frontiers | Frontiers in Anesthesiology

TYPE Original Research
PUBLISHED 13 October 2025
DOI 10.3389/fanes.2025.1631506

OPEN ACCESS

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RECEIVED 19 May 2025
ACCEPTED 26 August 2025
PUBLISHED 13 October 2025

CITATION
Schumacher CA, Choragudi RV, Mikolic JM, Boudreaux-Kelly MY and Williams BA (2025) A multi-variable, Veteran-centered study of PONV risk factors in separate regional vs. general anesthesia contexts.
Front. Anesthesiol. 4:1631506.
doi: 10.3389/fanes.2025.1631506

A multi-variable, Veteran-centered study of PONV risk factors in separate regional vs. general anesthesia contexts

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Background: Currently, perioperative stakeholders are guided to provide general anesthesia (GA) patients with either two or four antiemetic prophylaxis (AEPPx) medications based on the 1990s legacy risk factors (RFs). There are no Veteran-centric regional anesthesia (RA) or GA postoperative nausea and vomiting (PONV) RF studies, and only a few studies have explored these factors based on race/ethnicity. Thus, the currently accepted AEPPx in Veterans may be escalating symptoms, costs, and lengths of stay.
Methods: We first conducted institutional review board (IRB)-approved secondary analyses from a prospective Veteran-specific randomized trial to assess for RA-specific PONV RFs. Subsequently, we conducted IRB-approved retrospective analyses of observational quality improvement data from Veterans receiving GA with or without intrathecal morphine (ITM) preoperatively (with ITM cases accompanied by a five-drug AEPPx). The goal was to assess both Veteran-specific and anesthesia (RA and GA)-specific PONV RFs. For RA-specific PONV RF analyses in 115 Veterans, we queried electronic medical records (EMR) along with database-archived study data from case report forms. For GA-specific PONV RF analyses in 468 Veterans, we analyzed EMR data to compare PONV-free patients with PONV-positive patients, both for postoperative days 0–1 (POD#0–1 after surgery) and POD#2.
Results: Postoperative opioids were associated with increased PONV in both analyses. For RA, African-American Veterans were found to have more PONV despite lower overall opioid consumption than that in the race-referent group, while diabetic Veterans overall showed less PONV. For GA-specific analyses (informed by the risks and signals identified in RA analyses), African-American Veterans again had more PONV. Consensus-guided RFs added to the models were often non-predictive, particularly (i) smoking status and past PONV (RA-specific) and (ii) gender and past PONV (GA-specific). This may suggest underpowering in both limited sample sizes or, instead, indicate race as a profoundly overriding RF. RFs associated with POD#2 PONV after GA (after no PONV on POD#0–1) notably differed from factors driving POD#0–1 PONV.

Conclusion: Consensus-guided AEPPx may require reevaluation, particularly in Veterans undergoing RA or GA, if not population-wide. All Veterans could benefit from our 2023-described off-patent five-drug AEPPx before any anesthetic drug is administered, as described herein and elsewhere. Emerging RFs may have pharmacoequity and race-based implications.

KEYWORDS

PONV prophylaxis agents, regional anesthesia, general anesthesia, PONV risk factors, race/ethnicity, palonosetron, aprepitant

1 Introduction

Recent antiemetic prophylaxis (AEPPx) consensus guidelines (CG) (1), and predecessor guidelines, for the management/prevention of postoperative nausea and vomiting (PONV) have not dramatically shifted from their origins in 2003. The 2020 CG recommends the use of two non-specified medications of differing categories if two or fewer risk factors (RFs) are present and four medications if three or more RFs are present. However, recent reports (2), including our five-drug AEPPx for patients receiving intrathecal morphine (ITM), have demonstrated potential for remarkable outcome improvements. Furthermore, recent loss of patent protection for palonosetron and aprepitant (2), two of our five described AEPPx agents, seems to justify resource commitment toward more aggressive, low-cost prophylaxis, benefiting hospitals and patients alike (3). To our knowledge, (i) there have been no Veteran-centric studies on RFs for the development of PONV and (ii) there does not appear to be any recent work specifically addressing PONV after regional anesthesia (RA) in the absence of general anesthesia (GA), aside from the earlier reports by Borgeat et al. (4) and Williams et al. (5) in outpatient settings. There, otherwise, seems to be a paucity of literature addressing multimodal AEPPx after GA involving ITM. Therefore, we aimed to review, in Veterans, both RA-specific data from a previously reported prospective clinical trial (6) and GA-specific data derived from and expanded since a previously reported observational quality improvement (QI) study (2), to determine the robustness of traditional PONV RFs vs. other emerging factors potentially warranting routine clinical consideration.

