Fifth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting - Full Report

APPENDIX 1: FULL REPORT

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INTRODUCTION

Postoperative nausea and vomiting (PONV) is a common adverse event after surgery and anesthesia. It is distressing for patients, delays post-anesthesia recovery, and can sometimes lead to more serious complications. Optimal management of PONV requires a multidisciplinary approach, with evidence-based care and appropriate institutional infrastructure.[1] In the last consensus guideline, the expert panel recommended a general approach to multimodal PONV prophylaxis, and rescue treatment with antiemetics from a different pharmacological class.[2] Since the last guideline, there has been a plethora of studies on various novel antiemetic combinations. Additionally, there is a growing body of literature on the influence of genetic, socioeconomic, and diversity considerations on PONV management. The updated guidelines will address the emerging clinical evidence, as well as the novel considerations in the management of PONV.

METHODS

GOALS OF THE GUIDELINES

The goals of the current guidelines were established by the panel as follows: 1. Identify established as well as emerging risk predictors of PONV; 2. Evaluate the effectiveness of interventions in reducing baseline risk of PONV; 3. Provide updated evidence on PONV prophylaxis, including single antiemetic, combination therapy and nonpharmacological interventions; 4. Appraise the optimal timing and dose of PONV prophylaxis; 5. Highlight evidence based approaches to the treatment of PONV and post discharge nausea and vomiting (PDNV), with or without prior PONV prophylaxis; 6. Update the PONV management algorithm and infographics 7. Review the cost-effectiveness of strategies for PONV management; 8. Evaluate the management of PONV within enhanced recovery protocols (ERP); 9. Propose a research agenda for future studies.

ESTABLISHMENT OF THE EXPERT PANEL

The current guideline is prepared by a multidisciplinary expert panel, who were invited based on significant contributions in the field of PONV research or representation in professional societies with interest in PONV management. Many of the panel members were involved in the previous iterations of the guidelines. Panel members were divided into groups, each focused on a different aspect of PONV management. The groups provide input on the literature search strategy, review the literature identified from the search, and summarize the findings to be presented at the consensus meeting. At the meeting, the panel reviewed the presented evidence and reached a consensus on the grading and the clinical interpretation of the evidence. When a consensus was not reached, the majority view was accepted, and the lack of full agreement was noted in the manuscript.

LITERATURE SEARCH AND REVIEW

The searching process followed the Cochrane Handbook[3] for conducting the search, the PRISMA 2020[4] for reporting, and PRISMA-S[5] extension for searches.

An information specialist (ME) searched the following databases from inception via the Ovid platform: MEDLINE, MEDLINE ePubs and In-Process Citations, Embase Classic+Embase, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. All the databases were searched on the same day for each of the research topics, as noted in the search reports.

Preliminary searches were conducted, and full text literature was mined for potential keywords and appropriately controlled vocabulary terms (such as Medical Subject Headings for MEDLINE and EMTREE descriptors for Embase).
The search strategy concept blocks were built on the topics of: (Postoperative Nausea and Vomiting) AND (each of the topics noted in the search report) using both controlled vocabularies and text word searching for each component. Searches were limited to English language, humans, and adults (except for the topic on children). Conference material and non-journal materials were removed from results at source, where possible. The search results were limited to the update period, January 1, 2019, to present.

Panel members hand searched the included studies for other relevant studies. Continued literature surveillance was done through September 2024. The full search strategies and search reports were included as supplementary digital content (SDC) appendix 2.

GRADING OF EVIDENCE

To characterize the quality of evidence for each intervention, we used a grading system similar to that in the previous guidelines (SDC appendix 3).[1] This system was previously reported by the American Society of Anesthesiologists in their acute pain management practice guideline.[1,6] This provides an objective standard against which clinical evidence could be compared. The gradings are highlighted in **bold**.

RESULTS

GUIDELINE 1. IDENTIFY PATIENTS' RISK FOR PONV

PONV risk factors may be used for risk assessment (figure 1a and SDC table S1), to guide PONV management,[7,8] and have been advocated in previous versions of this guideline.[2] An analysis of various PONV prophylaxis algorithms supports the use of risk assessment tools or risk stratification protocols in reducing PONV (**B1**).[9]

Several recent publications have challenged the utilization of risk factors to guide management and have proposed a more liberal administration of PONV prophylaxis in patients with lower risk of PONV.[10] This approach is justified by the concern that a risk-stratified approach is not always implemented correctly, which tends to be most deleterious to high-risk patients.[11,12] Additionally, the lack of an evidence-based threshold for individual risk factors creates potential for ambiguity. For instance, it is not clear what dose of postoperative opioids and what amount of cigarette smoking significantly modifies the risk of PONV. Determination of a prior PONV history is also confounded by the nature of prior surgery, antiemetic prophylaxis and anesthetic management.

The National Anesthesia Clinical Outcomes Registry (NACOR) and the Anesthesiology Quality Institute (AQI) data found that lower socioeconomic status patients may receive fewer antiemetics even after adjusting for patient characteristics and for procedure and provider factors.[13] It may be assumed that a more general approach would reduce the incidence of inadequate PONV prophylaxis. As multimodal prophylaxis is increasingly adopted as part of enhanced recovery pathways,[14] it may be justified to ask why it is not the standard of care for all patients undergoing general anesthesia.

While the utility of a more general multimodal approach requires further validation, the argument for liberal antiemetic combination prophylaxis becomes all the stronger the more evidence grows that the established antiemetics are safe in the perioperative dosage.[15-18] If a strictly risk-based antiemetic prophylaxis regimen is implemented, previous studies have shown that reminder systems substantially increase guideline adherence.[19-21] For a risk-stratified approach, an objective assessment of risk factors should guide and optimize the prevention of PONV. Various tools may help to increase internal guideline adherence, such as reminders (**B1**), self-checklists (**B2**), and the use of more sophisticated electronic decision support tools (**B2**).

RISK SCORES

PONV risk scores can be used to inform and guide therapy. Such scores have been shown to reduce the rate of PONV at an institutional level[7,22,23].

Commonly used risk scores for inpatients undergoing anesthesia are the Koivuranta score and the Apfel score [24,25]. The Apfel simplified risk score is based on four predictors: female gender, history of PONV and/or motion sickness, nonsmoking status, and use of postoperative opioids (figure 1a). The incidence of PONV with the presence of 0, 1, 2, 3, and 4 risk factors is approximately 10%, 20%, 40%, 60%, and 80%, respectively.[24] The panel classifies patients with 0, 1-2, or 3-plus risk factors into "low," "medium," and "high" risk categories, respectively. Koivuranta's score includes the 4 Apfel risk predictors as well as length of surgery >60 minutes.[25]

A recent systematic review (SR) of PONV risk prediction[26] revealed sixty-two relevant publications with a total of 81,834 patients, and eight prediction models. The simplified Apfel score performed best, primarily because it was extensively validated. The Van den Bosch score [27] and Sinclair score [28] tied for second place. The simplified Koivuranta score was in third place.[25] This qualitative analysis highlights the strengths and weaknesses of each prediction system based on predetermined standardized quality criteria and may help choose appropriate scoring systems if PONV risk should be thoroughly classified, which becomes especially important in scenarios with no general multimodal prevention approach.

It should be noted that the shift in practice towards general, multimodal prophylaxis does not discredit the validity of PONV prediction scores,[22] nor an appropriately implemented risk-adapted PONV protocol.[7] Rather, a general multimodal approach may be used to overcome compliance issues and undetected risk factors. Such approach is increasingly adopted in enhanced recovery after surgery (ERAS) protocols.

NOVEL PONV RISK FACTORS

Preoperative physical status

After evaluation of more than 160,000 patients, a strong association was reported between preoperative physical fitness and decreased likelihood of developing PONV (hazard ratio 0.76 [0.71-0.82]) (**B1**).[29]

Preoperative hematocrit

Retrospective analysis demonstrated that higher hemoglobin and hematocrit were associated with less PONV (**B1**).[30] The prediction model cites sensitivity of 73.08% and 65.38% for Hb and Hct, respectively. Of note, patients with and without PONV had overlapping Hb/Hct values. An optimal Hct level of over 39.3% was associated with minimized PONV risk. Although these results have not been confirmed by further studies, they underline the importance of patient blood management in the perioperative context.

Preoperative neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR)

NLR was higher in patients who experienced PONV after thoracoscopic surgery (**B1**).[31] Studies suggest that NLR values > 2 are predictive of PONV and need for rescue antiemetic use.[32] In patients undergoing mammoplasty, PLR ratio of >137.2 slightly outperformed NLR, while NLR was more predictive for total knee arthroplasty.[33,34]

Intraoperative hemodynamic shifts

The avoidance of intraoperative hypotension may reduce the risk of PONV (**B1**). [35-37] Similarly, goal directed hemodynamic management may reduce the risk of PONV(**A1**).[38]

Body mass index

Kim et al identified statistically significant differences in odd ratio for PONV between patients with BMI 18.5 to 25 kg/m^2 and those with BMI>25 kg/m^2 with higher body mass index (BMI) being protective (**B1**).[39] This contrasts with older data showing no clinically relevant effect of BMI on the risk of PONV [40] and with some expert opinions suggest that obese patients have higher risks of PONV.

Type of surgery

Patients with high BMI undergoing bariatric surgery have higher rates of PONV than patients with normal BMI undergoing non-bariatric gastric surgery (**B1**).[41] The bariatric surgical population may have higher rates of PONV, but this does not appear to be attributable to the higher BMI of the patient population.[42,43] Certain other surgeries, such as laparoscopic cholecystectomy, urological procedures, and knee arthroplasty, may increase the risk of PONV (**B1**).[44,45] Breast, gynecologic and obstetric surgeries, are also associated with increased risk.[46] Among neurosurgical procedures, microvascular decompression and those with intraoperative cerebral spinal fluid loss are associated with the highest risk of PONV (**B1**).[47,48]

It should be noted that at the population level, adding selected individual risk factors to the prediction models is unlikely to improve the predictive properties of the risk models. This was the result of extensive modelling of different patient cohorts, as well as the occasional addition of potential risk factors of significant importance (odds ratio: 2-3).[49] If vomiting poses a significant medical risk, such as an increased intracranial pressure or in conjunction with wired jaws in the postoperative phase, these risks should be further considered.

