for decreasing baseline risk factors are presented in Table 2.

Table 2. Strategies to Reduce Baseline Risk

Avoidance of general anesthesia by the use of regional anesthesia (11,16) (randomized, controlled trial, RCT)
Use of propofol for induction and maintenance of anesthesia (4,14,41,42) (RCT/systematic review, SR)
Avoidance of nitrous oxide (3,4,43,44) (RCT/SR)
Avoidance of volatile anesthetics (15,28) (RCT)
Minimization of intraoperative (SR) and postoperative opioids (3,13,15,17,18,20,28,43) (RCT/SR)
Minimization of neostigmine (19,45) (SR)
Adequate hydration (46) (RCT)

Discussion

Reducing baseline risk factors can significantly decrease the incidence of PONV. Use of regional anesthesia is associated with a lower incidence of PONV than general anesthesia in both children and adults (11,16). Sinclair et al. (11) found the risk for PONV is nine times less among patients receiving regional anesthesia than those receiving general anesthesia. When general anesthesia is required, use of propofol for induction and maintenance of anesthesia decreases the incidence of early PONV (occurring within the first 6 h; number-needed-to-treat [NNT] = 5) (47). The IMPACT study evaluated several strategies to reduce PONV in 5199 high risk patients (4). The study reported a 59% incidence of PONV in patients treated with a volatile anesthetic or nitrous oxide. Use of propofol reduced PONV risk by 19%. Avoiding nitrous oxide reduced PONV risk by 12%. The combination of propofol and air/oxygen (total IV anesthesia) had additive effects, reducing PONV risk by approximately 25% (4). These findings are supported by two meta-analyses demonstrating that avoiding nitrous oxide reduces PONV risk (43,44) and a randomized, placebo-controlled trial showing that volatile anesthetics are the primary cause of early PONV (0–2 h), but that they do not have an impact on delayed PONV (2–24 h) (15). However, nitrous oxide has little impact when the incidence of PONV is low (44). Baseline risk for PONV can also be reduced by minimizing intraoperative and postoperative opioids (3,13,15,17,18,28,43,48). To achieve satisfactory analgesia without opioids, alternate modalities of pain management may be used. Randomized controlled trials and meta-analyses show that perioperative nonsteroidal antiinflammatory drugs and cyclooxygenase-2 inhibitors (49–51), and, less so, intraoperative ketamine (52), may have a morphine-sparing effect in the postoperative period. Theoretically, this decrease in opioid consumption could lead to a decrease in the incidence of opioid-related nausea and vomiting. Reducing the dose or avoiding neostigmine has been studied as a means for reducing baseline risk for PONV. Meta-analyses demonstrate that high-dose neostigmine (>2.5 mg) is associated with increased PONV and that reducing the dose can decrease PONV risk (19,45). However, the clinical importance of neostigmine's effects on PONV has been questioned (35).

Systematic reviews of randomized controlled trials show that supplemental oxygen has no effect on nausea or overall vomiting, although it may reduce the risk of early vomiting (53,54). As a result, supplemental oxygen is not recommended in these guidelines.

Guideline 3: Administer PONV Prophylaxis Using One to Two Interventions in Adults at Moderate Risk for PONV

Prophylactic doses and timing for administration of antiemetics in adults are shown in Table 3.

A treatment algorithm is presented in Figure 3.

Discussion

The recommended first- and second-line pharmacologic antiemetics for PONV prophylaxis in adults include the 5-hydroxytryptamine (5-HT3) receptor antagonists (ondansetron, dolasetron, granisetron, and tropisetron), steroid (dexamethasone), phenothiazines (promethazine and prochlorperazine), phenylethylamine (ephedrine), butyrophenones (droperidol, haloperidol), antihistamine (dimenhydrinate), and anticholinergic (transdermal scopolamine). These antiemetics are recommended for patients at moderate to severe risk for PONV. While PONV prevention is recommended in a subset of patients, current evidence does not support giving prophylactic antiemetics to all patients who undergo surgical procedures. However, with more inexpensive generics becoming available, properly conducted C/E studies need to be done to support more universal use of prophylactic antiemetics (see section on C/E). In the IMPACT trial, ondansetron 4 mg, droperidol 1.25 mg, and dexamethasone 4 mg were equally effective and each independently reduced PONV risk by approximately 25% (4). The recommended doses and timing of these drugs follow. (It should be noted that the recommendations given are evidence-based and that not all the drugs have a Food and Drug Administration [FDA] indication for PONV).