2 Methods

2.1 RA-specific analyses

We first conducted a retrospective secondary analysis of data from the aforementioned clinical trial (6) entailing nerve blocks/RA for joint replacement (primary hip or primary knee arthroplasty), but not involving ITM [as did our more recent report (2)]. This was an institutional review board (IRB)-approved amendment, exempt from patient research consent above and beyond original study consent, as well as original clinical surgery and anesthesia consent. Institutional approval was obtained (approval/exemption 1617210, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA), allowing for tracking and external reporting of the described, newly-queried outcome data. For $n = 115$ Veterans (6), both electronic medical records (EMR) and database-archived study data were queried. For PONV prophylaxis, these patients received standardized perphenazine 8 mg *per os* (PO) (before case), ondansetron 4 mg IV (end of case), and possibly discretionary aprepitant 40 mg PO (before case). Of the described $n = 115$ Veterans, 48 (42%) experienced at least one episode of PONV (of any severity) during the joint replacement hospitalization study period, and these cases were compared against those who were PONV-free on postoperative days (POD) #0–2. The novel factors explored were based on our prospective study data case report forms or informed by recent Veteran-centric and active duty-specific publications from 2021 to 2022 (see Supplementary Tables 1a,b) (7–9). This analysis was conducted using bivariate analyses via cross-tabular chi-square tests (or Fisher's exact tests, where appropriate; Supplementary Table 2) and then (due to the small sample size of available case data) multivariable parsimonious logistic regression (Table 1; SAS, SAS Institute Inc., Cary, NC, USA). Finally, despite the low number of African-American patients in the RA PONV ($n = 12$) retrospective analysis of prospective data, race was identified in the most parsimonious model as an associated predictor of PONV. Interaction terms of race with all other variables were explored during development of the most parsimonious model (data not shown), and no interaction terms were found to be associated with (or a signal of) PONV (with allowance of $P < 0.2$, for signals). Assuming low sample size as the most likely reason for these results, we then conducted exploratory bivariate analyses of race *with all other measures* from the most parsimonious model. The results of these analyses are presented in Supplementary Table 3.

2.2 GA-specific analyses

We then conducted analyses of data from an ongoing observational QI study (2) regarding Veterans receiving GA (entailing propofol induction as the institutional standard of care, at ~1–2 μg/kg over 30–60 s, depending on health status) with or without undergoing (before surgery) an ITM procedure

TABLE 1 Predictive factors and potential signals of PONV occurrence, by deriving the most parsimonious multivariable logistic regression model, regarding Veterans undergoing regional anesthesia without general anesthesia ($n = 115$).