PDNV RISK EVALUATION

PDNV presents a significant risk to discharged patients who no longer have access to fast-onset intravenous (IV) antiemetics or direct care. A study of 2,170 US outpatients reported the incidence of PDNV to be 37% in the first 48 hours after discharge and identified five independent predictors of PDNV, including female gender, age <50 years, history of PONV, opioid use in the post-anesthesia care unit (PACU), and nausea in the PACU.[50]

An observational study found that the strongest predictors of PDNV on days 3 to 7 were a previous history of PDNV, operating room time, use of ondansetron in the PACU, and pain during days 3 to 7.[51]

Validation of a simplified PDNV risk score based on these risk factors found that the incidence of PDNV with 0, 1, 2, 3, 4, or 5 of these risk factors to be about 10%, 20%, 30%, 50%, 60%, and 80%, respectively (figure 1b).[50]

GENOMICS, GENETICS AND POLYMORPHISM

There is emerging evidence that antiemetic efficacy may be influenced by gene polymorphisms as well as variation in gene expression (epigenetics). For example, cytochrome P450 (CYP $_2D_6$) is involved in the metabolism of several 5-hydroxytryptamine 3 (5-HT$_3$) receptor antagonists RA, and ultrarapid metabolizer phenotype may be associated with reduced antiemetic efficacy of ondansetron, tropisetron, and others.[52] Another example is the polymorphisms of the serotonin-transporter-linked polymorphic region, which have been associated with increased risk of PONV.[53] Dopamine receptor 2 gene polymorphism has also been linked to increased risk of PONV.[52]

SDC table S2 summarizes the main recent findings in the field. Particularly, in the genetic susceptibility to the development of PONV, two single nucleotide polymorphisms (SNPs), the CHRM3 rs2165870 and the KCNB2 rs349358 SNP, may have a major influence in Caucasians, and both SNPs were primary identified in a genome-wide association study.[54]

The translation of these interesting data on a large scale and in the everyday clinical practice is yet to be realized, along with the advances in personalized medicine.[55-57] A recent study suggests that the use of this polygenic risk score did not result in a clinically meaningful improvement in PONV prediction when added to traditional risk factors.[58]

THE IMPACT OF SEX/RACE/GENDER/SOCIAL DETERMINANTS ON PONV

Social determinants, such as sex, gender, race, and socioeconomic status may lead to disparities in health care access, treatment, and outcomes. However, they are not always considered in the analyses of Randomized controlled trials (RCTs).[59]

Race/Social Determinants

Social determinants of health are important to consider in the context of PONV. Andreae et al. reported that patients with lower socioeconomic status were less likely to receive antiemetics after controlling for confounders such as age, sex, ASA classification, anesthetics, practice patterns and insurance status[13].

The interaction between race/ethnicity and PONV risk is a topic of ongoing debate. While some retrospective studies have reported lower incidence of PONV in African American patients,[60] others have disputed the validity of such associations.[61] Nevertheless, several studies have reported that after adjustment for confounders, African American patients are more frequently undertreated when compared to white patients.[60,61] In high-risk patients (4 risk factors), Hispanic patients were more likely to experience PONV than white patients.[60] More studies are needed to investigate causes for such disparities and their associated impact. Racial, ethnic, and socioeconomic inequalities in perioperative care have been cited as a major driver of financial cost to hospital systems: Jotwani estimated that given the undertreatment of PONV in black patients, the average preventable cost per surgical case is $114 per surgical case in the United States.[62]

Racial disparity in perioperative management and resulting outcomes can be avoided through standardization of care, which was shown to minimize racial disparity in PONV management.[63]

Gender/Sex

Sex and gender may impact the perioperative management of PONV, and transgender patients represent a potentially vulnerable population.[64] In 282 transgender women receiving facial gender affirming surgery (GAS), the PONV incidence, after controlling for confounders including estrogen therapy holding before surgery, was found to be 37.6%. This is higher than the PONV rate in cisgender men (5.7%) and women (13.9%) undergoing rhinoplasty, who served as control groups ($p = 0.001$). The incidence of PONV in transgender patients is also higher than the reported rate of 25%–30% PONV after oral and maxillofacial surgery usually reported in the literature. Anesthesia providers may seek to pay special attention to antiemetic prophylaxis in this population.[65,66]

Pregnancy

In a retrospective study, 237 gravid women who underwent non-obstetric procedures with general anesthesia were compared with 474 non-gravid women. There was no significant difference in the incidence of PONV amongst gravid patients compared to non-gravid patients.[67] Fewer prophylactic antiemetics were given among gravid than non-gravid patients, which may be related to the lack of specific recommendations for PONV prophylaxis among gravid patients.

GUIDELINE 2. REDUCE BASELINE RISK FOR PONV

Approaches for decreasing baseline risk are presented in SDC table S3. Strategies recommended to reduce baseline risk for PONV include (1) minimization of perioperative opioids with the use of multimodal analgesic regimens; (2) preferential use of regional anesthesia; (3) preferential use of propofol infusions as the primary anesthetic;[68,69] (4) avoidance of volatile anesthetics; and (5) adequate hydration in patients undergoing surgery.

PROPOFOL TIVA

An systematic review and meta-analysis (SRMA) of RCTs showed that the PONV risk with propofol TIVA is comparable to volatile anesthesia plus 5-HT_3 RA or droperidol (**A1**).[68,69] Propofol TIVA is also effective when used in combination with other antiemetics (**A2**).[70,71] Lastly, subhypnotic dose propofol infusion is effective when used in combination with other antiemetics (**A2**), although the duration is limited to PACU duration.[72]

NITROUS OXIDE

A recent SRMA suggests that N_2O as maintenance anesthesia increases the incidence of PONV.[73] On the other hand, a RCT of patients undergoing laparoscopic hysterectomy found that 70% N_2O only during the last 30 minutes of surgery had comparable PONV risk to those receiving air/O_2 mixture throughout the case (**A3**).[74]

MULTIMODAL SYSTEMIC ANALGESIA

Prophylactic IV acetaminophen as part of a multimodal analgesic regimen reduces incidence of nausea when given before the onset of pain (**A1**).[75] Although oral acetaminophen has also been shown to reduce opioid requirement and is considerably less costly than other analgesics, its effect on PONV is not well-studied. RCTs and meta-analyses show that perioperative nonsteroidal anti-inflammatory drugs, (NSAIDs), cyclooxygenase-2 inhibitors[76-78] and, to a lesser extent, intraoperative ketamine[79] may have a morphine-sparing effect in the postoperative period (**A1**). A SRMA reported that, in patients with postoperative patient-controlled analgesia (PCA), IV or intramuscular (IM) NSAIDs significantly reduced the risk of PONV, and appears to be more effective than IV acetaminophen (**A1**).[80] However, nonselective NSAIDs may be associated with anastomotic leak in gastrointestinal (GI) surgery and their use should be carefully considered.[81-83]

NEURAXIAL AND REGIONAL ANESTHESIA

It is well established that epidural analgesia could reduce the risk of PONV,[84,85] on the other hand, the role of intrathecal opioids in the PONV risk modification remains unclear.[86] An earlier SRMA suggested that there may be a correlation between epidural local anesthetic dosage and PONV risk.[87]

A recent SRMA of patients undergoing abdominal surgery found that transversus abdominis plane (TAP) block significantly reduced the risk of PONV, specifically if TAP block was administered before surgery.[88] Quadratus lumborum block similarly reduced PONV risk within the first 24 hours (**A1**).[89]

Continuous wound infiltration is also effective in reducing postoperative opioid requirement and PONV risk (**A3**).[90] When regional anesthesia is implemented as a part of an enhanced recovery pathway, its benefit in preventing PONV is less apparent, likely because other enhanced recovery pathways include other opioid-sparing interventions.[91]

INTRAVENOUS LIDOCAINE

Weibel *et al*[16] conducted an SRMA on the use of IV lidocaine and PONV and reported that in laparoscopic abdominal procedures, the PONV risk is lower with lidocaine infusion. No benefit was seen with other surgery types.[92]

GABAPENTINOIDS

A large meta-analysis involving 281 RCTs reported a significant reduction in the risk of PONV with gabapentin and pregabalin (**A1**). This effect was seen with both low doses (defined as <300 mg pregabalin/day or <900 mg gabapentin/day) and higher doses, and also when given as a single or in multiple doses.[93] Their use was however associated with increased risk of dizziness and visual disturbances. The use of gabapentinoids as part of the multimodal analgesic regimen in ERAS protocols has been challenged due to concerns related to adverse events and the risk of respiratory depression when used in association with opioids.[94] Furthermore, the analgesic and opioid sparing efficacy of gabapentinoids may not be clinically relevant.[93]

ESMOLOL

In one study in patients undergoing ambulatory surgery, an intraoperative infusion of esmolol, in conjunction with PONV prophylaxis with droperidol and dexamethasone, was associated with reduced PACU opioid consumption and PONV compared with intraoperative infusion of remifentanil or placebo.[95] A subsequent study in patients undergoing laparoscopic cholecystectomy showed more PONV in patients who received esmolol bolus and infusion alone compared to those who received ramosetron alone or ramosetron combined with esmolol.[96]

OPIOID-FREE ANESTHESIA

Several studies demonstrate that opioid-free anesthesia reduces PONV and shortens PACU length of stay compared to opioid-based anesthesia (**A1**).[97-101] These effects lasted 24 hours. Bradycardia was seen more frequently in the opioid-free group and patients may have longer awakening times.[102] However, one SR showed no significant difference in PONV (**A1**) and another proposed that the choice of opioid is important for PONV risk evaluation (**A1**).[102,103] PONV occurred less in opioid-free anesthesia based on recent SR.[102] However, it is also unclear to what extent multimodal antiemetic prophylaxis can also achieve these effects in the context of opioid-sparing anesthesia or standard anesthetic approaches.

SUPPLEMENTAL OXYGEN

An SRMA of RCTs showed that supplemental oxygen was not associated with significant change in the overall risk of PONV (**A1**),[104] but the risk of early vomiting in abdominal surgery was lower and less PONV was seen when muscular tissue oxygen saturation was maintained above baseline (**B1**).[104-106]

SUGAMMADEX

Sugammadex reduces the incidence and severity of PONV (**A1**).[107] A SRMA of 40 RCTs found that sugammadex reduced PONV risk in PACU but not on the wards, and was effective regardless of the administration of other prophylactic antiemetics[108]. It however did not reduce PONV in the subgroup that received propofol TIVA. Furthermore, since the last iteration of the guideline, a new Cochrane SRMA identified 6 studies comparing the risk of PONV in patients, who had neuromuscular junction blockade reversed with sugammadex compared to neostigmine, and reported that the PONV risk is lower with sugammadex.[109] The quality of evidence was limited, however, due to inclusion of open-label studies as well as risk of bias due to unclear baseline PONV risk of the participants.

CARBOHYDRATE LOADING

There has been no general consensus on the use of carbohydrate loading prior to surgery and its impact on PONV. Adequate preoperative hydration contributes to less PONV but carbohydrate loading, which is used in many enhanced recovery protocols, shows no clear benefit in terms of PONV reduction in comparison to clear fluids (**C1**).[110] Carbohydrate loading may well improve circulatory dynamics (**A1**); it is more comfortable for the patient, and there is no increased risk with respect to aspiration (**A1**).[111] Therefore, taken together, the data suggest that this treatment may be overall beneficial despite the absence of PONV risk reduction.

