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Consensus Guidelines for the Management of Postoperative Nausea and Vomiting

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The present guidelines are the most recent data on postoperative nausea and vomiting (PONV) and an update on the 2 previous sets of guidelines published in 2003 and 2007. These guidelines were compiled by a multidisciplinary international panel of individuals with interest and expertise in PONV under the auspices of the Society for Ambulatory Anesthesia. The panel members critically and systematically 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. These guidelines identify patients at risk for PONV in adults and children; recommend approaches for reducing baseline risks for PONV; identify the most effective antiemetic single therapy and combination therapy regimens for PONV prophylaxis, including nonpharmacologic approaches; recommend strategies for treatment of PONV when it occurs; provide an algorithm for the management of individuals at increased risk for PONV as well as steps to ensure PONV prevention and treatment are implemented in the clinical setting. (Anesth Analg 2014;118:85–113)

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Postoperative nausea and vomiting (PONV) are common and distressing to patients. The general incidence of vomiting is about 30%, the incidence of nausea is about 50%, and in a subset of high-risk patients, the PONV rate can be as high as 80%.[9–11] Unresolved PONV may result in prolonged postanesthesia care unit (PACU) stay and unanticipated hospital admission that result in a significant increase in overall health care costs.[12–14] The goal of PONV prophylaxis is therefore to decrease the incidence of PONV and thus patient-related distress and reduce health care costs.[12–15]

Several guidelines on the management of PONV have been published.[1–7] However, they are either in non-English language,[4,5,7] targeted for a specific surgical population,[6] or have not been updated in recent years.[1–3] A recent update by the American Society of Anesthesiologists task force on postoperative care published practice guidelines for postoperative care.[8] Because the scope of the guidelines was broad, covering patient assessment, monitoring, and overall management of patients after anesthesia, and recommendations on the risk assessment and management of PONV were not adequately addressed. The present guidelines are the most recent data on PONV and an update on the 2 previous sets of guidelines published in 2003 and 2007.[1,2] A systematic literature search yielded several hundred publications on PONV since the 2007 guidelines, and a number of new antiemetics were introduced along with new data on PONV management strategies. This update includes new information on PONV risk factors including a risk scoring system for postdischarge nausea and vomiting (PDNV); recommendations

WHAT OTHER GUIDELINES ARE AVAILABLE ON THIS TOPIC?

Several guidelines on the management of postoperative nausea and vomiting (PONV) have been published.[1–7] Among them, 2 were the previous versions of the present guidelines by the same group, published in 2003 and 2007.[1,2] One set of guidelines was published by the American Society of Perianesthesia Nurses in 2006[3] and another published in the Canadian Journal of Obstetrics and Gynaecology in 2008.[6] Subsequently, 3 PONV guidelines were published in the French, Spanish, and German language.[4,5,7] A recent update on practice guidelines for postoperative care was published by the American Society of Anesthesiologists task force on postoperative care.[8]

WHY WAS THIS GUIDELINE DEVELOPED?

The goal of the current guidelines is to provide current and comprehensive information to practicing physicians, nurse anesthetists, anesthesiologist assistants, pharmacists, perianesthesia, perioperative and ward nurses as well as other health care providers about strategies to prevent and treat PONV in adults and children undergoing surgery.

HOW DOES THIS GUIDELINE DIFFER FROM EXISTING GUIDELINES?

A systematic literature search yielded several hundred publications on PONV since the 2007 Society for Ambulatory Anesthesia PONV guidelines, and a number of new antiemetics were introduced along with additional new data on PONV risk assessment and management strategies. The present guidelines are the most recent data on PONV and an update on 2 previous sets of guidelines published in 2003 and 2007 by the same group.[1,2] The 2 guidelines published in 2006 and 2008 focused primarily on perianesthesia nurses and gynecologists and did not have up-to-date information on the management of PONV.[3,6] The other 3 guidelines were published in non-English language.[4,5,7] The scope of the postoperative care guidelines published by the American Society of Anesthesiologists were broad, covering patient assessment, monitoring, and overall management of patients after anesthesia, and recommendations on the risk assessment and management of PONV were not adequately addressed.[8]

WHY DOES THIS GUIDELINE DIFFER FROM EXISTING GUIDELINES?

The present guidelines include new information on PONV risk factors; a risk scoring system for postdischarge nausea and vomiting; recommendations on new antiemetics, for example, neurokinin-1 receptor antagonists; changes in recommendations from previous guidelines based on new published information on efficacy and risk of antiemetics, including new data on QT prolongation; recommendation on a new antiemetic combination strategy and a multimodal prevention approach in adults and children to prevent PONV and implementation of PONV prevention and treatment strategies in the clinical setting.

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ESTABLISHMENT OF EXPERT GUIDELINES

The present guidelines were developed under the auspices of the Society for Ambulatory Anesthesia. While the previous 2 sets of guidelines were funded through educational grants, this update received no outside funding. Neither the society nor the experts received any funding from industry for this work. Panel members gathered during a Society for Ambulatory Anesthesia midyear meeting, a day before the commencement of the American Society of Anesthesiologists annual meeting. The primary author convened a multidisciplinary international panel of individuals, some of whom had previously developed the first and second guidelines,[1,2] and sought additional experts 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. Panel members were asked to review the medical literature on PONV (starting from 2007). Working in groups, the participants researched a specific topic and presented 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.

METHODS

We followed the guideline development process similar to that published in 2007.[2] A systematic review of the literature concerning PONV management in adult and pediatric patients undergoing surgery was conducted according to the protocol recommended by the Cochrane Collaboration.[16] We searched the Cochrane Controlled Trials Register, the Cochrane Library, MEDLINE, and EMBASE from January 2007 to October 2011. A reference librarian and a coauthor (FC) familiar with literature search protocol of the Cochrane Collaboration (Marina Englesakis, Toronto, Ontario, Canada) designed and conducted the electronic search strategy with input from members of the consensus panel. The search was divided into 6 areas: algorithms, prophylaxis, treatment effectiveness, nonpharmacological or alternative therapy, risk assessment, and risk reduction. The Medline search on algorithm of PONV protocols yielded 171 titles, prophylaxis 433 titles, treatment effectiveness 567 titles, and nonpharmacological or alternative therapy 320 titles. The search on risk assessment of PONV yielded 564 titles and risk reduction 549 titles. The search strategy and the keywords used are presented in Appendix 1 (see Supplemental Digital Content 1, http://links.lww.com/AA/A688). We hand-searched the reference lists from the already retrieved

articles to identify further trials. The search was limited to human trials but not limited by language. The librarian deleted duplicate records. Clinical studies reported by Fujii et al were excluded due to research misconduct.[17] The search results were screened by the authors in a stepwise manner to identify the eligible studies. In the first step, we screened the titles, and irrelevant papers were excluded. In the next step, we read the abstract or full text of the papers for inclusion. The number of and reason for excluded studies in this step were recorded. We selected all reviews, trials, or randomized controlled trials (RCTs) on PONV management (Appendix 1, see Supplemental Digital Content 1, http://links.lww.com/AA/A688).

Goals of Guidelines

The panel defined the following goals for the guidelines: (1) Understand who is at risk 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 single drug and combination therapy regimens for PONV/POV prophylaxis, including pharmacologic and nonpharmacologic approaches; (4) Ascertain the optimal approach to treatment of PONV and PDNV with or without PONV prophylaxis; (5) Determine the optimal dosing and timing of antiemetic prophylaxis; (6) Evaluate the cost-effectiveness of various PONV management strategies; (7) Create an algorithm to identify individuals at increased risk for PONV and suggest effective treatment strategies; and (8) Propose a research agenda for future studies.

Scientific Evidence Grading

A number of grading systems have been proposed to characterize the strength of evidence of the RCTs and observational studies supporting a treatment. The panel decided to use a scientific evidence grading system previously used by the American Society of Anesthesiologists in their practice guidelines for acute pain management in the perioperative setting (Appendix 2).[18] Study findings from published scientific literature were aggregated and are reported in summary form by evidence category, as described below. All literature (e.g., RCTs, observational studies, case reports) relevant to each topic was considered when evaluating the findings.

Guideline 1. Identify Patients' Risk for PONV

New information: Additional studies identify the younger age group (<50 years) as a significant risk factor for PONV (odds ratio, OR; 95% confidence interval [CI]): 1.79 (1.39–2.30) compared with those who are 50 years or older.[19] Type of surgery as a risk factor is still debated. New evidence suggests that cholecystectomy: 1.90 (1.36–2.68), gynecological surgery: 1.24 (1.02–1.52), and laparoscopic: 1.37 (1.07–1.77) approach are associated with a higher incidence of PONV when compared with general surgery as a reference group.[20] The contribution of intraoperative opioids to PONV is weak, and there is no difference among the different opioids. A recent meta-analysis reaffirmed previously known PONV risk factors but with somewhat different order of importance. Female gender was the strongest patient-specific predictor (OR 2.57, 95% CI, 2.32–2.84), followed by a history of PONV (2.09, 1.90–2.29), nonsmoking status (1.82, 1.68–1.98),

history of motion sickness (1.77, 1.55–2.04), and age (0.88 per decade, 0.84–0.92). The use of volatile anesthetics was the strongest anesthesia-related predictor (1.82, 1.56–2.13), followed by the duration of anesthesia (1.46 h^{-1}, 1.30–1.63), postoperative opioid use (1.47, 1.31–1.65), and nitrous oxide (1.45, 1.06–1.98).[19,20]

PDNV is a major concern for the anesthesia care provider with the growth in ambulatory surgeries. A new validated simplified risk score for adults for PDNV includes the risk factors of female sex, age <50 years, history of PONV, opioid use in PACU, and nausea in PACU.[19]

A simplified risk score for PONV in adults is shown in Table 1 and Figure 1. A simplified risk score for PDNV in adults is shown in Figure 2. A simplified risk score for POV in children is shown in Figure 3.

Patient Risk Assessment for PONV

A number of risk factors have been associated with an increased incidence of PONV. However, some of these factors may be only simple associations. For objective risk assessment, it is recommended to focus on those that independently predict PONV after accounting for other confounding factors. We identified those independent risk

Table 1. Risk Factors for PONV in Adults

Evidence	Risk factors
Positive overall	Female sex (B1)
	History of PONV or motion sickness (B1)
	Nonsmoking (B1)
	Younger age (B1)
	General versus regional anesthesia (A1)
	Use of volatile anesthetics and nitrous oxide (A1)
	Postoperative opioids (A1)
	Duration of anesthesia (B1)
	Type of surgery (cholecystectomy, laparoscopic, gynecological) (B1)
Conflicting	ASA physical status (B1)
	Menstrual cycle (B1)
	Level of anesthetist's experience (B1)
	Muscle relaxant antagonists (A2)
Disproven or of limited clinical relevance	BMI (B1)
	Anxiety (B1)
	Nasogastric tube (A1)
	Supplemental oxygen (A1)
	Perioperative fasting (A2)
	Migraine (B1)

PONV = postoperative nausea and vomiting; BMI = body mass index; MS = motion sickness.
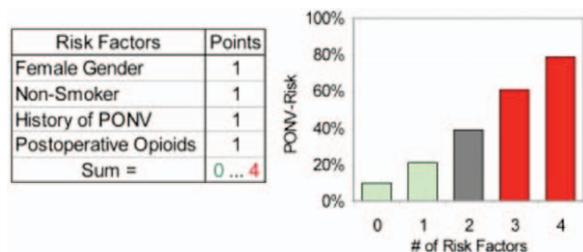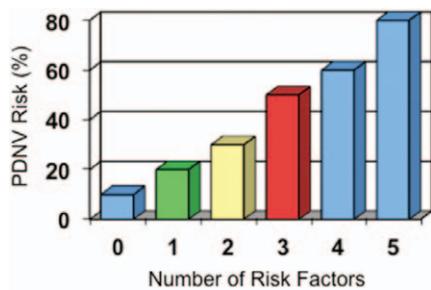

Figure 1. Risk score for PONV in adults. Simplified risk score from Apfel et al.[9] to predict the patient's risk for PONV. When 0, 1, 2, 3, and 4 of the risk factors are present, the corresponding risk for PONV is about 10%, 20%, 40%, 60%, and 80%, respectively. PONV = postoperative nausea and vomiting.

