



# Ondansetron for postoperative nausea and vomiting

*Ira Todd Cohen*

*Children's National Medical Center, George Washington University, Washington, DC, USA*

*Tel.: +1 202 884 2025*

*Fax: +1 202 884 5999*

*icohen@cnmc.org*

Postoperative nausea and vomiting, both early onset and delayed, continues to be a major concern of patients and practitioners. Postoperative nausea and vomiting is recognized as a debilitating and potentially dangerous occurrence during the recovery period. Extensive studies of the serotonin subtype 5-hydroxytryptamine<sub>3</sub> receptor antagonist ondansetron have demonstrated efficacy and safety in all age groups. Ondansetron has been shown to be most effective in preventing early postoperative vomiting in high-risk populations. Nausea and delayed postoperative nausea and vomiting are more effectively treated by combination therapies. Further understanding of patient-to-patient variability in the metabolism of ondansetron and the interaction of the different receptors in the nausea–vomiting neuroendocrine pathway may eventually greatly decrease the incidence of postoperative nausea and vomiting.

Postoperative nausea and vomiting (PONV) is a well recognized adverse outcome of anesthesia and surgery. It is one of the most common adverse events experienced by children and adults during the recovery period. In patient interviews and surveys, PONV has been repeatedly ranked higher than all other postoperative concerns, including pain [1,2]. Unrelieved symptoms have been described as disconcerting, distressing and debilitating. Persistent vomiting may result in prolonged recovery room stays, unanticipated hospital admissions, dehydration, electrolyte abnormalities, recurrence of surgical bleeding and increased risk of pulmonary aspiration [3]. The dissatisfaction and economic impact arising from these problems have been documented extensively [4,5]. When hypothetically given the choice, children and adults are both willing to tolerate some degree of pain rather than experience PONV [6,7].

Although vomiting poses greater risks, the discomfort and immobility frequently associated with nausea should not be minimized [8]. These symptoms, when lasting beyond the immediate postoperative period, can result in extended lengths of recovery and delayed resumption of work, school and other daily activities. Prolonged recovery can lead to an increase in concurrent surgical morbidity and decrease in return to preoperative levels of function.

## Physiology

Vomiting is characterized by the expulsion of gastric contents into the pharynx and mouth. Retching is described as having the same muscular

activity as vomiting without the expulsion of matter. Vomiting and retching can arise from multiple etiologies involving a complex series of humoral and neurological interactions stimulating a nucleus of cells in the medulla, referred to as the emesis center [9]. Neurotransmitters and receptors involved in this process include dopamine (D<sub>2</sub>), acetylcholine (M<sub>1</sub>), histamine (H<sub>1</sub>), endorphins ( $\sigma$ ), serotonin (5-hydroxytryptamine [5-HT]<sub>3</sub>) and neurokinin (NK)<sub>1</sub> [10]. The receptors are found in high concentration in the emesis center, chemoreceptor trigger zones (CTZs) and gastrointestinal (GI) tract. The emesis center receives input from at least four sources: the CTZ, the GI tract via the vagus, the vestibular apparatus and the cerebral cortex [11]. The CTZs, which lie in the brain stem beneath the fourth ventricle, sense chemical abnormalities in the body. Distention and inflammation of the GI tract and other internal organs stimulates the CTZs by the release of emetogenic substances into the systemic circulation and neurotransmission via the vagus. Vestibular and cerebral input may play a role in patient predisposition to PONV.

Nausea is a feeling of sickness or discomfort associated with the need or urge to vomit. The sensation is subjective and difficult to quantify or assess between different patients. Physiologically, nausea is typically associated with decreased gastric motility, intestinal hypertonia and reverse peristalsis [12]. The mechanisms and pathways, which modulate this uniquely human phenomenon, are understood poorly.

**Keywords:** 5-HT<sub>3</sub> receptor antagonists, antiemetics, ondansetron, postoperative nausea and vomiting



### Incidence & prevalence

Postoperative nausea and vomiting is defined as early (0–6 h) and delayed (6–48 h). PONV has been reported to occur in up to 27 and 70% of patients, respectively [13,14]. Premorbid conditions (history of PONV, motion sickness and obesity), anesthetic agents (opioids, anticholinesterases and nitrous oxide) and types of surgical procedures (gynecological, ophthalmological and otolaryngological) have all been implicated as causes of PONV (Box 1) [15,16].

### Guidelines

Guidelines for the prevention of PONV are based on these risk factors. Adult patients at moderate to high risk of PONV, determined by two or greater patient-specific risks and surgical procedure, should receive regional anesthesia or a 5-HT<sub>3</sub> receptor antagonist at the end of general anesthesia. Low-dose droperidol may also be considered in lieu of a 5-HT<sub>3</sub> receptor antagonist, however its side-effect profile must be taken into account [15].