FLUID MANAGEMENT

A Cochrane review involving 41 studies reported with moderate certainty of evidence that supplemental crystalloids, which ranged from 10-40 ml/kg, reduced the risk of early and late PONV as well as the need for rescue antiemetics (**A1**).[112] A SR comparing the impact of colloids versus crystalloids on PONV found that perioperative colloid administration did not reduce the incidence of PONV compared to crystalloids, except in major surgeries with anesthesia duration longer than 3 hours (**A1**).[113] Low quality evidence suggests that perioperative dextrose infusion might reduce the risk of postoperative nausea,[114] PONV and need for rescue antiemetics following laparoscopic surgery (**A1**).[115] Stroke volume-guided fluid therapy reduced the risk of PONV and antiemetic requirement in gastrectomy patients (**A3**).[116]

PROTON PUMP INHIBITORS

A study reported that PONV is higher in patients with gastroesophageal reflux and proton pump inhibitors may have some benefit in reducing PONV (**B1**).[117]

GUIDELINE 3. ADMINISTER PONV PROPHYLAXIS USING 2 INTERVENTIONS IN ADULTS AT ANY RISK FOR PONV

Although randomized controlled trials, meta-analyses, guidelines, and expert opinion recommend the use of combination therapy and administration of 2 antiemetics in patients with 1-2 risk factors for prevention of PONV, there continues to be a large number of studies investigating monotherapy with antiemetics from the 6 major pharmacological classes since the 2020 Guidelines (table 1).[2,16,118-148,8-13,15-24,27-29,31-42] The majority of single drug to single drug comparison studies for prevention of PONV are on the 5-HT_3 RA class of antiemetics. Safety profiles of antiemetics are summarized in the (SDC table S4).

5-HT3 RECEPTOR ANTAGONISTS

Elevated levels of the neurotransmitter serotonin induce nausea and vomiting by triggering the specific receptors in the gut and central nervous system. The 5-HT_3 RA inhibit serotonin receptors centrally and peripherally[118] and they have better anti-vomiting than anti-nausea efficacy.[16,118]

Ondansetron

Ondansetron was the first 5-HT_3 RA on the market and commonly used as the preferred antiemetic for PONV prophylaxis.[2] The drug was approved by the U.S. Food and Drug Administration (FDA), recommended dose was 4 mg by slow IV injection or 16 mg of the oral formulation (oral disintegrating tablets, given 1 hour before induction). The IV drug has a mean elimination half-life of 3.1-5.8 hours in adults and is extensively metabolized by the liver.[149-151] CYP 2D6 ultra-metabolizers are significantly more likely to develop PONV despite ondansetron prophylaxis.[152] In a 2021 Cochrane network meta-analysis (NMA) on drugs for PONV prophylaxis in adults after general anesthesia, 585 randomized trials enrolling 97,516 patients were included to evaluate 44 single drugs and 51 drug combinations. Ondansetron was the most investigated single drug followed by dexamethasone.[16,118]

Since the 2020 PONV Guideline, several studies have compared ondansetron 4 mg with dexamethasone 8 mg and concluded that ondansetron 4 mg is more effective for PONV prophylaxis. [119,120,153]

Ondansetron 4 mg is comparable to prochlorperazine 10 mg for PONV prophylaxis, with a trend towards greater risk of side effects in the prochlorperazine group.[121] A meta-analysis of 13 RCT's compared ondansetron (4-8 mg) versus droperidol (0.62-2.5 mg) and found that drowsiness incidences were significantly less with ondansetron.[122]

Nuttall conducted a single center retrospective safety study of 32,737 patients to determine incidence of torsades de pointes (TdP) or death following a prophylactic ondansetron 4 mg dose. Results showed that no patients died of TdP as a direct result of ondansetron. A subset of 4,331 patients had documented QTc>450msec and they did not experience TdP. Forty-six patients had monomorphic ventricular tachycardia that were precipitated by existing cardiovascular conditions.[123]

Palonosetron

Palonosetron was approved by the FDA in July 2003 with the recommended dose of 0.075 mg administered intravenously over 10 seconds. The agent is considered a 2nd generation 5-HT_3 RA. Palonosetron has an elimination half-life of 40 hours and a greater affinity for the 5-HT_3 receptor subtype than other 5-HT_3 RAs.[124,154]

Using a weight-based dosing strategy, 1mcg/kg palonosetron was more effective than ondansetron 0.1 mg/kg.[125-127] It has been suggested that the standardized dose of palonosetron 0.075 mg may lead to pharmacological underdosing in obese patients, and weight-based dosing adjustment for palonosetron was more efficacious without an increase in side effects.[127]

Palonosetron 0.075 mg was found to be more effective than ondansetron 4 mg in both abdominal and renal transplant surgery patients.[128,129] When compared to ondansetron 8mg, palonosetron 0.075 mg appears to have a lower incidence of PONV.[130,131] Patients who received subsequent redosing of ondansetron 8 mg had comparable PONV risk as those who received a single dose palonosetron,[132,133] although more headaches were noted in the ondansetron arm (26% vs 8%).[132] Palonosetron appears to be more effective when compared to ondansetron 4 mg or 8 mg, however when added doses of ondansetron are given, no differences were found between the two drugs. (**A3**)

Granisetron

Granisetron received FDA approval in 1993. The drug is 65% protein bound with an elimination half-life of 5-9hrs. The drug is metabolized by CYP_1A_1 and CYP_3A_4. Original labeling from the package insert recommended 1 mg IV push. More recently an adult dosing range of 0.1 to 3 mg IV at the end of surgery has been suggested for preventing PONV.[2,118,155-157]

In lower abdominal surgery patients, the incidence of 24-hour PONV was lower in those who received granisetron 3 mg (10%) compared to ondansetron 4 mg (26.7%) and metoclopramide 10 mg (53.3%).[134] Granisetron 2 mg was more effective than ondansetron 4 mg for late PONV.[135] Granisetron 10mcg/kg was more effective than ramosetron 0.3 mg.[136]

Ramosetron

Ramosetron is a newer 5-HT_3 RA for the management of PONV. The drug may have a higher binding affinity, slower receptor dissociation and longer duration of action than other first generation 5-HT_3 antagonists.[158] Ramosetron is not available in the U.S. however is available in Japan and several of the Southeast Asian countries.[2,118]

Several clinical trials have reported that ramosetron 0.3 mg was superior to ondansetron 4 mg, [137,138] while being comparable or superior to ondansetron 8 mg.[139-142] Clinical trials have also compared ramosetron 0.3 mg with palonosetron 0.075 mg.[143,144] A SRMA of 17 RCTs reported that palonosetron 0.075 mg is more effective in preventing late POV and retching than ramosetron 0.3 mg, but there were no differences between groups for PON, PONV, rescue, complete response (no vomiting or use of rescue antiemetic) and side effects. Notably, palonosetron was more effective when administered early in surgery and ramosetron was more effective when given later in surgery.[145]

Tropisetron

Tropisetron, one of the earlier 5-HT_3 RAs, is available in Europe and Asia but not in U.S. The drug is a 5-HT_3 RA with a recommended dose of 2 mg. Tropisetron can be given intravenously either as an infusion or as a slow injection and should be administered shortly before the induction of anesthesia. It has an elimination half-life of 6-8 hours.[2,118,147]
A meta-analysis of 14 RCT's, totaling 1,705 patients found that tropisetron (dose ranged from 2-5 mg) was more effective for POV prevention than ondansetron (doses ranged from 4-16 mg). However, there was no difference in PONV, PON and rescue antiemetic use. The incidence of dizziness was higher with ondansetron.[147] In patients undergoing middle ear surgeries, palonosetron 0.075 mg was more effective in preventing PONV than tropisetron 5 mg and ondansetron 8mg for up to 48 hours.[148]

In a large NMA on antiemetic drugs, the authors assessed primary outcomes for 24-hour POV, serious and any adverse event. The authors ranked the agents in terms of efficacy and safety and found 10 out of 28 single drugs lowered the risk of vomiting. Three of the 5-HT_3 RAs were included: ramosetron, granisetron, and ondansetron. Although tropisetron was ranked as one of the ten most clinically effective single drugs compared to placebo, it had a lower certainty of evidence. Palonosetron was minimally effective with also a lower certainty of evidence. The authors found that the recommended and high doses of granisetron, ondansetron, and tropisetron were similarly effective but more effective than lower doses of each agent. Therefore, the use of recommended doses of these drugs should be adequate for vomiting prevention. The 5-HT_3 RA's class of drugs increased the risk of headache.[118]

DEXAMETHASONE

Dexamethasone is commonly used for the prevention of PONV, the recommended dose is 4-8 mg. Dexamethasone was one of the five most effective single drugs for POV prevention in the large NMA,[159] and 8 mg dose seemed to have the optimal antiemetic and analgesic efficacy.[160] Also, in the large pragmatic RCT Perioperative Administration of Dexamethasone and Infection (PADDI) trial with 8,725 patients undergoing noncardiac surgeries, 8 mg IV dexamethasone significantly reduced the incidence of 24-hour PONV and rescue antiemetic requirement.[161] A sub study on patients reported outcomes found that dexamethasone 8 mg did not influence the incidence of clinically significant PONV, but did reduce the incidence of severe PONV.[161,162]

A 2018 Cochrane Database of SR examined the adverse side effects of dexamethasone in surgical patients, this included 38 studies involving a variety of surgical procedures. One intraoperative dose of dexamethasone did not increase the risk of postoperative (wound or systemic) infection compared to placebo, or active control with other antiemetics.[163] In the PADDI trial, a single 8 mg dose of dexamethasone was found to be noninferior to placebo with respect to surgical site infection within 30 days after surgery (P<0.001 for noninferiority).[161] This finding was true in all prespecified subgroups, including patients with or without diabetes mellitus, and for the individual subtypes of surgical-site infections.

A SR and meta-analysis of 11 studies with 2,567 patients found that dexamethasone led to transient postoperative hyperglycemia in patients with diabetes undergoing elective surgery when given as a single 4-10 mg IV dose for PONV prophylaxis.[17] The magnitude of hyperglycemia is small, and it may not have clinical relevance. In surgical patients with diabetes mellitus, another SRMA of 16 studies found that dexamethasone increased blood glucose by only 2 mmol/L (36 mg/dL) of peak glucose level within 24h of surgery, which had no effect on wound healing. [164]

Recently, studies that administered dexamethasone via an intraperitoneal route and found that it is effective in preventing PONV.[165-167] The clinical applicability of such technique is unclear.

