Upgrading intrathecal morphine for postoperative pain mitigation in abdominal surgery: an exploratory multiple regression analysis of observational data addressing co-administered spinal magnesium sulfate, *en route* to both enhanced systemic opioid sparing and opioid avoidance

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Background: For major abdominal surgery, we explored "usual" opioid-avoiding effects of spinal magnesium 25 mg added to intrathecal morphine (250+ µg in women, 300+ µg in men; ITM + Mg$^+$). We evaluated associated benefits of several integrated care "bundles": 5-drug antiemetic prophylaxis, multiple-day postoperative antiemetic boosters (perphenazine and aprepitant), boosters for non-opioid transitional analgesia, *and strategically-avoided* usual opioids intraoperatively (fentanyl, hydromorphone, etc.). We also explored antiemetic outcomes, and pruritus, on postoperative days 0−2. We hypothesized these bundles would independently and interactively influence associated outcomes.

Methods: We used a mixed-method framework to demonstrate whether these bundles, integrated with ITM + Mg$^+$, were *all* associated with one or more milestones *en route* to improving described outcomes [prevented postoperative nausea/vomiting (PONV), avoided postoperative opioids, etc.]. We did so via retrospective, case-matched quality improvement methodology for a single-hospital population of ITM-receiving Veterans, applying multiple regression to determine (i) PONV prevention success on days 0−1 separately from day 2, (ii) success of avoiding usual opioids (by withholding discretionary fentanyl/hydromorphone intraoperatively *en route* to avoiding the need for patient-requested hydromorphone/oxycodone postoperatively), and (iii) predictors/signals of itching, including related to the ITM-upgrade to ITM + Mg$^+$.

Results: ITM + Mg$^+$, at the described doses, supported by 5-antiemetic prophylaxis *and* three-drug non-opioid transitional analgesics, was associated with significant opioid-avoiding improvements. Postoperative avoidance of usual opioids was associated with *both* ITM + Mg$^+$ use *and* intraoperative and immediate postoperative avoidance of "usual opioids" (fentanyl, hydromorphone, etc.). PONV on days 0–1 (vs. day 2) appears to have differing predictor patterns, warranting *both* 5-MMAEPPx preoperatively, *and* future antiemetic upgrade from 2-drug booster prophylaxis (perphenazine/aprepitant) to also include palonosetron every 40 h. ITM historical control major abdominal surgery cases *before* ITM + Mg$^+$ had a 14% "usual opioid avoidance rate" (35/246), which showed significant associated improvements with ITM + Mg$^+$ use, usual opioid avoidance, and integration with the other described care bundles (34/60, 57%, $P < 0.001$).

Conclusion: Multiple "bundles" appear to address *both* sustained antiemetic success *and* "usual opioid avoidance." ITM-related pruritus requires further study regarding prophylaxis and treatment, in order to allow ITM + Mg$^+$ to achieve its full enhanced recovery potential, when trying to avoid postoperative exposure to usual opioids.

1 Introduction

This manuscript (a) addresses minimizing postoperative exposure by combining preservative-free magnesium sulfate (MgSO$_4$, or simply Mg$^+$; at a dose of 25 mg) to intrathecal morphine (ITM), and (b) follows our 2023 [1] and 2025 [2, 3] publications addressing postoperative nausea and vomiting (PONV) prevention with vs. without ITM, alongside an off-patent 5-drug Multimodal AntiEmetic ProPhylaxis (5-MMAEPPx) combination.

5-MMAEPPx has shown an associated ~95% PONV prevention success on Postoperative Day (POD) zero, and ~90% success on POD#1, without booster antiemetic dosing [1–3], but POD#2 PONV effects thereafter are unknown. 5-MMAEPPx was first [1–3] developed for our institution's intrathecal morphine (ITM) enhanced recovery protocol for major abdominal/truncal surgery under general anesthesia (GA) in early 2021. Our objectives now include extending further observations addressing whether our MMAEPPx/ITM successes could be further leveraged into both meaningful opioid-sparing and continued antiemetic benefits (e.g., POD#2).

Specifically, we presume that any "usual" opioid exposure intraoperatively may trigger *new persistent opioid use* (NPOU); we ask the necessary question of "how successful can we be in avoiding downstream opioids by *primary prevention* (of exposure) via *strategic avoidance* in the operating theater?" As a frame of reference, we previously reported [2] that ITM use with day-of-surgery (DOS) 5-MMAEPPx was associated with 17% success (10/58 cases) of averted need for any intravenous (IV) or *per os* (PO) opioids during/after bariatric surgery (on POD #0–1) in-hospital. Importantly, this 17% success in bariatrics [2] was observed when in-hospital postoperative follow-up (i.e., non-

opioid analgesic and antiemetic boosters) was fully systematized in a comprehensive enhanced recovery protocol [2]. We now aim to evaluate observations across other types of surgery (including bariatrics) regarding enhanced analgesic and antiemetic quality, via several interacting "bundles" in an enhanced recovery integrated care plan. First, (i) ITM would be supplemented by preservative-free magnesium sulfate (ITM + Mg$^+$) in the same spinal [4–6] without local anesthetic, while (ii) strategically withholding all "usual" intraoperative opioids (fentanyl/hydromorphone, etc.). Next (iii), 5-MMAEPPx routine preoperative dosing would be continued, while adding (iv) MMAEPPx scheduled booster dosing after surgery through at least POD#2 (we tested two drugs, but recommend three for future work). The next care bundle, (v), provides 3-drug, non-opioid, pre- and postoperative analgesic boosters to create necessary transitional analgesia once the ITM + Mg$^+$ analgesic dose effects dissipate. We consider these concepts (i–v) as separate but interacting care "bundles" informed by a "sixth bundle" care concept: (vi) that POD#2 AEPPx should incorporate any different risk factors that emerge for POD#2 separately from expected PONV risk factors on POD#0–1, and that pruritus should be tracked and addressed.

The aims are to quantify how (a) ITM + Mg$^+$ (and the described enhanced recovery multimodal booster dosing, i.e., bundles [i] and [ii–v]) may yield better associated antiemetic *and* analgesic outcomes, than does plain ITM and single-dose 5-MMAEPPx, (b) the extent to which POD#0–1 vs. POD#2 have differing PONV-predictor patterns and pruritus issues when ITM + Mg$^+$ is used (i.e., bundle [vi]), (c) ITM + Mg$^+$ in tandem with pre-and post-operative non-opioid multimodals (both analgesics and antiemetics, bundles [iv, v]) may be associated with a meaningful, associated significant downstream opioid

avoidance, higher than our reported 17% (2) success rate above with ITM-only, particularly when usual IV opioids (fentanyl, remifentanil, hydromorphone—bundle [ii]) are *deliberately avoided* in the operating room, and (d) avoiding after-OR IV opioids being achievable via better analgesia from ITM + Mg$^+$, and associated avoidance of opioid-induced itching (bundle [vi], as opposed to considering pruritus simply as a "fact of life" side effect from ITM ± Mg$^+$).

2 Materials and methods

2.1 Ethics approval

As in our prior (2) report, this was an IRB-approved quality improvement (QI) initiative, exempt from patient research consent above and beyond clinical surgery and anesthesia consent. Institutional approval (approval/exemption 1670098, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA, most recently on 19 February 2025) allowed for tracking and external reporting of QI outcome data. For this report, we focused specifically on GA patients undergoing ITM + Mg$^+$, and ITM case-matched controls.

