5-HT_3 receptor antagonists *vs* traditional agents for the prophylaxis of postoperative nausea and vomiting

Peter S. Loewen BSc (Pharm) Pharm.D,
Carlo A. Marra BSc (Pharm) Pharm.D,
Peter J. Zed BSc (Pharm) Pharm.D

Purpose: Numerous antiemetics have been studied for the prevention of postoperative nausea and vomiting (PONV) including traditional agents (metoclopramide, perphenazine, prochlorperazine, cyclizine and droperidol) and the 5-HT_3 receptor antagonists (ondansetron, dolasetron, granisetron and tropisetron). The results have been divergent and inconsistent. The purpose of this quantitative systematic review was to evaluate the effectiveness of 5HT_3 receptor antagonists compared to traditional antiemetics for the prevention of PONV.

Methods: A systematic search of the English language literature using computerized MEDLINE, EMBASE, and Pre-MEDLINE databases from 1966 to October 1999 and a manual search of references from retrieved articles were performed. Individual efficacy and adverse effect data was extracted from each of the studies according to a predefined protocol. The summary odds ratios were calculated using the Dersimonian and Laird method under a random effects model.

Results: A total of 41 trials met our pre-defined inclusion criteria and were included in our analysis. Results in the 32 studies examining PONV indicated a 46% reduction in the odds of PONV in the 5-HT_3-treated group (0.54 [95% CI 0.42-0.71], $P < 0.001$). Evaluation of PONV by traditional antiemetic agent demonstrated a 39% reduction compared with droperidol (0.61 [95% CI 0.42-0.89], $P < 0.001$) and a 56% reduction compared with metoclopramide (0.44 [95% CI 0.31-0.62], $P < 0.001$). Results in the 34 studies examining vomiting indicated a 38% reduction in the odds of vomiting in the 5-HT_3-treated group (0.62 [95% CI 0.48-0.81], $P < 0.001$).

Conclusions: The 5-HT_3 receptor antagonists are superior to traditional antiemetic agents for the prevention of PONV and vomiting. The reduction in the odds of PONV and vomiting is significant in the overall analysis and the subgroup analyses comparing 5-HT_3 receptor antagonists with droperidol and metoclopramide.

Objectif : La recherche de moyens de prévention des nausées et vomissement postopératoires (NVPO) a porté sur de nombreux antiémétiques incluant des médicaments traditionnels (métoclopramide, perphénazine, prochlorpérazine, cyclizine et dropéridol) et des antagonistes du récepteur 5-HT_3 (ondansétron, dolasétron, granisétron et tropisétron). Les résultats ont été divergents et contradictoires. La présente révision systématique quantitative évalue l'efficacité comparée des antagonistes du récepteur 5HT_3 et des antiémétiques traditionnels dans la prévention des NVPO.

Méthode : Une recherche systématique des documents de langue anglaise a été faite dans MEDLINE, EMBASE et Pre-MEDLINE, de 1966 à octobre 1999, suivie d'une recherche manuelle des articles retenus. Les données sur l'efficacité individuelle et les effets indésirables ont été extraites de chaque étude selon un protocole prédéfini. Les risques relatifs d'ensemble ont été calculés à l'aide de la méthode de Dersimonian et Laird d'après un modèle d'effet aléatoire.

Résultats : Quarante et un essais répondaient à nos critères d'inclusion prédéfinis et ont été retenus dans notre analyse. Les résultats de 32 études sur les NVPO ont indiqué une réduction de 46 % du risque relatif de NVPO chez les patients traités avec anti-5-HT_3 (0,54 [IC de 95 %; 0,42-0,71]; $P < 0,001$). Comparés aux autres antiémétiques traditionnels, les anti-5-HT_3 ont démontré une réduction du risque relatif de 39 % comparés au dropéridol (0,61 [IC de 95 %; 0,42-0,89]; $P < 0,001$) et de 56 % comparés au métoclopramide (0,44 [IC de 95 %; 0,31-0,62]; $P < 0,001$). Les résultats de 34 études sur les vomissements ont indiqué une réduction de 38 % du risque relatif chez les patients traités avec anti-5-HT_3 (0,62 [IC de 95 %; 0,48-0,81]; $P < 0,001$).

Conclusion : Les antagonistes du récepteur 5-HT_3 ont une action supérieure aux antiémétiques traditionnels pour prévenir les NVPO et les vomissements. La réduction de la probabilité de NVPO et de vomissements est significative dans l'analyse globale et dans les analyses de sous-groupes où on a comparé les antagonistes du récepteur 5-HT_3 avec le dropéridol et le métoclopramide.

From the Clinical Service Unit Pharmaceutical Sciences, Vancouver Hospital and Health Sciences Centre and Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, B.C., Canada.

Address correspondence to: Dr. Peter J. Zed, CSU Pharmaceutical Sciences, Vancouver Hospital & Health Sciences Centre, 855 West 12th Ave., Vancouver, BC, V5Z 1M9 Canada. Phone: 604-875-4077; Fax: 604-875-5267; E-mail: zed@interchange.ubc.ca

Presented at the American College of Clinical Pharmacy (ACCP) Annual Meeting, October 26th, 1999 in Kansas City, MO, USA.

Accepted for publication June 28, 2000.

POSTOPERATIVE nausea and vomiting (PONV) are commonly reported adverse reactions following surgery.[1] The incidence of PONV has been reported to be as high as 75% following some surgical procedures.[2] Besides the discomfort caused by nausea and vomiting following surgery, PONV can contribute to the development of aspiration, wound dehiscence and increased bleeding.[3] Patients who experience PONV consume more resources and require additional health care professional time than do those in whom these complications are avoided.[4] This increased resource consumption leads to a higher cost of care from the hospital perspective and a higher cost to the patient.

Prophylaxis with antiemetics has been shown to reduce the incidence of PONV in surgical procedures by 15-30% (absolute risk reduction).[5,6] The use of antiemetics for the prevention and optimal management of PONV has been shown to: (i) improve patient satisfaction; (ii) decrease recovery and discharge times; and (iii) reduce unanticipated hospital admissions.[7–10]

Numerous antiemetics have been studied for the prevention of PONV in surgery including traditional agents (metoclopramide, perphenazine, prochlorperazine, cyclizine and droperidol) and the 5-HT$_3$ receptor antagonists (ondansetron, dolasetron, granisetron and tropisetron), all of which have been associated with varying degrees of success.[11–51] Furthermore, the results of these trials have been divergent and inconsistent. There is a theoretical basis for a difference in efficacy between the 5-HT$_3$ antagonists and traditional agents because of their distinct mechanisms of action. The traditional agents are primarily dopamine receptor antagonists whereas the 5-HT$_3$ antagonist act on serotonin receptors.[52] The purpose of this quantitative systematic review was to evaluate the effectiveness of 5HT$_3$ receptor antagonists compared to traditional antiemetics for the prevention of PONV in all types of surgery.

