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Original Article

A meta-analysis of prevention of postoperative nausea and vomiting: randomised controlled trials by Fujii et al. compared with other authors

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Summary

The population sampling in randomised controlled trials by Fujii et al. have been shown to exhibit unusual distributions. This systematic review analysed the effectiveness of prophylactic antiemetics in trials by Fujii et al. compared with other authors. Granisetron was more effective in trials by Fujii et al., relative risk ratios (RRR (95% CI)): nausea 0.53 (0.42–0.67), p = 0.00021; vomiting 0.60 (0.50–0.73), p = 0.00094. Ramosetron was also more effective in studies by Fujii et al.: vomiting 0.60 (0.39–0.91), p = 0.02; nausea or vomiting 0.71 (0.56–0.91); p = 0.006. In comparison with granisetron, droperidol was less effective in trials by Fujii et al. than others: nausea 2.41 (1.72–3.36), $p = 2.5 \times 10^{-7}$; vomiting 1.73 (1.26–2.38), $p = 6.4 \times 10^{-4}$. Postoperative nausea and vomiting was less likely to trigger rescue antiemesis after granisetron and metoclopramide in studies by Fujii et al., 0.40 (0.27–0.60), $p = 9.7 \times 10^{-6}$. Triggered rates of rescue were not different in studies by others for droperidol, granisetron and metoclopramide, but were less common after granisetron than droperidol and metoclopramide in studies by Fujii et al., 0.50 (0.38–0.66), $p = 1.7 \times 10^{-6}$ and 0.47 (0.34–0.64), $p = 2.6 \times 10^{-6}$, respectively. There was no synergism between antiemetics in trials by other authors. In contrast, in studies by Fujii et al., postoperative nausea and vomiting was more likely if granisetron was administered alone: nausea 4.20 (1.94–9.08), $p = 2.6 \times 10^{-4}$; vomiting 4.50 (2.55–7.97), $p = 2.3 \times 10^{-7}$; nausea or vomiting 5.00 (2.84–8.81), $p = 2.5 \times 10^{-8}$. Similarly, droperidol was less effective in studies by Fujii et al. if administered alone: vomiting 2.76 (1.25–6.11), p = 0.01; nausea or vomiting 2.96 (1.46–6.00), $p = 2.7 \times 10^{-3}$. The conclusion is that if, as recommended, data with unusual distributions are removed from meta-analysis and articles by Fujii et al. excluded, then the antiemetic effects of granisetron and ramosetron are greatly reduced; further, there is no evidence of synergism between antiemetics and indeed, some evidence of antagonism between antiemetic agents.

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I previously analysed the very unusual data distributions from 168 randomised controlled trials (RCTs) published by one author group (Fujii et al.) [1], concluding (with others in accompanying editorials [2–4]) that the data showed such unusual distributions as to suggest that sampling had not been random and that, therefore, the data should be excluded from any meta-analysis. Indeed, in 2001 Kranke et al. calculated how the antiemetic effect of granisetron was affected by exclusion of Fujii et al.'s data following their observa-

tion of the unusual distribution of headache in some of their RCTs [5, 6].

I wished to extend that analysis by assessing the extent to which Fujii et al.'s data differ from those of other authors, and therefore how the estimated effect of prophylaxis – by dexamethasone, droperidol, granisetron, metoclopramide and ramosetron – change with the exclusion of data from RCTs authored by Fujii et al. In addition, I wished to explore whether the reported antiemetic effects of these drugs given alone or in combination with another antiemetic are consistent with synergism or antagonism, in particular by comparing data from Fujii et al. with other data. Finally, I planned to assess the relative rates of postoperative nausea and vomiting (PONV) and antiemesis. The PONV-to-rescue rate can be calculated for different drugs, and used to compare RCTs authored by Fujii et al. with RCTs authored by other authors.

Methods

My original intention had been to publish an update to the Cochrane review, *Drugs for preventing postoperative nausea and vomiting*, in 2010 [7]. This has been delayed by the discovery of unusual distributions in Fujii et al.'s data [1] and further developments arising from that controversy, including an open request by 23 Editors-in-Chief to Dr Fujii's employers to determine the data's authenticity [8].

Therefore, I did not include RCTs published after January 2009, except for a search to July 2011 of (a) RCTs authored by Fujii; and (b) RCTs by any author about PONV prophylaxis with ramosetron compared with placebo. I included RCTs that reported PONV after placebo vs prophylactic dexamethasone, droperidol, granisetron, metoclopramide, ramosetron or ondansetron (included for comparison). I also included RCTs that compared granisetron with either droperidol or metoclopramide (comparisons reported by Fujii et al.). I searched: The Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; CINAHL; ISI WOS; LILACS; and INGENTA. I retrieved full texts and extracted the rate of an outcome once for each RCT. For RCTs that did not report a rate for the total observation period, for instance when separate rates were reported for 0–3 h and 3–24 h after surgery, I used rates from the period in which the outcome was most common. I analysed separately the rates of postoperative nausea, vomiting, their composite (nausea or vomiting, or PONV), rescue antiemesis and the rates of side effects. I did not assume that someone categorised as vomiting was also nauseated. I included studies that compared a combination of two drugs vs one of those drugs (for instance dexamethasone and ondansetron vs dexamethasone) as 'drug vs placebo', in this example ondansetron vs placebo. The comparison of these RCTs with those in which an antiemetic was not given to the control group forms the basis for an assessment of synergism and antagonism.

Summary relative risks and relative risk ratios were generated using both fixed-effect (FE) and random-effects (RE) models. An additional hybrid result is reported for some comparisons based on subgroup heterogeneity, quantified with the I^2 statistic, using the RE model for subgroups with $I^2 > 25\%$ and the FE result for subgroups with $I^2 < 25.1\%$. I generated forest plots, funnel plots and L'Abbé plots for each comparison, some of which are illustrated in the Results.

I used RevMan 5.1 [9] to generate relative risks (RRs), their ratios (RRRs), forest plots and funnel plots, and Excel to test the equality of RRRs for PONV following prophylactic antiemetics in papers by Fujii et al. to articles by other authors [10]. I used Intercooled Stata® 12 (StataCorp LP, College Station, TX, USA) to generate L'Abbé plots.

Results

I assessed 593 full-text RCTs for inclusion, from which I excluded 59, leaving 534 for data extraction and analysis (Appendix S1 (online only), Fig. 1). The number of RCTs that assessed PONV following prophylaxis is shown in Table 1 and their heterogeneity is shown in Table 2. The lack of heterogeneity in Fujii et al.'s data is very striking; I^2 values of zero are highly unusual. Most of the RCTs for granisetron were published by Fujii et al.

Table S1 in Appendix S2 (online only) quantifies the effect of each antiemetic, for all RCTs and when grouped by authorship, Fujii et al. or other authors. Granisetron was 1.3–2.5 times more effective (RR 0.77–0.40) in RCTs by Fujii et al. than others, the magnitude of the finding varying with outcome and statistical model. Exclusion of RCTs by Fujii et al. therefore results in granisetron's still being effective, but less so.