2.2 External reporting precedents and guidance; patient identification/selection, and data collation

As previously (2) reported, following STROBE guidelines, we disclosed 5-MMAEPPx as institutional standard of care for ITM recipients, soon after our group's earliest case series (7) was accepted for publication [addressing joint replacement surgery (7) under bupivacaine spinal including ITM]. The *institutional standard of care* status was further reinforced after a subsequent publication (1). Patients having received both ITM (±Mg$^+$) and GA were then case-matched as follows. We retrospectively reviewed QI data from our single United States (US) Veterans Administration hospital. As with our previous publications (1, 2), case matching was by the lead author (BAW), described further below (Section 2.5). Consecutive ITM + Mg$^+$ cases from 1 February 2024 through 9 October 2024 ($n = 60$) were matched with ITM (without Mg$^+$) cases ($n = 246$) occurring no earlier than 9 March 2021. Of the $n = 246$, $n = 154$ were previously case-matched with GA-sans-ITM cases in a previous publication (1). The remaining 92 ITM cases (without Mg$^+$) were (a) not previously matched to non-ITM cases ($n = 71$), or (b) specifically matched to ITM + Mg$^+$ cases since February 2024, or previously reported (1, 2) ITM or non-ITM GA cases previously published ($n = 21$). Of the $n = 60$ ITM + Mg$^+$ cases, $n = 45$ cases were matched with the $n = 154$ previously-reported (1) ITM cases (in ratios most commonly ranging from 1:1 to 1:4). The remaining 15 ITM + Mg$^+$ cases were matched (in similar ratios) with previously unpublished $n = 71$ ITM cases. By the time that ITM + Mg$^+$ was initiated in February 2024, the following enhanced recovery processes were already co-established as

ITM-related local standards: (a) 2-drug antiemetic booster dosing (bundle [iv]), and (b) oral non-opioid analgesics entailing acetaminophen, a COX-2 inhibitor (usually celecoxib), and dextromethorphan (8) *both* pre- *and* post-operatively (bundle [v]).

2.3 Anesthesia and related enhanced-recovery procedures

2.3.1 Spinal/intrathecal analgesia: technical details

Our spinal needles were primarily pencil-point, 24–25G, selected for directionality of injectate flow, described by Urmey et al. (9), along with goals of avoiding post-dural puncture headache and/or diplopia (10). Preservative-free MgSO$_4$ (25–50 mg) was assumed to render injectates hyperbaric. Sterile water was the diluent, rendering a likely hypobaric effect (without Mg$^+$) when the usual 2–3 ml morphine-water volume was injected, so we anticipated ITM + Mg$^+$ in 3 ml to be hyperbaric, possibly imparting inadequate cephalad spread to achieve desired dermatome-focused analgesic effect. Future study will be needed to ultimately determine actual baricity with varying water diluent volumes. No local anesthetic was included in these injectates. Lead author BAW, based on decades of clinical experience with spinals, selected ∼8 ml as the volume start-point for water + ITM + Mg$^+$, with volume adjustments considered up or down if needed; no volume changes were deemed necessary after $n = 60$ recorded ITM + Mg$^+$ injections (or since then). "High spinal" was of relatively little concern (i.e., cardio-accelerator fiber anesthesia at T1-T4, or respiratory center anesthesia at C2–4), in the absence of bupivacaine/local anesthetics.

2.3.2 Enhanced recovery: established process details

In the process roll-out for ITM + Mg$^+$ (bundle [i]), we had already (contemporaneously) enhanced our preoperative (5-drug, bundle [iii]) and around-the-clock postoperative (2-drug, aprepitant and perphenazine "booster prophylaxis," bundle [iv]) MMAEPPx strategy, in tandem with the described non-opioid analgesics (and their daily [or more frequent] booster doses, bundle [v]). Our 5-MMAEPPx plan was "supersized" from palonosetron 75–150 μg IV, after early, ITM-induced pruritus tendencies (and anecdotal cumbersomeness) were observed with 50 mg MgSO$_4$. By this point, dexamethasone was already commonly "supersized" from 4 to 8 mg (IV), based on analgesic success with antiemetic doses approaching 0.1 mg/kg, reported elsewhere (11). We also directed focus to strategically avoiding "usual" intraoperative IV opioids (bundle [ii]) during and after surgery, in an effort to also avoid the need for "usual" PO opioids postoperatively, via IV opioid-induced acute hyperalgesia, particularly since ITM + Mg$^+$ would have already been in place. In the process, we opted for not only pan-prophylaxis against PONV, but also *deliberate avoidance of any exposure to "usual" opioids* during (bundle [ii]) or after surgery, specifically fentanyl, remifentanil, hydromorphone, and oxycodone/hydrocodone/tramadol, all of which we consider high abuse-liability opioids (HALO). We do not consider ITM ± Mg$^+$ as "HALO", given no

documented euphoria, tolerance, or hyperalgesia descriptions of such with single-injection ITM exposures (OVID Medline, last accessed 22 November 2024). All described interventions, regardless of *a priori* PONV risk factors, had already been actively implemented for consecutive cases in advance of February 2024, at the time of initiating ITM + Mg$^+$ (instead of plain ITM). Spinal procedures occurred in a separate location outside the operating room, as previously described (12), and as was the case in our most recent report in this journal (2).

2.4 Setting and participants, study size, and bias

As with our previous reports (1, 2), patients whose data were reviewed were already-hospitalized Veteran inpatients presenting for surgery, or were known in advance of surgery to be admitted to the hospital after surgery. ITM + Mg$^+$ cases ($n = 60$, bundle [i]) occurred after the February 2024 addition of MgSO$_4$ to our previous ITM program ($n = 246$). The total case number was a convenience sample, with no *a priori* power calculations. Regarding sample size and statistical power, our statistician co-author (MYBK) was consulted, and informed us regarding *post hoc* power analysis in such observational inquiries as being of questionable value (13–18). For this study, we could only (a) "case match" cases that were performed, and (b) assess similar historical control cases performed at the same institution as comparators. Based upon literature (13–18) focused on power analyses to assess reliability of research results, and to inform future research conducted, the application of *post hoc* power analysis seemed questionable due to concerns about the conceptual basis for such tests. We acknowledge *post hoc* power analyses as often being requested during peer review with the presence of *non-significant* results, to be able to assess if the same effect size would be statistically significant given a larger sample size, or to determine what effect size would have been required to be able to detect a difference between the same sample size groups. However, the purpose of these analyses for this specific query is unclear, and may be conceptually flawed, as described in the literature (13–18). No further efforts were made to address potential sources of bias, other than those listed above.

2.5 Quantitative variables, and statistical methods

2.5.1 Surgical setting

As reported (2), the setting was a single US Veterans hospital, this time with ITM + Mg$^+$ cases matched with prior (1, 2) ITM-only cases. The ITM ± Mg$^+$ cases represent a retrospective review of quality improvement (QI) data. Institutional approval (approval/exemption 1670098) within this report entailed tracking and external reporting of GA + ITM (or GA + ITM + Mg$^+$) data, while GA (without ITM) case-matched controls were previously (1) reported.

2.5.2 Bariatric-specific

Our queries first include a consecutive case cohort of Veterans undergoing ITM-only ($n = 60$) or ITM + Mg$^+$ ($n = 13$, bundle [i]) administration for bariatric surgery under GA. Sleeve gastrectomy and Roux-en-Y gastric bypass were the only "all-endoscopic" and/or "all-robotic" procedure types with necessary case volume for meaningful exploratory analysis. Descriptive statistics for these cases are presented in Supplementary Table S1. No PONV differences were seen based on ITM + Mg$^+$ in this limited sample, so we constructed logistic regression models for PONV occurrence(s), identifying bundles of potentially novel factors ($P \leq 0.05$) or signals ($P > 0.05$ but ≤ 0.175), as depicted in Table 1, Panels 1a,b, for PONV on POD#0–1 *and* POD#2, respectively. These factors and signals would then inform similar modeling across our entire ITM population (Table 2, Panels 2a,b, see below Section 2.5.3), i.e., not just restricted to bariatrics. Table 1, Panel 1c, addressed bundles of factors (or signals) associated with any downstream HALO opioid use (IV or PO) after bariatric operating room exit. After this, we addressed factors/signals associated with itching (Table 1, Panel 1d) requiring a nursing intervention.

