Chronic Atypical Antipsychotic Use Is Associated With Reduced Need for Postoperative Nausea and Vomiting Rescue in the Postanesthesia Care Unit: A Propensity-Matched Retrospective…

Article *in* Anesthesia & Analgesia · December 2018

DOI: 10.1213/ANE.0000000000003990

CITATIONS
3

READS
148

7 authors, including:

Dennis Gray
Vigilant Anesthesiology PC
14 PUBLICATIONS **215** CITATIONS
SEE PROFILE

Vikas O'Reilly-Shah
University of Washington Seattle
69 PUBLICATIONS **475** CITATIONS
SEE PROFILE

Chronic Atypical Antipsychotic Use Is Associated With Reduced Need for Postoperative Nausea and Vomiting Rescue in the Postanesthesia Care Unit: A Propensity-Matched Retrospective Observational Study

Craig S. Jabaley, MD,* Dennis W. Gray, DO, MPH,* Gaurav S. Budhrani, MD,* Grant C. Lynde, MD, MBA,* Panagiotis Adamopoulos, PhD,† George S. Easton, PhD,† and Vikas N. O'Reilly-Shah, MD, PhD*

BACKGROUND: Atypical antipsychotics are efficacious for chemoprophylaxis against chemotherapy-induced nausea and vomiting, but perioperative investigations have been scant. We sought to examine the association between chronic atypical antipsychotic therapy and the likelihood of postoperative nausea and vomiting.

METHODS: In this single-center, propensity-matched, retrospective, observational study, elective noncardiac surgical cases from January 2014 to December 2017 were examined with regard to the primary outcome of rescue antiemetic administration in the postanesthesia care unit as a measure of postoperative nausea and vomiting. Chronic administration of olanzapine, aripiprazole, and risperidone was the exposure of interest. Other independent variables included outpatient antiemetics, modified Apfel score, age, American Society of Anesthesiologists physical status score, case length, and exposures to emetogenic and chemoprophylactic agents. Logistic regression was performed using case-level data. Conditional logistic regression was performed after 1:2 propensity matching, sampling without replacement. Monte Carlo simulation was performed to compute the mean patient-level treatment effect on the treated.

RESULTS: Of 13,660 cases, 154 cases with patients receiving atypical antipsychotics were matched against 308 cases without, representing 115 and 273 unique patients, respectively. In a well-balanced cohort, the mean patient-level odds of being administered rescue antiemetic was lower for patients chronically taking the 3 atypical antipsychotics under consideration as compared to those not on atypical antipsychotics, with an odds ratio of 0.29 (95% CI, 0.11–0.75; $P = .015$).

CONCLUSIONS: Chronic atypical antipsychotic therapy is associated with reduced risk of postanesthesia care unit antiemetic administration. These findings support the need for prospective studies to establish the safety and efficacy of postoperative nausea and vomiting chemoprophylaxis with these agents. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

- **Question:** Are atypical antipsychotics protective against postoperative nausea and vomiting?
- **Findings:** Chronic atypical antipsychotic therapy is associated with reduced need for rescue antiemetic administration in the postanesthesia care unit.
- **Meaning:** These findings support and extend previous work demonstrating that atypical antipsychotics hold promise for postoperative nausea and vomiting chemoprophylaxis as chronic administration is also associated with a reduced rescue requirement.

Postoperative nausea and vomiting continues to be extremely common, despite well-developed knowledge of risk factors and development of management strategies.[1,2] The use of postoperative nausea and vomiting chemoprophylaxis and rescue antiemetics may be limited by cost, availability, side effects, or drug–drug interactions.[3] For example, aprepitant is highly effective but costly,[4] and associated inhibition of oral contraceptives complicates its use in young women.[5] Novel postoperative nausea and vomiting therapies are necessary to expand options for high-risk patients with contraindications to established agents.

The atypical antipsychotic olanzapine prevented chemotherapy-induced nausea and vomiting in a recent randomized controlled trial and improved the complete response rate among patients receiving highly emetogenic chemotherapy.[6] While olanzapine has been well studied in chemotherapy-induced nausea and vomiting,[7] perioperative

From the *Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia; and †Department of Information Systems and Operations Management, Emory University Goizueta Business School, Atlanta, Georgia.

Accepted for publication November 15, 2018.

Funding: V.N.O'.-S. is partially supported by a Synergy Grant from the Woodruff Health Sciences Center. Otherwise, this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The Emory University Department of Anesthesiology generously supported the time of the authors in producing this work.

The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

Reprints will not be available from the authors.

Address correspondence to Vikas N. O'Reilly-Shah, MD, PhD, Department of Anesthesiology, Emory University and Children's Healthcare of Atlanta, 3B S, 1364 Clifton Rd, NE, Atlanta, GA 30322. Address e-mail to voreill@emory.edu.

DOI: 10.1213/ANE.0000000000003990

investigations are lacking. Aripiprazole and risperidone may also have antiemetic effects.[8,9] Amisulpride has been demonstrated to reduce postoperative nausea and vomiting, although this drug is not yet approved for use in the United States.[10]

Together, these observations led us to hypothesize that atypical antipsychotic may be associated with reduced risk for postoperative nausea and vomiting. We designed this study to assess the rate at which patients receiving atypical antipsychotic agents previously demonstrated to have antiemetic activity (olanzapine, aripiprazole, and risperidone) on an outpatient basis ("chronic treatment") required rescue antiemetic therapy in the postanesthesia care unit (PACU), controlling for important confounders including baseline risk of postoperative nausea and vomiting and perioperative administration of agents known to affect its likelihood.