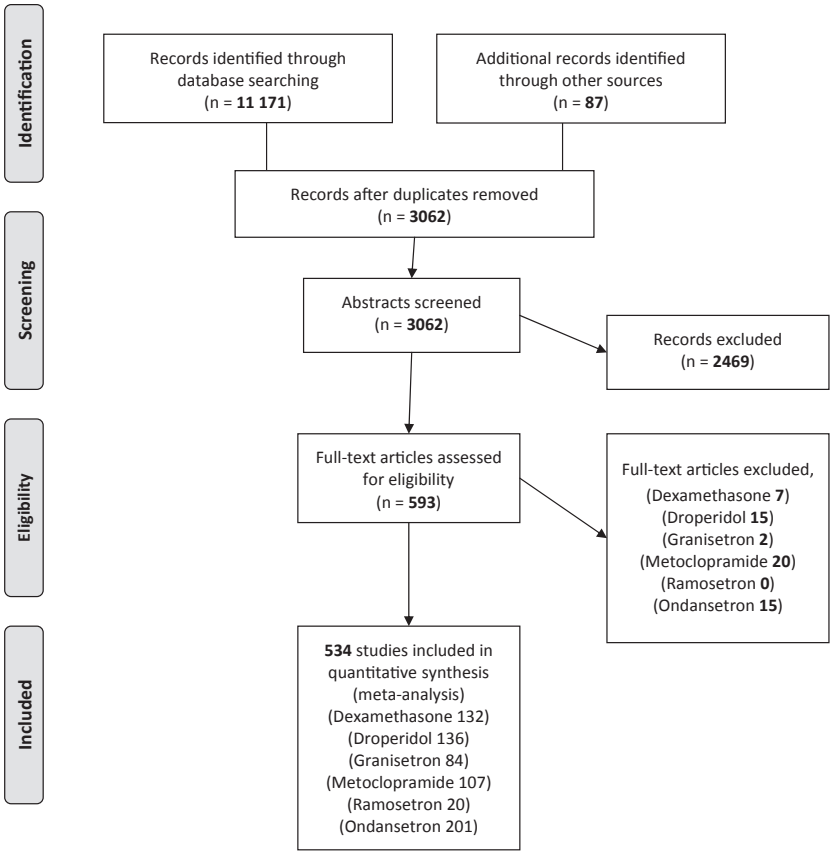

Figure 1 PRISMA flow diagram of the search, inclusion and exclusion of randomised controlled trials (http://www.prisma-statement.org/index.htm).

Table 1 The number of randomised controlled trials reporting rates of postoperative nausea and vomiting after prophylaxis with one of six drugs vs control, in studies by other authors and by Fujii et al.

	Nausea			Vomiting			Nausea or vomiting			Rescue		
	Others	Fujii	Total	Others	Fujii	Total	Others	Fujii	Total	Others	Fujii	Total
Dexamethasone	64	14	76	83	17	98	59	14	74	57	9	66
Droperidol	82	13	95	111	16	127	73	12	85	75	13	88
Granisetron	16	28	44	23	40	63	15	28	43	18	33	51
Metoclopramide	67	5	72	93	8	101	64	6	70	47	6	53
Ondansetron	143	0	143	175	0	175	105	0	105	130	0	130
Ramosetron	6	8	14	6	10	16	6	10	16	6	5	11

Figures 2–5 show the forest plots (a) and L'Abbé plots (b) for the effect of granisetron on nausea, vomiting, nausea or vomiting and rescue antiemesis. The forest plot shows the RR of an outcome (usually logarithmic horizontal axis) in one group compared with another, with the line of equality being vertical. The RCTs in a forest plot can be ordered as desired and a summary effect displayed. The horizontal lines running through each relative risk is its 95% CI. The visual impact of more precise results is less than that of imprecise results because of narrower 95% CI, a problem partly counteracted by larger symbols (squares) indicating RRs in more precise studies. The point of interest

Table 2 The heterogeneity (%, I^2 statistic) for randomised controlled trials (RCTs), drugs vs placebo, in studies by other authors and by Fujii et al.

	All RCTs (%)	Others (%)	Fujii (%)
Dexamethasone			
Nausea	43.2	48.6	0
Vomiting	14.5	21.8	0
Nausea or vomiting	38.6	42.7	18.7
Rescue	55.2	55.9	38.6
Droperidol			
Nausea	58.9	63	0
Vomiting	38	41.1	0
Nausea or vomiting	53.5	56.5	20.8
Rescue	51.5	54.6	0
Granisetron			
Nausea	60.4	65.6	0
Vomiting	43.5	47.3	0
Nausea or vomiting	72.8	66.1	40.4
Rescue	54.4	63.1	0
Metoclopramide			
Nausea	18.2	23.5	0
Vomiting	29.8	32.5	0
Nausea or vomiting	14.8	20.7	0
Nausea	18.2	23.5	0
Ondansetron			
Nausea	79.4	79.4	No RCTs
Vomiting	68.1	68.1	No RCTs
Nausea or vomiting	71.4	71.4	No RCTs
Rescue	59.4	59.4	No RCTs
Ramosetron			
Nausea	34	68	0
Vomiting	0	0	0
Nausea or vomiting	55	74	0
Rescue	65	77	0

in viewing the forest plots is that the studies of Fujii et al. demonstrate a larger effect of drug.

The L'Abbé plot is the rate in the control group on the horizontal axis and the rate in the test group on the vertical axis. Each axis therefore ranges from a rate of 0.0–1.0. If the outcome rate is the same in both groups the resultant plot lies on a diagonal line of equality, which is a ratio of risks of one. Each L'Abbé plot presents the RRs for more than one RCT, which are symbolised by a circle. The diameter of each circle is proportional to the statistical confidence ('weight') apportioned to the result of each study within the analysis, with more precise results represented by larger circles. This weight is determined by event rate and sample size (precision): it is not determined by data integrity. Generally, a beneficial effect of drug is indicated by the data points' lying below the line of equality (i.e. event rate with drug lower than control event rate). The points of interest are that Fujii et al.'s data exhibit narrower ranges for control event rate and/or drug event rate, and also that the data points' lie much lower in the graph below the line of equality than do data points from other authors.

Table S2 in Appendix S2 (online only) is similar to Table S1, but with results grouped according to whether or not the control and intervention groups received an antiemetic in addition to that under investigation, with Table S3 (Appendix S2 (online only)) detailing these results by authorship. Dexamethasone was 14% (FE model) to 18% (RE model) less effective in preventing postoperative nausea (Fig. 6) when given with another antiemetic, and 28% (FE) to 33% (RE) less effective in preventing the administration of rescue antiemesis (Fig. 7). In FE analyses dexamethasone was 24% less effective in preventing PONV and ondansetron was 18% less effective in preventing nausea and 20% less effective in preventing PONV, when given with another antiemetic. In contrast, granisetron was 1.5–3.7 times more effective in preventing postoperative nausea (Fig. 8), vomiting (Fig. 9) and nausea or vomiting (Fig. 10) when given with another antiemetic, the magnitude of the finding varying with outcome and statistical model. Table S3a shows that synergism between antiemetics was found only in RCTs by Fujii et al. (for both droperidol and granisetron), whereas antagonism with other antiemetics was found in RCTs by others for dexamethasone, droperidol and ondansetron (Table S3b).

Table 3 and Table S4 (Appendix S2 (online only)) detail the results of RCTs comparing droperidol vs granisetron, categorised by authorship. Granisetron was more effective in RCTs authored by Fujii et al., illustrated in Fig 11. Table 4 and Table S5 (Appendix S2 (online only)) detail the results of RCTs that compared granisetron vs metoclopramide, again categorised by authorship, with similar results for Fujii et al. and others.