2.5.3 Entire single-center ITM ± Mg$^+$ population

For the next analyses (after bariatrics-only, above), all ITM cases with GA (within or outside of bariatrics, including general/colorectal, and genitourinary major cancer) were queried to evaluate ITM without Mg$^+$ ($n = 246$) or with ITM + Mg$^+$ ($n = 60$, bundles [i–vi], all of which having been case-matched with at least one ITM-without-Mg$^+$ case). There were no non-ITM historical controls in this analysis (similar to the bariatrics analysis above in Section 2.5.2). Again, we constructed logistic regression models to identify novel factors ($P \leq 0.05$) or to signal potential predictors. These ($n = 306$) updated PONV outcomes are described below, along with HALO avoidance success and itching incidence. Descriptive statistics for these are presented in Supplementary Table S2. As with the Table 1 (*bariatric only*) panels described above, Table 2, Panels 2a,b address POD#0–1 and POD#2 PONV, respectively, while Table 2, Panel 2c, addressed downstream HALO opioid use (IV or PO) after operating room exit, and Table 2, Panel 2d addressed postoperative itching *across all ITM case types*.

2.5.4 Case-matching details

Similar to previous (1, 2) reports, for both bariatric-specific and expanded case analyses as described, case matching by lead author BAW utilized common procedural terminology codes, American Society of Anesthesiologists Physical Status designation, age, gender, surgery duration, and body mass index. Sleeve gastrectomy was coded separately from other bariatric (Roux-en-Y procedure) and general/genitourinary (usually colorectal or other cancer-related) surgery procedures. The sleeve gastrectomy nuance was incorporated based on statements from the International Society for Perioperative Care of the Patient with Obesity (ISPCPO) and the American Society for Metabolic and Bariatric Surgery (ASMBS), describing higher PONV risks for

TABLE 1 Panels 1a–d; multivariable logistic regression models after bariatric surgery (with ITM or ITM + Mg$^+$), outlining (1a) predictors of PONV on POD#0–1; (1b) predictors of PONV on POD#2 (after no PONV on POD#0–1); (1c) predictors of HALO Use on POD#0–2; and (1d) predictors of itching.

Panel 1a: Model coefficient for bariatric PONV on POD#0–1 (with 95% CI for factors/signals), P values	Excluded variables (P values)
Constant: 0.005; P = 0.33	Past PONV, per EMR (0.248)
Sleeve Gastrectomy: 94.0 (1.56–5,667), **P = 0.030**	Diabetes, vs. non-diabetic (0.286)
Interaction term of both Intraoperative HALO use, and any HALO IV opioid on POD#0–1: 23.4 (1.1–517), **P = 0.046**	5 drug AEPPx, vs. less than 5-drug (0.455)
Signals:	ITM + Mg$^+$, vs. ITM-only (0.586)
Age on DOS (per year): 0.88 (0.78–1.01), P = 0.061	POD#1 pain score (incremental points) difference from baseline (0.631)
BMI on DOS (per unit): 1.13 (0.98–1.31), P = 0.097	
POD#1 double-booster with oral perphenazine and aprepitant: 0.16 (0.02–1.41), P = 0.099	Intraoperative IV HALO use (0.698)
	Any HALO IV opioid on POD#0–1 (0.865)
Black American or Hispanic/Latino: 5.00 (0.73–34.46), P = 0.102	Taking preoperative GLP1-active agent (0.754)
	Volatile agent during surgery (0.850)
Surgical time (per minute): 1.02 (0.99–1.05), P = 0.168	ITM dose, per incremental μg (0.977)

PONV, postoperative nausea/vomiting; POD#, postoperative day(s); DOS, day of surgery; AEPPx, antiemetic prophylaxis; ITM, intrathecal morphine; ITM + Mg$^+$, ITM + intrathecal magnesium; EMR, electronic medical record; GLP1, glucagon-like peptide 1; IV, intravenous (or IV-administered); Model factor P values are in **bold italics**; HALO, high abuse-liability opioid, such as fentanyl, remifentanil, hydromorphone (but not methadone or buprenorphine).

Narrative interpretation: Underpowering in this bariatric sample rendered difficulty in evaluating the traditional risk factor of gender-based PONV effect on POD#0–1 (with early models showing higher PONV risk in men, and therefore gender being withheld from the final model above). Underpowering from small bariatric samples also affected possible nuanced factors, such as the patient being on baseline opioids, baseline marijuana-related product(s), and/or higher-consumption of alcohol at baseline (with an Audit C score of 4+/12, which is our nationwide institutional definition of potentially-problematic drinking). The non-smoker risk factor could not be evaluated since all bariatric patients at our institution must be nicotine-free (by urine cotinine testing) before undergoing elective bariatric surgery. Past history of PONV was not a predictor in this small, subspecialized sample with the described care plan interventions that included ITM and 5-MMAEPPx (before ITM/GA) as institutional standard of care. We re-verified (1, 19) sleeve gastrectomy as a potent, emetogenic surgical procedure, and observed a signal regarding potential benefit from perphenazine-aprepitant "double-booster" on POD#1 (after 5-MMAEPPx preoperatively in the vast majority of cases). Older age was associated with a signal of less PONV on POD#0–1, consistent with PONV consensus guideline narratives, and length of surgery was also a potential PONV signal: the longer the surgery, the potential for higher PONV burden on POD#0–1. We found it curious (and concerning) that non-Caucasian race/ethnicity (entailing African-Americans and Hispanic-Latino) was a signal of increased PONV despite 5-drug AEPPx; such findings should be further explored in PONV race-based epidemiologic research worldwide. Opioid-related factors (consistent with Apfel risk factors and variations on opioid categorization) were indeed predictive in this small sample, particularly IV opioids having been given (on a discretionary basis) during surgery despite the presence of ITM in these cases, specifically followed (as an interaction term) by further IV opioids on POD#0–1. Coexisting postoperative pain scores (above baseline values) was not an associated PONV factor on POD#1. It appears that ITM dosing (with or without Mg$^+$) was less of a PONV risk than IV opioids given intraoperatively and followed by POD#0–1 IV opioids, in the backdrop of 5-MMAEPPx, but this particular bariatric data set remains underpowered at present to determine this issue confidently. GLP-1 agonists in this sample did not appear to escalate PONV risks in this small bariatric sample, those patients commonly having been on such agents preoperatively, but having not received treatment for at least 1 week before surgery.

Panel 1b: Model coefficient for bariatric PONV on POD#2 (with 95% CI for factors/signals), P values	Excluded variables (P values)	
Constant: <0.001; P = 0.008	POD#1 pain score (incremental points) difference from baseline: (0.225)	Age on DOS (per year): (0.563)
Dextromethorphan used every 12 h, from preop through POD#2, with no missed doses in that interval: 13.4 (1.3–136), **P = 0.029**	Sleeve Gastrectomy: (0.241)	POD#1 double-booster with oral perphenazine and aprepitant: (0.612)
	ITM + Mg$^+$, vs. ITM-only: (0.260)	Demographic history of EtOH or marijuana-related misuse/use:(0.633)
	Baseline history of active preoperative opioids: (0.270)	
BMI on DOS (per BMI unit): 1.17 (1.00–1.36), **P = 0.045**	POD#0 pain score (incremental points) different from baseline: (0.296)	ITM dose, per μg: (0.677)
		Gender: (0.746)
Signals:	Surgical time (per minute): (0.314)	Black American or Hispanic/Latino: (0.800)
Diabetes, vs. non-diabetic: 0.20 (0.02–1.76), P = 0.147	Propofol + Volatile agent during surgery: (0.463)	Propofol without Volatile agent during surgery: (0.866)
	HALO IV opioid on POD#0–1: (0.549)	Past PONV, per EMR: (0.912)

PONV, postoperative nausea/vomiting; POD#, postoperative day(s); BMI, body mass index (in kg·m^{-2}); DOS, day of surgery; AEPPx, antiemetic prophylaxis; EtOH, ethanol; ITM, intrathecal morphine; ITM + Mg$^+$, ITM + intrathecal magnesium; EMR, electronic medical record; IV, intravenous (or IV-administered); Model factor P values are in **bold italics**; HALO, high abuse-liability opioid, such as fentanyl, remifentanil, hydromorphone (but not methadone or buprenorphine).

