


# Prevention and Treatment of Postoperative Nausea and Vomiting (PONV): A Review of Current Recommendations and Emerging Therapies

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**Abstract:** Postoperative nausea and vomiting is one of the most frequent adverse events after surgery and anesthesia. It is distressing for the patient and can lead to other post-operative complications. Management of PONV involves a framework of risk assessment, multimodal risk reduction, and prophylactic measures, as well as prompt rescue treatment. There has been a significant paradigm shift in the approach towards PONV prevention. There have also been several emerging therapeutic options for PONV prophylaxis and treatment. In this review, we will discuss the up-to-date PONV management guidelines and highlight novel therapeutic options which have emerged in the last few years.

**Keywords:** antiemetics, enhanced recovery after surgery, postoperative care, postoperative nausea and vomiting

## Introduction

Postoperative nausea and vomiting (PONV) remains one of the most common adverse events after surgery. It is distressing for patients, increases the risk of other adverse events such as readmission, and has a financial impact for the healthcare institution.<sup>1</sup> Management of PONV involves a framework of risk assessment, multimodal risk reduction, and prophylactic measures, as well as prompt rescue treatment. In this review, we aim to summarize up-to-date recommendations on PONV management, as well as the evidence on newer treatment options.

## Epidemiology and Healthcare Cost of PONV in the USA

The risk of PONV in the general surgical population is approximately 30%.<sup>2</sup> In high-risk patient groups, or high-risk surgical procedures, the risk of PONV can be as high as 80%.<sup>3</sup> PONV is a distressing experience for the patient and can have a significant impact on patient satisfaction.<sup>4,5</sup> PONV may prolong post-anesthesia care unit (PACU) stay and increase the risk of postoperative complications. Parra-Sanchez et al<sup>6</sup> conducted a prospective observational study and analyzed the healthcare resource utilization associated with PONV in the ambulatory surgical population. They found, on average, the occurrence of PONV increases the PACU

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stay by an hour and cost by 74 US dollars. PONV has also been shown to be the most common reason for unplanned readmission in bariatric patients.<sup>7</sup>

In recent years, healthcare remuneration in the United States of America (USA) has transitioned from volume-based systems to value-based systems. This means healthcare institutions are financially incentivized to provide care according to evidence based best practice, and assume financial responsibility for the occurrence of potentially avoidable complications.<sup>8</sup> In the context of PONV management, institutions are now paid under the Merit-based Incentive Payment System for administering appropriate PONV prophylaxis based on risk factors.<sup>9</sup> However, the introduction of Bundled Payments for Care Improvement means the institution will receive a fixed remuneration for a surgical procedure, regardless of any delay in discharge or readmission that occurs due to PONV.<sup>8</sup>