Since pediatric patients are 50–75% more likely to develop PONV than their adult counterparts, factors specific to this age group are highlighted in Box 1. It is recommended that children at moderate to high risk of PONV should receive a long-acting corticosteroid after

induction and a 5-HT<sub>3</sub> receptor antagonist near the completion of general anesthesia. Droperidol is not recommended in children, secondary to the risk of extrapyramidal symptoms and high level of sedation associated with its use [15].

### Overview of the market

Prior to the introduction of 5-HT<sub>3</sub> receptor antagonists, prophylaxis and treatment of PONV was attempted with several classes of agents with limited success. Studies of anticholinergics (scopolamine) [17], antihistamines (dimenhydrinate) [18], phenothiazines (promethazine) [19], butyrophenones (droperidol) [20–22], benzamides (metoclopramide) [23] and corticosteroids (dexamethasone) [24,25] have demonstrated a wide range of responses and side effects. These medications are compared with 5-HT<sub>3</sub> receptor antagonists in Table 1. Clinical efficacy of each medication, in their standard intravenous dose, is presented as the number needed to treat (NNT), which is the number of treated subjects required to avoid a single additional adverse outcome. The NNT for early and delayed PONV is included for medications in which data are available.

Adverse drug events (ADEs) are common in these older classes of used antiemetics. In ambulatory patients, ADEs, such as sedation, dizziness and blurred vision, are of particular concern, delaying or preventing hospital discharge. Extrapyramidal symptoms can be disconcerting to patients and healthcare providers, but are typically ameliorated by intravenous administration of diphenhydramine. Prolongation of the QT interval is reported with droperidol use, and is included on the package insert as a Black Box Warning. Although prolonged QT is associated with an increased risk of developing the arrhythmia Torsade des Pointes, there are no known incidents of this phenomenon occurring with droperidol.

The incidence of PONV in high-risk patients receiving ondansetron prophylaxis (~25–30%) is clinically significant and of concern [26,27]. Treatment of breakthrough PONV with ondansetron has been studied less extensively than its prophylactic use. Analysis of existing studies has determined that follow-up doses of ondansetron are no more effective than placebo in patients with established PONV. Since repeat dosing with ondansetron is ineffective, medications with greater receptor affinity or different mechanisms of action

#### Box 1. Risk factors for postoperative nausea and vomiting [13–16].

##### Patient specific

- + Female gender
- + History of postoperative nausea and vomiting (patient and/or family)
- + History of motion sickness
- + Nonsmoker
- + Age ≥3 years\*

##### Anesthetic specific

- ± Volatile agents
- ± Nitrous oxide
- + Opioid use (postoperative administration\*)
- + Duration ≥30 min

##### Surgery specific

- + Strabismus\*
- ± Laparoscopy
- ± Gynecological
- Ear-nose-throat‡
- Plastics‡
- Laparotomy‡
- Neurosurgery‡

\*Pediatric age group-specific.

‡Nausea specific.

**Table 1. Antiemetic medications for the prevention of postoperative nausea and vomiting.**

Medication	Dose (mg/kg)	Number needed to treat			
		Early vomiting	Early nausea	Delayed vomiting	Delayed nausea
Ondansetron	0.1–0.15	2.5–4.5	7	13	
Dolasetron*	1.8	3–4	13	3–5	
Granisetron	0.02	3–5	NS		
Dexamethasone	0.5	4 (7) <sup>¶</sup>	4	4	4
Dimenhydrinate	0.5–1	8		5	
Droperidol	0.05–0.075	6 (4) <sup>¶</sup>	5	7–12	
Metoclopramide	0.15	9	13	10	12
Promethazine	0.25–0.5	7			
Propofol <sup>‡</sup>	2–3	3	3	NA	NA
Scopolamine <sup>§</sup>	NA	7	5	NA	NA
Ondansetron and dexamethasone		2.5	4	6	4

\*Metabolite is activate component.

<sup>‡</sup>Propofol versus sevoflurane for induction of anesthesia.