METHODS

Approval from the Emory University Institutional Review Board (IRB00088166) was obtained before data acquisition and analysis, and a waiver of written informed consent was granted owing to the investigation's retrospective observational design. We conducted a propensity-matched, retrospective, observational cohort study to ascertain the association between chronic atypical antipsychotic therapy and the likelihood of PACU rescue antiemetic administration. This manuscript was prepared in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology statement and guidelines for improved reporting of observational studies and propensity score analyses.[11]

Inclusion/Exclusion Criteria

Inclusion criteria were (1) elective noncardiac surgical procedures (2) performed under general anesthesia (3) from January 2014 to December 2017 with (4) American Society of Anesthesiologists (ASA) physical status classification I–III patients (5) at Emory University Hospital (Atlanta, GA) who were (6) evaluated in the preoperative clinic and (7) admitted to the PACU postoperatively. Patients were seen in the anesthesia preoperative clinic no greater than 30 days before their procedure. Preoperative clinic evaluation ensured a high-quality source of information for preoperative outpatient prescriptions and a modified Apfel score routinely recorded in that clinic. The modified Apfel score documented in the preoperative history and physical is based on female gender, history of postoperative nausea and vomiting, nonsmoker, and emetogenic surgery. Emetogenic surgeries are defined in our preoperative clinic note as "cholecystectomy, laparoscopic surgery, or gynecologic surgery." The authors did not write this definition nor did they have control of the language; it is up to the provider whether to assign the point for known emetogenic surgeries outside of these explicit examples.

Procedures where the anesthetic record was documented on paper were excluded from the analysis. Only cases for which the complete set of variables were available were included in the analysis. The primary unit of analysis was at the surgical case level; as such, patients who underwent >1 surgery during the study period had >1 surgical case in the final dataset. These were treated as independent encounters as the nature of the surgery, exposures, and prophylaxis may have differed during each procedure; however, a sensitivity analysis was also performed at the patient level as described below.

Data Collection

The Emory Healthcare Clinical Data Warehouse was queried for patient demographic data, surgical case data, and all medications recorded in the medication administration record from 2 hours before the start time to the PACU stop time (see below). These data included exposure to potent inhalational anesthetic agents (specifically, isoflurane, sevoflurane, and desflurane) and nitrous oxide.

Primary Outcome

The primary outcome (dependent variable) in this study was the administration of rescue antiemetics in the PACU. At our institution, rescue antiemetic administration is at the discretion of an attending anesthesiologist dedicated to the PACU with no specific protocol in place. Bounds for the PACU length of stay were defined as the time at which the primary anesthesia team ended responsibility (anesthesia stop time) to the time at which the patient achieved readiness for discharge as documented by the PACU nursing staff. Specific criteria documented in the PACU Discharge Assessment at our institution include minimum length of stay, stable vital signs, control of nausea/vomiting/dizziness, control of pain, Aldrete score 9–10,[12] swallowing, voiding, ambulation, surgical dressing assessment, no bleeding, and soft abdomen. This is routinely documented regardless of barriers to physical discharge from the PACU due to bed availability or other logistical reasons. We then used the medication administration record to determine if any of the following medications were administered in PACU: ondansetron, promethazine, haloperidol, diphenhydramine, propofol, and ephedrine. If so, they were deemed to have been administered a rescue antiemetic.

Independent Variables

Outpatient medications were documented in the preoperative history and physical. The primary independent variable (exposure) of interest in our study was chronic treatment with atypical antipsychotic agents previously demonstrated to have antiemetic activity: olanzapine, aripiprazole, and risperidone. Amisulpride is not yet available in the United States, and no patients in our study pool were taking this medication. A determination was similarly made as to whether patients were prescribed outpatient preoperative antiemetic therapy, specifically, haloperidol, droperidol, ondansetron, granisetron, dolasetron, palonosetron, alosetron, diphenhydramine, hydroxyzine, promethazine, and metoclopramide.

Independent variables included in this analysis were <50 years of age, ASA physical status score, outpatient preoperative antiemetic therapy, modified Apfel score, log (surgical case length), exposure to nitrous oxide, exposure to potent inhalational agents, exposure to opioids in the PACU, and number of agents administered for postoperative nausea and vomiting prophylaxis within the period 2 hours before anesthesia start time and anesthesia stop time. Agents counted for postoperative nausea and vomiting

prophylaxis were ondansetron, dexamethasone, transdermal scopolamine, aprepitant, diphenhydramine, haloperidol, and propofol at a total dose >5 mg/kg for the entire case to capture total IV anesthesia or infusion for postoperative nausea and vomiting chemoprophylaxis.

Univariate Statistical Methods

Statistical analysis was performed in R v3.3.2 (R Core Team, Vienna, Austria) using the RStudio platform v1.1.423 (R Studio Team, Boston, MA).[13,14] Comparing the atypical antipsychotic group with the non–atypical antipsychotic group, demographic characteristics were compared using *t* test for age; χ^2 for modified Apfel score; Wilcoxon rank-sum test for body mass index and surgical case length; and Fisher exact test for gender, outpatient preoperative antiemetic therapy, exposure to potent inhalational agent, exposure to nitrous oxide, chronic atypical antipsychotic therapy, ASA physical status score, exposure to opioids in the PACU, and postoperative nausea and vomiting prophylaxis agents. Surgical case length was defined as the span of time between surgery start and surgery stop, as routinely recorded by intraoperative staff.

Multiple Variable Regression Analysis

To test the association between the independent variables described above with the primary outcome, multiple variable logistic regression was performed on the entire dataset. Interaction terms were included to test for nonlinearity due to an interaction between the number of postoperative nausea and vomiting prophylaxis agents and <50 years of age, modified Apfel score, log (surgical case length), exposure to nitrous oxide, exposure to potent inhalational agents, exposure to opioids in the PACU, and outpatient preoperative antiemetic therapy. Although a normal distribution is not strictly necessary for logistic regression, surgical case length was log transformed due to skew with improvement in symmetry and linearity as assessed by examination of quantile–quantile plots. Gender and surgery type were explicitly not included in the regression or matching models due to multicollinearity with the modified Apfel score.[15] *P* values for standalone independent variables (noninteraction terms) were calculated using the likelihood ratio test to ensure consistency with the *confint* function of the MASS package,[16] which uses the likelihood ratio test to calculate 95% CIs from glm family models implemented in the "stats" package in R.[17]

Propensity Matching

Propensity matching was performed for the purpose of confounder control and was planned as the primary analysis approach a priori. This approach is more effective than multiple variable regression in mitigating bias while improving the precision of the treatment effect in situations, like ours, where the number of outcomes is relatively small compared to the number of confounders.[18] Propensity matching was performed using the MatchIt package for R.[19,20] This package is capable of performing propensity matching using a variety of algorithms. After sensitivity analysis to optimize final balance, we selected optimal matching, which minimizes the global average absolute distance across all matched pairs, sampling without replacement.[21]

