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Current therapy for management of postoperative nausea and vomiting: the 5-HT_3 receptor antagonists

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Abstract

The control of postoperative nausea and vomiting (PONV) remains a problem in spite of the improvements achieved with newer anesthetic agents, such as propofol, and newer antiemetics. Management of PONV is difficult, this is most likely due to the multiple receptors and neurotransmitters in the central nervous system that mediate the emetic response, and to the multifactorial etiology of PONV. Studies of the four major 5-hydroxytryptamine (serotonin) subtype-3 (5-HT_3) receptor antagonists suggest that they have similar safety and efficacy for prevention and treatment of PONV. These drugs lack the significant side effects observed with traditional antiemetics. Combination regimens of 5-HT_3 receptor antagonists and traditional antiemetics can improve antiemetic efficacy. Areas of future study include comparing the cost effectiveness of these agents and determining optimal combinations of antiemetics to further reduce the incidence of PONV.

Keywords: Antiemetic; Postoperative nausea and vomiting; PONV; 5-HT_3 receptor antagonist

1. Introduction

The introduction of propofol, avoidance of routine antagonism of residual neuromuscular block, and the abandonment of required liquid intake before patient discharge has decreased the incidence of postoperative nausea and vomiting (PONV) [1]. Nevertheless, PONV still occurs frequently; the reported incidence is highly variable, ranging from 8–92% [2]. On average, approximately 20–30% of patients experience PONV after surgery [3]. Patients rank freedom from PONV high and are willing to accept some pain and drowsiness in return [1]. Postoperative emesis also can cause detrimental effects, including wound bleeding and dehiscence, esophageal tears, aspiration pneumonitis, dehydration, and electrolyte imbalances (e.g. hypochloremia, hypokalemia, metabolic alkalosis). When these occur after outpatient surgery, emergency admissions to the hospital can result [4]. The 5-hydroxytryptamine (serotonin) subtype-3 (5-HT_3) receptor antagonists represent a major advance in the management of PONV. They are highly effective and lack the sedative and dysphoric effects of traditional antiemetics such as droperidol, the cardiovascular effects of phenothiazines, and the extrapyramidal symptoms associated with high-dose metoclopramide [5–7].

Dolasetron mesilate is the most recent 5-HT_3 receptor antagonist to be approved in the USA. Similar to ondansetron, dolasetron is indicated for the prevention of chemotherapy-induced nausea and vomiting (CINV) and PONV, and for treatment of established PONV. Two other 5-HT_3 receptor antagonists, granisetron and tropisetron, are approved for the prevention of CINV and are under evaluation for use in managing PONV.

Many publications describe the effectiveness of the 5-HT_3 receptor antagonists for management of PONV

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versus placebo, older antiemetics, and other agents in the class. In this report, we attempt to provide a comprehensive overview of current PONV management.

1.1. Etiology and incidence of PONV

The mechanisms underlying PONV are not well understood and it is likely that several factors are involved. Little is certain about the etiology of nausea and its subjective nature makes measurement difficult [2,8]. Mechanical disturbances of 5-HT-containing cells in the intestinal wall may contribute to emesis. In addition, certain anaesthetic drugs and opiate analgesics increase the likelihood of PONV [1,2,9]. Opioids and anaesthetics act directly on the chemoreceptor trigger zone (CTZ), which is rich in neural fibers possessing muscarinic M_1, histaminic H_1, dopaminergic D_2, serotonergic 5-HT_3, and vasopressinergic receptors. All of these receptors mediate message transmission to the vomiting center and blocking these receptors is the mode of action of many antiemetic drugs [9,10]. In some cases, optical or vestibular signals to these receptors may be involved. Motion sickness, thought to be the result of aberrant optical and vestibular symptoms [11], is not well controlled by 5-HT_3 receptor antagonists but responds to vestibular histamine receptor antagonists (e.g. meclizine) or vestibular muscarinic receptor antagonists (e.g. scopolamine) [10].

Much information has been accumulated regarding the various factors affecting the incidence of PONV, including the patient's physical traits, general health, mental state, surgery type and site, premedications, type of anaesthesia used, and postoperative pain treatment [2,10,12,13]. Some variables that correlate positively with incidence of PONV are listed in Table 1. Conversely, some factors are associated with a reduced occurrence of PONV, for example, chronic alcohol use. Because so many variables influence the likelihood of PONV and because efficacy endpoints differ among clinical trials, comparisons of antiemetic agents from published reports are problematic.

