# Serotonin Receptor Antagonists for the Prevention and Treatment of Pruritus, Nausea, and Vomiting in Women Undergoing Cesarean Delivery with Intrathecal Morphine: A Systematic Review and Meta-Analysis

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**BACKGROUND:** We performed a systematic review to determine the overall efficacy of serotonin (5-$HT_3$) receptor antagonists for the prevention and treatment of pruritus, nausea, and vomiting in women receiving spinal anesthesia with intrathecal morphine for cesarean delivery.

**METHODS:** Reports of randomized, controlled trials that compared prophylaxis or treatment of pruritus and/or nausea, and vomiting using one of the 5-$HT_3$ receptor antagonists or placebo in women undergoing cesarean delivery were reviewed. The articles were scored for validity and data were extracted by the authors independently and summarized using relative risks (RR) with 95% confidence intervals (CI).

**RESULTS:** Nine randomized, controlled trials were included in the systematic review. The nine trials had a total of 1152 patients enrolled; 539 received 5-$HT_3$ receptor antagonists, 413 received placebo, and 200 received other antiemetics and were not included in the analysis. The incidence of pruritus was not reduced with 5-$HT_3$ receptor antagonists prophylaxis compared with placebo (80.7% vs 85.8%, RR [95% CI] = 0.94 [0.81–1.09]). However, their use reduced the incidence of severe pruritus and the need for treatment of pruritus (number-needed-to-treat = 12 and 15, respectively). Their use for the treatment of established pruritus showed improved efficacy compared with placebo with a number-needed-to-treat of three. There was a significant reduction in the incidence of postoperative nausea (22.0% vs 33.6%, RR [95% CI] = 0.75[0.58–0.96]) and vomiting (7.7% vs 16.8%, RR [95% CI] = 0.49 [0.30–0.81]), and the need for postoperative rescue antiemetic treatment with the use of 5-$HT_3$ receptor antagonists when compared with placebo (9% vs 23%, RR [95% CI] = 0.38 [0.21–0.68]).

**CONCLUSIONS:** Although prophylactic 5-$HT_3$ receptor antagonists were ineffective in reducing the incidence of pruritus, they significantly reduced the severity and the need for treatment of pruritus, the incidence of postoperative nausea and vomiting, and the need for rescue antiemetic therapy in parturients who received intrathecal morphine for cesarean delivery. They were also effective for the treatment of established pruritus. Although more studies are warranted, the current data suggest that the routine prophylactic use of those drugs should be considered in this patient population.

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Intrathecal morphine is commonly used to enhance postoperative analgesia in women undergoing cesarean delivery under spinal anesthesia. However, its use is associated with a frequent incidence of side effects, including pruritus, nausea, and vomiting.[1]

Serotonin (5-$HT_3$) receptor antagonists were specifically developed for the management of nausea and vomiting. Their favorable side effect profile, in particular, lack of sedation, confers an advantage over older generation antiemetics. The efficacy of those drugs for the prophylaxis of postoperative nausea and vomiting in the general surgical population has been established.[2–5] Some studies also suggested that these drugs might be effective for the prophylaxis and treatment of opioid-induced pruritus.[6]

We therefore performed this systematic review to assess the efficacy of 5-$HT_3$ receptor antagonists for the prevention and treatment of intrathecal morphine-induced pruritus, nausea, and vomiting in women undergoing cesarean delivery under spinal anesthesia.

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## METHODS

The current meta-analysis adhered to the QUOROM guidelines for reporting meta-analyses.[7] A systematic search was performed for full reports of randomized, controlled trials that compared prophylaxis or treatment of pruritus and/or nausea, and vomiting using one of the 5-$HT_3$ receptor antagonists (ondansetron, granisetron, tropisetron, and dolasetron) versus placebo in women undergoing cesarean delivery under spinal anesthesia. Relevant trials had to report the main end points, namely the incidence of pruritus, and/or nausea, and/or vomiting in all study groups. The spinal anesthetic technique in both the treatment and control groups had to be standardized and include the administration of intrathecal morphine.

The databases of MEDLINE (1966–2008), the Cochrane Central Register of Controlled Trials, EMBASE, Web of Science, and CINAHL were searched without language restriction. Furthermore, the reference lists of retrieved reports and review articles were screened. Data from abstracts, letters, retrospective trials, case reports, and unpublished data were not considered. Keywords used in the search were "ondansetron," "granisetron," "tropisetron," "dolasetron," "pruritus," "nausea," "vomiting," "postoperative nausea and vomiting," and "cesarean." Both medical subject headings and text words were used. The date of the last computer search was June 2008.

The articles meeting the inclusion criteria were scored independently by two authors (RG and TA) for methodological validity using the 4-item, 7-point, Modified Oxford scale (Appendix).[8] Any discrepancies were resolved by discussion with the third author (AH).

All three authors extracted data independently. A data collection form was used to collect the following data: i) surgical procedure, ii) anesthesia technique, iii) intrathecal opioid, iv) therapeutic allocation, v) outcome measures including the incidence and severity of postoperative pruritus, incidence and severity of nausea and vomiting, and need for rescue treatment of pruritus, nausea, and vomiting, vi) side effects, and vii) for treatment studies, success of treatment. When event rates were reported over multiple time intervals and not over the entire duration of the study, the authors were contacted and asked to provide such information. If the authors did not respond, the highest recorded incidence over the duration of the study was used in the analysis. If any other additional data were required, the authors were contacted and asked to provide the additional information.