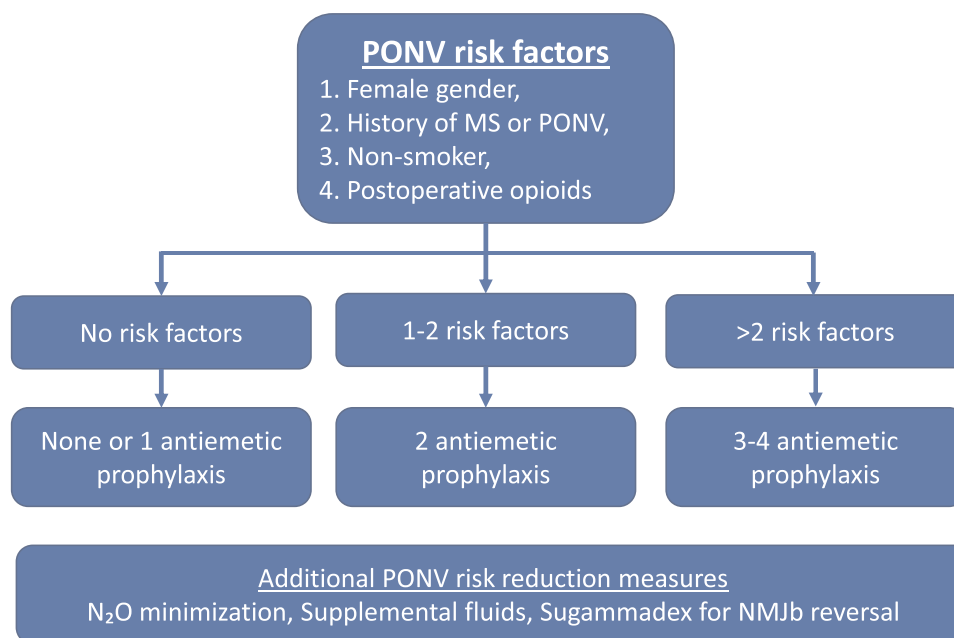
## Summary of Current Recommendations

Gan et al<sup>2</sup> have published several evidence-based guidelines on the management of PONV, based on a comprehensive literature search and the consensus of an international panel of experts. The proposed framework for PONV management involves the assessment of risk factors, risk reduction interventions, PONV prophylaxis, and rescue treatment. Patient risk factors (including female gender, non-smoker, history of PONV, or motion sickness)

could be quantified using risk scores such as the Apfel score and the Koivuranta score,<sup>3,10</sup> while surgical procedures such as laparotomy and cholecystectomy confer additional PONV risk.<sup>11</sup> Other perioperative risk factors of PONV includes the length of surgery, the use of volatile anesthesia, including nitrous oxide, as well as perioperative opioid administration.<sup>3,10,12</sup> Perioperative risk reduction interventions include multimodal, opioid sparing anesthesia, avoidance of volatile anesthetic, as well as nitrous oxide exposure. Gan et al<sup>2</sup> have extensively reviewed various options for PONV prophylaxis and rescue treatment, which includes pharmacological and non-pharmacological interventions. The authors acknowledged that currently the biggest challenge in PONV management is often low compliance to the guidelines.

## Implementation of General Multimodal Prophylaxis

There has been a paradigm shift towards the use of general multimodal prophylaxis for PONV, that is the administration of multiple antiemetics, as a standard of care (Figure 1).<sup>1,13,14</sup> This represents a significant change from the previous approach of administering none or one PONV prophylaxis in patients who are considered low risk. Reasons for this paradigm shift include: 1) PONV risk scores only provide an estimated risk stratification;<sup>3</sup> 2) patients identified as low risk may still develop PONV;<sup>3</sup> 3) PONV scores do not take



**Figure 1** Summary of the expert consensus guidelines on postoperative nausea and vomiting (PONV) management.<sup>2</sup>

**Abbreviations:** MS, motion sickness; NMJb, neuromuscular junction blocker; N<sub>2</sub>O, nitrous oxide.

into account factors such as the emetogenic risk of the surgical procedure;<sup>11</sup> and 4) anti-emetics effectiveness varies between patients.<sup>13,14</sup> Instituting multimodal prophylaxis as a standard of care also reduces the practice variability that is commonly seen in perioperative care. As there are now robust clinical data supporting the safety and efficacy of multimodal PONV prophylaxis,<sup>15</sup> this practice is now considered a standard of care.

## Novel Risk Reduction Measures

In addition to the well-known PONV risk associated with volatile inhalational agents and opioid use, recent literature has highlighted several other potentially modifiable perioperative risk factors. These are discussed below.

### Propofol

Propofol is an intravenous general anesthesia agent. Clinical trials and meta-analyses have shown that intravenous anesthesia (TIVA) with propofol is associated with significantly lower risk of PONV than volatile anesthesia.<sup>16,17</sup> On the other hand, it is not clear if propofol, when used as an induction only, is less emetogenic when compared with other intravenous agents.<sup>18,19</sup> Interestingly, sub-hypnotic doses of propofol (20–40 mg) is also effective as a rescue treatment for PONV.<sup>20,21</sup> However, this should be done with caution considering the sedative effects of propofol.

### Nitrous Oxide Sparing Anesthesia

Nitrous oxide is a gaseous anesthetic agent with mild analgesic effect. On the other hand, it is also commonly associated with PONV risk. Peyton and Wu<sup>12</sup> conducted a meta-analysis and meta-regression on the efficacy of nitrous oxide avoidance for PONV prevention; they found that the number needed to treat (NNT) in anesthesia lasting more than 2 hours was nine; whereas the NNT in anesthesia less than 1 hour is 128. This suggests that nitrous oxide avoidance may not be an effective strategy in shorter surgeries.