DOPAMINE RECEPTOR ANTAGONISTS

Amisulpride

Amisulpride, originally developed as an antipsychotic oral medication, is a D2, D3 antagonist.[168] An IV formulation was recently approved for PONV. While amisulpride 5 mg was more effective vs. placebo (complete response, nausea severity (**A2**),[169,170] amisulpride 1 and 2 mg were not (**A3**).[169] As PONV treatment rescue in prophylaxis naïve patients, amisulpride 5 and 10 mg were more effective than placebo (**A3**).[171] However, for PONV treatment, the amisulpride 10 mg dose was more effective than 5 mg in patients who had prior PONV prophylaxis with a non-antidopaminergic agent (**A3**).[172] While amisulpride was associated with a mild increase in the level of prolactin, the clinical significance is not clear. For the PONV dose, amisulpride is unlikely to cause QTc prolongation or extrapyramidal side effects.[169-174]

In a safety analysis of ECGs for QTc effects, Fox et al[175] reported that amisulpride 10 mg IV, given alone or in combination with ondansetron did not have a clinically significant effect on the QTc interval. In addition, a single preoperative oral dose of amisulpride 25 mg, given two hours before craniotomy for intercranial tumor surgery decreased the incidence and severity of PONV in patients with no adverse effects.[176]

Droperidol

For PONV prophylaxis, the recommended dose of droperidol is 0.625–1.25 mg (**A1**),[177,178] and optimal timing is the end of surgery (**A1**).[178] Meta-analyses support its efficacy,[16,179] specifically related to vomiting.[16] For patients having bimaxillary surgery, droperidol 0.3-1 mg had equal efficacy as granisetron 1.0 mg; however, both were less effective than a droperidol and granisetron combination.[180]

The FDA issued a black box warning in 2001 restricting the use of droperidol due to the risk of sudden cardiac death.[181] However, at the doses used for PONV, droperidol's QT prolongation potential is similar to ondansetron.[182,183] When ondansetron is used in combination with droperidol, the risk of QT prolongation is comparable to either drug alone.[184] A large retrospective PONV prophylaxis study found that patients who received droperidol 0.625 mg had no increase in the risk of ventricular tachycardia.[185] The risk of akathisia is also comparable between ondansetron 4 mg, droperidol 0.625 mg, and droperidol 1.25 mg.[186]

Retrospective studies of droperidol use in morphine IV patient controlled analgesia support its PONV efficacy,[187,188] without significant adverse events,[187] and a low rate (0.9%) of adverse events such as extrapyramidal effects (**B1**).[188] However, a NMA demonstrated low to very low confidence in adverse event and droperidol was associated with decreased severe and overall adverse events (**A1**).[16] Doses less than 1 mg have been found effective.[189] Even though there may be a dose related cause for adverse effects, a dose of 0.625 mg was recommended by the panel.

In a SR of antiemetic use after failed prophylaxis, droperidol 1-1.25 mg had equal efficacy as ondansetron 4-8 mg and both were better than propofol. Sedation was a main side effect occurring in 25% of patients who received droperidol.[190]

Haloperidol

After droperidol's FDA black box warning, haloperidol's use in PONV increased.[191] For PONV prophylaxis, haloperidol 0.5–2 mg IV has been found effective. Efficacy and side effects (QT prolongation) are comparable with the 5-HT3 receptor antagonists (**A1**).[192,193] Given after anesthesia induction, haloperidol 1 mg had efficacy and side-effects comparable to droperidol 0.625 mg.[194] For PONV prophylaxis, haloperidol 2 mg at anesthesia induction or end of surgery did not change its 24 hour effectiveness.[195] For PONV treatment, haloperidol 1 mg had comparable complete response rate to ondansetron 4 mg at the 4- and 24-hour post surgery, but with more sedation.[196]

For PONV prophylaxis after laparoscopic abdominal hysterectomy, a dose ranging study of haloperidol 0.35, 0.5, 1.0 and 2.0 mg showed effectiveness at all doses except the 0.35 mg dose. No QTc effects, neurologic or extrapyramidal symptoms were observed.[197] Haloperidol 5 mg was found comparable to metoclopramide 10 mg, dexmedetomidine 25 mcg, and ginger for prevention of PONV in laparoscopic cholecystectomy surgery.[198] To decrease postoperative nausea, haloperidol 1 mg was more effective than 5 mg dexamethasone, with no difference in the POV risk.[199]

Metoclopramide

As a monotherapy for PONV prophylaxis, 10 mg of metoclopramide has shown efficacy (A1).[200] However, metoclopramide conferred no additional PONV prevention when used in addition to dexamethasone.[201] In combination with dexamethasone 8 mg, one study showed that metoclopramide 25 or 50 mg (not 10 mg) showed efficacy, but the higher doses were associated with a small increase in extrapyramidal side effects.[200] In addition, for PONV prophylaxis through 24 hours, a meta-analysis demonstrated metoclopramide to be significantly inferior to dexamethasone, droperidol, and droperidol/metoclopramide (**A1**).[179]

In cesarean delivery under spinal anesthesia, if administered after cord clamping, metoclopramide provided faster onset of intraoperative antiemetic efficacy than dexamethasone.[202] Alternately, compared to metoclopramide, further studies reported that other antiemetics (ondansetron, dexamethasone, glycopyrrolate) were more effective as single-agent prophylaxis.[203-205] While metoclopramide may be an alternate choice when other dopamine antagonists are not available, it is not recommended for PONV prophylaxis.

NEUROKININ-1 RECEPTOR ANTAGONISTS

Aprepitant

Aprepitant is a neurokinin-1 (NK-1) receptor antagonist with a half-life of approximately 40 hours, available in oral and parenteral (aprepitant & fosaprepitant) forms (**A1**).[2] Aponvie®, a polysorbate 80–free injectable aprepitant, is the most recently released NK-1 receptor antagonist agent for intravenous use and is the only NK-1 IV formulation with the FDA indication for PONV prophylaxis. The drug is available in a 32 mg dose and administered as a 30-second IV injection. The IV aprepitant is bioequivalent to the oral form of aprepitant but each in a different dosage form (IV vs. oral). The IV formulation has a quicker onset of action than the oral formulation and 97% of receptor occupancy is achieved within 5 min of administration.[206,207]

Previous work has demonstrated greater efficacy of all dosages (40, 80, and 125 mg) in vomiting over nausea.[2] Previous work has also demonstrated similar or improved PONV prevention efficacy of 40 and 80 mg doses of aprepitant and 150 mg dose of fosaprepitant compared to 5-HT_3 receptor antagonists.[2] In recent years, there has been an increased focus on 80 mg dosing, likely due to availability in particular geographic regions, but there is absence of direct head to head comparisons of 40 mg to 80 mg.[2]

Meta-analyses found that aprepitant alone[208] or added to a multimodal regimen,[209] significantly reduced the risk of PONV. An NMA also supports a high certainty benefit over placebo. Additionally, the analysis found a single neurokinin-1 receptor antagonist was as effective as some combination therapy for prevention of POV (**A1**).[16]

Multiple randomized trials found that aprepitant is comparable or superior to ondansetron for PONV prophylaxis.[210-214] A meta-analysis concluded that aprepitant (40 and 80 mg) is more effective for POV prevention compared to 5-HT_3 receptor antagonists.[215] There is limited evidence suggesting that aprepitant is comparable to ramosetron[211] and palonosetron in efficacy.[216] In a retrospective study, patients who received fosaprepitant (75 mg IV preoperatively with 75 mg after 24 hours) required less antiemetic rescue than patients who received a multimodal prophylactic regimen (scopolamine patch, intraoperative dexamethasone, ondansetron and promethazine).[217] Another meta-analysis of several regimens reported fosaprepitant (150 mg) as the most effective prophylaxis related to vomiting in the first 48 hours, and may be even more effective when combined with dexamethasone.[218] (**A1**)

Rolapitant

Rolapitant is a long-acting, NK-1 receptor antagonist which may be effective in PDNV because of its half-life of 180 hours.[2] A NMA demonstrated with very low certainty an uncertain benefit of rolapitant over placebo.[16]

Vestipitant

Previous work demonstrated possible efficacy for PONV similar to other NK-1 receptor antagonists (**A3**).[2]

Casopitant

Casopitant is being removed from recommendations secondary to lack of widespread global availability.

ANTIHISTAMINES

A 2002 SRMA of 18 trials with 3,045 patients reported that dimenhydrinate was effective for PONV prophylaxis. The optimal dose, time of administration, and side-effect profile when used for PONV prophylaxis are however unclear (**A1**).[219] Side effects associated with the use of dimenhydrinate include drowsiness/ sedation,[220,221] dizziness,[118] headache[221] and dry mouth.[220]

De Oliveira et al. reported that after ambulatory gynecologic surgery, diphenhydramine 50 mg but not 25 mg, reduced the risk of PONV compared to placebo, this was associated with improved quality of recovery.[222] In patients undergoing ear, nose and throat surgery, 30 mg of diphenhydramine significantly reduced the risk of PONV and need for rescue analgesia in the recovery room compared to placebo.[223] Similarly, when combined with ondansetron in patients undergoing laparoscopic sleeve surgery, preinduction 0.4 mg/kg of diphenhydramine reduced the risk of PONV, pain scores and analgesic rescue compared with ondansetron alone (**A2**).[224] Drowsiness and sedation are the main side effects reported with the use of diphenhydramine.[224]

There is limited data investigating the antiemetic efficacy of promethazine. Higher doses of promethazine (12.5-50 mg) are effective as monotherapy[225] or as a part of multimodal regimen, but their use was also associated with greater sedation which delayed mobilization.[226]

Lower doses of promethazine are effective for both the prophylaxis and treatment of PONV. In women undergoing abdominal hysterectomy, promethazine 0.1 mg/kg before induction or at the end of surgery reduced the risk of nausea, vomiting and need for rescue, compared to placebo.[227] Promethazine-granisetron combination resulted in higher complete response rate than promethazine alone.[157] Promethazine is also effective for the rescue treatment of established PONV,[228] with the 6.25 mg dose being as effective as higher doses and associated with less sedation.[229,230] This dose has also been reported to be significantly more effective than metoclopramide 10 mg for the treatment of PONV in PACU.[231] Side effects associated with promethazine include drowsiness/sedation, and potential for skin necrosis with IV extravasation, particularly at high concentrations.

ANTICHOLINERGICS

Transdermal scopolamine reduces the risk of PONV in PACU and for 24 hours after surgery. The onset of action is 2-4 hours following its transdermal application, and with a duration of effect of 72 hours, it can be applied on the day of surgery or the night before surgery.[232,233] There is some evidence that scopolamine may reduce intraoperative nausea in women having regional anesthesia for cesarean section.[234] It is generally well tolerated with the most common side effects reported being visual disturbances, dry mouth, and dizziness (**A1**).[232,233] Recent evidence suggests that transdermal scopolamine may increase the risk of postoperative urinary retention, especially following urogynecologic procedures.[235,236] In this patient population, other antiemetics option may be considered to reduce the incidence of urinary retention (**A3**).