If the studies included three groups and the third group did not include a placebo or a 5-$HT_3$ receptor antagonist, data from this third group were not included in the analysis. If two 5-$HT_3$ receptor antagonist groups were included in addition to placebo, data from all the groups were extracted. Drug specific and pooled analyses combining all the 5-$HT_3$ receptor antagonists were then performed.

Dichotomous data were extracted and summarized using relative risks (RR) with 95% confidence intervals (CI). If the 95% CI included a value of 1, it was assumed that there was no significant difference between the 5-$HT_3$ receptor antagonist and placebo. A fixed effects model was used by default. If the statistical test for heterogeneity was significant ($P < 0.1$), a random effects model was used and the reason for heterogeneity was explored. Analyses were performed using the Review Manager Software (Review Manager [Revman] Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Forrest plots were used to graphically represent and evaluate treatment effects. The number-needed-to-treat (NNT) was calculated to estimate the overall clinical impact of statistically significant interventions.

We performed a subgroup analysis of the incidence of postoperative pruritus by including only studies that used intrathecal morphine without lipophilic opioids. Dose responsiveness was assessed using assumptions previously published in similar analyses.[3,9,10] First, if the 95% CI of the RR of one dose did not overlap with the 95% CI of another dose, we assumed that these two doses were significantly different. Second, if the lower dose was not significantly different than control but the higher doses were more effective than control and the NNT decreased by more than 20%, this was considered dose responsive.

## RESULTS

Twenty-four potentially relevant articles were identified (Fig. 1). Fifteen were excluded[11–25] leaving nine randomized, controlled trials included in the systematic review. Six of these trials contained results regarding prophylaxis against pruritus,[26–31] six contained data regarding prophylaxis against nausea and vomiting,[26–29,32,33] and one presented results for the treatment of pruritus.[34] The trials' details are outlined in Table 1. All studies investigating prophylaxis against pruritus and/or nausea, and vomiting had an observation period of 24 h[26–30,33] except for one study which lasted for 28 h.[31] The dose of intrathecal morphine ranged from 0.1 to 0.2 mg. There were no studies investigating the efficacy of 5-$HT_3$ receptor antagonists for the treatment of established nausea and vomiting. Methodological validity scores ranged from 3 to 7. The nine trials had a total of 1152 patients enrolled, 539 received 5-$HT_3$ receptor antagonists, 413 received placebo, and 200 patients received non-5-$HT_3$ receptor antagonist drugs. These data were not included in this review. Tropisetron,[28] granisetron,[29,32] and ondansetron[26–31,33] were the 5-$HT_3$ receptor antagonists used. All trials used a fixed dose of 5-$HT_3$ receptor drugs, except a single trial which used ondansetron 0.1 mg/kg.[31] For analysis purposes, this trial was included in the 8 mg category.