5-HT_3 Receptor Antagonists

The 5-HT_3 receptor antagonists, ondansetron, dolasetron, granisetron, and tropisetron, are most effective in the prophylaxis of PONV when given at the end of surgery (67–70). However, some data on dolasetron administration suggest timing may have little effect on efficacy (80). Most of the research available about the 5-HT_3 receptor antagonists involves ondansetron, which has greater antivomiting than antinausea effects (81). The recommended prophylactic dose of ondansetron is 4 mg, which has a NNT of approximately 6 for the prevention of vomiting (0–24 h) and a NNT of approximately 7 for the prevention of nausea (81). The recommended prophylactic dose of dolasetron is 12.5 mg (61). A meta-analysis of placebo-controlled studies provides support for the efficacy of dolasetron for preventing PONV (82). Granisetron, 0.35 to 1.5 mg IV (5–20 μg/kg), is effective for PONV

Table 3. Antiemetic Doses and Timing for Prevention of Postoperative Nausea and Vomiting (PONV) in Adults

Drugs	Dose	Evidence	Timing	Evidence
Dexamethasone	4–5 mg IV	SR (55–57)	At induction	RCT (57)
Dimenhydrinate	1 mg/kg IV	SR (58) RCT (59,60)		
Dolasetron	12.5 mg IV	RCT (61)	End of surgery; timing may not affect efficacy	RCT (61)
Droperidol[a]	0.625–1.25 mg IV	RCT (62,63)	End of surgery	SR (64)
Ephedrine	0.5 mg/kg IM	RCT (65,66)	End of surgery	RCT (65,66)
Granisetron	0.35–1.5 mg IV	RCT (67–71)	End of surgery	RCT (68–70)
Haloperidol	0.5–2 mg IM/IV	SR (72)		
Prochlorperazine	5–10 mg IM/IV	RCT (73)	End of surgery	RCT (73)
Promethazine[b]	6.25–25 mg IV	RCT (74,75)	At induction	RCT (74,75)
Ondansetron	4 mg IV	RCT (76)	End of surgery	SR (67)
Scopolamine	Transdermal patch	SR (77,78)	Prior evening or 4 h before surgery	RCT (78)
Tropisetron	2 mg IV	RCT (79)	End of surgery	Expert opinion

Note: These recommendations are evidence-based and not all the drugs have a FDA indication for PONV.

Drugs are listed alphabetically.

[a] See Food and Drug Administration (FDA) "black box" warning.

[b] FDA Alert: Should not be used in children less than 2 years old.

RCT = randomized, controlled trial; SR = systematic review.

