Guidelines for the Management of **PONV**

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Postoperative nausea and vomiting (PONV) is a common complication following surgery and is associated with patient dissatisfaction during the postoperative period. Persistent PONV can result in further serious adverse events after surgery (eg, aspiration pneumonitis, dehydration, esophageal rupture, wound dehiscence, loss of vision[1]) and a prolonged hospital stay or an unanticipated hospital admission.[2]

Despite ongoing research and new pharmacologic therapies, 25% to 30% of patients continue to experience PONV within 24 hours after surgery.[3,4]

The following guidelines for the prevention and treatment of PONV were developed by a multidisciplinary panel that convened in 2003. However, important updates are incorporated into this review of the 2003 consensus guidelines, based on more recent published data.

Guideline 1: Identify Adults at High Risk for PONV

Antiemetic prophylaxis is not appropriate for every patient. Patients at moderate to high risk for PONV are most likely to benefit from prophylactic antiemetic therapy. It is therefore crucial to identify these patients. Risk factors related to patient characteristics, anesthesia, and surgery have been determined.

Patient-related risk factors[5-7] include female sex, history of PONV or motion sickness, and nonsmoking status. Anesthesia-related risk factors include the intraoperative use of volatile anesthetics,[8] the intraoperative and postoperative use of opioids,[5,9-12] and the use of nitrous oxide (NO).[10] Surgical risk factors can involve the type and duration of surgery. Patients undergoing long surgical procedures,[6] or a procedure such as neurosurgery, breast surgery, laparoscopy, or plastic surgery,[6,13,14] may be at greater risk for PONV. A simplified risk score based on female sex, nonsmoking status, history of PONV or motion sickness, and postoperative opioid use provides adequate predictive power.[5,9,15] The incidence of PONV associated with zero, 1, 2, 3, or all 4 of these risk factors is about 10%, 20%, 40%, 60%, and 80%, respectively.[5]

Table 1 summarizes risk factors for adult PONV.

Table 1. Risk Factors for PONV in Adults

Patient-specific risk factors
- Female sex
- Nonsmoking status
- History of PONV/motion sickness

Anesthetic risk factors
- Intraoperative use of volatile anesthetics
- Use of nitrous oxide
- Intraoperative and postoperative use of opioids

Surgical risk factors
- Duration of surgery (each 30-min increase in duration increases PONV risk by 60%, so that a baseline risk of 10% is increased to 16% after 30 min)

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Table 2. Risk Factors for POV in Children

Risk factors for children are similar to those for adults, with the following differences:
- Studies in children are often limited to vomiting and do not address nausea
- Vomiting is twice as frequent among children as among adults
- Risk increases as children age, decreasing after puberty
- Sex differences in POV are not seen before puberty
- Risk increases more consistently with specific operations

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Table 3. Strategies To Reduce Baseline Risk for PONV

- Use of regional anesthesia
- Use of propofol for induction and maintenance of anesthesia
- Use of intraoperative supplemental oxygen*
- Use of hydration
- Avoidance of nitrous oxide†
- Avoidance of volatile anesthetics
- Minimization of intraoperative and postoperative opioids
- Minimization of neostigmine (Prostigmin, Valeant)

* In 2 recent trials, supplemental oxygen did not help prevent PONV in patients undergoing strabismus repair or thyroidectomy.[24,25]

† Minor contribution, about 15% reduction in risk. Weigh benefits and risks of using nitrous oxide.

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Guideline 2: Identify Children at High Risk for Postoperative Vomiting

Because nausea is difficult to diagnose in younger patients, vomiting is studied and treated in pediatric patients. Children at high risk for postoperative vomiting (POV) benefit from prophylactic antiemetic therapy. Although POV is rare in patients younger than age 2, the incidence increases with age until puberty and then tapers. In children age 3 and older, the incidence of POV is 40% or greater.[3] A gender difference in risk for POV is not noted in preadolescent patients.[16] Certain surgical procedures are associated with a higher incidence of POV in children: adenotonsillectomy, strabismus repair, orchiopexy, penile surgery, and hernia repair.[3]

Revised PONV consensus guidelines include a simplified risk score to determine the degree of POV risk in children. The degree of risk is based on the number of the following risk factors that are present: 1) duration of surgery longer than 30 minutes[4]; 2) age older than 3 years[4]; 3) strabismus surgery; and 4) history of POV or PONV among relatives. Risk for POV/PONV is elevated as the number of risk factors increases, with 1 representing a 10% risk and 4 representing a 70% risk for POV/PONV.