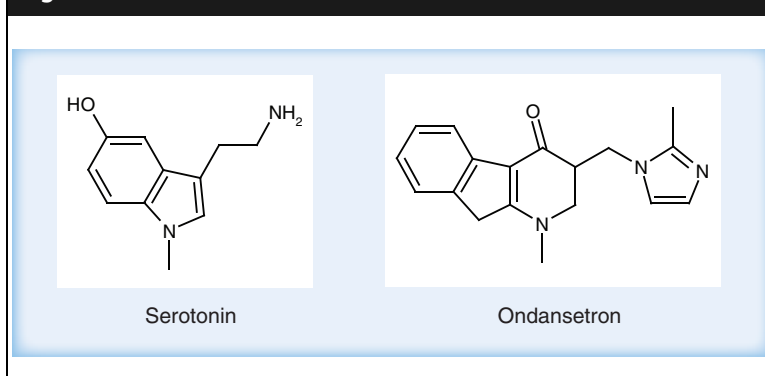
<sup>§</sup>Transdermal patch.

<sup>¶</sup>Pediatric results.

are indicated. Granisetron and promethazine have been suggested to be more effective in this setting [28,29].

### Chemical properties

Ondansetron (2, 3-dihydro-9-methyl- 3-[(2-methylimidazol-1-yl)methyl] carbazol-4) is a competitive antagonist of induced 5-HT<sub>3</sub> receptor depolarization. It has the chemical formula C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O (Figure 1) and a molecular weight of 325.9. *R*- and *S*-isomers are approximately equipotent with pKB values ranging from 8.0 to 8.7 [30]. Ondansetron has a bioavailability of 60–90%, depending on commercial formulations, which include tablet, dissolving wafer, syrup, suppository and intravenous preparations.

**Figure 1. Serotonin and ondansetron.**

### Pharmacodynamics

Pharmacodynamics are mediated by drug–receptor and receptor–cell interactions. Theoretically, activation of 5-HT<sub>3</sub> serotonin receptors leads to the opening of Na<sup>+</sup> channels, which in turn results in further release of serotonin and activation of afferent neurons [31]. Blockade of these receptors will prevent direct and indirect stimulation of vagal structures, brain stem nuclei and the CTZ, decreasing stimulation of the vomiting centers. Structural difference in known 5-HT<sub>3</sub> receptor antagonists may give rise to differences in receptor affinity and specificity. Ondansetron binds to several types of serotonin receptors, although its affinity to 5-HT<sub>3</sub> is 250–500-times greater. The relative looser binding by ondansetron may be the reason why repeat treatment for breakthrough vomiting with ondansetron is unsuccessful, while crossover treatment with granisetron is successful in establishing control of vomiting.

### Pharmacokinetics & metabolism

The pharmacokinetics of ondansetron are summarized in Table 2 [32–34]. Hepatic oxidation via the cytochrome P450 system accounts for 95% of drug metabolism. The major metabolites are 7-hydroxy and 8-hydroxyondansetron, which appear to have little pharmacodynamic activity when compared with the parent drug. Excretion of metabolites in humans is almost

**Table 2. Ondansetron pharmacokinetics by age groups.**

Parameter	Preschool 3–7 years	School age 7–12 years	Adult 18–60 years	Older adult 61–74 years	Aged adult 75–82 years
Cl (l/h/kg)	0.5	0.40	0.35	0.28	0.21
V <sub>D</sub> (l/kg)	1.7	1.61	1.81	1.94	1.71
t <sub>1/2</sub> (h)	2.6	3.10	3.50	4.50	5.50

Cl: Clearance; t<sub>1/2</sub>: Half life; V<sub>D</sub>: Volume of distribution.

Data from [33–35].

exclusively renal. Metabolism of ondansetron tends to be slower in females and older patients, accounting for slightly longer elimination times but minimal clinical effect. In patients with severe hepatic insufficiency, clearance decreases and half-life increases.

Metabolism of ondansetron can also be altered by medications that induce or inhibit the cytochrome P450 system. Cytochrome 2D6 enzyme (CYP2D6) is inhibited by the following medications: amiodarone, bupropion, chlorpheniramine, cimetidine, doxorubicin, methadone, quinidine, ranitidine, ritonavir and selective serotonin reuptake inhibitors, and is induced by dexamethasone and rifampin. Several pharmacogenetic studies have revealed a patient subpopulation that rapidly metabolizes ondansetron, negating its antiemetic action [35–37]. Ultrarapid metabolizers have been shown to have an increased number of the alleles that code for CYP2D6. Patients with three or more copies of the CYP2D6 allele experience treatment failure with ondansetron.

### Animal studies

Preclinical safety studies conducted in rats and dogs using ondansetron doses 30–100-times those used in humans demonstrated no end-organ toxicity. Only at near lethal doses did animals develop neurological signs, such as sedation, ataxia and seizures [38]. Subsequent evaluations including multiple dosing, reproductive, oncogenicity and allergy studies have confirmed the excellent safety profile of ondansetron [39].