Figure 12 is a funnel plot that shows the relative risks (vertical axis) of side effects in placebo and intervention groups for RCTs authored by others and by Fujii et al. The funnel plot shows the relative risk (usually logarithmic scale) of RCTs vs their certainty or precision, usually calculated by the inverse of the

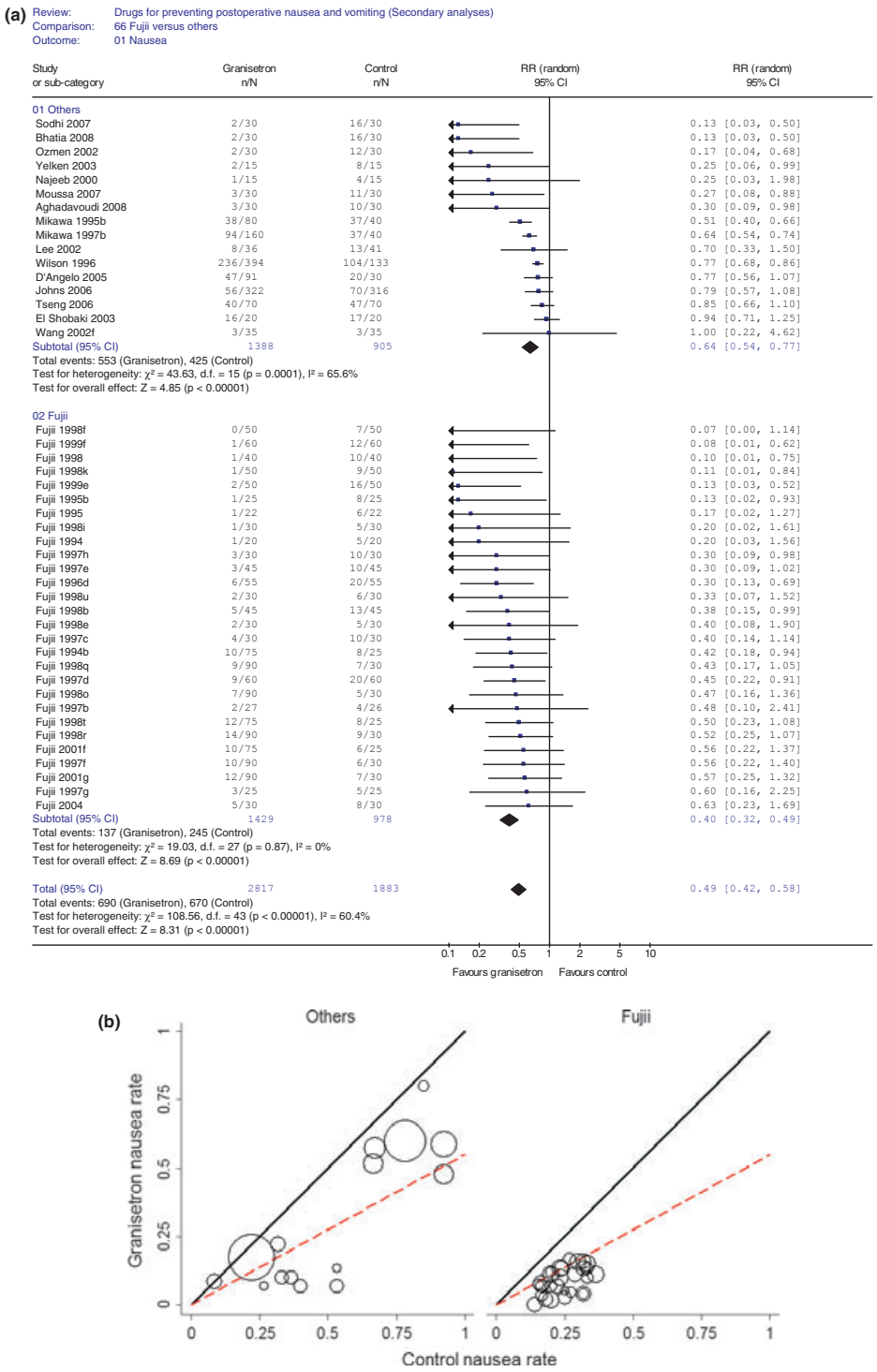

Figure 2 (a) Forest plots for postoperative nausea after granisetron vs control, in randomised controlled trials by other authors (top) and by Fujii et al. (bottom). The summary statistic is the solid diamond below each subgroup. There is a greater effect of granisetron in studies by Fujii et al. than others. Trials are listed in Appendix S1. (b) L'Abbé plots for postoperative nausea after granisetron vs control, in randomised controlled trials by other authors and by Fujii et al. The solid diagonal black line indicates no effect (RR = 1). The dashed red line indicates the combined relative risk (RR = 0.55), with studies by Fujii et al. predominantly below this line and studies by others above.