Most risk factors for vomiting are similar in adult and pediatric patients; however, several important differences exist (Table 2).

Guideline 3: Reduce Baseline Risk Factors for PONV

The use of I.V. propofol in place of inhaled agents to induce and maintain anesthesia has been demonstrated to reduce the incidence of early PONV (0-6 hours after surgery) in numerous randomized controlled trials.[17-19] The incidence of PONV has also been reduced when the use of NO[20,21] was avoided. In the previously discussed factorial trial, the use of propofol in place of volatile anesthetics reduced the risk for PONV by about 19% (odds ratio [OR], 0.69), and the use of nitrogen instead of NO reduced the risk by approximately 12% (OR, 0.81).[15] On the other hand, the use of remifentanil (Ultiva, Abbott) rather than fentanyl—another intervention that was expected to reduce risk—did not reduce the risk for PONV.

According to systematic reviews and results of randomized and nonrandomized trials,[5,9-12] minimizing the intraoperative and postoperative use of opioids also reduces the incidence of PONV. The use of intraoperative/supplemental oxygen (80% oxygen) may or may not reduce the risk for PONV. In 2 randomized controlled trials, supplemental oxygen halved the risk for PONV in patients undergoing colon resection or gynecologic laparoscopy.[22,23] However, in 2 more

Table 4. Antiemetic Doses and Timing of Administration in Adults

Drug	Dose*
Timing: before or on induction of anesthesia	
Aprepitant	40 mg PO 1-3 h before induction
Dexamethasone	4-8 mg I.V. on induction
Ondansetron	8 mg PO 1 h before induction
Prochlorperazine	5-15 mg PO 1 h before induction
Promethazine	12.5-25 mg PO 1 h before induction
Timing: at end of surgery	
Dolasetron	12.5 mg I.V.
Droperidol	0.625-1.25 mg I.V.
Granisetron	0.1-1 mg I.V.†
Ondansetron	4 mg I.V.
Prochlorperazine	5-10 mg I.V.
Promethazine	6.25-12.5 mg I.V.
Timing: applied prior evening or 4 h before end of surgery	
Scopolamine	Transdermal patch
Timing: not known	
Dimenhydrinate	1-2 mg/kg I.V.
Ephedrine	0.5 mg/kg IM

* When a dose range is presented, the lowest dose is recommended.

† A recent study found granisetron 0.1 mg plus dexamethasone 8 mg to be noninferior to ondansetron 4 mg plus dexamethasone 8 mg.[32]

Modified from Gan TJ, et al. *Anesth Analg*. 2003;97:66.

recent randomized controlled trials, supplemental oxygen did not help to prevent PONV in patients undergoing strabismus repair or thyroidectomy.[24,25] It is possible that oxygen is effective only in abdominal surgery because it counteracts emetogenic mediators released during relative intestinal hypoperfusion and ischemia.

Table 3 outlines key strategies for reducing baseline risks for PONV.

Multimodal Approach

A multimodal approach that incorporates both baseline risk reduction and antiemetic therapy should be adopted for PONV prophylaxis.[26] A recent prospective, double-blind, randomized controlled trial compared 3 strategies for the prevention of PONV in patients undergoing laparoscopic cholecystectomy: 1) a multimodal approach using ondansetron, droperidol, and total I.V. anesthesia (TIVA) with propofol; 2) combination therapy with ondansetron and droperidol, with isoflurane and NO-based anesthesia; and 3) TIVA with propofol alone.[27] The rate of complete response was highest in the multimodal group compared with the combination and TIVA-only groups (90%, 63%, and 66%, respectively), as was the degree of patient satisfaction.