### Reversal of Neuromuscular Blockade with Sugammadex

Prior to the introduction of sugammadex for the reversal of amino-steroid neuromuscular blockers (NMJB), neostigmine was routinely used. Neostigmine is an acetylcholine esterase inhibitor, which has a parasympathomimetic effect on the gastrointestinal tract, such as increasing gastrointestinal motility and secretion. Cheng et al<sup>22</sup> conducted a meta-analysis of clinical trials comparing NMJB reversal with

neostigmine and those who did not receive NMJB reversal, and found while the incidence of nausea was slightly higher on the neostigmine arm with a trend towards dose correlation, neither were statistically significant.

With the introduction with sugammadex for NMJB reversal, several clinical trials and a recent Cochrane meta-analysis have investigated the effect of sugammadex vs neostigmine on PONV risk. They found that PONV risk is lower with sugammadex compared to neostigmine reversal [numbers needed to treat (NNT)=16]. The quality of evidence was deemed low due to the risk of study bias and, therefore, further research is warranted.<sup>23</sup>

### Lidocaine Infusion

Studies have demonstrated that intravenous lidocaine is an effective analgesic in several major abdominal procedures.<sup>24,25</sup> It has been proposed that the opioid sparing effect of lidocaine infusion may also result in a lower incidence of PONV. Weibel et al<sup>26</sup> conducted a recent systematic review and meta-analysis (SRMA) on the use of intravenous lidocaine and included PONV as a secondary outcome; the PONV analysis included a total of 35 studies and 1,903 patients. The authors reported that lidocaine infusion reduced the incidence of postoperative nausea, but there was no significant difference in the incidence of postoperative vomiting; there was also a significant risk of publication bias.

The meta-analysis included a range of procedures, included laparoscopic abdominal and pelvic surgeries, as well as thyroid, breast, and spinal surgeries; and did not conduct a subgroup analysis according to the procedure type. In a previous iteration of the meta-analysis, lidocaine significantly reduced the risk of PONV in patients undergoing laparoscopic abdominal procedures only.<sup>27</sup> More surgery-specific data are needed to assess if a lidocaine infusion may be beneficial in certain procedure types.

### Dexmedetomidine

Dexmedetomidine is a highly selective  $\alpha$ -2 adrenergic agonist with sedative and analgesic properties. It can be administered intravenously or as a regional anesthesia adjunct.<sup>28,29</sup> When administered intravenously, dexmedetomidine is thought to reduce postoperative pain and opioid requirement. Jin et al<sup>30</sup> conducted a meta-analysis of 24 clinical trials, and reported that single bolus and continuous infusion of dexmedetomidine both reduced the risk of PONV. As a regional anesthesia adjunct, dexmedetomidine have been shown to prolong the duration of analgesia, which may translate to an opioid-sparing effect.<sup>31</sup>

## Supplemental Fluids

It has been suggested that perioperative fluid status is an important risk factor for the development of PONV. The role of preoperative carbohydrate solution is currently unclear. Awad et al<sup>32</sup> conducted a meta-analysis which included abdominal, thyroid, and cardiac surgeries, and found limited evidence that preoperative carbohydrate alters the risk of PONV. A more recent meta-analysis by Xu et al<sup>33</sup> looking into laparoscopic cholecystectomy reported that carbohydrate beverage before surgery was associated with significantly lower risk of postoperative vomiting.

Intraoperative fluid administration may affect the risk of PONV. A recent Cochrane review found that a 10–30 mL/kg intraoperative crystalloids infusion significantly reduces the risk of both early and late PONV and the need for rescue antiemetics.<sup>34</sup> Due to the heterogeneity of the surgical procedures included, there was no consensus on the optimal volume of intravenous fluid administration. Colloid solutions (such as hydroxyethyl starch) contain macromolecules which are thought to remain in the intravascular component for a longer period of time. A recent meta-analysis by Kim et al<sup>35</sup> reported that, compared to fluid supplementation with crystalloids, colloids significantly reduced the risk of PONV in longer surgeries (>3 hours) when compared to shorter surgeries (<3 hours).