Table 1
Variables with positive correlation to PONV

Variable	Most likely to experience PONV
Age	Younger
Gender	Female
Menstruation	Time of cycle
Weight	Obesity
Pre-existing disease	Diabetes, renal disease
Surgery duration	Longer than 3 h
Premedication	Opiates
Balanced anaesthesia	Opiate analgesic use, etomidate
Previous history	Motion sickness, PONV, allergies
Type of surgery	Gynecologic; ear, nose and throat; laparoscopy; intra-abdominal; breast operations (females); testicular operations (males); strabismus operations (children)
Postoperation/ recovery room	Pain, movement, hypotension

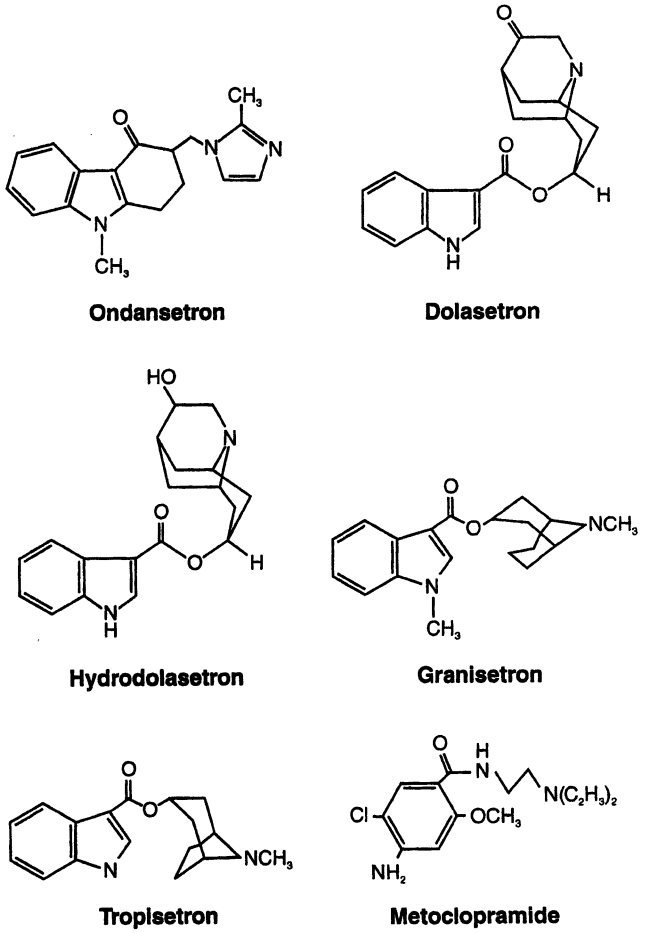

Fig. 1. Chemical structures of the 5-HT_3 receptor antagonists.

2. 5-HT_3 receptor antagonists

2.1. Pharmacology

Ondansetron, dolasetron, granisetron, and tropisetron are all highly selective at the 5-HT_3 receptor with receptor specificity and binding greater than 100:1 (Fig. 1) [5,14–17]. These agents do not affect histaminic, dopaminergic, or cholinergic receptors, hence, their lack of side effects such as drowsiness, dry mouth, tardive dyskinesia, and extrapyramidal effects [5]. Table 2 shows several pharmacokinetic parameters of the four 5-HT_3 receptor antagonists. Ondansetron is a carbazole; derived from a modification of the serotonin molecule [15]. Systemic clearance of ondansetron is slower in females, the elderly, pediatric patients, and cancer pa-

Table 2
Pharmacokinetics of 5-HT_3 receptor antagonists in healthy volunteers

5-HT_3 Receptor antagonist	$t_{1/2}$ (h)	$AUC_{(0\rightarrow\infty)}$	CL	V_d
Ondansetron [5,13,63]				
Oral (4–8 mg)	3.2	133 h ng/ml	541 ml/min	1.8 l/kg
IV (8 mg)	3.5	229 h ng/ml	578 ml/min	
Dolasetron [19–22]				
Oral (50 mg)	5–10	469 μg/l h	—	5.5 l/kg
IV (12.5 mg)	4–8	—	0.61–0.94 l/h/kg	
Granisetron [5,16]				
IV (40 μg/kg)	10–12	350 h ng/ml	33.4–75.7 l/h	174–258 l
Tropisetron [14]				
IV (5 mg)	7.3[a] 30.3[b]	239[a] 1192[b] μg/l h	0.96[a] 0.20[b] l/min	554[a] 463[b] l[b]