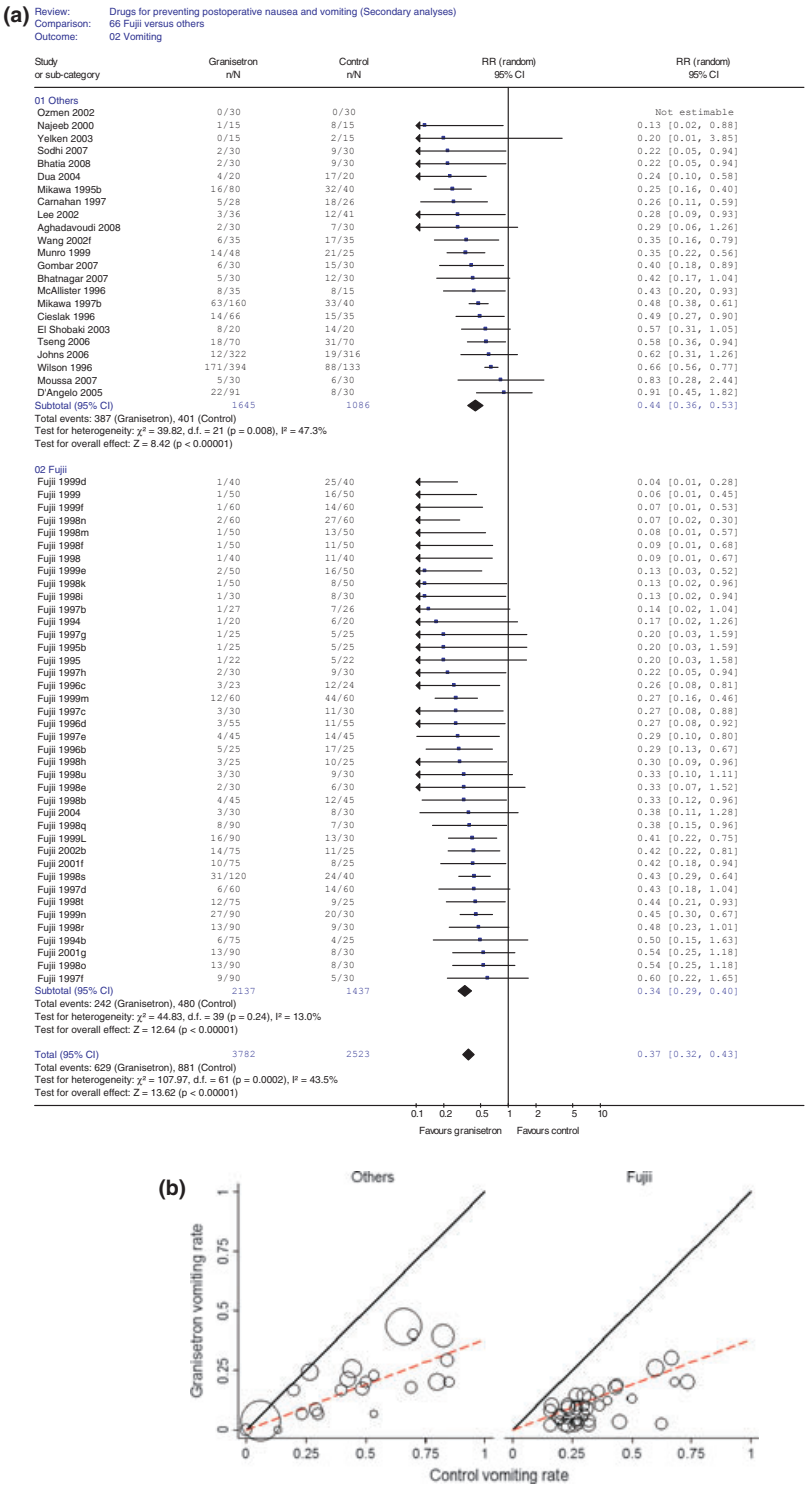

Figure 3 (a) Forest plots for postoperative vomiting after granisetron vs control, in randomised controlled trials by other authors (top) and by Fujii et al. (bottom). The summary statistic is the solid diamond below each subgroup and combined; it shows a greater effect of granisetron in studies by Fujii et al. than others. Trials are listed in Appendix S1. (b) L'Abbé plots for postoperative vomiting after granisetron vs control, in randomised controlled trials by other authors and by Fujii et al. The solid diagonal black line indicates no effect (RR = 1). The dashed red line indicates the combined relative risk (RR = 0.38), with studies by Fujii et al. predominantly below this line and studies by others above.

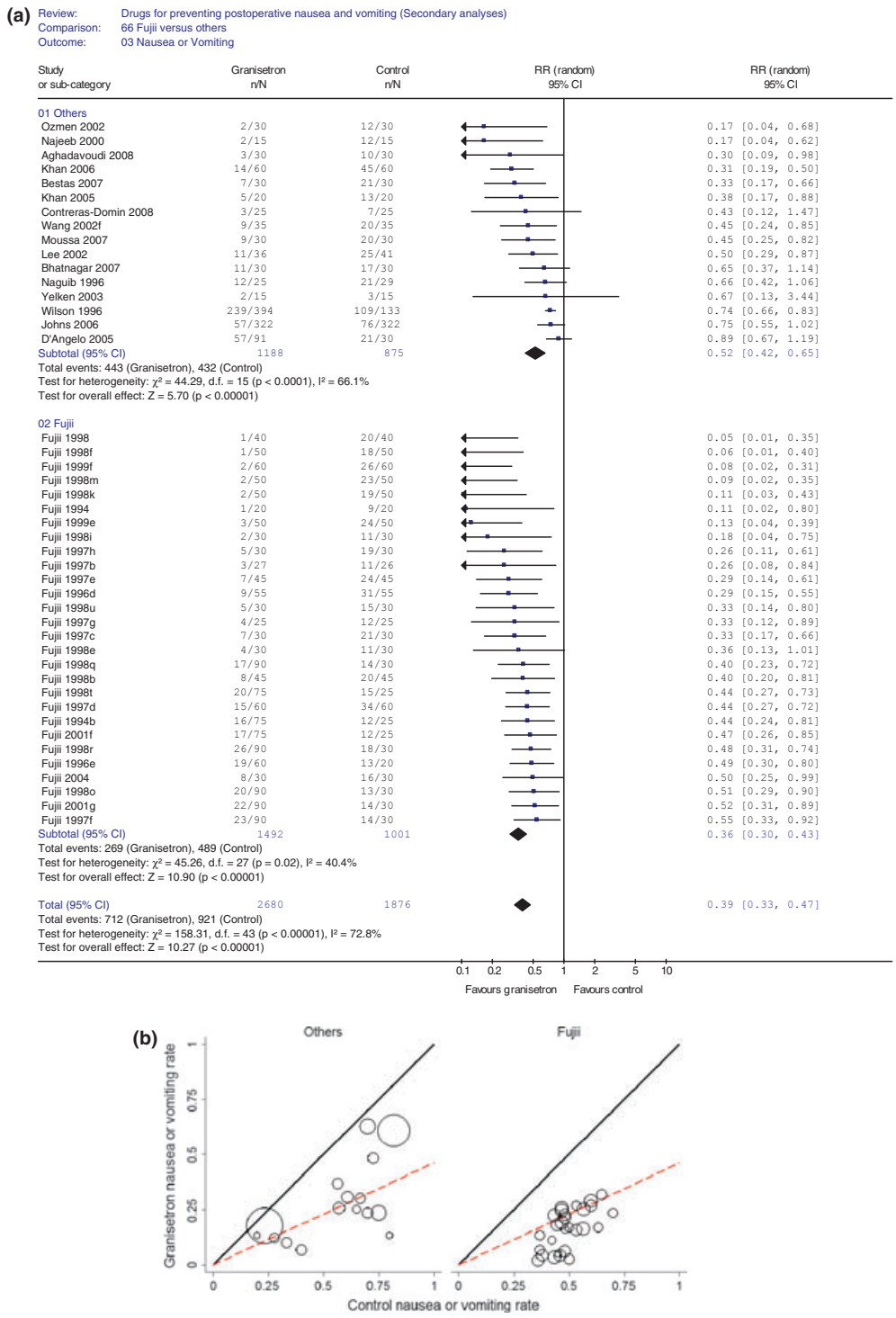

Figure 4 (a) Forest plots for postoperative nausea or vomiting (PONV) after granisetron vs control, in randomised controlled trials by other authors (top) and by Fujii et al. (bottom). The summary statistic is the solid diamond below each subgroup and combined; it shows a greater effect of granisetron in studies by Fujii et al. than others. Trials are listed in Appendix S1. (b) L'Abbé plots for PONV after granisetron vs control, in randomised controlled trials by other authors and by Fujii et al. The solid diagonal black line indicates no effect (RR = 1). The dashed red line indicates the combined relative risk (RR = 0.46), with studies by Fujii et al. predominantly below this line and studies by others above.