Materials and Methods

Data sources

A systematic search of the English language literature using computerized MEDLINE, EMBASE, and PreMEDLINE databases from 1966 to October 1999 and a manual search of references from retrieved articles were performed. Search terms included: *nausea, vomiting, emesis, postoperative, surgery, ondansetron, granisetron, tropisetron, dolasetron, metoclopramide, droperidol, prochlorperazine, perphenazine, dimenhydrinate, and cyclizine.*

Study selection

Randomized, double-blinded, controlled clinical trials evaluating agents for prophylaxis of PONV in adults (>18 yr) receiving general anesthesia were considered for inclusion. Only studies that evaluated PONV, vomiting, or nausea as an endpoint were eligible for inclusion. Of these, studies comparing any 5-HT$_3$ receptor antagonist (ondansetron, dolasetron, tropisetron, granisetron) with at least one other prophylactic drug therapy were included. Exclusion criteria were previously published data, studies that compared only combinations of antiemetics, data published only in abstract form and unpublished data.

Outcome definitions

PONV was defined as nausea or emetic episodes (including vomiting or retching) occurring less than 48 hr after surgery. The individual trialists' definitions of PONV and vomiting were assumed to be similar and combinable. Adverse reactions to antiemetics were subcategorized as headache, dizziness and sedation.

Data extraction

Each report was read by all three authors independently to assess adequacy of randomization and blinding and to assess description of withdrawals. Assessment of methodological quality was built into the inclusion/exclusion criteria; therefore, another formal assessment was not completed.

Data extracted included sample size, patient characteristics, surgery type, dose, timing and route of administration of antiemetic agents, anesthetic regimens, incidences of PONV, vomiting, nausea, and adverse events. Attempts were made to acquire additional information from investigators as required. Discrepancies of data extraction were resolved by group consensus.

Statistical methods and sensitivity analysis

The incidences of PONV, nausea, vomiting and adverse events were analyzed separately. Odds ratios (OR) with 95% confidence intervals (CI) and the summary odds ratios were calculated using the Dersimonian and Laird method under a random-effects model.[53] A statistically significant result was assumed when the 95% CI of the OR did not include 1. Tests for heterogeneity of the OR was performed using the Cochrane Q method.[54] Homogeneity was assumed when P was > 0.10.[55] Heterogeneity was also evaluated visually using Galbraith plots.[56] Where heterogeneity was detected, accepted methods for exploration of statistical heterogeneity using clinical parameters were used.[57] Trials were subgrouped by surgery type, traditional antiemetic agent, induction agent, previous history of PONV,

and induction anesthetic. Publication bias was investigated through visual inspection of funnel plots whereby ORs were plotted against study sample size.[54] Cumulative analysis ordered by publication date was also performed on the PONV and vomiting endpoints to determine the contribution of successive trials to the pooled results. The number needed to treat (NNT) was calculated for the efficacy outcomes of PONV and vomiting and the number need to harm (NNH) was calculated for the toxicity parametres.

Sensitivity analyses were performed by exploring for extremes of outcomes grouped by traditional antiemetic and surgery type. Robustness of the analysis was further evaluated using a technique based upon the "file drawer" problem.[58] This technique is based upon the premise that published journals are filled with only 5% of studies whereas a further 95% reside in "file drawers" due to lack of statistical significance of their results. Therefore, the number of unretrieved studies averaging null results required to bring the new overall *P*-value to the brink of significance ($P = 0.05$) was calculated for each endpoint. Robustness is typically set at 5k+10 studies where k is equal to the number of originally identified studies.

Results

Study selection and characteristics

Our search strategy identified 45 articles which, before review, appeared to meet our inclusion criteria. One trial was excluded due to obvious duplication of publication[59] and one due to uninterpretable results.[60] Two trials were excluded because patients did not receive general anesthesia.[61,62] Thus, a total of 41 trials met our pre-defined inclusion criteria and were included in our analysis.[11–51] Although our search evaluated the literature since 1966 all of the trials included in this analysis were published since 1992.

We excluded the nausea endpoint from further analysis because of the lack of a standard definition across trials. The trialists were inconsistent in their definition of nausea in that some considered episodes of vomiting as both nausea and emesis whereas others classified such episodes as vomiting alone. Secondly, methods of nausea determination varied widely among the trials from patient report to investigator elicited to request for rescue therapy. Each of these methods has been shown to yield different rates of nausea.[63] Characteristics of the included studies are summarized in Table I.

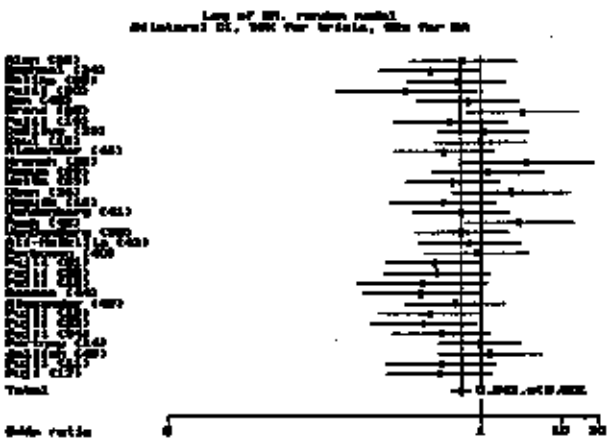

FIGURE 1 For each trial (represented by a vertical dash) the log of the odds ratio for effect size is plotted, with values to the left of the equal effect vertical line (OR=1) indicating that the trial found 5-HT antagonists to be more effective and values to the right of the equal effect vertical line indicating that the trial found traditional antiemetic to be more effective. 95% confidence intervals are shown (horizontal lines) for each trial. The summary odds ratio using the random effects model is indicated by "TOTAL". The dashed vertical line also indicates the summary odds ratio. References are indicated by the bracketed number after the trial. Trials are shown in order of year of publication in ascending order.

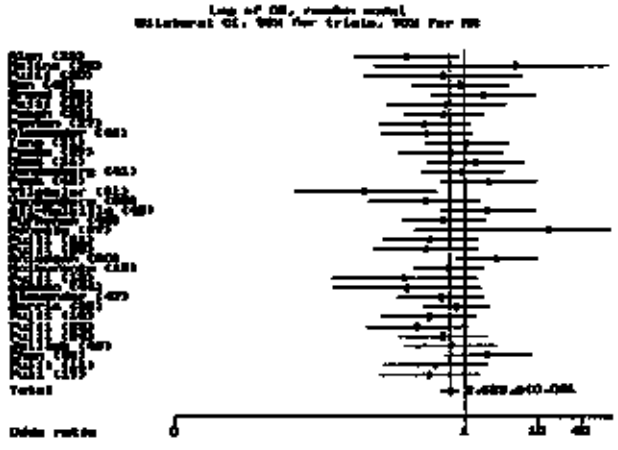

FIGURE 2 For each trial (represented by a vertical dash) the log of the odds ratio for effect size is plotted, with values to the left of the equal effect vertical line (OR=1) indicating that the trial found 5-HT antagonists to be more effective and values to the right of the equal effect vertical line indicating that the trial found traditional antiemetic to be more effective. 95% confidence intervals are shown (horizontal lines) for each trial. The summary odds ratio using the random effects model is indicated by "TOTAL" . The dashed vertical line also indicates the summary odds ratio. References are indicated by the bracketed number after the trial. Trials are shown in order of year of publication in ascending order.