IV, intravenous; h, hour; min, minute; l, liter; ml, milliliter; kg, kilogram; mg, milligram; ng, nanogram; μg, microgram.
a Extensive metabolizers.
[b] Poor metabolizers.

tients; however, dosage adjustments are usually not necessary for these patients [1,15]. A small study in healthy volunteers showed intramuscular (IM) injection of ondansetron to have the same systemic availability as intravenous (IV) dosing [18]. Dolasetron mesylate is a pseudopelletierine-derivative [17,19]. Dolasetron has a serum half-life of 9 min and is rapidly reduced by ubiquitous plasma reductase to its major metabolite, hydrodolasetron, which is responsible for the drug's antiemetic effect [20,21]. Pharmacokinetics of hydrodolasetron in elderly patients are similar to those in younger patients [22]. Greater mean apparent clearances and shorter terminal half-lives of hydrodolasetron were detected in children [23] and longer elimination times were seen in patients with renal dysfunction [24]; however, dosage need not be adjusted for either population group. Granisetron, a derivative of metoclopramide [5], has an elimination half-life of approximately 4 h in healthy volunteers and 10–12 h in cancer patients [16]. It has not been determined whether these divergent findings are due to differences in drug elimination due to the underlying disease process, drug interactions with antineoplastic agents, changes in plasma protein binding, or the relative older age of cancer patients compared with healthy volunteers [16]. Like ondansetron, tropisetron was originally derived from the serotonin molecule [5]. Because it is metabolized by the hepatic cytochrome P450 2D6 enzyme system, polymorphism may cause some patients to metabolize tropisetron faster than others [14].

2.2. Clinical trials

2.2.1. Patients

Because of their propensity of developing PONV [1,2], female patients undergoing gynecologic surgery with general, balanced anaesthesia have been predominately studied in clinical trials of antiemetics. Females are two to three times as likely to experience emesis as males, perhaps due to variations in serum gonadotropin (or other hormonal) levels [1]. Moreover, gynecologic surgeries-whether due to proximity to abdominal vagus nerves, insufflation of CO_2 into the abdominal cavity during laparoscopy, or type of anaesthesia (usually general balanced)-are associated with a high incidence of emesis [1]. Relatively few male patients have been studied in PONV trials of the 5-HT_3 receptor antagonists. A notable exception is a recently reported trial of ondansetron in male outpatients ($n = 468$) [25]. This trial indicated prognostic factors thought to be associated with increased PONV in males: (1) history of motion sickness; (2) previous PONV; (3) longer surgery duration (> 3 h); and (4) non-orthopedic surgery.

2.2.2. Study design/efficacy measures

Efficacy measures used in PONV trials vary among agents, and rarely, among clinical trials of the same agent [26–28]. Almost all 5-HT_3 receptor antagonist clinical trials have used a 24-h period after administration of study drug. In outpatient surgery, the patient is often evaluated across two intervals: an acute, 2-3 h period after receipt of antiemetic prevention or treatment in the postanesthesia care unit (PACU), and the remaining 21- or 22-h interval when PONV is recorded by the patient at home. In most 5-HT_3 antagonist clinical trials, retching (unproductive emesis) and vomiting are each considered primary efficacy endpoints, and nausea presence and severity are evaluated as secondary efficacy endpoints. In some trials, endpoints such as patient satisfaction are also measured.

Table 3
5-HT_3 receptor antagonist dosing

Drug	IV and oral	IV dose: prevention	IV dose: treatment	Oral dose: prevention
Ondansetron	Yes/yes	4 mg Prior to induction[a]	4 mg	16 mg (1–2 h before anesthesia)
Dolasetron	Yes/yes	12.5 mg Prior to emergence	12.5 mg	100 mg (1–2 h before anesthesia)
Granisetron[b]	Yes/?	40 μg/kg After emergence	0.1 mg[c]	N/A
Tropisetron[b]	Yes/?	5 mg Before induction or at emergence	N/A	N/A

N/A, Not applicable.
[a] Results of recent studies suggest administration prior to emergence may provide better effect [47,48].
[b] Oral dosage form available for prevention of chemotherapy-induced nausea and vomiting.
[c] Only one IV granisetron treatment study [57].