DEXMEDETOMIDINE

Systemic α2 agonists (clonidine or dexmedetomidine) administration decreases the risk of PONV (**A1**).[237] The reduction in the risk of PONV has been demonstrated in various surgical procedures including laparoscopic cholecystectomy,[238,239] thoracic surgery,[240] gynecological surgery,[241] bariatric surgery[242,243] and strabismus surgery.[244] The use of dexmedetomidine has however been associated with increased risk of bradycardia[238,245] and hypotension.[237,238,243] Interestingly, dexmedetomidine was associated with reduced risk of oculocardiac reflex following strabismus surgery.[244] When added to a PCA regimen with opioids, dexmedetomidine was associated with a reduction in opioid consumption, pain scores, PONV and pruritus (**A1**).[246] When compared with remifentanil infusion for controlled hypotension, dexmedetomidine was associated with less pain, PONV and shivering in PACU (**A1**).[247]

In patients undergoing laparoscopic cholecystectomy, dexmedetomidine 1 μg/kg before skin incision was comparable to dexamethasone 8 mg for PONV prevention, while also reduced postoperative pain.[87] The combination of intraoperative dexmedetomidine and lidocaine infusions reduced PONV risk, postoperative pain and improved postoperative quality of recovery following laparoscopic hysterectomy, but this was at the expense of increased risk of sedation and bradycardia and prolongation of the duration of PACU stay.[248,249]

EPHEDRINE

When given towards the end of surgery, ephedrine 0.5 mg/kg IM was more effective than placebo and as effective as droperidol 0.04 mg/kg IM for PONV prophylaxis.[250,251] In one study the antiemetic effect was confined to the early postoperative period (3 hours).[251] Another study suggested that IM ephedrine 0.5 mg/kg is less effective than dexmedetomidine or dexamethasone for the prophylaxis against PONV.[252] When administered IM before reversal of neuromuscular blockade, 30 mg IM ephedrine was found to be more effective than a 15 mg dose for PONV prophylaxis in patients undergoing laparoscopic tubal ligation (**A2**).[253]

OLANZAPINE

Olanzapine is an atypical antipsychotic drug that is used for the prophylaxis against chemotherapy-induced nausea and vomiting (CINV). It acts as an antagonist on dopaminergic, serotonergic and histaminergic receptors. When combined with ondansetron and dexamethasone, the addition of 10 mg olanzapine decreased the risk of PONV in the first 24h by 60% after ambulatory surgery [254] and by 59% in patients at high-risk for PONV and a history of CINV undergoing cancer surgery.[255] The reduction in the risk of PONV was confirmed in a meta-analysis involving 4 studies, which reported 49% reduction with doses of 10 mg.[256]

BENZODIAZEPINES

A recent meta-analysis of 119 RCTs reported with moderate certainty of evidence that the use of benzodiazepines was associated with a 33% reduction in the risk of PONV, 28% reduction in the risk of nausea and 26% reduction in the risk of vomiting.[257] The meta-analysis could not however assess optimal dosing and time of administration or whether there are differences in antiemetic efficacy between the different benzodiazepines (**A1**). Given the risk of sedation, the panel does not recommend the use of benzodiazepines solely for the indication of PONV prophylaxis.

NON-PHARMACOLOGICAL OPTIONS

Aromatherapy

A Cochrane SR with 16 studies (n=1036) reported that, overall, aromatherapy reduced the need for rescue antiemetics but the incidence or severity of nausea, with low to very low quality of evidence. Peppermint aromatherapy did not reduce the severity of nausea (low level of evidence). When compared to a standard antiemetic, isopropyl alcohol inhalation, reduced the time to 50% reduction in nausea scores, and reduced the need for rescue antiemetics with no difference in patient satisfaction between the groups (moderate level of evidence). On the other hand, there was no difference in the need for rescue antiemetics between isopropyl alcohol inhalation and placebo.[258] A recent SR involving thirteen RCTs (11 in PACU, 8 treatment, 3 prophylaxis, and 3 in the emergency department, n=1253) concluded that the evidence for the use of isopropyl alcohol for PONV is low and more large studies are needed to evaluate its effectiveness.[259] A recent study reported that lemon aromatherapy started the morning of surgery was effective for reducing the frequency and severity of PONV as well as the need for rescue antiemetics (**A3**).[260] More studies are needed to confirm those findings.

Ginger

Ginger might have benefit for PONV prophylaxis but data regarding the benefits of ginger are inconsistent. Further well-designed studies are needed to outline several use considerations including dose, frequency, and efficacy in various populations.[261,262]

Acupoint stimulation

A Cochrane review including 59 trials with 7,667 subjects reported a significant reduction in the risk of nausea, vomiting, and the need for rescue antiemetics with the 6th point of the pericardial meridian (PC6) stimulation compared with sham (**A1**). PC6 stimulation was also as effective as other antiemetics for PONV prophylaxis. Timing of stimulation (before or after induction of anesthesia) did not impact antiemetic efficacy. [263] The reduction in the risk of PONV with acupoint stimulation has also been associated with improved quality of recovery after surgery.[264] Application of the neuromuscular function electrodes over the median nerve is effective in reducing the incidence of early PONV, especially when tetanic stimulation is used.[265]

Chewing Gum

Chewing gum has been investigated for both the prophylaxis and treatment for PONV. When used for treating established PONV, a small pilot study suggested that chewing gum was non-inferior to ondansetron following laparoscopic or breast surgery (**A3**).[266] On the other hand, chewing gum does not appear to be an effective modality for prophylaxis,[267,268] but large well-designed studies are needed (**A2**).

COMBINATION THERAPY

Since the last Consensus Guideline, there has been an exponential increase in the number of antiemetic combinations reported in the literature (table 2). The panel continues to recommend the use of general multimodal PONV prevention in adults. There is robust evidence that appropriate use of combination therapy is likely to be more effective than monotherapy[269-292]. However, not all combination therapies have demonstrated superiority when compared to their individual component drugs.

A NMA by Weibel et al reviewed an extensive number of monotherapy and combination options for the prevention of PONV. This analysis has facilitated indirect comparisons between combination therapies and their respective component drugs.[16] Based on the primary outcome of 24-hour POV, options which demonstrated superiority over at least one constituent antiemetic included NK-1 receptor antagonist plus 5-HT_3 receptor antagonist, NK-1 receptor antagonist plus dexamethasone, and 5-HT_3 antagonists plus dexamethasone.

The combination of 5-HT_3 antagonists and dexamethasone remains the most well-studied combination for PONV prophylaxis.[16,293] An earlier meta-analysis of 17 studies and 1,402 participants reported that combination prophylaxis resulted in significantly less PONV and rescue antiemetic requirements.[286] Subgroup analysis according to individual drugs showed that ondansetron and palonosetron demonstrated significant reduction in PONV (**A1**). This result was followed by a subsequent meta-analysis evaluating the efficacy of dexamethasone in addition to palonosetron. The pooled data from 12 RCTs demonstrated a marginal, albeit statistically significant reduction in rescue antiemetic requirements.[294] Palonosetron is also effective when used in combination with methylprednisolone.[295] Tropisetron in addition to dexamethasone was effective in reducing PONV in both thyroidectomy and gynecological procedures (**A2**).[296,297] As covered in the 2020 guideline, ramosetron is also effective in combination with dexamethasone (**A2**).[279,283]

The previous guideline supported the use of aprepitant in combination with 5-HT_3 antagonists. The NMA on PONV prevention reported that aprepitant was effective when used in addition to ondansetron, ramosetron, and palonosetron (**A1**).[16] The same study also reported that aprepitant is effective in addition to dexamethasone (**A1**).[16] A SRMA evaluated the efficacy of aprepitant in combination with other antiemetics; in a subgroup analysis of 3 studies, the addition of aprepitant 80 mg to ondansetron, dexamethasone, and propofol TIVA resulted in significantly lower incidence of PONV.[209] Similarly, fosaprepitant is also effective when used in addition to other antiemetics.[298] The panel notes that while several recent studies administered 80 mg aprepitant,[299,300] the FDA currently recommends 40 mg for the PONV prevention. However, this formulation is not uniformly available worldwide.

The previous guideline cited an RCT of 1,147 patients, which reported that amisulpride in addition to ondansetron or dexamethasone resulted in lower PONV and rescue antiemetic than ondansetron or dexamethasone monotherapy.[173] A more recent study reported that PO amisulpride before surgery in addition to ondansetron resulted in significantly less rescue antiemetic requirement (**A2**).[176] Neither study reported any cases of extrapyramidal side effects associated with amisulpride use.

Olanzapine has a relatively long half-life and appears to be promising for preventing PDNV.[254] Two recent RCTs reported that 10 mg PO olanzapine, in addition to ondansetron and dexamethasone significantly reduced PONV.[254,255] The most common side effect is sedation, while transient visual changes have also been reported.[254] Neither trial reported any cases of extrapyramidal side effects.

The NMA on PONV prevention reported that haloperidol is effective when used in addition to ondansetron (**A1**).[16] Two recent RCTs of patients with moderate PONV risk undergoing gynecological procedures reported that droperidol in addition to dexamethasone is effective for reducing PONV (**A2**).[296,301] As reported in the prior guideline, droperidol is effective when used in combination with ondansetron,[302] granisetron, [303] and palonosetron.[304] Haloperidol is effective when used in combination with dexamethasone (**A2**)[275,284] and midazolam (**A2**).[270,274]

The recommendation regarding antihistamines as a part of combination therapy remains largely unchanged. Betahistine is effective when added to ondansetron (**A2**).[273,282] Dexamethasone 8 mg plus dimenhydrinate 1mg/kg was more effective than dexamethasone 8 mg plus ondansetron 4 mg (**A3**) in a small RCT of rhinoplasty patients.[305] A recent RCT of patients undergoing sleeve gastrectomy reported that diphenhydramine in addition to ondansetron was effective in reducing PONV (**A3**).[224]

In a SRMA by Grant et al, midazolam is effective when used in addition to other antiemetics (**A1**). The authors reported that lower (<0.05 mg/kg) doses of midazolam are as effective for PONV and may minimize side effects.[306] A NMA of PONV prevention strategies after cholecystectomy reported that droperidol in addition to midazolam resulted in higher complete response rate when compared to midazolam alone (**A1**).[179] On the other hand, two RCTs evaluated the efficacy of 0.05 mg/kg midazolam in addition to 0.075 mg palonosetron and reported that the addition of midazolam was not effective in reducing PONV.[307,308]

Combination therapy with more than two agents was a relatively novel research topic at the time of the last guideline. Since then, there have been several studies that introduced a third or a fourth antiemetic and demonstrated clinical benefits. Aprepitant 40 mg PO before surgery as a fourth prophylactic intervention (in addition to ondansetron, dexamethasone and propofol TIVA) significantly reduced the incidence of PONV.[209] Olanzapine 10 mg PO before surgery in addition to ondansetron 8 mg and dexamethasone 8 mg also resulted in lower PONV incidence[254,255]. Haloperidol in addition to ondansetron and dexamethasone was more effective than promethazine plus ondansetron and dexamethasone.[309] In an RCT of patients undergoing sleeve gastrectomy, patients received ondansetron plus dexamethasone, with or without aprepitant 80 mg, scopolamine patch, and propofol TIVA. The combination of the 5 antiemetic interventions resulted in significantly lower PONV severity, but it is not clear whether the three additional interventions all contributed to the clinical benefit.[300] More research is required on the efficacy of adding a third or fourth antiemetic in high-risk patients.