TABLE I Characteristics of included studies.

Study, year, reference	*5-HT$_3$ antagonist(s)*	*Traditional agent(s)*	*Number of patients receiving 5-HT$_3$ antagonist/ traditional agents(s)*	*OR for PONV (95% CI)*	*OR for vomiting (95% CI)*
Breast					
Fujii, 1998[11]	Granisetron	Droperidol, Metoclopramide	30/60	0.30 (0.06 - 1.46)	0.39 (0.08 - 1.97)
General					
Fujii, 1997[12]	Granisetron	Droperidol	20/20	0.18 (0.03 - 1.18)	0.15 (0.02 - 1.42)
Koivuranta, 1997[13]	Ondansetron	Droperidol	195/193	N/A	0.61 (0.20 - 1.82)
Fortney, 1998[14]	Ondansetron	Droperidol	505/1012	0.94 (0.29 - 3.01)	N/A
Kaul, 1995[15]	Ondansetron	Metoclopramide	81/80	0.98 (0.26 – 3.64)	N/A
Naguib, 1996[16]	Ondansetron, Granisetron, Tropisetron	Metoclopramide	79/24	0.33 (0.07 - 1.49)	N/A
Gynecologic					
Fujii, 1998[17]	Granisetron	Droperidol	50/50	0.22 (0.05 - 0.99)	0.33 (0.08 - 1.42)
Fujii, 1998[18]	Granisetron	Droperidol	50/50	0.29 (0.06 - 1.32)	0.32 (0.07 - 1.50
Fujii, 1995[19]	Granisetron	Droperidol	25/50	0.41 (0.08 – 2.05)	0.58 (0.09 - 3.70)
Fujii, 1994[20]	Granisetron	Metoclopramide	20/20	0.11 (0.01 – 0.87)	0.53 (0.04 - 6.30)
Fujii, 1997[21]	Granisetron	Metoclopramide, Droperidol	45/90	0.25 (0.06 - 1.02)	0.34 (0.08 - 1.48)
Fujii, 1997[22]	Granisetron	Metoclopramide, Droperidol	30/60	0.27 (0.06 - 1.21)	0.30 (0.06 - 1.50)
Fujii, 1998[23]	Granisetron	Metoclopramide, Droperidol	30/60	0.18 (0.04 - 0.84)	0.22 (0.04 - 1.09)
Fujii, 1998[24]	Granisetron	Metoclopramide, Droperidol	40/80	0.30 (0.07 - 1.23)	0.51 (0.13 - 1.96)
Grond, 1995[25]	Ondansetron	Droperidol	40/40	3.37 (0.66 – 7.17)	1.86 (0.37 - 9.38)
Paech, 1995[26]	Ondansetron	Droperidol	83/89	N/A	0.53 (0.16 - 1.81)
Paxton, 1995[27]	Ondansetron	Droperidol	32/58	N/A	0.29 (0.07 - 1.20)
Wrench, 1996[28]	Ondansetron	Droperidol	20/20	3.78 (0.56 – 25.4)	N/A
Pueyo, 1996[29]	Ondansetron	Droperidol	25/25	1.18 (0.24 – 5.89)	0.65 (0.13 - 3.30)
Sniadach, 1997[30]	Ondansetron	Droperidol	80/78	N/A	2.73 (0.78 - 9.61)
Tang, 1996[31]	Ondansetron	Droperidol	40/81	N/A	1.09 (0.30 - 3.92)
Alon, 1992[32]	Ondansetron	Droperidol, Metoclopramide	22/44	0.58 (0.12 – 2.71)	0.17 (0.03 - 0.87)
DeSilva, 1995[33]	Ondansetron	Droperidol, Perphenazine, Metoclopramide	58/170	1.07 (0.29 – 3.95)	N/A
Raphael, 1993[34]	Ondansetron	Metoclopramide	61/62	0.22 (0.05 – 0.96)	N/A
Malins, 1994[35]	Ondansetron	Metoclopramide	50/50	0.49 (0.12 – 2.02)	5.10 (0.06 - 425.2)
Chen, 1996[36]	Ondansetron	Metoclopramide	25/24	2.40 (0.43 - 13.4)	1.49 (0.33 - 6.68)
Monagle, 1997[37]	Ondansetron	Metoclopramide	45/46	N/A	14.23 (0.21 - 954.8)
Morris, 1998[38]	Ondansetron	Metoclopramide	465/462	N/A	0.77 (0.28 - 2.13)
Watts, 1996[39]	Ondansetron	Metoclopramide, Cyclizine	59/107	0.43 (0.11 - 1.68)	N/A
Purhonen, 1997[40]	Tropisetron	Droperidol	48/49	0.87 (0.20 - 3.83)	0.52 (0.14 - 1.88)
Nasal					
VanDenBerg,1996[41]	Ondansetron	Prochlorperazine	55/110	0.55 (0.14 - 2.10)	0.29 (0.05 - 1.64)
Neurologic					
Pugh, 1996[42]	Ondansetron	Metoclopramide	30/30	3.05 (0.64 - 14.62)	2.15 (0.49 - 9.43)
Ophthalmologic					
Ali-Melkkila, 1996[43]	Ondansetron	Metoclopramide	40/40	0.70 (0.16 – 3.13)	2.11 (0.48 - 9.17)
Ascaso, 1997[44]	Ondansetron	Metoclopramide	116/51	0.17 (0.03 - 0.90)	0.16 (0.02 - 1.62)
Orthopedic					
Gan, 1994[45]	Ondansetron	Droperidol	42/38	0.68 (0.16 – 2.92)	0.89 (0.20 - 3.98)
Alexander, 1995[46]	Ondansetron	Droperidol	43/43	0.34 (0.08 – 1.45)	0.31 (0.07 - 1.31)
Alexander, 1997[47]	Ondansetron	Metoclopramide	42/42	0.46 (0.11 – 2.0)	0.48 (0.13 - 1.83)
Chen, 1998[48]	Ondansetron	Prochlorperazine	37/41	N/A	2.02 (0.53 - 7.73)
Otic					
Jellish, 1998[49]	Ondansetron	Droperidol	40/40	1.26 (0.29 - 5.54)	0.64 (0.15 - 2.75)
Vandenberg, 1996[50]	Ondansetron	Prochlorperazine	37/74	0.55 (0.13 - 2.23)	0.95 (0.26 - 3.47)
Thyroid					
Yilmazlar, 1996[51]	Tropisetron	Metoclopramide	20/20	N/A	0.04 (0.01 - 0.41)
TOTAL			2855/3783	0.54 (0.42-0.71)	0.62 (0.48-0.81)

N/A: Trial did not study or report this endpoint.