Variables	Reference group	PONV on POD#0–2: odds ratio (95% CI)	*P*-value	Interpretation
Associated predictors of PONV				
Diabetes mellitus	No diabetes	0.13 (0.04–0.47)	0.002	Our enrolled study Veterans with diabetes had an associated ~87% lower odds of PONV than those of Veterans without diabetes
0–24 h oral morphine equivalent increments (per milligram)	No opioids consumed	1.02 (1.00–1.03)	0.014	Per milligram increase in oral morphine equivalents, our enrolled study Veterans had an associated 2% greater odds ratio for PONV
African-American	Not African-American	6.53 (1.25–34.14)	0.026	Our enrolled study Veterans who were African-American had an associated ~6.5 times greater odds of PONV than did enrolled Veterans of other races (predominantly Caucasian)
Potential signals of PONV predictability				
Recent N/V, per study survey responses 1–4 weeks preop	No recent (preop) N/V	4.98 (0.89–27.89)	0.068	Our enrolled study Veterans indicating any recent (N/V) on preoperative study surveys signaled ~5 times greater odds ratio of PONV than did enrolled Veterans without recent preoperative N/V reports
Marijuana-related use, or unhealthy patterns of EtOH use, at preoperative baseline	Neither current nor recent EtOH or marijuana-related consumption in the EMR considered problematic	2.41 (0.88–6.61)	0.088	Our enrolled study Veterans with recent/concurrent marijuana-related or alcohol use signaled a ~2.4 times greater odds ratio of PONV than did enrolled Veterans without such use
Baseline opioid use at the time of surgery	No baseline opioids preop	3.53 (0.81–15.47)	0.094	Our enrolled study Veterans with baseline opioid use before surgery signaled a ~3.5 times greater odds ratio of PONV than did enrolled Veterans without baseline opioid use
History of vomiting listed in EMR, but unrelated to specific surgical encounters	No EMR listing of non-surgical vomiting	8.14 (0.68–96.96)	0.097	Our enrolled study Veterans with an EMR listing of vomiting unrelated to surgery/anesthesia signaled an ~8 times greater odds ratio of PONV than did enrolled Veterans without such a listing
Female gender	Male	3.15 (0.72–13.83)	0.129	Our enrolled study Veterans who were female signaled a ~3 times greater odds ratio of PONV than did enrolled male Veterans

All patients received regional anesthesia (spinal with peripheral nerve blocks), intraoperative propofol sedation, no general anesthesia, perphenazine 8 mg *per os* (before surgery), and ondansetron 4 mg IV (end of surgery), per protocol. PONV, postoperative nausea and vomiting; POD, postoperative day; CI, confidence interval; EMR, electronic medical record(s); EtOH, ethanol; N/V, nausea/vomiting (of any etiology, not restricted to PONV). Based on all measures and bivariate analyses listed in Supplementary Table 2a, predictive factors ($P < 0.05$, and gender, based on prior literature) and signals ($P \geq 0.05$, rounded up to $P \leq 0.2$) of PONV were identified and modeled using most parsimonious multivariable logistic regression (shown above), to obtain odds ratio estimates of each included measure, while simultaneously adjusting for all other variables included in the model. It should be noted that peptic/gastric ulcer ($P = 0.068$, signaling more PONV) and epilepsy/seizure variables ($P = 0.138$, signaling less PONV), both from Supplementary Table 2a, were excluded from the modeling above, due to too small sample sizes for those conditions. The sequence of removing variables chosen from Supplementary Table 2a to create the most parsimonious model, beginning from the least predictive, is bullet-listed below. The *P*-values for these bulleted measures (in the full model, before parsimonious transformation) were all >0.1 (data not shown). Sequence of removed variables from the full model to the most parsimonious model. The following bullet point factors were excluded ($P > 0.1$, but <0.2) from the parsimonious multivariable model above, in order of least to most statistically signaling (i–v, below), and should be interpreted (from our limited sample) as factors or signals for PONV still to be determined (likely related to underpowering). (i) Day 1, maximum pain score with movement (0–10). (ii) History of non-surgical nausea, per EMR review. (iii) Smoking history, baseline/preoperatively—only 7 of 115 Veterans were contemporaneous smokers at the time of surgery, due to a surgical requirement for being a non-smoker (non-user of any nicotine) at the time of the surgery; this requirement was enforced soon after study recruitment began. (v) Surgical procedure (hip vs. knee arthroplasty). (iv) Past PONV, per history or per EMR review.