## Opioid Free Anesthesia/Analgesia

With the advances in regional anesthesia techniques and non-opioid analgesia options, several authors have discussed the feasibility of opioid free anesthesia or analgesia.<sup>36,37</sup> While the two terms are often used interchangeably, the American Society for Enhanced Recovery and Perioperative Quality Initiative joint consensus defined opioid free anesthesia as “the absolute avoidance of opioids from induction of anesthesia until complete emergence”; and opioid free analgesia as “the absolute avoidance of opioids in the pre and postoperative periods”.<sup>38</sup> Avoidance of opioids in the perioperative period eliminates the risk of any opioid related adverse events, this includes PONV, as well as respiratory depression and ileus.<sup>39</sup> Bakan et al<sup>40</sup> conducted a clinical trial of patients undergoing laparoscopic cholecystectomy, and compared propofol/remifentanyl anesthesia to propofol/lidocaine/dexmedetomidine anesthesia, and reported that the latter technique had significantly lower PONV and pain. It should be noted, however, that fentanyl PCA was

used for postoperative pain control. Hakim and Wahba<sup>41</sup> conducted a similar study, and found that propofol/dexmedetomidine anesthesia was associated with significantly less antiemetic requirement than propofol/fentanyl anesthesia. Again, this did not eliminate the need for postoperative opioid (tramadol) analgesia. Opioid-free postoperative analgesia is also possible with the use of regional anesthesia, Becchi et al<sup>42</sup> conducted a clinical trial comparing the use of continuous Psoas compartment block for postoperative analgesia to continuous morphine infusion, and reported that the opioid free continuous block was associated with comparable analgesia but significantly less PONV. As the study did not employ a placebo catheter technique, patients and clinicians were not blinded. It is worth noting that opioid free anesthesia and analgesia are only suitable in selected patient/surgery combinations, and often rely on the use of regional anesthesia. The benefit of absolute opioid avoidance will need to be balanced with issues such as risk of block failure and undesired motor block. In addition, most available literature did not compare opioid free anesthesia/analgesia to an opioid sparing approach. In their consensus statement, the American Society for Enhanced Recovery and Perioperative Quality Initiative concluded that there is limited evidence that an opioid free approach is superior to an opioid minimizing approach.<sup>38</sup> As such, the routine adoption of opioid free anesthesia/analgesia require further studies.

## Novel Chemoprophylaxis

The combination of ondansetron and dexamethasone is one of the most studied and utilized multimodal PONV prophylaxis.<sup>15</sup> In recent years, evidence has emerged for novel therapeutic options for PONV prophylaxis, as summarized below.

### Palonosetron

Palonosetron is a second generation 5-HT<sub>3</sub> receptor antagonist, first licensed in 2003, for use in acute and delayed chemotherapy-induced nausea and vomiting. It is only available as a solution for intravenous administration. Palonosetron has 100-fold higher affinity to the 5-HT<sub>3</sub> receptor, when compared to ondansetron, and a terminal half-life of 40 hours, which is ten-times longer than ondansetron.<sup>43</sup> It has been postulated that palonosetron causes irreversible, allosteric inhibition of the 5-HT<sub>3</sub> receptor,<sup>44</sup> and receptor internalization.<sup>45</sup>

Candiotti et al<sup>46</sup> and Kovac et al<sup>47</sup> reported in moderate-to-high risk female patients undergoing high risk surgeries that 0.075 mg palonosetron prophylaxis was associated with a significantly lower incidence of PONV for 72 hours after surgery.

Palonosetron monotherapy for PONV prophylaxis is more effective than other 5-HT<sub>3</sub> antagonists, including ondansetron, granisetron, ramosetron,<sup>48–50</sup> it is also more effective than dexamethasone.<sup>51,52</sup> Palonosetron has comparable efficacy to aprepitant.<sup>53</sup>

Palonosetron has additional advantages in ambulatory surgeries. Post-discharge nausea and vomiting is a common complication after ambulatory surgeries, and often patients will not have access to rescue anti-emetics. The long duration of action means that intraoperative palonosetron may reduce the risk of nausea and vomiting for an extended period of time after surgery, and patients are less likely to experience post-discharge nausea and vomiting.<sup>47</sup>

One of the factors which likely limited the use of palonosetron was its cost. However, since 2018, generic versions of palonosetron have been approved for use by the FDA. This will likely make palonosetron more cost-effective.