Since the last consensus guideline, there has been an exponential increase in the number of different antiemetic combinations reported within the literature. However, not all combination antiemetic studies adequately addressed the question of whether the additional antiemetic led to clinical benefit (for example, combination of antiemetics A+B compared to monotherapy with antiemetic C). While these comparisons may reflect changes in practice for specific clinical scenarios, they offer limited insight into the efficacy of the additional antiemetic. A list of experimental combinations tested in clinical trials are summarized in SDC table S5. Experimental evaluation of antiemetics used in conjunction with risk reduction interventions are summarized in SDC table S6.

The NMA by Weibel et al indicate that some antiemetic combinations may be more effective than others in preventing PONV (e.g. aprepitant + palonosetron is more effective than dexamethasone + metoclopramide).[16] While it does not contain every possible antiemetic combination, their findings provide an evidence-based approach to designing combination antiemetic regimens beyond using agents from a different pharmacologic class.[310] As discussed in the previous guideline, there are currently limited data regarding whether antiemetics could be administered at lower doses when used as a part of multimodal prophylaxis. On the other hand, several clinical trials administered antiemetics at doses higher than the current recommendation, e.g. aprepitant 80 mg vs. 40 mg, droperidol 1-1.25 mg vs. 0.625 mg, and tropisetron 5-10 mg vs. 2 mg.[285,296,299-302,311]

Lastly, several studies have reported the use of nonpharmacological interventions as part of combination therapies.[312] Needle acupuncture at PC6 reduces 24-hour PONV when used in addition to ondansetron and dexamethasone.[313] Electrostimulation of PC6 and ST36 acupoints reduced PONV and antiemetic requirement when used in addition to multimodal pharmaco-prophylaxis with tropisetron and dexamethasone.[314,315] Electroacupuncture at PC6 and ST36 is also effective when used in addition to dexamethasone, 5-HT_3 antagonists and propofol TIVA.[316] Two prior meta-analyses concluded that while acupoint stimulation is effective when used in addition to pharmacological prophylaxis, the quality of evidence is low due to study limitations and heterogeneity.[317,318] In an RCT of patients undergoing laparoscopic surgery, aromatherapy with isopropyl alcohol before surgery in addition to intraoperative ondansetron did not significantly reduce the risk of PONV.[319]

GUIDELINE 4. PROVIDE ANTIEMETIC TREATMENT TO PATIENTS WITH PONV WHO DID NOT RECEIVE PROPHYLAXIS OR WHEN PROPHYLAXIS FAILED

In the review of the literature in adults since the 2020 Consensus Guidelines, the recommendation remains unchanged for rescue antiemetics. The panel continues to recommend patients should receive antiemetic treatment from a different agent and/or pharmacological class to the PONV administered prophylactic agents. Redosing agents of the same class does not provide a benefit. If more than 6 hours has elapsed, administration of a second dose of a 5-HT_3 receptor antagonist or butyrophenone may be considered if no alternatives are available.[1,2,320-322] We propose an algorithmic approach to risk assessment, mitigation, PONV prophylaxis and rescue treatment (figure 2).

Antiemetics such as aprepitant, fosaprepitant, and palonosetron, have a prolonged action and clinicians should avoid re-dosing these agents in the recovery area.[154,323,324] If the anesthesia professional is considering a second dose of a long-acting agent, they should follow package insert information on redosing. The drug effect/duration for dexamethasone for the prevention of PONV is unclear and assumed to have a longer duration of action. Dexamethasone is used in combination with other antiemetics for prevention and is not commonly repeated as treatment therapy for breakthrough PONV.[325] Transdermal scopolamine is another long-acting antiemetic that would typically not be used in the recovery area since the onset of action is approximately 2-4 hours and breakthrough PONV should be treated with agents that have quick/immediate onset of action for patient comfort. [326] A new IV injection formulation of aprepitant (Aponvie®) provides an alternative to oral aprepitant for treatment of PONV in the PACU, though no specific rescue study has been performed.

There is inadequate published evidence on PONV rescue treatment. The lack of evidence presents a challenge in developing evidence-based guidelines or recommendations on the optimal agent, dose, route, tolerability, and safety profile.[327]

Because of the lack of RCTs, higher-grade evidence, and current studies with today's practices and medications, it may be tempting to assume that drugs which are effective for PONV prophylaxis would also be effective for rescue treatment. This may not be the best approach but it is the option used by frontline anesthesia professionals without more research in this area.[190]

A recent SR focused on PONV rescue treatments after failed prophylaxis or no prophylaxis. Forty-five RCTs were included.[190]

For the treatment of PONV in antiemetic naive patients, the review found:[190]

- Dose adjustments may not be needed when treating breakthrough PONV with the 5-HT_3 receptor antagonists above the doses used for prophylaxis.
- Newer 5-HT_3 agents did not show improved efficacy over ondansetron. (**A3**, moderate certainty)
- Droperidol 1 to 1.25 mg has comparable efficacy as ondansetron at the recommended dose of 4 to 8 mg, (**A3**, low certainty)
- Droperidol was found to be more effective than dexamethasone 8 mg and metoclopramide 10 mg (**A3**, low certainty)
- Metoclopramide 10 mg is significantly less effective than ondansetron and droperidol (**A2**, moderate certainty).
- Propofol 20-40 mg is effective as treatment for PONV (**A3**, low certainty)

The more important findings of the review were from trials where prophylaxis was given but failed.

The studies indicate:[190]

- For patients failing ondansetron prophylaxis, redosing with ondansetron or other 5-HT_3 antagonists did not provide further benefits (**A3**, low certainty)
- Promethazine 6.25 mg and higher shows to be more effective in patients who failed ondansetron prophylaxis over the redosing of ondansetron (**B1**, low certainty).
- For promethazine, there is not an apparent dose response in the range of 6.25-25 mg, hence the lowest dose is recommended.
- The higher doses of promethazine in this range have been associated with sedation.

POST-DISCHARGE NAUSEA AND VOMITING

Post-discharge nausea and vomiting (PDNV) presents a significant risk to discharged postoperative patients who no longer have access to fast onset IV antiemetics or direct care after being discharged from the hospital or medical facility. The management of PDNV can be categorized into extended prophylaxis and extended treatment.

A study of 2,170 US outpatients reported the incidence of PDNV to be 37% in the first 48 hours after discharge and identified five independent predictors of PDNV: female gender, age <50 years, history of PONV, opioid use in the PACU, and nausea in the PACU.[50] Validation of a simplified PDNV risk score based on these risk factors found that the incidence of PDNV with 0, 1, 2, 3, 4, or 5 of these risk factors to be about 7%, 20%, 28%, 53%, 60%, and 89%, respectively (figure 1b).

Extended Prophylaxis

Extended nausea and vomiting prophylaxis is essential to the prevention of PDNV. Options for extended prophylaxis include single-dose long-acting antiemetics, or post-discharge oral antiemetics.

In the first RCT, Hyman et al[254] report that olanzapine PO 10 mg combined with ondansetron and dexamethasone decreased the risk of 24-hour PDNV by approximately 60%, as compared to placebo, after discharge from ambulatory surgery. However, there was a slight increase in sedation (**A3**).

Another RCT found that ramosetron 0.1 mg orally disintegrating tablets (ODT) significantly reduced the incidence and severity of 24-hour PDNV in female patients undergoing ambulatory surgery (**A3**).[328] ODT may be a valuable option for the management of PDNV after ambulatory surgery.

The administration of palonosetron, a long-acting antiemetic, significantly reduced the incidence of PDNV and use of rescue antiemetics on POD 1 and 2, when compared to placebo. [329] Palonosetron arm also had significantly lower incidence of PDNV and use of rescue antiemetics on POD 1 and 2. However, palonosetron did not reduce total incidence of PDNV in the first two postoperative days. Palonosetron may be beneficial for patients at high risk for PDNV, although further investigation is needed (**A3**).[329,330] In summary, patients at high risk of PDNV should be given prophylactic, long acting antiemetics before discharge (**B1**).[51]

GUIDELINE 5. POSTOPERATIVE NAUSEA AND VOMITING IN PEDIATRIC PATIENTS – RISK PREDICTION, MITIGATION, AND PROPHYLAXIS

In the pediatric literature, POV and PONV are considered distinct entities. POV is a more objective outcome, where the subjective assessment of nausea is more difficult. Moreover, risk assessment for POV/PONV in pediatric patients differs from that in the adult population. Predictive models for PONV developed in adults, such as the Apfel score, are poorly suited to pediatric POV, exhibiting low discriminating power and inconsistent calibration.[331]

Since the publication of the previous guidelines, no new pediatric-specific risk models for POV/PONV have been developed. Currently, two general models exist: the Vomiting in the Postoperative Period (VPOP) score (figure 3a) [332] and the Postoperative Vomiting in Children (POVOC) score (figure 3b).[333] Both models show modest discriminating ability in internal validation. However, predicted risk values for POV differ across these two scores, particularly as each increase towards its maximum.

While the discriminating capabilities of both the POVOC and VPOP scores are only modest, they are comparable to that of the most widely used adult models, such as the simplified Apfel score and Koivuranta score.[334] Beyond the risk factors identified by these two models, other factors have been recognized, including post-pubertal female status, use of anticholinesterases, and the use of volatile anesthetics (compared to TIVA).[2] Although using validated multivariable models such as POVOC and VPOP for risk prediction is the ideal approach, the age of these models and potential significance of additional risk factors justify an *ad hoc* approach to defining risk, combining elements from both scores with other risk factors through a simple additive approach (**B1**). These risk factors are outlined in figure 3. However, when employing this approach (e.g., using a non-validated prediction model), calibration and discrimination remain undefined, precluding numerical risk estimation and permitting only a relative categorization of risk.