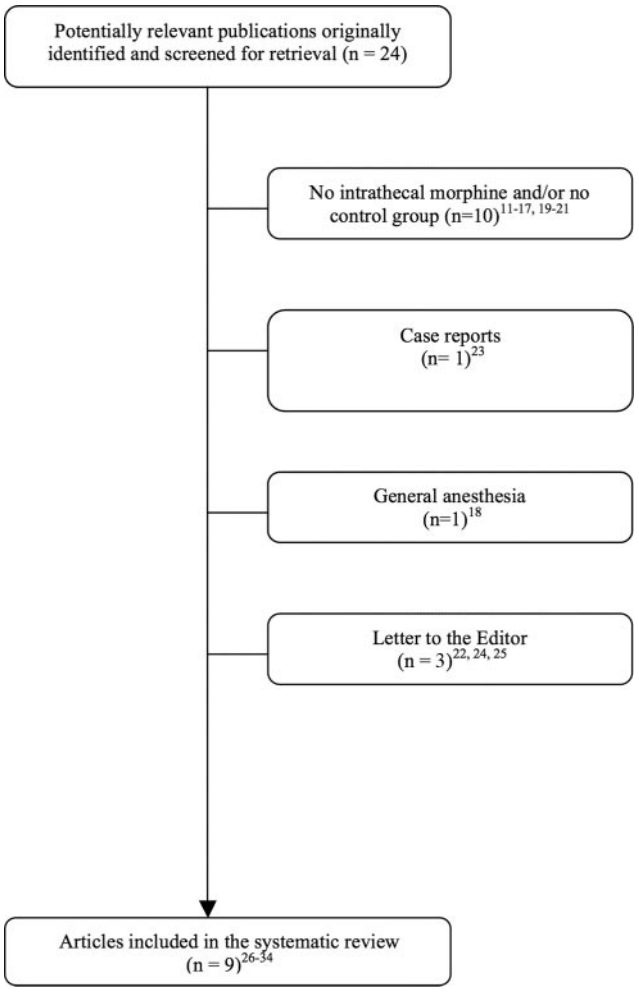


**Figure 1.** Flow diagram of screened, excluded, and analyzed studies.

## Pruritus

### Incidence of Pruritus

The effect of prophylaxis with 5-$HT_3$ receptor antagonists on the incidence of pruritus was reported in five studies.[26,28–31] Ondansetron 4 mg was tested in one study,[26] ondansetron 8 mg in five studies,[26,28–31] tropisetron 5 mg in one study,[28] and granisetron 3 mg in one study.[29] Results are presented in Table 2. There was no reduction in the incidence of pruritus with any of the 5-$HT_3$ receptor antagonists compared with placebo, nor was there a difference when all trials reporting pruritus were combined (Table 2 and Fig. 2). Ondansetron was the only drug used in more than one dose. Data did not suggest that there was dose responsiveness when ondansetron was used for the prophylaxis of pruritus. Similarly, there was no difference in the incidence of pruritus when the analysis was limited to the trials using intrathecal morphine only without lipophilic drugs (81.2% vs 89.6%, RR [95% CI] = 0.86 [0.66–1.12]). Statistical heterogeneity was observed. Excluding the study by Yeh et al.[31] eliminated the statistical heterogeneity ($P = 0.63$, $I^2 = 0\%$) but did not significantly change the overall incidence of pruritus in either group (84.3% vs 85.9%, RR [95% CI] = 0.97 [0.90–1.05]).

### Need for Treatment

Six of the nine studies published data regarding the need for treatment of pruritus.[26–31] Treatment of pruritus consisted of propofol,[26,31] diphenhydramine,[29,30] naloxone,[28] nalbuphine,[27] and hydroxyzine.[28] In three studies, treatment was offered to patients with "severe" pruritus,[26,30,31] in two studies pruritus was treated on patients' request,[28,29] and in one study, the trigger for the treatment of pruritus was not defined.[27]

There was a reduction in the need for treatment of pruritus with ondansetron 4 mg (NNT = 7) and when all doses of ondansetron were combined (NNT = 17). There was no evidence of dose responsiveness for prophylactic ondansetron when need for treatment of pruritus was the outcome. Tropisetron and granisetron, each used in one trial, were not more effective than placebo at reducing the need for treatment of pruritus. When all trials which reported the need for treatment of pruritus were combined, 5-$HT_3$ receptor antagonist prophylaxis was significantly more effective than placebo at reducing the need for treatment of pruritus (Table 2).

### Severity of Pruritus

The severity of pruritus was reported in six studies.[26,28–31,33] Sarvela et al.[28] graded pruritus with a numeric rating scale between 0 and 10 and chose to treat subjects who requested treatment for their pruritus. Data were reported as median and range and showed no significant differences between the treatment and placebo groups in the severity of pruritus. Data from this study were not included in the pooled analysis. One trial used a 4-point scale (0 = no pruritus, 1 = perioral, 2 = diffuse moderate, 3 = diffuse intense).[33] Results were reported as mean with standard deviation and were not included in the pooled analysis. Two trials used a 4-point scale (1 = no pruritus, 2 = mild pruritus, 3 = moderate pruritus, 4 = severe pruritus) with subjects receiving treatment on request[29] or moderate to severe pruritus.[26] Two trials used a 3-point scale (0 = no pruritus, 1 = mild/mild to moderate pruritus, 2 = severe pruritus) and treated patients who had severe pruritus.[30,31] For analysis, we converted the 4-point scale into a 3-point scale by combining Grades 3 and 4 into one grade (severe pruritus) and compared the incidence of severe pruritus between the placebo and 5-$HT_3$ receptor antagonists groups in these four studies.[26,29–31] Combined data showed that ondansetron 4 mg and combined ondansetron doses were effective in reducing the incidence of severe pruritus (Table 2). There was no evidence of dose responsiveness in the effect of ondansetron on the severity of pruritus. Granisetron and tropisetron were not effective in reducing the severity of pruritus. When combining all drugs and doses, 5-$HT_3$ receptor antagonists were effective in reducing the incidence of severe pruritus compared with placebo.

**Table 1.** Trials of 5-$HT_3$ Receptor Antagonists for Prophylaxis and Treatment of Intrathecal Morphine-Induced Pruritus, Nausea, and Vomiting