## Aprepitant

Aprepitant is a competitive Neurokinin (NK)-1 receptor antagonist which was also initially approved for the treatment of chemotherapy-induced nausea and vomiting. It is administered orally, although an intravenous equivalent is also available, in the form of a pro-drug Fosaprepitant. It has a half-life of 9–13 hours,<sup>54</sup> and it has been suggested that its duration of action may be as long as 40 hours.<sup>55</sup> Fosaprepitant is approved only for chemotherapy-induced nausea and vomiting.

Singh et al<sup>56</sup> conducted a meta-analysis, and included trials of various design, including aprepitant compared to placebo, and aprepitant compared to other anti-emetics as a part of multimodal prophylaxis. While they concluded that 40–125 mg aprepitant had significantly lower incidence of vomiting on both postoperative days 1 and 2, the clinical significance of the findings are not clear when considering the heterogeneity in study design.

As a single agent prophylaxis, 40 mg aprepitant has similar efficacy as 0.075 mg palonosetron.<sup>53</sup> Clinical trials and meta-analyses have reported that aprepitant is more effective in preventing PONV when compared to ondansetron.<sup>57,58</sup>

Similar to palonosetron, the aprepitant is also shown to be beneficial in ambulatory surgery due to its long duration of action and lower risk of postdischarge nausea and vomiting. Vallejo et al<sup>59</sup> conducted a clinical trial of 150 patients with moderate-to-high risk undergoing ambulatory plastic surgery, and found that aprepitant plus ondansetron was associated with significantly lower incidence of postdischarge nausea and vomiting than ondansetron alone.

## Amisulpride

Amisulpride is a dopamine receptors antagonist. While initially licensed as an antipsychotic, in February 2020 the FDA approved its IV formulation for prophylactic and rescue therapy of PONV. The anti-emetic dose for prophylaxis is 5 mg IV, 10 mg IV for rescue treatment, whereas its antipsychotic dose is 50–1,200 mg/day orally.

Several clinical trials have reported that, when compared to placebo, amisulpride significantly reduces the incidence of PONV as well as rescue anti-emetic requirement.<sup>60,61</sup> In addition, at the dosage used for PONV prophylaxis, amisulpride is not associated with significant risk of prolonged QT interval or extrapyramidal side-effects.<sup>61</sup> There are currently limited head to head studies comparing amisulpride to other anti-emetics.

## Midazolam

Midazolam is a short acting benzodiazepine primarily used as an anxiolytic premedication. Meta-analysis showed that midazolam administration at induction reduces the risk of PONV,<sup>62</sup> the efficacy is comparable to ondansetron prophylaxis.<sup>63,64</sup> Again, it is not recommended to use midazolam solely for its antiemetic effect due to the risk of sedation.

## Acupressure/Acupuncture

Pericardium 6 (PC6) is an acupoint located on the palmar aspect of the forearm, between the palmaris longus and flexor carpi radialis tendons, approximately 6 cm proximal to the wrist. Clinical trials and a Cochrane review have concluded that stimulation of the acupoint with a variety of instruments (including needle acupuncture, acupressure devices, nerve stimulator, electrical stimulation needles, and laser) are effective in reducing the risk of PONV and antiemetic requirement.<sup>65</sup> Trial sequential analysis indicates that currently data has exceeded the information required for moderate strength evidence (defined as type 1 error of <5%, power at >80%).