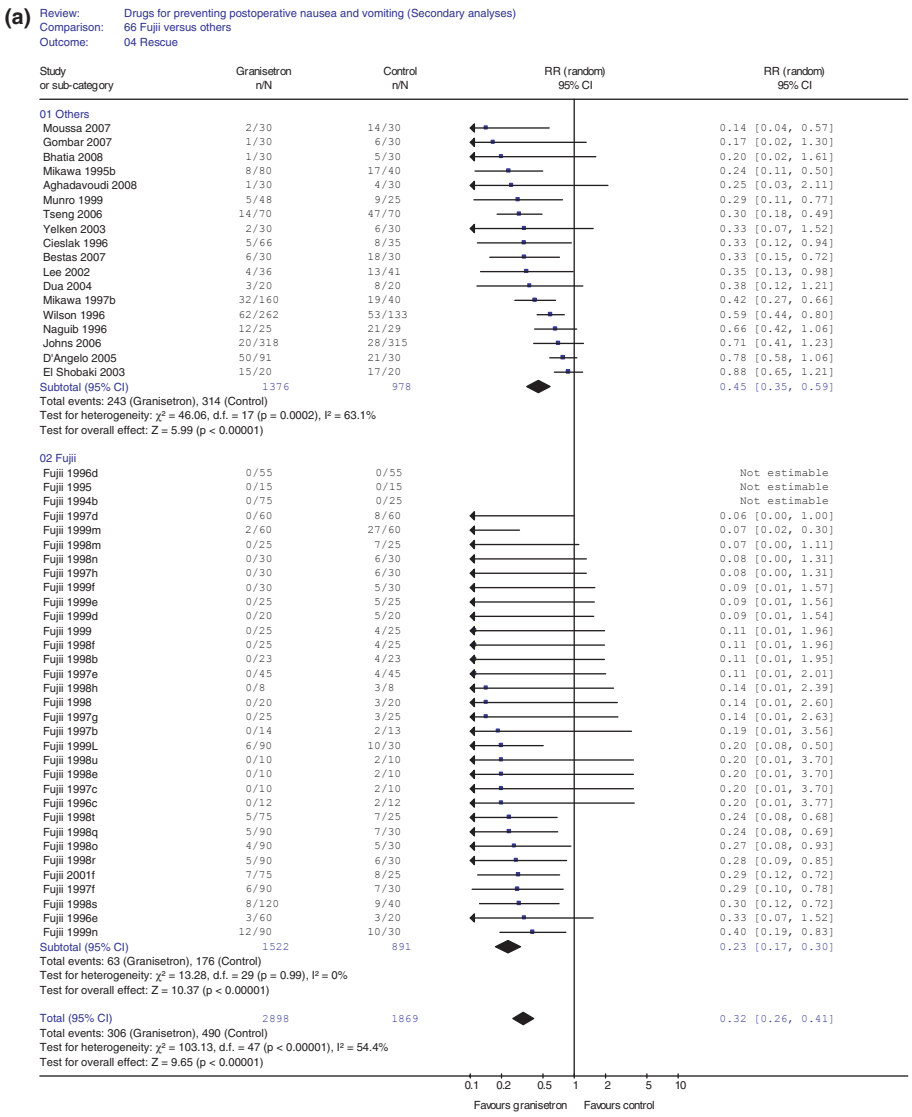

Figure 5 (a) Forest plots for postoperative rescue antiemesis after granisetron vs control, in randomised controlled trials by other authors (top) and by Fujii et al. (bottom). The summary statistic is the solid diamond below each subgroup and combined; it shows a greater effect of granisetron in studies by Fujii et al. than others. Trials are listed in Appendix S1. (b) L'Abbé plots for postoperative rescue antiemesis after granisetron vs control, in randomised controlled trials by other authors and by Fujii et al. The solid diagonal black line indicates no effect (RR = 1). The dashed red line indicates the combined relative risk (RR = 0.37), with studies by Fujii et al. predominantly below this line and studies by others above.

logarithm of the standard error of the relative risk. Normally, due to the effects of random sampling, it is expected that smaller RCTs have wider standard errors, so the relative risks scatter more widely around the average effect as their precision decreases, giving the appearance of a triangle or 'funnel'. This appears to be the case with the data of other authors (Fig. 12, top panel). However, the data reported by Fujii et al. fail to conform to this expected shape. Of 159 rates, 128 (80.5%) are the same in each experimental group from studies by Fujii et al.; by comparison, the rate of side effects reported by others was the same in both groups for just 12 of 102 rates (11.8%). These rates are different, $p = 1.5 \times 10^{-29}$.

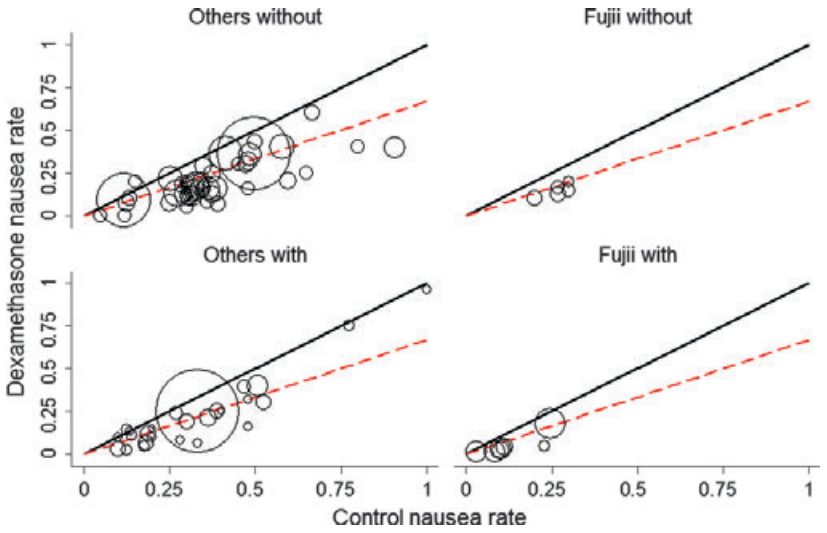

Figure 6 L'Abbé plots for postoperative nausea after dexamethasone vs control, in randomised controlled trials by other authors and by Fujii et al. (columns), and according to whether dexamethasone was given with another antiemetic (rows). The solid diagonal black line indicates no effect (RR = 1). The dashed red line indicates the combined RR: the spread of studies around this line is similar by author (column) and antiemetic co-administration (row).

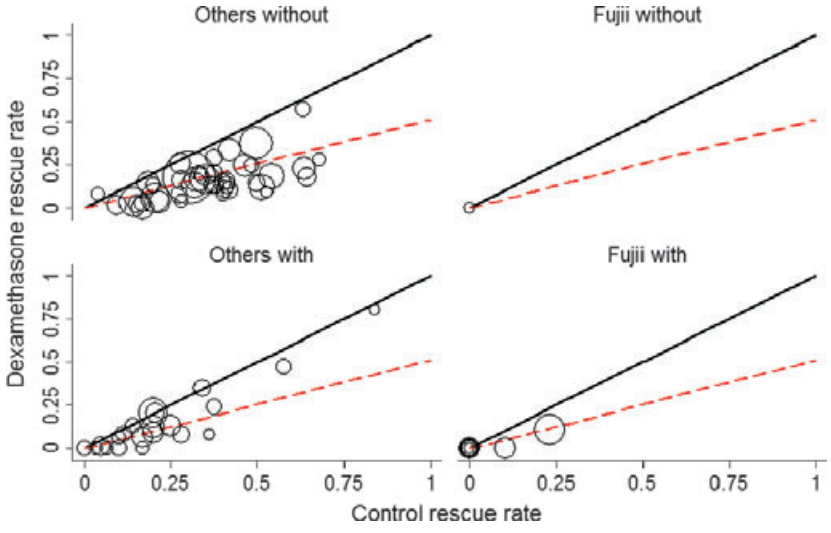

Figure 7 L'Abbé plots for postoperative rescue after dexamethasone vs control, in randomised controlled trials by other authors and by Fujii et al. (columns), and by whether dexamethasone was given with another antiemetic (rows). The solid diagonal black line indicates no effect (RR = 1). The dashed red line indicates the combined RR: the spread of studies around this line is similar by author (column) and antiemetic co-administration (row).