Guideline 4: Antiemetic Therapy for PONV Prophylaxis in Adults

Serotonin (5-HT$_3$)–Receptor Antagonists

These agents, used for both the prevention and treatment of PONV, are given toward the end of surgery for greatest efficacy.[28,29] The 5-HT$_3$–receptor antagonists are more effective in preventing vomiting than in preventing nausea. Dolasetron (Anzemet, Organon), granisetron (Kytril, Roche), and ondansetron (Zofran, GlaxoSmithKline, and generic formulations now available) all have favorable side-effect profiles. The panel agreed that there is no evidence of any differences in efficacy and safety among 5-HT$_3$–receptor antagonists used for PONV prophylaxis.[30,31] A recent study demonstrated the equivalent efficacy and safety of granisetron and ondansetron when used in combination antiemetic therapy.[32] In this study, low-dose granisetron (0.1 mg) plus dexamethasone 8 mg was found to be noninferior to ondansetron 4 mg plus dexamethasone 8 mg in patients undergoing abdominal hysterectomy with general anesthesia. The combinations prevented vomiting in 94% and 97% of patients, respectively, in the first 2 hours after tracheal extubation, and in 83% and 87% of patients, respectively, in the 24 hours postextubation.

Dexamethasone

The mechanism of action of the antiemetic properties of corticosteroids is not well understood. Dexamethasone has been found to be effective for the management of PONV. It has a slow onset but a prolonged duration of action and therefore should be administered on induction of anesthesia.[33] The most commonly used dose for adults is 8 to 10 mg I.V.[34] Smaller doses of 2.5 to 5 mg have also been used and found to be as effective.[35,36] Based on a quantitative, systematic review of the data, no adverse side effects have been noted following a single antiemetic dose of dexamethasone.[34]

Droperidol

The neuroleptic drug droperidol is widely used for PONV prophylaxis and is comparable to ondansetron as a prophylactic antiemetic.[37] For greatest efficacy, droperidol is administered at the end of surgery[38] or concomitantly with morphine via patient-controlled analgesia (PCA) systems.[39] The use of low doses

Table 5. Antiemetic Doses for Children

Drug	I.V. Dose
Dexamethasone	0.15 mg/kg up to 5 mg
Dimenhydrinate	0.5 mg/kg up to 12.5 mg
Dolasetron	0.35 mg/kg up to 12.5 mg
Droperidol	0.015-0.03 mg/kg up to 1.25 mg
Ondansetron	0.05-0.1 mg/kg up to 4 mg
Perphenazine	0.07 mg/kg
Promethazine	6.25 mg

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(0.625-1.25 mg) of droperidol has not been associated with the typical side effects caused by higher doses of this drug (hypotension, extrapyramidal symptoms, sedation, akathisia, dysphoria).[40]

In 2001, the FDA began requiring that droperidol labeling include a "black box" warning stating that the drug may cause death or life-threatening events associated with QTc prolongation and torsades de pointes. The labeling requirement was based on 10 reported cases associated with droperidol use (at doses of 1.25 mg or lower) during its approximately 30 years on the market.[41] However, no case reports in peer-reviewed journals have associated droperidol use with QTc prolongation, cardiac arrhythmias, or death at doses used for the management of PONV.[26] This year, in a randomized, double-blind, placebo-controlled trial, droperidol was not associated with a significant increase in the QTc interval compared with saline.[42] Additionally, another recent study found that droperidol increased the QTc interval no more than did ondansetron.[43]

The original New Drug Application submitted was only for doses of droperidol at or above 2.5 mg, which are well above the effective antiemetic doses (0.625-1.25 mg).

Novel Antiemetic

NK1 receptor antagonists (RA) are a new class of antiemetic that exhibit efficacy in the prevention of PONV. In a recent study, the NK1 RA aprepitant (Emend, Merck) at a dose of 40 mg was more effective than ondansetron for the prevention of PONV in high-risk patients undergoing abdominal procedures. The OR for no vomiting was 2.5 (P<0.001), and for total response (no nausea, vomiting, or use of rescue antiemetic) was 1.3 (P<0.03) when aprepitant was compared with ondansetron at 24 hours. The drug appears to retain its antiemetic properties even at 48 hours.[44,45]

Aprepitant is available as an oral capsule and should be administered 1 to 3 hours before induction of anesthesia.