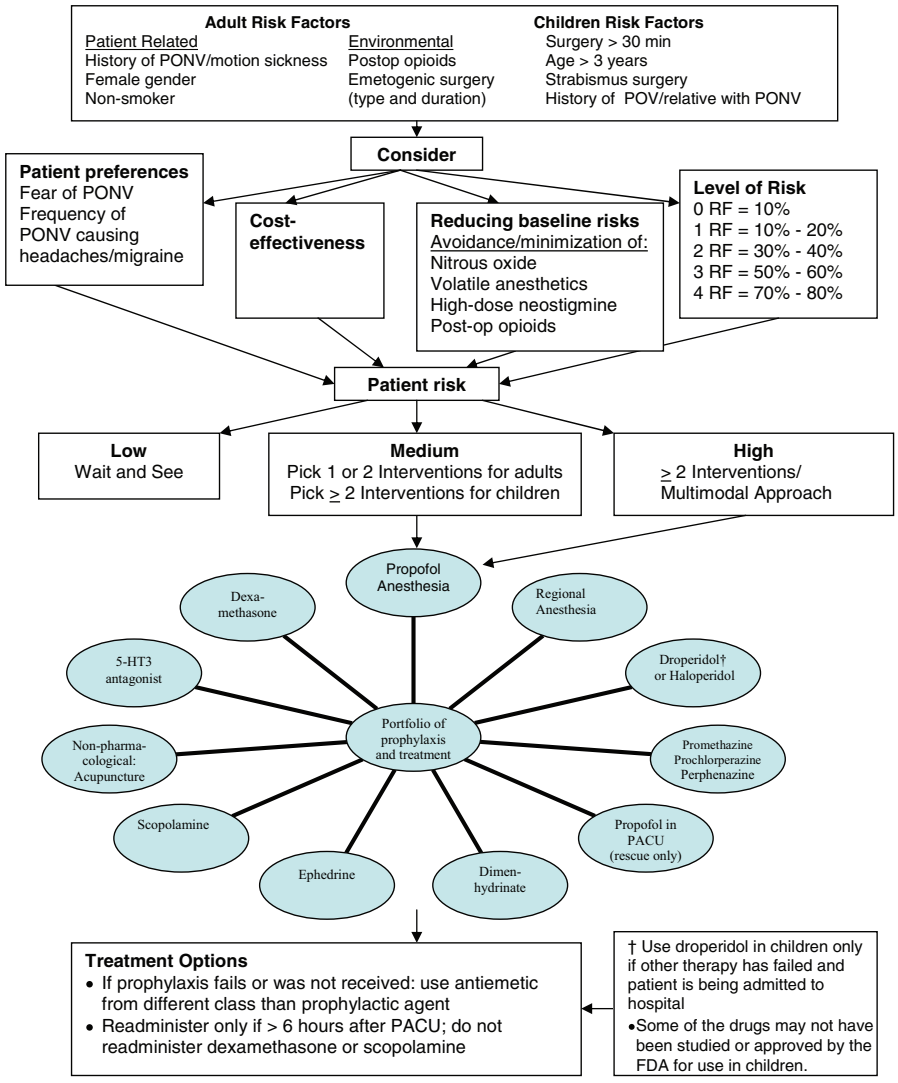

Figure 3. Algorithm for management of postoperative nausea and vomiting (PONV).

prophylaxis, although a systematic review shows that some of the data on granisetron may be less reliable than others (61,68–70,80–83). Tropisetron, 2 mg IV, shows significant efficacy for reducing risk for nausea and vomiting and is recommended for PONV prophylaxis (79,84). The 5-HT_3 antagonists have a favorable side effect profile and are considered equally safe. The number-needed-to-harm (NNH) with a single dose of

ondansetron is 36 for headache, 31 for elevated liver enzymes, and 23 for constipation (81). All the 5-HT_3 antagonists have been found equally antiemetic for the treatment of established PONV (85).

Dexamethasone

The corticosteroid, dexamethasone, effectively prevents nausea and vomiting (55,56). It is recommended at a prophylactic dose of 4–5 mg IV (depending on the dosage formulation in different countries) for patients at increased risk for PONV. For PONV prophylaxis, the efficacy of dexamethasone 4 mg IV seems to be similar to that of ondansetron 4 mg IV and droperidol 1.25 mg IV (4). The recommended timing for administration is at induction of anesthesia rather than at the end of surgery (57). Adverse events have not been noted after a single bolus dose of dexamethasone (55).

Butyrophenones

Prophylactic doses of droperidol, 0.625–1.25 mg IV, are effective for the prevention of PONV (62,63). The efficacy of droperidol is equivalent to that of ondansetron for PONV prophylaxis, with an NNT of approximately 5 for prevention of nausea and vomiting (0–24 h) (2,4). Droperidol is most effective when administered at the end of surgery (64). It also effectively reduces the risk for opioid-induced nausea and vomiting, with a NNT of approximately 3, when given concomitantly with patient-controlled analgesia (PCA) (86,87). Many physicians have stopped using droperidol due to the FDA "black box" restrictions on its use. However, the droperidol doses used for the management of PONV are extremely low, and at these dosing levels droperidol is unlikely to be associated with significant cardiovascular events (88–90). The panel expressed considerable concern about the quality and quantity of evidence and the validity of the FDA conclusion. If it were not for the black-box warning, droperidol would have been the panel's overwhelming first choice for PONV prophylaxis.

Haloperidol, which has antiemetic properties when used in low doses, has been investigated as an alternative to droperidol (72,91). A meta-analysis of published and unpublished randomized trials suggests that at doses much lower than those used to treat psychiatric disorders, 0.5–2 mg IM or IV, haloperidol effectively reduces PONV risk with a NNT of between 4 and 6 (72). At these doses, sedation did not occur, and cardiac arrhythmias were not reported. Of 806 patients exposed to haloperidol, 1 (0.1%) had extrapyramidal symptoms with 4 mg. There are no reports in the medical literature about optimal timing of haloperidol administration. Haloperidol carries a risk of QTc prolongation in its label and thus it is not recommended as first-line therapy. However, it can be considered as an alternative to droperidol if the black box warning precludes use of that drug.