The study also investigated the use of PC6 stimulation in combination with pharmacoprophylaxis (ondansetron, droperidol, or ondansetron plus dexamethasone), compared to pharmacoprophylaxis alone. The addition of PC6 stimulation was associated with lower risk of vomiting and rescue anti-emetic requirement. However, the reliability of the findings were limited by the heterogeneity of the included studies.<sup>65</sup>

Several other acupoints have also been investigated for PONV prophylaxis. Large intestine 4 (LI4) is an acupoint on the dorsal aspect of the hand between the first and second metacarpal. In an RCT of patients undergoing high emetogenic surgeries, acupuncture at the LI4 point in addition to PC6 point significantly reduced the incidence of PONV compared to PC6 acupuncture alone.<sup>66</sup> Stomach 36 (ST36) is another acupoint infero-lateral to the tibial tuberosity. A RCT of patients undergoing laparoscopic surgeries, bilateral ST36 acupoint injection of vitamin B1 was associated with significantly lower incidence of PONV.<sup>67</sup>

## Use of Novel Therapy as Part of a Multimodal Prophylaxis Regimen

With the implementation of the general multimodal prophylaxis, the pressing clinical question is whether the novel therapies are effective when used in combination with other prophylactic agents. While it is well established that multimodal prophylaxis is more effective than monotherapy, questions remain as to what the margin of gain from each additional antiemetic is.<sup>15</sup>

As a NK-1 receptor antagonist, aprepitant can be used in combination with 5-HT<sub>3</sub> antagonists as well as other antiemetics. Vallejo et al<sup>59</sup> conducted a clinical trial of 150 patients with moderate-to-high risk undergoing ambulatory plastic surgery, and found that aprepitant plus ondansetron was associated with significantly lower incidence and severity of PONV than ondansetron alone. Similarly, Lee et al<sup>68</sup> conducted a clinical trial of 84 female patients with low-to-moderate risk undergoing gynecological surgeries, and found that aprepitant plus ramosetron was associated with significantly lower incidence and severity of PONV than ramosetron alone.

On the other hand, Yoo et al<sup>69</sup> conducted a clinical trial of 100 moderate risk female patients undergoing moderate-to-high risk surgeries, and reported that aprepitant plus palonosetron did not significantly reduce the incidence of PONV or the rescue anti-emetic requirement when compared to

palonosetron alone. One possible explanation is that, as palonosetron is intrinsically more effective than the other 5-HT<sub>3</sub> antagonists, the marginal gain of adding aprepitant is diminished.

Aprepitant could also be used in combination with dexamethasone. While Aprepitant monotherapy is more effective than ondansetron, its benefit as a part of the combination therapy is unclear. Habib et al<sup>70</sup> conducted a clinical trial of 104 low-to-moderate risk patients undergoing craniotomy, and reported that aprepitant plus dexamethasone significantly reduced the incidence of PONV compared to ondansetron plus dexamethasone. On the other hand, Bilgen et al<sup>71</sup> conducted a clinical trial of 67 moderate-to-high risk patients undergoing laparoscopic surgeries, and reported that aprepitant plus dexamethasone did not significantly reduce the incidence of PONV or the rescue anti-emetic requirement when compared to ondansetron and dexamethasone.

In addition, there is limited evidence that aprepitant is effective as a third additional agent. Holder-Murray et al<sup>72</sup> conducted a clinical trial of 498 patients with low-to-moderate PONV risk undergoing colorectal surgeries, and found that when used in addition to ondansetron and dexamethasone prophylaxis, aprepitant did not significantly reduce the incidence of PONV or the rescue antiemetic requirement when compared to perphenazine. Bergese et al<sup>73</sup> conducted a clinical trial of 95 patients with low-to-moderate PONV risk undergoing craniotomy, and found that when used in addition to dexamethasone and promethazine prophylaxis, aprepitant did not significantly reduce the incidence of PONV or the rescue antiemetic requirement when compared to ondansetron.

The diminished return associated with multimodal prophylaxis regimens is also seen with palonosetron. While multimodal prophylaxis 5-HT<sub>3</sub> antagonist and dexamethasone is used extensively in clinical practice, the efficacy of palonosetron plus dexamethasone combination is unclear. Two clinical trials have reported that palonosetron plus dexamethasone prophylaxis was associated with lower risk of PONV.<sup>74,75</sup> Most other clinical trials reported trends favoring the combination prophylaxis, but the results were not statistically significant.<sup>76-81</sup>