Figure 2. Simplified risk score for PDNV in adults. Simplified risk score from Apfel et al.[19] to predict the risk for PDNV in adults. When 0, 1, 2, 3, 4, and 5 risk factors are present, the corresponding risk for PDNV is approximately 10%, 20%, 30%, 50%, 60%, and 80%, respectively. PDNV = postdischarge nausea and vomiting; PONV = postoperative nausea and vomiting; PACU = postanesthesia care unit.
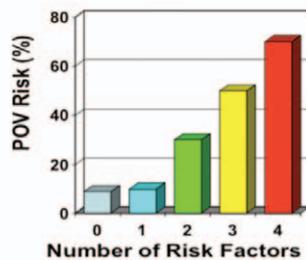

Figure 3. Simplified risk score for POV in Children. Simplified risk score from Eberhart et al.[48] to predict the risk for POV in children. When 0, 1, 2, 3, or 4 of the depicted independent predictors are present, the corresponding risk for PONV is approximately 10%, 10%, 30%, 50%, or 70%, respectively. POV = postoperative vomiting; PONV = postoperative nausea and vomiting.

factors that remain significant in multivariable analyses of large cohort studies (Table 1).

The most likely causes of PONV are volatile anesthetics, nitrous oxide, and postoperative opioids.[21,22] The effect of volatile anesthetics on PONV is dose-dependent and particularly prominent in the first 2 to 6 hours after surgery.[21] Irrespective of the specific drug given,[23,24] postoperative opioids also increase the risk for PONV in a dose-dependent manner,[25] and this effect appears to last for as long as opioids are used for pain control in the postoperative period.[19] This most likely explains why the incidence of PONV is lower with opioid-free regional anesthesia[26] and reduced opioid consumption through the use of non-opioid analgesics,[27] perioperative alpha-2 agonists,[28] and beta-blockers.[29]

Despite the triggers mentioned above, many patients do not experience PONV, most likely because the development of PONV also depends on the individual patient's susceptibility.[30] Patient-specific risk factors for PONV in adults include female sex, a history of PONV and/or motion sickness, nonsmoking status, and young age.[9–11,19,21,31,32] Type of surgery is strongly believed to be a risk factor for PONV, yet it is difficult to prove that it is an independent risk factor. Certain types of surgery may be associated with a frequent incidence of PONV (e.g., abdominal surgeries), not because of a specific emetogenic pathway, but could be as a result of a long exposure to general anesthesia and higher doses of opioids. More recent studies suggest laparoscopic, gynecological surgery, and cholecystectomy are risk factors that independently increase the risk for PONV.[11,21,31,33–35] However, the reference groups used differed widely among studies, which may have led to a bias toward positive results.

Evidence for other commonly believed risk factors is either: (1) Not clinically relevant for the prediction of PONV (e.g., anxiety),[36] (2) Uncertain (e.g., menstrual cycle,[37] neostigmine,[38,39] and perioperative fasting),[40] or (3) Disproven (e.g., nasogastric tube, obesity, and supplemental oxygen).[41–43]

Risk Score

Like all drugs, antiemetics carry some risk for adverse effects, which range in severity from mild headache to possibly more meaningful QTc prolongations that may rarely be associated with cardiac arrest.[44] Therefore, a patient's baseline risk for PONV should be objectively assessed using a validated risk score that is based on independent predictors, so the number and choice of prophylactic antiemetics can be titrated against the patient's risk.

Even though there is strong evidence for a couple of truly independent risk factors for PONV, none of those risk factors taken alone as a single predictor is clinically sufficient for a risk assessment or to make clinical decisions about the need for prophylactic antiemetics.[21] Therefore, a patient's baseline risk for PONV should be objectively assessed using a validated risk score that is based on these independent predictors. Indeed, use of PONV risk scores has been demonstrated to significantly reduce the institutional rate of PONV.[45–47] The 2 most commonly used risk scores for inpatients undergoing balanced inhaled anesthesia are the Koivuranta score and the Apfel score.[9,10] The Apfel simplified risk score is based on 4 predictors: female sex, history of PONV and/or motion sickness, nonsmoking status, and use of postoperative opioids (Fig. 1).[9] The incidence of PONV with the presence of 0, 1, 2, 3, and 4 risk factors is about 10%, 20%, 40%, 60%, and 80%, respectively.[9] The panel considers patients with 0–1, 2 or 3, and more risk factor as "low," "medium," and "high" risk categories, respectively.

Given that several antiemetics are now generic and inexpensive, some experts suggest it may be appropriate to give 1 or 2 antiemetics to all patients. However, this strategy puts the low-risk patients at unnecessary risk for rare but well-described side effects. Although risk scores are an objective approach to assessing the patient's risk for PONV or PDNV, they are not completely predictive, with sensitivity and specificity of between 65% and 70%. In addition, other clinically relevant aspects should also be taken into consideration by the anesthesia care provider, such as whether vomiting would pose a significant medical risk, for example, in patients with wired jaws, increased intracranial pressure, and after gastric or esophageal surgery.

Because ambulatory procedures are typically shorter and less invasive than inpatient procedures, they are associated with a lower risk of PONV in the PACU.[19] However, PDNV presents a significant risk to discharged patients who, by definition, no longer have access to fast-onset IV antiemetics or monitored care. A recent study on 2170 U.S. outpatients reported that the incidence of PDNV is 37% in the first 48 hours after discharge and identified 5 independent predictors of PDNV including female sex, age<50 years, history of PONV, opioid use in the PACU, and nausea in the PACU.[19] Validation of a simplified PDNV risk score based on these risk factors showed that the incidence of PDNV with 0, 1, 2, 3, 4, or 5 of these risk factors was about 10%, 20%, 30%, 50%, 60%, and 80%, respectively (Fig. 2).[19]

Assessment for POV in Children
In the 2007 Guidelines,[2] we referred to a single center study by Eberhart et al.[48] who identified 4 independent predictors of POV in children: duration of surgery >30 minutes; age >3 years; history of POV in patient, parent, or sibling; and strabismus surgery. Based on the presence of 0, 1, 2, 3, and 4 factors, the risk of POV was 9%, 10%, 30%, 55%, and 70%, respectively (Fig. 3). Kranke et al.[49] performed an external validation of this score in a different institution in children not undergoing strabismus surgery. They noted the actual incidence of POV when prophylaxis was not used was 3.4%, 11.6%, 28.2%, and 42.3%, respectively in the presence of 0, 1, 2, or 3 factors. These findings support the earlier recommendation of using a simplified score to estimate the child's risk of POV.

Guideline 2. Reduce Baseline Risk Factors for PONV
New Information: Minimization of neostigmine dosage has been removed from the list of strategies to reduce baseline risk as new evidence did not find this to be helpful, and the evidence is contradictory. In children, subhypnotic doses of propofol infusion in combination with an antiemetic significantly reduce incidence of PONV.[50,51]

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

DISCUSSION
Reducing baseline risk factors can significantly decrease the incidence of PONV. Strategies recommended to reduce baseline risk include: (1) The avoidance of general anesthesia by the use of regional anesthesia; (2) Preferential use of propofol infusions; (3) Avoidance of nitrous oxide; (4) Avoidance of volatile anesthetics; (5) Minimization of perioperative opioids; and (6) Adequate hydration (Table 2).[2]

Use of regional anesthesia was associated with a lower incidence of PONV than general anesthesia in both children and adults.[11,52] Sinclair et al.[11] found the risk for PONV was 9 times less among patients receiving regional anesthesia than those receiving general anesthesia. When general anesthesia was required, use of propofol for induction and maintenance of anesthesia decreased the incidence of early PONV (occurring within the first 6 hours; number-needed-to-treat [NNT] = 5).[53]

The IMPACT study evaluated 6 strategies to reduce PONV in 5199 high-risk patients.[47] They found that a combination of propofol and air/oxygen (total IV anesthesia [TIVA]) had additive effects, reducing PONV risk by approximately 25%.[47] These findings are supported by 2 meta-analyses demonstrating that avoiding nitrous oxide reduced PONV risk[54,55] and a randomized, placebo-controlled trial showing that volatile anesthetics were the primary cause of early PONV (0–2 hours after surgery), but that they did not have an impact on delayed PONV (2–24 hours after surgery).[21] However, nitrous oxide had little impact when the baseline risk for PONV is low.[55]

Baseline risk for PONV can also be reduced by minimizing postoperative opioids.[9,21,25,54,56–58] To achieve satisfactory analgesia without opioids, alternate modalities of pain management may be used. RCTs and meta-analyses show that perioperative nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 inhibitors[27,59,60] and less so intraoperative ketamine[61] may have a morphine-sparing effect in the postoperative period. The decrease in opioid consumption using opioid analgesic adjuncts has been demonstrated to decrease the incidence of opioid-related nausea and vomiting.[62]

Reducing the dose or avoiding neostigmine had been shown to reduce the baseline risk for PONV. Meta-analyses demonstrate that high-dose neostigmine (>2.5 mg) was associated with increased PONV and that reducing the dose can decrease PONV risk.[39,63] However, more recent data disputed the clinical importance of neostigmine's effects on PONV.[38] Hence, minimization of neostigmine dosage has been removed from the list of strategies to reduce the baseline risk.

Systematic reviews of RCTs show that supplemental oxygen had no effect on nausea or overall vomiting, although it may reduce the risk of early vomiting.[64] As a result, supplemental oxygen is not recommended for the prevention of PONV in these guidelines.