APPROACH TO POV/PONV PREVENTION IN PEDIATRIC PATIENTS

For evidence-based prevention of POV/PONV in children, we propose a multi-step, algorithmic approach as outlined in figure 4. This begins with an assessment of baseline risk, considering both patient and procedural details, and can take the form of basic risk factor summation in the absence of new robust multivariable prediction models. This assessment is then used to define the relative level of risk for each patient, which in turn determines the approach to: (1) baseline risk mitigation (SDC table S7) and (2) administration of prophylactic agents (table 3). For patients without clear risk factors, we recommend using one prophylactic antiemetic agent, unless otherwise contraindicated, given the similar rates of POV seen in these patients compared to those with one risk factor (figure 3). Patients with 1-2 risk factors should receive combination prophylactic therapy with two agents, most commonly ondansetron and dexamethasone. Higher risk patients (3+ risk factors) should receive at least two-agent combination prophylactic therapy. Given the lack of sufficient evidence for addition of a third agent in these patients, attention should instead be focused on sufficient risk mitigation techniques.

RISK MITIGATION

Total Intravenous Anesthesia (TIVA)

No new studies have examined the effects of propofol-based TIVA on POV/PONV since publication of the previous guidelines. Two previous meta-analyses found that TIVA reduces POV and PONV rates compared to inhalational anesthesia with single-agent prophylaxis[335] or inhalational anesthesia alone (**A1**, SDC table S7).[336] Two smaller studies—one retrospective and one prospective randomized—suggest a protective role for subhypnotic propofol during volatile agent maintenance, with doses ranging from <100 mcg/kg/min to 20 mcg/kg/min (**A3**).[337,338] Therefore, if full TIVA is not feasible, a subhypnotic infusion of propofol may serve as a risk mitigating strategy (**A3**).

Fluid Therapy and Dextrose Loading

Traditionally, “liberal” fluid therapy has been regarded as protective against POV/PONV in children, a view supported by small RCTs comparing different fluid administration methods.[339] A meta-analysis consolidating these trials evaluated “liberal” versus “standard” fluid therapy, finding that “liberal” fluid therapy reduced POV and PONV.[340] Notably, though, there was substantial heterogeneity across trials with respect to the definition of both liberal and control groups. An earlier Cochrane meta-analysis[341] similarly found that, compared to adults, intravenous crystalloids in pediatric patients were somewhat effective in lowering the risk of POV but were less effective in reducing the need for pharmacological treatment for PONV. This evidence base suggests that adequate hydration is protective in pediatric patients, although the optimal regimen remains unclear (**A1**).

Carbohydrate loading and dextrose therapy were investigated in three heterogeneous randomized trials. One trial found that a carbohydrate drink two hours prior to induction did not reduce the rate of POV when compared to a similar volume of flavored water.[342] A second study found administration of a carbohydrate drink reduced gastric content volume and PONV when compared to a standard fasting protocol.[343] This study did *not* use a sham pre-operative drink, and thus the control group was allowed *ad lib* PO intake based on fasting guidelines. The discrepant findings across these studies may be due to the difference in volume and not a true protective effect of carbohydrates (**C2**). A third trial examined the use of intraoperative 5% dextrose maintenance fluids combined with dexamethasone compared to dual-agent prophylaxis (ondansetron and dexamethasone), finding a non-statistically significant *increase* in POV in the dextrose group.[344] Based on these findings, intraoperative dextrose-containing fluids, when combined with dexamethasone, is not protective against PONV when compared to dual-agent prophylaxis (**A3**). Finally, one small RCT indicates that early oral fluid intake in the post-anesthesia care unit (PACU) is preferable to restrictive intake for reducing opioid requirement and PONV (**A3**).[345]

Neuraxial and Regional Anesthesia

The efficacy of neuraxial and regional anesthesia as opioid-minimizing strategies for perioperative pain management and their role in PONV prevention remain challenging to evaluate due to underreporting and the lack of PONV as the primary outcome focus on most studies. We encountered several meta-analyses comparing various neuraxial and regional techniques to conventional care, yet these studies show wide variation in protocols and sometimes produce contradictory outcomes. In a comprehensive NMA of inguinal hernia repairs, specific regional and neuraxial methods, such as the transversus abdominis plane block, quadratus lumborum block, and caudal block, were more effective than systemic opioid administration in preventing PONV, albeit their advantage over local wound infiltration was uncertain.[346] Two additional meta-analyses reported conflicting findings: a reduction in PONV with the use of erector spinae plane blocks and no benefit of serratus anterior plane blocks.[347,348] Overall, while regional and neuraxial anesthesia offer varying degrees of protection against PONV, the adoption of these approaches as part of a risk mitigation strategy should be tailored to the type of surgical intervention and individual patient factors (**C1**).

Adjuvant Therapies

A recent meta-analysis found a protective effect of lidocaine against POV, but not PONV, with the overall quality of evidence rated as 'very low'.[349] Importantly, the trials not finding a reduction in PONV utilized a single lidocaine bolus, in contrast to one of the trials reporting POV prevention using both a bolus and a continuous infusion. These observations align with subsequent research indicating a lidocaine bolus followed by an infusion may decrease POV, though this regimen's superiority to monotherapy with agents like dexamethasone is not definitive (**C1**).[350]

Two randomized studies have demonstrated that intravenous acetaminophen decreases PONV rates in pediatric patients undergoing strabismus surgery, although its effect outside the strabismus surgery demographic remains to be established (**A2**).[351,352]

Alpha-2 agonists (clonidine and dexmedetomidine) have been studied as risk mitigating interventions for PONV in children. Premedication with intranasal dexmedetomidine reduces PONV rates compared to intranasal midazolam or clonidine (**A1**).[353] In meta-analytic data, intravenous dexmedetomidine (0.25 to 1 mcg/kg) reduces both PONV and risk for the oculocardiac reflex during strabismus procedures (**A1**).[354] Oral clonidine pre-medication (4 mcg/kg) is also effective compared to placebo and oral midazolam; an effect not observed at lower (2 mcg/kg) doses (**A1**).[355] Notably, these studies predominantly involve strabismus surgery and their effectiveness beyond this specific population warrants further exploration.

Miscellaneous Factors

Since the release of the previous guidelines a limited number of studies appraising additional risk reduction strategies have been published. A randomized study investigating the influence of intraoperative fractional inspired oxygen (FiO2) found that varying levels of FiO2—80% compared to 30%—did not result in differences in PONV.[356] A small RCT assessed the timing of fentanyl administration and its effect on PONV following adenotonsillectomy and found no difference when fentanyl was given 10-15 minutes prior to, versus at the conclusion of, the procedure[357]. The benefit of hypopharyngeal packing during adenotonsillectomy was examined in a recent randomized trial in pediatric patients with obstructive sleep apnea,[358] finding a negligible difference in PONV rate. In summary, based on available evidence, intraoperative FiO2 levels, timing of intraoperative opioid administration, and use of hypopharyngeal packing do not appear to have a major impact on PONV in the pediatric population (**C2**).

PROPHYLACTIC ANTIEMETICS: AN ALGORITHMIC PERSPECTIVE

Historical guidelines have favored a risk-tailored iterative approach for prophylactic antiemetic administration, adjusting the number of agents prescribed based on the patient's baseline risk. However, studies highlight that clinicians' adherence to risk-based adjustments in PONV prophylaxis is suboptimal.[359] Moreover, recent findings indicate low-risk patients appear to benefit from prophylaxis that aligns with guideline recommendations, while high-risk patients do not show improvement from additional prophylactic measures.[360] This is underlined by the fact that major pediatric risk prediction models show a negligible difference in the predicted risk for POV between patients with zero and one risk factors (9% and 5% versus 10% and 6%, respectively), and the lack of robust evidence for prophylactic regimens with greater than two pharmacologic agents. The absence of pragmatic RCT makes it difficult to establish an optimal algorithmic prophylaxis approach in pediatric settings. Nevertheless, given the existing data and the favorable safety profiles of widely researched agents such as ondansetron and dexamethasone, we advocate for a blended strategy. For pediatric patients without risk factors, the use of a single prophylactic agent (preferably ondansetron or dexamethasone) is recommended, while escalating to a two-agent regimen (typically combining ondansetron and dexamethasone) is advisable for patients with one or two risk factors. For patients presenting with three or more risk factors, the current evidence does not conclusively favor the routine addition of a third agent. In these high-risk scenarios, emphasis should be placed on modifying baseline risk factors through various interventions (such as elimination of nitrous oxide, use of propofol-based total intravenous anesthesia, administration of local and regional anesthesia techniques, incorporation of multimodal analgesia, and minimization of opioid use).

PROPHYLACTIC ANTIEMETIC AGENTS

Propofol

Evidence supporting the role of propofol as an antiemetic and risk mitigation strategy is outlined in the risk mitigation section.

5-HT$_3$ Receptor Antagonists:

The effectiveness and safety of 5-HT$_3$ receptor antagonists, particularly ondansetron (0.05 mg/kg to 0.1 mg/kg) in children are well established (**A1**, table 3).[2] Regarding QTc prolongation concerns, a study comparing ondansetron (0.2 mg/kg) to dexamethasone (0.1 mg/kg) in children receiving cochlear implants found significant PONV reduction without notable QTc changes, although caution continues to be advised in patients with existing cardiac conduction issues.[361]

Dexamethasone:

Dexamethasone (0.1-0.5 mg/kg) is a highly effective antiemetic in pediatric patients (**A1**), with meta-analyses confirming its superiority over placebo. Although a dose-response relationship was qualitatively observed in one such study, no significant dose-based subgroup differences were statistically significant.[362] This finding is consistent with several retrospective and randomized trials across varied surgeries.[363-367] The recommended dose of dexamethasone for PONV prophylaxis in children is 0.15 mg/kg up to 4 mg.

NK1 Receptor Antagonists:

Updated pharmacokinetic data on weight-based dosing of aprepitant in pediatric patients suffering CINV, indicate adolescent plasma concentrations are akin to those observed in adults on fixed-dose regimens (**A3**).[368] Robust efficacy data for POV/PONV are limited in this population, however, and should be the subject of future investigation.

COMBINATION THERAPY:

Combination therapy in pediatric patients is often superior to single agent prophylaxis (table 3). The evidence for such superiority is particularly strong for dexamethasone with ondansetron (**A1**), and more limited for other combinations such as dexamethasone with tropisetron, and ondansetron with droperidol (**A3**).[2] However, dexamethasone and droperidol are noted to be less effective than a dexamethasone and ondansetron pairing.[369] In high-risk pediatric groups (3+ risk factors), a single retrospective study suggests a benefit when adding a third agent (scopolamine or diphenhydramine) to ondansetron and dexamethasone.[370] This finding from a retrospective analysis using historical controls necessitates cautious interpretation, further evidence on three agent regimens is necessary.