Stables and colleagues reported the efficacy of ondansetron in reducing the incidence of cisplatin-induced vomiting in ferrets [40]. Based on the evidence that cisplatin selectively increases the levels of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) in the small intestine, they concluded that ondansetron selectively blocks 5-HT<sub>3</sub> receptors on vagal afferents. Further

investigations demonstrated the efficacy of ondansetron in reducing emesis in ferrets, dogs and rats exposed to other emetogenic agents, including cyclophosphamide, doxorubicin, radiation and morphine [41]. *In vitro*, ondansetron has been shown to interact with serotonin receptors found in the rat vagus nerve and superior cervical ganglion and in the guinea pig ileum longitudinal smooth muscle [42].

### Clinical efficacy & postmarketing surveillance

Phase I and II trials for ondansetron were performed in populations at risk of nausea and vomiting secondary to treatment with emetogenic antineoplastic medications. Since establishing the dose, effectiveness and safety profile of ondansetron in this setting, 90 randomized clinical trials and eight meta-analyses have examined ondansetron efficacy in reducing and treating PONV [20,24,29,43–47]. Clinical studies, which initially focused on the early phase of PONV, have now extended their focus to include patient data regarding delayed PONV. The safety and efficacy of ondansetron in infants aged 1–24 months has confirmed recently [48]. The effectiveness of ondansetron against nausea and delayed vomiting is enhanced, in high-risk patients and surgical procedures, when combined with long-acting corticosteroids

### Safety & tolerability

Adverse drug events associated with ondansetron compared with antiemetics (Table 3) are rare and, when reported, mild and transitory. Headaches are the most common side effect of ondansetron. Rare complications include constipation, diarrhea, fever, tremors, dizziness, nervousness and thirst. Ondansetron, as with droperidol, has been shown to cause prolongation of electrocardiographic intervals. Prolonged QT segments may arise from alteration in cardiac muscle Na<sup>+</sup> and K<sup>+</sup> channels secondary

**Table 3. Antiemetic medications – adverse events, cost and half life.**

Medication	Adverse drug events Common/infrequent (perioperative use)	Cost (US\$/dose)	t <sub>1/2</sub> (h)
Ondansetron	Headache/dizziness	12.00	3–5
Dolasetron	Headache/dizziness	25.00	6
Granisetron	Headache/dizziness	50.00	7
Dexamethasone	Euphoria, dysphoria	0.50	36–56
Dimenhydrinate	Sedation, Dizziness	0.50	1–4
Droperidol	Sedation, Dysphoria, eps	1.50	1–2
Metoclopramide	Sedation, EPS/dizziness	2.00	3–6
Promethazine	Sedation, ↓BP/dizziness, dry mouth	4.00	9–16
Propofol	Sedation, ↓BP	10.00	2–4
Scopolamine	Dry mouth, blurred vision/dysphoria	3.00	Patch

↓BP: Hypotension; EPS: Extrapyramidal symptoms; t<sub>1/2</sub>: Half-life.

Data from [22,103].

to blockade in serotonin receptors [49–51]. The clinical significance of these changes is unclear [52].

#### Regulatory affairs

Ondansetron first received US FDA approval in 1991 for the treatment of chemotherapy-induced nausea and vomiting. In 1997, approval was extended to children aged 2–12 years and in 2005 to children aged as young as 6 months. Ondansetron is the only 5-HT<sub>3</sub> antagonist approved for use in infants. On November 18, 2005, the FDA approved a generic formulation of ondansetron oral disintegrating tablets but later rescinded this action when the US District Court for the District of New Jersey found the medication patent was still active. The patent on ondansetron is set to expire on June 24, 2006. On December 15, 2005, February 24, 2006 and April 14, 2006, the FDA granted tentative approval for generic formulations of ondansetron [101]. The anticipated decrease in drug cost should allow for a wider range of clinical application.

In 2004, sales of ondansetron were US\$1.2 billion in the USA and US\$1.6 billion (£837 million) worldwide [102]. Ondansetron was the 42nd top-selling prescribed drug in the USA, a remarkable statistic in light of the fact that most of the other top-selling drugs were daily at-home medications. Owing to the relative expense of ondansetron compared with older antiemetics, investigators have compared the financial reward and burden of its prophylactic use [53–56]. Taking into account efficacy, antiemetic acquisition cost, duration of action, rescue medication costs,

recovery room stay charges and hospital staff labor and salaries, several economic-based conclusions have been reached:

- Antiemetic prophylaxis for PONV is only justified in moderate- to high-risk patients;
- ‘Older’ and less expensive antiemetics are more cost effective;
- The major expense incurred secondary to PONV is recovery room charges and staff salary;
- Patient satisfaction and willingness to bear the expense for PONV prophylaxis is difficult to quantify and measure consistently.