A number of recently published studies demonstrate that reducing baseline risk factors is also effective for decreasing the incidence of POV in children. In the pediatric patient population, regional anesthesia is usually performed while the child is receiving general anesthesia to reduce stress associated with inserting needles. A major benefit of a combined general and regional anesthetic technique is the reduction in perioperative opioid requirements and consequently, reduced postoperative emesis. Children randomized to a wrist block during hand surgery had less emesis than those receiving perioperative opioids.[65] Similarly, children receiving a peribulbar block or topical lidocaine during strabismus repair had less emesis than a control group.[66] In another study, there were fewer incidents of POV when children receive a bupivacaine-induced subtenon block

Table 2. Strategies to Reduce Baseline Risk
Avoidance of general anesthesia by the use of regional anesthesia[11,52] (A1)
Use of propofol for induction and maintenance of anesthesia[47] (A1)
Avoidance of nitrous oxide[43,54,55] (A1)
Avoidance of volatile anesthetics[47,21,21,47] (A2)
Minimization of intraoperative (A2) and postoperative opioids[9,21,25,54,56–58] (A1)
Adequate hydration[261,325] (A1)

GA = general anesthesia.

during strabismus surgery compared with a sham block with saline.[67] However, in a study of children undergoing cataract surgery, the reduction in emesis rates in those receiving a subtenon block with a lidocaine–bupivacaine mixture did not reach statistical significance, although this group had significantly less pain and drowsiness and required less rescue analgesia compared with those receiving a sham block.[68]

The benefit of propofol infusions during tonsillectomies in pediatric patients has been studied.[50,51] Children receiving intraoperative propofol in subhypnotic doses (bolus of 1 mg/kg followed by an infusion at 20 mcg/kg/min) combined with dexamethasone had less emesis than those receiving dexamethasone alone.[50] Similarly, treatment with a combination of subhypnotic propofol and tropisetron provided better prophylaxis against POV than tropisetron alone in this patient population.[51]

NSAIDs are used in the perioperative period with the aim of reducing opioid requirements, but there are concerns about increased postoperative bleeding with their use. In a systematic review, Cardwell et al.[69] concluded that NSAIDs do not increase bleeding after tonsillectomy/adenoidectomy procedures. In 12 trials evaluating the effect of NSAIDS on POV in 928 children, less emesis was noted in the treated groups (OR 0.49, 95% CI, 0.29–0.83).

Adequate hydration is another simple strategy to reduce emesis. Goodarzi et al.[70] showed that high dose IV fluids at 30 mL/kg were associated with less emesis than the standard 10 mL/kg therapy during strabismus repair. However, routine gastric decompression and limiting oral intake after surgery were ineffective in reducing emesis in the postoperative period in children.[71–73]

Guideline 3. Administer PONV Prophylaxis Using 1 to 2 Interventions in Adults at Moderate Risk for PONV

New Information: Clinically approved drugs that are new or with further studies since the last guidelines are: (1) $5HT_3$ receptor antagonists: ramosetron and palonosetron; (2) NK-1 receptor antagonist: aprepitant, casopitant, and rolapitant;

(3) corticosteroid: methylprednisolone; (4) butyrophenone: haloperidol; and (5) antihistamine: meclizine. Concerns have been raised regarding the effects of the first generation $5HT_3$ receptor antagonists on the QTc interval. Dolasetron is no longer marketed in the United States because of its risk of QTc prolongation and torsade de pointes. However, the use of droperidol in combination with a $5HT_3$ receptor antagonist, such as ondansetron, did not increase the risk of QT prolongation. Recent studies raised concerns about the effect of dexamethasone on postoperative infection and blood glucose levels 6 to 12 hours postoperatively.

Strategies not evaluated in the 2007 guidelines and found to be not effective for PONV prophylaxis include music therapy, isopropyl alcohol inhalation, intraoperative gastric decompression, the proton pump inhibitor esomeprazole, ginger root, nicotine patch to nonsmokers, cannabinoids (nabilone and tetra-hydrocannabinol), and intraoperative supplemental oxygen. Morindal citrofolin linn (noni fruit) showed effectiveness in reducing early postoperative nausea. A small dose (2 mg) of midazolam when given toward the end of surgery is effective in reducing PONV. Since the publication of the last guideline, a new meta-analysis on P6 stimulation has been published. The timing of acupoint P6 electrical stimulation did not impact PONV with similar reductions in PONV achieved when the stimulation was initiated either before or after anesthesia induction. Neuromuscular stimulation over the median nerve reduced PONV in the early postoperative period, particularly when tetanic stimulation was used. While adequate IV fluid hydration was effective to reduce PONV, the type of fluid (crystalloid versus colloid) did not have an effect on PONV when similar volumes were used in surgeries with minimal fluid shifts.

Prophylactic doses and timing for administration of antiemetics in adults are shown in Table 3. A treatment algorithm is presented in Figure 4.

DISCUSSION

The recommended pharmacologic antiemetics for PONV prophylaxis in adults include the 5-hydroxytryptamine

Table 3. Antiemetic Doses and Timing for Prevention of PONV in Adults

Drugs	Dose	Evidence	Timing	Evidence
Aprepitant	40 mg per os	A2[113,115]	At induction	A2[113]
Casopitant	150 mg per os	A3[117,118]	At induction	
Dexamethasone	4–5 mg IV	A1[121]	At induction	A1[326]
Dimenhydrinate	1 mg/kg IV	A1[152–154]		
Dolasetron	12.5 mg IV	A2[84,85]	End of surgery; timing may not affect efficacy	A2[85]
Droperidol[a]	0.625–1.25 mg IV	A1[138,139]	End of surgery	A1[140]
Ephedrine	0.5 mg/kg IM	A2[223,224]		
Granisetron	0.35–3 mg IV	A1[91–93]	End of surgery	A1[108–110]
Haloperidol	0.5–<2 mg IM/IV	A1[146]		
Methylprednisolone	40 mg IV	A2[137]		
Ondansetron	4 mg IV, 8 mg ODT	A1[74,75]	End of surgery	A1[107]
Palonosetron	0.075 mg IV	A2[105,106]	At induction	A2[105,106]
Perphenazine	5 mg IV	A1[162]		
Promethazine	6.25 - 12.5 mg IV	A2[222,295]		
Ramosetron	0.3 mg IV	A2[102]	End of surgery	A2[102]
Rolapitant	70–200 mg per os	A3[119]	At induction	
Scopolamine	Transdermal patch	A1[157,158]	Prior evening or 2 h before surgery	A1[157]
Tropisetron	2 mg IV	A1[97]	End of surgery	Expert opinion

These recommendations are evidence-based, and not all the drugs have an FDA indication for PONV. Drugs are listed alphabetically.
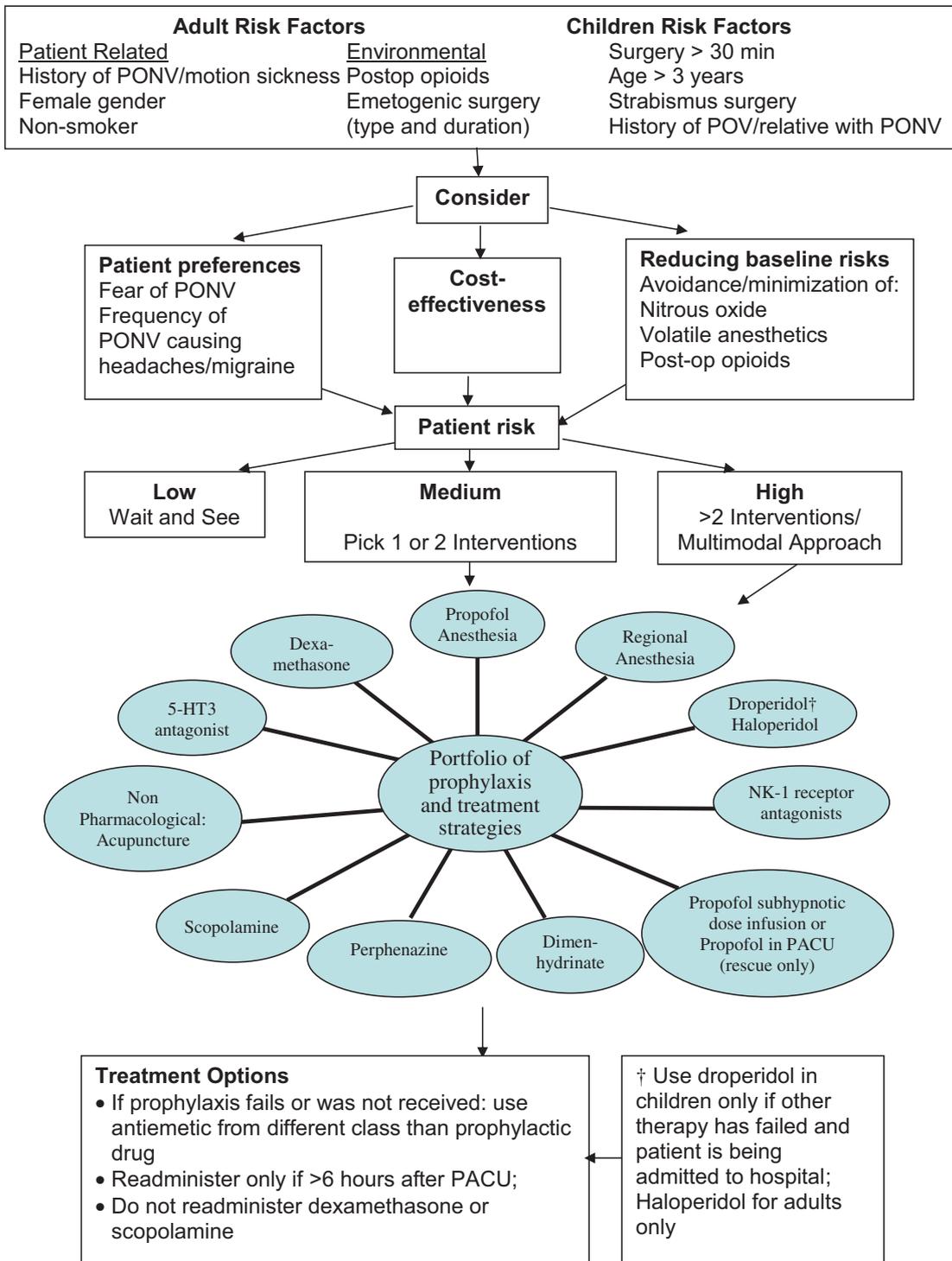[a]See FDA Black box warning.

Figure 4. Algorithm for management of postoperative nausea and vomiting. PONV = postoperative nausea and vomiting.

(5-HT$_3$) receptor antagonists (ondansetron, dolasetron, granisetron, tropisetron, ramosetron, and palonosetron), neurokinin-1 (NK-1) receptor antagonists (aprepitant, casopitant, and rolapitant), corticosteroids (dexamethasone and methylprednisolone), butyrophenones (droperidol and haloperidol), antihistamines (dimenhydrinate and meclizine), and anticholinergics (transdermal scopolamine [TDS]). 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 cost-effectiveness (C/E) studies need to be done to support the more universal use of prophylactic antiemetics. Ondansetron 4 mg, droperidol 1.25 mg, and dexamethasone 4 mg were equally effective, and each independently reduced PONV risk by approximately 25%.[47] The recommended doses and timing of these drugs are listed in Table 3. Recommendations given

are evidence based, and not all the drugs have a Food and Drug Administration (FDA) indication for PONV.

