Mirtazapine for Postoperative Nausea and Vomiting: Systematic Review, Meta-analysis, and Trial Sequential Analysis

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Purpose: *Patients rank postoperative nausea and vomiting (PONV) as the most undesirable outcome of anesthesia. Mirtazapine is hypothesized to be effective in PONV prophylaxis via 5HT3 receptor antagonism.*
Design: *Systematic review and meta-analysis.*
Methods: *We identified seven randomized controlled trials by systematically searching electronic databases that compare the efficacy of mirtazapine versus placebo or ondansetron in reducing PONV.*
Findings: *Mirtazapine reduced PONV overall versus placebo in three studies (risk ratio [RR] = 0.44; 95% confidence interval [CI] 0.32 to 0.62) both on conventional meta-analysis and trial sequential analysis. One study comparing mirtazapine with ondansetron found similar rates of PONV (RR = 0.96; 95% CI 0.48 to 1.94). Mirtazapine reduced preoperative anxiety versus placebo or ondansetron (standardized mean difference −1.4; 95% CI −2.56 to −0.23) but increased sedation (RR = 22.47; 95% CI 5.61 to 89.93). The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) quality of evidence was moderate to low.*
Conclusions: *This meta-analysis suggests that mirtazapine reduces PONV overall versus placebo. We found evidence of reduction in preoperative anxiety, although mirtazapine increased the risk of sedation.*

Keywords: *mirtazapine, nausea and vomiting, perioperative care, PONV.*

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POSTOPERATIVE NAUSEA AND VOMITING (PONV) has previously been identified as the most undesirable outcome of anesthesia.[1] As serious adverse outcomes of anesthesia are rare, consideration must be given by clinicians to improving the patient experience by minimizing this common adverse event (one in three patients).[2] Multiple antiemetics are currently in use for the treatment of PONV; the "setrons" are commonly used in clinical practice. Consensus guidelines recommend the use of methods for prophylaxis of PONV rather than simply rescue treatment of PONV during the perioperative period.[3-5] Mirtazapine, commonly used as an antidepressant, has been postulated to be an effective antiemetic. It may have additional benefits such as reductions

in preoperative anxiety and pain. These additional beneficial effects of mirtazapine have been observed in contexts such as oncology and obstetrics and are derived from pharmacologic principles (eg, 5HT3 receptor antagonism as one mechanism). Given this premise, we investigated the effectiveness of the preoperative use of mirtazapine in the prevention of PONV. We thus aimed to evaluate the use of a drug, which is well established in the pharmaceutical industry for other indications, in a novel context.

Aims

The primary aim of this study was to compare the effect of preoperative administration of mirtazapine versus preoperative administration of placebo or no treatment or another antiemetic on incidence of PONV (incidence measured as composite or individually). A secondary aim was to compare the effect of preoperative use of mirtazapine versus preoperative administration of placebo/no treatment or another antiemetic on the following perioperative outcomes:

1. Postoperative pain
2. Morphine consumption
3. Preoperative anxiety
4. Pruritus
5. Adverse events such as sedation and dry mouth

Design and Methods

Study Registration

We report this review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[6] The PRISMA statement consists of the PRISMA checklist (the minimum set of items that should be reported in a systematic review and meta-analysis) and the PRISMA flow diagram (applied to our study in Figure 1). We prospectively registered this review on the PROSPERO database using the registration number CRD42016047502.

Literature Search and Information Sources

Author B.D. searched MEDLINE, EMBASE, CINAHL, AMED, and Cochrane Central Register of Controlled Trials (CENTRAL) databases from their inception to May 2017. Key words searched include "mirtazapine" OR "Remeron" AND "nausea," OR "vomiting." The term "POSTOPERATIVE NAUSEA AND VOMITING" was exploded and combined with the terms mentioned previously (using Boolean operator "OR"). To help reduce the likelihood of publication bias, B.D. searched for unpublished studies in Clinicaltrials.gov and the World Health Organization (WHO) clinical trials registries. We did not exclude any studies on the basis of language or publication status. We planned to send non-English language articles for professional translation. We also screened the reference lists of all included articles to identify any additional studies.

Study Selection

We included all randomized controlled trials with all years considered, comparing mirtazapine at any dose versus placebo/no treatment or other antiemetic medication. The study population in all studies was adult patients (older than 15 years) undergoing any type of surgical procedure. All included studies evaluated the primary outcome: Incidence of PONV (either individually or as composite outcomes or both).