| Ref | Oxford scale (R/C/B/F)[a] | Intrathecal morphine | Randomized groups | *n* | Outcomes (P/N/V)[b] | Observation period |
|---|---|---|---|---|---|---|
| Charuluxananan et al.[26] | 7 (2/1/2/2) | 0.2 mg | Normal saline (4 mL) | 60 | P/N/V | 24 h |
| | | | Nalbuphine (4 mg) | 60 | | |
| | | | Ondansetron (4 mg) | 60 | | |
| | | | Ondansetron (8 mg) | 60 | | |
| Harnett et al.[27] | 4 (2/0/2/0) | 0.2 mg (+10 μg ITF[c]) | Normal saline (10 mL) | 81 | P/N/V | 24 h |
| | | | Ondansetron (4 mg) | 79 | | |
| | | | Scopolamine (1.5 mg) | 80 | | |
| Sarvela et al.[28] | 6 (2/0/2/2) | 0.16 mg (+15 μg ITF[c]) | Normal saline (5 mL) | 29 | P | 24 h |
| | | | Ondansetron (8 mg) | 30 | | |
| | | | Tropisetron (5 mg) | 28 | | |
| Siddik-Sayyid et al.[29] | 5 (2/0/1/2) | 0.2 mg | Normal saline | 45 | P/N/V | 24 h |
| | | | Granisetron (3 mg) | 42 | | |
| | | | Ondansetron (8 mg) | 42 | | |
| Yazigi et al.[30] | 4 (2/0/2/0) | 0.1 mg (+2.5 μg ITS[d]) | Normal saline (5 mL) | 50 | P | 24 h |
| | | | Ondansetron (8 mg) | 50 | | |
| Yeh et al.[31] | 3 (1/0/2/0) | 0.15 mg | Normal saline | 20 | P | 28 h |
| | | | Ondansetron (0.1 mg/kg) | 20 | | |
| | | | Diphenhydramine (30 mg) | 20 | | |
| Peixoto et al.[33] | 7 (2/1/2/2) | 0.1 mg (+20 μg ITF[c]) | Normal saline | 40 | N/V | 24 h |
| | | | Ondansetron (4 mg) | 40 | | |
| | | | Droperidol (1.25 mg) | 40 | | |
| Balki et al.[32] | 6 (2/0/2/2) | 0.1 mg (+10 μg ITF[c]) | Normal saline (1 mL) | 88 | N/V | PACU |
| | | | Granisetron (1 mg) | 88 | | |
| Charuluxananan et al.[34] | 7 (2/1/2/2) | 0.2 mg | Normal saline (2 mL) | 39 | P | 4 h |
| | | | Ondansetron (4 mg) | 41 | | |

PACU = postanesthesia care unit.

[a] R/C/B/F—randomization/concealment allocation/blinding/flow of subjects. Numbers represent points allocated for each quality indicator (see Appendix).

[b] P/N/V—pruritus/nausea/vomiting.

[c] ITF—intrathecal fentanyl.

[d] ITS—intrathecal sufentanil.

**Table 2.** The Effect of 5-$HT_3$ Receptor Antagonists Prophylaxis on the Incidence, Need for Treatment and Severity of Pruritus

| | Risk of treatment group | Risk of control group | RR (95% CI) | NNT (95% CI) |
|---|---|---|---|---|
| Incidence of pruritus | | | | |
| Ondansetron 4 mg[26] | 52/60 (86.7%) | 56/60 (93.3%) | 0.93 (0.82–1.05) | |
| Ondansetron 8 mg[26,28–31a] | 157/202 (77.7%) | 175/204 (85.8%) | 0.94 (0.79–1.11) | |
| Combined ondansetron doses | 209/262 (79.8%) | 175/204 (85.8%) | 0.93 (0.80–1.10) | |
| Tropisetron 5 mg[28a] | 22/28 (78.6%) | 22/29 (75.9%) | 1.04 (0.78–1.37) | |
| Granisetron 3 mg[29] | 37/42 (88.1%) | 39/45 (86.7%) | 1.02 (0.87–1.19) | |
| *All studies combined* | *268/332 (80.7%)* | *175/204 (85.8%)* | *0.94 (0.81–1.09)* | |
| Need for treatment of pruritus | | | | |
| Ondansetron 4 mg[26,27] | 52/139 (37.4%) | 74/141 (52.5%) | 0.71 (0.55–0.92) | 7 (4–29) |
| Ondansetron 8 mg[26,28–31a] | 77/202 (38.1%) | 94/204 (46.1%) | 0.83 (0.66–1.03) | |
| Combined ondansetron doses | 129/341 (37.8%) | 125/285 (43.9%) | 0.79 (0.66–0.95) | 17 (8 to −59) |
| Tropisetron 5 mg[28a] | 11/28 (39.3%) | 9/29 (31.0%) | 1.27 (0.62–2.58) | |
| Granisetron 3 mg[29] | 12/42 (28.6%) | 18/45 (40.0%) | 0.71 (0.39–1.30) | |
| *All studies combined* | *152/411 (38.0%)* | *125/285 (43.9%)* | *0.80 (0.64–0.96)* | *15 (7 to −186)* |
| Incidence of severe pruritus | | | | |
| Ondansetron 4 mg[26] | 28/60 (46.7%) | 43/60 (71.7%) | 0.65 (0.48–0.89) | 4 (3–13) |
| Ondansetron 8 mg[26,29–31] | 70/172 (40.7%) | 85/175 (48.6%) | 0.84 (0.67–1.05) | |
| Combined ondansetron doses | 98/232 (42.2%) | 85/175 (48.6%) | 0.80 (0.65–0.98) | 16 (6 to −29) |
| Granisetron 3 mg[29] | 14/42 (33.3%) | 18/45 (40.0%) | 0.83 (0.48–1.46) | |
| *All studies combined* | *112/274 (40.9%)* | *85/175 (48.6%)* | *0.79 (0.65–0.97)* | *13 (6 to −58)* |

RR = relative risk; CI = confidence interval; NNT = number needed to treat.

[a] Sarvela et al.[28]—The highest recorded incidence over the duration of the study was used as the 24 h incidence.

### Time to Onset of Pruritus

Only a single prophylaxis trial published the interval from morphine administration until the onset of pruritus after prophylaxis with ondansetron 0.1 mg/kg.[31] The average time to the onset of pruritus was not significantly different in the placebo compared with the ondansetron group (183 vs 187 min, weighted mean difference [95% CI] = 4.00 [−28.87 to 36.87]).