Dimenhydrinate

Dimenhydrinate is an antihistamine with antiemetic effects. Data from placebo-controlled trials suggest that its degree of antiemetic efficacy may be similar to the 5-HT_3 receptor antagonists, dexamethasone, and droperidol (58). The recommended dose is 1 mg/kg IV (58–60). However, not enough data are available to establish the optimal timing and dose response for dimenhydrinate administration or its side effect profile. Direct comparisons with other antiemetic drugs are lacking.

Transdermal Scopolamine

A systematic review of transdermal scopolamine shows that it is useful as an adjunct to other antiemetic therapies (77). The patch effectively prevents nausea and vomiting postoperatively (NNT = 6). It is applied the evening before surgery or 4 h before the end of anesthesia due to its 2–4 h onset of effect, which may be problematic in some centers (78). Adverse events associated with transdermal scopolamine are generally mild; the most common being visual disturbances (NNH = 5.6), dry mouth (NNH = 13), and dizziness (NNH = 50) (77). Transdermal scopolamine has been found useful for control of nausea in the setting of PCA (92,93).

Combination Therapy

Adults at moderate risk for PONV should receive combination therapy with one or more prophylactic drugs from different classes. In general, combination therapy has superior efficacy compared with monotherapy for PONV prophylaxis (94,95). Drugs with different mechanisms of action should be used in combination to optimize efficacy. The 5-HT_3 antagonists, which have better antivomiting than antinausea efficacy (yet are associated with headache), can be used in combination with droperidol, which has greater antinausea efficacy and a protective effect against headache (96). The 5-HT_3 antagonists can also be effectively combined with dexamethasone (55). One study found no difference in efficacy for preventing PONV when low-dose granisetron (0.1 mg) in combination with dexamethasone 8 mg was compared with ondansetron 4 mg plus dexamethasone 8 mg (97). In a single study, the combination of a 5-HT_3 antagonist and promethazine significantly reduced both the frequency and severity of nausea and vomiting (74). Optimal antiemetic dosing with combination therapy needs to be established. Combination therapy regimens using ondansetron with either droperidol or dexamethasone are the most widely studied. It has been suggested that, with combination therapy, dexamethasone doses should not exceed 10 mg IV and that droperidol doses should not exceed 1 mg IV (96). When used in combination with another drug, ondansetron doses in adults typically should not exceed 4 mg, and can be much lower (96).

Lack or Limited Evidence of Effect

Some therapies have proven ineffective for PONV prophylaxis. These include metoclopramide when used in standard clinical doses (10 mg IV), ginger root, and cannabinoids (nabilone, tetra-hydrocannabinol) which, although promising in the control of chemotherapy-induced sickness, are not effective in PONV (98–102). In two randomized trials, the phenothiazines, promethazine, 12.5–25 mg IV, administered at the induction of surgery, and prochlorperazine, 5–10 mg IV, given at the end of surgery were shown to have some antiemetic efficacy (73,74). Similarly, it was suggested that the phenylethylamine, ephedrine, 0.5 mg/kg IM, may have an antiemetic effect when administered at the end of surgery (65,66). Due to a paucity of data, evidence is not as strong as for the other, well documented antiemetic drugs; therefore, further research is warranted before these drugs can be recommended as first-line therapy. There is inadequate evidence to suggest that hypnosis is a promising modality for PONV prophylaxis.

Nonpharmacologic Prophylaxis

A meta-analysis of nonpharmacologic PONV prophylaxis demonstrated antiemetic efficacy with acupuncture, transcutaneous electrical nerve stimulation, acupoint stimulation, and acupressure (NNT [≤6 h after surgery] ≈ 5) (103). A systematic review of 26 trials by Lee and Done (104) showed that stimulation of the P6 acupuncture point reduced the incidence of nausea, vomiting, and need for rescue medication. In a randomized, controlled trial, P6 electro-acupoint stimulation led to a complete response rate as high as that of ondansetron when compared with controls ($P = 0.006$) (105). P6 stimulation was particularly effective at reducing the incidence and severity of nausea (19%) compared with ondansetron (40%) and placebo (79%). Stimulation of Korean hand acupoints proved effective in preventing PONV as well, reducing the incidence of postoperative vomiting in two randomized controlled trials by approximately half (106,107).

Cost Effectiveness

The C/E of therapy is one of the primary considerations in determining whether to use PONV prophylaxis. However studies assessing C/E of PONV interventions have several drawbacks; they use variable methodologies, they are often too small to be reliable, and many are not specifically designed for that purpose. This panel recommends that future C/E studies be conducted according to established guidelines (108–111). Such guidelines address components of the numerator and denominator of a C/E ratio. The numerator should measure resource use and the denominator should provide a value of health consequences.