(with the ITM procedure typically accompanied by a five-drug AEPPx, vs. case-matched historical controls *not* receiving ITM and *not* receiving a five-drug AEPPx). Institutional approval was obtained recently on 19 February 2025 (approval/exemption 1670098, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA), allowing for tracking and external reporting of QI outcome data. In the previous publication (2), we had shown in this retrospective, case-matched QI series that a five-drug AEPPx was significantly protective against PONV (vs. non-ITM and typically four drugs or less for PONV prophylaxis). The five-drug AEPPx regimen included (predominantly) palonosetron, perphenazine, aprepitant, diphenhydramine, and dexamethasone (2). After VA Pittsburgh IRB approval/exemption, for $n = 468$ Veterans, we collated and analyzed EMR and subsequently used SPSS (Version 29, IBM, Armonk, NY, USA) to generate cross-tabular chi-square tests (data not shown) and multivariable logistic regression (data shown below), with a liberal *P*-value ($P < 0.1$) to also identify potential signals ($P \geq 0.05$ and $P < 0.1$), to inform future risk factor research, and to compare PONV-free patients with patients that experienced PONV, first on POD#0–1 after surgery and (separately) on POD#2 (after no PONV on POD#0–1). The overview of results from both the RA and GA analyses (Table 2) is displayed adjacent to each other.

The inclusion and exclusion criteria for the RA and GA studies are previously described (2, 6).

TABLE 2 Summary of associated predictors and potential signals of PONV in Veterans undergoing RA POD#0–2, adjacent to Veterans factors/signals when undergoing GA (from Tables 3, 4, with separate GA assessments across POD#0–1 and POD#2, after no PONV on POD#0–1), for thorough evaluation of both contemporary and historical predictors of PONV risks.

Variables	PONV after RA POD#0–2	PONV after GA POD#0–1	PONV after GA POD#2 (after no PONV on POD#0–1)
Associated predictors of PONV			
Diabetes mellitus (if diabetes, then *less* PONV)	Y	Y	TBD
Oral morphine equivalent increments (0–24 h)[a]	Y	TBD	TBD
African-American/not Caucasian	Y	Y	TBD
Age (year increments; if *younger* age, then *more* PONV)	TBD	Y	TBD
"Bundle" of intrathecal morphine (ITM), five-drug AEPPx, and no IV opioids on POD#0 (if bundle, then *less* PONV)	TBD	Y	TBD
Any upper GI conditions	TBD/Y[b]	Y	TBD
Alcohol use	TBD/Y[c]	Y	TBD
Vietnam War Veteran	TBD	TBD	Y
ITM dose (per incremental microgram)[a]	TBD	TBD	Y
Anxiety diagnosis in EMR	TBD	TBD	Y
Potential signals/predictors of PONV predictability			
Past PONV[a]	Y (signal)	TBD	Y (signal)
Recent nausea or vomiting, per study survey responses 1–4 weeks in advance of surgery	Y	TBD	TBD
History of nausea listed in EMR, but unrelated to specific surgical encounters	Y (signal)	Y (predictor)	TBD
Marijuana-related use, or unhealthy patterns of EtOH use, at preoperative baseline	Y	TBD	TBD
Baseline opioid use at the time of surgery[a]	Y	TBD	TBD
History of vomiting listed in EMR, but unrelated to specific surgical encounters	Y	TBD	Y (predictor)
Female gender[a]	Y (signal)	TBD	TBD
History of any vertigo-related diagnoses[a]	TBD	Y (signal)	Y (predictor)
History of any headache diagnoses	TBD	Y (signal of less PONV)	Y (predictor of more PONV)
Highest pain score difference from baseline on POD#1	TBD	Y (signal)	TBD
Smoking history, baseline preoperatively	Y (signal)	TBD	TBD
Surgical procedure as hip but not knee arthroplasty	Y (signal)	N/A	N/A

See Supplementary Tables 1a,b for all potential predictors evaluated, since those not included in Table 1 herein may simply have been underpowered.
[a]Indicates PONV risk factors expressed or implied by the original criteria of Apfel et al. (11). TBD, to be determined, with respect to either (i) data not analyzed in the report herein or (ii) data analyzed, showing no predictive or signaling relationship, but potentially underpowered in the datasets reported herein.
[b]Indicates (from Supplementary Table 2) that peptic/gastric ulcer was a signal of PONV ($P = 0.068$) after RA, but "any upper GI condition" was not a signal or predictor as an all-encompassing factor/variable for RA PONV.
[c]Indicates (from Supplementary Table 2) that alcohol/marijuana use was a factor predicting more PONV in the RA group. PONV, postoperative nausea and vomiting; RA, regional anesthesia; GA, general anesthesia; ITM, intrathecal morphine; AEPPx, antiemetic prophylaxis; GI, gastrointestinal; EMR, electronic medical record; POD, postoperative day.