Other Antiemetics

Low-dose naloxone (0.25 mcg/kg per hour) reduced nausea and vomiting and lowered the need for rescue medication compared with placebo in adult patients,[46] and significantly reduced opioid-related side effects including nausea in children and adolescents.[47] Another opioid antagonist, nalmefene, proved effective in reducing opioid-induced nausea, vomiting, and need for rescue medication in patients receiving PCA.[48]

Transdermal scopolamine (Transderm Scop, Novartis Consumer/Baxter) has an antiemetic effect when applied the evening before surgery or 4 hours before the end of anesthesia. The phenothiazines promethazine and prochlorperazine have been shown to be effective antiemetics when administered intravenously at the end of surgery.[49,50] All 3 drugs may cause sedation, dry mouth, and dizziness.

Palonosetron (Aloxi, MGI Pharma) is a 5-HT_3–receptor antagonist approved in 2003 for the prevention and treatment of chemotherapy-induced nausea and vomiting. Palonosetron is currently in Phase III trials for safety and efficacy in the management of PONV.

Table 4 lists the commonly used prophylactic antiemetics in adults, with appropriate doses and timing of administration. Some therapies have proved ineffective for PONV prophylaxis. These include metoclopramide when used in standard clinical doses (10 mg intravenously) and often in larger doses, ginger root, and cannabinoids (nabilone, tetrahydrocannabinol). There is inadequate evidence to suggest that hypnosis is a promising modality for PONV prophylaxis.

Nonpharmacologic Therapies

Acupuncture, acupressure, transcutaneous electrical nerve stimulation, acupoint stimulation, and hypnosis are examples of nonpharmacologic therapies that have shown antiemetic efficacy when used before surgery.[51] In a study by Gan et al in 2004, patients receiving general anesthesia for major breast surgery were randomized to receive electro-acupoint stimulation, ondansetron 4 mg, or placebo.[52] The complete response rates were significantly higher in the active treatment groups than in the placebo group, and patient satisfaction was greater in the active treatment groups. The incidence and severity of nausea were significantly higher in patients who received ondansetron or placebo than in those who received electro-acupoint stimulation, which suggests that this alternative therapy may be more effective in preventing postoperative nausea than are 5-HT_3–receptor antagonists.

Guideline 5: Antiemetic Therapy for POV Prophylaxis in Children

Children, perhaps more than adults, are candidates for POV prophylaxis; the POV rate in children can be