Willingness to pay is a recommended measure in cost benefit analyses. Gan et al. determined that patients are willing to pay approximately $100 to prevent experiencing PONV and Diez found parents are willing to spend approximately $80 to prevent POV in their children (112,113). Reducing baseline risk can be a cost-effective strategy. For example, it is more cost-effective to use a propofol/isoflurane regimen, which is associated with the lowest cost per episode of PONV avoided, than either propofol/sevoflurane or sevoflurane/sevoflurane (114). C/E assessments for PONV prophylaxis are more difficult and depend on the specific model and assumptions chosen. It is estimated that each episode of emesis delays discharge from the postanesthesia care unit (PACU) by approximately 20 min (115). However, in a retrospective study of patients who underwent ambulatory surgery, Dexter and Tinker (116) demonstrated that if PONV could have been eliminated in patients who suffered this complication, the length of PACU stay for all patients would only have been reduced by <5%. Hill et al. (117) found prophylaxis in high-risk patients was more cost-effective than placebo due to increased costs associated with nausea and vomiting. The additional costs associated with PONV in placebo patients were up to 100 times higher compared with prophylaxis with a generic antiemetic and the cost of treating vomiting was three times more than the cost of treating nausea. Similarly, a study evaluating dolasetron, droperidol, or no prophylaxis in high-risk patients found that prophylaxis with either of the two antiemetics was more cost-effective than no prophylaxis and subsequent rescue therapy (118). On the other hand, in a study that did not assess C/E but evaluated factors affecting cost, there was no difference in the time to discharge, rate of unanticipated admission, or time to return to normal activity between the prophylaxis and treatment groups in an ambulatory setting, apart from the highest risk group (female patients with a history of motion sickness or PONV who were undergoing highly emetogenic procedures) who reported high patient satisfaction when prophylaxis was given (119). It has been suggested that PONV prophylaxis is cost-effective with the older, less expensive drugs when patients have a 10% or more risk of emesis (120). In another model, treatment of PONV with ondansetron was more cost-effective than prevention in both a low (30%) and a high (60%) risk setting (121). This was due to the high success rate of treating established PONV, even with low doses of ondansetron (1 mg). When using a willingness-to-pay rate of $100 per case avoided, PONV prophylaxis proved cost-effective in groups with a 40% risk of PONV. Lower drug acquisition costs support PONV prophylaxis in patient groups at a lower risk for PONV (122). The decision about whether or not to use PONV prophylaxis, or to treat patients with established symptoms, not only depends on the efficacy of the drug but also on the baseline risk for PONV, adverse effects of the antiemetics, and drug acquisition costs, which will vary from one setting to another. For instance, anesthesiologists may be more likely to administer prophylaxis with an inexpensive

Table 4. Pharmacologic Combination Therapy for Adults and Children

Adults
Droperidol + dexamethasone (4)
5-HT_3 receptor antagonist + dexamethasone (4,55,95,97,130,131)
5-HT_3 receptor antagonist + droperidol (4,64,95,130,131)
5-HT_3 receptor antagonist + dexamethasone + droperidol (4)
Combinations in children
Ondansetron, 0.05 mg/kg, + dexamethasone, 0.015 mg/kg (132,133)
Ondansetron, 0.1 mg/kg, + droperidol, 0.015 mg/kg (134)
Tropisetron, 0.1 mg/kg, + dexamethasone, 0.5 mg/kg (135)

See Table 5 for maximum doses for children.

generic antiemetic even if the baseline risk is low and, consequently, many patients must be treated prophylactically for one to benefit.