2.2.3. Ondansetron

In ondansetron trials, efficacy was defined by the number of emetic episodes (retching was included in the definition of emesis in some studies but not all) [26]. Complete response was defined as no emetic episodes and no receipt of rescue antiemetic medication. In most studies, nausea was patient-assessed as present or absent. When present, nausea severity was rated by patients on an 11-point linear scale (0 = 'no nausea' and 10 = 'nausea as bad as it can be'), at frequent intervals throughout the evaluation period [12,15,18,25,26,29–32].

2.2.4. Dolasetron

Efficacy measures were standardized across all dolasetron PONV clinical trials [33–40]. Complete response was the primary efficacy measure, defined as no emetic episodes (vomiting or retching) and no rescue medication. Patient-assessed nausea severity, evaluated via a 100-mm visual analog scale (VAS) (0 = no nausea and 100 = severe nausea) frequently during the acute period, at discharge, and at 24 h. Patient satisfaction was also recorded using the 100-mm VAS at 24 h. Total response (complete response with no nausea, < 5 mm VAS) was also measured.

2.2.5. Granisetron

In two PONV prevention trials, efficacy was measured by anaesthetist interview across two time intervals: 0–3 and 3–24 h following recovery. A single score indicated only the presence or absence of nausea or vomiting: 0 = no emetic symptoms, 1 = nausea, and 2 = vomiting [27,41]. In another PONV prevention trial, granisetron efficacy was defined by the number of emetic episodes (vomiting and/or retching) and patient self-assessed nausea on a 100-mm VAS across one 24-h interval [28].

2.2.6. Tropisetron

Efficacy of tropisetron in two trials was measured by the number of emetic episodes (vomiting and/or retching) and severity of nausea as rated by the investigator (absent to severe, on a 0–3 rating scale) [8,42]. Complete response was defined as no vomiting, retching, or nausea during the 24-h study period. In another trial, nausea and vomiting were rated by nurse observation, by anaesthetist interview, and by patient self-report on a 100-mm VAS. Patient satisfaction with antiemetic treatment was also assessed in this trial [43].

2.3. Dosing

Seemingly, the doses of the 5-HT_3 receptor antagonists studied in dose-response trials for PONV management have all been on the plateau of the response curve. Dose-ranging studies of ondansetron have shown IV and oral doses of 4 and 8 mg, and 8 and 16 mg, respectively, to be equally effective [29,44]. The lowest IV dolasetron dose tested, 12.5 mg, was as effective as the 100 mg IV dose when administered prior to emergence from anaesthesia [33–35]. Data have also shown a flat dose–response relationship across the 20, 40, and 160 μg IV doses of granisetron [27,41]. Finally, tropisetron PONV trials have used a 5 mg IV dose, based on the finding in CINV studies that a 5 and 10 mg dose were equally effective [45]. More recently, however, a 2-mg dose of tropisetron has been shown to have similar efficacy to a 4-mg dose of ondansetron in female patients (Table 3) [46].

The difficulty in determining an optimal antiemetic dose for prevention of PONV is further confounded by the timing of study drug administration. Early trials dosed the IV 5-HT_3 receptor antagonists before the emetic stimuli of anaesthesia and surgery. More recent studies have reported equivalent rates of PONV prevention with substantially lower doses when the antiemetic is administered just prior to emergence from anaesthesia. Dolasetron 12.5 mg IV administered prior to emergence from anaesthesia appears as effective as 50 mg dolasetron IV administered prior to induction of anaesthesia [33–36]. Recent studies indicate similar findings with ondansetron when administered at the end of anaesthesia [47,48].

3. Efficacy

3.1. IV PONV prevention

3.1.1. Ondansetron

A number of dose-finding studies have shown 4 mg IV ondansetron to be optimal for prevention of PONV, although an 8 mg dose may be more effective in women, undergoing laparoscopy, with a history of PONV, as well as patients who weigh more than 80 kg [13,31]. In placebo-controlled clinical trials, complete response rates achieved with 4 mg IV ondansetron were 16–30% better than those seen with placebo in adult patients [13,15,18,29–32]. In comparative trials, 4 mg IV ondansetron was statistically superior to 10 mg IV metoclopramide [49,50] but not different from 1.25 mg IV droperidol [51] in controlling emesis. Ondansetron was significantly less effective than 2.5 mg droperidol in another trial [52]. Table 4 lists several trials in which a 5-HT_3 receptor antagonist was compared with traditional antiemetics.

