Title of Study or Project:	The Association of Race with Utilization of Antiemetic Prophylaxis in the Multicenter Perioperative Outcomes Group
Primary Institution:	Weill Cornell Medicine
Principal Investigator:	Robert S. White MD, MS
Co-Investigators:	Kane O. Pryor MD (mentor), Michael H. Andreae MD, Anna S. Nachamie BS, Zachary A. Turnbull MD, Noelle S. Arroyo BA
Type of Study:	Retrospective Observational, Cross Sectional
IRB Number/Status:	The project has been submitted to Weill Cornell Medicine's IRB for expedited approval with limited dataset. Approval is pending (Protocol #: 1802019004).
Hypothesis:	Our hypothesis is that social determinants of health (race) are associated with the utilization of antiemetic prophylaxis as marker of intraoperative anesthesia quality, after controlling for PONV risk as well as patient and anesthesia case characteristics.
Number of Patients/Participants:	The MPOG database will be queried for all anesthesia cases of adult (≥18 years of age) patients undergoing elective surgery between January 1, 2013 to the present. We will exclude trauma and cardiac surgery, anesthesia for labor and delivery, and endoscopic procedures. We will limit procedures to the CPT codes specified in the MPOG PONV 01 (MIPS 430)
Power Analysis:	Needed sample size: 5,885 More specifics are outlined in the Statistical Analysis section below.
Proposed statistical test/analysis:	Our outcome of interest is the utilization of antiemetic medications (count measure). We will investigate differences in utilization not justified by risk factors for postoperative nausea and vomiting. A priori, we chose a mixed regression models. However, we will compare our primary model with bivariate, stratified, multivariate logistic regression models, and mixed effects hierarchical Bayesian models to investigate the association in different datasets with more or less missing data on known PONV risk factors and confounders. More specifics are outlined in the Statistical Analysis section below.
Resources (Brief summary of resources for data collection, personnel, financial):	The MPOG database will be queried for the specified concept IDs with programmatic support. Statistical analyses and operational oversight will be funded from the Center for Perioperative Outcomes in the Department of Anesthesiology at Weill Cornell Medicine.

Antiemetic prophylaxis as an anesthesia quality marker and its association with race in the Multicenter Perioperative Outcomes Group

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Introduction

Health care disparities continue to persist, despite countermeasures, in the United States and they have been linked to wealth and wealth distribution, race, language, health insurance primary payer status, and geography [1-8]. Uninsured and underinsured patients (those whose health insurance benefits do not adequately cover their medical expenses) have been shown to have worse outcomes following medical care of chronic pain, acute care surgery, and major surgeries, in both adult and pediatric populations [1, 2, 7-12]. Meghani et al. performed a meta-analysis and systematic review that quantified the magnitude and raised alarm towards the analgesic treatment disparities present in subgroups of minorities, in particular Blacks/African Americans[14]. We previously identified language as a potentially modifiable barrier to access chronic pain services for underserved inner-city populations [2, 7, 9].

What current gaps exist in the understanding of this problem?

Racial and ethnic disparities have also been described in neuraxial and labor anesthesia [15-18]. However, healthcare disparities in intraoperative anesthesia care have not been well studied and in particular the contribution of individual anesthesia providers to healthcare disparities remains unclear [1, 19, 20].

We investigated the contribution of individual intraoperative anesthesia providers to healthcare disparities in the administration of antiemetic prophylaxis [1, 21]. We chose antiemetic prophylaxis (administration of drugs ondansetron and dexamethasone) as a marker of anesthesia quality because antiemetic prophylaxis is patient-centered and improves outcomes, is given relatively independently of patient comorbidities, its indication is contingent on specific measurable risk factors for postoperative nausea and vomiting (PONV), it is a standard of care with explicit guidelines that are widely accepted, and administration is the sole responsibility of anesthesia providers. We examined the association of social determinants of health and the utilization of the most frequent antiemetics (ondansetron and dexamethasone) in the subset of 173,133 anesthesia records in the National Anesthesia Clinical Outcomes Registry (NACOR), uploaded from six academic centers. Our multiple statistical models consistently demonstrated a large and statistically significant association between the socioeconomic status (insurance status median income in patients' home zip code) and the utilization of antiemetic medication. This points to healthcare disparities for which individual anesthesia providers would be accountable. However, our NACOR study had many limitations. We failed to control for several important risk factors for PONV like smoking, which may themselves be associated with social status and could have confounded the association. Our findings need to be confirmed in another larger

registry (MPOG), consider other social determinants of health (race), controlling for all known risk factors of PONV (in particular smoking).

How will this project address this gap and advance clinical care and/or research knowledge?