#### Conclusion

The introduction of 5-HT<sub>3</sub> receptor antagonists, in general, and ondansetron in particular, has revolutionized the prevention of PONV. Ondansetron has been studied extensively over the past 10 years across all age groups and in a multitude of settings. It has been shown to be extremely effective and superior to other available antiemetics by significantly reducing the incidence of early postoperative vomiting in high-risk populations. Side effects are infrequent and rarely problematic. Concomitant use of intraoperative corticosteroids greatly enhances effectiveness of ondansetron in preventing early nausea and delayed PONV. The remarkable success of 5-HT<sub>3</sub> receptor antagonists in reducing the incidence of PONV has dramatically changed patient outcome. A reduction in the acquisition cost secondary to the availability of a generic form of ondansetron may result in an even use in this setting.

### Outlook

Three broad areas of ongoing study offer the possibility for an extensive reduction in the incidence of postoperative nausea and vomiting: pharmacogenetics, selective receptor therapy and nonpharmacologic interventions. Identification of genetic differences among patients that lead to treatment failures or greater susceptibility for PONV will, in the future, enable physicians to specifically select anesthetics and antiemetics tailored to their patient's genetic make up. The identification of patients with multiple alleles for CYP2D6 is only the beginning. Greater understanding of the different receptors and their interactions in the nausea–vomiting pathway will help design multidrug modalities that will help patients avoid PONV successfully. For

example, initial experience with the NK<sub>1</sub> receptor antagonist aprepitant suggests an additive or synergic action with ondansetron [57,58]. The ability to selectively block receptors and pathways will enable practitioners to fine-tune antiemetic therapy. An approach that blocks specific receptors being stimulated by specific emetogenic substances may result in superior management. Nonpharmacological approaches, including acupuncture, acupressure and acustimulation, have shown great promise in adults. [59–61] These new approaches (genetic analyses, selective receptor blockade and complementary medicine treatments), along with continued refinement of anesthetics [62] and intraoperative management, offer great hope to banish PONV to oblivion.

### Highlights

- Postoperative nausea and vomiting (PONV) continues to be a major concern for patients and healthcare providers.
- Serotonin subtype 5-hydroxytryptamine (5-HT)<sub>3</sub> receptor antagonists have dramatically improved patient outcome.
- Ondansetron, extensively studied in pediatric and adult patients, has an excellent therapeutic index for early postoperative vomiting.
- Combination therapy, specifically with long-acting corticosteroids, is effective in reducing the incidence of nausea and delayed vomiting.
- From a cost-effective prospective, 5-HT<sub>3</sub> receptors should be reserved for patients at moderate to high risk of PONV.
- Generic formulations of ondansetron have received approval by the US FDA.

### Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Eberhart LH, Morin AM, Wulf H, Geldner G. Patient preferences for immediate postoperative recovery. *Br. J. Anaesth.* 89, 760–761 (2002).
2. Jenkins K, Grady D, Wong J, Correa R, Armanious S, Chung F. Post-operative recovery: day surgery patients' preferences. *Br. J. Anaesth.* 86(2), 272–274 (2001).
3. Board T, Board R.:The role of 5-HT<sub>3</sub> receptor antagonists in preventing postoperative nausea and vomiting. *AORN J.* 83(1), 209–216, 219–220 (2006).
4. Sennaraj B, Shende D, Sadhasivam S, Ilavajady S, Jagan D. Management of post-strabismus nausea and vomiting in children using ondansetron: a value-based comparison of outcomes. *Br. J. Anaesth.* 89(3), 473–478 (2002).
5. Tang J, Wang B, White PF, Watcha MF, Qi J, Wender RH. The effect of timing of ondansetron administration on its efficacy, cost–effectiveness, and cost–benefit as a prophylactic antiemetic in the ambulatory setting. *Anesth. Analg.* 86(2), 274–282 (1998).
6. Rashiq S, Edlund D, Dick BD. Utilities of the post-anesthesia state derived by the standard gamble method in surgical patients. *BMC Med. Inform. Decis. Mak.* 15, 6–8 (2006).
7. Cucchiaro G, Farrar JT, Guite JW, Li Y. What postoperative outcomes matter to pediatric patients? *Anesth. Analg.* 102(5), 1376–1382 (2006).
8. Richards CA, Andrews PL. Food refusal: a sign of nausea? *J. Pediatr. Gastroenterol. Nutr.* 38(2), 227–228 (2004).
9. Andrews PL, Hawthorn J. The neurophysiology of vomiting. *Res. Clin. Gastroenterol.* 2(9), 141–168 (1988).
10. Pisters KM, Kris MG. Treatment-related nausea and vomiting. In: *Principles and Practice of Supportive Oncology.* Berger A, Portenoy RK, Weissman DE (Eds). Lippincott-Raven Publishers, Philadelphia, PA, USA (1998).
11. Naylor RJ, Inall FC. The physiology and pharmacology of postoperative nausea and vomiting. *Anaesthesia* 49, 2–5 (1994).
12. Hasler WL. Nausea, gastroparesis, and aerophagia. *J. Clin. Gastroenterol.* 39(5), 223–229 (2005).
13. Eberhart LH, Geldner G, Kranke P *et al.* The development and validation of a risk score to predict the probability of postoperative vomiting in pediatric patients. *Anesth. Analg.* 99(6), 1630–1637 (2004).
14. Apfel CC, Kranke P, Eberhart LH, Roos A, Roewer N. Comparison of predictive models for postoperative nausea and vomiting. *Br. J. Anaesth.* 88(2), 234–240 (2002).
- Extensive comparison of the effectiveness of different antiemetics in preventing postoperative nausea and vomiting (PONV). The authors present profound evidence regarding the appropriateness of medication selections and prophylactic use.