Secondary outcomes included:

1. Postoperative pain (early less than 6 hours and late 24 hours).
2. Morphine consumption (at latest time reported in milligrams).
3. Preoperative anxiety (on continuous scale).
4. Pruritus (incidence).
5. Adverse events such as sedation (incidence or on a continuous scale) and dry mouth (incidence).

Two authors (D.B. and B.D.) reviewed the titles and abstracts from all the studies retrieved from the search to select those studies potentially meeting eligibility criteria for full text review. Full texts were available for eight of the nine studies retrieved from the search. Full text was not available for one study retrieved[7] although on abstract review by two independent authors as described previously, this study met the inclusion or exclusion criteria for this meta-analysis and was therefore included. We found one unpublished study from searching clinical trial registries, although we received no response for further data from the study investigators (JPRN-UMIN000003822). Full text review was also conducted independently by two authors (D.B. and B.D.).

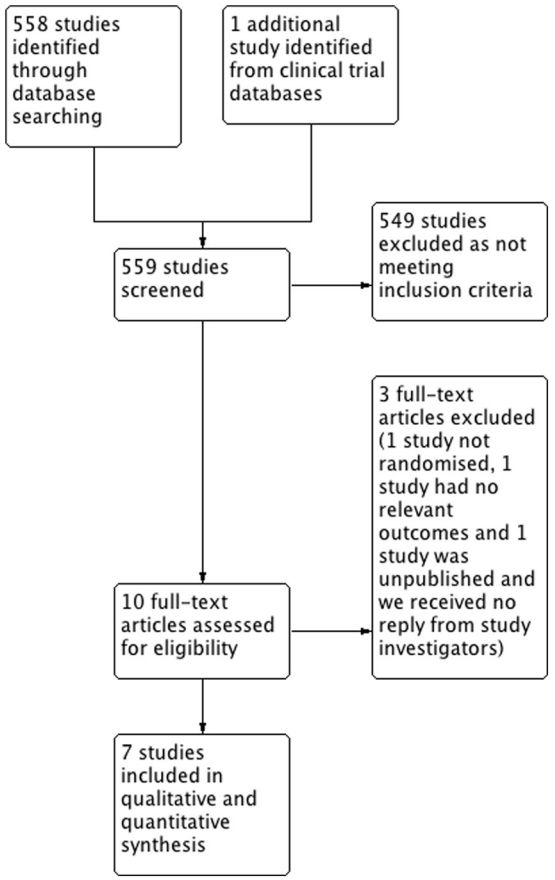

Figure 1. Flow diagram of search results.

Data Extraction and Data Items

D.B. and B.D. extracted data independently and in duplicate. Data extraction disagreements were resolved by consensus. We initially followed the Population, Intervention, Comparator, Outcome model for data extraction. Extracted data included population (percentage female, American Society of Anesthesiologists [ASA] grade, previous PONV, previous motion sickness, Apfel score, smoker status, postoperative opioids used), intervention dose and route, control used, type of surgery, types of anesthesia and other agents used (such as nitrous oxide), sample size, outcomes, and the country the study was conducted in.

Risk of Bias Assessment

Risk of bias was conducted independently and in duplicate by D.B. and B.D. using the Cochrane Risk of Bias tool.[8] Disagreements regarding quality assessment were resolved by consensus.

Statistical Analysis

We report continuous outcomes as differences in means and dichotomous outcomes using risk ratios (RRs). If noncomparable scales were used, we report effect estimates as standardized mean differences. Precision of results is reported using 95% confidence intervals (CIs). We aggregated results using a random-effects model. Statistical heterogeneity was assessed using the I^2 statistics. We planned to perform assessment for publication bias and investigation of heterogeneity using a random-effects meta-regression. However, the low number of studies precluded this. We assessed the quality of evidence using the GRADE criteria.[9,10] The GRADE criteria allow rating of the quality of evidence according to the certainty that the true effect is similar to the estimated effect size. According to the GRADE criteria, there are four levels of quality of evidence: very low, low, moderate, and high. We also conducted sensitivity analysis including low risk of bias studies (low risk for randomization, allocation concealment, blinding, and attrition bias). Finally, we conducted trial sequential analysis (TSA) for the primary outcome of PONV. We used O'Brien-Fleming monitoring boundaries adjusted for multiple comparisons. Analyses were conducted using a $1 - \beta = 80\%$ and an $\alpha = 0.05$. We used empiric estimates of diversity (D^2) and estimated incidences from the included studies with a relative risk reduction of 50%. All meta-analyses were conducted using STATA version 14.2, and TSA was conducted using TSA software from the Copenhagen Trial Unit.