TABLE II Effects of 5-HT_3 antagonists *vs* traditional antiemetics on PONV

5-HT_3 antagonist(s)	*Trials*	*Number of patients receiving 5 HT_3 antagonist/traditional agent(s)*	*OR for PONV (95% CI) [test for heterogeneity]**	*OR for vomiting (95% CI) [test for heterogeneity]**
vs all traditional agents	PONV: 32 Vomiting: 34	PONV: 1858/2715 Vomiting: 1992/2308	0.54 (0.42 – 0.71) [*P* = 0.21] NNT=10 (95% CI 7-15)	0.62 (0.48 – 0.81) [*P* = 0.19] NNT=16 (95% CI 10-44)
vs metoclopramide	PONV: 19 Vomiting: 18	PONV: 908/782 Vomiting: 1132/1061	0.44 (0.31 – 0.62) [*P* = 0.36] NNT=6 (95% CI 5-10)	0.50 (0.32 –0.77) [*P* = 0.24] NNT=10 (95% CI 7-23)
vs droperidol	PONV: 18 Vomiting: 20	PONV: 1113/1639 Vomiting: 960/1022	0.61 (0.42 – 0.89) [*P* = 024] NNT=14 (95% CI 8-46)	0.56 (0.41 – 0.76) [*P* = 0.48] NNT=12 (95% CI 7-32)

*Cochrane's Q test for heterogeneity
NNT = Number needed to treat

TABLE III Effects of 5-HT_3 antagonists *vs* traditional antiemetics on PONV by surgery type.

Surgery type	*Trials*	*Number of patients receiving 5 HT_3 antagonist/traditional agent(s)*	*OR for PONV (95% CI) [test for heterogeneity]**	*OR for vomiting (95% CI) [test for heterogeneity]**
Gynecologic	PONV: 18 Vomiting: 20	PONV: 698/1051 Vomiting: 1245/1506	0.51 (0.34 – 0.76) [*P* = 0.27] NNT=7 (95% CI 5-13)	0.61 (0.44 – 0.85) [*P* = 0.33] NNT=22 (95% CI 11-)
General	PONV: 4 Vomiting: 2	PONV: 685/1136 Vomiting: 215/213	0.64 (0.36 – 1.15) [*P* = 0.23]	0.43 (0.13 – 1.43) [*P* = 0.32]
Orthopedic	PONV: 3 Vomiting: 4	PONV: 127/123 Vomiting: 164/164	0.47 (0.28 – 0.79) [*P* = 0.54] NNT=6 (95% CI 3-97)	0.73 (0.32 – 1.66) [*P* = 0.41]
Ophthalmologic	PONV: 2 Vomiting: 2	PONV: 156/91 Vomiting: 156/91	0.36 (0.09 – 1.48) [*P* = 0.32]	0.68 (0.06 – 8.34) [*P* = 0.32]
Otic	PONV: 2 Vomiting: 2	PONV: 77/114 Vomiting: 77/114	0.80 (0.35 – 1.80) [*P* = 0.32]	0.81 (0.42 – 1.59) [*P* = 0.58]

*Cochrane's Q test for heterogeneity
NNT = Number needed to treat

PONV

The summary of results of the thirty-two studies examining PONV indicated a 46% reduction in the odds of PONV in the 5-HT_3-treated group (OR 0.54 [95% CI 0.42-0.71], $P < 0.001$, NNT = 10, [95% CI 7-15]) (Figure 1, Table II). The test for heterogeneity of treatment effect of PONV studies was not significant, ($P = 0.21$). Visual inspection of the corresponding funnel plot revealed no evidence of publication bias.

Table III summarizes the results when the PONV endpoint was analysed by surgery type. A significant benefit favouring 5-HT_3 antagonists was found for gynecological and orthopedic surgery. Table II depicts the PONV outcomes grouped by traditional antiemetic (metoclopramide and droperidol). There were insufficient trials involving other traditional antiemetics to justify further pooling. Evaluation of PONV by traditional antiemetic agent demonstrated a beneficial effect of 5-HT_3 over droperidol (OR 0.61 [95% CI 0.42-0.89], $P < 0.001$, NNT = 14, [95% CI 8-46]) and metoclopramide (OR 0.44 [95% CI 0.31-0.62], $P < 0.001$, NNT = 6, [95% CI 5-10]). Cumulative meta-analysis by year revealed that the benefit of 5-HT_3 antagonists over traditional therapy achieved terminal significance at the advent of the trial by Fujii *et al.* in 1997.[22]

Vomiting

The summary of results of the 34 studies examining vomiting indicated a 38% reduction in the odds of vomiting in the 5-HT_3-treated group (OR 0.62 [95% CI, 0.48-0.81], $P < 0.001$, NNT = 16 [95% CI 10-44]) (Figure 2, Table II). The test for heterogeneity

TABLE IV Adverse effects associated with 5-HT$_3$ antagonists and traditional antiemetics.

Intervention	*Trials*	*All ADRs (95% CI) [test for heterogeneity]**	*Headache (95% CI) [test for heterogeneity]**	*Sedation (95% CI) [test for heterogeneity]**	*Dizziness (95% CI) [test for heterogeneity]**
5 HT$_3$ *vs* traditional agents	All ADR's: 24 Headache: 12 Sedation: 11	1.0 (0.79 – 1.26) [*P* = 0.34]	1.65 (1.35 – 2.02) [*P* = 0.97] NNH=28 (95% CI 15-200)	0.47 (0.34 – 0.64) [*P* = 0.91] NNH=14 (95% CI 9-26)	1.12 (0.86 – 1.45) [*P* = 0.99]
5 HT$_3$ *vs* metoclopramide	All ADR's: 8 Headache: 5 Sedation: 5 Dizziness: 5	0.94 (0.62 – 1.44) [*P* = 0.39]	1.34 (0.75 – 2.40) [*P* = 0.99]	0.56 (0.20 – 1.60) [*P* = 0.84]	1.13 (0.63 – 2.00) [*P* = 1.0]
5 HT$_3$ *vs* droperidol	All ADR's: 19 Headache: 10 Sedation: 9 Dizziness: 10	0.73 (0.51 – 1.05) [*P* = 0.47]	1.68 (1.34 – 2.11) [*P* = 0.92] NNH=15 (95% CI 10-35)	0.39 (0.29 – 0.54) [*P* = 0.78] NNT=12 (95% CI 8-20)	1.11 (0.84 – 1.48) [*P* = 0.99]

*Cochrane's Q test for heterogeneity
NNH = Number needed to harm

of treatment effect in vomiting studies was not significant, ($P = 0.19$). As with the PONV endpoint, visual inspection of the corresponding funnel plot revealed no evidence of publication bias.

