ANESTHESIOLOGY

Olanzapine for the Prevention of Postdischarge Nausea and Vomiting after Ambulatory Surgery

A Randomized Controlled Trial

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ABSTRACT

Background: Postdischarge nausea and vomiting after ambulatory surgery is a common problem that is not adequately addressed in current practice. This prospective, randomized, double-blind, parallel-group, placebo-controlled study was designed to test the hypothesis that oral olanzapine is superior to placebo at preventing postdischarge nausea and vomiting.

Methods: In a single-center, double-blind, randomized, placebo-controlled trial, the authors compared a single preoperative dose of olanzapine 10 mg to placebo, in adult female patients 50 years old or less, undergoing ambulatory gynecologic or plastic surgery with general anesthesia. All patients received standard antiemetic prophylaxis with dexamethasone and ondansetron. The primary composite outcome was nausea and/or vomiting in the 24 h after discharge. Secondary outcomes included severe nausea, vomiting, and side effects.

Results: A total of 140 patients were randomized and evaluable. The primary outcome occurred in 26 of 69 patients (38%) in the placebo group and in 10 of 71 patients (14%) in the olanzapine group (relative risk, 0.37; 95% CI, 0.20 to 0.72; $P = 0.003$). Severe nausea occurred in 14 patients (20%) in the placebo group and 4 patients (6%) in the olanzapine group (relative risk, 0.28; 95% CI, 0.10 to 0.80). Vomiting occurred in eight patients (12%) in the placebo group and two patients (3%) in the olanzapine group (relative risk, 0.24; 95% CI, 0.05 to 1.10). The median score for sedation (scale 0 to 10, with 10 being highest) in the 24 h after discharge was 4 (interquartile range, 2 to 7) in the placebo group and 6 (interquartile range, 3 to 8) in the olanzapine group ($P = 0.023$).

Conclusions: When combined with ondansetron and dexamethasone, the addition of olanzapine relative to placebo decreased the risk of nausea and/or vomiting in the 24 h after discharge from ambulatory surgery by about 60% with a slight increase in reported sedation.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Nausea and vomiting after discharge from ambulatory surgery remains common despite use of current antiemetics.

What This Article Tells Us That Is New

- The authors randomized women having day surgery to olanzapine 10 mg or placebo. All were also given both dexamethasone and ondansetron.
- Olanzapine reduced nausea and vomiting in the 24 h after hospital discharge from 38% to 14%, corresponding to a number-needed-to-treat of just four patients.

Approximately 35 million ambulatory surgeries are performed in the United States each year, including one third under general anesthesia.[1] Postdischarge nausea and vomiting after these ambulatory surgeries is a common problem, with an overall incidence of 37%.[2] This outcome is associated with significant patient distress and dissatisfaction, especially since patients at home no longer have access to rescue intravenous antiemetic medications.[3] Vomiting is rated by patients as the least desirable outcome after anesthesia, even relative to pain.[4]

Prevention of postoperative and postdischarge nausea and vomiting requires a multimodal management approach using both pharmacologic and nonpharmacologic interventions.[5] The short half-life of ondansetron (approximately 3 h) effectively covers the typical ambulatory postanesthesia care unit stay, but does not reduce the risk of nausea and vomiting after discharge.[2] Similarly, the avoidance of volatile anesthetics in favor of a total intravenous anesthetic technique with propofol reduces postoperative nausea and vomiting in the postanesthesia care unit but does not affect

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the incidence of postdischarge nausea and vomiting.[6] By comparison, intraoperative dexamethasone, with its relatively longer half-life, does appear to have a small protective effect against postdischarge nausea and vomiting.[2]

Olanzapine is an atypical antipsychotic medication in the thienobenzodiazepine class that antagonizes several receptors implicated in the pathogenesis of nausea and vomiting, including dopamine (D_1, D_2, D_4), serotonin ($5HT_{2A}$, $5HT_{2C}$, $5HT_3$), alpha-1 adrenergic, histamine (H_1), and multiple muscarinic receptors.[7] Several studies have already demonstrated the antiemetic effectiveness of olanzapine for both the prevention and treatment of chemotherapy-induced nausea and vomiting.[8–13] Importantly, the pharmacologic properties of olanzapine including a peak plasma time of 6 h and a half-life of 30 h, make it potentially well-suited for management of postdischarge nausea and vomiting *via* a single preoperative oral dose.