Timing of ondansetron administration was evaluated in two recent clinical trials. In patients undergoing otolaryngologic surgery, 4 mg IV ondansetron was not more effective than placebo in preventing emesis, which was likely due to stimulation of the vestibular labyrinthine system [12]. Nevertheless, patients, who received 4 mg IV ondansetron at emergence of anaesthesia, received rescue medication less often than those who received ondansetron before induction of anaesthesia [47]. A trial in women undergoing laparoscopic surgery reported similar results when ondansetron was administered near the end of anaesthesia [48].

3.1.2. Dolasetron

An 8-fold range of IV dolasetron doses was tested (12.5–100 mg IV) in four placebo-controlled randomised PONV prevention studies [33–36] (Table 5). The majority of patients in these studies (78%) were females undergoing gynecological surgeries under general anaesthesia. Combined data from these studies indicated an 18 to 22% increase in complete response rates with dolasetron compared with placebo in this patient population [53]. In three of the four studies, dolasetron was administered just prior to emergence from anaesthesia; the lowest dose, 12.5 mg, was as effective as higher doses (25–100 mg) [33–35]. The fourth trial was a comparative study in which IV dolasetron (25 or 50 mg), IV ondansetron (4 mg), or placebo was administered before induction of anaesthesia [36]. In this study, the 50 mg dolasetron dose was as effective as the approved ondansetron dose, and both drugs were significantly superior to placebo. No clinical trials comparing dolasetron with metoclopramide or droperidol for management of PONV have been reported. Further research is need to determine dolasetron's efficacy in relation to metoclopramide and to droperidol.

3.1.3. Granisetron

A dose-finding trial of granisetron in patients undergoing major gynecologic surgery under general anaesthesia showed 40 and 60 μg/kg IV doses to be equally effective and both were superior to placebo and a 20 μg/kg granisetron dose [41]. This trial suggested 40 μg/kg granisetron was the optimal dose in this patient group. In another trial, fixed-dose granisetron 3 mg IV was compared with metoclopramide 10 mg IV and placebo in females undergoing general anaesthesia for major gynecological surgery [27]. Granisetron was administered immediately after recovery from anaesthesia. Granisetron and metoclopramide were not statistically different for preventing acute (0–3 h) emesis (both were superior to placebo). However, granisetron was statistically superior to both metoclopramide and placebo during the 3–24 h interval. A comparison trial of granisetron and droperidol showed both antiemetics were superior to placebo, but there was no statistical difference between efficacy rates of 40 μg/kg granisetron and 1.25 or 2.5 mg droperidol at 0–3 h [54]. During the 3–24 h interval, 40 μg/kg granisetron and 2.5 mg droperidol had similar efficacy rates and both were statistically superior to the lower dose of droperidol and placebo.

3.1.4. Tropisetron

Three trials of 5 mg IV tropisetron showed statistical significance versus placebo for preventing PONV. In one trial, tropisetron was administered before induction of anaesthesia to women who were undergoing gynecologic surgery with 65% of tropisetron patients vs 40% of placebo patients experiencing a complete response (no nausea, emesis, or rescue medication) [42]. In a second trial, tropisetron was administered 15 min before emergence from anaesthesia to a similar patient population with 74% of tropisetron-treated patients vs 41% of placebo-treated patients not experiencing emesis [8]. However, 69% of patients in the tropisetron group and 88% of placebo-treated patients experienced nausea. In a third trial, tropisetron was compared with droperidol, metoclopramide, and placebo in a 36-h trial for prevention of PONV associated with patient-controlled analgesia with morphine after orthopedic surgery [43]. Tropisetron reduced the incidence and severity of emesis for 18 h compared with 36 h for droperidol. Metoclopramide had only a marginally significant effect on emesis. Only droperidol significantly reduced the need for rescue medication in this trial; however, compared with tropisetron, droperidol use was more often associated with sleepiness and anxiety.