Within the RCTs by Fujii et al. the rescue rate for droperidol was no different to that for metoclopramide; however, the rate of each was approximately double that of granisetron, unlike RCTs authored by others (Table 5). Similarly, in participants experiencing PONV the rates for a single dose of rescue antiemetic are significantly greater in RCTs by Fujii et al. compared with RCTs by other authors for metoclopramide and in particular granisetron (Fig. 13). Within RCTs authored by Fujii et al. the rate of rescue antiemesis for droperidol was no different to

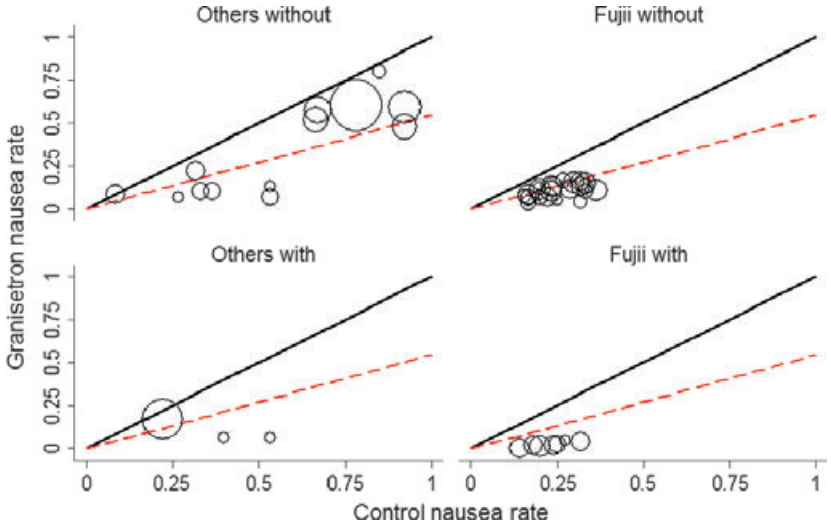

Figure 8 L'Abbé plots for postoperative nausea after granisetron vs control, in randomised controlled trials by other authors and by Fujii et al. (columns) and by whether granisetron was given with another antiemetic (rows). The solid diagonal black line indicates no effect (RR = 1). The dashed red line indicates the combined RR: granisetron was more effective in studies by Fujii et al. (right column), in which co-administration with another antiemetic increased granisetron's effectiveness (bottom row).

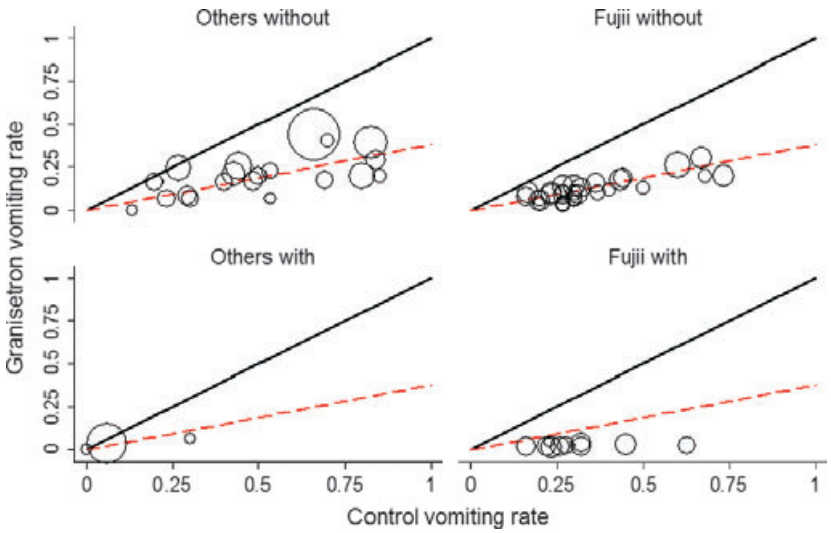

Figure 9 L'Abbé plots for postoperative vomiting after granisetron vs control, in randomised controlled trials by other authors and by Fujii et al. (columns) and by whether granisetron was given with another antiemetic (rows). The solid diagonal black line indicates no effect (RR = 1). The dashed red line indicates the combined RR: granisetron was more effective in studies by Fujii et al. (right column), in which co-administration with another antiemetic increased granisetron's effectiveness (bottom row).

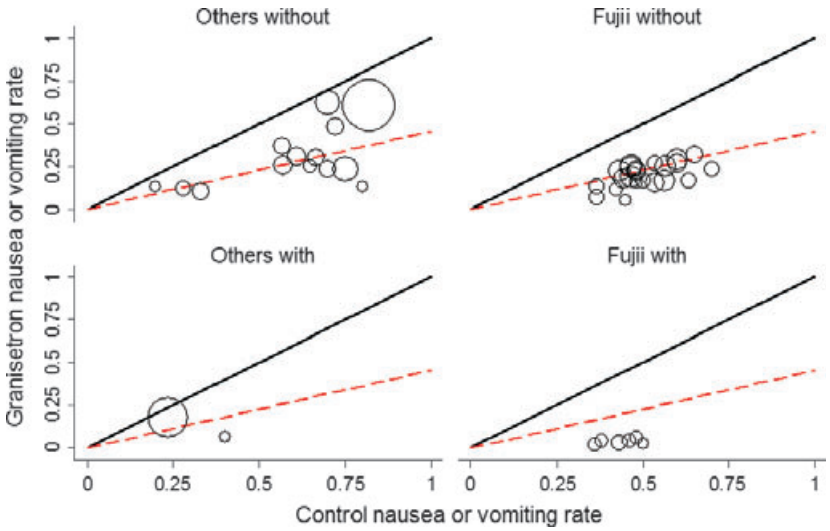

Figure 10 L'Abbé plots for postoperative nausea or vomiting after granisetron vs control, in randomised controlled trials by other authors and by Fujii et al. (columns) and by whether granisetron was given with another antiemetic (rows). The solid diagonal black line indicates no effect (RR = 1). The dashed red line indicates the combined RR: granisetron was more effective in studies by Fujii et al. (right column), in which co-administration with another antiemetic increased granisetron's effectiveness (bottom row).

metoclopramide, but both had higher rates of rescue per PONV episode than granisetron (Fig. 14).

Discussion

Inclusion of data from Fujii et al. in a systematic review of drugs for prevention of PONV leads to the following conclusions, derived from this article and the unpublished update of the Cochrane review [7]:

- Direct comparisons of one antiemetic with another show that granisetron is more effective than both droperidol and metoclopramide for all PONV outcomes (nausea, vomiting, nausea or vomiting, rescue). No other antiemetic is different from any other for all four outcomes.
- Against placebo, granisetron is the most effective antiemetic, an indirect demonstration of granisetron's superiority.
- About one out of two patients who experience PONV after prophylaxis (with any antiemetic) go on to receive a rescue antiemetic, with the exception of granisetron, after which only one out of five patients who experience PONV go on to receive rescue antiemesis.
- Granisetron is the only antiemetic potentially synergistic with another, whereas dexamethasone and droperidol, as well as ondansetron, potentially antagonise other antiemetics.