We conducted this study to assess the effectiveness and side effects of a single oral dose of olanzapine for the prevention of postdischarge nausea and vomiting in patients receiving standardized prophylaxis with two other antiemetics, ondansetron and dexamethasone. We hypothesized that olanzapine would be superior to placebo in the prevention of postdischarge nausea and vomiting in the first 24 h after discharge from ambulatory surgery with general anesthesia.

Materials and Methods

Study Design

This single-center, double-blind, randomized, parallel-group, placebo-controlled trial was conducted from April 2016 through September 2019. The trial protocol was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board/Program for Protection of Human Subjects (New York, New York), and the study was registered at ClinicalTrials.gov before enrollment (NCT02755116, Principal Investigator: Jaime Hyman, M.D., April 28, 2016, https://clinicaltrials.gov/ct2/show/NCT02755116). The full trial protocol is available by request from the corresponding author. Patients were recruited and signed written informed consent from the outpatient offices of gynecologic and plastic surgeons during preoperative consultations. A 10-mg dose of olanzapine was chosen based on its effectiveness for the prevention of chemotherapy-induced nausea and vomiting.[14]

Eligible patients were females, age 18 to 50 yr, scheduled to undergo ambulatory surgery under general anesthesia. Patients were excluded if they were unable to swallow pills, were taking antipsychotic medications, were pregnant or lactating, had a preoperative corrected QT interval greater than 450 ms, or had a history of torsades de pointes. Patients with diabetes mellitus or cardiovascular conditions manifested as hypertension requiring medication, previous myocardial infarction or unstable angina, arrhythmia, congestive heart failure, a recent history of postural hypotension or vasovagal syncope, or hypotension on the day of surgery (systolic blood pressure less than 90 mmHg) were also excluded. Patients with a contraindication to olanzapine were excluded, including known drug allergy, Parkinson's disease, or Lewy body dementia.

Randomization and Blinding

The randomization schedule was prepared by the Investigational Drug Service of the Mount Sinai Hospital Pharmacy (New York, New York) independent of the blinded study investigators. A total of 140 subjects were randomized into 35 blocks. Olanzapine and placebo tablets were compounded into matching blinded capsules by the pharmacy. After enrollment at a preoperative office visit by a study investigator, one capsule was dispensed per subject by the pharmacy to an investigator on the day of surgery. Participants, investigators, anesthesiologists caring for the patient, and surgeons were blinded to treatment group throughout the entire enrollment period.

Study Treatments

Participants took the study medication in the preoperative holding area within 1 h before entering the operating room. All participants received premedication with intravenous midazolam 2 mg once in the operating room. If tracheal intubation was indicated, general anesthesia was induced using propofol 1.5 to 2.5 mg/kg, and neuromuscular blockade was achieved with succinylcholine 1 to 2 mg/kg or rocuronium 0.6 mg/kg, at the discretion of the attending anesthesiologist. Rocuronium was administered as needed to maintain neuromuscular blockade during the case. If a supraglottic airway was to be used, anesthesia was induced with propofol 1.5 to 2.5 mg/kg. Regardless of the method of airway management, anesthesia was maintained with sevoflurane, and fentanyl was administered at doses deemed appropriate by the anesthesia provider. All patients received dexamethasone 8 mg immediately after anesthetic induction, and ondansetron 4 mg and ketorolac 30 mg approximately 30 min before emergence from anesthesia. Patients with tracheal intubation received neuromuscular blockade reversal with neostigmine 0.4 to 0.7 mg/kg before tracheal extubation. In the postanesthesia care unit, ondansetron 4 mg intravenously every 4 h as needed was ordered as per a standard departmental order set.

Outcomes

Patients were provided with a standardized diary (appendix) to record severity of nausea using an 11-point numerical rating scale (with 0 = "no nausea" and 10 = "worst nausea imaginable"), episodes of vomiting, and pain medication taken in 8-h intervals, beginning at the time of hospital discharge for a total of 24 h. The diary also included an 11-point numerical rating scale for sedation (with 0 = "no undesired

sedation at all" and 10 = "undesired sedation as bad as it can be") more than the 24-h period after discharge. Information entered into the subject's diary was obtained during a telephone interview performed by one of two blinded investigators (J.H. or C.P.) on the first or second postoperative day, a minimum of 24 h after hospital discharge. All patients were reached by telephone within 1 or 2 days.