5-HT₃ Receptor Antagonists

Ondansetron

Most of the available research on the 5-HT₃ receptor antagonists involves ondansetron, which has greater antivomiting than antinausea effects. Ondansetron is the "gold standard" compared with other antiemetics. It has a recommended dose of 4 mg, a NNT of approximately 6 for prevention of vomiting (0–24 hours), and a NNT of approximately 7 for prevention of nausea.[74] The effect of the ondansetron 8 mg oral disintegrating table is equivalent to the 4 mg IV dose.[75,76] Ondansetron is as effective as other 5-HT₃s[74] including ramosetron 0.3 mg.[77] It is also as effective as dexamethasone[47] and haloperidol 1 mg IV,[78–80] with no difference in effect on the QTc interval.[81] However, it is less effective than aprepitant[81] for reducing emesis and palonosetron for the incidence of PONV.[82]

Dolasetron

Prospective RCTs show a prophylactic dose of 12.5 mg dolasetron effectively prevents PONV.[83–85] That prophylactic dose is as effective as ondansetron 4 mg.[86,87] Other data show dolasetron is more effective than droperidol in preventing PONV after surgery for prognathism.[88] A study by Janicki et al.[89] found granisetron is more effective in preventing PONV than dolasetron. These differences may be due to duplication of the CYP2D6 allele causing ultrarapid metabolism of dolasetron. In December 2010, the FDA announced that IV dolasetron should no longer be used for chemotherapy-induced nausea and vomiting in adults and children because of concerns of QT prolongation and torsade de pointes.[90] At present, dolasetron is no longer marketed in the United States but may be available in other countries.

Granisetron

Granisetron, 0.35 to 3 mg IV (5–20 mcg/kg), is as effective as other first generation 5HT₃ receptor antagonists.[91–93] Granisetron, 3 mg IV, is also as effective as dexamethasone 8 mg, and the combination is better than either drug alone.[94] Similarly, granisetron 1 mg plus cyclizine 40 mg is more effective than granisetron 1 mg or cyclizine 50 mg alone.[95] However, compared with palonosetron 0.075 mg, granisetron 2.5 mg is as effective at 3 hours and 3 to 24 hours but less effective at 24 to 48 hours.[96]

Tropisetron

Tropisetron 2 mg IV is effective for PONV prophylaxis.[97] It is as effective as ondansetron, granisetron,[98] and droperidol and more effective than metoclopramide.[99] The combination of tropisetron plus dexamethasone is more effective than either drug alone.[100] Tropisetron is not approved in the United States.

Ramosetron

Ramosetron is not approved in the United States but available in other parts of the world. It is more effective with IV versus PO dosing (1–24 hours postoperatively).[101] Ramosetron 0.3 mg IV is the most effective dose to prevent

vomiting and decrease nausea for patients receiving fentanyl patient-controlled analgesia (PCA).[102]

Palonosetron

Palonosetron is a second generation 5HT₃ receptor antagonist with a half-life of 40 hours.[103,104] The most effective dose is 0.075 mg IV approved for 24 hours.[105,106] Palonosetron 0.075 mg is more effective than granisetron 1 mg[96] and ondansetron 4 mg[82] in preventing PONV.

Timing of Administration

Ondansetron, dolasetron, granisetron, and tropisetron are most effective in the prophylaxis of PONV when given at the end of surgery,[85,107–110] although some data on dolasetron suggest timing may have little effect on efficacy.[111] Palonosetron is typically given at the start of surgery.[105,106]

Adverse Events

The 5-HT₃ receptor antagonists have a favorable side effect profile, and while generally considered equally safe, all except palonosetron affect the QTc interval. In June 2012, the U.S. FDA recommended the dose of ondansetron for chemotherapy-induced nausea and vomiting should not exceed 16 mg in a single dose because of risks of QT prolongation. In December 2012, the FDA notified that the 32 mg single IV dose will no longer be marketed.[112] However, there was no change in the recommended dose of ondansetron 4 mg to prevent PONV.[90] 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.[54]

NK-1 Receptor Antagonists

Aprepitant

Aprepitant is an NK-1 receptor antagonist with a 40-hour half-life. In 2 large RCTs, aprepitant (40 and 80 mg per os) was similar to ondansetron in achieving complete response (no vomiting and no use of rescue antiemetic) for 24 hours after surgery. However, aprepitant was significantly more effective than ondansetron for preventing vomiting at 24 and 48 hours after surgery and in reducing nausea severity in the first 48 hours after surgery.[81,113] It also has a greater antiemetic effect compared with ondansetron. When used in combination, aprepitant 40 mg per os, plus dexamethasone, is more effective than ondansetron plus dexamethasone in preventing POV in patients undergoing craniotomy.[114] A dose-ranging study for gynecologic laparotomy patients found a 80 mg per os dose of aprepitant is the most appropriate dose and is more effective than a 40 mg dose.[115] The clinical experience with the use of aprepitant is still limited, and its role in routine prophylaxis is not established.[116]

Casopitant

A Phase 3 study of casopitant shows the combination of casopitant, 50 to 150 mg per os, plus ondansetron 4 mg, is more effective than ondansetron alone.[117,118] Casopitant has not been approved for use.

Rolapitant

Rolapitant has a 180-hour half-life and better PONV prophylaxis than placebo. A clinical trial by Gan et al.[119] showed no difference between groups receiving oral rolapitant and

ondansetron 4 mg IV at 24 hours, but more patients experienced no emesis with the rolapitant 70 and 200 mg doses at 72 and 120 hours, respectively. Rolapitant has not been approved for use.

Corticosteroids

Dexamethasone

The corticosteroid dexamethasone effectively prevents nausea and vomiting in postoperative patients.[120,121] A prophylactic dose of 4 to 5 mg IV for patients at increased risk for PONV is recommended after anesthesia induction rather than at the end of surgery.[121] For PONV prophylaxis, the efficacy of dexamethasone 4 mg IV is similar to ondansetron 4 mg IV and droperidol 1.25 mg IV.[47] More recent studies increasingly use the higher dose of dexamethasone 8 mg IV rather than the minimum effective dose of 4 to 5 mg.[122–126]

Preoperative dexamethasone 8 mg enhances the postdischarge quality of recovery in addition to reducing nausea, pain, and fatigue.[127] Dexamethasone also has dose-dependent effects on quality of recovery. At 24 hours, patients receiving dexamethasone 0.1 vs 0.05 mg/kg required less opioid and reported less nausea, sore throat, muscle pain, and difficulty falling asleep.[128] A meta-analysis evaluating the dose-dependent analgesic effects of perioperative dexamethasone found that doses >0.1 mg/kg are an effective adjunct in multimodal strategies to reduce postoperative pain and opioid consumption.[129,130] With these additional benefits of pain relief and better quality of recovery, a prophylactic dose of dexamethasone 0.1 mg/kg or 8 mg in adults may be considered though further confirmation is needed for this larger dose.

Data on safety of perioperative dexamethasone are inconclusive. In most studies, a single dose of perioperative dexamethasone does not appear to increase the risk of wound infection.[120,129] However, a recent study reported that intraoperative dexamethasone 4 to 8 mg may confer an increased risk of postoperative infection.[131] Weighing the risk-benefit ratio, a recent editorial suggests a single dose of dexamethasone 4 to 8 mg is safe when used for PONV prophylaxis.[132] In addition, recent studies showed significant increases in blood glucose that occur 6 to 12 hours postoperatively in normal subjects,[133,134] those with impaired glucose tolerance,[134] and type 2 diabetic[135] and obese[134] surgical patients who receive dexamethasone 8 mg. In view of this evidence, use of dexamethasone in labile diabetic patients is relatively contraindicated.

Methylprednisolone

Methylprednisolone 40 mg IV is effective for the prevention of late PONV.[136,137] There is no evidence to suggest that the adverse effect of methylprednisolone is any different from dexamethasone.

Butyrophenones

Droperidol

Prophylactic doses of droperidol 0.625 to 1.25 mg IV are effective for the prevention of PONV.[138–140] The efficacy of droperidol is similar to ondansetron for PONV prophylaxis, with an NNT of approximately 5 for prevention of nausea and vomiting (0–24 hours).[140] Droperidol is most effective when administered at the end of surgery.[140] For PONV

prevention, droperidol is superior to metoclopramide doses of <20 mg.[141] A recent meta-analysis suggests that with prophylactic low-dose droperidol (<1 mg or 15 μg/kg IV) in adults, there is still significant antiemetic efficacy with a low risk of adverse effects.[142]

Many physicians stopped using droperidol in 2001 due to the FDA "black box" restrictions on its use. However, the droperidol doses used for the management of PONV are extremely low, and it is believed that at these dosing levels, droperidol is unlikely to be associated with significant cardiovascular events. Several studies have documented the equal QTc effects of droperidol versus ondansetron.[44,143] In an in vitro electrophysiological drug interaction study, ondansetron did not further increase the QT prolongation caused by droperidol when used in clinically relevant concentrations.[144] In a clinical study, droperidol plus ondansetron combination was more effective than either drug alone, and QT prolongation with the combination versus placebo was equivalent to either drug alone.[145] Due to the 2001 black box warning, droperidol is not the first choice for PONV prophylaxis in many countries. However, a recent survey suggested that in 19 of 24 European countries, representing an estimated 73,000 anesthesiologists, droperidol is regularly used as an antiemetic.[142]

Haloperidol

Haloperidol has antiemetic properties when used in low doses and has been investigated as an alternative to droperidol.[146,147] At doses much lower than those used to treat psychiatric disorders, 0.5 to 2 mg IM or IV, haloperidol effectively reduced PONV risk with a NNT of between 4 and 6.[146] At these doses, sedation does not occur, and cardiac arrhythmias are not reported. Haloperidol carries a risk of QTc prolongation in its label and is not recommended as first-line therapy. Haloperidol 1 mg IM or IV may be regarded as an alternative to droperidol. Of potential interest, haloperidol may be given IM or orally. Its efficacy can be increased when combined with other antiemetics such as dexamethasone or ondansetron. As with droperidol, the combination of haloperidol with the 5-HT$_3$ receptor antagonists does not increase the risk of QT prolongation.[148] Only one of 806 patients (0.1%) exposed to haloperidol 4 mg had extrapyramidal symptoms.[146]

When haloperidol 1 mg was compared with ondansetron 4 mg and placebo, there was no difference in QTc effect among the 3 groups. There was no difference in PONV incidence between haloperidol and ondansetron given before the end of surgery, but both were not significantly better than placebo at 24 hours.[78] There was no difference in early antiemetic efficacy between haloperidol 1 mg and ondansetron 4 mg and no difference in the risk of QT prolongation.[80] Comparing haloperidol 2 mg IV vs ondansetron 4 mg IV given before the end of surgery, there was no difference in effect on early versus late PONV or QTc prolongation.[79] However, Meyer-Massetti et al.[149] recently reviewed the literature and all FDA Med Watch reports of haloperidol-associated adverse events and recommended doses of haloperidol <2 mg to reduce the risk of side effects and QT prolongation. Low-dose haloperidol 1 mg vs droperidol 0.625 mg given after induction showed no difference in early or late PONV and no extrapyramidal symptoms with

either drug.[150] The timing of haloperidol 2 mg IV at induction versus end of surgery administration did not make a difference.[151] It should be noted that the use of haloperidol as an antiemetic or the IV route of administration is not an FDA-approved indication.