Findings

We identified 559 studies from searching electronic databases and clinical trial databases (Figure 1). After excluding studies that did not meet inclusion criteria, 10 studies underwent full text review and 7 were included in the final review. Study characteristics of the seven studies included in this meta-analysis are presented in Table 1.[5,7,11-15] In total, 581 subjects were represented in our systematic review and meta-analysis. The intervention in all studies was preoperative administration of oral mirtazapine. The control in five of the studies was

Table 1. Study Characteristics

Studies Included in Meta-analysis	% Female	ASA Physical Status	Previous PONV/ Motion Sickness	Apfel Score	Smoker	Postoperative Opioids Used	Intervention	Control	Type of Surgery	Type of Anesthetic Used	Year, Country
Akhan et al[11] Sample size = 80 patients	20%	I and II	Patients with history of PONV were excluded. Previous motion sickness = no information	No information	No information	None, patients using opioids postoperative were excluded from study	Mirtazapine 30 mg orally 2 h before surgery	3 comparators: Group 1: preoperative ondansetron Group 2: preoperative gabapentin Group 4: placebo sugar pills	Unilateral inguinal hernia repair or pilonidal sinus surgery	Spinal anesthesia: 0.5% hyperbaric bupivacaine 15 mg (3 mL), and 0.2 mg (0.1 mL) morphine	2016, Turkey
Chang et al[12] Sample size = 97 patients	15.5%	I and II	Previous PONV = 10/97 participants overall. 5 (10%) in each group Previous motion sickness = 11/97 participants overall. 5(10%) in mirtazapine group, 6(12%) in placebo group	Apfel score 0/1/2/3: mirtazapine group: 15/23/9/2, placebo group: 13/24/8/3. In the whole population, 29% of patients had Apfel score 0, 48% had Apfel score 1, overall low Apfel risk scores for PONV	71/97 (73%) of overall participants were current smokers. 75% in the mirtazapine group and 70% in the placebo group were current smokers	None mentioned.	Orally disintegrating tablet of 30 mg mirtazapine 1 h before surgery	Placebo: orally disintegrating tablet of identical size, shape and color to mirtazapine but without active ingredient—1 h before surgery	Lower limb orthopaedic surgery	Spinal anesthesia: 15 mg isobaric bupivacaine 0.5% along with 0.2 mg preservative-free morphine	2010, Taiwan
Chang and Sheen[7] Sample size = 80 patients *only abstract available*	100%	Not mentioned in abstract	Previous PONV = not mentioned in abstract Previous motion sickness = not mentioned in abstract	Not mentioned in abstract	Not mentioned in abstract	Not mentioned in abstract	30 mg mirtazapine orally 1 h before surgery	Placebo 1 h before surgery	Elective caesarean section	Spinal anesthesia: intrathecal injection of 10 mg of 0.5% hyperbaric bupivacaine and 0.2 mg preservative free morphine	2011, Taiwan
Chen et al[5] Sample size = 80 patients	100%	I and II	47.5% in mirtazapine + dexamethasone group 37.5% in placebo + dexamethasone group	Apfel's PONV risk factors (2/3/4) (Only patients who had at least two risk factors were enrolled): mirtazapine + dexamethasone group = 1/21/18, placebo + dexamethasone group: 3/24/13	2.5% in mirtazapine + dexamethasone group, 0% in placebo + dexamethasone group	Postoperative opioids used % (IV PCA morphine or IM meperidine): 90% in mirtazapine + dex group. 80% in placebo + dex group	An oral disintegrating mirtazapine (Remeron SolTab) 30 mg was given 1 h before surgery	Placebo tablet was given 1 h before surgery	Patients undergoing gynecologic procedures, including abdominal total hysterectomy, myomectomy, laparoscopic myomectomy, and laparoscopic oophorectomy, were recruited	General anesthesia: Induction: fentanyl 2 mcg/kg, xylocaine 0.5 mg/kg, and propofol (infused at the rate of 200 mL/h). Rocuronium 0.8 mg/kg was given to facilitate tracheal intubation. Maintenance of GA: sevoflurane in oxygen and air (FiO_2 0.6).	2008, Taiwan

(Continued)