Novel Therapies

Preliminary data on novel therapies for PONV prophylaxis and treatment show promising results with opioid antagonists and neurokinin-1 (NK_1) receptor antagonists, suggesting that confirmatory studies are warranted. Low-dose naloxone, 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$, reduced nausea and vomiting and decreased the need for rescue medication compared with placebo in adult patients (123), and significantly reduced opioid-related side effects including nausea in children and adolescents (124). Another opioid antagonist, nalmefene, proved effective in reducing opioid-induced nausea, vomiting, and need for rescue medication in patients receiving PCA (125). Alvimopan, 6 mg, an opioid antagonist that does not cross the blood–brain barrier effectively reduced nausea and vomiting in patients undergoing abdominal surgery compared with placebo (126). An alternative therapy, the NK_1 receptor antagonist, CP-122,721, significantly reduced emesis over a 24-h period, both alone and in combination with ondansetron, compared with ondansetron alone (127). Another NK_1 receptor antagonist, GR205171, significantly controlled emesis ($P < 0.01$) and reduced nausea in established PONV compared with placebo (128). The NK_1 antagonist, aprepitant 40 mg PO, was equivalent to ondansetron 4 mg IV in the incidence of nausea and reducing the need for rescue in the initial 24 h postoperatively, but was significantly better than ondansetron for preventing vomiting in the 24 and 48 h after surgery ($P < 0.001$) (129).

Guideline 4: Administer Prophylactic Therapy with Combination (≥2) Interventions/Multimodal Therapy in Patients at High Risk for PONV

Recommended combination therapy is shown in Table 4.

A treatment algorithm is presented in Figure 3.

Discussion

Patients who are at high risk for PONV should receive prophylaxis with combination therapy or a multimodal approach that includes two or more interventions. Regional anesthesia should be considered for patients at high risk for PONV. If general anesthesia is used, baseline risk factors should be reduced when possible. Nonpharmacologic therapies should be considered as adjuncts to pharmacologic therapy. Antiemetics recommended for prophylaxis in adults and children are shown in Tables 3 and 5. When used in combination, drugs from different classes should be selected to optimize their effects.

For PONV prophylaxis, the efficacy of dexamethasone 4 mg IV, ondansetron 4 mg IV, and droperidol 1.25 mg IV appear to be similar (4). Systematic reviews addressing specific therapeutic combinations have shown the combination of a 5-HT_3 receptor antagonist and either dexamethasone or droperidol is more effective than monotherapy with any of the drugs (4,55,95,130,131). Similarly, droperidol combined with dexamethasone is more effective than either drug alone (4). When the different combinations were compared, no differences were found between 5-HT_3 receptor antagonist plus droperidol; 5-HT_3 receptor antagonist plus dexamethasone; and droperidol plus dexamethasone (4,130). Combinations involving metoclopramide were not found to reduce PONV to a greater extent than monotherapy (94,136,137).

A multimodal approach to minimize PONV combines nonpharmacologic and pharmacologic prophylaxis as well as interventions that reduce baseline risk (46,88). Scuderi et al. (46) tested the efficacy of a multimodal approach to reducing PONV. Their multimodal approach consisted of preoperative anxiolysis and aggressive hydration; oxygen; prophylactic antiemetics (droperidol and dexamethasone at induction and ondansetron at end of surgery); total IV anesthesia with propofol and remifentanil; and ketorolac. No nitrous oxide or neuromuscular blockade was used. Patients who received multimodal therapy had a 98% complete response rate compared with a 76% response rate among patients receiving antiemetic monotherapy and a 59% response rate among those receiving routine anesthetic plus saline placebo.

Guideline 5: Administer Prophylactic Antiemetic Therapy to Children at Increased Risk for POV; as in Adults, Use of Combination Therapy Is Most Effective

The prophylactic antiemetic doses recommended for children at risk for POV are shown in Table 5.

Recommended combination therapy is shown in Table 4.

Discussion

In children, the POV rate can be twice as high as in adults, which suggests a greater need for POV prophylaxis in this population (145). The prophylactic antiemetics recommended for children are shown in

Table 5. Antiemetic Doses for Prophylaxis of Postoperative Vomiting (POV) in Children

Drug	Dose	Evidence
Dexamethasone	150 μg/kg up to 5 mg	SR (55,138,139)
Dimenhydrinate	0.5 mg/kg up to 25 mg	SR (58,140)
Dolasetron	350 μg/kg up to 12.5 mg	RCT (141,142)
Droperidol[a]	10–15 μg/kg up to 1.25 mg	SR (64)
Granisetron	40 μg/kg up to 0.6 mg	RCT (71)
Ondansetron[b]	50–100 μg/kg up to 4 mg	SR (81,146)
Perphenazine[c]	70 μg/kg up to 5 mg	RCT (143,144)
Tropisetron	0.1 mg/kg up to 2 mg	SR (84)

Note: These recommendations are evidence-based and not all the drugs have an FDA indication for postoperative nausea and vomiting (PONV).

Drugs are listed alphabetically.

[a] See Food and Drug Administration (FDA) "black box" warning. Recommended doses 10 to 15 μg/kg.