15. Biedler A, Wermelt J, Kunitz O *et al.* A risk adapted approach reduces the overall institutional incidence of postoperative nausea and vomiting. *Can. J. Anaesth.* 51(1), 13–19 (2004).
16. Gan TJ, Meyer T, Apfel CC *et al.* Consensus guidelines for managing postoperative nausea and vomiting. *Anesth. Analg.* 97(1), 62–71 (2003).
- **Most complete and up-to-date set of PONV prevention guidelines, as determined by evidence-based medicine and expert opinion.**
17. Kranke P, Morin AM, Roewer N, Wulf H, Eberhart LH. The efficacy and safety of transdermal scopolamine for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth. Analg.* 95(1), 133–143 (2002).
- **Systematic review of an older but popular antiemetic. The authors provide an evidence-based opinion regarding continued use of this medication in this setting.**
18. Kranke P, Morin AM, Roewer N, Eberhart LH: Dimenhydrinate for prophylaxis of postoperative nausea and vomiting: a meta-analysis of randomized controlled trials. *Acta Anaesthesiol. Scand.* 46(3), 238–44 (2002).
19. Moser JD, Caldwell JB, Rhule FJ. No more than necessary: safety and efficacy of low-dose promethazine. *Ann. Pharmacother.* 40(1), 45–48 (2006).
- **Systematic review of an older but popular antiemetic. The authors provide an evidence-based opinion regarding continued use of this medication in this setting**
20. Domino KB, Anderson EA, Polissar NL, Posner KL. Comparative efficacy and safety of ondansetron, droperidol, and metoclopramide for preventing postoperative nausea and vomiting: a meta-analysis. *Anesth. Analg.* 88(6), 1370–1379 (1999).
21. Eberhart LH, Morin AM, Seeling W, Bothner U, Georgieff M. Meta-analysis of controlled randomized studies on droperidol for prevention of postoperative phase vomiting and nausea. *Anesthesiol. Intensivmed. Notfallmed. Schmerzther.* 34(9), 528–536 (1999).
22. Kovac AL. Benefits and risks of newer treatments for chemotherapy-induced and postoperative nausea and vomiting. *Drug Saf.* 26(4), 227–259 (2003).
- **Comprehensive review of adverse events experienced with commonly used antiemetic medications.**
23. Henzi I, Walder B, Tramer MR. Metoclopramide in the prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized, placebo-controlled studies. *Br. J. Anaesth.* 83(5), 761–771 (1999).
24. Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth. Analg.* 90(1), 186–194 (2000).
25. Goldman AC, Govindaraj S, Rosenfeld RM. A meta-analysis of dexamethasone use with tonsillectomy. *Otolaryngol. Head Neck Surg.* 123(6), 682–686 (2000).
26. Kazemi-Kjellberg F, Henzi I, Tramer MR. Treatment of established postoperative nausea and vomiting: a quantitative systematic review. *BMC Anesthesiol.* 1(1), 2 (2001).
- **One of the few systematic reviews and metaanalysis of antiemetic effectiveness in treating breakthrough PONV.**
27. Gupta A, Wu CL, Elkassabany N, Krug CE, Parker SD, Fleisher LA. Does the routine prophylactic use of antiemetics affect the incidence of postdischarge nausea and vomiting following ambulatory surgery? A systematic review of randomized controlled trials. *Anesthesiology* 99(2), 488–495 (2003).
28. Kovac AL. Meta-analysis of the use of rescue antiemetics following PONV prophylactic failure with 5-HT<sub>3</sub> antagonist/dexamethasone versus single-agent therapies. *Ann. Pharmacother.* 40(5), 873–887 (2006).