Table 1. Continued

Studies Included in Meta-analysis	% Female	ASA Physical Status	Previous PONV/ Motion Sickness	Apfel Score	Smoker	Postoperative Opioids Used	Intervention	Control	Type of Surgery	Type of Anesthetic Used	Year, Country
Mansour[13] Sample size = 60 patients	35%	I and II	Previous PONV = no data Previous motion sickness = no data	No data	No data	No data	Mirtazapine 30 mg chewable tablet, which was ground and mixed with 20 mL of water in an opaque cup	Placebo—20 mL of plain water in an opaque cup	Variety of elective surgical procedures, duration of surgery in mirtazapine group: mean 44.6 ± 17.3 min (SD), duration of surgery in placebo group: mean 43.8 ± 19.2 min (SD)	Continuous IV infusion of propofol solution 1% mixed with 2 mL of lignocaine 1% at a rate of 300 mL/h by a syringe pump till a BIS value of 45 was reached, then propofol infusion was stopped. After that 2 mcg/kg of fentanyl was given and 0.15 mg/kg of cisatracurium to facilitate tracheal intubation. Maintenance of anesthesia: sevoflurane and oxygen/air mixture (FiO_2 = 0.6)	2013, Saudi Arabia
Omran et al[14] Sample size = 80 patients	100%	I and II	Previous PONV = no specific data Previous motion sickness = no specific data	Apfel score: 2.6 (mean) SD = 0.5 in mirtazapine group 2.7 (mean) SD = 0.5 in ondansetron group	All smokers excluded	Postoperative pain relief was prescribed as nalbuphine 20 mg IM 4 hourly PRN if VAS ≥ 4	Orally disintegrating tablet of 30 mg mirtazapine 1 h before surgery	Orally disintegrating tablet of ondansetron 16 mg 1 hour before surgery	Prophylactic mastectomy	General anesthesia induction: fentanyl .5 mcg/kg and propofol 1.5-2.5 mg/kg until loss of eyelash reflex. Tracheal intubation was facilitated with rocuronium 0.5 mg/kg. Maintenance of anesthesia with isoflurane (1-2.5%), nitrous oxide in 40% oxygen, and intermittent doses of muscle relaxants if needed throughout	2011, Egypt
Sheen et al[15] Sample size = 104 patients	5.8%	I	Previous PONV = not mentioned Previous motion sickness = not mentioned	Not mentioned	No data	Nalbuphine was used as rescue treatment for postoperative pruritus	An orally disintegrating mirtazapine 30 mg tablet was given 1 h before surgery	Orally disintegrating placebo tablet 1 h before operation	Lower limb orthopaedic surgery—cruciate ligament reconstruction, open reduction, removal of implant, arthroscopy	Subarachnoid anesthesia: 15 mg of isobaric bupivacaine plus 0.2 mg of preservative free morphine. Fentanyl 50 mg was given to each patient before surgery	2008, Taiwan

ASA, American Society Anesthesiologists; BIS, bispectral index; IM, intramuscular; IV, intravenous; PONV, postoperative nausea and vomiting; PRN, pro re nata; VAS, visual analog scale; PCA, patient controlled analgesia.

placebo, in two of the studies[11,14] the comparator was ondansetron. In three of the studies[5,7,14] all participants were female, with the types of surgery in these studies being either gynecologic operations or prophylactic mastectomy. Five of the seven studies included had participants with ASA physical status 1 to 2[5,11-14] and a variety of types of anesthesia were included ranging from spinal anesthesia, general anesthesia to continuous intravenous anesthesia. In terms of risk of bias, most of the included studies were at unclear risk of bias for allocation concealment and only two studies were low risk of bias for blinding (Figure 2).

Postoperative Nausea and Vomiting

In terms of mirtazapine versus placebo, when reported as a composite outcome, mirtazapine reduced PONV in three studies (Figure 3; moderate quality evidence). TSA showed that the results for this outcome crossed the α adjusted monitoring boundary and information size reducing both type I and II errors in analyses (Figure 4). There was no reduction in nausea (RR = 0.59; 95% CI 0.29 to 1.23; two studies; $I^2 = 0\%$; low quality evidence), although there was a significant reduction in vomiting in one study (RR = 0.25; 95% CI 0.08 to 0.82; low quality evidence). When compared with ondansetron in one study, mirtazapine resulted in similar rates of nausea (RR = 0.67; 95% CI 0.31 to 1.45; low quality evidence), vomiting (RR = 0.5; 95% CI 0.16 to 1.53; low quality evidence), and PONV (RR = 0.96; 95% CI 0.48 to 1.94; low quality evidence).