Patients read out loud to the investigator what had been recorded in the study diary. Side effects were assessed using the 11-point numerical rating scale for level of sedation, inquiring about the occurrence of lightheadedness or dizziness during the study period, and asking an open-ended question regarding any other negative experiences during the study period, all of which were recorded in the study database.

Relevant intraoperative and postoperative data was obtained from the anesthesia record (CompuRecord, Philips, USA), the hospital electronic medical record (Epic Systems Corporation, USA), and the telephone interviews, and was recorded in the Research Electronic Data Capture tool (REDCap; Vanderbilt University, USA).

The primary outcome was the occurrence of nausea and/or vomiting in the 24 h after discharge from ambulatory surgery. Secondary outcomes included incidence of severe postdischarge nausea (defined as any numerical rating scale score greater than 3 for nausea during the 24 h after discharge), vomiting, and side effects. An additional secondary outcome that was not prespecified, nausea and/or vomiting in the 24 h after completion of surgery, is also reported to facilitate comparison to other studies.

Statistical Analysis

Assuming a rate of postdischarge nausea or vomiting of 35% and considering that a 20% decrease in this rate would be clinically significant and similar to alternative interventions used to reduce the risk of postoperative nausea and vomiting, we calculated that we would need to enroll 140 patients to achieve 80% power to detect this difference at a two-sided alpha level at 0.05. The baseline and intraoperative characteristics were compared between the groups with the use of chi-square and Wilcoxon tests. Baseline characteristics are described as numbers (percent), mean ± SD and the absolute standardized mean difference between the groups (*i.e.,* absolute mean difference divided by the SD of the placebo group). Intra- and postoperative outcomes are described as numbers (percent) and medians (interquartile ranges). Differences were considered significant if the *P* values were less than 0.05 (two-tailed).

The evaluable population was defined as those patients who were randomized, received study drug, and were successfully discharged from the postanesthesia care unit, and thus able to be assessed for the primary outcome. Patients in whom a change in operative plan necessitated unplanned inpatient hospitalization were replaced with a new randomization block created by the Investigational Drug Service pharmacy.

The primary outcome and secondary outcomes were compared between groups with the use of a log-binomial regression model to estimate the relative risk. Empirical standard error was used to construct the 95% CI. No adjustment was made for multiple comparisons of outcomes; thus, *P* values are reported only for the primary outcome and adverse events.

A difference in opioid administration in the postanesthesia care unit was observed despite randomization. As postoperative opioid administration is an established independent risk for postdischarge nausea or vomiting, a *post hoc* sensitivity analysis based on postanesthesia care unit opioid exposure (binary outcome: yes/no) was also performed. The primary and secondary outcomes were compared between groups with the use of a log-binomial regression model adjusted for the covariate of opioid administration in the postanesthesia care unit. We chose the log-binomial models because our primary and secondary outcomes are not uncommon. It has been advocated in recent medical and public health literature to report the relative risk rather than the odds ratio since there is a growing differential between relative risk and odds ratio with increasing incidence rates, and there is a tendency for some to interpret odds ratios as if they are relative risks.[15–17] The log-binomial model belongs to the class of the generalized linear model that assumes outcome data were from a binomial distribution, but the link between outcome variable and covariates is through the log function rather than the logit function. The relative risk of the treatment effect can be obtained by exponentiating the beta coefficient of the treatment group variable, while adjusting for all the other covariates in the model. Unadjusted and adjusted risk ratios are reported. All analyses were performed in SAS, version 9.4 (SAS Institute, USA).

Results

Trial Participants

From April 2016 through September 2019, consent was obtained from a total of 180 patients who were subsequently randomized as shown in figure 1. On the day of surgery, 36 patients were excluded before study drug administration due to cancellation of surgery, an exclusion criterion not previously identified, or withdrawal of consent. Four patients, three in the olanzapine group and one in the placebo group, were excluded after study drug administration due to conversion from laparoscopic to open surgery and subsequent inpatient hospital admission. Enrollment ceased when the target sample size of evaluable patients was obtained. In total, 140 patients (69 in the placebo group, 71 in the olanzapine group) completed the study and were evaluable for all study outcomes. No patients were lost to follow-up, and there were no missing data.