The treatment group for propensity matching was the group of cases in which the patient was taking chronic atypical antipsychotic therapy. Match cases were drawn from the control group in which patients were not taking atypical antipsychotics. A ratio of 1:2 for matching was selected on the basis of previous work recommending ratios of 1:1 or 1:2 as larger ratios decrease the standard error of the estimate but at the cost of possibly introducing bias due to matching of increasingly dissimilar subjects.[22] Propensity scores were generated on the basis of the following independent variables: <50 years of age, ASA physical status score, outpatient preoperative antiemetic therapy, modified Apfel score, log (surgical case length), exposure to nitrous oxide, exposure to potent inhalational agents, exposure to opioids in the PACU, and number of agents administered for postoperative nausea and vomiting prophylaxis. Balance in the propensity-matched population was assessed using absolute standardized mean differences for each covariate included in the model, calculated using the "tableone" package.[23] A standardized difference of <0.1 was considered to indicate an acceptable balance between the treatment cases and the matched controls for that covariate.[24]

After propensity matching, we created a dummy variable to identify each treatment case with its matched control cases in a unique stratum. We then performed multiple variable conditional logistic regression using the *clogit* function of the "survival" package in R to estimate the treatment effect. Variables were eliminated from the final model using a backward stepwise selection. Forward stepwise regression and selection were then used as a check to ensure that no significant variables were excluded.[25]

As propensity matching was performed at the surgical case level, there were some patients who had >1 case represented in the propensity-matched cohort. We performed a 1000 iteration basic Monte Carlo simulation in which we randomly selected a single unique case per unique patient in the propensity-matched cohort, and then used this subsample to perform conditional logistic regression using the final 2-variable model (Supplemental Digital Content, Figure 1, http://links.lww.com/AA/C685). The significance and CI were calculated for the association of interest between chronic atypical antipsychotic treatment and administration of rescue antiemetic in the PACU. The mean and SEM of the *P* values and CIs were calculated and reported. For sensitivity analysis, 2 additional analogous Monte Carlo simulations were performed in which (1) only the treatment variable of interest was included in the conditional logistic regression (univariate conditional logistic regression) and (2) in which all independent variables were included in the conditional logistic regression (multiple-variable conditional logistic regression without selection).

RESULTS

Demographic information for the complete cohort of cases used in the analysis is shown in Table 1, and a flow diagram outlining exclusions is shown in Figure 1. Data from 13,660 cases were analyzed in the multiple variable logistic regression. In the propensity-matched analysis, data from 154 cases where the patient was taking chronic atypical antipsychotics were matched with 308 cases where the patient was not. This represented a cohort of 115 unique treated patients and 273 unique untreated patients.

Table 1. Summary of Baseline Case-Level Demographics and Exposures Comparing Treated Versus Untreated With Atypical Antipsychotic

	All Patients	No Atypical Antipsychotic	Atypical Antipsychotic	Absolute Standardized Mean Difference	*P* Value
N (cases, row percent)	13,660	13,506 (98.9%)	154 (1.1%)	-	-
N (unique patients)	10,880	10,765	115	-	-
Age (y), median (25th/75th quartile)	57 (44–67)	57 (44–67)	51 (41.25–63)	0.279	<.001
Females (%)	8370 (61.3%)	8267 (61.2%)	103 (66.9%)	0.118	.158
Body mass index ($kg \cdot m^{-2}$), median (25th/75th quartile)	25.8 (19.6–30.9)	25.8 (19.6–30.9)	25.4 (17.7–31.5)	0.044	.611
Outpatient antiemetic therapy	1404 (10.3%)	1366 (10.1%)	38 (24.7%)	0.391	<.001
Exposed to potent inhalational anesthetic (isoflurane, sevoflurane, desflurane)	11,754 (86.0%)	11,622 (86.1%)	132 (85.7%)	0.010	.907
Exposed to nitrous oxide	4691 (34.3%)	4629 (34.3%)	62 (40.3%)	0.124	.125
Surgical case length (min), median (25th/75th quartile)	112 (55–181)	112 (56–181)	87.5 (37.5–145.5)	0.170	<.001
Opioids administered in PACU	7290 (53.4%)	7213 (53.4%)	77 (50%)	0.068	.417
Treatment in PACU with rescue antiemetic	1834 (13.4%)	1823 (13.5%)	11 (7.1%)	-	.023
ASA classification				0.212	.013
I/II	5435 (39.8%)	5389 (39.9%)	46 (29.9%)	-	-
III	8225 (60.2%)	8117 (60.1%)	108 (70.1%)		
Modified Apfel score, median (25th/75th quartile)	3 (2–4)	3 (2–4)	3 (2–3)	0.078	.561
0	882 (6.5%)	872 (6.5%)	10 (6.5%)	-	-
1	4208 (30.8%)	4171 (30.9%)	37 (24%)		
2	4976 (36.4%)	4893 (36.2%)	83 (53.9%)		
3	3132 (22.9%)	3109 (23%)	23 (14.9%)		
4	462 (3.4%)	461 (3.4%)	1 (0.6%)		
Number of postoperative nausea and vomiting prophylaxis agents				0.165	.609
0	959 (7.0%)	947 (7%)	12 (7.8%)	-	-
1	5308 (38.9%)	5238 (38.8%)	70 (45.5%)		
2	4079 (29.9%)	4036 (29.9%)	43 (27.9%)		
3	2215 (16.2%)	2194 (16.2%)	21 (13.6%)		
4	821 (6.0%)	815 (6%)	6 (3.9%)		
5	238 (1.7%)	236 (1.7%)	2 (1.3%)		
6	40 (0.3%)	40 (0.3%)	0 (0%)		

Abbreviations: ASA, American Society of Anesthesiologists; PACU, postanesthesia care unit.