Antihistamines

Dimenhydrinate

Dimenhydrinate is an antihistamine with antiemetic effects. The recommended dose is 1 mg/kg IV.[152–154] Data from placebo-controlled trials suggest that its antiemetic efficacy may be similar to the 5-HT$_3$ receptor antagonists, dexamethasone, and droperidol.[154] 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.

Meclizine

Meclizine has a longer duration of PONV effect than ondansetron.[155] Meclizine 50 mg per os plus ondansetron 4 mg IV is more effective than either ondansetron or meclizine alone.[155]

Anticholinergic

Transdermal Scopolamine

A systematic review of TDS showed that it is useful as an adjunct to other antiemetic therapies.[156] The patch effectively prevented nausea and vomiting postoperatively up to 24 hours with a NNT of 6. It can be applied the evening before surgery or 2 to 4 hours before the start of anesthesia due to its 2- to 4-hour onset of effect.[156,157] Adverse events associated with TDS are generally mild, the most common being visual disturbances (NNH = 5.6), dry mouth (NNH = 13), and dizziness (NNH = 50).[158] Dry mouth occurs mostly on the first day of use. A higher prevalence of visual disturbances can be observed at 24 to 48 hours.[156] TDS is useful for control of nausea in the setting of PCA.[159,160] New data show equal effectiveness with single drug therapy using TDS, ondansetron, or droperidol.[161]

Phenothiazines

Perphenazine

Perphenazine is a phenothiazine derivative that has been used for the prevention of PONV at doses between 2.5 mg to 5 mg IV or IM.[162] A recent systematic review from 6 RCTs demonstrated a relative risk reduction (RRR) of 0.5 (95% CI, 0.37–0.67) for PONV with a recommended dose of 5 mg IV, with no increase in sedation and drowsiness when compared with placebo.[162]

Metoclopramide

Metoclopramide is a weak antiemetic and at a dose of 10 mg is not effective in reducing the incidence of nausea and vomiting.[163] In a study with >3000 patients, metoclopramide had an antiemetic effect when given in doses larger than 20 mg. Metoclopramide's dose-response curve was evaluated in the presence of dexamethasone 8 mg IV administered 30 to 60 minutes before the end of surgery. Metoclopramide in 25 and 50 mg doses had an effect similar to ondansetron 4 mg for early PONV but a smaller effect than ondansetron for late PONV. The NNT for metoclopramide 10, 25, and 50 mg for PONV at 24 hours is 30, 16, and 11, respectively. Dyskinesia or extrapyramidal symptoms were 0.3%, 0.6%, and 0.6%, respectively, and can increase with increasing metoclopramide doses. The NNH for extrapyramidal symptoms with the 25 or 50 mg doses is 140.[35]

Other Antiemetics

Propofol

Propofol is a sedative-hypnotic widely used for induction and maintenance of general anesthesia and monitored anesthesia care sedation with local or regional anesthesia.[164] Numerous studies have demonstrated propofol has antiemetic properties. The median plasma propofol concentration associated with an antiemetic response was 343 ng/mL, which is much lower than the concentration ranges associated with general anesthesia (3–6 mcg/mL) or sedation (1–3 mcg/mL), allowing propofol to have antiemetic properties in the subhypnotic dose range.[165]

Propofol used as part of TIVA is recommended to reduce baseline risk for PONV. The use of propofol for induction and maintenance of anesthesia decreases the incidence of early PONV (occurring within the first 6 hours), with the NNT = 5.[53,166] The combination of propofol and air/oxygen (TIVA) reduces the PONV risk by approximately 25%.[47] A systematic review of 58 studies demonstrated that use of propofol versus inhaled anesthesia also reduced the incidence of PDNV.[167]

The benefit of a small dose propofol infusion (bolus of 1 mg/kg followed by an infusion at 20 mcg/kg/min), either by itself or in combination with other antiemetics, has been shown to reduce PONV.[50,51]

Propofol, in small doses (20 mg as needed), can be used for rescue therapy for patients in the direct care environment, for example, PACU, and has been found as effective as ondansetron.[168,169] However, the antiemetic effect with low doses of propofol is likely brief.

Alpha2-Agonists

In a meta-analysis, perioperative systemic alpha2-adrenoceptor agonists (clonidine and dexmedetomidine) showed a significant albeit weak and short-lived antinausea effect.[170] This effect may be explained by direct antiemetic properties of alpha2-agonists or its opioid-sparing effect, although the biological basis remains obscure.

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant.

Prophylactic mirtazapine delays the onset of PONV.[171] Mirtazapine 30 mg per os plus dexamethasone 8 mg reduces the incidence of late PONV by >50% compared with dexamethasone 8 mg alone. Less rescue medication is needed with the combination of antiemetics.

Gabapentin

Gabapentin doses of 600 mg per os given 2 hours before surgery effectively decreases PONV.[172–174] Given 1 hours before surgery, gabapentin 800 mg per os is as effective as dexamethasone 8 mg IV, and the combination is better than either drug alone.[175]

Midazolam

Midazolam decreases nausea and vomiting compared with placebo.[176,177] Midazolam 2 mg when administered 30 minutes before the end of surgery was as effective against PONV as ondansetron 4 mg.[178] While there was no significant difference using midazolam 0.075 mg/kg or dexamethasone 10 mg, their combination provided a more favorable effect than either drug alone.[179,180] Midazolam 1 mg/h was as effective as a subhypnotic dose of propofol 1 mg/kg/h when given at the end of surgery.[177] For PONV prophylaxis, midazolam was more effective than metoclopramide 10 mg.[181,182] Midazolam 2 mg given 30 minutes before end of surgery decreased PONV more effectively than midazolam 35 mcg/kg premedication.[183]

Combination Antiemetic Therapy

Combination therapy for PONV prophylaxis is preferable to using a single drug alone.[47,122,145,155,184–189] Apfel et al.[47] demonstrated that the effects of antiemetics acting on different receptors are additive. Adults at moderate risk for PONV should receive combination therapy with drugs from different classes as the efficacy is optimized when a combination of drugs with different mechanisms of action are administered. The 5-HT$_3$ antagonists have better antiemetic than antinausea efficacy but are associated with headache. These drugs can be used in combination with droperidol, which has greater antinausea efficacy and is associated with lower risk of headache.[190] The 5-HT$_3$ antagonists can also be effectively combined with dexamethasone.[120]

Optimal antiemetic dosing with combination therapy needs to be established. Combination therapy regimens using ondansetron with either droperidol or dexamethasone are most widely studied. It has been suggested that when used as combination therapy, dexamethasone doses should not exceed 10 mg IV, droperidol doses should not exceed 1 mg IV, and ondansetron doses in adults should not exceed 4 mg and can be much lower.[191]

Multiple studies confirm the effectiveness of combination therapy with dexamethasone.[179,180,185,186,192–195] In particular, many have evaluated the combination of dexamethasone plus granisetron or ondansetron[186,196–198] with one demonstrating that low-dose granisetron, 0.1 mg, combined with dexamethasone 8 mg is as effective as ondansetron 4 mg plus dexamethasone 8 mg.[192] Another study evaluating low-dose ondansetron showed similar rates of PONV between dexamethasone 8 mg and ondansetron 0.1 mg/kg and dexamethasone 8 mg and granisetron 40 mcg/kg.[199]

The combination of haloperidol 2 mg plus dexamethasone 5 mg was more effective than haloperidol or dexamethasone alone,[200] and combination therapy with haloperidol 1.5 mg plus dexamethasone 8 mg effectively prevented PONV.[126] Moreover, less nausea and vomiting occurred in the dexamethasone combination groups than with ondansetron,[184] granisetron,[201] or haloperidol[200] alone. When dexamethasone 4 mg was used in combination with droperidol 0.625 mg, there was no increase in the incidence of side effects.[191] When propofol 0.5 mg/kg was combined with dexamethasone 8 mg, the regimen had twice the effectiveness as propofol alone.[122] Similarly, combining TDS with other drugs such as ondansetron[187] or dexamethasone[202] was better than using a single drug alone.

Combination therapy with ondansetron has also been widely studied. When ondansetron was combined with casopitant[117,118] or TDS,[187] the combination therapy was more effective than single drug therapy. A study evaluating ondansetron plus haloperidol at 8 hours postoperatively showed that the combination was better than either drug alone.[203] The difference is primarily one of antinausea rather than antivomiting efficacy. The combination was also not associated with any increase in adverse events such as dystonia, akathisia, or QT prolongation.

Patient-Controlled Analgesia

Approximately one-third of patients who are treated with opioids for postoperative pain will have nausea and vomiting.[204] Droperidol effectively reduced the risk of nausea and vomiting, with a NNT of approximately 3, when given concomitantly with morphine in a PCA device.[204,205] Other studies evaluating the effects of various other antiemetics on PCA-related PONV showed a benefit. Ramosetron was more effective than ondansetron in preventing vomiting and reducing nausea in relation to fentanyl-based PCA.[102] The combination of metoclopramide 50 mg plus dimenhydramine 60 mg added to PCA decreased the severity of PCA-related PONV.[206] TDS plus dexamethasone 8 mg was more effective than ramosetron 0.3 mg plus dexamethasone 8mg in patients receiving epidural PCA.[202] Ondansetron, 8 mg, proved more effective than metoclopramide for controlling opioid-induced emesis and nausea in this population.[207]

Lack or Limited Evidence of Effect

The following strategies are not effective for PONV prophylaxis: music therapy,[208,209] isopropyl alcohol inhalation,[210] intraoperative gastric decompression,[41] the proton pump inhibitor esomeprazole,[211,212] and administration of nicotine patch 7 mg to nonsmokers.[215] The latter modality may actually increase the incidence and severity of PONV.[215,216]

There is insufficient evidence regarding the efficacy of hypnosis for PONV prophylaxis.[217] Cannabinoids (nabilone, tetra-hydrocannabinol), although promising in the control of chemotherapy-induced sickness, are not effective for PONV.[218,219]

Two meta-analyses have addressed the impact of intraoperative supplemental oxygen on the incidence of PONV.[64,220] There is no convincing evidence that high inspired oxygen fraction reduces PONV.