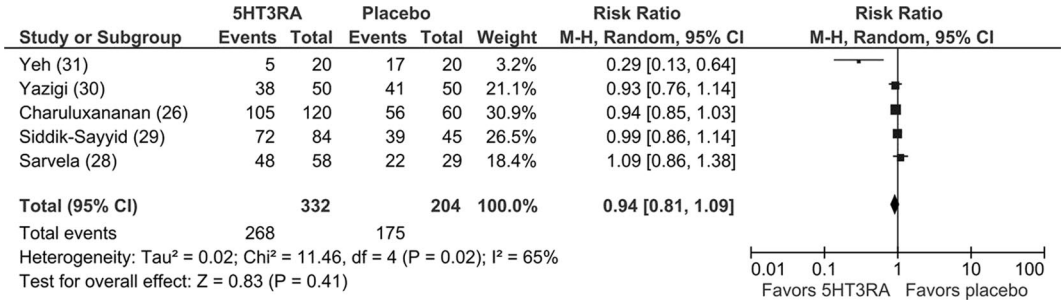


**Figure 2.** Incidence of pruritus. A relative risk (RR) less than one indicates less pruritus with 5-$HT_3$ receptor antagonists compared with control. When the 95% confidential interval (CI) does not include 1, the difference is considered statistically significant. $\hat{o}^2$, $\chi^2$, and $I^2$ refer to the tests for statistical heterogeneity, M–H = Mantel–Haenszel test; 5-HT3RA = 5-$HT_3$ receptor antagonist.

### Treatment of Established Pruritus

Only one study compared ondansetron 4 mg with placebo for the treatment of pruritus after cesarean delivery using 0.2 mg intrathecal morphine.[34] A 4-point scale to assess the severity of pruritus was used. Patients who had a pruritus score of 3 or 4 were randomized and treated; treatment success was achieved if the pruritus score was decreased to 1 or 2 after treatment. Ondansetron was significantly more effective than placebo in successfully treating pruritus (80% vs 36%, RR [95% CI] = 0.30 [0.16–0.59], NNT = 3).

## Nausea and Vomiting

### Intraoperative Nausea and Vomiting

Data on intraoperative nausea and vomiting were reported in four studies.[27,28,32,33] Two reported nausea and vomiting separately,[27,32] whereas the remainder reported nausea and vomiting collectively.[28,33] Of the former studies, one reported the incidence over the whole intraoperative period,[27] whereas the other reported predelivery and postdelivery data separately.[32] Therefore, we were unable to combine data on the incidence of intraoperative nausea and vomiting quantitatively and these data were not included in the review.

### Postoperative Nausea

Four studies reported the incidence of postoperative nausea after prophylactic 5-$HT_3$ receptor antagonists compared with placebo.[26,27,29,33] The results are summarized in Table 3. Ondansetron 8 mg reduced postoperative nausea when compared with placebo. This reduction was also significant when these data were combined with data from the three trials investigating ondansetron 4 mg. There was no evidence of dose responsiveness for ondansetron. The study investigating granisetron 3 mg did not demonstrate a significant reduction in the incidence of postoperative nausea.[29] Overall, when all drugs and doses of 5-$HT_3$ receptor antagonists were combined, there was a significant reduction in the incidence of postoperative nausea when compared with placebo (Fig. 3).

### Postoperative Vomiting

The four studies investigating postoperative nausea also reported the incidence of postoperative vomiting (Table 3).[26,27,29,33] Ondansetron 4 mg significantly reduced postoperative vomiting when compared with placebo. When combined with the studies investigating ondansetron 8 mg, the reduction was still significant. There was no evidence of dose responsiveness for ondansetron. The only study investigating the use of granisetron 3 mg was unable to demonstrate any efficacy in preventing postoperative vomiting.[29] When all drugs and doses were combined, the 5-$HT_3$ receptor antagonists significantly reduced the incidence of postoperative vomiting when compared with placebo (Fig. 4).

### Need for Postoperative Rescue Antiemetic Treatment

Three studies reported the need for postoperative rescue antiemetic therapy.[28,29,33] Metoclopramide or naloxone,[33] droperidol or metoclopramide,[28] or metoclopramide only[29] were the rescue antiemetics of choice. Results are summarized in Table 3. A significant reduction in the need for rescue occurred with ondansetron 4 mg, and with all ondansetron doses combined. When all drugs and doses were combined, the need for postoperative rescue antiemetic was significantly reduced when 5-$HT_3$ receptor antagonists were compared with placebo.