There were significant differences in underlying patient characteristics between treated and untreated with an atypical antipsychotic in the overall sample population (Table 1). In terms of the underlying predictors of postoperative nausea and vomiting chosen, there was a monotonic increase in the rate of rescue antiemetic in the PACU with increasing modified Apfel score (Supplemental Digital Content, Table 1, http://links.lww.com/AA/C685). There was a nonmonotonic relationship between the number of agents administered and the percentage of patients administered PACU antiemetic. The breakdown of the specific agents administered for prophylaxis is shown in Supplemental Digital Content, Table 2, http://links.lww.com/AA/C685. A breakdown of specific agents administered in the PACU that were considered to evidence PACU antiemetic administration is shown in Supplemental Digital Content, Table 3, http://links.lww.com/AA/C685.

Adjusted Risk of Rescue Antiemetic in PACU

For each of the independent variables included in our multiple variable regression model, the adjusted odds ratios for receiving rescue antiemetics in the PACU are illustrated in Figure 2A; the specific odds ratios and *P* values for this regression model are available in Supplemental Digital Content, Table 4, http://links.lww.com/AA/C685. This analysis demonstrates evidence for an association between chronic atypical antipsychotic therapy and reduced odds of receiving rescue antiemetics in the PACU, with an odds ratio of 0.51 (95% CI, 0.26–0.91; $P = .034$).

This analysis also demonstrates, as expected, that age <50 years and increasing modified Apfel score are associated with increased odds of rescue antiemetics administration. Exposure to potent inhalational anesthetic agents was just above the threshold for statistical significance for the association with the need for rescue ($P = .059$), while nitrous oxide exposure was not statistically significant ($P = .222$). Outpatient therapy with antiemetics was also just above the threshold for statistical significance for the association with the need for rescue ($P = .053$), while surgical case length ($P < .001$) and administration of opioid in PACU ($P < .001$) were significantly associated with the need for rescue antiemetics. Again, the specific odds ratios and *P* values for this regression model are available in Supplemental Digital Content, Table 4, http://links.lww.com/AA/C685. There was an increased risk of rescue relative to the number of prophylaxis agents administered, likely reflecting provider assessment that the patient was at greater risk for postoperative nausea and vomiting, increasing the number of associated interventions performed. The interaction terms between postoperative nausea and vomiting prophylaxis and age were significant and protective. This confirmed that increasing prophylaxis reduced the odds of rescue for these exposure categories.

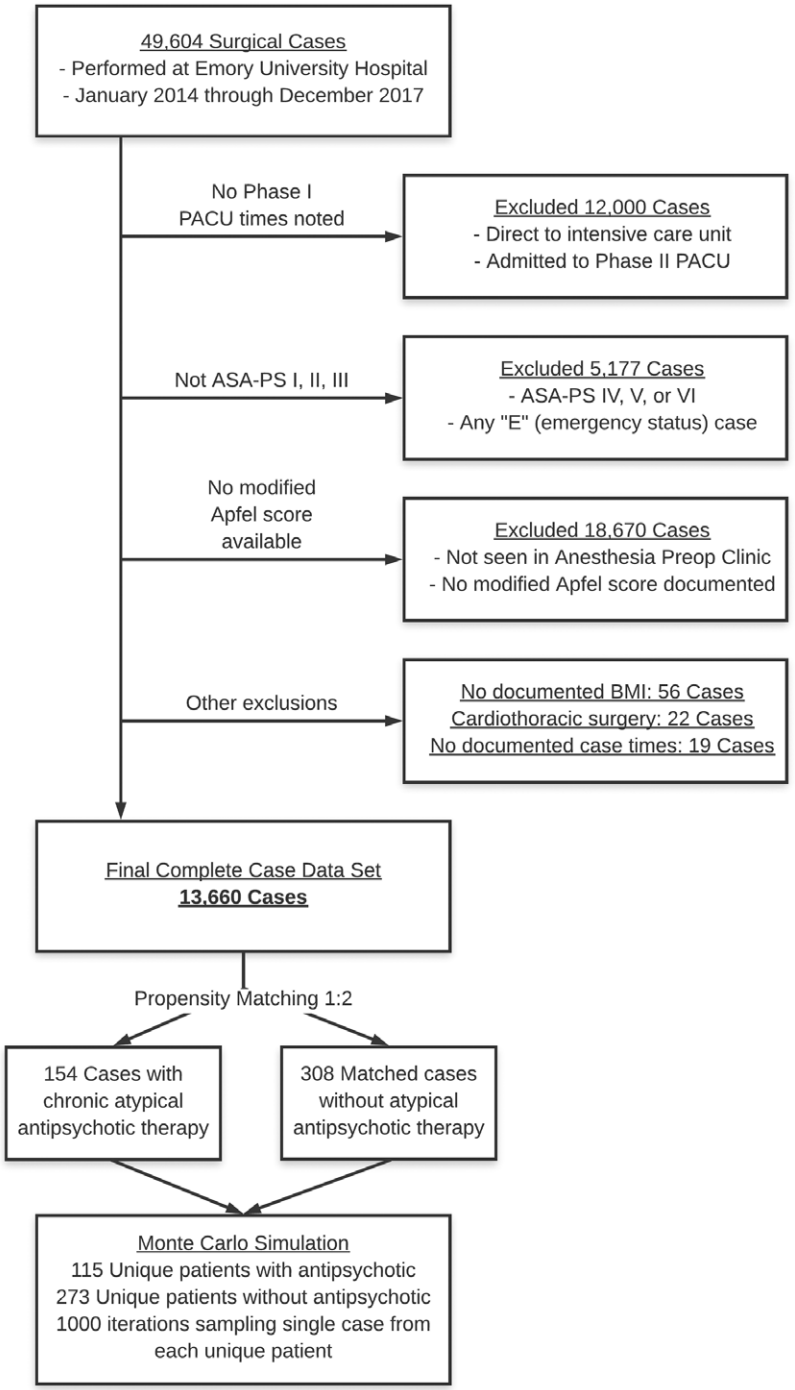

Figure 1. Case-level flow diagram outlining exclusions and case counts. ASA-PS indicates American Society of Anesthesiologists physical status; BMI, body mass index; PACU, postanesthesia care unit.