However, if we exclude the data of Fujii et al., as has been recommended elsewhere [1], we conclude:

- Granisetron remains more effective than metoclopramide for all four outcomes, with significant differences vs droperidol persisting for two outcomes (vomiting, rescue) but disappearing for nausea and the combined 'nausea and vomiting' outcomes.
- Against placebo, the effects of granisetron and ramosetron are less, for instance the amended RR for vomiting vs placebo changes to 0.48 from 0.38, and for ramosetron to 0.65 from 0.49.
- Postoperative nausea and vomiting after granisetron triggers rescue antiemesis at the same rate as droperidol and metoclopramide, instead of less often.
- The unique characteristic of granisetron to act synergistically with other antiemetics disappears.

Table 3 The number of randomised controlled trials (RCTs) by other authors and by Fujii et al. reporting rates of postoperative nausea and vomiting after prophylaxis with droperidol vs granisetron and subgroup heterogeneity (I^2 statistic). The lack of heterogeneity in Fujii et al. is striking.

	Others		Fujii		Total	
	RCTs	I^2 (%)	RCTs	I^2 (%)	RCTs	I^2 (%)
Nausea	4	24	16	0	20	51
Vomiting	4	0	21	0	25	0
Nausea or vomiting	5	37	15	0	20	72
Rescue antiemesis	2	0	17	0	19	44

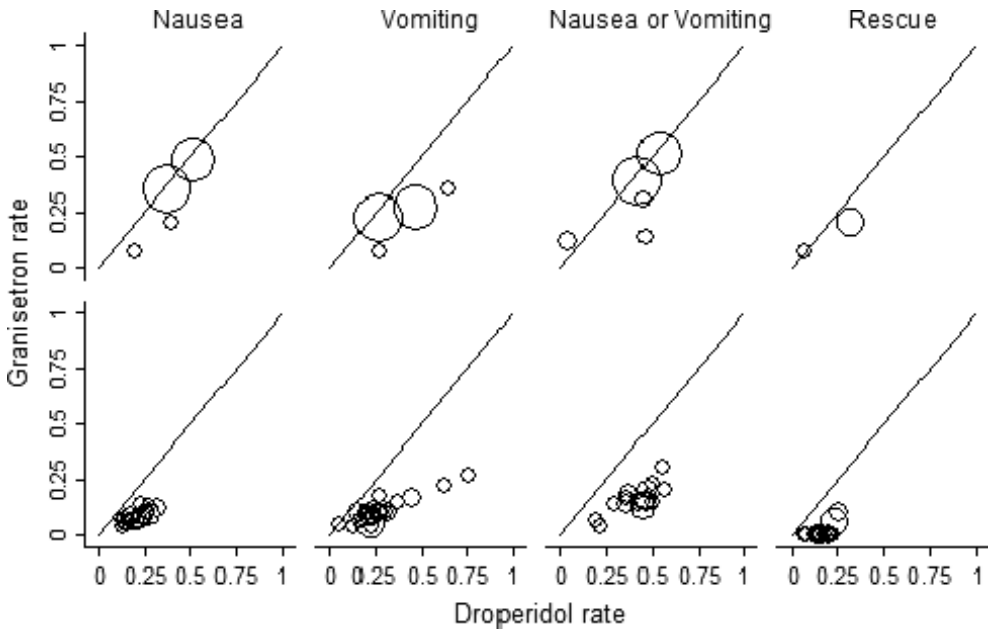

Figure 11 L'Abbé plots for postoperative nausea and vomiting after droperidol vs granisetron, in randomised controlled trials arranged by outcome (column) and by authorship (rows, others top and Fujii bottom). The solid diagonal black line indicates no effect (RR = 1). Granisetron was comparatively more effective than droperidol in studies by Fujii et al.

Postoperative nausea and vomiting rarely cause long-term morbidity or death, so one might consider that these distinctions are inconsequential. However, PONV is a common and feared postoperative complication [11]. When considering the annual number of operations (~3 million general anaesthetics in the United Kingdom alone), one cannot dismiss lightly the burden of misery that results from the fear and experience of PONV. This burden is lessened by interventions that prevent PONV. Although granisetron reduces PONV, it has been an expensive option whilst produced under exclusive licence, ten times the cost of other drugs: the 2009 British National Formulary cost for 1 mg intravenous granisetron was £11.46, whereas the cost for 20 mg intravenous metoclopramide was £0.56. If these drugs are equipotent then in fact there is potential for huge cost savings. Although the expense of new drugs sometimes deters their use, this is often counterbalanced by the casual clinician's assuming that new is better. Patients have been denied the opportunity to reduce their risk of PONV through the mistaken beliefs that cheaper antiemetics like metoclopramide and cyclizine are ineffective, and that their side-effect profiles are worse than, or as uncertain as, newer drugs.

I have shown previously that the distribution of group means and categorical rates sampled from populations in RCTs by Fujii et al. are very unlikely to have occurred naturally, by chance, supporting the earlier work of Kranke et al. [1, 6]. This current article, again following on from work by Kranke et al., shows that the effects of antiemetics reported in Fujii et al.'s RCTs were systematically different from the results of other authors [5]. Taken together, these analyses lead to the conclusion that

Table 4 The number of randomised controlled trials by other authors and by Fujii et al. reporting rates of postoperative nausea and vomiting after prophylaxis with granisetron vs metoclopramide and subgroup heterogeneity (I^2 statistic). The lack of heterogeneity in Fujii et al. is striking.

	Others		Fujii		Total	
	RCTs	I^2 (%)	RCTs	I^2 (%)	RCTs	I^2 (%)
Nausea	4	46	10	0	14	0
Vomiting	4	5	13	0	17	0
Nausea or vomiting	5	49	10	0	15	10
Rescue antiemesis	4	51	10	0	14	55

RCTs, randomised controlled trials.