In 2 RCTs, the phenothiazines, promethazine, 12.5 to 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.[221,222] Similarly, it is suggested that the phenylethylamine, ephedrine, 0.5 mg/kg IM, has an antiemetic effect when administered at the end of surgery.[223,224] However, 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 or techniques can be recommended as first-line therapy. It should be noted that there is an FDA black box warning on promethazine hydrochloride injection. Promethazine should neither be administered into an artery nor administered under the skin because of the risk of severe tissue injury, including gangrene. There is also a risk that the drug can leach out from the vein during IV

Nonpharmacologic Prophylaxis

A meta-analysis of 40 articles including 4858 subjects[226] concluded that P6 stimulation with 10 different acupuncture modalities reduces nausea, vomiting, and the need for rescue antiemetics compared with sham stimulation (Evidence A1). The efficacy of P6 stimulation is similar to that of prophylactic antiemetics such as ondansetron, droperidol, metoclopramide, cyclizine, and prochlorperazine. In subgroup analysis, there was no difference in effectiveness in adults compared with children or invasive versus noninvasive modalities for P6 stimulation. The timing of transcutaneous acupoint electrical stimulation does not impact PONV, with similar reductions being achieved with stimulation initiated before or after induction of anesthesia.[227,228] Neuromuscular stimulation over the median nerve also reduces the incidence of PONV in the early postoperative period, particularly when tetanic stimulation is used.[229,230]

Other Methods and Alternative Therapies

Adequate IV fluid hydration is an effective strategy for reducing the baseline risk for PONV (Evidence A2).[231,232] However, there was no difference in efficacy between crystalloids and colloids when similar volumes were used in surgeries associated with minimal fluid shifts.[233,234]

Low-dose naloxone, 0.25 mcg/kg/h, reduced nausea and vomiting and decreased the need for rescue medication compared with placebo in adult patients[235] and significantly reduced opioid-related side effects including nausea in children and adolescents.[236] Lower infusion rates of 0.05, 0.1, and 0.2 mcg/kg/h were also effective in reducing the incidence of nausea and sedation induced by tramadol infusion with the highest rate of 0.2 mcg/kg/h showing efficacy in reducing the incidence of vomiting.[237] Another opioid antagonist, nalmefene (no longer available in the United States), reduced opioid-induced nausea, vomiting, and need for rescue medication in patients receiving PCA.[238]

While earlier meta-analyses did not find ginger to be an effective modality for PONV prophylaxis (Evidence A1),[48,239] a more recent meta-analysis concluded that fixed dose of at least 1g per os administered 1 hour before induction of anesthesia is more effective than placebo (Evidence A1).[240] A recent study suggested that Morinda Citrifolia Linn (Noni fruit) in a dose of 600 mg might be effective in reducing nausea in the early postoperative period (Evidence A3).[241]

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 and 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.[242–244] 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.[245] found that patients are willing to pay approximately $100 to prevent experiencing PONV, and Diez[246] found parents are willing to spend approximately $80 to prevent POV in their children. 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.[247] However, generic sevoflurane is now available that will reduce the costs.

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 PACU by approximately 20 minutes.[248] However, in a retrospective study of patients who underwent ambulatory surgery, Dexter and Tinker[249] 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.[14] found that prophylaxis in high-risk patients is more cost-effective than placebo due to increased costs associated with nausea and vomiting. The additional costs associated with PONV in placebo patients are up to 100 times higher compared with prophylaxis with a generic antiemetic, and the cost of treating vomiting is 3 times higher than the cost of treating nausea. Similarly, a study evaluating dolasetron, droperidol, or no prophylaxis in high-risk patients showed that prophylaxis with either of the 2 antiemetics is more cost-effective than no prophylaxis and subsequent rescue therapy.[250] However, 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.[251] It has been suggested that PONV prophylaxis is cost-effective with the older, less expensive drugs when patients have a 10% or greater risk of emesis.[252] These studies were conducted before the availability of generic ondansetron. In another model, treatment of PONV with ondansetron proved more cost-effective than prevention in both a low- (30%) and a high-risk (60%) setting.[253] 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 would generally support PONV prophylaxis in patient groups at a lower risk for PONV. 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 1 setting to another. For instance, anesthesiologists may be more likely to administer prophylaxis with an inexpensive generic antiemetic even if the baseline risk is low and, consequently, many patients must be treated prophylactically for one to benefit.

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

New Information: New antiemetic combination therapies have been reported. These include midazolam and dexamethasone,[177,180] dexamethasone 8 mg IV at induction plus ondansetron 4 mg IV at the end of surgery plus ondansetron 8 mg PO postoperatively[254] and haloperidol 2.5 mg plus dexamethasone 5 mg IV after induction.[200] Among the NK_1 RAs, aprepitant (40 mg) in combination with dexamethasone 10 mg proved superior to ondansetron 4 mg and dexamethasone 10 mg in preventing vomiting in neurosurgical patients up to 48 hours after surgery.[114] The combination of casopitan and ondansetron proved more effective than ondansetron alone.[117,118] (Additional details of the study are described in the PDNV section.

Recommended combination therapy is shown in Table 4. A treatment algorithm is presented in Figure 4.

DISCUSSION

Patients who are at high risk for PONV should receive prophylaxis with combination therapy or a multimodal approach that includes 2 or more interventions (Table 4). When considering anesthesia, use regional anesthesia or TIVA with propofol if patients are at high risk for PONV.

Table 4. Pharmacologic Combination Therapy for Adults and Children

Adults
  Droperidol + dexamethasone[47] (A1)
  5-HT3 receptor antagonist + dexamethasone[47,120,189,192,32747,120,189,192 327](A1)
  5-HT3 receptor antagonist + droperidol[47,140,188,257] (A1)
  5-HT3 receptor antagonist + dexamethasone + droperidol (A2)
  Ondansetron + casopitant[118 117117,118] or TDS[187] (A1)
Combinations in children
  Ondansetron, 0.05 mg/kg, + dexamethasone, 0.015 mg/kg[328,329] (A1)
  Ondansetron, 0.1 mg/kg, + droperidol, 0.015 mg/kg[330] (A1)
  Tropisetron, 0.1 mg/kg, + dexamethasone, 0.5 mg/kg[331](A1)

See Table 5 for dose ranges for children.

Table 5. Antiemetic Doses for Prophylaxis of POV in Children

Drug	Dose	Evidence
Dexamethasone	150 mcg/kg up to 5 mg	A1[332]
Dimenhydrinate	0.5 mg/kg up to 25 mg	A1[154]
Dolasetron	350 mcg/kg up to 12.5 mg	A2[333]
Droperidol[a]	10–15 mcg/kg up to 1.25 mg	A1[140]
Granisetron	40 mcg/kg up to 0.6 mg	A2[334]
Ondansetron[b]	50–100 mcg/kg up to 4 mg	A1[335]
Tropisetron	0.1 mg/kg up to 2 mg	A1[97]

These recommendations are evidence based, and not all the drugs have an FDA indication for PONV. Drugs are listed alphabetically.
[a]See FDA black box warning. Recommended doses 10 to 15 mcg/kg.
[b]Approved for POV in pediatric patients aged 1 month and older.

If general anesthesia is used, reduce baseline risk factors when possible. Nonpharmacologic therapies as adjuncts to pharmacologic therapy should be considered. Antiemetics recommended for prophylaxis in adults and children are shown in Table 3 and Table 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 appears to be similar.[47] Systematic reviews addressing specific therapeutic combinations showed the combination of a 5-HT$_3$ receptor antagonist with either dexamethasone or droperidol was more effective than monotherapy with any of the drugs[255,188,189,256] Similarly, droperidol combined with dexamethasone was more effective than either drug alone.[47] When the different combinations are compared, no differences are found between 5-HT$_3$ receptor antagonist plus droperidol, 5-HT$_3$ receptor antagonist plus dexamethasone, and droperidol plus dexamethasone.[47,257] Combinations involving metoclopramide are not found to reduce PONV to a greater extent than monotherapy.[258–260]

A multimodal approach to minimize PONV combined nonpharmacologic and pharmacologic prophylaxis as well as interventions that reduced baseline risk.[261,262] Habib et al.[263] evaluated a multimodal approach to reduce PONV that consisted of preoperative anxiolysis (midazolam), prophylactic antiemetics (droperidol at induction and ondansetron at end of surgery), TIVA with propofol, and local anesthetic infiltration and ketorolac. No nitrous oxide was used. Patients who received multimodal therapy had a 80% complete response rate compared with a 43% to 63% response rate among patients receiving either inhaled drug or TIVA alone.

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

New Information: Numerous appropriately powered studies add additional support for the use of combination antiemetics for children at high risk for POV, with a large volume of data to suggest that prophylaxis with a combination of a 5-HT$_3$ antagonist and a steroid should be administered for most pediatric patients at high risk for POV unless there is a contraindication. New data on pharmacokinetics of ondansetron in children <2 years of age are now available. Dolasetron is not promoted in the United States because of the risks of cardiac arrhythmias. Concerns have been raised about the use of steroids in children at risk for tumor lysis syndrome and the use of 5-HT$_3$ antagonists in children with prolonged QT syndrome.

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.[264] Children who are at moderate or high risk for POV should receive combination therapy with at least 2 prophylactic drugs from different classes (Table 5).

There are now many studies that confirmed the efficacy of 5 HT$_3$ antagonists as prophylactic antiemetics in the pediatric patient population, including studies of oral disintegrating tablets of ondansetron.[265,266] However, in contrast to the data in adult studies, the efficacy of ondansetron in preventing emesis after craniotomy was not established in children, probably because the sample size was too small, even after pooling data from 2 pediatric studies.[267,268]

The evidence supporting the prophylactic use of ondansetron in reducing POV has been extended to children aged 1 to 24 months.[269] Newer data on the pharmacokinetics of ondansetron in children aged 1 to 48 months showed clearance was decreased by 76%, 53%, and 31%, respectively for 1-, 3-, and 6-month-old subjects.[270] Simulations show that a dose of 0.1 mg/kg in the infant younger than 6 months produces levels similar to that of 0.15 mg/kg in older children. This is attributed to the immaturity of the cytochrome P450 enzymes, particularly CYP3A4 that increases from 30% at 1 month to adult values by 6 to 12 months, and CYP1A2 that reaches 35% of adult values at 1 year. The authors concluded that children younger than 4 months should be monitored more closely after receiving ondansetron but did not make specific recommendations on the duration or modality of monitoring.[270]

Ondansetron and Other 5 HT3 Antagonists

There is now good evidence to suggest that 5 HT$_3$ antagonists and dexamethasone are the most effective antiemetics in the prophylaxis of pediatric POV. A study by Bolton et al.[271] evaluating 557 children undergoing tonsillectomy/adenoidectomy found ondansetron was more effective than metoclopramide in preventing POV. A systematic review in children undergoing tonsillectomies also found that the 5 HT$_3$ antagonists and dexamethasone were the most effective prophylactic antiemetics with insufficient evidence for the efficacy of dimenhydrinate, droperidol, or perphenazine (Table 1).[73] In a more recent quantitative systematic review of children undergoing a variety of surgical procedures, Schnabel et al.[162] concluded that perphenazine is an effective antiemetic compared with placebo, but a 5 HT$_3$ antagonist (ondansetron or granisetron) was more effective. In a Bayesian meta-analysis of 6 single drug therapy and 5 combinations of antiemetics in children, Engelman et al.[272] note that the most pessimistic expectations are that single drug prophylaxis with the 5 HT$_3$ receptor antagonists or dexamethasone result in a 50% to 60% RRR and that the expected RRR of the combination is 80%. In this study, the risk reduction with droperidol was 40%.

Dexamethasone

The dose-effect relationship of dexamethasone is unclear. Most studies use a dose of 0.5 mg/kg.[73] Kim et al.[195] found no differences in POV rates or secondary outcomes in children receiving 0.0625, 0.125, 0.25, 0.5, or 1 mg/kg (maximum dose 24 mg) during adeno-tonsillectomy procedures. Thus, they concluded there is no justification for using higher doses than 0.0625 mg/kg. However, another study of the same patient population showed a dose-dependent reduction in POV with the best response in children receiving 0.5 mg/kg.[273] Steward et al.[274] in an updated Cochrane review of steroids for tonsillectomy patients stated that "the

question of appropriate dosing remains unanswered and final recommendations must await randomized dose-control trials."