[b] Approved for POV in pediatric patients aged one month and older.

[c] IV formulation of perphenazine is no longer available in the United States, only oral formulation.

RCT = randomized, controlled trial; SR = systematic review.

Table 5. Children who are at moderate or high risk for POV should receive combination therapy with two or three prophylactic drugs from different classes.

Ondansetron has been studied extensively for POV prophylaxis in children and has recently been approved for use in children as young as one-month-of-age (76,146). It is recommended at a dose range of 50–100 μg/kg (76). Compared with placebo, the NNT to prevent early (0–6 h) and late (0–24 h) vomiting is between 2 and 3 (76). Ondansetron is the only 5-HT_3 antagonist that has been approved for a pediatric (age <2) indication. Dolasetron is also recommended for POV prophylaxis, but only in children aged 2 yr and older. The optimal dose of dolasetron for POV prophylaxis is 350 μg/kg (20,141,142,147).

Granisetron at a dose of 40 μg/kg and tropisetron at a dose of 0.1 mg/kg have significantly reduced the incidence of POV in children (71,84). However, the data available about use of these 5-HT_3 antagonists in the pediatric population are slim. Because the 5-HT_3 antagonists as a group have greater efficacy for the prevention of vomiting than nausea, they are the drugs of first choice for prophylaxis in children.

Studies of PONV in children have been limited to the measurement of vomiting, as the reliable, effective evaluation of nausea in nonverbal children is difficult. This methodological limitation may explain some of the reported differences in efficacy of interventions in children and adults. Meta-analyses and single studies have shown that the 5-HT_3 antagonists are superior to droperidol and metoclopramide for the prophylaxis of POV in children. Therefore, the panel recommends the use of 5-HT_3 antagonists as the first choice for prophylaxis of POV in children. However, no pediatric study has demonstrated superior efficacy of any one 5-HT_3 antagonist over another for the prophylaxis of POV.

Dexamethasone has been used in children at a dose of 150 μg/kg, with a NNT to prevent early and late vomiting of about four (55,138,139). A systematic review of dimenhydrinate demonstrates an antiemetic efficacy in children at a dose of 0.5 mg/kg (58). When given at a dose of 70 μg/kg, perphenazine demonstrated antiemetic efficacy in children, although only the oral formulation can be used as the IV formulation is no longer available in the United States (143,144). Droperidol can also be used for the prophylaxis of POV and is administered in a dose range of 50–75 μg/kg. Although these doses correspond to the officially tested doses, the panel considered them too high in a child. If we assume that the pediatric doses on a per kg body weight basis may be extrapolated from adult doses (i.e., 0.625–1.25 mg), the dose range in children should correspond to 10–15 μg/kg. The NNT for prevention of early vomiting is approximately 5 and is between 4 and 5 for prevention of late vomiting (64). Due to the potential increased risk for extrapyramidal symptoms and high levels of sedation found with droperidol, the panel recommended that this drug be reserved for pediatric patients who have failed all other therapies and are being admitted to the hospital.

Numerous, small randomized trials have compared the efficacy of combination therapy with monotherapy for POV prophylaxis. Most have found combination therapy more effective (132–135). Many of the studies that did not find combination therapy superior to monotherapy were under-powered to adequately show a difference between treatment groups (148–150). Combinations that showed efficacy for reducing POV are shown in Table 4. It has been suggested that, with combination therapy in children, dexamethasone doses should not exceed 150 μg/kg and droperidol doses should not exceed 50 μg/kg (96). (See comments above regarding droperidol dosing.) When used in combination with another drug, ondansetron doses should not exceed 50 μg/kg. Combinations with metoclopramide proved no better outcomes than monotherapy alone (151,152).

Guideline 6. Provide Antiemetic Treatment to Patients with PONV Who Did Not Receive Prophylaxis or in Whom Prophylaxis Failed

A treatment algorithm is presented in Figure 3.

Discussion

When PONV occurs postoperatively, treatment should be administered with an antiemetic from a pharmacologic class that is different from the prophylactic drug initially given, or, if no prophylaxis was given, the recommended treatment is a low-dose 5-HT_3 antagonist (85,153). The 5-HT_3 antagonists are the only drugs that have been adequately studied for the treatment of existing PONV (85,154). The doses of 5-HT_3 antagonists used for treatment are smaller than those used for prophylaxis: ondansetron 1.0 mg; dolasetron 12.5 mg; granisetron 0.1 mg; and tropisetron 0.5 mg (NNT = 4–5) (85,76). Smaller doses of dolasetron have not been studied. Alternative treatments

for established PONV include dexamethasone, 2–4 mg IV, droperidol, 0.625 mg IV, or promethazine 6.25–12.5 mg IV (75,153,155). Propofol, 20 mg as needed, can be considered for rescue therapy in patients still in the PACU and has been found as effective as ondansetron (156–158). However, the antiemetic effect with low doses of propofol is probably brief (159).