Narrative interpretation: This bariatric sample exploring PONV on POD#2, after not having encountered PONV on POD#0–1, revealed a striking pattern of non-predictive traditional PONV risk factors. Gender, past PONV, and opioid-related parameters did not approach "signal" status, in what could simply be attributed to underpowering. Again, in our institution, smokers are excluded from elective bariatric surgery, so this risk factor could not be evaluated. Our efforts entailed use of multimodal non-opioid analgesics to enhance and prolong the ITM (or ITM + Mg$^+$) analgesic durations, and we were somewhat surprised that preoperative and POD#0–2 oral dextromethorphan (sustained release preparations every 12 h) predicted PONV tendencies on POD#2; however, the nausea/vomiting side effect is consistent with listings on the package insert of most dextromethorphan preparations. Each additional BMI unit (this already being a signal in our bariatric population for POD#0–1) rendered higher POD#2 PONV tendencies. Diabetes, which we (1) previously identified as a predictor of less PONV on POD#1, remained a signal of less PONV of POD#2. None of our POD#0–1 PONV predictors or signals continued as a predictor or signal on POD#2. We did not record booster dosing of perphenazine-aprepitant on POD#2 in our data query of nearly 500 patients overall, so future research should certainly explore whether POD#2 "double-booster" dosing signals or predicts less-associated PONV on POD#2. Including magnesium in the morphine spinal did not appear to signal PONV patterns one way or the other, but this may have been underpowered. Preceding days' pain scores (compared to baseline) again did not show signals of PONV effects on POD#2, again indicating possible underpowering.

Panel 1c: Model coefficient for bariatric HALO use on POD#0–2 (with 95% CI for factors/signals), *P* values	Excluded variables (*P* values)	
Constant: 0.600; *P* = 0.469	Demographic history of EtOH or marijuana-related misuse/use: (0.206)	POD#1 double-booster with oral perphenazine and aprepitant: (0.648)
POD#1 pain score (incremental points) difference from baseline: 1.70 (1.22–2.37), **P = 0.002**	Intraoperative IV HALO use: (0.232)	Black American or Hispanic/Latino: (0.656)
	All three multimodal non-opioidson-schedule, through POD#0–2: (0.316)	Past PONV, per EMR: (0.854)
		ITM dose, per µg (0.941)
	Gender: (0.329)	Sleeve Gastrectomy: (0.951)
ITM + Mg$^+$, vs. ITM-only: 0.097 (0.01–0.87), **P = 0.037**	Surgical time (per minute): (0.371)	Propofol without Volatile agent during surgery: (0.710)
	Diabetes, vs. non-diabetic: (0.374)	
Signals: none	Baseline history of activepreoperative opioids: (0.378)	Propofol + Volatileduring surgery: (0.855)
	Age on DOS (per year): (0.526)	

HALO, high abuse-liability opioid, such as fentanyl, remifentanil, hydromorphone (but not methadone or buprenorphine); EtOH, ethanol; POD#, postoperative day(s); DOS, day of surgery; ITM, intrathecal morphine; ITM + Mg$^+$, ITM + intrathecal magnesium; PONV, postoperative nausea/vomiting; EMR, electronic medical record; IV, intravenous (or IV-administered); Model factor *P* values are in **bold italics**.

Narrative interpretation: Underpowering in this bariatric sample renders potential uncertainty with respect to completeness of the model. Our treatment goal was to use ITM (later ITM + Mg$^+$), along with 5-MMAEPPx, and followed by both multimodal non-opioid analgesics and booster antiemetics (described above) in a coordinated, holistic, whole-health effort to avoid "downstream" opioid exposure after endoscopic/robotic bariatric surgery. Our prediction was that this sustained and multifaceted antiemetic strategy would potentially facilitate enteral adherence to (and absorption of) the primarily oral analgesic regimen. Adding Mg$^+$ to ITM was favorably associated with reducing associated downstream opioid exposure, while pain scores on POD#1 (compared to baseline pain score before surgery) logically (and confidently) predicted associated opioid use, in a step function that increased with each additional pain score unit. There were no race/ethnicity-based, age-based, surgical time-based, anesthetic agent-based, or gender-based factors, rendering the two associated predictors identified as seemingly quite robust, There were no apparent cross-substance or care plan issues (baseline opioids, ITM dose used, POD#1 double-booster antiemetics with perphenazine and aprepitant, baseline marijuana-related substance, and/or baseline ethanol) that would have traditionally been considered to escalate opioid dosing after surgery, when compared to other expected factors/signals regarding postoperative opioid. Smoking status could not be evaluated since all bariatric patients at our institution must be nicotine-free (by urine cotinine testing) before undergoing elective bariatric surgery. It seems possible that ITM + Mg$^+$ may be a prime (yet under-appreciated) opioid sparing opportunity dominating many other conventional factors, warranting future research regarding whether the spinal procedure includes local anesthetic (as in a lower extremity total joint replacement procedure) along with ITM + Mg$^+$, or not.

Panel 1d: Model coefficient for bariatric itching (with 95% CI for factors/signals), *P* values	Excluded variables (*P* values)	
Constant: 0.007; *P* = 0.017	Acetaminophen used every 6–8 h, from preop through POD#2, with no missed doses in that interval: (0.197)	Dextromethorphan used every 12 h, from preop through POD#2, with no missed doses in that interval: (0.641)
HALO IV opioid on POD#0–1:12.23 (2.5–59.9), **P = 0.002**		
Celecoxib used every 12 h, from preop through POD#2, with no missed doses in that interval:10.72 (1.96–58.73), **P = 0.006** (another non-steroidal anti-inflammatory may have been used "around the clock" instead of celecoxib)	Baseline history of active preoperative opioids: (0.476)	POD#1 double-booster with oral perphenazine and aprepitant: (0.808)
	Demographic history of EtOH or marijuana-related misuse/use: (0.561)	Sleeve Gastrectomy: (0.838)
Gender (if male) 0.104 (0.02–0.48), **P = 0.030**	Black American or Hispanic/Latino: (0.586)	ITM + Mg$^+$, vs. ITM-only: (0.890)
Preoperative "super-size" with dexamethasone 8 mg (not 4) and palonosetron 100+µg (not 75): 0.175 (0.03–0.91), **P = 0.038**	HALO oral opioid on POD#0–2:(0.592)	Diabetes, vs. non-diabetic: (0.953)
ITM dose, per mg: 1.02 (1.00–1.03), **P = 0.044**		
Signals: Volatile agent during surgery: 2.4 (0.68–8.46), *P* = 0.174		

POD#, postoperative day(s); IV, intravenous (or IV-administered); EtOH, ethanol; HALO, high abuse-liability opioid, such as fentanyl, remifentanil, hydromorphone (but not methadone or buprenorphine); ITM, intrathecal morphine; ITM + Mg$^+$, ITM + intrathecal magnesium. Model factor *P* values are in **bold italics**.

Narrative interpretation: We presumed before this query that women had higher associated ITM-pruritus risks than did men (which proved to be a strong predictor), and that either the escalating ITM dose or addition of Mg$^+$ (50 mg) to the spinal morphine (or both) likely promoted itching (the ITM dose was ultimately an associated predictor, but the spinal Mg$^+$ hay have been an underpowered factor; we had also reduced the Mg$^+$ dose to 25 mg without apparent adverse analgesic benefit based on anecdotal observation). Our most common pre- and postoperative non-steroidal anti-inflammatory drug (NSAID) was the COX-2 inhibitor celecoxib, and the surprisingly-potent itching association invokes the possibility of the sulfa moiety in the celecoxib molecule being problematic (while acetaminophen and dextromethorphan did not appear to be problematic in the realm of pruritus). At roughly the midpoint of data collection, we had learned of anti-itching benefit of higher-than-PONV doses of palonosetron (with our then increasing routine palonosetron doses from 75 to 150 µg, simultaneously with an increase of dexamethasone pre-emptive dose from 4 to 8 mg IV, aiming for additional analgesic benefits atop known antiemetic benefit). IV opioids on POD#0–1 were a profoundly-associated predictor of pruritus, but oral opioids (on POD#0–2) did not carry pruritus associations. Another potentially interesting signal in this model occurring (along with the factors already described) is the possibility of volatile agents enhancing itching risk (as a dichotomous yes/no function). Baseline opioid consumption, or that of other substances (THC/CBD or ethanol), did not appear to desensitize our subjects to ITM pruritus risks. Again, underpowering in this bariatric sample rendered difficulty in evaluating the completeness of this model. The non-smoker risk factor could not be evaluated since all bariatric patients at our institution must be nicotine-free (by urine cotinine testing) before undergoing elective bariatric surgery. Non-Caucasian race/ethnicity (entailing African-Americans and Hispanic/Latino) and diabetes status did not appear to influence pruritus occurrence, but one or both of these could be underpowered.