3 Results

3.1 RFs for both RA and GA

Significant RFs for higher PONV risk, common to both RA and GA on POD#0–1, included (i) absence of diabetes mellitus, (ii) African-American/non-Caucasian race/ethnicity, (iii) peptic ulcer/gastric ulcer/any upper gastrointestinal conditions, and (iv) alcohol use (Table 2 and Supplementary Table 2).

3.2 RFs relevant to RA only (without GA)

Significant RFs relevant and specific to RA on POD#0–2 (Table 2) included (i) oral morphine equivalents consumed postoperatively, as an incremental (step) function, (ii) any recent nausea or vomiting (within ~2 weeks of the joint replacement nerve block study date), (iii) baseline opioid use, (iv) history of any vomiting that was not related to PONV, and (v) female gender.

3.3 RFs relevant to GA (with or without ITM)

We identified significant RFs relevant to GA on *both* POD#0–1 and POD#2 (separately, specifically when there was no PONV POD#0–1; Tables 2–4). These RFs, both POD#0–1 and POD#2, included (i) history of any headache diagnosis and (ii) vertigo or history of any vertiginous diagnoses (such as Ménière's disease, associated with *more* PONV). Significant RFs relevant to GA on POD#0–1 specifically (Tables 2, 3) included (i) younger age on date of surgery (associated with *more* PONV); (ii) a "bundled" factor entailing ITM, five-drug AEPPx, and no IV opioids on day 0 (associated with *less* PONV); (iii) history of past nausea (on EMR query) not necessarily occurring in the postoperative

TABLE 3 Predictive factors and potential signals of PONV prediction on POD#0–1 in Veterans undergoing general anesthesia: a multivariable logistic regression model.

Variables	Reference group	PONV on POD#0–1: odds ratio (95% CI)	*P*-value
Associated predictors of PONV			
Age (per-year increments)	N/A	0.96 (0.94-0.98)	<0.001
"Bundle" of ITM, five-drug AEPPx, and no IV opioids on POD#0	"Partial bundle" or "no components of bundle"	0.34 (0.18–0.64)	<0.001
History of nausea listed in EMR, but unrelated to specific surgical encounters	No history of nausea	2.23 (1.24–4.02)	0.008
Not Caucasian	Caucasian	2.30 (1.18–4.49)	0.015
Any upper GI conditions	No upper GI conditions	2.12 (1.14–3.91)	0.017
Diabetes mellitus	No diabetes	0.46 (0.23–0.91)	0.025
Alcohol use	Audit C score ≤3/12	0.42 (0.19–0.92)	0.031
Potential signals of PONV predictability			
History of any vertigo-related diagnoses	No prior vertigo-related diagnoses	1.84 (0.92–3.69)	0.083
History of any headache diagnoses	No prior headache diagnoses	0.54 (0.26–1.10)	0.089
Highest pain score difference from baseline on POD#1	n/a	1.07 (0.99–1.17)	0.103