There were no significant differences in the baseline characteristics of the patients between groups (table 1). There were no significant differences in intraoperative management between groups, with the exception of the amount of propofol

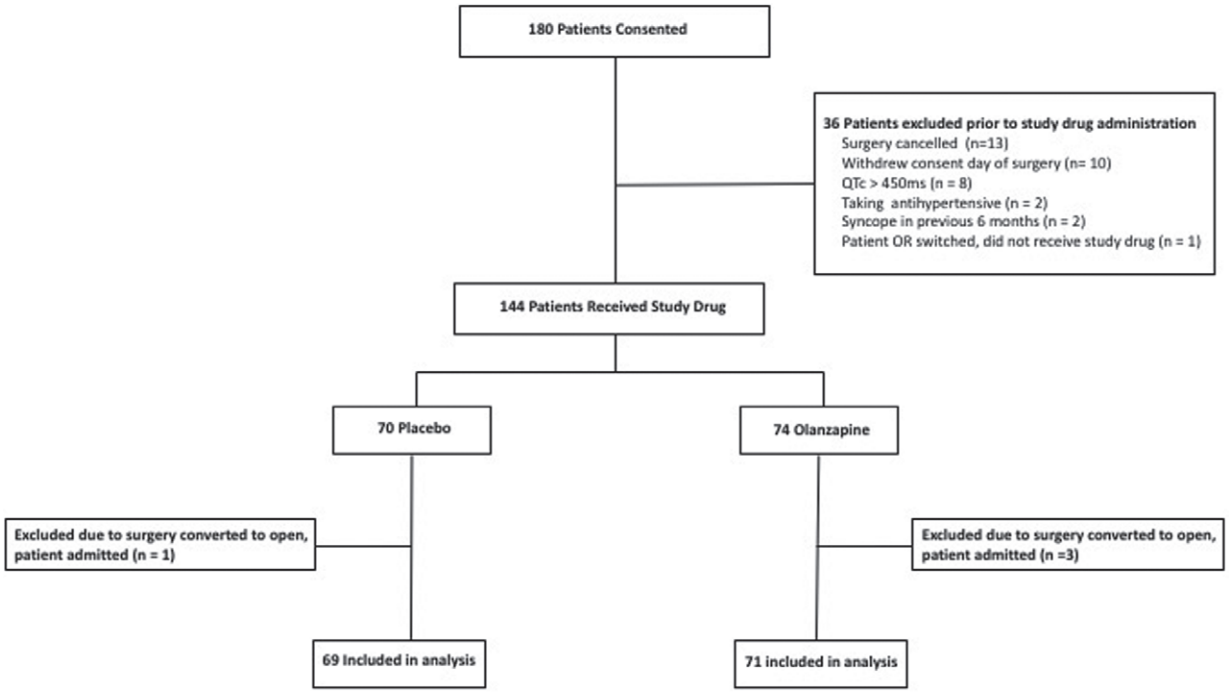

Fig. 1. Patient flow diagram depicts patients who were consented, received study drug, and were included in the analysis. OR, operating room; QTc, corrected QT interval.

administered during anesthetic induction (table 2). There was a significant difference between groups in opioids administered in the postanesthesia care unit, with a median opioid equivalent dose of 7.5 mg (interquartile range, 2.5 to 15) in the placebo group and 5 mg (interquartile range, 0 to 9) in the olanzapine group, $P = 0.003$ (table 3). There was no significant difference in the number of oxydocone/acetaminophen tablets taken in the 24 h after discharge between groups, with a median of 3 (interquartile range, 0 to 4) in the placebo group and 2 (interquartile range, 1 to 3) in the olanzapine group, $P = 0.477$.