### Severity of Nausea/Vomiting

Five studies assessed the severity of nausea and vomiting in patients receiving 5-$HT_3$ receptor antagonists.[26–30] In one study, nausea severity was assessed postoperatively using a 100 mm unlabeled visual analog scale.[27] No difference in nausea scores was reported between the placebo and 5-$HT_3$ receptor antagonist groups; data from this study were not included in the pooled analysis. Two studies used a 4-point scale (1 = absent nausea, 2 = queasy, 3 = severe nausea, 4 = vomiting) for assessing the severity of postoperative nausea and vomiting.[26,29] Yazigi et al.[30] used a 3-point scale (0 = no nausea and vomiting, 1 = mild to moderate nausea or vomiting not needing treatment, and 2 = severe nausea or vomiting needing treatment) as did Sarvela et al.[28] (0 = none, 1 = nausea, 2 = disturbing nausea or vomiting). For the purposes of comparison, we converted the 4-point scales to a 3-point scale by combining Grades 3 and 4 into a single severe group and compared

**Table 3.** The Effect of 5-$HT_3$ Receptor Antagonists on the Incidence of Postoperative Nausea and Vomiting and the Need for Rescue Antiemetic Therapy

| | Risk of treatment group | Risk of control group | RR (95% CI) | NNT (95% CI) |
|---|---|---|---|---|
| Incidence of postoperative nausea | | | | |
| Ondansetron 4 mg[26,27,33a] | 50/179 (27.9%) | 67/181 (37.0%) | 0.76 (0.58–1.00) | |
| Ondansetron 8 mg[26,29] | 12/102 (11.8%) | 25/105 (23.8%) | 0.49 (0.26–0.93) | 8 (4–56) |
| Combined ondansetron doses | 62/281 (22.1%) | 92/286 (32.2%) | 0.69(0.53–0.89) | 10 (6–35) |
| Granisetron 3 mg[29] | 9/42 (21.4%) | 9/45 (20.0%) | 1.07 (0.47–2.44) | |
| *All studies combined* | *71/323 (22.0%)* | *76/226 (33.6%)* | *0.75 (0.58–0.96)* | *9 (5–25)* |
| Incidence of postoperative vomiting | | | | |
| Ondansetron 4 mg[26,27,33a] | 36/179 (20.1%) | 63/181 (34.8%) | 0.59 (0.43–0.80) | 7 (4–18) |
| Ondansetron 8 mg[26,29] | 9/102 (8.8%) | 11/105 (10.5%) | 0.85 (0.37–1.96) | |
| Combined ondansetron doses | 21/281 (7.4%) | 42/286 (14.5%) | 0.52 (0.32–0.85) | 14 (8–48) |
| Granisetron 3 mg[29] | 4/42 (9.5%) | 7/45 (15.6%) | 0.61 (0.19–1.94) | |
| *All studies combined* | *25/323 (7.7%)* | *38/226 (16.8%)* | *0.49 (0.30–0.81)* | *12 (7–30)* |
| Need for postoperative rescue antiemetic therapy | | | | |
| Ondansetron 4 mg[33] | 2/40 (5.0%) | 10/40 (25.0%) | 0.16 (0.03–0.78) | 5 (3–20) |
| Ondansetron 8 mg[28,29] | 8/72 (11.1%) | 16/74 (21.6%) | 0.46 (0.19–1.15) | |
| Combined ondansetron doses | 10/112 (8.9%) | 26/114 (22.8%) | 0.39(0.20–0.78) | 7 (4–22) |
| Granisetron 3 mg[29] | 5/42 (11.9%) | 13/45 (28.9%) | 0.33 (0.11–1.03) | |
| Tropisetron 5 mg[28] | 1/28 (3.6%) | 3/29 (10.3%) | 0.32 (0.03–3.29) | |
| *All studies combined* | *16/182 (8.8%)* | *26/114 (22.8%)* | *0.38 (0.21–0.68)* | *7 (4–19)* |
| Incidence of severe postoperative nausea and vomiting | | | | |
| Ondansetron 4 mg[26] | 5/60 (8.3%) | 14/60 (23.3%) | 0.36 (0.14–0.93) | 7 (4–45) |
| Ondansetron 8 mg[26,28–30] | 23/182 (12.6%) | 43/184 (23.4%) | 0.54 (0.34–0.87) | 10 (5–34) |
| Combined ondansetron doses | 28/242 (11.6%) | 57/244 (23.4%) | 0.50 (0.30–0.75) | 9 (5–20) |
| Granisetron 3 mg[29] | 8/42 (19.0)% | 10/45 (22.2%) | 0.86 (0.37–1.96) | |
| Tropisetron 5 mg[28] | 1/28 (3.5%) | 4/29 (13.8%) | 0.26 (0.03–2.18) | |
| *All studies combined* | *37/315 (11.7%)* | *43/184 (23.4%)* | *0.55 (0.33–0.76)* | *9 (5–22)* |

RR = relative risk; CI = confidence interval; NNT = number-needed-to-treat.

[a] Harnett et al. [27]—The author provided unpublished data regarding the overall 24 h incidence of postoperative nausea and vomiting.

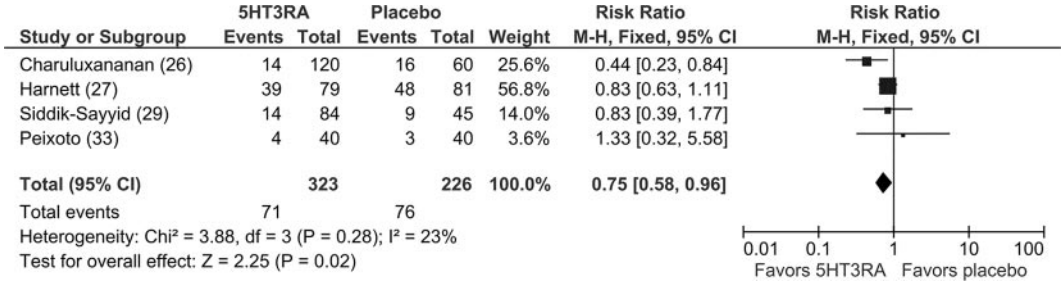


**Figure 3.** Incidence of postoperative nausea. A relative risk (RR) less than one indicates less postoperative nausea with 5-$HT_3$ receptor antagonists compared with control. When the 95% confidential interval (CI) does not include 1, the difference is considered statistically significant. $\delta^2$, $\chi^2$, and $I^2$ refer to the tests for statistical heterogeneity; M–H = Mantel–Haenszel test; 5-$HT_3$RA = 5-$HT_3$ receptor antagonist.