NON-PHARMACOLOGIC INTERVENTIONS

A recent SRMA[371] assessed the efficacy of acupuncture and acupressure, particularly at acupoint PC6, for reducing PONV in pediatric patients. This review found evidence for a benefit in early POV, albeit with high heterogeneity and moderate to very-low evidence quality. Additional single center trials[372] and case series[373] have investigated acupuncture in pediatric patients, with some evidence for early improvement in PONV. Overall, evidence appears to suggest acupuncture, particularly at PC6, may provide relief from early PONV in pediatric patients (**A1**).

Aromatherapy, using substances like isopropyl alcohol and peppermint oil, has garnered interest as a non-invasive prophylactic measure against PONV. A Cochrane review[258] reported a tentative benefit of aromatherapy, though evidence is of low to moderate quality.

GUIDELINE 6. ENSURE MULTIMODAL PONV PREVENTION AND TIMELY RESCUE TREATMENT ARE IMPLEMENTED IN THE CLINICAL SETTING

ECONOMICS OF PONV MANAGEMENT

Cost containment policy in the hospital environment has typically focused upon drug acquisition cost and the cost of an undesirable outcome should the drug not be used. There are, however, additional considerations when assessing the cost effectiveness. Values to consider include clinical outcomes, quality (patient safety, experience of care), patient-reported outcomes (quality of life, functional outcomes), and operational efficiency (personnel/space/operational outcomes), while additional costs includes resources and personel.[374] The authors go on to discuss enabling principles which include efficient deployment of resources, having a culture of safety and appropriate patient selection and perioperative risk stratification. Hirsch additionally suggested that in addition to analyzing the typical health care system direct, indirect and opportunity costs we should also evaluate costs from the patient perspective.[375] These include direct costs (cost of additional visits) and indirect costs (lost income and caregiver costs).[376]

Jotwani et. al. analyzed the cost of racial disparities in perioperative care. They found a 15% reduced antiemetic prophylaxis in Black vs. non-Black patients. They found an increase in direct and indirect costs as a result of this disparity.[62] Not all countries have the resources to routinely administer PONV prophylaxis. Fentie et al described that 37.6% of health professionals in Ethiopian referral hospitals practiced prophylaxis based on availability and cost of the medications.[377]

Providers do not always know the costs involved with administering various anti-emetics. Mehallow and team investigated departmental cost-awareness and likelihood to consider cost for PONV medications. Presentation of data to their department increased the likelihood for the providers to consider acquisition costs of PONV medications. No evidence was provided that this intervention changed provider practices or patient outcomes.[378]

There are also many low-cost non-pharmacologic therapies to prevent and treat PONV, e.g. herbals, mindfulness and acupuncture. Although their impact on PONV may be small and clinically modest in many cases, it can be more meaningful in other cases. Mindfulness for patients undergoing surgery may be a cost-effective and potentially underrated tool for improving outcomes.[198,379] Many studies have demonstrated that enhanced recovery pathways lead to a reduction in PONV rates and cost of care.[380-382] These evidence-based examples of PONV prophylaxis as part of ERAS lead to decreased costs of care. The direct impact of PONV reduction on the length of stay is not discussed: PONV prophylaxis forms an important part of many ERAS interventions.

PONV is associated with poorer postoperative quality of life and is associated with both institutional and patient costs. More studies are needed to examine cost economic benefits associated with rescue treatment for PONV.

GUIDELINE 7. INCLUSION OF MULTIMODAL PROPHYLACTIC ANTIEMETICSAS ENHANCED RECOVERY ELEMENTS

Enhanced recovery protocols provide multimodal approaches to minimize the stresses of surgery with the aim of improving recovery, decreasing complication rates, and shortening the length of hospital stays. Enhanced recovery pathways (ERPs) do not exist in a vacuum but rather span a continuum of various elements, starting from preoperative counseling and carbohydrate loading to intraoperative components such as euvolemia, normothermia, multimodal analgesia, adjunct peripheral nerve blocks to postoperative considerations such as early mobilization and removal of drains.[383]

Multimodal PONV prophylaxis constitutes a major cornerstone of enhanced recovery protocols, with risk mitigating interventions such as the use of propofol-based TIVA, adequate hydration, opioid-sparing analgesia, and regional anesthesia.[384] Management of ERP patients should include at least two antiemetics for PONV prophylaxis and additional antiemetics as needed for patients at higher risk. Various studies have included PONV management in the context of ERP protocols. The key studies representing different surgical subspecialties are summarized in SDC table S8.

Although most studies did not investigate the impact of a specific ERP element on PONV rates and there was a variability in ERP protocols, the implementation of ERPs appears to play a prominent role in minimizing PONV. It is the panel's consensus that risk mitigation, prophylaxis, and treatment are important components of ERPs.

RESEARCH AGENDA FOR PONV

Table 4 summarizes themes as basis for the future research agenda. Modern approaches to PONV started with generic ondansetron. For the first time, risk identification became actionable - clinicians had an effective, safe and cost-accessible antiemetic. We have come a long way since then, but the need for further improvement exists, for research in both knowledge and practice.

One future research area is the refinement of risk assessment. Wide inter-individual variability in PONV experience has long been observed. Genome-wide association studies have identified several candidate SNPs in Caucasian and East Asian populations.[54,385]

Inflammation also may contribute to risk for PONV, and early research suggests that elevated preoperative peripheral blood neutrophil/lymphocyte ratios may be markers for individual risk.[34]

Further investigations of the genetic and internal environment predispositions to PONV could personalize preventive strategies, particularly in ethnicities not yet studied. The developing field of pharmacogenomics in relation to antiemetic efficacy is of equal clinical interest.

There is yet a paucity of research on PONV risk and management in special patient populations, including children, pregnant patients, and patients having cesarean delivery.

There is rising incidence of obesity, bariatric surgery worldwide; and a recent dramatic increase in the use of glucagon-like peptide 1 (GLP-1) receptor agonists. How these factors influence PONV risk assessment and treatment is not yet clearly understood.

The current armamentarium of antiemetic drugs provides a solid approach to reduce PONV for most patients. Further research could look to enhance efficacy and reduce side effects. The NK-1 receptor antagonist class is of particular interest, because of high efficacy and reasonable duration, as well as potential anxiolytic, antidepressant and antipruritic effects.[386,387]

A combination drug of long acting netupitant with palonosetron is approved in the US for CINV. Research in combination or co-administration of drugs for PONV indications should be done, focusing on the synergistic effects of different antiemetic classes, while monitoring clinical and drug-interaction (CYP450) side effects.

Non-pharmacological interventions to prevent or treat PONV hold perennial appeal because of their perceived lack of toxicity and low cost. Research is needed to validate those assumptions and to further explore the efficacy of non-pharmacological interventions such as herbal medicine, acupuncture, acupressure, and transcutaneous electrical nerve stimulation, particularly in combination with pharmacologic approaches.[388]

Research on aromatherapy has shown low efficacy for PONV, but further research could focus on the effects of isopropyl alcohol sniffs, which have shown limited but positive effects (distinct from the essential oils aromatherapy e.g., peppermint). Isopropyl alcohol's possible immediate but short-term effects could be investigated in combination with slower onset pharmacologic interventions.

Future management of PONV would also benefit from the integration of novel technology. System-integrated digital health solutions could potentially predict, monitor, and manage PONV. Personal digital health solutions such as wearable devices could be utilized to provide real-time symptom tracking, direct patient engagement, and facilitate follow-up beyond the hospital stay. Artificial intelligence and machine learning are likely to be useful to assess risk and optimize patient outcomes. Also, advances in surgical technology may contribute to PONV risk reduction; our surgical colleagues should be encouraged to include PONV outcomes in their research.[389]

Future PONV research should expand to include more patient-reported outcome measures, thus better representing the impact of PONV on patient satisfaction, quality of life, and recovery. New devices and data systems may be needed to follow patients along the full trajectory of perioperative PONV care, until their return to "wellness". There is limited research to date on the economic burden of PONV to patients (and facilities). Better research to assess the efficacy of individual components of ERAS protocols is warranted.

Future PONV research will benefit from interaction with policy makers. The FDA has a guidance document on CINV: Developing Drugs for Prevention-Guidance for Industry.[390] A parallel guidance for PONV management could include data and outcomes of interest, with input from clinician experts, as well as pharmacoeconomic measures. Such a document could set the standards of PONV related research, thus growing the evidence base in a meaningful direction.

How can we encourage practitioners to embrace and implement up-to-date knowledge? This is the field of healthcare system implementation research. The most effective ways to implement evidence-based guidelines for PONV prevention and management across different healthcare settings need to be further investigated.[391-393]

The realities of resource variability must be part of implementation research. Some countries have severely limited choices in anesthetics, analgesics and antiemetics, so access to risk reductions and therapies via those pathways will necessarily be constrained. Even the well-resourced US and Europe struggle with critical drug shortages and struggle with balance in cost-effectiveness decision making.[394-396]

CONCLUSIONS

With the widespread implementation of general, multimodal PONV prophylaxis, it is now imperative to adopt evidence based antiemetic combination for prophylaxis, as well as appropriate rescue antiemetics. While there is now evidence that individual antiemetics differ in their efficacy, it is not yet clear how this translates to the efficacy of combination prophylaxis. There are robust PONV risk scores that are accurate for risk stratification at a population level, clinicians should be cognizant of additional factors which could modify individuals' PONV risks and management. There is now a growing body of literature on the management of PONV in children. As in adults, PONV management in children should follow algorithmic approach, using evidence-based interventions. The paradigm shift towards personalized medicine brings opportunities for further research in refining the approaches to PONV risk assessment and intervention algorithm. Lastly, research and institutional policy on PONV management should include considerations to the socioeconomic and equity aspects of healthcare delivery.

PROFESSIONAL SOCIETY ENDORSEMENTS

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

- American Society for Enhanced Recovery
- American Academy of Anesthesiologist Assistants
- American Association of Nurse Anesthesiology
- American Academy of Ambulatory Care Nursing (AAACN)
- American College of Clinical Pharmacy
- American Society of Health Systems Pharmacists
- American Society of Peri Anesthesia Nurses
- Australian and New Zealand College of Anesthetists
- Australian Society of Anesthetists
- Canadian Anesthesiologists' Society
- College of Anesthesiologists of Ireland
- European Society of Anesthesiology
- German Society of Anesthesiology
- Hong Kong College of Anesthesiologists
- Indian Society of Anesthesiology
- Indonesian Society of Anesthesiologists and Intensive Therapy
- Japanese Society of Anesthesiologists
- Korean Society of Anesthesiologists
- Malaysian Society of Anesthesiologists
- Royal College of Anesthesiologist Thailand
- Royal College of Anaesthetists United Kingdom
- Singapore Society of Anesthesiologists
- Society for Ambulatory Anesthesia
- Society for Pediatric Anesthesia
- South African Society of Anesthesiologists

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