Outcomes

The primary outcome, nausea and/or vomiting in the 24 h after hospital discharge, occurred in 26 patients (38%) in the placebo group and in 10 patients (14%) in the olanzapine group (relative risk, 0.37; 95% CI, 0.20 to 0.72; $P = 0.003$). Severe postdischarge nausea (numerical rating scale score greater than 3) occurred in 14 patients (20%) in the placebo group and 4 patients (6%) in the olanzapine group (relative risk, 0.28; 95% CI, 0.10 to 0.80; fig. 2). Postdischarge vomiting occurred in eight patients (12%) in the placebo group, and in two patients (3%) in the olanzapine group (relative risk, 0.24; 95% CI, 0.05 to 1.10). Before discharge from the postanesthesia care unit, nausea and/or vomiting occurred in 23 patients (33%) in the placebo group and 14 patients (20%) in the olanzapine group (relative risk, 0.61; 95% CI, 0.34 to 1.08). In the 24 h after completion of surgery, 35 patients (51%) had nausea and/or vomiting in the placebo group compared to 22 patients (31%) in the olanzapine group (relative risk, 0.61; 95% CI, 0.40 to 0.93). In that same time period, the number of patients with severe nausea was 26 (38%) in the placebo group and 12 (17%) in the olanzapine group (relative risk, 0.45; 95% CI, 0.25 to 0.82; table 4).

Adjusting for opioid exposure in the postanesthesia care unit, the relative risk for the primary outcome of nausea and/or vomiting in the 24 h after discharge was 0.38 (95% CI, 0.20 to 0.72) in the olanzapine group. The adjusted relative risk for severe postdischarge nausea was 0.30 (95% CI, 0.10 to 0.80) and for postdischarge vomiting was 0.24 (95% CI, 0.06 to 0.89) in the olanzapine group. The adjusted relative risk for nausea and/or vomiting before discharge from the postanesthesia care unit was 0.59 (95% CI, 0.33 to 1.05). The adjusted relative risk for nausea and/or vomiting in the 24 h after completion of surgery was 0.62 (95% CI, 0.41 to 0.95) and for severe nausea was 0.46 (95% CI, 0.26 to 0.83).

Adverse Events

The median 11-point numerical rating scale score for sedation was 4 (interquartile range, 2 to 7) in the placebo group and 6 (interquartile range, 3 to 8) in the olanzapine group in the 24 h after discharge ($P = 0.023$). Dizziness or lightheadedness was reported by 27 patients (39%) in the placebo group and 21 patients (30%) in the olanzapine group

Table 1. Baseline Characteristics

Characteristics	Olanzapine (N = 71)	Placebo (N = 69)	Absolute Standardized Differences
Mean age, yr ± SD	37 ± 7	37 ± 7	0.013
Ethnic group, no. (%)*			
Hispanic	26 (37)	27 (39)	0.517
Race, no. (%)*			
White	26 (37)	28 (41)	0.082
Black	10 (14)	14 (20)	0.177
Other	35 (49)	27 (39)	0.202
ASA Physical Status, no. (%)			
I	19 (27)	24 (35)	0.180
II	49 (69)	41 (59)	0.206
III	3 (4)	4 (6)	0.078
Mean BMI, kg/m^2 ± SD	27.8 ± 6.3	27.7 ± 5.9	0.011
History of postoperative nausea/vomiting, no. (%)	19 (27)	17 (25)	0.048
Motion sickness, no. (%)	21 (30)	25 (36)	0.145
Nonsmoker, no. (%)	67 (94)	62 (90)	0.194
Risk Factors, no (%)†			
2	4 (6)	7 (10)	0.194
3	43 (60)	35 (51)	0.200
4	24 (34)	27 (39)	0.112
Surgery type, no. (%)			
Laparoscopic gynecologic	54 (76)	58 (84)	0.614
Hysteroscopy	11 (16)	9 (13)	0.267
Vaginal	3 (4)	1 (1)	0.082
Plastics	3 (4)	1 (1)	0.028

*Race and ethnic group were self-reported. †Risk factors are (1) female, (2) history of postoperative nausea/vomiting or motion sickness, (3) nonsmoker, (4) received postoperative opioids.

ASA, American Society of Anesthesiologists; BMI, body mass index.