- **Much-needed systemic review and meta-analysis of antiemetic effectiveness in treating breakthrough PONV after ondansetron prophylaxis.**
29. Habib AS, Gan TJ. The effectiveness of rescue antiemetics after failure of prophylaxis with ondansetron or droperidol: a preliminary report. *J. Clin. Anesth.* 17(1), 62–65 (2005).
30. Butler A, Hill JM, Ireland SJ, Jordan CC, Tyers MB. Pharmacological properties of GR38032F, a novel antagonist at 5-HT<sub>3</sub> receptors. *Br. J. Pharmacol.* 94(2), 397–412 (1988).
31. Gan TJ. Selective serotonin 5-HT<sub>3</sub> receptor antagonists for postoperative nausea and vomiting: are they all the same? *CNS Drugs* 19(3), 225–238 (2005).
32. Spahr-Schopfer IA, Lerman J, Sikich N, Palmer J, Jorch U. Pharmacokinetics of intravenous ondansetron in healthy children undergoing ear, nose, and throat surgery. *Clin. Pharmacol. Ther.* 58(3), 316–321 (1995).
33. Pritchard JF. Ondansetron metabolism and pharmacokinetics. *Semin. Oncol.* 19(4), 9–15 (1992).
34. Pritchard JF, Bryson JC, Kernodle AE, Benedetti TL, Powell JR. Age and gender effects on ondansetron pharmacokinetics: evaluation of healthy aged volunteers. *Clin. Pharmacol. Ther.* 51(1), 51–55 (1992).
35. Candiotti KA, Birnbach DJ, Lubarsky DA *et al.* The impact of pharmacogenomics on postoperative nausea and vomiting: do CYP2D6 allele copy number and polymorphisms affect the success or failure of ondansetron prophylaxis? *Anesthesiology* 102(3), 543–549 (2005).
36. Blower PR. Related 5-HT<sub>3</sub>-receptor antagonists and the cytochrome P450 system: clinical implications. *Cancer J.* 8(5), 405–414 (2002).
37. Kaiser R, Sezer O, Papias A *et al.* Patient-tailored antiemetic treatment with 5-hydroxytryptamine type 3 receptor antagonists according to cytochrome P-450 2D6 genotypes. *J. Clin. Oncol.* 20(12), 2805–2811 (2002).
- **Clear and concise report regarding the genetics of ondansetron metabolism and its role in the prevention of PONV.**
38. Finn AL. Toxicity and side effects of ondansetron. *Semin. Oncol.* 19(4), 53–60 (1992).
39. Tucker ML, Jackson MR, Scales MD *et al.* Ondansetron: pre-clinical safety evaluation. *Eur. J. Cancer Clin. Oncol.* 25(1), 79–93 (1989).
40. Stables R, Andrews PL, Bailey HE *et al.* Antiemetic properties of the 5HT<sub>3</sub>-receptor antagonist, GR38032F. *Cancer Treat. Rev.* 14(3–4), 333–336 (1987).
41. Eglen RM, Lee CH, Smith WL, Johnson LG, Whiting RL, Hegde SS. A novel and potent 5-HT<sub>3</sub> receptor antagonist, *in vitro* and *in vivo*. *J. Pharmacol. Exp. Ther.* 266(1), 535–543 (1993).
42. Butler A, Hill JM, Ireland SJ, Jordan CC, Tyers MB. Pharmacological properties of GR38032F, a novel antagonist at 5-HT<sub>3</sub> receptors. *Br. J. Pharmacol.* 94(2), 397–412 (1988).
43. Figueredo E, Canosa L. Prophylactic ondansetron for post-operative emesis: meta-analysis of its effectiveness in patients with and without a previous history of motion sickness. *Eur. J. Anaesthesiol.* 16(8), 556–564 (1999).
44. Figueredo E, Canosa L. Prophylactic ondansetron for postoperative emesis. Meta-analysis of its effectiveness in patients with previous history of postoperative nausea and vomiting. *Acta Anaesthesiol. Scand.* 43(6), 637–644 (1999).