There are no new data to base a recommendation on the timing of administration of these drugs. There are no differences in POV in children who receive tropisetron immediately after induction or at the end of surgery during short tonsillectomy procedures.[275] There are also no published pediatric data to make recommendations on the use of palonosetron or the NK-1 antagonists in pediatric POV. A RCT without a placebo arm found no differences in the 48-hour rates of POV in children receiving 0.5, 1.0, or 1.5 mg/kg palonosteron.[276]

Based on this evidence, we would recommend the prophylactic use of a combination of dexamethasone and ondansetron in most pediatric patients at high risk for POV unless there are contraindications. This is similar to the recommendation by the Association of Pediatric Anaesthetists of Great Britain and Ireland.[277]

SIDE EFFECTS OF DRUGS
Ondansetron

Cardiovascular complications have been reported after ondansetron therapy. An 11-year-old child undergoing a thyroglossal duct cyst excision developed ventricular tachycardia after receiving ondansetron and dimenhydrate.[278] Subsequent studies showed she had an undiagnosed long QT syndrome. There is a report of a death from ventricular tachycardia in a patient receiving ondansetron in the emergency department[279] and another report of severe bradycardia during incision and drainage of an abscess.[280] The effects of droperidol and ondansetron on myocardial repolarization have been studied when given alone or in combination to healthy children.[281] There were clinically insignificant changes with lengthening of the QT intervals by 10 to 17 millisecond and of the Tp-e intervals by 0 to 7 millisecond without any differences between the groups. These data suggest clinicians should be aware of these risks especially in children with prolonged QT syndrome.

Steroids

Tumor lysis syndrome has been reported in children with leukemia who received intraoperative dexamethasone.[282,283] One patient with an undiagnosed acute lymphoblastic leukemia developed hyperkalemia and a fatal cardiac arrest during a tonsillectomy procedure.[282] A study of steroids in children undergoing tonsillectomies was terminated early because of increased bleeding in patients receiving dexamethasone.[273] There has been considerable discussion about this unexpected finding as it was a secondary outcome and was not adjusted for other risk factors.[284] The statistical significance of increased bleeding was lost when primary hemorrhage cases, which are largely related to surgical technique, were excluded. Other studies including a meta-analysis and retrospective reviews have failed to show increased postoperative bleeding between patients receiving dexamethasone and controls in both meta-analyses and retrospective reviews.[285–287] Although the incidence of bleeding may not increase, there was an increased incidence of operative reintervention for bleeding episodes in a systematic review of

children receiving steroids during adenotonsillectomy.[288] In the updated Cochrane review, Steward et al.[274] stated "any suggestion that single-dose dexamethasone increases bleeding risk needs to be substantiated with further studies." The most recent clinical practice guidelines from the American Academy of Otolaryngology-Head and Neck Surgery continue to make a strong recommendation for the use of a single dose of dexamethasone in children undergoing tonsillectomy.[289] This guideline was based on a preponderance of benefit over harm, including benefits from decreased throat pain, POV, and earlier resumption of oral intake.[289]

Nonpharmacologic Therapy

Two meta-analyses showed acupuncture and acustimulation were effective in reducing POV in children.[290,291] Pooled data from 12 studies showed all modalities reduce vomiting (risk reduction 0.69, 95% CI, 0.59–0.8). There were no differences between acustimulation and medications in reducing POV. However, therapeutic suggestion through earphones during anesthesia for tonsillectomy/adenoidectomy was ineffective.[292]

Guideline 6. Provide Antiemetic Treatment to Patients With PONV who did not Receive Prophylaxis or in whom Prophylaxis Failed

A treatment algorithm for adults is presented in Figure 4.

New information: Additional studies on the use of isopropyl alcohol for the treatment of established PONV are discussed. Further data suggest the futility of repeat antiemetic when administered within 6 hours of the previous antiemetic administration.

DISCUSSION

When nausea and vomiting occur 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.[190,293] The 5-HT$_3$ antagonists are the only drugs that have been adequately studied for the treatment of existing PONV.[190,294] The doses of 5-HT$_3$ antagonists used for treatment are smaller than those used for prophylaxis: ondansetron 1.0 mg; granisetron 0.1 mg; and tropisetron 0.5 mg (NNT = 4–5).[54,190] All the 5-HT$_3$ antagonists, except palonosetron (that has not been studied for PONV treatment), are equally antiemetic for the treatment of established PONV.[190]

Alternative treatments for established PONV include dexamethasone, 2 to 4 mg IV, droperidol, 0.625 mg IV, or promethazine 6.25 to 12.5 mg IV.[293,295,297] Propofol, 20 mg as needed, can be considered for rescue therapy in patients still in the PACU and is as effective as ondansetron.[165,169,298] However, the antiemetic effect with low doses of propofol is probably brief.[165,298]

Although isopropyl alcohol inhalation is not effective for the prophylaxis of PONV,[210] aromatherapy with isopropyl alcohol was effective in achieving a quicker reduction in nausea severity compared with promethazine or ondansetron when used for the treatment of PONV (Evidence A2).[299–301] However, since studies investigating its use had limitations, it is not clear whether it is an effective modality

for the complete control of PONV. Better-designed studies investigating the use of isopropyl alcohol for the treatment of PONV are needed.

Repeating the medication given for PONV prophylaxis within the first 6 hours after the initial dose conferred no additional benefit.[302] During the first 4 postoperative hours, patients who failed PONV prophylaxis with ondansetron 4 mg did not respond either to a second administration of ondansetron 4 mg or to crossover with granisetron 0.1 or 1 mg.[302,303] If >6 hours 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 longer-acting drugs, for example, dexamethasone, TDS, aprepitant, and palonosetron 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 an opioid PCA, blood draining down the throat, or an abdominal obstruction. There is no large-scale study to base recommendations on the use of rescue antiemetics in children who have failed prophylactic antiemetics.

Postdischarge Nausea and Vomiting

As many as one-third to one-half of patients who undergo ambulatory surgery experience PDNV.[304] Such patients often do not have access to treatment for their 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%).[305]

Since ambulatory surgery constitutes about 60% of all surgical procedures in the United States, many studies are focusing on how to prevent PDNV.[83,84,103] As these studies show, PDNV is still a significant problem. New research in this area is centered on mixing IV and per os doses of different drugs, administered at various time points, to evaluate the effects on reducing PDNV. The results show that mixing IV and per os antiemetics at various perioperative times decreases PDNV. For instance, 1 study found that dexamethasone 8 mg IV at induction plus ondansetron 4 mg IV at the end of surgery plus ondansetron 8 mg per os postoperatively had a greater effect on decreasing PDNV than ondansetron 4 mg IV alone at the end of surgery.[254]

Other studies evaluated different combinations for PDNV. The combination of haloperidol 2.5 mg plus dexamethasone 5 mg IV after induction was more effective than droperidol 1.25 mg, haloperidol 2 mg, or dexamethasone 5 mg alone, all of which were more effective than placebo.[200] Aprepitant 40 mg, 120 mg, and ondansetron 4 mg decreased PONV to a similar extent during the 0- to 24-hour postoperative period; however, 24 to 48 hours postoperatively, aprepitant 40 mg and 120 mg had an equal effect, which was more effective than ondansetron 4 mg.[113] In other PDNV trials, the combination of casopitant plus ondansetron was more effective than ondansetron alone,[118] and ondansetron 4 mg IV was equivalent to granisetron 1 mg per os.[92]

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 to 13 for ondansetron 4 mg or dexamethasone 4 to 10 mg alone.[304] 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 anesthetics also reduced the incidence of PDNV ($P < 0.05$).[167] Small RCTs have demonstrated efficacy in preventing PDNV with orally disintegrating ondansetron tablets, acupoint stimulation of P6, and transdermal scopolamine.[157,306,307]

Guideline 7. Ensure PONV Prevention and Treatment Is Implemented in the Clinical Setting

New information: This section is new to emphasize the importance of implementing PONV prevention and treatment strategies in the clinical setting.

Measures must be put in place to determine whether suggested algorithms for the management of PONV are actually implemented as standard operating procedure in clinical settings and that these practices lead to improvement of PONV management.

Clinical PONV Protocols and Algorithms to Implement PONV Policies

Recommendations for the administration of antiemetic interventions traditionally support the application of a "valid assessment of the patient´s risk for POV or PONV."[2] Furthermore, when developing a management strategy for each individual patient, the choice should be based on patient preference, cost-efficiency, level of PONV risk, and patient's preexisting condition (e.g., avoid QT prolonging antiemetics in patients with prolonged QT syndrome and TDS in closed angle glaucoma patients).[2] Such recommendations are based on the goal that antiemetics and other interventions reduce the baseline risk for PONV in "high-risk patients," that is, patients who actually need antiemetic prevention. This would save costs and prevent pharmacological exposure among patients who will not vomit anyway. Assuming that each antiemetic intervention is associated with a defined RRR that has been determined by clinical trials and meta-analyses, this RRR translates into an absolute risk reduction (ARR) that depends mainly on the control event rate (CER) in a given patient population. If the CER is high (e.g., 60%), then an antiemetic with a RRR of 30% reduces the incidence in that population to 42% (ARR = 18). This means that approximately 6 patients (1/0.18) need to be treated with antiemetics for one to stay completely free from PONV. If, using the same antiemetic with similar efficacy, the CER is 10%, the ARR would equal 3%, and approximately 33 patients (33 = 1/0.03) need to be treated for one to benefit from the administration of antiemetics in that population (= NNT).[308]

The validity of these assumptions in a clinical scenario rests on: (1) The ability to correctly classify the PONV risk; (2) The acquisition costs of antiemetics; (3) The potential of antiemetics to cause adverse effects as well as; (4) The clinical applicability and compliance with guidelines depending on their structure (e.g., general multimodal prevention versus various risk-adapted approaches or a combination of these approaches).

Classifying PONV Risk With Risk Model

Clinical risk models have made substantial contributions to eliminate presumed risk factors, so more reasonable risk assessment is now feasible for patients.[9,10,48] However, it is important to note "that no risk model can accurately predict the likelihood of an individual having PONV," rather they allow us "to estimate the risk for PONV among patient groups."[2,309] Furthermore, problems may arise in the prospective determination of what constitutes "opioid therapy," "motion sickness," "smoking status" or even "PONV history" (e.g., patient developed PONV after one of previous 3 anesthetics). However, for patient populations, it has been shown in observational trials that:

1. (a) the allocation of patients to risk groups was successful,[45] and (b) a risk-adapted PONV protocol effectively reduced the institutional PONV incidence.[46] (B2)

THE ACQUISITION COSTS OF ANTIEMETICS

These costs of some of the antiemetics have decreased dramatically during recent years as generic versions have become available and also vary to a large extent from country to country and among different institutions. Published analyses suggest that "PONV prophylaxis is cost-effective with the older, less expensive drugs when patients have a 10% or more risk of emesis."[252] Lower drug acquisition costs may even "support PONV prophylaxis in patient groups at a lower risk for PONV."[2] Newer substances that entered the pharmaceutical market are associated with significant costs, but older molecules should not per se constitute a relevant obstacle to a liberal administration of antiemetics.