Table 2. Intraoperative Management Characteristics

Characteristics	Olanzapine (N = 71)	Placebo (N = 69)	*P* Value
Airway management, no. (%)			0.229
Tracheal tube	69 (97)	64 (93)	
Supraglottic airway	2 (3)	5 (7)	
Medications			
Median fentanyl, mcg (IQR)	250 (200–350)	250 (200–400)	0.847
Median propofol, mg (IQR)	200 (150–200)	160 (150–200)	0.025
Median rocuronium, mg (IQR)	50 (40–70)	50 (40–70)	0.641
Median neostigmine, mg (IQR)	3 (2–4)	3 (2.5–4)	0.893
Median surgery length, min (IQR)	111 (55–144)	97 (53–136)	0.788

Reported from two-sided chi-square and Wilcoxon–Mann–Whitney tests.
IQR, interquartile range.

Table 3. Postanesthesia Care Unit Characteristics

Characteristics	Olanzapine (N = 71)	Placebo (N = 69)	*P* Value
Median opioid equivalent, mg (IQR)	5 (0–9)	7.5 (2.5–15)	0.003
Nausea, no. (%)	14 (20)	23 (33)	0.068
Vomiting, no. (%)	2 (3)	5 (7)	0.307
Received rescue antiemetic, no. (%)	14 (20)	17 (27)	0.483
Median length of stay, min (IQR)	195 (124–287)	173 (93–267)	0.214

Reported from two-sided chi-square and Wilcoxon–Mann–Whitney tests
IQR, interquartile range.

(relative risk, 0.76; 95% CI, 0.48 to 1.20; $P = 0.237$). Two patients in the olanzapine group reported visual disturbance that resolved within 24 h. One patient in the olanzapine group visited the emergency room after discharge with urinary retention after laparoscopic gynecologic surgery. There were no other adverse events reported (table 5).

Discussion

In this double-blind, randomized, placebo-controlled trial, we found that in patients having ambulatory gynecologic or plastic surgery requiring general anesthesia who received two-drug combination postoperative nausea and vomiting prophylaxis, the addition of olanzapine relative to placebo significantly decreased the rate of nausea and/or vomiting in the 24 h after discharge from 38% to 14%. This corresponds to an absolute risk reduction of 24% and a relative risk reduction of 63%, translating to a number needed to treat of approximately four to prevent postdischarge nausea and/or vomiting in one patient in this population. The olanzapine group had a modest increase in median score for sedation on an 11-point numerical rating scale from 4 in the placebo group to 6 in the olanzapine group.

Current consensus guidelines make no specific recommendations for prevention of postdischarge nausea and vomiting.[5] Of note, many commonly used agents are not optimally suited to this purpose given their short half-life. Some strategies have demonstrated promise in preventing postdischarge nausea and vomiting. These include ondansetron orally disintegrating tablets administered postoperatively[18,19] or long-acting serotonin $5HT_3$ antagonists.[20] Studies of these long-acting agents, however, have to date not specifically evaluated for prevention of postdischarge nausea and vomiting. Studies of neurokinin-1 receptor antagonists have found that these agents do reduce vomiting but not nausea.[21–23] By comparison, transdermal scopolamine decreases the incidence of postoperative and postdischarge nausea and vomiting,[24,25] but its use is associated with substantial side effects including visual disturbances, dry mouth, and agitation.[26] Finally, acupuncture[27] and acustimulation[28] have demonstrated effectiveness for postoperative and postdischarge nausea and vomiting.

Antidopaminergic antiemetics have not previously been evaluated specifically for the prevention of postdischarge nausea and vomiting. However, as postdischarge nausea is believed to be predominantly opioid-induced and mediated through dopamine D_2 receptors in the chemoreceptor