Table III summarizes the results when the vomiting endpoint was analysed by surgery type. A benefit favouring 5-HT$_3$ antagonists was found only for gynecological surgery (OR 0.61 [95% CI 0.44-0.85], < 0.001, NNT =22 [95% CI 11-∞). Table II depicts the vomiting outcomes grouped by traditional antiemetic (metoclopramide and droperidol). As with the PONV endpoint there were insufficient trials involving other traditional antiemetics to justify further pooling. Evaluation of vomiting by traditional antiemetic agent demonstrated a beneficial effects of 5-HT$_3$ over droperidol (OR 0.56 [95% CI 0.41-0.76], $P < 0.001$, NNT = 12 [95% CI 7-32]) and metoclopramide (OR 0.50 [95% CI 0.32-0.77], $P < 0.001$, NNT = 10 [95% CI 7-23]).

Adverse events

Table IV summarizes the common adverse events associated with each of the study drugs. There was no difference between the 5-HT$_3$ antagonists and the traditional agents in the overall rate of adverse reactions. Headache was the most common adverse experience occurring in 14.6% of patients in whom it was evaluated (12 trials) and was more common in the 5-HT$_3$ group (17.0%) than in the traditional antiemetic group (13.0%) (OR 1.65 [95% CI 1.35-2.02], $P < 0.001$, NNH = 28 [95% CI 15-200]). Sedation occurred in 9.6% of patients evaluated (11 trials) and was more common in the traditional antiemetic groups (11.9%) than in the 5-HT$_3$ group (5.6%) (OR 0.47 [95% CI 0.32-0.64], $P < 0.001$, NNH = 14 [95% CI 9-26]). Finally, dizziness was found in 7.6% of patients evaluated (10 trials) and the incidence was not different between the two groups.

We also evaluated the individual traditional agents. Compared with droperidol, 5-HT$_3$ antagonists were associated with a higher incidence of headache (OR 1.68 [95% CI 1.34-2.11], $P < 0.001$, NNH = 15 [95% CI 10-35]) and a lower incidence of sedation (OR 0.39 [95% CI 0.29-0.54], $P < 0.001$, NNH = 12, 95% CI 8-20). No differences were detected between 5-HT$_3$ antagonists and metoclopramide for the adverse effects evaluated.

Heterogeneity analyses

The Galbraith plots for the PONV endpoint (Figure 3) and the vomiting endpoint (Figure 4) are provided. The regions delimited by the dotted lines represent areas in which, in the absence of statistical heterogeneity, 95% of trials would be expected to lie.[5,6] Thus, for the PONV endpoint, the seven trials that fell outside this region were thought to be statistically heterogeneous.[14,23,25,28,33,36,42] On closer inspection of these trials, there was no factor determined to be common among them which would explain their dissimilar results from the aggregate. For the vomiting endpoint, five trials fell outside the region of homogeneity.[30,37,42,48,51] Similarly, no common factor was found among them that would explain these differences. The overall analyses of these two endpoints were repeated without the anomalous trials which further strengthened the estimated beneficial effects of 5-HT$_3$ antagonists on PONV (OR 0.44 [95% CI 0.35 – 0.55]; test

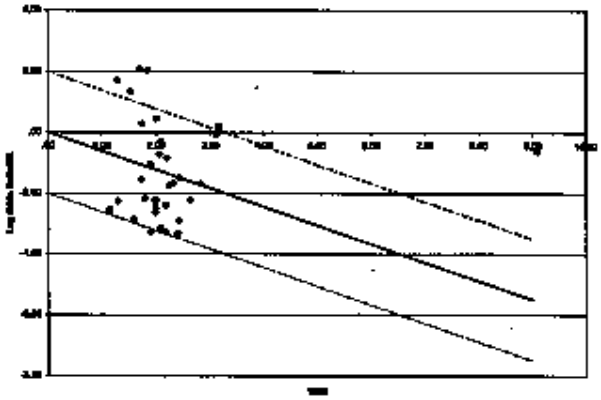

FIGURE 3 For each trial evaluating PONV as an endpoint (represented by a point in the plot), the ratio of the log odds ratio to its standard error (the Z statistic) has been plotted against the reciprocal of the standard error. The least precise results from small trials appear towards the left of the figure and results from larger trials appear towards the right. The slope of the solid line through the origin represents an overall log odds ratio. The dotted lines, two units above and below the solid line, represent an area between which 95% of the trial results would be expected to lie. The trials lying outside of these boundaries have been investigated for heterogeneity.

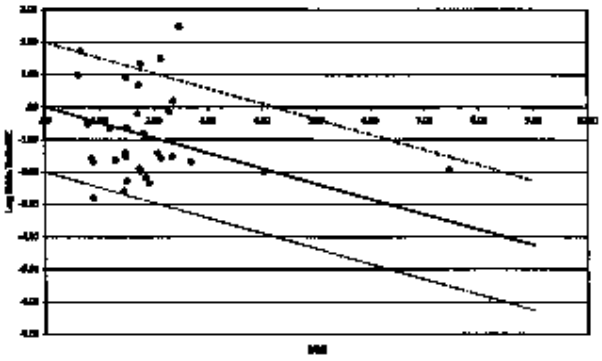

FIGURE 4 For each trial evaluating vomiting as an endpoint (represented by a point in the plot), the ratio of the log odds ratio to its standard error (the Z statistic) has been plotted against the reciprocal of the standard error. The least precise results from small trials appear towards the left of the figure and results from larger trials appear towards the right. The slope of the solid line through the origin represents an overall log odds ratio. The dotted lines, two units above and below the solid line, represent an area between which 95% of the trial results would be expected to lie. The trials lying outside of these boundaries have been investigated for heterogeneity.

for heterogeneity P = 0.46; NNT = 6) and vomiting (OR 0.57 [95% CI 0.46 – 0.70]; test for heterogeneity P = 0.42; NNT=13) compared to traditional agents.

Sensitivity analyses

The results of all analyses were robust to varying the extremes of outcomes when grouped by traditional antiemetic and type of induction anesthetic. When the results were pooled by surgery type, only in gynecologic surgery were the 5-HT_3 receptor antagonists superior to traditional agents for both the PONV and vomiting endpoints.

Techniques used to solve for the "file drawer" problem revealed that the number of unretrieved trials averaging null results that would be required to bring the P-value up to 0.05 were 598 and 245 for PONV and vomiting, respectively. The limit for robustness for this review was defined as 5k + 10 trials where k equals the number of trials included in the analysis. By this method, the threshold values for PONV and vomiting would be 170 and 180 trials, respectively, and therefore our results are robust.

Discussion

The findings of this quantitative systematic review indicate that 5-HT_3 receptor antagonists are superior to conventional antiemetic agents for the prevention of PONV and vomiting. The reduction in the odds of PONV and vomiting is significant in the overall analysis and the subgroup analyses comparing 5-HT_3 receptor antagonists to droperidol and metoclopramide. The evidence suggests that the inconsistencies among the results of randomized trials comparing 5-HT_3 receptor antagonists with traditional agents are most likely due to small sample sizes. These results remained robust to the sensitivity analyses we conducted.