We propose to replicate our preliminary NACOR study now in the Multicenter Perioperative Outcomes Group (MPOG) electronic anesthesia record registry with expanded antiemetic medications and to examine socioeconomic patient characteristics associated with reduced quality of anesthesia care [22], addressing the many limitations acknowledged by the former [1]. In our statistical models, we will examine patient-identified race as our socioeconomic patient characteristic of interest, further solidifying our hypothesis that social determinants of health drive utilization of antiemetic prophylaxis as a marker of anesthesia quality. With advanced statistical modeling, we will explore the variability across individual anesthesia providers and try to delineate their influence on the observed disparity.

The specific aims of our projects are therefore to:

1. Investigate the association of social determinants of health and utilization of antiemetic prophylaxis as a proxy for anesthesia quality in the Multicenter Perioperative Outcomes Group (MPOG) electronic perioperative record database with mixed regression models.
2. Fit and develop novel, transparent, and reproducible Bayesian hierarchical regression models to delineate/demonstrate the contribution of individual anesthesia providers to this disparity and to explore potential mechanisms of perioperative healthcare disparities to identify potential targets to address them.
3. Explore novel (Bayesian) modeling approaches to impute missing data with additional patient and case characteristics.
4. Investigate the relative contribution and influence of institutional culture and or attending supervision an anesthesia (resident and CRNA) provider utilization of antiemetic prophylaxis and explore if hierarchical modeling can delineate if and how the influence of anesthesia attendings or institutional factors mediates the effects of social determinants of health on utilization of antiemetic prophylaxis.

5. Can anesthesia attendings be held responsible for the described disparity anesthesiology or are residents, nurse anesthetists primarily responsible for disparities in antiemetic prophylaxis? Are local practice specific cultures and practice habits driving provider choices? These findings are hypothesis generating and will serve as preliminary data for future interventional trials and further mechanistic investigations.

Our proposed work would provide additional evidence to support the notion that social determinants of health impact provider performance and hence outcomes also in anesthesia.

Furthermore, we will seek to develop novel statistical approaches to overcome the challenge of missing data in large electronic medical record registries and to attribute the driving influence of disparities to the correct level in our contemporary hierarchical healthcare system. Our hypothesis is that patient race is associated with provider performance as evidenced by reduced utilization of antiemetic prophylaxis medications after controlling for accepted risk factors for PONV and other patient and case characteristics.

Methods

Study Database and Population

We will utilize the Multicenter Perioperative Outcomes Group (MPOG), a non-profit academic consortium of more than 100 investigators representing more than 8.2 million anesthetic cases integrated across 50 hospitals across 18 states and 2 countries. MPOG uses electronic health record and administrative data to analyze the interplay between patient comorbidities, surgical procedure, perioperative care, interventions, and postoperative outcomes and represents the most comprehensive and detailed global perioperative anesthesiology registry. We will utilize a MPOG Public User File, enriched with data on antiemetic utilization and race.

Our unit of analysis will be the anesthesia case. Our dataset will contain information about the utilization of the antiemetics (as a count measure) medications; patient demographics and American Society of Anesthesiologists Physical Status Classification; provider identifier; institution and location; procedure codes; and other case characteristics. As previously mentioned, we will limit our analysis to the most frequent volume procedures performed in the MPOG database. Antiemetics used will be measured according to the Anesthesiology Performance Improvement and Reporting Exchange (ASPIRE) Post-Operative Nausea and Vomiting quality measure (PONV 01). The MPOG database contains information pertaining to a patient's self-identified race. Variables abstracted for each anesthesia case include patient, procedure, and provider characteristics. We will extract information about antiemetic medication administered pre-, intra, and postoperatively. Patient characteristics included race (as our primary predictor/ independent variable of interest), patient age, gender, and American Society of Anesthesiologists Physical Status Classification. MPOG also specifically contains information on smoking status and on past history of postoperative nausea or motion sickness and vomiting. Neither median income nor primary insurance payer are recorded in the MPOG database. Procedure types and indications include billing code, modifiers, and international classification of disease codes. Provider characteristics include information on the anesthetist (nurse anesthetist versus resident versus attending alone; adjustments for individual provider's tendancy to administer antiemetics), the supervising anesthesiologist if any, institutional data (geographic location, academic versus private versus government institution) and provider demographics as available.

Detailed Statistical Approach

IRB statement

The project has been submitted to Weill Cornell Medicine's IRB for expedited approval with limited dataset. Approval is pending (Protocol #: 1802019004).

Study type

Observational (cross-sectional). The STROBE guidelines have been referenced and our proposal is in accordance with the checklist.

Primary outcome

The primary outcome of our study is the administration of antiemetic prophylaxis medications (overall count measure) by patient race as defined by PONV 01 (MIPS 430).

Patient inclusion/exclusion criteria

All anesthesia cases of adult (≥18 years of age) patients undergoing elective surgery between January 1, 2013 to the present. We will exclude trauma and cardiac surgery, anesthesia for labor and delivery, and endoscopic procedures. We will focus our investigation on the most frequent interventions to reduce outliers and enhance the homogeneity of our population. We will limit the procedure included to the CPT codes listed in MPOG PONV 01 (MIPS 430).