TABLE 2 Panels 2a–d; multivariable logistic regression models after all surgery types in our institution (with ITM or ITM + Mg$^+$) outlining (2a) predictors of PONV on POD#0–1; (2b) predictors of PONV on POD#2 (after no PONV on POD#0–1); (2c) predictors of HALO Use on POD#0–2; and (2d) predictors of itching.

Panel 2a: Model coefficient for POD#0–1 PONV after ITM (with 95% CI for factors/signals), *P* values	Excluded variables (*P* values)	
Constant: 0.051; *P* < 0.001	Age on DOS (per year): (0.255)	POD#1 double-booster with oral perphenazine and aprepitant: (0.686)
Sleeve Gastrectomy: 12.0 (3.7–38.8), ***P < 0.001***	Taking preoperative GLP1-active agent: (0.282)	POD#0 pain score (incremental points) difference from baseline: (0.769)
Interaction term of *both* intraoperative IV HALO use, *and* any HALO IV opioid on POD#0–1: 6.473 (2.03–20.6), ***P = 0.002***	Intraoperative IV HALO use: (0.455)	Demographic history of EtOH or marijuana-related misuse/use: (0.799)
	POD#1 pain score (incremental points) difference from baseline: (0.481)	
	Demographic history of baseline smoking: (0.572)	Surgical time (per minute): (0.850)
		Preoperative "super-sized" doses with dexamethasone 8 mg (not 4), and palonosetron 100+ μg (not 75): (0.860)
Diabetes, vs. non-diabetic: 0.192 (0.059–0.624), ***P = 0.006***	Baseline history of active preoperative opioids: (0.601)	
Past PONV, per EMR: 3.45 (1.25–9.55), ***P = 0.017***	HALO IV opioid on POD#0–1: (0.631)	Volatile agent during surgery: (0.879)
	ITM + Mg$^+$, vs. ITM-only: (0.646)	5 drug AEPPx, vs. less than 5-drug: (0.895)
Open (not all-endoscopic) surgery: 2.90 (1.16–7.22), ***P = 0.022***	Gender: (0.648)	ITM dose, per incremental μg: (0.941)
Signals: Black American or Hispanic/Latino: 2.24 (0.94–5.30), *P* = 0.068		

PONV, postoperative nausea/vomiting; ITM, intrathecal morphine; POD#, postoperative day(s); DOS, day of surgery; GLP1, glucagon-like peptide 1; AEPPx, antiemetic prophylaxis; ITM + Mg$^+$, ITM + intrathecal magnesium; HALO, high abuse-liability opioid, such as fentanyl, remifentanil, hydromorphone (but not methadone or buprenorphine); EMR, electronic medical record; IV, intravenous (or IV-administered); EtOH, ethanol; Model factor *P* values are in **bold italics**.

Narrative interpretation: Underpowering seems less likely (in this institution-wide ITM case sample), but interpretation is cautioned because of surgical case type variability (e.g., open vs. endoscopic), unlike the relative uniformity of the previously-presented bariatric data Table 1 and Supplementary Table S1). Traditional risk factors of gender-based PONV effects and nonsmoker status did not affect POD#0–1 PONV predictions, when several other factors were considered. Sleeve gastrectomy was again a strong independent predictor, remaining from the earlier bariatric analysis (Table 1). Past PONV (per EMR review) was an Apfel-based predictor in this model, and non-Caucasian race/ethnicity status was a notable signal that remained in the model (i.e., separate from "past PONV"). While being on baseline opioids was not an associated predictor during this POD#0–1 time segment, the interaction term of in-OR discretionary IV opioids (despite ITM use already) and POD#0–1 use of IV opioids was a significant Apfel-based predictor of PONV. All patients had ITM, but neither the ITM dose nor the MgSO4 additive was found to be predictive of POD#0–1 PONV in this sample. Age and length of surgery were not predictive, but open procedures (as opposed to endoscopic surgery) were predictive of POD#0–1 PONV. Cross-substance use (CBD/THC-related product(s), and/or higher-consumption of alcohol at baseline, with an Audit C score of 4+/12, which is our nationwide institutional definition of potentially-problematic drinking) was not predictive in this sample. The perphenazine-aprepitant "double-booster" on POD#1 (after 5-MMAEPPx preoperatively) was not predictive in this model (as it had been in our earlier, bariatric-specific model), nor was the higher-combined "super-sized" dose of preoperative palonosetron (e.g., 100–150 μg instead of 75 μg) and dexamethasone (8 mg instead of 4 mg). Coexisting postoperative pain scores above baseline were non-predictive of PONV occurrence on POD#0–1, but again this finding may have been underpowered, and should continue to be explored as a risk factor worth minimizing. It appears that ITM (with or without Mg$^+$) may be of less PONV risk (on POD#0–1) than in-OR IV opioids and POD#0–1 IV opioids (*P* = 0.002) in the backdrop of 5-MMAEPPx. GLP-1 agonists in this larger sample did not appear to escalate PONV risks, these patients having been on such agents, but having not received treatment for at least 1 week before surgery.

such cases (19). Medical records of all described cases were audited for rescue antiemetic administration on POD#0–2, and/or health professional electronic medical record (EMR) narrative notes indicating nausea and/or vomiting (e.g., nurses, physicians, other advanced care providers) on POD#0–2. POD#0–1 vs. POD#2 data were analyzed separately using multivariable logistic regression (of PONV predictors including ITM ± Mg$^+$ use), to provide a preliminary assessment for factors' (and bundles') robustness and "believability" of 5-MMAEPPx (bundle [iii]) success, co-administered with ITM + Mg$^+$ (bundle [i]), daily antiemetic booster doses (perphenazine and aprepitant, bundle [iv]), and scheduled postoperative multimodal analgesic/anti-hyperalgesic booster doses of acetaminophen, celecoxib, and dextromethorphan (bundle [v]). Prophylactic booster doses of ondansetron (after preoperative palonosetron) were not utilized, out of fear of creating "rebound PONV," previously described (20, 21); rescue ondansetron doses were permitted only 40+ h following the initial palonosetron dose before surgery.

In determining factors/signals in the regression analyses (Tables 1, 2), or when evaluating clusters of 2–3 variables

(e.g., two individual variables and a third interaction term), a factor with *P* < 0.2 was either retained in the multivariable model as a viable signal, or such variables/clusters were removed if the outcome of the multivariable model was opposite of expectation. For example, "increases in IV opioid use yielding *less* PONV" *would be excluded* from a subsequent iterative model, *as an unexpected result*. To re-run the model with a logical array (or bundle) of predictive factors and signals, the final models excluded variables (as potential signals) with *P* ≥ 0.2. In addition, if a variable was found to be a significant associated predictor on the multivariable PONV models (bundle [vi]) of POD#0–1 vs. POD#2, the factor/signal variable was similarly run in the other multivariable time-based model (and vice-versa), for completeness.