Table 4
5-HT_3-receptor antagonists vs other antiemetics for PONV prophylaxis

Reference	Drug doses	Results	
		Percentage with emesis	
Alon and Himmelseher [69] 66 women	IV OND 8 mg	13[b]	
	METO 10 mg	54	
	DROP 1.25 mg	45	
		Percentage no severe emetic sequelae	
Desilva et al. [70] 360 female inpatients	IV OND 4 mg	63[a]	
	DROP 1.25 mg	76[a]	
	Perphenazine 5 mg	70[a]	
	METO 10 mg	50	
	Placebo	43	
		Percentage no emesis in PACU	Percentage naseau in PACU
Sun et al. [71] 125 adult outpatients (58 women 67 men)	IV OND 4 mg	8[a]	60
	METO 20 mg	35	52
	DROP 1.25 mg	25	56
	METO 20 mg + DROP 0.625 mg	20	76
	Placebo	20	72
		Percentage no PONV	
Grond et al. [52] 80 adult female inpatients	IV OND 8 mg	68[c]	
	DROP 2.5 mg	88	
		Percentage emesis	Percentage nausea
Gan et al. [51] 120 patients undergoing orthopedic surgery	IV OND 4 mg	17[a]	23
	DROP 1.25 mg	18[a]	29
	Placebo	45	21
		Percentage emesis and nausea	
		0–3 h postop	3–24 h postop
Fujii et al. [54] 100 adult female inpatients	IV GRAN 40 pg/kg	12[a]	8[a]
	DROP 1.25 mg	16[a]	36[a]
	DROP 2.5 mg	12[a]	12[a]
	Placebo	60	44
		Mean PONV score (0–2)	
		0–3 h	3–24 h
Fujii et al. [27] 60 adult female inpatients	IV GRAN 3 mg	0.1[a]	0.1[a]
	METO 10 mg	0.1[a]	0.5
	Placebo	0.8	0.6

PONV, postoperative nausea and vomiting; OND, ondansetron; GRAN, granisetron; TROP, tropisetron; METO, metoclopramide; DROP, droperidol; PACU, postanesthesia care unit
[a] Statistical significance ($P<0.05$) compared with placebo.
[b] Statistical significance ($P<0.05$), OND compared with DROP.
[c] Statistical significance ($P<0.05$), DROP compared with OND.
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Table 5
Dolasetron PONV trials: complete response rates (%)

Clinical trial	Dolasetron dose (% mg)					
	Placebo	12.5	25	50	100	200
IV prevention (overall, $n = 2332$)	36	54	54	54	58	
Graczyk et al. [33]	31	50	52	56	—	
Diemunsch et al. [34]	43	54	67	59	59	
Kovac et al. [35]	49	60	55	58	58	
Korttila et al. [36]	59	—	51	71	—	
P value*		$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	
Oral preventation (overall, $n = 1167$)	33	42	52	52	48	
Diemunsch et al. [39]	35	—	45	57	51	47
Warriner et al. [40]	29	—	36	41	54	49
P value*		$P = 0.056$	$P < 0.0001$	$P = 0.0001$	$P = 0.0014$	
IV treatment (overall, $n = 957$)	11	32	28	32	28	
Diemunsch et al. [37]	11	24	28	37	25	
Kovac et al. [38]	11	35	28	29	29	
P value*		$P < 0.0001$	$P = 0.0027$	$P < 0.0001$	$P = 0.0001$	

* Overall P value compared with placebo.

3.2. 5-HT_3 comparison trials

Several head-to-head trials of IV 5-HT_3 receptor antagonists have been conducted (Table 6). Korttila et al. reported results of a trial showing comparable efficacy between IV dolasetron 50 mg and ondansetron 4 mg when administered prior to the induction of anaesthesia (both drugs were statistically superior to placebo) [36]. In a similar study, Scholz et al. reported that IV ondansetron 4 mg and IV tropisetron 2 mg produced similar reductions in PONV incidence compared with placebo [46]. Among female patients, administration of tropisetron or ondansetron was associated with similar decreases in emesis compared with placebo. However, in male patients, neither drug appeared to be effective, regardless of the type of surgery. Finally, a study comparing ondansetron, granisetron, tropisetron, metoclopramide, and placebo was reported by Naguib and colleagues [50]. The three 5-HT_3 receptor antagonists had similar effectiveness and all were superior to placebo ($P < 0.05$). Only ondansetron was also more effective than metoclopramide ($P = 0.02$).

3.3. IV treatment of established PONV

3.3.1. Ondansetron

In treatment studies, patients were eligible to receive ondansetron or placebo if they: (1) experienced nausea and/or vomiting; (2) requested PONV medication; or (3) were judged by study or PACU personnel to need treatment within 2 h of entry into the PACU. A recently published systematic review [55] of seven ondansetron treatment trials (four placebo-controlled and three comparison studies) reported that treatment with ondansetron was more effective than placebo in approximately 25% of patients for ameliorating established PONV. There was no clinically relevant dose response between 1, 4, and 8 mg doses. Two of the comparison studies with droperidol indicated no statistical difference in complete response rates between ondansetron and droperidol (8 mg IV ondansetron three times a day vs 1.25 mg IV droperidol, $n = 100$; and 100 μg/kg ondansetron vs 20 μg/kg droperidol, $n = 29$) [55]. However, a large comparative trial with metoclopramide ($n = 746$) showed ondansetron (4 mg) was superior to metoclopramide (10 mg) for treatment of established emesis [56].