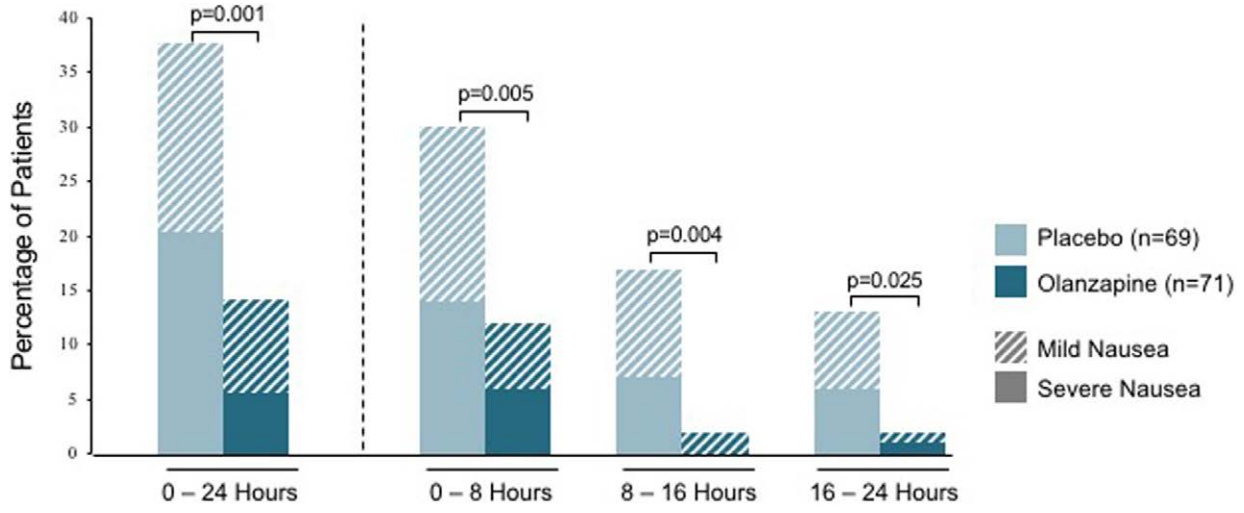

Fig. 2. Percentage of patients with mild nausea (scores 1 to 3) and severe nausea (scores 4 to 10) in the olanzapine (N = 71) and placebo (N = 69) groups in 8-h intervals over the 24 h after discharge from ambulatory surgery. Differences were compared between groups with the use of a chi-square test.

Table 4. Nausea and Vomiting Outcomes

Outcome	Olanzapine (n = 71)	Placebo (n = 69)	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)†
Primary outcome				
Nausea and/or vomiting in 24 h after discharge, no. (%)	10 (14)	26 (38)	0.37 (0.20–0.72)*	0.38 (0.20–0.72)*
Secondary outcomes				
Severe‡ postdischarge nausea, no. (%)	4 (6)	14 (20)	0.28 (0.10–0.80)	0.30 (0.11–0.80)
Postdischarge vomiting, no. (%)	2 (3)	8 (12)	0.24 (0.05–1.10)	0.24 (0.06–0.89)
PONV in first 24 h, no (%)	22 (31)	35 (51)	0.61 (0.40–0.93)	0.62 (0.41–0.95)
Severe‡ PONV in first 24 h, no %	12 (17)	26 (38)	0.45 (0.25–0.82)	0.46 (0.26–0.83)

*P = 0.003. †Adjusted relative risk was calculated using a log-binomial regression model adjusting for the covariate of opioid use in the postanesthesia care unit. ‡Defined as numerical rating scale score greater than 3.

PONV, postoperative nausea and/or vomiting.

trigger zone,[29] agents in this class may be best suited for this purpose. The first generation antipsychotics droperidol and haloperidol are effective in the prevention of nausea and vomiting,[30–34] but their utility after discharge is limited by both short half-lives and concerns over the risk of torsades de pointes.[5] Atypical antipsychotics, in contrast, have not been associated with torsades de pointes,[35] and have recently been proposed as alternatives for postoperative nausea prevention.[36] Amisulpride is an investigational intravenous atypical antipsychotic that, when combined with either a corticosteroid or ondansetron, improved the rate of patients without emesis or need for rescue medication in the 24 h after wound closure from 46.6% in those who received placebo to 57.7%.[37] Although this study did not specifically evaluate postdischarge nausea and vomiting in ambulatory surgery patients, it provides further evidence that long-acting atypical antipsychotic agents have a potentially important role in the management of this common postoperative complication.