Propensity-Matched Risk of Rescue Antiemetic

Propensity matching yielded a well-balanced cohort (Table 2), with 2 cases where the patient had not been exposed to chronic atypical antipsychotic therapy for every case where the patient had been. Matched cases were drawn from the pool of cases with complete data per the inclusion criteria; as such, no cases had missing data. Absolute standardized mean differences showed no significant remaining imbalance on the matched variables, as defined by a cutoff of 0.1. Single-variable conditional logistic regression demonstrated significant differences for outpatient preoperative antiemetic therapy, log (surgical case length), and chronic atypical antipsychotic therapy; exposure to opioids in the PACU was also just above the threshold for statistical significance. Although the remaining imbalance was <0.1 for modified Apfel score, visual inspection of this covariate showed a potential imbalance. However, on single-variable conditional logistic regression, there was no significant association between the risk of PACU rescue antiemetics and modified Apfel score. We, therefore, concluded that there was no significant residual imbalance in modified Apfel scores.

We proceeded to perform multiple-variable conditional logistic regression to analyze the case-level effect. After backward selection and forward selection testing, only 2

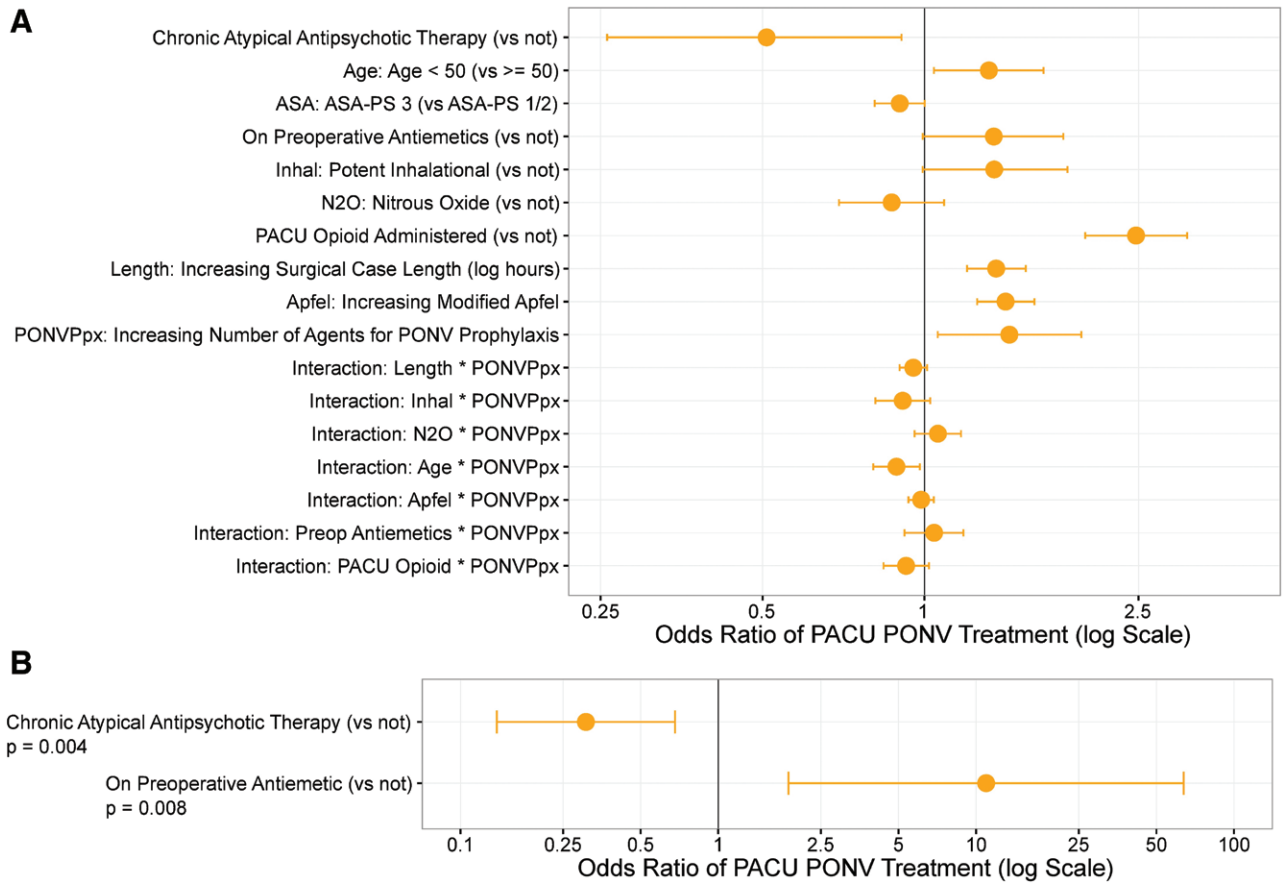

Figure 2. Odds ratio of receiving rescue medication for postoperative nausea and vomiting in the postanesthesia care unit for (A) all included cases and (B) a propensity-matched cohort of cases testing the association with chronic atypical antipsychotic therapy. ASA-PS indicates American Society of Anesthesiologists physical status; N_2O, nitrous oxide; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting; PONVPpx, PONV prophylaxis.

variables remained significant: chronic atypical antipsychotic therapy and outpatient preoperative antiemetic therapy. The results of this regression are shown in Figure 2B. The case-level odds ratio of PACU rescue antiemetics administration associated with chronic atypical antipsychotic therapy was 0.31 (95% CI, 0.14–0.68; P = .004).

To account for bias due to the inclusion of multiple surgeries on single patients, we performed a 1000-iteration Monte Carlo simulation in which a single case per unique patient was sampled, and 2-variable conditional logistic regression performed. The odds ratio of PACU antiemetic therapy from this analysis was estimated to be 0.283 ± 0.003 (0.108 ± 0.002 to 0.747 ± 0.001, each expressed as the mean ± SEM). The mean P value obtained from this analysis was 0.014 ± 0.001 (mean ± SEM). Therefore, the mean patient-level odds of being administered rescue antiemetic was lower for patients chronically taking the 3 atypical antipsychotics under consideration as compared to those not on atypical antipsychotics. Sensitivity analyses performed using single-variable conditional logistic regression and unselected multiple-variable conditional logistic regression demonstrated that the statistical significance of these findings was robust.