3.3.2. Dolasetron

The eligibility criteria in dolasetron treatment trials were similar to those in ondansetron trials. Combined results of two placebo-controlled, randomised clinical trials showed 12.5 mg IV dolasetron to be superior to placebo for complete response (32 vs 11%, respectively, $P < 0.0001$) [53]. The 12.5 mg IV dose was as effective as the three higher doses (25, 50, and 100 mg) studied in these trials.

3.3.3. Granisetron

At the time of this report, there is one reported abstract of the use of IV granisetron for the treatment of PONV [57]. Patients received 0.1, 1.0 or 3.0 mg IV granisetron or placebo if they experienced nausea or emesis within 6 h after surgery. Complete response rates of 38, 46, and 49% in the granisetron 0.1, 1.0 and 3.0 mg groups, respectively, were statistically significant compared to the placebo (20%) group.

Table 6
Comparison trials of 5-HT_3-receptor antagonists

Reference	Drug doses	Results	
Korttila et al. [36]		Percentage no emesis	Percentage no emesis, no nausea
514 Adults	IV DOL 25 mg	51	43
(484 women,	IV DOL 50 mg	71*	60*
30 men)	OND 4 mg	64*	54*
	Placebo	49	36
Naguib et al. [50]		Percentage no emesis	
132 adults	IV OND 4 mg	65.5**	
(108 women,	GRAN 3 mg	52	
24 men)	TROP 5 mg	48	
	METO 10 mg	29.2	
	Placebo	27.6	
Scholz et al. [46]	Abdominal surgery ($n = 504$), percentage emesis		
842 adults	All	Women	Men
IV OND 4 g	29*	31*	19
TROP 2 mg	30*	36*	8
Placebo	42	42	15
	Nonabdominal surgery ($n = 338$), percentage emesis		
	All	Women	Men
IV OND 4 g	21	24	14
TROP 2 mg	27	22	18
Placebo	23	25	20

PONV, postoperative nausea and vomiting; OND, ondansetron; GRAN, granisetron; TROP, tropisetron; METO, metoclopramide; DROP, droperidol; PACU, postanesthesia care unit.
* Statistical significance ($P < 0.05$) compared with placebo.
** Statistical significance compared with METO ($P < 0.05$).
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Information regarding IV tropisetron for treatment of established PONV is not available at this time.

3.4. Oral prevention

3.4.1. Ondansetron

Early clinical trials showed multiple oral doses of ondansetron (8 mg three times daily and 16 mg twice daily), administered before anaesthesia and after recovery, were effective for PONV prevention [44,58]. Subsequent trials in female inpatients confirmed the effectiveness of a single 16 mg oral dose before surgery [32]. A comparative trial in women undergoing gynecological laparoscopy showed a 4 mg oral ondansetron dose to be more effective than 10 mg oral metoclopramide [59]. In this study, 26% of patients who received 4 mg oral ondansetron experienced PONV compared with 42% of patients who received 10 mg metoclopramide and 50% of placebo-treated patients.

3.4.2. Dolasetron

Pooled data from two large, placebo-controlled, dose-finding studies in females undergoing gynecologic surgery ($n = 1167$) showed oral doses of 50 mg dolasetron administered 1–2 h prior to anaesthesia to be superior to placebo for complete response (52 vs 33%, respectively, $P < 0.0001$) [53]. Higher doses did not confer greater efficacy.

Information regarding oral granisetron or tropisetron for prevention of PONV is not available at this time.

3.5. Combination studies

Research has shown increased efficacy can be achieved when a 5-HT_3 receptor antagonist is used in combination with an antiemetic agent from a different class, for example, dexamethasone. Two studies conducted by McKenzie et al. showed that the addition of 8 or 20 mg dexamethasone to 4 mg IV ondansetron

Table 7
Studies of combination regimens with an IV 5-HT_3-receptor antagonist

Reference	Drug dose	Results		
McKenzie et al. [59]		Percentage complete response		
180 adult female inpatients	OND 4 mg	38		
	OND 4 mg + DEX 8 mg	52*		
McKenzie et al. [60]		Percentage complete response		
80 adult female inpatients	PROP + OND 4 mg + DEX 20 mg	53*		
	PROP + OND 4 mg + placebo	38		
Fujii et al. [61]		Percentage no vomiting		
88 women	GRAN 20 pg/kg + DEX 8 mg	95*		
	GRAN 20 pg/kg	77		
	DEX 8 mg	77		
	Placebo	77		
Belo and Koutsoukos [62]		Percentage nausea/emesis		
		0–6 h	6–12 h	12–24 h
80 adult female inpatients	OND 4 mg	7*	21	18
	DROP 1.25 mg	7*	40	18
	OND 4 mg + DROP 1.25 mg	7*	40	18
	Placebo	34	43	34