45. Tramer MR, Walder B. Efficacy and adverse effects of prophylactic antiemetics during patient-controlled analgesia therapy: a quantitative systematic review. *Anesth. Analg.* 88(6), 1354–1361 (1999).
46. McQuay HJ, Moore RA. Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review. *Health Technol. Assess.* 2(12), 1–236 (1998).
47. Tramer MR, Reynolds DJ, Moore RA, McQuay HJ. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. *Anesthesiology* 87(6), 1277–1289 (1997).
48. Khalil SN, Roth AG, Cohen IT, Simhi E, Ansermino JM *et al.* A double-blind comparison of intravenous ondansetron and placebo for preventing postoperative emesis in 1- to 24-month-old pediatric patients after surgery under general anesthesia. *Anesth. Analg.* 101(2), 356–361 (2005).
49. Charbit B, Albaladejo P, Funck-Brentano C, Legrand M, Samain E, Marty J. Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. *Anesthesiology* 102(6), 1094–1100 (2005).
50. Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine<sub>3</sub> receptor antagonists. *Ann. Pharmacother.* 37(9), 1276–1286 (2003).
51. Kuryshv YA, Brown AM, Wang L, Benedict CR. Interactions of the 5-hydroxytryptamine 3 antagonist class of antiemetic drugs with human cardiac ion channels. *J. Pharmacol. Exp. Ther.* 295(2), 614–620 (2000).
52. Scuderi PE. You (still) can't disprove the existence of dragons. *Anesthesiology* 102(6), 1081–1082 (2005).
53. van den Bosch JE, Bonsel GJ, Moons KG, Kalkman CJ. Effect of postoperative experiences on willingness to pay to avoid postoperative pain, nausea, and vomiting. *Anesthesiology* 104(5), 1033–1039 (2006).
54. Pueyo FJ, Lopez-Olaondo L, Sanchez-Ledesma MJ, Ortega A, Carrascosa F. Cost-effectiveness of three combinations of antiemetics in the prevention of postoperative nausea and vomiting. *Br. J. Anaesth.* 91(4), 589–592 (2003).
55. Olutoye O, Jantzen EC, Alexis R, Rajchert D, Schreiner MS, Watcha MF. A comparison of the costs and efficacy of ondansetron and dolasetron in the prophylaxis of postoperative vomiting in pediatric patients undergoing ambulatory surgery. *Anesth. Analg.* 97(2), 390–396 (2003).
56. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A *et al.* A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N. Engl. J. Med.* 350(24), 2441–2451 (2004).
57. Jordan K. Neurokinin-1-receptor antagonists: a new approach in antiemetic therapy. *Onkologie* 29(1–2), 39–43 (2006).
58. Diemunsch P, Schoeffler P, Bryssine B *et al.* Antiemetic activity of the NK1 receptor antagonist GR205171 in the treatment of established postoperative nausea and vomiting after major gynaecological surgery. *Br. J. Anaesth.* 82(2), 274–276 (1999).
59. Streitberger K, Diefenbacher M, Bauer A *et al.* Acupuncture compared to placebo-acupuncture for postoperative nausea and vomiting prophylaxis: a randomized placebo-controlled patient and observer blind trial. *Anaesthesia* 59(2), 142–149 (2004).
60. White PF, Issioui T, Hu J *et al.* Comparative efficacy of acustimulation (ReliefBand) versus ondansetron in combination with droperidol for preventing nausea and vomiting. *Anesthesiology* 97(5), 1075–1081 (2002).
61. Coloma M, White PF, Ogunnaike BO *et al.* Comparison of acustimulation and ondansetron for the treatment of established postoperative nausea and vomiting. *Anesthesiology* 97(6), 1387–1392 (2002).
62. Joo HS, Perks WJ. Sevoflurane versus propofol for anesthetic induction: a meta-analysis. *Anesth. Analg.* 91(1), 213–219 (2000).

**Website**

101. Annual Review GlaxoSmithKline (2005) [www.gsk.com/investors/rep05/annual\\_review\\_2005/business\\_operating\\_review.htm](http://www.gsk.com/investors/rep05/annual_review_2005/business_operating_review.htm)
102. Center for Drug Evaluation and Research, Food and Drug Administration Department of Health and Human Services [www.fda.gov/cder/](http://www.fda.gov/cder/)
103. Minutes of the Department of Defense Pharmacy and Therapeutics Executive Council Meeting [www.tricare.osd.mil/pharmacy/PT\\_Cmte/PT\\_C/Nov\\_03\\_PT\\_Exec\\_Minutes.pdf](http://www.tricare.osd.mil/pharmacy/PT_Cmte/PT_C/Nov_03_PT_Exec_Minutes.pdf)

**Affiliation**

*Ira Todd Cohen, MD, MEd, Associate Professor of Anesthesiology and Pediatrics, Children's National Medical Center, George Washington University, Washington, DC, USA*  
 Tel.: +1 202 884 2025  
 Fax: +1 202 884 5999  
[icohen@cnmc.org](mailto:icohen@cnmc.org)