DISCUSSION

This propensity-matched retrospective investigation suggests that chronic atypical antipsychotic therapy with the 3 agents under consideration is associated with a reduced rate of rescue antiemetic administration in the PACU for ASA physical status I–III patients undergoing elective noncardiac surgery. Reduction in this surrogate for postoperative nausea and vomiting is consistent with previous literature demonstrating antiemetic efficacy of atypical antipsychotics in other contexts.[7,26] Factors and exposures known to increase the risk of postoperative nausea and vomiting were demonstrated to increase the risk of PACU rescue antiemetic administration. This confirmed the value of this measure as a proxy for postoperative nausea and vomiting while demonstrating the value of these variables as important confounders to include in the propensity-matched analysis. Simple exposure to nitrous oxide was not predictive of rescue antiemetic administration; we did not assess duration of nitrous oxide exposure and therefore could not test for consistency with previous reports that only exposures >45 minutes resulted in emetogenic effects.[27]

Atypical antipsychotics, also referred to as second-generation antipsychotics, antagonize the serotonin 2A receptor (5-HT2A) to a greater degree than the dopamine 2 receptor,[28] which mediates their antidepressant effect.[29] However, these agents have effects on a broad range of receptors.[30] The atypical antipsychotic olanzapine has demonstrated efficacy in prophylaxis against chemotherapy-induced nausea and vomiting,[26] possibly mediated by antagonism

Table 2. Summary of Propensity-Matched Case-Level Demographics and Exposures Comparing Treated Versus Untreated With Atypical Antipsychotic

	No Atypical Antipsychotic	Atypical Antipsychotic	Absolute Standardized Mean Difference	*P* Value (Univariate Conditional Logistic Regression)
N (cases, row percent)	308	154	-	-
N (unique patients)	273	115	-	-
Age (y), median (25th/75th quartile)	54 (41.75–66)	51 (41.25–63)	-	.142
Age <50 (%)	141 (45.8%)	75 (48.7%)	0.059	.905
Females (%)	216 (70.1%)	103 (66.9%)	0.070	.888
Body mass index ($kg \cdot m^{-2}$), median (25th/75th quartile)	24.7 (17.9–29.8)	25.4 (17.7–31.5)	0.042	.848
Outpatient antiemetic therapy	82 (26.6%)	38 (24.7%)	0.045	.046
Exposed to potent inhalational anesthetic	262 (85.1%)	132 (85.7%)	0.018	.280
Exposed to nitrous oxide	117 (38%)	62 (40.3%)	0.047	.906
Surgical case length (min), median (25th/75th quartile)	84 (36–148)	87.5 (37.5–145.5)	0.049	.034
Opioids administered in PACU	163 (52.9%)	77 (50%)	0.058	.065
Treatment in PACU with rescue antiemetic	45 (14.6%)	11 (7.1%)	-	.020
ASA classification			0.084	.789
I/II	104 (33.8%)	46 (29.9%)	-	-
III	204 (66.2%)	108 (70.1%)		
Modified Apfel score, median (25th/75th quartile)	3 (2–3)	3 (2–3)	0.029	.791
0	29 (9.4%)	10 (6.5%)	-	-
1	80 (26%)	37 (24%)		
2	125 (40.6%)	83 (53.9%)		
3	66 (21.4%)	23 (14.9%)		
4	8 (2.6%)	1 (0.6%)		
Number of postoperative nausea and vomiting prophylaxis agents			0.006	.413
0	33 (10.7%)	12 (7.8%)	-	-
1	130 (42.2%)	70 (45.5%)		
2	84 (27.3%)	43 (27.9%)		
3	42 (13.6%)	21 (13.6%)		
4	15 (4.9%)	6 (3.9%)		
5	4 (1.3%)	2 (1.3%)		
6	0 (0%)	0 (0%)		

Abbreviations: ASA, American Society of Anesthesiologists; PACU, postanesthesia care unit.

Table 3. Raw Postoperative Nausea and Vomiting Rescue Rate by Atypical Antipsychotic and Summary of Drug Affinities at the Specified Receptor Sites Using K_i Data

	Cases Requiring Postoperative Nausea and Vomiting Rescue	Literature Demonstrating Antiemetic Effect	Receptor Affinities				
			D2	D3	5-HT3	H1	H2
Amisulpride	Not approved in the United States	Yes, high quality	+++	+++	0	0	0
Olanzapine	4/42 (9.5%)	Yes, high quality	++	++	++	+++	++
Aripiprazole	6/62 (9.7%)	Minimal	+++	++++	+	++	0
Risperidone	1/53 (1.9%)	Minimal	+++	++	0	+++	+
Ziprasidone	0/15 (0%)	No	+++	+++	0	+	0
Quetiapine	19/151 (12.6%)	No	+	+	0	+++	0
Clozapine	2/6 (33.3%)	No	+	+	+	+++	+
No exposure to atypical antipsychotic	1802/13,344 (13.5%)	…	…	…	…	…	…

0: no affinity; +: $100 < K_i < 1000$; ++: $10 < K_i < 100$; +++: $1 < K_i < 10$; ++++: $K_i < 1$; D2, D3: dopamine receptor subtypes; 5-HT3: serotonin receptor subtype; H1, H2: histamine receptor subtypes.

of 5-HT3.[31] We categorize in Table 3 the inhibitory effect of common atypical antipsychotics on receptors where antagonism has been associated with antiemetic effects based on the Psychoactive Drug Screening Program K_i Database (specific number available in Supplemental Digital Content, Table 5, http://links.lww.com/AA/C685).[32,33] These receptors include the dopamine D2 receptor, the serotonin 5-HT3 receptor, and the histamine H1 receptor.[34,35]

In Table 3, we also provide the raw rate of postoperative nausea and vomiting rescue antiemetic administration we observed for patients taking these medications. A small trial of olanzapine in postoperative nausea and vomiting has been reported,[36] and amisulpride has demonstrated efficacy in postoperative nausea and vomiting prophylaxis.[10,37] Our work provides additional evidence for the potential role of certain atypical antipsychotics as prophylactic agents in postoperative nausea and vomiting management. If the mechanism underlying postoperative nausea and vomiting indeed involves antagonism at the mentioned receptors, then differences in receptor inhibition by different members

of this drug class may correspond with differential efficacy for postoperative nausea and vomiting prophylaxis.