All data collation and statistical analysis utilized SPSS version 28 (IBM SPSS Statistics, Armonk, NY, USA), and all reported *P*-values are two-sided. In this report, other sociodemographic determinants of health were included in these analyses, such as race/ethnicity (Caucasian/not Latino vs. not, taking baseline opioids immediately before surgery, regularly using marijuana-related

Panel 2b: Model coefficient for POD#2 PONV after ITM (with 95% CI for factors/signals), P values	Excluded variables (P values)	
Constant: 0.082; $P < 0.001$	Volatile agent during surgery: (0.288)	Age on DOS (per year): (0.541)
Dextromethorphan used every 12 h, from preop through POD#2, with no missed doses in that interval: 3.58 (1.48–8.66), **P = 0.005**	POD#1 pain score (incremental points) difference from baseline: (0.309)	HALO oral opioid on POD#0–2: (0.545)
	Demographic history of EtOH or marijuana-related misuse/use: (0.324)	Sleeve Gastrectomy: (0.575)
		ITM dose, per μg (0.604)
Celecoxib used every 12 h, from preop through POD#2, with no missed doses in that interval: 2.57 (1.03–6.42), **P = 0.043** (another non-steroidal anti-inflammatory may have been used "around the clock" instead of celecoxib)	Black American or Hispanic/Latino: (0.345)	Surgical time (per minute): (0.615)
	BMI on DOS (per BMI unit): (0.362)	POD#1 double-booster with oral perphenazine and aprepitant: (0.624)
	Taking preoperative GLP1-active agent: (0.365)	Open (not all-endoscopic) surgery: (0.771)
	HALO IV opioid on POD#0–1: (0.438)	Intraoperative IV HALO use: (0.803)
Signals: ITM + Mg$^+$, vs. ITM-only: 0.27 (0.07–1.04), $P = 0.057$	Preoperative "super-sized" dose with dexamethasone 8 mg (not 4) and palonosetron 100+ μg (not 75): (0.496)	Gender: (0.925)
Past PONV, per EMR: 3.061 (0.90–10.36), $P = 0.072$	Baseline history of active preoperative opioids: (0.521)	Acetaminophen used every 6–8 h, from preop through POD#2, with no missed doses in that interval: (0.990)
Diabetes, vs. non-diabetic: 0.50 (0.19–1.31), $P = 0.157$	5 drug AEPPx, vs. less than 5-drug: (0.525)	

POD#, postoperative day(s); PONV, postoperative nausea/vomiting; ITM, intrathecal morphine; EtOH, ethanol; BMI, body mass index (in $kg \cdot m^{-2}$); DOS, day of surgery; AEPPx, antiemetic prophylaxis; HALO, high abuse-liability opioid, such as fentanyl, remifentanil, hydromorphone (but not methadone or buprenorphine); ITM + Mg$^+$, ITM + intrathecal magnesium; EMR, electronic medical record; IV, intravenous (or IV-administered); Model factor P values are in **bold italics**.

Narrative interpretation: Multivariable Logistic Regression—POD#2 PONV Predictors. This wider, all-ITM sample exploring PONV on POD#2, after not having encountered PONV on POD#0–1, revealed a differing pattern of PONV risk factors and signals from those explored in the PONV context of POD#0–1. First, including magnesium in the morphine spinal yielded a signal of less PONV on POD#2, perhaps related to opioid-sparing benefit that may have dominated any particular opioid-specific category of variables considered. Gender, smoking status, and opioid-related Apfel parameters did not approach "signal" status, but "past PONV" status yielded a logical signal of higher PONV risk on POD#2 (after no PONV on POD#0–1, and this "past PONV" factor/signal not presenting in the bariatric-specific models earlier). Race/ethnicity had no apparent influence on POD#2 PONV, after having been a signal for POD#0–1 PONV. Diabetes was an associated, somewhat protective signal, but was non-predictive of POD#2 PONV in our earlier bariatric surgery model. Bariatric sleeve gastrectomy did not persist as a factor/signal in POD#2 PONV (nor did it in the earlier bariatric-specific POD#2 model), after being a potent predictor in POD#0–1. Our efforts entailed use of multimodal non-opioid analgesics to enhance and prolong the ITM (or ITM + Mg$^+$) analgesic durations, and we were again surprised that preoperative and POD#0–2 oral dextromethorphan (sustained release preparations every 12 h, as a non-immediate but presumed cumulative effect) predicted PONV tendencies by POD#2; however, the nausea/vomiting side effect is consistent with listings on the package insert of most dextromethorphan preparations. COX-2 inhibitors (primarily celecoxib)/NSAIDs (rare, but when used, primarily ketorolac) emerged as a surprise predictor of POD#2 PONV, which could be tantamount to a gastritis side effect. Diabetes, which we (1) previously identified as a predictor of less PONV on POD#1 overall, but having not emerged as protective in our earlier bariatric analyses herein, was a weak overall signal of less PONV on POD#2 in this model. None of our POD#0–1 PONV predictors or signals continued as a predictor or signal on POD#2 (other than Apfel-based "past PONV"). We did not record booster dosing of perphenazine/aprepitant on POD#2 in our data query of nearly 500 patients overall, so future research could certainly explore whether POD#2 "double-booster" dosing signals or predicts less-associated PONV on POD#2, as the POD#1 double-booster appeared as a protective signal in bariatric-specific contexts, and particularly if dextromethorphan and/or celecoxib are to be used as non-opioid multimodal analgesics. The preceding day's peak pain scores (compared to baseline, i.e., on POD#1) did not show signals of PONV effects on POD#2; we excluded POD#0 pain since it gave a reverse-from-logical prediction in multiple model trials (data not shown).

substance[s] and/or unhealthy alcohol consumption at baseline before surgery, etc.).

3 Results

3.1 Participants and descriptive data

As detailed and itemized in Supplementary Tables S1, S2, the number of patients per analyzed observational condition are summarized as follows. There were 60 bariatric ITM cases (without Mg$^+$) and 13 bariatric ITM + Mg$^+$ cases (bundle [i]) in Supplementary Table S1. Supplementary Table S2 shows 246 ITM cases overall (without Mg$^+$), and 60 ITM + Mg$^+$ cases (bundle [i]) overall (with Supplementary Table S2 including the aforementioned bariatric cases from Supplementary Table S1). One relevant raw data outcome (from Supplementary Table S2) that we will not discuss further below is the perceived longer analgesic duration of ITM + Mg$^+$ (42 h, 95% CI 36–49 h) over plain ITM (31 h, 95% CI 28–33 h, $P < 0.001$ per t-test), likely explainable by local enhancement [e.g., N-methyl-D-aspartate (NMDA)-antagonism] of ITM by Mg$^+$ (bundle [i]), particularly at the spinal cord level.

3.2 Raw data analysis of avoided downstream opioid when intrathecal Mg$^+$ is added to ITM

In Section 1, we cited our recent observation (2) that ITM-only use, with day-of-surgery 5-MMAEPPx followed by 2-drug AEPPx boosters (bundles [iii, iv]), was associated with 17% success (10/58 cases) of averted need for any IV or PO HALO opioids during and after bariatric surgery (on POD#0–1). This was observed when in-hospital postoperative follow-up (i.e., non-opioids [bundle [v]] and antiemetic boosters [bundle [iv]]) was fully systematized in a comprehensive bariatric enhanced recovery protocol (2). In the current data set incorporating ITM + Mg$^+$ and all described bundles, 9/13 (69%) of our bariatric cases with ITM + Mg$^+$ did not need or receive downstream opioids after the initial ITM + Mg$^+$, compared to 11/60 (18%, Supplementary Table S1) in bariatric cases receiving ITM only [i.e., one numerator and two denominator bariatric cases having been added to the previously-published (2) cases that entailed 10 of 58 cases at the time].