Data source

MPOG Database

Statistical analysis

Our primary approach will be a Bayesian Hierarchical Model. Similar to the models built for our previous paper, we will build hierarchical Bayesian models for the subset with complete data on race, PONV risk factors and other case and patient characteristics. We will study the utilization of antiemetic prophyaxis as defined by MPOG PONV 01 (MIPS 430) as primary outcomes (overall count measure). We will control for patient characteristics, in particular the four accepted PONV risk factors and other patient, procedure, or anesthetic-related confounders. We will include random effects to control for the potential confounding influence of procedure type or provider behavior and institutional culture, by allowing each procedure, institution, and each provider to have an individual intercept. Our unit of analysis is the anesthesia case, not the patient. We will focus our analysis on the most frequent procedures performed and limit the cases by CPT code as defined in MPOG PONV 01 (MIPS 430). A priori, we will declare findings statistically significant if the *P* value was less than the type I error rate of .01, deliberately choosing a more stringent criterion, given the size of our populations of interest. Still, given the large number of anesthesia cases included, we acknowledge that the *size, consistency and robustness* of the association between social determinants of health as predictors

and utilization of antiemetic prophylaxis as our primary outcome will be more important for our inferences than admittedly arbitrary p-value cutoffs.

To corroborate our findings and to explore if the associations are consistent across all datasets, regardless of missing data and to investigate the sensitivity of our inference to our modeling choices and assumptions, will perform various sensitivity analyses:

1. *Bivariate and stratified analysis.* We will present demographic characteristics and case information for patients who received antiemetic prophylaxis and those who did not. Categorical variables will be compared using Pearson's χ^2 tests or Fisher's exact tests; continuous variables will be compared using analysis of variance (ANOVA) or Kruskal-Wallis tests, for non-normally distributed variables, as appropriate. We will repeat our investigation of the association of social determinants of health versus utilization of antiemetic prophylaxis using stratification by gender, age, and other demographics and case characteristics.

2. *Multivariate logistic regression.* To examine the effect of markers of racial and socioeconomic disparities on antiemetic prophylaxis, we will conduct multivariate logistic regression analyses for dichotomous outcome administration of antiemetic prophylaxis. These models will serve to control for potential confounders including patient characteristics, provider characteristics, and procedure type and indication. Race and ethnicity is a categorical variable; possible values are (unordered) Hispanic White, Hispanic Black, Hispanic Color Unknown, Black not of Hispanic Origin, White not of Hispanic origin, American Indian or Alaska Native, Asian or Pacific Islander, Bi or Multiracial, Middle Eastern.

3. *Sensitivity analysis.* Besides comparing the results of our 3 models (bivariate, logistic regression, and Bayesian analysis) to confirm the robustness of our findings, we will use different prior and vary other model parameters to investigate the influence of our modelling choices on our results. We will perform this sensitivity analysis of our model assumptions and choices with various data subsets.

Statistical tests and analysis will be performed using SAS version 9.4 (SAS Institute, Cary, NC), Stata version 15 SE (StataCorp, LLC, College Station, TX), and R/Rstudio (RStudio, Vienna, Austria).

Power analysis

Sample size is 5,885

- 80% power, two-sided alpha = 0.01
- Baseline probability that Y = 1 (use of ondansetron) was 51%
- Odds Ratio for Medicaid vs. Private (from the frequentist model) was 0.70 (conservative roundup from 0.63)

- R-Squared of the insurance variable with the other independent variables was 0.70

Power	N	Pcnt N X=1	P0	P1	Odds Ratio	R Squared	Alpha	Beta
0.79976	2904	30.000	0.510	0.384	0.600	0.700	0.01000	0.20024
0.79969	4055	30.000	0.510	0.404	0.650	0.700	0.01000	0.20031
0.79984	5885	30.000	0.510	0.421	0.700	0.700	0.01000	0.20016

Adapted from: Andreae, M.H., et al., *Antiemetic Prophylaxis as a Marker of Health Care Disparities in the National Anesthesia Clinical Outcomes Registry*. Anesthesia & Analgesia, 2018. 126(2): p. 588-599.

PASS 13 Power Analysis and Sample Size Software (2014). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass

Variables to be collected

See details in query specification.

Handling of missing data

A priori, we have devised a rigorous and robust statistical analysis approach to analyze different data subsets with varying degrees of missing data to demonstrate that the association is consistent across all data. We will employ concurrent statistical analysis including bivariate analysis, stratified analysis, multivariate logistic regression models, and mixed effects hierarchical Bayesian models comparing the different statistical approaches provided in sensitivity and subgroup analysis. Besides, we will explore Bayesian approaches to impute missing data using additional patient and case characteristics to enhance the generalizability and validity of our findings.

Areas for discussion/known limitations

- Validity of the primary data collection of race and risk factors at participating institutions
- Missing data and resulting unknown selection bias
- MPOG population may differ from general population undergoing anesthesia in the US
- CPT/ICD code exclusions
- Elective surgery coding practices

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