Potential for Adverse Effects

The safety of antiemetics is well established considering the huge amount of clinical data available and their summary in valid meta-analyses.[310] Limited adverse effects have been associated with the use of minimum effective doses of most recommended antiemetics.

Clinical Applicability and Compliance With Guideline

A risk-adapted PONV protocol effectively reduced institutional PONV incidence.[46] (B2). However, it has to be considered that the results of such a protocol were obtained in a clinical study that had good compliance with proposed algorithms, in contrast to clinical implementation in the routine busy setting.

Clinical Effectiveness of PONV Protocols

As observed with other settings and pharmacological preventive measures, effectiveness may be different from efficacy evaluations. The latter may be partly due to poor

compliance with existing protocols. This seems to be true in the setting of PONV, where irrespective of tremendous amounts of research findings observational studies investigating whether PONV prevention based on existing clinical guidelines (even if present in the intranet or in the format of a booklet) are poorly implemented (B2). This phenomenon was detected for adults[311] and pediatric patients.[312] Therefore, some studies suggest the introduction of electronic reminders to improve compliance with standard operating procedures.[313,314]

The argument that poor education is the root cause for the reluctance to administer appropriate antiemetic prophylaxis seems to be invalid, since the problem persists even after intense educational activities.[315] In 1 study, even after training and continuous provider feedback, only 47% and 37% of moderate (2 risk factors present) or high-risk patients (3 risk factors present) received the scheduled prophylactic treatment using a very simple algorithm that suggested administering 1 antiemetic per risk factor found in the preoperative assessment.[315] Instead, almost all patients received single antiemetic prophylaxis that was the de facto standard at the site where the study took place.[315]

Arguing that treating PONV only after symptoms occur is as effective and as appropriate for patients as prevention, disregards the findings of a recent trial showing that PONV symptoms, and nausea in particular, are frequently missed in a busy clinical scenario. This observational study shows only 42% and 29% of PONV episodes were actually detected by the regular staff in the PACU and on the ward, respectively.[316]

Guideline 8. Use General Multimodal Prevention to Facilitate Implementation of PONV Policies

New information: This is a new section to recommend a multimodal prevention approach to facilitate implementation of PONV (Tables 6 and 7).

In view of the poor guideline compliance with risk-adapted approaches and no general preventive measures, multimodal prevention strategy (adjusted with additional measures in high-risk patients) may be an option to facilitate clinical implementation. This is especially true for high-risk patients in which the latter procedure may overcome the hurdle to provide multimodal prevention (Tables 6 and 7).

In 1 study, despite intense educational strategies that resulted in fewer institutional PONV incidences, it was surprising to note that no significant difference in the rate of administration of antiemetic prophylaxis was observed between the overall "before" and "after" patient populations (31.4% vs 36.8%).[317] The only difference was in the rate of administration of antiemetic prophylaxis in the high-risk group (with an Apfel simplified score >2), which reached statistical significance (36.4% to 52.8%). This underscores the observed extremely low compliance with institutional PONV policies. In another report, it was stated that only 37% of medium and high-risk patients received the specified prophylaxis, leading to suboptimal PONV prevention in moderate and high-risk patients.[318]

As a result, fast-track protocols often incorporate multimodal preventive PONV strategies.[319,320] General multimodal strategies may well be a starting point to facilitate clinical implementation of better PONV protection of patients.[321] Such approaches may prove more effective than

Table 6. Risk-Adapted PONV-Prevention Algorithm (With No Prevention in Low-Risk Patients)

	Estimated risk for PONV, for example, as determined by a risk score		
	Low	**Medium**	**High**
Interventions for prophylaxis	No prevention ("wait and see")	Drug A + Drug B or TIVA	Drug A + Drug B + TIVA On a case-by-case decision: further interventions
Interventions for treatment	1. Drug B 2. Drug C (in case of ineffectiveness of treatment in stage 1) (i.e., Drug B)	1. Drug C 2. Drug D (in case of ineffectiveness of treatment in stage 1) (i.e., Drug C)	1. Drug C 2. Drug D (in case of ineffectiveness of treatment in stage 1) (i.e., Drug C)

Example interventions: Drug A = Dexamethasone 4 mg in adults/0.15 mg/kg of body weight in children; Drug B = Ondansetron 4 mg in adults/0.1 mg/kg of body weight in children; Drug C = Droperidol 1 mg in adults/10 to 15 µg/kg of body weight in children; Substance D = Dimenhydrinate 1 mg/kg of body weight in adults/0.5 to 1.0 mg/kg of body weight in children. Given drug examples are used to illustrate how the algorithm may be actually implemented but may not represent the most favorable approach. The latter may be context-sensitive (children, adults, or other issues). In the event of treatment failure, a timely assessment and alternative antiemetics should be used. A multimodal treatment approach may be appropriate to increase the likelihood of success.
TIVA = total intravenous anesthesia, that is, propofol induction and maintenance, no nitrous oxide.

Table 7. PONV-Prevention Algorithm in All Patients Including Low-Risk Patients Plus Additional Interventions for High-Risk Patients

	Estimated risk for PONV, for example, as determined by a risk score		
	Low	**Medium**	**High**
Interventions for prophylaxis	Drug A + (Drug B or TIVA)	Drug A + (Drug B or TIVA)	Drug A + drug B + TIVA On a case-by-case decision: further interventions
Interventions for treatment	1. Drug C 2. Drug D (in case of ineffectiveness of treatment in stage 1) (i.e., Drug C)	1. Drug C 2. Drug D (in case of ineffectiveness of treatment in stage 1) (i.e., Drug C)	1. Drug C 2. Drug D (in case of ineffectiveness of treatment in stage 1) (i.e., Drug C)

Example interventions: Drug A = Dexamethasone 4 mg in adults/0.15 mg/kg of body weight in children; Drug B = Ondansetron 4 mg in adults/0.1 mg/kg of body weight in children; Drug C = Droperidol 1 mg in adults/10 to 15 mcg/kg of body weight in children; Drug D = Dimenhydrinate 1 mg/kg of body weight in adults/0.5 to 1.0 mg/kg of body weight in children. Given drug examples are used to illustrate how the algorithm may be actually implemented but may not represent the most favorable approach. The latter may be context-sensitive (children, adults or other issues). In the event of treatment failure, a timely assessment and alternative antiemetics should be used. A multimodal treatment approach may be appropriate to increase the likelihood of success.
TIVA = total intravenous anesthesia, that is, propofol induction and maintenance, no nitrous oxide.

strictly risk-based approaches that rely on no prevention in low-risk patients. The goal, therefore, is for antiemetic multimodal prevention to become an integral part of anesthesia.[322]

Research Agenda for PONV

PONV has been extensively studied, and there is an excellent evidence base to guide clinical practice. Perhaps, the biggest problem is that many anesthesia care providers fail to translate this knowledge into changes in practice.[315,323] One of the obstacles to widespread adoption of previous guidelines may be the lack of conviction regarding the clinical importance of PONV and/or unresolved aspects of the risk-benefit of PONV prophylaxis or treatment. One way the latter issue might be clarified is to obtain accurate data regarding the incidence of PONV and the clinical and psychological implications of suffering from nausea and vomiting. The incidence of adverse effects of antiemetics, such as headache, prolonged QT interval, hyperglycemia, and sepsis will better assist clinicians in the management decision-making process. Risk-benefit can be summarized by calculating the likelihood of harm, expressed as the NNT divided by the NNH.[324] Such a statistic would only be valid however when both benefit and harm are comparable in their intensity and duration.

There are too many unhelpful PONV studies, many of which address questions that are already known, such as efficacy of many of the established antiemetics, or include too few patients when analyzing risk factors for PONV. We strongly advise against such redundant research.

CONCLUSIONS

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 using available risk scores leads to the most effective use of therapy and the greatest cost-efficacy. Although antiemetic prophylaxis cannot 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 on 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 moderate and 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, and potentially one with a different mode of administration. If PONV occurs within 6 hours postoperatively, patients should not receive a repeat dose of the prophylactic antiemetic. An emetic episode more than 6 hours postoperatively can be treated with any of the drugs used for prophylaxis except dexamethasone, TDS, aprepitant, and palonosetron.

There are significant challenges in implementing an institution-wide, comprehensive PONV prevention protocol based on a detailed risk-adapted approach. A more practical risk assessment using a more liberal preventive strategy may be a better alternative in a busy clinical environment such that it becomes an integral part of anesthesia. ■

APPENDIX 2
Category A: Supportive Literature

Randomized controlled trials report statistically significant ($P < 0.01$) differences between clinical interventions for a specified clinical outcome.

Level 1: The literature contains multiple randomized controlled trials, and aggregated findings are supported by meta-analysis.

Level 2: The literature contains multiple randomized controlled trials, but the number of studies is insufficient to conduct a viable meta-analysis for the purpose of these guidelines.

Level 3: The literature contains a single randomized controlled trial.

Category B: Suggestive Literature

Information from observational studies permits inference of beneficial or harmful relationships among clinical interventions and clinical outcomes.

Level 1: The literature contains observational comparisons (e.g., cohort, case-control research designs) of clinical interventions or conditions and indicates statistically significant differences between clinical interventions for a specified clinical outcome.

Level 2: The literature contains noncomparative observational studies with associative (e.g., relative risk, correlation) or descriptive statistics.

Level 3: The literature contains case reports.

Category C: Equivocal Literature

The literature cannot determine whether there are beneficial or harmful relationships among clinical interventions and clinical outcomes.

Level 1: Meta-analysis did not find significant differences ($P > 0.01$) among groups or conditions.

Level 2: The number of studies is insufficient to conduct meta-analysis, and (1) randomized controlled trials have not found significant differences among groups or conditions, or (2) randomized controlled trials report inconsistent findings.

Level 3: Observational studies report inconsistent findings or do not permit inference of beneficial or harmful relationships.

Category D: Insufficient Evidence from Literature

The lack of scientific evidence in the literature is described by the following terms.

Inadequate: The available literature cannot be used to assess relationships among clinical interventions and clinical outcomes. The literature either does not meet the criteria for content as defined in the "Focus" of the Guidelines or does not permit a clear interpretation of findings due to methodological concerns (e.g., confounding in study design or implementation).

Silent: No identified studies address the specified relationships among interventions and outcomes.

APPENDIX 3

This set of guidelines have been officially endorsed by the following societies:

American Academy of Anesthesiologist Assistants
American Association of Nurse Anesthetists
American Society of Anesthesiologists
American Society of Health Systems Pharmacists
American Society of PeriAnesthesia Nurses
Australian and New Zealand College of Anaesthetists
Chinese Society of Anesthesiology
CongresoLationoamericano de Sociedades de Anestesia
European Society of Anaesthesiology
Hong Kong College of Anaesthesiologists
Malaysian Society of Anaesthesiologists
Singapore Society of Anaesthesiologists
South African Society of Anaesthesiologists

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