Postoperative Pain

In one study,[5] there was no difference in pain scores within the first 6 hours on a 0 to 100 scale (differences in mean 4.3; 95% CI −6.34 to 14.94). Mansour[13] reported pain as medians; there was no significant difference in pain scores at 6 hours (3 vs 3; $P = .72$) or 24 hours (2.5 vs 3; $P = .93$).

Morphine Consumption

Chen et al[5] reported no difference in morphine consumption between groups (29 vs 32 mg; $P > .05$), although it was unclear which group these values belonged to.

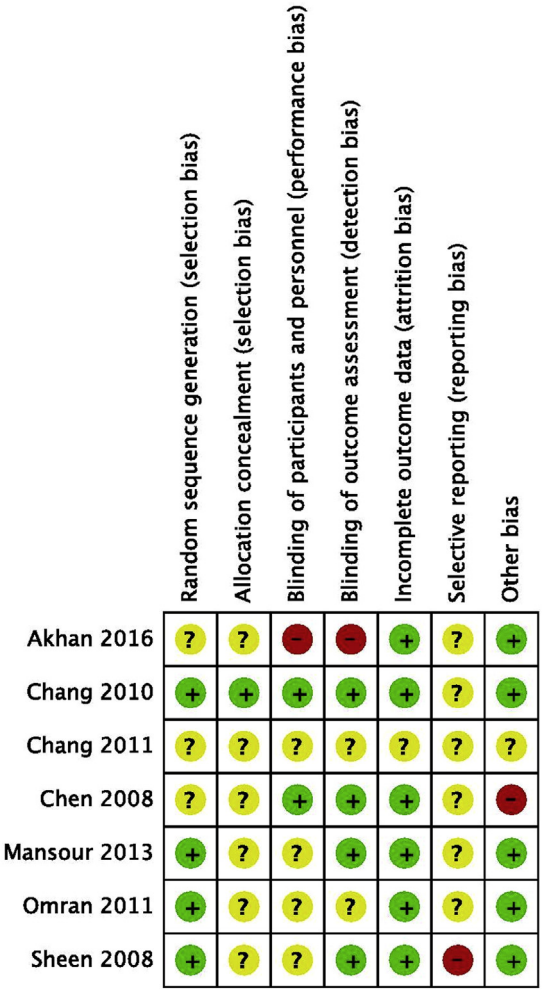

Figure 2. Risk of bias summary from the Cochrane Risk of Bias tool. Red is high risk, yellow unclear risk, and green low risk of bias. Please refer to the Cochrane Risk of Bias tool.[8] Domains for risk of bias include sequence generation (randomization), allocation concealment, blinding, and attrition bias (loss to follow-up). Reporting bias required preregistration of the clinical trial and no selective outcome reporting to score low risk of bias. This figure is available in color online at www.jopan.org.

Preoperative Anxiety

Mirtazapine reduced preoperative anxiety when compared with placebo or ondansetron (standardized mean difference −1.4; 95% CI −2.56 to −0.23; two studies; $I^2 = 91\%$; low quality evidence). Mansour[13] reported anxiety scores as medians. They found lower anxiety, three in the mirtazapine group and eight in the placebo group ($P < .001$).