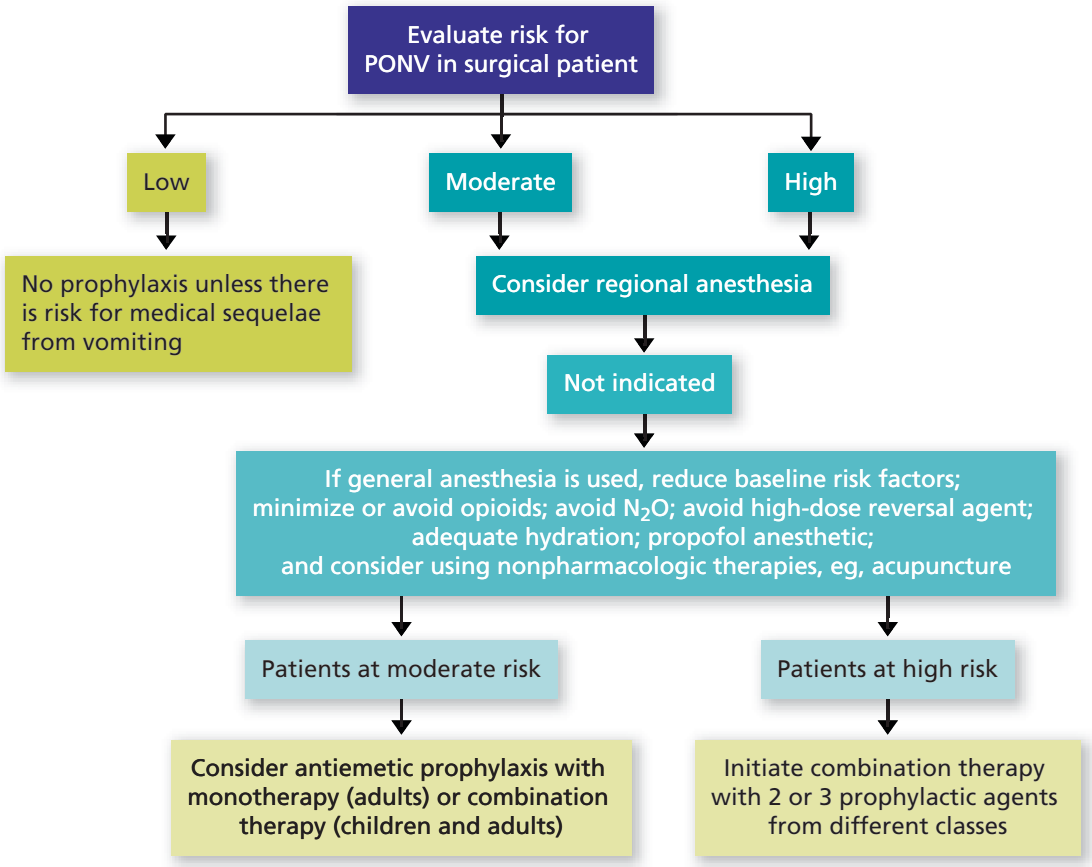

Figure. Algorithm for the prevention of PONV.

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double the rate in adults.[3] As a group, the 5-HT_3–receptor antagonists are the first-line prophylactics for vomiting in children. Perphenazine (based on the results of 2 large, randomized controlled trials[53,54]), dimenhydrinate, and dexamethasone (the latter 2 based on meta-analyses[34,55]) are also effective prophylactics for pediatric POV. The use of droperidol, with an increased risk for extrapyramidal side effects in children, should be reserved for hospital patients who have failed all other therapies.

Since the publication of the first guidelines, ondansetron has been approved for use in children as young as 1 month of age and granisetron (40 mg/kg) and tropisetron (0.1 mg/kg) have been added as therapeutic options. Because the 5-HT_3–receptor antagonists as a group have greater efficacy in the prevention of vomiting than of nausea, these drugs are the first choice for prophylaxis in children.

An updated guideline recommends that children who are at moderate or high risk for POV should receive combination therapy with 2 or 3 prophylactic drugs from different classes. When rescue therapy is required, the antiemetic should not be chosen from the same therapeutic class as the agents used for prophylaxis.

Table 5 lists commonly used prophylactic antiemetics in children, with appropriate doses.

Guideline 6: Use Prophylaxis in Patients at High Risk for PONV and Consider Prophylaxis In Patients at Moderate Risk for PONV

Patients at high or moderate risk for PONV are most likely to benefit from prophylaxis. Patients at low risk for PONV are usually not candidates for prophylaxis unless potentially compromised by medical sequelae of vomiting. Those at moderate risk for PONV should receive antiemetic monotherapy (adults) or combination therapy (adults and children). Those at high risk should receive combination therapy with 2 or 3 antiemetics from different classes.[56,57] Drugs with different mechanisms of action can be combined for optimal efficacy. For example, the 5-HT_3–receptor antagonists (more effective against vomiting) can be combined with droperidol (more effective against nausea).