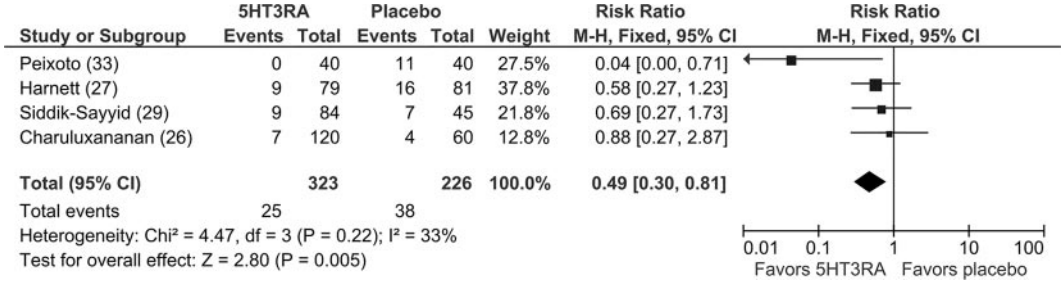


**Figure 4.** Incidence of postoperative vomiting. A relative risk (RR) less than one indicates less postoperative vomiting with 5-$HT_3$ receptor antagonists compared with control. When the 95% confidential interval (CI) does not include 1, the difference is considered statistically significant. $\delta^2$, $\chi^2$, and $I^2$ refer to the tests for statistical heterogeneity; M–H = Mantel–Haenszel test; 5-$HT_3$RA = 5-$HT_3$ receptor antagonist.

the incidence of severe postoperative nausea and vomiting between the 5-$HT_3$ receptor antagonists and placebo groups. Combined data showed that ondansetron was effective in reducing the incidence of severe postoperative nausea and vomiting when compared with placebo (Table 3). Overall, when combining all drugs and doses, 5-$HT_3$ receptor antagonists were still effective in reducing the incidence of severe postoperative nausea and vomiting when compared with placebo.

### Side Effects

Headache, cardiac arrhythmias, and extrapyramidal side effects were the most commonly investigated side effects of 5-$HT_3$ receptor antagonists. Four studies evaluated patients for headache after the administration of 5-$HT_3$ receptor antagonists.[29–32] In one study, there were no reported cases of headache directly related to the administration of 5-$HT_3$ receptor antagonists.[30] Yeh et al.[31] did not report the actual incidence of headaches but reported no difference between the treatment and placebo groups. In the two remaining studies, the incidence of headaches were reported quantitatively.[29,32] Both studies reported no difference between the treatment and placebo groups. Combined data also showed no difference in the risk of headache with the 5-$HT_3$ receptor antagonists compared with placebo (6% vs 2%, RR [95% CI] = 2.78 [0.83–9.29]).

Five studies evaluated patients for cardiac dysrrhythmias.[26,29–32] The single study reporting quantitative differences found no difference in the incidence of dysrhythmias (3.4% vs 4.6%), tachycardia (0% vs 1.1%), or bradycardia (6.7% vs 10.2%) between the treatment and control groups.[32] Yeh et al.[31] reported no significant difference in the incidence of dysrhythmias between the treatment and the placebo group. In the remaining three studies, cardiac dysrhythmias were not observed in any patient.[26,29,30]

Four studies evaluated patients for extrapyramidal side effects[26,29–31] and reported that these side effects were not observed in any patient.

## DISCUSSION

The results of this systematic review indicate that the 5-$HT_3$ receptor antagonists do not significantly reduce the incidence of pruritus in women undergoing spinal anesthesia with intrathecal morphine. Their use, however, was associated with a significant reduction in the severity and need for treatment of pruritus. Ondansetron was effective for the treatment of established pruritus. 5-$HT_3$ receptor antagonists were effective for the prophylaxis against postoperative nausea and vomiting in this patient population. There was no dose responsiveness with ondansetron 4 or 8 mg when used for the prophylaxis against nausea, vomiting, and pruritus. 5-$HT_3$ receptor antagonists were not associated with a higher incidence of side effects when compared with placebo.