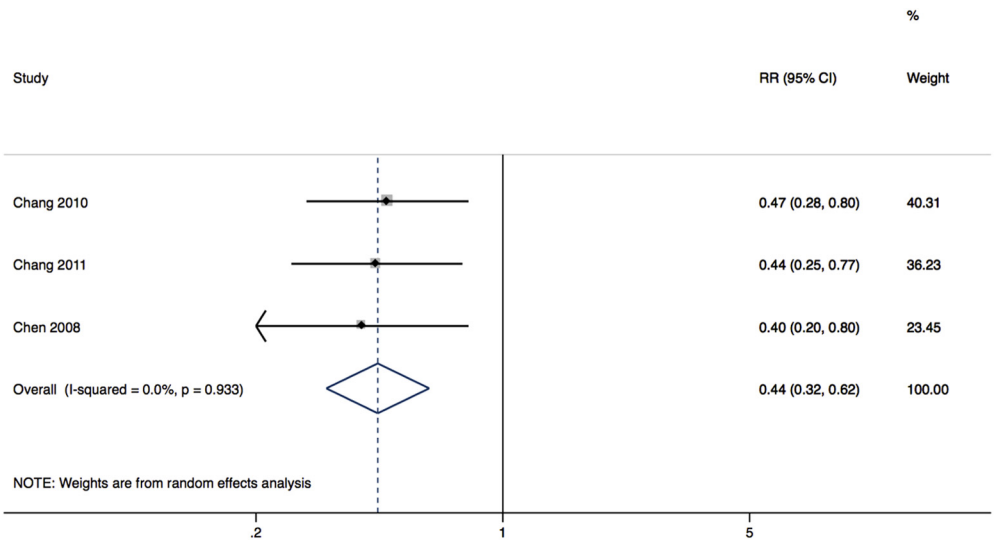

Figure 3. Meta-analysis Forest plot with PONV reported as a composite outcome. The diamond indicating overall relative risk lies to the left of 1. This suggests that there is overall a decrease in risk of PONV with the intervention used in the included studies (mirtazapine preoperatively) compared with the control used in the included studies (placebo). As the CI does not cross 1, this suggests that this result is statistically significant. CI, confidence interval; PONV, postoperative nausea and vomiting; RR, risk ratio. This figure is available in color online at www.jopan.org.

Pruritus

For pruritus, mirtazapine reduced the incidence of postoperative pruritus when compared with placebo (RR 0.65; 95% CI 0.50 to 0.86; two studies; I^2 = 0%; moderate quality evidence) and similar to ondansetron in one study (RR = 0.64; 95% CI 0.31 to 1.30; low quality evidence).

Adverse Events

Mirtazapine increased the risk of sedation when compared with placebo (RR = 22.47; 95% CI 5.61 to 89.93; two studies; I^2 = 0%; low quality evidence). Omran et al[14] reported data as medians and found no difference in sedation scores at 24 hours (1 vs 1; P = .12). There was no difference in the incidence of dry mouth (RR = 1.41; 95% CI 0.76 to 2.61; two studies; I^2 = 0%; low quality evidence).

We could not use data from Omran et al[14] for pain, opioid consumption, or adverse effects as the table was incorrectly labeled. Despite attempts to contact the authors, we received no response.

Conclusions

In our meta-analysis, when comparing PONV between mirtazapine and placebo three of the seven studies showed that there was a significant reduction (RR = 0.44; 95% CI 0.32 to 0.62) in PONV with mirtazapine. Furthermore, these benefits were confirmed on TSA, reducing the likelihood of type I and II errors in our analysis. Mirtazapine appeared equivalent to ondansetron for PONV although this conclusion was based on low quality evidence and only a single study. In addition, we found mirtazapine may also reduce preoperative anxiety and pruritus although it increased the risk of sedation. With regards to other preoperative outcomes, we found that mirtazapine did not significantly reduce early or late postoperative pain or postoperative morphine consumption. For reducing pruritus, mirtazapine was superior to placebo in two studies, based on moderate quality evidence but in a single study, mirtazapine was equivalent to ondansetron for this outcome. Mirtazapine was equivalent to placebo and ondansetron in two studies for incidence of dry mouth, based on low quality evidence.

5HT3 receptor antagonists, particularly ondansetron, are commonly used for prophylaxis and treatment of PONV. In a randomized, double-blind placebo-controlled study, Yazigi et al[16] found that prophylactic ondansetron significantly reduced the frequency and severity of PONV after caesarean section. Frost et al,[17] in their meta-analysis of six