When the results were pooled by surgery type, only in gynecological surgery were the 5-HT_3 receptor antagonists superior to traditional agents for both the PONV and vomiting endpoints. This finding may be due to the fact that many more trials were completed in this surgical category (Table III). For example, although the cumulative numbers of patients in the studies of other surgical procedures were similar to that of gynecological surgery (i.e. general surgery), the overall number of trials was so small such that one negative trial could be sufficient to obviate the 5-HT_3 antagonists' superiority over traditional agents. However, from the results of our analysis, it is possible that the absolute risk reduction associated with the prophylactic using a 5-HT_3 antagonist over a conventional agent may be greater with some surgical procedures, specifically

major gynecological and orthopedic surgery, which are thought to be highly emetogenic surgery types.[45,48] In surgical procedures where there is a high baseline event rate, there is much more scope to show a statistically significant difference among comparators.[64]

In a meta-analysis, it is important to investigate the presence and source of statistical heterogeneity.[57] We utilized a random-effects model that accounted for heterogeneity among the ORs of pooled studies. In addition, we utilized Cochran's Q to test for the presence of statistical heterogeneity and were unable to identify its presence via this method. However, statistical tests for heterogeneity have low power and, thus, heterogeneity cannot be ruled out solely through their use; thus other methods should also be utilized.[57] By utilizing Galbraith plots (Figures 3,4), heterogeneity in our results was revealed for both the PONV and vomiting endpoints. Although we could not identify any common factors which could explain the heterogeneity, when the analyses were repeated without the results from these outlying studies, our original results of 5-HT_3 superiority were further strengthened as the ORs and the 95% confidence intervals became smaller. Therefore, we can be confident that our overall analyses are conservative and any heterogeneity present in the trials is influencing the overall ORs in a negative direction.

We assumed that the efficacy of the four 5-HT_3 antagonists is equivalent and thus the results of trials utilizing these agents are readily combinable. This assumption is supported by several comparative trials of 5-HT_3 receptor antagonists for the prophylaxis of PONV in which there have been no difference in efficacy.[16,65] Although not all of the 5-HT_3 receptor antagonists have been directly compared, available evidence suggests that there are no clinical advantages of any one agent over the others when used for the prophylaxis of PONV. It should be noted that the majority of 5-HT_3-treated patients in this analysis received ondansetron (Table I).

Most trials evaluating the prophylactic value of antiemetic agents consider the occurrence of PONV (i.e. either nausea or vomiting) as the primary endpoint. Typically, secondary endpoints of the trials include the separate outcomes of nausea or vomiting. We could not combine the results from nausea across the trials due to the lack of a standard definition used by investigators. However, although we recognize this as a limitation in our analysis, we do not perceive that this omission influenced the applicability of our results as the PONV endpoint is sufficiently broad to include incidences of nausea in its definition and thus is the most relevant.

Several important limitations of this meta-analysis should be recognized. As in any meta-analysis of previously published results, this analysis relied on information from trials that was reported in a variety of ways. Consequently, although every effort was made to standardize the extraction of relevant information, available data and definitions of outcomes varied among studies. We also did not account for differences in dosage regimens among trials and combined results based solely upon the type of antiemetic utilized. A limitation in this approach is that possible dose-related differences in effect are not considered. We did not perform sensitivity analysis on this parameter as there were not enough trials utilizing high doses of agents to quantitate this effect on the overall OR and differences in dosing regimens between trials did not explain the statistical heterogeneity that was observed in the Galbraith plots.

The influence of publication bias must be considered in any meta-analysis.[66] We attempted to detect this source of bias through the construction of funnel plots.[54] This plot allowed us to assess, through visual inspection, whether most of the articles that were included in our analysis reported positive results. Fortunately, it appeared that there were an approximately equal number of both positive and negative trials making publication bias less likely. In addition, we utilized calculations for the "file drawer" problem to determine the number of papers averaging null results that would be required to have been overlooked to bring our results to the brink of significance.[58] Finally, because we limited our search strategy to include only articles published in English language journals, it is possible that we excluded some literature that would have otherwise been included in our analysis. However, there is no reason to believe that the results of these studies would have been so divergent from the published English language literature as to change the results of this analysis.

Covert duplicate publication is a direct threat to meta-analyses.[67] We were able to locate one trial that contained information that had obviously been previously published.[59] However, in the trials that we included in our analysis, many investigators completed more than one study. Therefore, it is possible that there was some overlap in the data reported in each of these trials although there was no obvious similarity between these trials (i.e. number of patients evaluated, identical event rates reported). We attempted to contact several authors of more than one study but were unsuccessful in determining if any of the data was duplicated in multiple publications.

During the completion of this meta-analysis, Domino *et al.*[68] published a similar meta-analysis comparing ondansetron to droperidol and metoclopramide in the prevention of PONV. They found that

ondansetron and droperidol were both more effective than metoclopramide in preventing vomiting but there was no difference between ondansetron and droperidol in the adult patients studied. Several differences between this meta-analysis and our study should be addressed. First, ondansetron was the only 5-HT_3 receptor antagonist evaluated resulting in the exclusion of a number of trials evaluating dolasetron, granisetron and tropisetron. This resulted in the exclusion of over 1100 patients comparing 5-HT_3 receptor antagonists other than ondansetron with traditional antiemetics.[11,12,16-24,40,51] As mentioned earlier we have no reason to believe these agents are pharmacologically different which is also supported by several comparative trials of 5-HT_3 receptor antagonists for the prophylaxis of PONV in which there have been no difference in efficacy.[16,65] Although not all of the 5-HT_3 receptor antagonists have been directly compared, available evidence suggests that there are no clinical advantages of any one agent over the others when used for the prophylaxis of PONV. Second, both pediatric and adult patients were included resulting in a heterogeneous patient population limiting the external validity of the overall analysis. Third, PONV as an endpoint was not used, making comparisons with our primary endpoint difficult. Fourth, heterogeneity testing was not as extensive and important factors such as surgery type were not evaluated by Domino *et al.*[68] Finally, our analysis included all traditional agents and was not limited to droperidol and metoclopramide. As a result of these differences, Domino *et al.*[68] failed to demonstrate an overall benefit of ondansetron over droperidol in adults as was the case in our analysis. Due to a smaller population of adult patients included in their analysis, there may have been insufficient power to detect a clinically important difference.

Based on the results of this analysis, it appears that the 5-HT_3 antagonists are superior to traditional antiemetics in the prevention PONV. When compared with droperidol and metoclopramide, 5-HT_3 receptor antagonists would prevent one patient from developing PONV for every 14 and six patients treated, respectively. It appears that these agents are associated with a higher incidence of headache but a lower incidence of sedation then with traditional antiemetic agents.