PONV, postoperative nausea and vomiting; GI, gastrointestinal; POD, postoperative day; ITM, intrathecal morphine; EMR, electronic medical record; AEPPx, antiemetic prophylaxis; "five-drug," palonosetron, perphenazine, aprepitant, diphenhydramine, and dexamethasone: the now-recommended (15) doses of the five drugs to be given before operating room entry are palonosetron (150–250 μg IV), perphenazine 8 mg PO (4 mg if over age 75, and none if Parkinson's/related), aprepitant (40 mg PO), diphenhydramine (12–20 mg IV), and dexamethasone (8 mg IV). Interpretation: We identified factors and signals relevant to GA-related PONV on POD#0–1. Signals were (i) history of any headache diagnosis (associated signal of less PONV), (ii) vertigo or history of any vertiginous diagnoses (such as Ménière's disease, associated signals of more PONV), and (iii) the highest pain score difference from baseline on POD#1 (associated signal of more PONV). Significant factors on POD#0–1 were (i) younger age on date of surgery (associated with more PONV); (ii) a "bundled" combined factor entailing ITM, five-drug AEPPx, and no IV opioids on day 0 (associated with less PONV); (iii) history of nausea listed in EMR, but unrelated to specific surgical encounters (associated with more PONV); (iv) non-Caucasian race/ethnicity (associated with more PONV); (iv) any upper GI conditions (associated with more PONV); (v) diabetes mellitus (associated with less PONV) and problematic alcohol use contemporaneously with the surgical date (associated with *less* PONV). We acknowledge that problematic alcohol use or cannabis use (as a merged variable) was a signal (in Table 1) of *more* POD#0–2 PONV after regional anesthesia (without GA).

TABLE 4 Predictive factors and potential signals of PONV prediction on POD#2 in Veterans undergoing general anesthesia, specifically after no PONV on POD#0–1: a multivariable logistic regression model.

Variables	Reference group	PONV on POD#2: odds ratio (95% CI)	*P*-value
Associated predictors of PONV			
Vietnam War Veteran	Not a Vietnam War Veteran	3.60 (1.68–7.70)	0.001
ITM dose (per incremental microgram)	No ITM used	1.00 (1.00–1.01)	0.002
History of any headache diagnoses	No prior headache diagnoses	3.05 (1.37–6.78)	0.006
History of vomiting listed in EMR, but unrelated to specific surgical encounters	No EMR history of vomiting	2.37 (1.21–4.66)	0.012
History of vertigo-related diagnoses	No history of vertigo-related diagnoses	0.23 (0.06–0.83)	0.025
Anxiety	No anxiety diagnoses	2.07 (1.00–4.28)	0.049
Potential signals of PONV predictability			
Past PONV	No history of PONV	2.57 (0.99–6.68)	0.054

PONV, postoperative nausea and vomiting; ITM, intrathecal morphine; POD, postoperative day; AEPPx, antiemetic prophylaxis; EMR, electronic medical record; "any vomiting," any vomiting, *neither* related to PONV *nor* corresponding to contemporaneous surgery. Interpretation: Significant risk factors relevant to increasing PONV risks after GA on POD#2 specifically (after encountering no PONV POD#0–1) were all associated with more PONV and entailed (i) Vietnam War Veteran; (ii) step function related to higher ITM doses; (iii) history of headache per EMR, forecasting more likely PONV on POD#2; (iv) history of any vomiting (in EMR review) that was not PONV; (v) anxiety; and (vi) past PONV. A "ping-pong" possible effect is noted regarding headache reported in the EMR, in that on POD#0–1, headache was a signal of possibly less PONV (Table 3), whereas on POD#2, headache was an associated predictor of more PONV (Table 4). It is conceivable that our patients may have taken their headache medications on the day of (or day before) surgery, leading to less associated PONV on POD#0–1, but that repeat doses of headache prevention measures postoperatively may have been missed and therefore associated with a headache recurrence also manifesting as PONV. Finally, patients with vertigo-related diagnoses may have had less PONV on POD#2 (odds ratio 0.23) after having had no PONV on POD#0–1 because their antivertigo medications may have been continued on schedule throughout the perioperative process. Future study of this signal-then-reversed-predictor interaction may be relevant for future patient care.

setting (associated with *more* PONV); and (iv) postoperative peak pain score difference from baseline pain score preoperatively (*higher* pain scores above baseline associated with *more* PONV). Signals/RFs, all relevant to *increasing* PONV risks after GA on POD#2 specifically (Tables 2, 4) after encountering *no* PONV POD#0–1, entailed (i) Vietnam War Veteran, (ii) step function related to higher ITM doses, (iii) history of any vomiting (in EMR review) *not* related to PONV, (iv) anxiety, (v) past PONV, and (vi) headache diagnoses (per EMR).