While palonosetron monotherapy is more effective than other 5-HT<sub>3</sub> antagonists, the advantage of palonosetron as a part of the multimodal prophylaxis is also not clear. Choi et al<sup>82</sup> conducted a clinical trial of 88 female patients with moderate-to-high PONV risk undergoing laparoscopic cholecystectomy, and found that palonosetron

plus aprepitant was associated with significantly lower risk of PONV than ramosetron plus aprepitant. On the other hand, several studies have compared the efficacy of palonosetron plus dexamethasone to ondansetron plus dexamethasone, while the results appear to favor palonosetron plus dexamethasone, and the difference was not statistically significant.<sup>83–88</sup>

In summary, while the novel therapies are more effective as monotherapy, it appears that the benefit is diminished when used as a part of multimodal prophylaxis regimens. In their consensus guidelines, Gan et al<sup>2</sup> suggested that the use of multimodal prophylaxis may allow for a lower dose of the individual anti-emetics, thereby further reducing the risk of adverse reactions. This is an area which requires further study.

## Novel Rescue Treatment

In patients with established PONV (with or without prior PONV prophylaxis), common rescue treatment includes ondansetron, promethazine, and droperidol.<sup>89–91</sup> Several additional rescue treatments have been proposed, as summarized below.

Palonosetron administration resulted in a higher rate of PONV resolution when compared to placebo.<sup>92</sup> In patients who received ondansetron prophylaxis, administration of palonosetron resulted in complete response in 25% of the patients, this was not significantly different from administration of additional ondansetron dose as rescue.<sup>93</sup> Hence, we do not recommend redosing of 5-HT<sub>3</sub> receptor antagonists if a previous dose was administered within 6 hours.

Intravenous vestipitant is also an effective rescue treatment for established PONV. In patients who developed PONV despite ondansetron prophylaxis, rescue IV vestipitant resulted in a comparable complete response rate to IV ondansetron, and significantly lower incidence of further vomiting episodes.<sup>94</sup>

Amisulpride may also be effective for treating established PONV. In patients who did not receive PONV prophylaxis, 5 mg (and 10 mg) amisulpride resulted in a significantly higher complete response rate compared to placebo.<sup>64</sup> A further multicenter study reported that, compared to placebo, 5 mg amisulpride resulted in a significantly lower rate of further vomiting episode; however, the overall complete response rate was not statistically different.<sup>95</sup> Hence, a 10 mg dose is recommended.

PC6 acupoint stimulation may also be effective as a rescue treatment for PONV. Coloma et al<sup>96</sup> conducted

a clinical trial of moderate risk patients undergoing laparoscopic surgeries, who developed PONV despite droperidol or metoclopramide prophylaxis. Electrical stimulation of PC6 resulted in a comparable complete response rate to ondansetron rescue, and addition of PC6 acu-stimulation to ondansetron rescue resulted in a significantly better complete response rate.

A wide range of aromatherapy treatments have been proposed for the treatment of PONV, including peppermint, ginger, isopropyl alcohol, and various aromatherapy blends. Hines et al<sup>97</sup> conducted a Cochrane review on the use of aromatherapy, and reported that isopropyl alcohol reduced the duration as well as the severity of nausea. No benefits were observed with aromatherapy blends. Another meta-analysis by Tóth et al<sup>98</sup> investigated the use of ginger for the treatment of PONV, that ginger aromatherapy was associated with slightly reduced nausea severity. Further studies are warranted.

## Application of PONV Guidelines to Enhanced Recovery Pathways

PONV management is becoming an increasingly integral aspect of enhanced recovery pathways. This is reflected in the American Society for Enhanced Recovery (ASER) Expert Opinion Statement that all patients should receive PONV prophylaxis during the perioperative period. The numbers of medications used for treatment and prophylaxis should be determined by the number of modifiable and non-modifiable risk factors; medications used should be from different pharmacological classes, with different mechanisms of action, in an attempt to achieve multimodal benefit.<sup>99</sup> The approach to managing PONV as part of the enhanced recovery pathway is similar to the multimodal approach discussed above, and should include measures to reduce baseline emetogenic risks, and the use of general multimodal prophylaxis with at least two agents. In patients who develop PONV, prompt rescue treatment should be started.<sup>100</sup> The specific components can vary between different surgeries due to factors such as the emetogenic risk of the surgical procedure, special anesthesia considerations (such as in neurosurgery), viability of regional anesthesia techniques, as well as any special considerations for postoperative recovery.