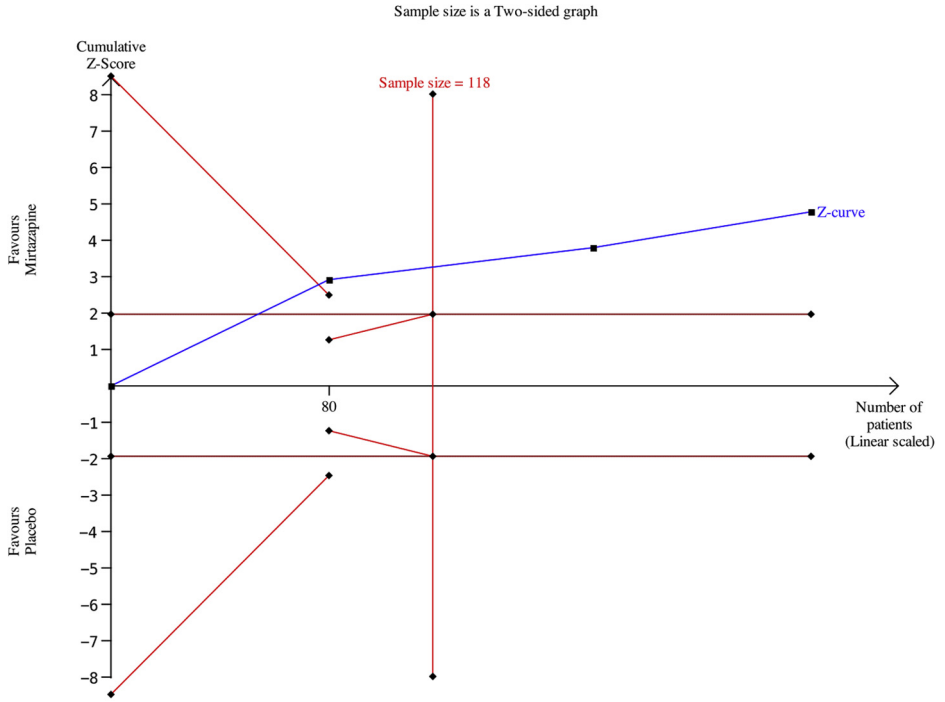

Figure 4. Trial sequential analysis. Blue line indicates cumulative *Z* score, which shows the results for PONV cross the O'Brien-Fleming monitoring boundary (diagonal red line) and information size (vertical red line). Once O'Brien-Fleming monitoring boundary is crossed, this suggests statistical significance for results adjusted for multiple comparisons (which occurs when each new study has been published). The vertical red line is the information size which when crossed suggests adequate power has been achieved in the current meta-analysis. PONV, postoperative nausea and vomiting. This figure is available in color online at www.jopan.org.

randomized, double-blinded placebo-controlled trials, found that preoperative ondansetron reduced both nausea and vomiting 24 hours after surgery in adults undergoing craniotomy.

Although mirtazapine has traditionally been used as an antidepressant, like ondansetron, it also antagonizes 5HT3 receptors. Mirtazapine's action on specific receptors is thought to explain its mechanism of action for different indications: it acts as an antagonist on presynaptic alpha-2 receptors on autonomic noradrenergic and serotonergic axons and additionally blocks postsynaptic serotonin receptors (5HT2 and 5HT3 receptors). The resulting net increase in synaptic noradrenaline and specific increased serotonergic activity is thought to underlie its efficacy as an antidepressant with the added benefit of reduced adverse reactions such as the risks of cardiotoxicity with tricyclic antidepressants and the absence of serotonergic effects associated with selective serotonin reuptake inhibitors (SSRIs).[18] Mirtazapine therefore generally has a good safety profile.

Spread of morphine, injected intrathecally during anesthesia, to the chemoreceptor trigger zone and subsequent activation of 5HT3 receptors has been hypothesized to be a mechanism of PONV related to intrathecal morphine.[19] Because of its antagonism of serotonergic receptors, particularly 5HT3 (similar to ondansetron), it has been hypothesized that mirtazapine may be an effective drug in the prevention of PONV. Chang et al[12] have also proposed multiple other mechanisms for the antiemetic effect of mirtazapine, including its action as an antihistaminic agent and modulation of preoperative anxiety and depression levels, which are known psychological factors thought to contribute to PONV.[12]

This hypothetical effectiveness of mirtazapine as an antiemetic generated from pharmacologic principles has been supported in several clinical settings. Mirtazapine has been noted to be an effective treatment of hyperemesis gravidarum[20] and has proven effective in oncology in treatment of both nausea and pain.[21,22] Mirtazapine as a

treatment for PONV, in particular, is supported as effective in postgastric bypass surgery.[23] Another proposed hypothesis is that mirtazapine may be used as a prevention rather than treatment of PONV. Consensus guidelines recommend the use of prophylactic antiemetics for the prevention of PONV for high-risk patients.[3] This meta-analysis does indeed support the evidence for the effectiveness of the use of mirtazapine for PONV prophylaxis compared with placebo.

Mirtazapine has properties that are amenable for its use in the preoperative period. Oral absorption for mirtazapine is known to be rapid and reaches peak plasma concentrations within 2 hours (faster in fasted patients),[24] hence the suggestion of administration of mirtazapine approximately 2 hours before anesthesia. The elimination half-life of mirtazapine ranges from 20 to 40 hours, suggesting that beneficial effects as an antiemetic would cover the immediate postoperative period. Because of its other known beneficial effects such as anxiolysis[25] and reports of effectiveness as an analgesic (particularly noted to be beneficial in chronic pain[26]), it is hypothesized that preoperative administration of mirtazapine may bring about multiple benefits along with prevention of PONV. Supporting the previously mentioned hypothesis, this meta-analysis found that the preoperative use of mirtazapine has additional benefits such as reduction in preoperative anxiety when compared with both placebo and ondansetron and also postoperative pruritus when compared with placebo.