4 Discussion

4.1 PONV as a potential race/ethnicity inclusion/pharmacoequity issue

Based on the results, some existing and some novel PONV RFs seem to warrant further attention. To date, non-Caucasian race has not been associated with an increased risk of PONV [except for the recently declared higher risk in the Chinese population

(10); patients of Asian descent were not present in our case series described]. In our analyses, non-Caucasian race/ethnicity status was statistically significant for more PONV associations in both RA and GA contexts, compelling future analyses in both Veteran and civilian populations to uncover potential pharmacoequity-related considerations.

4.2 Could race/ethnicity RFs, and other novel findings, now dominate traditional RFs, particularly if "new customers" have had no known PONV history, since they had not previously undergone anesthesia/surgery?

Some traditional RFs for PONV remained significant for some of the analyses run, but no traditional Apfel factors (11) were found predictive across all analyses. Other traditional RFs, such as non-smoker, were not significant in our models, which may introduce the possibility of some of these Veteran-centric (or RA-related) factors being potentially more dominating than some traditional RFs (11), pending further study. Again, we are not aware of either the Veterans or the RA populations having had representative RF-based analyses regarding PONV. Further refinement of these factors in Veterans, including those which appear to be novel, may prove to be more statistically robust than traditional (11) factors, which then could compel re-examination of these novel RFs in the general population.

4.3 Recently identified other predictors of PONV, including PONV on POD#2 after not encountering PONV on POD#0–1

Recent studies have shown other predictors of PONV, not necessarily specific to POD#2, after not encountering PONV on POD#0–1. First would be semaglutide and glucagon-like peptide-1 (GLP-1) agonists promoting PONV (12), and another would be cannabis-related products (13, 14). Our group's work showed oral sustained-release dextromethorphan as a POD#2 PONV predictor after no PONV on POD#0–1 (15), particularly (consistent with its package insert) related to cumulative doses of opioid-sparing dextromethorphan over consecutive days. This suggests the potential meaningful value of proposed booster AEPPx throughout the hospital stay, as non-opioid analgesic efforts, such as the dextromethorphan and celecoxib, still appear to be associated with unwanted PONV at POD#2 (15). Furthermore, the same recent study (15) found that a "bundle" of ITM including magnesium, as well as diabetes mellitus, was associated with protectors against PONV on POD#2 (15) after no PONV on POD#0–1.

4.4 Limitations

Intraoperative "usual opioids" (i.e., fentanyl and hydromorphone) and our efforts to reduce or eliminate their use intraoperatively over time are reported elsewhere (15). Strategies for ITM dosing are also reported elsewhere (16).

Larger-sample prospective analyses involving newly identified predictive variables, and potential signals, may be warranted in both Veteran/active duty and civilian populations undergoing RA and/or GA to allow for better generalizability. It is also important to recognize that RFs differed significantly from POD#0–1 to POD#2 when analyzing the GA population, and one limitation of the data included herein is the lack of such analysis in the RA population. However, the RA risk factor query (which took place in 2023) was, in part, designed to inform our future queries in the wider, larger-sample GA population (with these GA case EMR reviewed in 2024).

Veterans may be anecdotally considered a low-risk population for PONV. However, Veterans have not been specifically studied in the present or past PONV consensus guidelines, nor have patients who specifically received ITM. Therefore, forecasts of five-drug PONV prophylaxis success in ITM cases may differ in the non-Veteran (with or without ITM) population. To offset this limitation, we allowed for signals (with $P \geq 0.05$ but ≤ 0.1) into our final regression equations, often representing non-traditional but potentially interacting risk factors, to query for potential epidemiologic influence (or "bedside habit" influence) beyond traditional PONV risk factors.