References

1 *Wetchler BV.* Postoperative nausea and vomiting in day-case surgery. Br J Anaesth 1992; 69: 33S–9.

2 *Haigh CG, Kaplan LA, Durham JM, Dupeyron JP, Harmer M, Kenny GNC* Nausea and vomiting after gynaecological surgery: a meta-analysis of factors affecting their incidence. Br J Anaesth 1993; 71: 517–22.

3 *Madej TH, Simpson KH.* Comparison of the use of domperidone, droperidol, and metoclopramide in the prevention of nausea and vomiting following major gynaecological surgery. Br J Anaesth 1986; 58: 884–7.

4 *Sanchez LA, Hirsch JD, Carroll NV, Miederhoff PA.* Estimation of the cost of postoperative nausea and vomiting in an ambulatory surgery center. J Res Pharm Econ 1995; 6: 35–44.

5 *Graczyk SG, McKenzie R, Kallar S, et al.* Intravenous dolasetron for the prevention of postoperative nausea and vomiting after outpatient laparoscopic surgery. Anesth Analg 1997; 84: 325–30.

6 *Helmers JH, Briggs L, Abrahamsson J, et al.* A single *iv* dose of ondansetron 8 mg prior to induction of anaesthesia reduces postoperative nausea and vomiting in gynaecological patients. Can J Anaesth 1993; 40: 1155–61.

7 *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 1998; 86: 274–82.

8 *Gold BS. Kitz DS, Lecky JH, Neuhaus JM.* Unanticipated admission to the hospital following ambulatory surgery. JAMA 1989; 262: 3008–10.

9 *Fancourt-Smith PF, Hornstein J, Jenkins LC.* Hospital admissions from the Surgical Daycare Centre of Vancouver General Hospital 1977-1987. Can J Anaesth 1990; 37: 699–704.

10 *Fortier J, Chung F, Su J.* Unanticipated admission after ambulatory surgery - a prospective study. Can J Anaesth 1998; 45: 612–9.

11 *Fujii Y, Tanaka H, Toyooka H.* Prevention of nausea and vomiting in female patients undergoing breast surgery: a comparison with granisetron, droperidol, metoclopramide and placebo. Acta Anaesthesiol Scand 1998; 42: 220–4.

12 *Fujii Y, Tanaka H, Toyooka H.* Granisetron reduces the incidence and severity of nausea and vomiting after laparoscopic cholecystectomy. Can J Anaesth 1997; 44: 396–400.

13 *Koivuranta M, Läärä E, Ranta P, Ravaska P, Alahuhta S.* Comparison of ondansetron and droperidol in the prevention of postoperative nausea and vomiting after laparoscopic surgery in women. Acta Anaesthesiol Scand 1997; 41: 1273–9.

14 *Fortney JT, Gan TJ, Graczyk S, et al.* A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. Anesth Analg 1998; 86: 731–8.

15 *Kaul HL, Rao U, Mandal NG, Rahman A* Comparative evaluation of single dose oral ondansetron and metoclopramide in a placebo-controlled study for

prevention of post-operative nausea and vomiting. J Anaesth Clin Pharmacol 1995; 12: 27–30.

16 *Naguib M, El Bakry AK, Khoshim MHB, et al.* Prophylactic antiemetic therapy with ondansetron, tropisetron, granisetron and metoclopramide in patients undergoing laparoscopic cholystectomy: a randomized, double-blind comparison with placebo. Can J Anaesth 1996; 43: 226–31.

17 *Fujii Y, Toyooka H, Tanaka H.* Prevention of postoperative nausea and vomiting with a combination of granisetron and droperidol. Anesth Analg 1998; 86: 613–6.

18 *Fujii Y, Saitoh Y, Tanaka H, Toyooka H.* Prophylactic antiemetic therapy with granisetron-droperidol combination in patients undergoing laparoscopic cholecystectomy. Can J Anaesth 1998; 45: 541–4.

19 *Fujii Y, Tanaka H, Toyooka H.* Prevention of postoperative nausea and vomiting with granisetron: a randomized, double-blind comparison with droperidol. Can J Anaesth 1995; 42: 852–6.

20 *Fujii Y, Tanaka H, Toyooka H.* Reduction of postoperative nausea and vomiting with granisetron. Can J Anaesth 1994; 41: 291–4.

21 *Fujii Y, Tanaka H, Toyooka H.* The effects of dexamethasone on antiemetics in female patients undergoing gynecologic surgery. Anesth Analg 1997; 85: 913–7.

22 *Fujii Y, Toyooka H, Tanaka H.* Prevention of PONV with granisetron, droperidol and metoclopramide in female patients with history of motion sickness. Can J Anaesth 1997; 44: 820–4.

23 *Fujii Y, Saitoh Y, Tanaka H, Toyooka H.* Prevention of PONV with granisetron, droperidol or metoclopramide in patients with postoperative emesis. Can J Anaesth 1998; 45: 153–6.

24 *Fujii Y, Toyooka H, Tanaka H* Prevention of postoperative nausea and vomiting in female patients during menstruation: comparison of droperidol, metoclopramide and granisetron. Br J Anaesth 1998; 80: 248–9.

25 *Grond S, Lynch J, Diefenbach C, Altrock K, Lehmann KA.* Comparison of ondansetron and droperidol in the prevention of nausea and vomiting after inpatient minor gynecologic surgery. Anesth Analg 1995; 81: 603–7.

26 *Paech MJ, Pavy TJG, Evans SF.* Single-dose prophylaxis for postoperative nausea and vomiting after major abdominal surgery: ondansetron versus droperidol. Anaesth Intensive Care 1995; 23: 548–54.

27 *Paxton LD, McKay AC, Mirakhur RK.* Prevention of nausea and vomiting after day case gynaecological laparoscopy. A comparison of ondansetron, droperidol, metoclopramide and placebo. Anaesthesia 1995; 50: 403–6.

28 *Wrench IJ, Ward JEH, Walder AD, Hobbs GJ.* The prevention of postoperative nausea and vomiting using a combination of ondansetron and droperidol. Anaesthesia 1996; 51: 776–8.

29 *Pueyo FJ, Carrascosa F, Lopez L, Iribarren MJ, García-Pedrajas F, Saez A.* Combination of ondansetron and droperidol in the prophylaxis of postoperative nausea and vomiting. Anesth Analg 1996; 83: 117–22.

30 *Sniadach MS, Alberts MS.* A comparison of the prophylactic antiemetic effect of ondansetron and droperidol on patients undergoing gynecologic laparoscopy. Anesth Analg 1997; 85: 797–800.

31 *Tang J, Watcha MF, White PF.* A comparison of costs and efficacy of ondansetron and droperidol as prophylactic antiemetic therapy for elective outpatient gynecologic procedures. Anesth Analg 1996; 83: 304–13.

32 *Alon E, Himmelseher S.* Ondansetron in the treatment of postoperative vomiting: a randomized, double-blind comparison with droperidol and metoclopramide. Anesth Analg 1992; 75: 561–5.