Ours is the first systematic review and meta-analysis that has investigated the use of mirtazapine for prevention of PONV when used preoperatively. Although the use of mirtazapine in anxiety and depression is well established in national guidelines[27] and has been supported in one previous meta-analysis,[28] the novel uses of mirtazapine in other areas of psychiatry such as in the treatment of negative symptoms of schizophrenia have also been investigated through the methodology of systematic review and meta-analysis of randomized controlled trials.[29] Many other hypothesized beneficial effects of mirtazapine are still undergoing research and evaluation. Understanding the pharmacologic properties of mirtazapine and its observed benefits for other indications has therefore prompted research into its potential benefits for novel indications such as preoperative prophylaxis of PONV, the question addressed in this meta-analysis.

Our meta-analysis has several limitations. The small number of studies included in this meta-analysis may limit the power of some of the outcomes studied, although for our primary outcome of PONV, TSA showed our analysis reached the required information size (minimum 118 participants giving a power of 80%). The randomized controlled studies included in this meta-analysis were conducted in different clinical populations undergoing different types of surgery with different types of anesthesia, which may have affected PONV incidence. Most of the studies included in this meta-analysis were conducted in the context of elective surgery and the results of this meta-analysis may therefore not be generalizable to emergency surgery. Moreover, most studies included only participants of ASA grade 1 to 2, therefore study results may not be generalizable to patients with more severe systemic disease, who would have increased vulnerability to adverse effects of mirtazapine, including the risk of sedation. Objective assessment using the Cochrane Risk of Bias tool and the GRADE criteria suggested some evidence of low quality in our analyses because of the presence of risk of bias, imprecision, and statistical heterogeneity of the included studies.

Because of the observed significant reduction in PONV rates with the preoperative use of mirtazapine compared with placebo, we argue that mirtazapine may be good choice for routine prophylaxis of PONV, a postanesthetic side effect that is known to be highly undesirable among patients. We showed no significant difference in PONV between preoperative use of mirtazapine versus ondansetron. However, because of the additional benefits that mirtazapine brings, including reduction in preoperative anxiety versus both placebo and ondansetron, it could be argued that mirtazapine may be a choice drug for preoperative use. The increased risk of sedation, however, may limit its use. Future studies may wish to investigate whether these increases in sedation affect clinically important outcomes such as opioid-induced respiratory depression. Weight gain, a known adverse effect of the long-term use of mirtazapine, is unlikely to be a clinical significant issue as we are suggesting the use of only a single dose of mirtazapine in the context of prophylaxis of PONV.

Because of its antagonism of peripheral alpha-1 receptors, postural hypotension may be a clinically important side effect of the use of mirtazapine in the perioperative period. The patient may need to be monitored for this side effect in recovery. Moreover, to utilize the beneficial effects of mirtazapine while minimizing potential for harm from adverse effects, the perioperative nurse may have a key role to play in monitoring for the adverse effects of mirtazapine, such as postural hypotension and sedation, and escalating appropriately. Given we are suggesting the use of a drug for a novel indication, the perioperative nurse would also be invaluable in reporting other adverse effects of mirtazapine observed after its perioperative use, which have not been evaluated in the current literature. Stemming from the increased risk of sedation observed in this study, closer and longer postoperative monitoring may be required in recovery after preoperative use of mirtazapine. This may require more intensive input from the postanesthesia nursing team, linking into workforce planning issues and bed management. The overall benefit gained from decreasing risk of PONV but increasing risk of sedation on the length of recovery can be evaluated in further studies. Larger future studies are also required to address whether mirtazapine is similar in efficacy to other setron antiemetics.

In conclusion, from the findings of this meta-analysis, we conclude that mirtazapine when used preoperatively is effective in reducing PONV when compared with placebo, with a possible similar efficacy to ondansetron. Moreover, our meta-analysis found additional beneficial effects of preoperative mirtazapine use including reduction in preoperative anxiety and postoperative pruritus, further strengthening the argument for its use in the preoperative period to reduce undesirable perioperative outcomes. Further studies are needed to investigate comparative effects with other antiemetics, improve methodological conduct, and determine whether the sedative effects of mirtazapine affect clinically important outcomes such as respiratory depression.

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