In colorectal surgeries, postoperative pain can be significant, which is associated with high opioid requirement; in addition, postoperative ileus is also a common adverse event. Postoperative pain can be managed effectively

through the use of techniques such as epidural analgesia, transverse abdominis plane (TAP) block and bupivacaine infiltration. Postoperative ileus risk can be managed using minimally invasive surgical technique whenever possible, as well as maintaining euvoemia and early mobilization.<sup>101,102</sup> General multimodal prophylaxis for PONV is recommended in several enhanced recovery consensus guidelines.<sup>103</sup> The principles of colorectal enhanced recovery pathway could also be adapted to other abdominal or gastrointestinal procedures, such as esophageal, gastric, pancreatic, and hepatic procedures.<sup>104–106</sup>

Similar to major abdominal surgeries, major pelvic surgeries are also associated with significant emetogenic risk due to pain and ileus. The enhanced recovery guideline for radical cystectomy recommends the use of minimally invasive surgery, early oral intake, liberal use of antiemetics, chewing gum, prokinetic agents and opioid sparing analgesia to minimize PONV and postoperative ileus.<sup>107</sup> In addition, the stenting of the uretero-ileal anastomosis have also been shown to reduce the risk of PONV.<sup>108–110</sup> For gynecologic/oncologic surgery, general multimodal PONV prophylaxis is again recommended; regional interventions (e.g., TAP blocks) may decrease opioid use and postoperative pain, but this may not directly translate into a PONV advantage in all cases.<sup>111,112</sup>

For cesarean delivery, specific risk factors include neuraxial anesthesia associated hypotension, reduced cardiac output from aortocaval compression, surgical stimulation, use of uterotonics, and the use of neuraxial opioids.<sup>113</sup> PONV risk reducing measures specific to cesarean delivery include intravenous fluid loading, lower limb compression stocking, and the use of phenylephrine and ephedrine to prevent hypotension, and should be administered in addition to general multimodal PONV prophylaxis.<sup>113</sup>

In orthopedic surgery, pain is the main postoperative adverse event and can result in high opioid requirement. Effective analgesic techniques are available for most procedures, including spinal anesthesia, peripheral nerve block, and liposomal bupivacaine infiltration for the joint capsule.<sup>114</sup> General multimodal PONV prophylaxis is again recommended.<sup>115</sup> In a prospective before-and-after study, introduction of standardized multimodal, opioid sparing analgesia, and general PONV prophylaxis significantly decreased the risk PONV.<sup>116</sup>

Similarly in breast surgeries, effective postoperative analgesia techniques including paravertebral block (PVB) or pectoral nerves block (PECs) can reduce the risk of

PONV;<sup>117–119</sup> and should be used in addition to nonopioid analgesia and multimodal PONV prophylaxis.<sup>120–122</sup>

Head and neck surgeries are considered high risk for the development of PONV, and a recent clinical trial has demonstrated that preoperative assessment and multimodal prophylaxis are effective in reducing the risk of PONV.<sup>123</sup> A expert consensus statement on enhanced recovery for head and neck surgeries also supported the use of multimodal PONV prophylaxis.<sup>124</sup>

Enhanced recovery pathways for several other surgical procedures have also included general multimodal PONV prophylaxis as part of their PONV management component.<sup>125–127</sup> It could therefore be summarized that multimodal PONV prophylaxis is applicable to most enhanced recovery pathways; while surgery specific considerations include the emetogenicity of the procedure, risk of postoperative ileus, applicability of regional anesthesia techniques, and whether PONV is associated with any procedure specific risks (such as with neurosurgical procedures).

## Conclusions

In recent years, the approach to PONV management has shifted from administering none or one PONV prophylaxis to low risk patients to administering multimodal PONV prophylaxis as a standard of care. The introduction of novel therapies will allow for a greater number of prophylaxis and rescue anti-emetic combinations. There are also emerging evidence for several non-pharmacological risk management strategies, such as the minimizing fasting time, use of supplemental IV fluids and acupressure/acupuncture. As such, there is a greater number of potential therapeutic options for PONV than ever before. However, the efficacy of the different therapy combinations will require further studies.

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