These agents are widely available and relatively inexpensive. However, their safety profile must be considered. When administered chronically, these medications are associated with insulin resistance and weight gain, hypercholesterolemia, hyperprolactinemia, QT prolongation, dystonia, and dyskinesia.[38] More work is needed to determine whether such side effects can occur with short-term administration, for example, for a small number of perioperative doses. There is evidence for amisulpride that short-term use may be safe; there was no increase in the incidence of side effects (specifically, QT prolongation, extrapyramidal symptoms, or sedation) compared to controls in the aforementioned clinical trial examining amisulpride for postoperative nausea and vomiting prophylaxis.[37] Aripiprazole is particularly interesting because there is a low reported incidence of QTc prolongation.[39] Options are limited in patients when concerned about QTc, as both 5-HT3 antagonists and butyrophenones are known to prolong QTc and are therefore generally avoided.

The significance of our result is limited by our retrospective observational study design. Selection and observation bias are inherent to the approach. Propensity matching was performed to limit the impact of measured confounders. However, propensity matching does not imitate true randomization; therefore, systematic selection bias may present for other unmeasured confounders playing an explanatory role in the observed association. In addition, propensity matching can only estimate the average treatment effect on the treated; combined with our limited sample size, generalizability is somewhat limited. Analysis at the case level results in duplication of information; the estimate provided by the case-level propensity-matched conditional logistic regression is therefore biased toward overestimating the treatment effect of atypical antipsychotics. The estimate provided by the Monte Carlo simulation capturing the spectrum of outcomes from analysis at the individual case level is imprecise, but more accurately captures the probability and magnitude range for the treatment effect.

There may be specific factors associated with patients who are receiving atypical antipsychotics that may be protective against postoperative nausea and vomiting, such as the well-known association between schizophrenia and tobacco smoking status.[40] The retrospective approach also inherently fails to capture certain specific details including whether the patients were actually taking their outpatient prescription antiemetics or atypical antipsychotics. We had no high-quality source of information as to the duration of atypical antipsychotic use. Some patients treated with agents we included as antiemetics (diphenhydramine, ephedrine) could have received these agents for other indications (itching, hypotension).

Another limitation is that the modified Apfel score recorded in our preoperative clinic evaluations was not tightly defined; for example, the verbiage does not specifically reflect all emetogenic surgeries or include motion sickness as a consideration. However, the performance of the score in predicting PACU antiemetic administration strengthens the case that the score reflected underlying postoperative nausea and vomiting risk. A potentially greater limitation is that our absolute rate of rescue antiemetic administration in the PACU was fairly low, which may be due to factors related to the specific population of patients cared for at our institution, the types of surgeries performed here, or local approaches to chemoprophylaxis. In addition, the lack of a specific PACU postoperative nausea and vomiting rescue protocol at our institution limits specific conclusions about the type postoperative nausea and vomiting being treated; some patients may have experienced only mild postoperative nausea and vomiting but requested medication, while others may have truly had severe postoperative nausea and vomiting absolutely requiring rescue antiemetics.

Last, we were unable to control for the potential influence of chemotherapy-induced nausea and vomiting on postoperative nausea and vomiting as has been previously investigated, although chemotherapy-induced nausea and vomiting could be reflected in the modified Apfel or otherwise be partially reflected by outpatient preoperative antiemetic therapy, both of which were included in the final model as potential confounders.[41]

In conclusion, atypical antipsychotics have promise for the chemoprophylaxis of postoperative nausea and vomiting. Demonstrating a protective effect of chronic therapy with these agents adds to the existing literature supporting this role. More work is needed in the form of a prospective trial to validate these findings. We anticipate with interest the results of an ongoing phase 2 clinical trial of olanzapine for postoperative nausea and vomiting prophylaxis due to complete enrollment in 2020.[42] As the use of these medications for this indication would be off-label in the United States and elsewhere, their adoption cannot be recommended without additional safety and efficacy data.

ACKNOWLEDGMENTS

The authors thank Lisa Cogdill, MPH (Data Analyst, Research and Woodruff Health Sciences Information Technology, Emory University, Atlanta, GA) for her invaluable expertise in data extraction from the Emory Healthcare Clinical Data Warehouse.

DISCLOSURES

Name: Craig S. Jabaley, MD.
Contribution: This author helped provide critical input into the statistical analysis plan, interpret the data, critical revision of the manuscript, and approve the final version.
Name: Dennis W. Gray, DO, MPH.
Contribution: This author helped interpret the data, critical revision of the manuscript, and approve the final version.
Name: Gaurav S. Budhrani, MD.
Contribution: This author helped interpret the data, critical revision of the manuscript, and approve the final version.
Name: Grant C. Lynde, MD, MBA.
Contribution: This author helped interpret the data, critical revision of the manuscript, and approve the final version.
Name: Panagiotis Adamopoulos, PhD.
Contribution: This author helped provide critical input into the statistical analysis plan, critical revision of the manuscript, and approve the final version.
Name: George S. Easton, PhD.
Contribution: This author helped provide critical input into the statistical analysis plan, critical revision of the manuscript, and approve the final version.
Name: Vikas N. O'Reilly-Shah, MD, PhD.
Contribution: This author helped conceive the work, acquire the data, write the statistical analysis plan, clean and analyze the data, and draft the manuscript. He is the guarantor.
This manuscript was handled by: Tong J. Gan, MD.