OND, ondansetron; DEX, dexamethasone; GRAN, granisetron; DROP, droperidol; PROP, propofol
* Statistical significance ($P < 0.05$) compared with placebo.
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improved antiemetic efficacy, as measured by complete response rate (Table 7) [60,61]. Similarly, Fujii et al. determined that the addition of 8 mg IV dexamethasone improved the effectiveness of 20 mg/kg IV granisetron when compared with granisetron alone, dexamethasone alone, or placebo [62]. Belo and Koutsoukos reported that the administration of 4 mg IV ondansetron with 1.25 mg IV droperidol significantly decreased incidence of PONV for the first 6 h after surgery compared with placebo, but the combination provided no benefit compared with either antiemetic used alone [63].

3.6. Safety

The 5-HT_3 antagonists are generally well tolerated with few adverse effects. Because they have little or no affinity for α_1, α_2, and β_1-adrenergic receptors; 5-HT_{1A}, 5-HT_{1B}, 5-HT_2, D_2, and D_3 dopaminergic receptors; benzodiazepine receptors; cholinergic receptors; or histamine (H_1) receptors, the 5-HT_3 antagonists do not interfere with surgical anaesthesia [1,5]. For the same reasons, they are not associated with extrapyramidal effects, sedation, or anticholinergic effects [5,10].

Headache is the most commonly reported adverse event in clinical trials of the 5-HT_3 receptor antagonists. Other known side effects of these agents include light-headedness, flushing, and constipation [64]. All members of this drug class are known to cause asymptomatic and transient treatment-related ECG changes [65–68]. No cardiovascular sequelae have been attributed to these changes.

4. Discussion

Comparing the efficacy of drugs to prevent or treat PONV is difficult due to the variety of efficacy parameters, surgical procedures, and anaesthetic techniques employed in various clinical trials. Moreover, there are myriad of patient variables that influence PONV within a study, not to mention between studies. Nevertheless, many clinical trials have tried to minimize confounding patient-related factors by examining the same type of patients: females undergoing gynecologic surgery. The high frequency of PONV in these patients also lends statistical power to study group comparisons.

Given that exact comparisons are not possible, when 5-HT_3 receptor antagonists are compared with traditional antiemetics the 5-HT_3 receptor antagonists are shown to be as effective as, and in many cases, more effective than, antiemetics commonly used in clinical practice such as droperidol (lower doses), metoclopramide, and perphenazine [49,50,69–71]. They also

have fewer side effects than the older agents. Comparisons among drugs within the 5-HT_3 receptor antagonist class suggest that all four have similar safety and efficacy. A benefit of comparison studies will be determining equipotent doses of the different 5-HT_3 receptor antagonists so that the relative cost-effectiveness of each drug may be determined.

Demonstrating cost effectiveness is important because the 5-HT_3 receptor antagonists are considerably more expensive than traditional antiemetics. However, their relative lack of side effects and quick administration when needed for treating established PONV can result in improved health outcomes for patients. Two recent reports indicate that, compared with placebo, use of IV dolasetron resulted in decreased resource utilization when administered as prophylaxis [72] or as treatment for established PONV [73]. Routine PONV prevention may not be an option at many surgical sites; however, providing prophylaxis for the highest risk patients (e.g. females undergoing laparoscopic surgery or patients with a previous history of PONV) may prove cost effective. Further study is needed to gauge actual cost savings in caregiver time and resources expended to prevent and/or treat PONV.

Another area that merits continued research is the utility of combination therapy for management of PONV [74]. Combination therapies were avoided with early antiemetics due to concern about additive central nervous system toxicity [10]. However, because numerous neurotransmitters (dopaminergic, histaminic (H_1), cholinergic muscarinic, and serotonergic) appear to play roles in the emetic response, and many different receptors send input to the vomiting center, no single drug has been able to completely block the emetic pathway and act as a universally effective antiemetic agent [10,11]. This may explain the demonstrated improvements in efficacy with combination therapy [60–62].

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