One-third of patients who are treated with opioids for postoperative pain will have nausea or vomiting (87). In this group of patients, the addition of droperidol, 2.5 mg, to every 100 mg morphine in a PCA device was effective for reducing PONV (87). Ondansetron, 8 mg, also proved more effective than metoclopramide for controlling opioid-induced emesis and nausea in this population (160).

Repeating the medication given for PONV prophylaxis within the first 6 h after the patient has left the PACU confers no additional benefit (156). If more than 6 h has elapsed, it may be possible to achieve some effect with a second dose of a 5-HT_3 antagonist or butyrophenone (droperidol or haloperidol), but this has not been demonstrated in clinical trials and should only be attempted if triple therapy has been used for prophylaxis and if no alternatives are available for rescue that have not been used for prophylaxis. Readministration of dexamethasone or transdermal scopolamine is not recommended.

The attempt at rescue should be initiated when the patient complains of PONV and, at the same time, an evaluation should be performed to exclude an inciting medication or mechanical factor for nausea and/or vomiting. Contributing factors might include a morphine PCA, blood draining down the throat, or an abdominal obstruction.

Postdischarge Nausea and Vomiting

After ambulatory surgery, approximately one-third of patients experience PONV, many of whom did not experience PONV prior to discharge (161,162). Such patients often do not have access to treatment for their postdischarge nausea and vomiting (PDNV). A systematic review of all studies assessing PDNV after outpatient surgery found that, on discharge, 17% of patients experience nausea (range, 0%–55%) and 8% have vomiting (range, 0%–16%) (163). Administration of prophylactic antiemetics may be warranted in patients at high risk for PDNV; however, many of the available antiemetics have a short half-life and may not be suitable for this purpose. A meta-analysis assessing prophylactic therapy for PDNV after ambulatory surgery found a NNT of approximately 5 with combination therapy versus a NNT of approximately 12–13 for ondansetron, 4 mg, or dexamethasone, 4–10 mg alone (161). Droperidol was ineffective at preventing PDNV at a dose <1 mg, and there was insufficient evidence to evaluate droperidol >1 mg. A systematic review of 58 articles demonstrated that use of propofol versus inhaled anesthesia also reduced the incidence of PDNV ($P < 0.05$) (164). Small randomized controlled trials have demonstrated efficacy in preventing PDNV with orally disintegrating ondansetron tablets, acupoint stimulation of P6, and transdermal scopolamine (78,165,166).

CONCLUSION

These guidelines provide a comprehensive, evidence-based reference tool for the management of patients undergoing surgical procedures who may be at risk for PONV. Not all surgical patients will benefit from antiemetic prophylaxis; thus identification of patients who are at increased risk leads to the most effective use of therapy and the greatest cost-efficacy. Although antiemetic prophylaxis can not eliminate the risk for PONV, it can significantly reduce the incidence. When developing a management strategy for each individual patient, the choice should be based on patient preference, C/E, and level of PONV risk.

Among the interventions considered, a reduction in baseline risk factors and use of nonpharmacologic therapy are least likely to cause adverse events. PONV prophylaxis should be considered for patients at moderate to high risk for PONV. Depending upon the level of risk, prophylaxis should be initiated with monotherapy or combination therapy using interventions that reduce baseline risk, nonpharmacologic approaches, and antiemetics. Antiemetic combinations are recommended for patients at high risk for PONV. All prophylaxis in children at moderate or high risk for POV should include combination therapy using a 5-HT_3 antagonist and a second drug. Because the effects of interventions from different drug classes are additive, combining interventions has an additive effect in risk reduction.

When rescue therapy is required, the antiemetic should be chosen from a different therapeutic class than the drugs used for prophylaxis. If PONV occurs within 6 h postoperatively, patients should not receive a repeat dose of the prophylactic antiemetic. An emetic episode more than 6 h postoperatively can be treated with any of the drugs used for prophylaxis except dexamethasone and transdermal scopolamine.

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