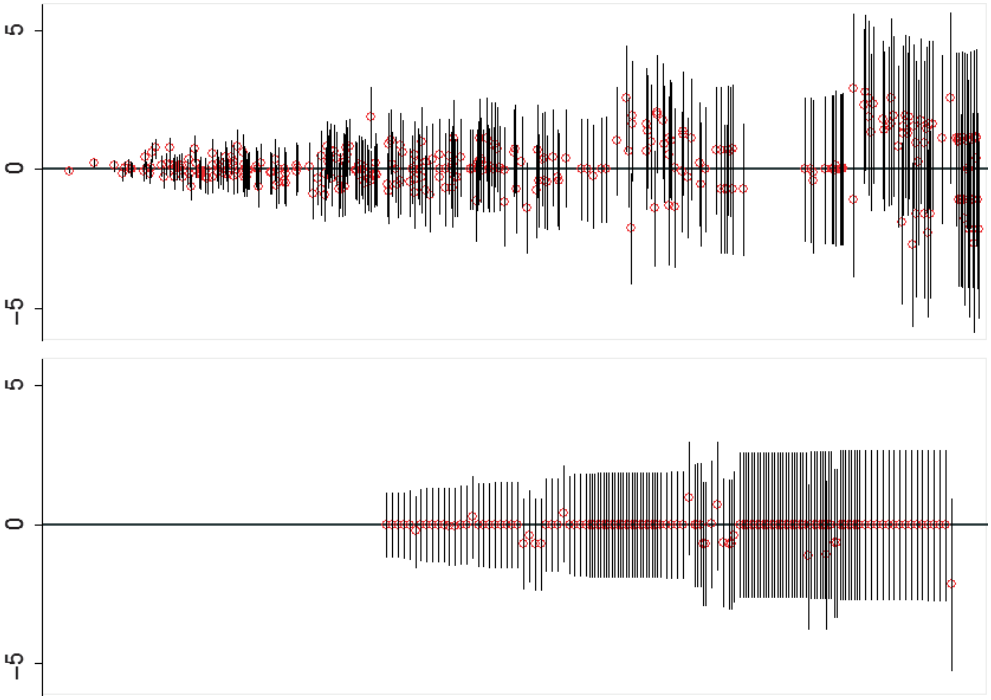

Figure 12 Funnel-type plot of log relative risks (RRs; vertical axis, red circles), with 95% CI (black vertical lines) of side effects in placebo and intervention groups for randomised controlled trials by other authors (top) and by Fujii et al. (bottom). The horizontal axis is similar to the vertical funnel plot axis (log standard error), modified to allow coincident log RRs (up to 30 with the same log standard error coordinates) to be spread out horizontally, which is why there is no horizontal scale. The point of interest is that the relative risk of side effects was the same in nearly all Fujii groups (lnRR = 0).

Table 5 Rates of rescue antiemetics for participants with nausea or vomiting in trials by other authors and by Fujii et al. Values are number (95% CI).

	Relative risk for rescue		Relative risk ratio	p value
	Others	Fujii		
Droperidol	0.49 (0.41–0.60)* (n = 46)	0.40 (0.35–0.47)† (n = 26)	0.82 (0.64–1.04)	0.10
Granisetron	0.50 (0.36–0.69) (n = 20)	0.20 (0.16–0.26) (n = 48)	0.40 (0.27–0.60)	9.7×10^{-6}
Metoclopramide	0.63 (0.55–0.73)‡ (n = 57)	0.43 (0.35–0.53)§ (n = 14)	0.68 (0.53–0.88)	0.003

n, number of discrete observation periods (some trials reported rates for more than one discrete observation period).
*Relative risk ratio compared to granisetron within trials by other authors 1.02 (0.70–1.49); p = 0.92.
†Relative risk ratio compared to granisetron within trials by Fujii et al. 2.00 (1.51–2.66); $p = 1.7 \times 10^{-6}$.
‡Relative risk ratio compared to granisetron within trials by other authors 0.79 (0.56–1.13); p = 0.20.
§Relative risk ratio compared to granisetron within trials by Fujii et al. 2.15 (1.56–2.96); $p = 2.6 \times 10^{-6}$.

the effects of antiemetics and other interventions should be gauged without inclusion of Fujii et al.'s RCTs. The Joint Editors-in-Chief request to the institutions in which Fujii et al. conducted their research will help to determine whether or not any work can be salvaged to contribute as evidence for the effect of an intervention [8].

Competing interests

No external funding and no competing interests declared. JBC is an Editor of *Anaesthesia* and this manuscript has undergone an additional external review as a result.

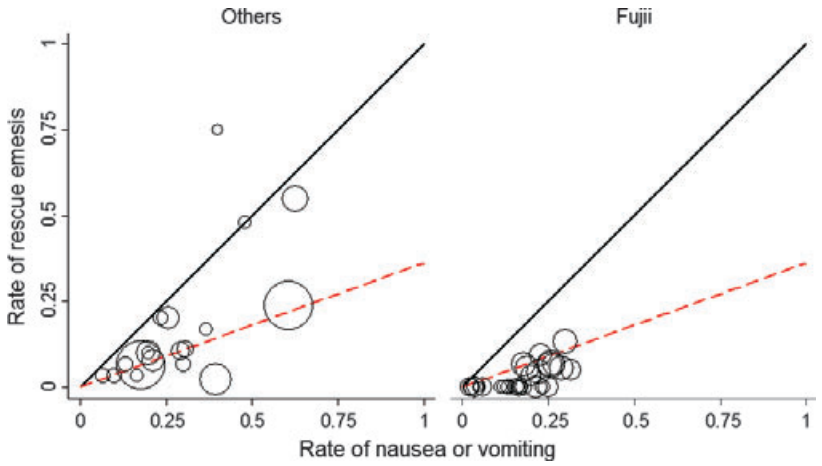

Figure 13 L'Abbé plots for rates of rescue antiemetic vs postoperative nausea or vomiting in randomised controlled trials of granisetron vs placebo by other authors and by Fujii et al. The solid diagonal black line indicates no effect (RR = 1). Many groups experienced postoperative nausea and vomiting after receiving granisetron but did not receive rescue antiemetics in trials published by Fujii et al. (aligned along the *x*-axis), and none in studies by other authors ($p = 9.7 \times 10^{-6}$).

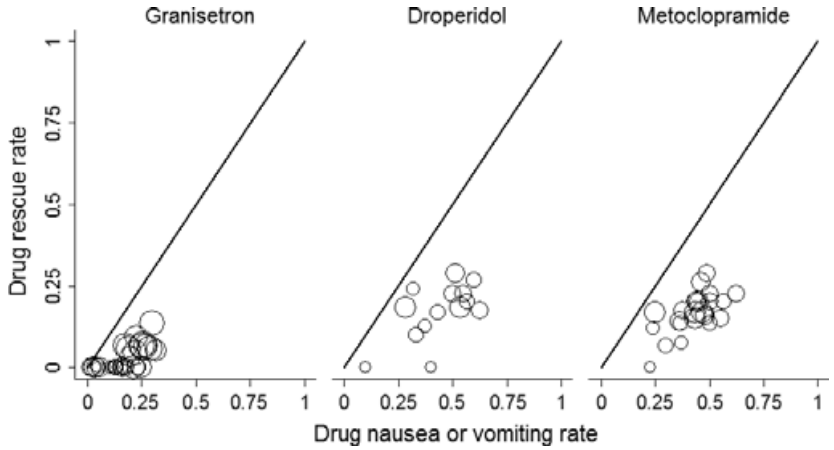

Figure 14 L'Abbé plots for rates of rescue antiemetic vs postoperative nausea or vomiting in in randomised controlled trials by Fujii et al., categorised by drug. The solid diagonal black line indicates no effect (RR = 1). Many groups experienced postoperative nausea and vomiting after receiving granisetron but did not receive rescue antiemetics, in contrast with droperidol and metoclopramide.

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Supporting information

Additional Supporting information may be found with the online version of this article:

Table S1. The effect (relative risk, RR) for antiemetics vs control, in randomised controlled trials by other authors and by Fujii et al.

Table S2. The effect (relative risk, RR) for antiemetics vs control.

Table S3. The effect (relative risk, RR) for antiemetics vs control, with results grouped by whether both control and intervention groups received an effective antiemetic, which meant the intervention group received two antiemetics.

Table S4. The effect (relative risk, RR) for droperidol vs granisetron, in randomised controlled trials by other authors and by Fujii et al.

Table S5. The effect (relative risk, RR) for granisetron vs metoclopramide, in randomised controlled trials by other authors and by Fujii et al.

Appendix S1. RCT references.

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