Table 6. Antiemetic Treatment for Patients With PONV Who Have Not Received Prophylaxis or in Whom Prophylaxis Has Failed

If Initial Therapy Was:	Then Treat With:
No prophylaxis or dexamethasone	Low-dose 5-HT_3–receptor antagonist*
5-HT_3–receptor antagonist* plus second agent†	Agent from a different class
Triple therapy with 5-HT_3–receptor antagonist* plus 2 other agents†	When PONV occurs <6 h after surgery: Use agent from a different class or propofol 20 mg in PACU (adults) When PONV occurs 6 h after surgery: Repeat 5-HT_3–receptor antagonist and droperidol (except dexamethasone or scopolamine) Use agent from a different class

* Low-dose 5-HT_3–receptor antagonist I.V. dosing: dolasetron 12.5 mg, granisetron 0.1 mg, ondansetron 1.0 mg, and tropisetron 0.5 mg.

† Alternative therapies for rescue: dexamethasone 2-4 mg I.V., droperidol 0.625 mg I.V., and promethazine 12.5 mg I.V.

PACU, postanesthesia carre unit

Modified from Gan TJ, et al. *Anesth Analg*. 2003;97:68.

An algorithm for the management of PONV is presented in the Figure.

Guideline 7: Provide Antiemetic Treatment To Patients With PONV Who Did Not Receive Prophylaxis or in Whom Prophylaxis Failed

Nausea and vomiting may persist in some patients after they leave the postanesthesia care unit. After medication and mechanical causes of PONV have been excluded, rescue therapy with antiemetics can be initiated. For patients who receive no prophylaxis, low-dose therapy with 5-HT_3–receptor antagonists may be initiated.[58] Some of the doses of 5-HT_3–receptor antagonists used for the treatment of PONV have been one-fourth the doses used for prophylaxis.[59]

The consensus panel developed antiemetic treatment recommendations for the following 3 scenarios. For patients in whom dexamethasone prophylaxis has failed, low-dose therapy with a 5-HT_3–receptor antagonist is recommended. For patients in whom initial 5-HT_3–receptor antagonist prophylaxis has failed, 5-HT_3–receptor antagonist rescue therapy should not be given within the first 6 hours after surgery. Similarly, patients in whom prophylactic combination therapy with a 5-HT_3–receptor antagonist plus dexamethasone has failed should be treated with an antiemetic from a different class.

As a general guideline, patients who experience PONV within 6 hours after surgery should be treated with an antiemetic other than the one used for prophylaxis. For the treatment of patients who experience PONV more than 6 hours after surgery, drugs from the prophylactic antiemetic regimen may be repeated—except for dexamethasone and transdermal scopolamine, which have a longer duration of action. Propofol may be used in small doses (20 mg as needed) for the treatment of PONV in a supervised environment.[60,61]

The preliminary results of a recent analysis support the recommendation that a rescue antiemetic should be from a class other than that of the original antiemetic agent.[62] This analysis of a previous trial reported that in patients who failed prophylaxis with ondansetron or droperidol, promethazine was significantly more effective in controlling PONV than the original agent. Dimenhydrinate was also more effective than droperidol in patients who failed prophylaxis with droperidol.

Table 6 outlines recommended treatment regimens for PONV patients who have not received prophylaxis or in whom prophylaxis has failed.

Summary

Consensus guidelines for the optimal management of PONV were developed as an evidence-based tool for clinicians. This review incorporates recent findings and published data in the area of PONV management. Evidence for newer and novel antiemetics has been added. The guidelines recommend that clinicians first identify surgical patients at high or moderate risk for PONV, then reduce baseline risk factors in these patients. Combination antiemetic therapy is recommended for all adult patients at high risk for PONV and for pediatric patients at high or moderate risk for POV. A multimodal approach for the prevention of PONV, including the use of antiemetics, analgesics, anxiolytics, hydration, and total I.V. anesthesia, has been shown to be most effective.

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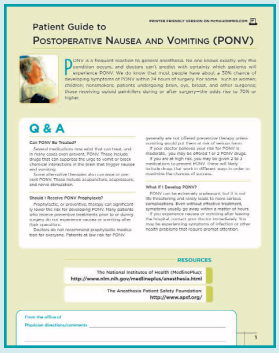
Patient Guide to
Postoperative Nausea and Vomiting (PONV)

Q & A

RESOURCES

Please see AnesthesiologyNews.com for a guide on talking to patients and their family members about PONV.