Neuraxial opioid-induced pruritus is likely due to cephalad migration of neuraxial opioids to the medulla where the "itch center" is thought to be located and where they interact with the trigeminal nucleus.[35] Interactions between the serotonin and opioid receptors in the central nervous system have been suggested as a mechanism of opioid-induced pruritus.[36] Specifically, the 5-$HT_3$ receptor has been implicated and this stimulated interest in investigating the potential for the 5-$HT_3$ receptor antagonists to reduce the incidence of this bothersome complication of intrathecal morphine. Parturients appear to be more susceptible to neuraxial opioid-induced pruritus compared with the general surgical population with a reported incidence of 60%–100%.[37] An interaction of estrogen with the opioid receptors has been suggested as a reason for this increased sensitivity.[38] Although our analysis demonstrated the prophylactic use of 5-$HT_3$ receptor antagonists was associated with a reduction in the severity and the need for treatment of pruritus, this reduction was modest with a NNT of 12 and 15, respectively. Only one study investigated the use of ondansetron for the treatment of established pruritus and reported that it was more effective than placebo.[34]

The incidence and severity of pruritus increases with increasing doses of intrathecal morphine.[39] In this review, the average incidence of pruritus was 90%, 82%, and 76% with the use of 0.2, 0.1, and 0.16 mg intrathecal morphine, respectively. It has been suggested that the combination of intrathecal morphine with a lipophilic opioid may decrease the efficacy of the 5-$HT_3$ receptor antagonist in reducing the incidence of pruritus, due to activation of the serotonin receptors by the lipophilic opioid before being blocked by the 5-$HT_3$ receptor antagonist.[24] However, our study found no efficacy in reducing the incidence of pruritus, even when we limited our analysis to studies in which patients did not receive lipid soluble opioids.

Our results regarding pruritus differ from those of Bonnet et al.[40] who recently published a quantitative systematic review of the efficacy of 5-$HT_3$ receptor antagonists for the prophylaxis of neuraxial opioids (morphine, fentanyl, and sufentanil)-induced pruritus in patients undergoing a wide variety of surgical procedures and labor. They concluded that 5-$HT_3$ receptor antagonists were effective in reducing the incidence of pruritus. This agrees with a previous report showing a benefit of those drugs for the prophylaxis against neuraxial opioid-induced pruritus in the general surgical population.[41] They also performed a subgroup analysis of patients receiving neuraxial opioids for cesarean delivery and concluded that the incidence of pruritus was reduced with 5-$HT_3$ receptor antagonists' prophylaxis in this patient population. However, they included a trial in which fentanyl alone was used[16] in addition to trials using intrathecal morphine. Our analysis only included patients who had intrathecal morphine, because we believe that this results in a more clinically homogeneous patient population. We also included the highest incidence of pruritus recorded during the 24 h duration of the study in one of the included trials,[28] whereas Bonnet et al. used the incidence of pruritus reported at 4–12 h after surgery (69%), which was lower in the 5-$HT_3$ group than the incidence that we included (83%).

Our systematic review had several limitations. There were only a limited number of studies available for review that investigated pruritus, nausea, and vomiting in the obstetric population. Several of these studies had small sample sizes. In addition, these studies used different scoring systems for reporting the severity of pruritus and nausea. The trigger for treating pruritus was also different in the included studies. Therefore, data on the severity of pruritus and severity of postoperative nausea and vomiting, and the need for treatment of pruritus, should be interpreted with caution. Also, the duration of pruritus and nausea and vomiting episodes was not assessed in several studies. None of the studies reported complete response to antiemetic prophylaxis. We combined data on all drugs and doses because it was previously suggested that the antiemetic effect of the 5-$HT_3$ receptor antagonists is similar when adequate doses are used.[42] However, it is not clear if this also applies to their antipruritic effect. Publication bias cannot be excluded. However, funnel plots and statistical tests for detection of publication bias are unreliable in the presence of a small number of studies as is the case in our review and therefore were not performed.[43–45] A strong point of our analysis was the consistent anesthetic technique in the included studies and comparable periods of follow-up.

Larger studies with adequate power are required to further investigate the use of the 5-$HT_3$ receptor antagonists for the prophylaxis against pruritus, intraoperative, and postoperative nausea and vomiting in the obstetric population. Specifically, future studies need to use validated and consistent scoring systems for assessing the severity of pruritus and nausea. These studies also need to have clearly defined consistent end points for the treatment of pruritus. Nausea and vomiting also need to be reported separately rather than collectively. Reporting of intraoperative nausea and vomiting also needs to be improved. Reporting should differentiate events that occur before delivery or after delivery because the etiology might be different at those different stages of the procedure. The usefulness and efficacy of the 5-$HT_3$ receptor antagonists for the treatment of established pruritus also requires further investigation.

In conclusion, the 5-$HT_3$ receptor antagonists significantly reduce the severity and need for treatment of pruritus, the incidence and severity of postoperative nausea and vomiting and the need for postoperative rescue antiemetic therapy in patients who have received intrathecal morphine as part of spinal anesthesia for cesarean delivery. However, they did not reduce the overall incidence of neuraxial opioid-induced pruritus but were effective for the treatment of established pruritus. They also had a favorable side effects profile, and therefore the results of this review suggest that the prophylactic use of 5-$HT_3$ receptor antagonists in this patient population should be considered. However, the current studies had limitations, and therefore further studies are warranted.

## APPENDIX

Modified Oxford score[8]
Validity Score (0–7)
Randomization
0–None
1–Mentioned
2–Described and adequate
Concealment of allocation
0–None
1–Yes
Double blinding
0–None
1–Mentioned
2–Described and adequate
Flow of patients
0–None
1–Described but incomplete
2–Described and adequate
R/C/B/F–randomization/concealment allocation/blinding/flow of subjects (Table 1)

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