Other "mixed signals" from our data include seizure disorder (possibly PONV-protective, data not shown) and peptic/gastric ulcer history (possibly PONV-predictive) and should be queried during history-taking (Table 2). Another recommendation, related to our recent report (2), is that a low-cost, off-patent five-drug AEPPx could be administered before any/every anesthetic, to offset insufficient sensitivity/specificity of past and present PONV consensus guidelines not yet incorporating these emerging factors, further promoting equity and inclusion, via *primary prevention* (pending further refinement of data).

Next, the RA cohort had case report form data that were completed in real time (including graded severity by the patient), while the GA cohort's PONV was only determined via *post hoc* EMR QI review (without patient-reported severity grading). This forced a simpler overall dichotomous capture (no/yes) for all PONV data presented, although it seems conceivable that RA-based nausea would likely seem less severe than GA-based nausea if coexisting opioid load was otherwise constant.

Finally, we acknowledge that we were unable to derive and present expected *a priori* sample size determinations and power analyses. Our observations are limited to a single-center US Veterans Affairs population, which may not generalize to broader, diverse patient populations. For the GA/QI observational study, we could only "case match" cases that were performed and assess similar historical control cases performed at the same institution in the described time periods as comparators. It is difficult to expand an observational sample size (with limited resource support) to cases that are neither present in one's institution nor present in the institution's medical record archive. Future work by other research teams expanding the cohort and including non-Veteran populations

would likely enhance applicability. Using the described consecutive caseload, our goal was to provide preliminary data for external researchers to create their own cohorts (such as in non-Veteran populations) or prospective randomized study groups incorporating the described paradigm shifts, as soon as the significant findings and signals were noted in analysis.

5 Conclusions

CG-AEPPx decisions based on restricted consideration of 1990s-generated RFs (11) may require new attention to detail, particularly in African-Americans, Veterans, and/or patients undergoing procedures with RA (with or without GA). We recommend that all Veterans and all RA and GA patients (if not patients overall) could first benefit from more detailed history-taking (querying all listed factors and signals in Table 2) to include diabetes status, *recent* nausea/vomiting unrelated to surgery/anesthesia, *any* past vomiting unrelated to surgery/anesthesia, regular consumption of any marijuana-related substances (13, 14), unhealthy patterns of alcohol consumption (based on data herein), baseline opioid use (therapeutic or illicit), or history of any headache or vertiginous diagnoses (based on data herein). We confidently suggest that race/ethnicity [(i) African-American (Tables 1–3), based on our data; (ii) Chinese, as recently (10) reported; and (iii) Hispanic, other races and ethnicities, and those with US Medicaid health coverage (17)] represents an opportunity to properly address pharmacoequity for, what now appears to be, a largely preventable symptom complex. Specific to the GA analysis (Tables 3, 4), the proportion of Veterans who *did not* experience PONV on POD#0–1, but experienced PONV on POD#2, prompts the need for further investigation of a possible "rebound PONV" phenomenon (18, 19), querying further for associated RFs extending beyond the Veteran population.

Because of the vast array of new predictors identified, it may instead be more reasonable to simply entrust the recently described (2, 15) five-drug AEPPx for all patients as a rational and inexpensive centerpiece of compassionate care, instead of querying the somewhat complex and interwoven new RFs identified. As a corollary, it may be acceptable to "let go" of legacy PONV CG RFs as the sole driver of AEPPx decisions, due to possibly insufficient sensitivity/specificity of said legacy CG RFs, described before the inexpensive options that palonosetron and aprepitant now represent in the tool box of the anesthesia team and other stakeholders, and before any other studies (observational or otherwise) incorporated a fifth drug/category.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the VA Pittsburgh Healthcare System, Pittsburgh, PA, USA. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

CS: Data curation, Investigation, Methodology, Resources, Software, Writing – review & editing, Writing – original draft. RC: Conceptualization, Data curation, Investigation, Methodology, Resources, Software, Writing – original draft, Writing – review & editing. JM: Data curation, Investigation, Methodology, Resources, Writing – review & editing. MB-K: Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Writing – review & editing. BW: Conceptualization, Data curation, Investigation, Formal analysis, Supervision, Methodology, Resources, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fanes.2025.1631506/full#supplementary-material

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