REFERENCES

1. Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology*. 1999;91:693–700.
2. Gan TJ, Diemunsch P, Habib AS, et al; Society for Ambulatory Anesthesia. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2014;118:85–113.
3. Cao X, White PF, Ma H. An update on the management of postoperative nausea and vomiting. *J Anesth*. 2017;31:617–626.
4. Singh PM, Borle A, Rewari V, et al. Aprepitant for postoperative nausea and vomiting: a systematic review and meta-analysis. *Postgrad Med J*. 2016;92:87–98.
5. Merck. Emend Package Insert. [Cited March 13, 2018]. Available at: https://www.merck.com/product/usa/pi_circulars/e/emend/emend_pi.pdf. Accessed March 13, 2018.
6. Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2016;375:134–142.
7. Yoodee J, Permsuwan U, Nimworapan M. Efficacy and safety of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2017;112:113–125.
8. Shiokawa M, Narita M, Nakamura A, Kurokawa K, Inoue T, Suzuki T. Usefulness of the dopamine system-stabilizer aripiprazole for reducing morphine-induced emesis. *Eur J Pharmacol*. 2007;570:108–110.
9. Okamoto Y, Tsuneto S, Matsuda Y, et al. A retrospective chart review of the antiemetic effectiveness of risperidone in refractory opioid-induced nausea and vomiting in advanced cancer patients. *J Pain Symptom Manage*. 2007;34:217–222.
10. Kranke P, Bergese SD, Minkowitz HS, et al. Amisulpride prevents postoperative nausea and vomiting in patients at high risk: a randomized, double-blind, placebo-controlled trial. *Anesthesiology*. 2018;128:1099–1106. Available at: http://anesthesiology.pubs.asahq.org/article.aspx?articleid=2675570&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-Anesthes&utm_content=olf&utm_term=031418. Accessed March 17, 2018.
11. Yao XI, Wang X, Speicher PJ, et al. Reporting and guidelines in propensity score analysis: a systematic review of cancer and cancer surgical studies. *J Natl Cancer Inst*. 2017;109. DOI: http://dx.doi.org/10.1093/jnci/djw323.
12. Aldrete JA. The post-anesthesia recovery score revisited. *J Clin Anesth*. 1995;7:89–91.
13. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2015. Available at: http://www.R-project.org/. Accessed March 13, 2018.
14. RStudio Team. RStudio: Integrated Development Environment for R. Boston, MA: RStudio, Inc; 2015. Available at: http://www.rstudio.com/. Accessed March 13, 2018.
15. Allen MP, ed. The problem of multicollinearity. In: *Understanding Regression Analysis*. Boston, MA: Springer US; 1997:176–180.
16. Venables WN, Ripley BD. Modern Applied Statistics with S. New York, NY: Springer New York; 2002.
17. Agresti A. An introduction to categorical data analysis. New York, NY: Wiley; 1996.
18. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol*. 2003;158:280–287.
19. Ho S, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Softw*. 2011;42:1–28.
20. Keller B, Tipton E. Propensity score analysis in R. *J Educ Behav Stat*. 2016;41:326–348.
21. Austin PC. A comparison of 12 algorithms for matching on the propensity score. *Stat Med*. 2014;33:1057–1069.
22. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol*. 2010;172:1092–1097.
23. Yoshida K, Bohn J. Tableone: create 'Table 1' to describe baseline characteristics v0.9.3. 2018. Available at: https://CRAN.R-project.org/package=tableone. Accessed August 23, 2018.
24. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424.
25. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York, NY: Springer Science & Business Media; 2013.
26. Navari RM, Loprinzi ChL. Olanzapine for chemotherapy-induced nausea and vomiting. *N Engl J Med*. 2016;375:1396.
27. Peyton PJ, Wu CY. Nitrous oxide-related postoperative nausea and vomiting depends on duration of exposure. *Anesthesiology*. 2014;120:1137–1145.
28. Seeman P. Atypical antipsychotics: mechanism of action. *Can J Psychiatry*. 2002;47:27–38.
29. Guiard BP, Di Giovanni G. Central serotonin-2A (5-HT2A) receptor dysfunction in depression and epilepsy: the missing link? *Front Pharmacol*. 2015;6:46.
30. Mauri MC, Paletta S, Maffini M, et al. Clinical pharmacology of atypical antipsychotics: an update. *EXCLI J*. 2014;13:1163–1191.
31. Kast RE, Foley KF. Cancer chemotherapy and cachexia: mirtazapine and olanzapine are 5-HT3 antagonists with good antinausea effects. *Eur J Cancer Care (Engl)*. 2007;16:351–354.
32. American Association for the Advancement of Science. NetWatch: 'pharmacokinetics unbound'. *Science*. 2000;287:543.
33. Roth BL, Lopez E, Patel S, Kroeze WK. The multiplicity of serotonin receptors: uselessly diverse molecules or an embarrassment of riches? *Neuroscientist*. 2000;6:252–262.
34. Wiesmann T, Kranke P, Eberhart L. Postoperative nausea and vomiting: a narrative review of pathophysiology, pharmacotherapy and clinical management strategies. *Expert Opin Pharmacother*. 2015;16:1069–1077.
35. Kovac AL. Update on the management of postoperative nausea and vomiting. *Drugs*. 2013;73:1525–1547.
36. Ibrahim M, Eldesuky HI, Ibrahim TH. Oral olanzapine versus oral ondansetron for prevention of post-operative nausea and vomiting: a randomized, controlled study. *Egypt J Anaesth*. 2013;29:89–95.
37. Gan TJ, Kranke P, Minkowitz HS, et al. Intravenous amisulpride for the prevention of postoperative nausea and vomiting: two concurrent, randomized, double-blind, placebo-controlled trials. *Anesthesiology*. 2017;126:268–275.
38. Uçok A, Gaebel W. Side effects of atypical antipsychotics: a brief overview. *World Psychiatry*. 2008;7:58–62.
39. Belgamwar RB, El-Sayeh HGG. Aripiprazole versus placebo for schizophrenia. *Cochrane Database Syst Rev*. 2011:CD006622.
40. Cather C, Pachas GN, Cieslak KM, Evins AE. Achieving smoking cessation in individuals with schizophrenia: special considerations. *CNS Drugs*. 2017;31:471–481.
41. da Silva HB, Sousa AM, Guimarães GM, Slullitel A, Ashmawi HA. Does previous chemotherapy-induced nausea and vomiting predict postoperative nausea and vomiting? *Acta Anaesthesiol Scand*. 2015;59:1145–1153.
42. Hyman JB, Demaria S. Olanzapine for Nausea After Surgery - Full Text View - ClinicalTrials.gov. [Cited April 14, 2018]. Available at: https://clinicaltrials.gov/ct2/show/NCT02755116. Accessed April 14, 2018.