When considering the entire ITM + Mg$^+$ vs. ITM-only cohorts at our center (Supplementary Table S2), ITM + Mg$^+$ (34/60, 57%) was

Panel 2c: Model coefficient for POD#0–2 HALO use after ITM (with 95% CI for factors/signals), P values	Excluded variables (P values)	
Constant: 0.172; $P = 0.581$	Interaction term for ITM dose by ITM + Mg$^+$: (0.237)	Volatile agent during surgery: (0.761)
POD#1 pain score (incremental points) different from baseline: 1.28 (1.15–1.44), **$P < 0.001$**	Age on DOS (per year): (0.258)	Sleeve Gastrectomy: (0.764)
All three multimodal non-opioids on-schedule, through POD#0–2: 0.29 (0.12–0.71), **$P = 0.007$**	Diabetes, vs. non-diabetic: (0.440)	Preoperative "super-sized" doses with dexamethasone 8 mg (not 4) and palonosetron 100+ µg (not 75): (0.828)
	Demographic history of baseline smoking: (0.445)	
Intraoperative IV HALO use: 14.05 (1.72–114.82), **$P = 0.014$**	POD#0 pain score (incremental points) difference from baseline: (0.534)	POD#1 double-booster antiemetics with perphenazine and aprepitant: (0.852)
ITM + Mg$^+$, vs. ITM-only: 0.30 (0.11–0.82), **$P = 0.019$**	BMI on DOS (per unit): (0.570)	Demographic history of EtOH or marijuana-related misuse/use: (0.867)
Taking preoperative GLP1-active agent: 4.09 (1.10–15.25), **$P = 0.036$**	Surgical time (per minute): (0.612)	Gender: (0.935)
Current-case PONV, per EMR: 0.16 (0.03–0.91), **$P = 0.038$**	Past PONV, per EMR: (0.752)	
Open (not all-endoscopic) surgery: 2.20 (1.03–4.70), **$P = 0.041$**		
Signals:		
Baseline opioid use: 1.96 (0.77–4.99), $P = 0.159$		
Black American or Hispanic/Latino: 2.06 (0.71–5.98), $P = 0.182$		

HALO, high abuse-liability opioid, such as fentanyl, remifentanil, hydromorphone (but not methadone or buprenorphine); ITM, intrathecal morphine; IV, intravenous (or IV-administered); ITM + Mg$^+$, ITM + intrathecal magnesium; POD#, postoperative day(s); GLP1, glucagon-like peptide 1; PONV, postoperative nausea/vomiting; BMI, body mass index (in kg·m^{-2}); DOS, day of surgery; EMR, electronic medical record; EtOH, ethanol; Model factor P values are in **bold italics**.

Narrative interpretation: Not surprising in this wider sample was the finding that arbitrary IV opioid use in the OR (with ITM already administered) yields an associated predictor of any downstream opioid use (IV and/or PO) on POD#0–2, consistent with Curry et al. (23). Other logical independent findings included (i) all 3 multimodal analgesics (most commonly acetaminophen, celecoxib vs. ketorolac, and dextromethorphan) as an associated predictor of HALO opioid avoidance on POD#0–2, (ii) the association of open (vs. endoscopic) surgery with higher use of any HALO opioid on POD#0–2, (iii) combined ITM + Mg$^+$ showing associated protective value against the need for any HALO opioids on POD#0–2, and (iv) the incremental association of each escalating pain score unit (on POD#1, above baseline preoperative pain) predicting any HALO opioids on POD#0–2. Two surprising factors were (i) concomitant GLP-1 agents associated with more POD#0–2 HALO use/requirement, and (ii) any PONV on POD#0 seeming to curb associated opioid use at any point throughout POD#0–2. Our treatment goal was to use ITM (and later ITM + Mg$^+$), along with 5-drug AEPPx, and followed by both multimodal non-opioid analgesics and booster antiemetics (described above) in a coordinated, holistic, whole-health effort to avoid "downstream" opioid exposure after the described surgeries. We forecasted that that our sustained and multifaceted antiemetic booster strategy would potentially facilitate enteral adherence to (and absorption of) the primarily oral analgesic regimen, which appeared to be true in these observational data [with the vast majority (94%) of these patients having received 5-MMAEPPx]. Baseline preoperative opioid consumption and non-Caucasian race/ethnicity were signals consistent with other models presented herein. There were no age-based, surgical time-based, anesthetic agent-based, or gender-based factors, rendering the seven associated predictors (and two signals) identified as reasonably robust. There were no apparent cross-substance, overall health, or care plan issues (baseline tobacco, baseline THC/CBD and/or baseline ethanol, diabetes status, ITM dose used when combined with Mg$^+$, POD#1 double-booster antiemetics with perphenazine/and aprepitant) that would have traditionally been considered to escalate opioid dosing after surgery. It seems possible that ITM + Mg$^+$ may be a prime (yet under-appreciated) opioid sparing opportunity dominating many other usual/expected factors, warranting future research regarding whether the spinal procedure including local anesthetic with ITM + Mg$^+$ (as in a lower extremity total joint replacement procedure), or not, may provide further benefit. Meanwhile we are unaware of any prior reports of GLP-1 agents leading to either a higher pain score warranting opioid consumption, or stimulating opioid consumption when patients on these metabolism-altering medications are given access to opioids.

significantly more successful than was ITM-only (35/246, 14%, $P < 0.001$ by Chi-square test) on the "avoided HALO" parameter.

3.3 Models addressing clustered PONV occurrences across POD#0−1 (as a no/yes dichotomous variable)

When considering the bariatric (Table 1) and overall ITM cohort (Table 2) models incorporating comparisons of ITM against ITM + Mg$^+$, as an aggregate exploration to inform potentially-predictive PONV bundles on POD#0–1 (Panels 1a, 2a, respectively), we observed logical prediction and signaling patterns. First (a), sleeve gastrectomy was profoundly emetogenic (19); (b) outside of sleeve gastrectomy, daily postoperative booster doses of perphenazine/aprepitant were of relatively little value [i.e., at least until booster doses of palonosetron (every 40 h) are added in future enhanced recovery QI work]. This latter point is based on Apfel's statements (20, 21) regarding ondansetron and *rebound nausea* risk. Continuing, (c) there may be a separate, race-based PONV risk factor distinct from the classic Apfel factor of "past PONV"; (d)

operating room IV HALO, followed by ongoing IV HALO, appears to be profoundly associated with PONV risk on POD#0–1; and (e) younger age and higher BMI may be PONV-predictive factors, along with open (not endoscopic) surgery. Readers are directed to the fully descriptive captions and footnotes of Tables 1, 2, Panels 1a, 2a.

3.4 Models and predictive bundles addressing any PONV occurrence on POD#2 (dichotomous variable), specifically after no PONV on POD#0−1

When considering PONV predictors on POD#2, and addressing (among other comparisons) ITM vs. ITM + Mg$^+$, we observed: (a) oral, slow-release dextromethorphan contributing cumulative analgesic effects as a non-opioid (Panel 2c), but also appearing to emerge as a POD#2 PONV factor (Panels 1b, 2b). This PONV side effect after associated analgesic benefit renders as reasonable the daily incorporation of not only oral booster antiemetics (perphenazine and aprepitant), but also palonosetron booster doses every 40 h, since incorporating 3 boosters (bundle

Panel 2d: Model coefficient for POD#0–2 itching after ITM (with 95% CI for factors/signals), *P* values	Excluded variables (*P* values)	
Constant: 0.024; *P* = 0.003	Acetaminophen used every 6–8 h, from preop through POD#2, with no missed doses in that interval: (0.258)	Sleeve Gastrectomy: (0.604)
Gender (if male) 0.146 (0.062–0.341), **P < 0.001**		
ITM dose, per μg 1.01 (1.003–1.017), **P = 0.003**	ITM + Mg$^+$, vs. ITM-only (0.287)	Past PONV, per EMR: (0.684)
Signals:	Taking preoperative GLP1-active agent: (0.307)	
Surgical time (per minute): 0.997 (0.994–1.000), *P* = 0.072	Demographic history of baseline smoking: (0.338)	Dextromethorphan used every 12 h, from preop through POD#2, with no missed doses in that interval: (0.857)
Volatile agent during surgery: 2.1 (0.9–4.7), *P* = 0.074	Celecoxib or non-steroidal anti-inflammatory used every 12 h, from preop through POD#2, with no missed doses in that interval: (0.398)	Any HALO IV opioid on POD#0–1 (0.885)
BMI on DOS (per BMI unit): 1.0 (0.99–1.09), *P* = 0.090		Intraoperative IV HALO use: (0.897)
Demographic history of EtOH misuse or marijuana-related use: 0.482 (0.202–1.145), *P* = 0.098	Black American or Hispanic/Latino: (0.456)	HALO oral opioid on POD#0–2: (0.904)
	Age on DOS (per year): (0.479)	
Diabetes, vs. non-diabetic: 0.573 (0.244–1.341), *P* = 0.199	Baseline history of active preoperative opioids: (0.518)	Open (not all-endoscopic) surgery: (0.906)
	Preoperative "super-sized" doses with dexamethasone 8 mg (not 4) and palonosetron 100+ μg (not 75): (0.552)	POD#1 double-booster with oral perphenazine and aprepitant: (0.808)

POD#, postoperative day(s); ITM, intrathecal morphine; ITM + Mg$^+$, ITM + intrathecal magnesium; GLP1, glucagon-like peptide 1; HALO, high abuse-liability opioid, such as fentanyl, remifentanil, hydromorphone (but not methadone or buprenorphine). IV, intravenous (or IV-administered); BMI, body mass index (in kg·m^{-2}); DOS, day of surgery; EtOH, ethanol. Model factor *P* values are in **bold italics**.