33 *Desilva PHDP, Darvish AH, McDonald SM, Cronin MK, Clark K* The efficacy of prophylactic ondansetron, droperidol, perphenazine, and metoclopramide in the prevention of nausea and vomiting after major gynecologic surgery. Anesth Analg 1995; 81: 139–43.

34 *Raphael JH, Norton AC.* Antiemetic efficacy of prophylactic ondansetron in laporoscopic surgery: randomized, double-blind comparison with metoclopramide. Br J Anaesth 1993; 71: 845–8.

35 *Malins AF, Field JM, Nesling PM, Copper GM.* Nausea and vomiting after gynaecologocal laparoscopy: a comparison of premedication with oral ondansetron, metoclopramide and placebo. Br J Anaesth 1994; 72: 231–3.

36 *Chen PP, Chui PT, Gin T.* Comparison of ondansetron and metoclopramide for the prevention of post-operative nausea and vomiting after major gynaecologic surgery. Eur J Anaesthesiol 1996; 13: 485–91.

37 *Monagle J, Barnes R, Goodchild C, Hewitt M.* Ondansetron is not superior to moderate dose metoclopramide in the prevention of post-operative nausea and vomiting after minor gynecological surgery. Eur J Anaesthesiol 1997; 14: 604–9.

38 *Morris RW, Aune H, Feiss P, et al.* International, muticentre, placebo-controlled study to evaluate the effectiveness of ondansetron vs. metoclopramide in the prevention of post-operative nausea and vomiting. Eur J Anaesthesiol 1998; 15: 69–79.

39 *Watts SA.* A randomized double-blinded comparison of metoclopramide, ondansetron and cyclizine in day-case laparoscopy. Aust Soc Anaesth 1996; 24: 546–51.

40 *Purhonen S, Kauko M, Koski EMJ, Nuutinen L.* Comparison of tropisetron, droperidol, and saline in the prevention of postoperative nausea and vomiting after gynecologic surgery. Anesth Analg 1997; 84: 662–7.

41 *van den Berg AA.* The prophylactic antiemetic efficacy of prochlorperazine and ondansetron in nasal septal surgery: a randomized double-blind comparison. Aust Soc Anaesth 1996; 24: 538–45.
42 *Pugh SC, Jones NC, Barsoum LZ.* A comparison of prophylactic ondansetron and metoclopramide administration in patients undergoing major neurosurgical procedures. Anaesthesia 1996; 51: 1162–4.
43 *Ali-Melkkilä T, Kanto J, Katevuo R.* Tropisetron and metoclopramide in the prevention of postoperative nausea and vomiting. Anaesthesia 1996; 51: 232–5.
44 *Ascaso FJ, Ayala I, Carbonell P, Castro FJ, Palomar A.* Prophylactic intravenous ondansetron in patients undergoing cataract extraction under general anesthesia. Ophthalmologica 1997; 211: 292–5.
45 *Gan TJ, Collis GR, Hetreed M.* Double-blind comparison of ondansetron, droperidol and saline in the prevention of postoperative nausea and vomiting. Br J Anaesth 1994; 72: 544–7.
46 *Alexander R, Lovell AT, Seingry D, Jones RM.* Comparison of ondansetron and droperidol in reducing postoperative nausea and vomiting associated with patient-controlled analgesia. Anaesthesia 1995; 50: 1086–8.
47 *Alexander R, Fennelly M.* Comparison of ondansetron, metoclopramide and placebo as premedicants to reduce nausea and vomiting after major surgery. Anaesthesia 1997; 52: 695–703.
48 *Chen JJ, Frame DG, White TJ.* Efficacy of ondansetron and prochlorperazine for the prevention of postoperative nausea and vomiting after total hip replacement or total knee replacement procedures. Arch Intern Med 1998; 158: 2124–8.
49 *Jellish WS, Leonetti JP, Fluder E, Thalji Z.* Ondansetron versus droperidol or placebo to prevent nausea and vomiting after otologic surgery. Otolaryngol Head Neck Surg 1998; 118: 785–9.
50 *van den Berg AA.* A comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after tympanoplasty. Can J Anaesth 1996; 43: 939–45.
51 *Yilmazlar A, Yilmazlar T, Gürpinar E, Korun N, Kutlay O.* Anti-emetic efficacy of tropisetron and metoclopramide. J Int Med Res 1996; 24: 266–70.
52 *Watcha MF, White PF.* Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992; 77: 162–84.
53 *Dersimonian R, Laird N.* Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–88.
54 *Cook DJ, Sackett DL, Spitzer WO.* Methodologic guidelines for systematic reviews of randomized controlled trials in health care from the Potsdam consultation on meta-analysis. J Clin Epidemiol 1995; 48: 167–71.
55 *Fleiss JL.* Analysis of data from multiclinic trials. Control Clin Trials 1986; 7: 267–75.
56 *Galbraith RF.* A note on graphical presentation of estimated odds ratios from several clinical trials. Stat Med 1988; 7: 889–94.
57 *Thompson SG.* Why sources of heterogeneity in meta-analysis should be investigated. BMJ 1994; 309: 1351–5.
58 *Rosenthal R.* Meta-analysis: a review. Psychosomatic Medicine 1991; 53: 247–71.
59 *Jellish WS, Thalji Z, Fluter E, Leonetti JP.* Ondansetron versus droperidol or placebo when given prophylactically for prevention of postoperative nausea and vomiting in patients undergoing middle ear procedures. J Clin Anesth 1997; 9: 451–6.
60 *Doe EA, Jones P, O'Hara MA.* A comparison of prophylactic ondansetron hydrochloride and droperidol for strabismus repair in adults. J Pediatr Ophthmal Strabismus 1998; 35: 264–9.
61 *Pitkänen MT, Numminen MK, Tuominen MK, Rosenberg PH.* Comparison of metoclopramide and ondansetron for the prevention of nausea and vomiting after intrathecal morphine. Eur J Anaesthesiol 1997; 14: 172–7.
62 *Pan PH, Moore CH.* Intraoperative antiemetic efficacy of prophylactic ondansetron versus droperidol for Cesarean section patients under epidural anesthesia. Anesth Analg 1996; 83: 982–6.
63 *Kortilla K* The study of postoperative nausea and vomiting. Br J Anaesth 1992; 69(7Suppl1): 20S–3.
64 *Tramèr MR, Reynolds DJM, 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 1997; 87: 1277–89.
65 *Kortilla K, Clergue F, Leeser J, et al.* Intravenous dolasetron and ondansetron in prevention of postoperative nausea and vomiting: a multicenter, double-blind, placebo-controlled study. Acta Anaesthesiol Scand 1997; 41: 914–22.
66 *Stern JM, Simes RJ.* Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ 1997: 315: 640–5.
67 *Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ.* Impact of covert duplicate publication on meta-analysis: a case study. BMJ 1997; 315: 635–40.
68 *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 1999; 88: 1370–9.