Although not prespecified in the original study design, we also found that olanzapine use resulted in a 39% relative risk reduction in the rate of nausea and/or vomiting in the 24 h after the completion of surgery (51% *vs.* 31% in placebo *vs.* olanzapine groups, respectively). Unlike the primary outcome of this study, this metric spans both the pre- and postdischarge periods. By comparison, other prophylactic antiemetic interventions currently in use achieve an approximate 26% reduction in relative risk with each additional medication used.[32] Given that the trial was not specifically designed to address this outcome, additional studies will be necessary to determine whether olanzapine

Table 5. Adverse Events

Variables	Olanzapine (N = 71)	Placebo (N = 69)	Relative Risk (95% CI)	*P* Value
Sedation scale, median (IQR)	6 (3–8)	4 (2–7)	—	0.023*
Lightheadedness/dizziness, no. (%)	21 (30)	27 (39)	0.76 (0.48–1.20)	0.237
Visual disturbance, no. (%)	2 (3)	0	—	—
Urinary retention, no. (%)	1 (1)	0	—	—

*Wilcoxon test was used to compare sedation scores between groups (scale 0–10).
IQR, interquartile range

outperforms other antiemetics for this use. Additionally, while there was a trend toward a reduction in predischarge nausea and vomiting, the baseline incidence of nausea in the postanesthesia care unit tends to be lower in the ambulatory surgical patient population,[2] so a larger study is necessary to evaluate this outcome in ambulatory patients.

This current study has some important strengths as well as limitations. In addition to utilizing a randomized, double-blinded design, standardized inclusion of two additional antiemetics already commonly used permitted assessment of the additive value of olanzapine. Moreover, this study specifically evaluated nausea and vomiting occurring after discharge, the area of greatest unmet need where patients are unable to use rescue intravenous agents. Limitations include the single-center design at an academic medical center that may limit generalizability to other ambulatory surgical patient populations. Another limitation is that despite randomization, more patients in the placebo group received opioid medication in the postanesthesia care unit. This is an independent risk factor for postdischarge nausea, and this imbalance between groups represents a source of potential bias, and therefore a *post hoc* adjusted analysis was performed.

Because we only studied patients at the highest historic risk of the primary outcome, female patients ages 18 to 50 yr, and the study was limited to gynecologic and plastic surgery, these results may not be generalizable to other patient populations. Finally, general anesthesia was maintained with sevoflurane; thus, we do not know how olanzapine would perform in patients receiving total intravenous anesthesia.

Though it did not reach significance, there was a trend toward increased length of stay in the postanesthesia care unit in the olanzapine group compared to the placebo group. It is possible that increased sedation could impact the discharge readiness of ambulatory patients after receiving olanzapine. This could have an impact on care delivery and should be evaluated in future studies.

In summary, we find that a single preinduction dose of olanzapine is highly effective for the reduction in risk of postdischarge nausea and vomiting with a slight increase in reported sedation. Future studies could evaluate whether a lower dose of olanzapine is effective in postdischarge nausea and vomiting prevention with a better side effect profile. Studies that are multicenter and involve a more diverse surgical population to better assess both effectiveness and side effects are warranted.

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Competing Interests

Dr. Fenske is on the speaker's bureau for Abbvie Pharmaceuticals (Chicago, Illinois). Dr. Ascher-Walsh serves as an expert witness, is on the medical board of Trophikos (Atlanta, Georgia), maker of cranberry extract supplements, and is the owner of Expert Alternatives (New York, New York), maker of a vitamin supplement for the treatment of uterine fibroids. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: jaime.hyman@mountsinai.org. Raw data available at: jaime.hyman@mountsinai.org.

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Appendix. Olanzapine Study Nausea and Vomiting Diary

From time leaving hospital plus 8 hours:
Nausea Severity Scale:

0	1	2	3	4	5	6	7	8	9	10

No nausea — Worst nausea imaginable

Number of vomiting episodes at least 1 minute apart _____
Number of retching episodes at least 1 minute apart _____
Number of Percocet pills taken _____

Hours 8–16 at home:
Nausea Severity Scale:

0	1	2	3	4	5	6	7	8	9	10

No nausea — Worst nausea imaginable

Number of vomiting episodes at least 1 minute apart _____
Number of retching episodes at least 1 minute apart _____
Number of Percocet pills taken _____

Hours 16–24 at home:
Nausea Severity Scale:

0	1	2	3	4	5	6	7	8	9	10

No nausea — Worst nausea imaginable

Number of vomiting episodes at least 1 minute apart _____
Number of retching episodes at least 1 minute apart _____
Number of Percocet pills taken _____

Please rate any undesired sedation trouble that you had over the past 24 hours:

0	1	2	3	4	5	6	7	8	9	10

No undesired sedation at all — Undesired sedation as bad as it can be

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