Narrative interpretation: Before proceeding with this analysis, we forecasted that women would have higher associated ITM-pruritus risks than would men (which held as true in the model), and that either the escalating ITM dose or addition of Mg$^+$ to the spinal morphine (or both) likely promoted itching (the ITM dose was ultimately an associated predictor, but the spinal Mg$^+$ may have been an underpowered factor, with 16/60 ITM + Mg$^+$ patients with pruritus and not differing between 25 and 50 mg Mg$^+$ doses). Our surprising bariatric surgery finding regarding NSAID selection as an itching predictor (primarily entailing the COX-2 inhibitor celecoxib) did not hold in this wider model, while acetaminophen and dextromethorphan again did not appear to be problematic in the realm of pruritus. At roughly the midpoint of data collection, we had learned of anti-itching benefit of higher doses of palonosetron (than the 75 μg dose used for PONV prophylaxis; with our decision at that point to increase routine palonosetron doses from 75 to 150 μg, simultaneously with an increase of dexamethasone pre-emptive dose from 4 to 8 mg IV, aiming for additional analgesic benefits atop known antiemetic benefit), but this did not appear to be predictive or serve as a signal preventing itching in this wider model. IV opioids on POD#0–1, a logical predictor of associated pruritus in the bariatric model above (Panel 1d), was non-predictive (and a non-signal) in this wider-scope model, while oral opioids on POD#0–2 were both non-predictive and non-signaling in this wider model and in the earlier bariatric model. Another potentially interesting signal in this wider model occurring along with the factors already described, and already identified as a weaker signal in the bariatrics model earlier, is the possibility of volatile agents enhancing itching risk. Baseline opioid consumption was neither a signal in this wider model, nor in the earlier bariatric model, but other substances at baseline (marijuana-related, or ethanol) may be associated (as a signal) with desensitizing patients to ITM-related pruritus risks in this wider model. Tobacco use (which could not be evaluated in the bariatric analyses, since all cases entailed non-smokers) was a non-signal in this wider model. Non-Caucasian race/ethnicity (entailing African-Americans and Hispanic/Latino) and diabetes status did not appear to influence pruritus occurrence, neither in this wider model, nor in the earlier bariatrics model. Higher BMI signaled an incremental function of higher itching risk, while surgical duration signaled an incrementally lower itching risk, in this wider model (neither of these signals had emerged in our earlier bariatrics model).

[iv]) into the 5-MMAEPPx plan (bundle[iii]) should help avoid hospital cost escalations associated with usual rescue/work-up PONV care, and extended length of stay (22). Continuing, (b) ITM + Mg$^+$ (bundle [i]) signals POD#2 PONV reduction and/or protection (Panel 2b), presumably via strategic avoidance of other/HALO opioids (bundle [ii] extended postoperatively). Next, (c), diabetes appears to be a PONV-protective factor [POD#0–1 Panel 2a, which has been previously reported (1)], along with diabetes signaling (Panels 1b, 2b) lower PONV risks into POD#2. Further, (d), Apfel factor "Past PONV" remains as a logical signal of PONV prediction on POD#2 (Panel 2b). Readers are directed to the fully descriptive captions and footnotes of Tables 1, 2, Panels 1b, 2b.

3.5 Models addressing any HALO use on POD#0−2 (dichotomous variable)

When considering both models (Tables 1, 2) and comparing ITM and ITM + Mg$^+$ (among other comparisons), for identifying HALO use predictors on POD#0–2 (Panels 1c, 2c), we observed the following. First (a), ITM + Mg$^+$ (bundle [i]) appearing to be a confident predictor of opioid sparing, in that the co-administered intrathecal MgSO$_4$ may attenuate "rebound pain" possibilities (or pain severity) as initial-dose ITM effects dissipate. Next, (b), intraoperative HALO (Panel 2c)

appears to induce hyperalgesia/tolerance (opposite of the objectives of bundle [ii]), as described elsewhere (23), including in rodent models (24), even with only brief exposure. Further, (c), any non-opioid analgesic (bundle [v]) reducing POD#1 pain scores seem likely to provide associated HALO avoidance; while (d), baseline opioid use preoperatively being a possibly overrated signal with ITM + Mg$^+$ use. Next, (e), Current-case PONV (POD#0, Panel 2c) appears to curb opioid dosing thereafter, which may reflect (1) the care team withholding opioids with known new PONV, or (2) a patient not wanting opioids based on current PONV. Further, (f), all three (and not less than three) of our oral multimodal non-opioids on-schedule, started preoperatively (Panel 2c), appear to be predictive of less frequent future HALO use/need. Finally, (g), Agents such as semaglutide (Panel 2c) may warrant evaluation for possibly worsening postoperative pain perception and/or opioid requirement/utilization. Readers are directed to the fully descriptive captions and footnotes of Tables 1, 2, Panels 1c, 2c.

3.6 Models addressing pruritus on POD#0−2 (dichotomous variable)

When considering bundles of predictors (Panels 1d, 2d) evaluating ITM ± Mg$^+$ and pruritus, we observed the following.

First, (a), female gender and ITM dose, not surprisingly, were predictive of pruritus, but higher-dose preoperative palonosetron (e.g., 150 µg instead of 75 µg, Panel 1d) may be protective, based on bariatric observations. Next, (b), any IV HALO on POD#0–1 (in bariatrics) appeared to increase the occurrence of associated pruritus. Further, (c), volatile agents may signal more postoperative itching, perhaps via sensitization, while (d), celecoxib (in bariatrics) may enhance itching, along with marijuana and/or ethanol consumption (in all ITM cases) having signals of desensitization associated with fewer itching occurrences. Readers are directed to the fully descriptive captions and footnotes of Tables 1, 2, Panels 1c, 2c.

4 Discussion

4.1 Specific aims, and future recommended bundles for hypothesis testing and compassionate care

The specific aims, using multivariable logistic regression analyses, were to present bundles of integrated potential predictors related to (a) POD#0–1 PONV (Panels 1a, 2a) when evaluating an intrathecal analgesia plan entailing ITM ± Mg$^+$; (b) POD#2 PONV (Panels 1b, 2b) when there had been no PONV on POD#0–1; (c) greater associated avoidance of downstream HALO after ITM ± Mg$^+$ use (Panels 1c, 2c); and (d) POD#0–2 pruritus (Panels 1d, 2d). More compelling than the bundles of predictors and signals, however, was the raw data observation of 69% downstream opioid avoidance after bariatric surgery with ITM + Mg$^+$ (bundle [i], compared with 18% after ITM-only and bundles [ii–v]), and 57% downstream opioid avoidance in our entire ITM + Mg$^+$ cohort (bundles [i–v], vs. 14% after ITM-only). All of these outcomes entail routine use of off-patent products not carrying excessive expense or side effect burden. Also compelling (from raw data in Supplementary Table S2) were confirmations in follow-up to previously published (1) PONV and related outcome data: 5% POD#0 PONV after ITM with 5-MMAEPPx [vs. 14% in discretionary PONVCG-guided practice in pre-ITM Veteran historical controls (1)], 11% POD#1 PONV after ITM with 5-MMAEPPx [vs. 24% (1) in the same Veteran historical controls], and 15% PONV across POD#0–1 after ITM with 5-MMAEPPx [vs. 27% (1) in the same previously-reported Veteran historical controls].

4.1.1 The 5-MMAEPPx preoperative "bundle (iii)", and its postoperative prophylactic boosters ("bundle [iv]")

To restate and clarify next steps in hypothesis testing, from herein and from previous publications, the 5-MMAEPPx bundle had first entailed palonosetron (now recommending IV 250 µg, vs. data herein using 150 µg). Next in 5-MMAEPPx was perphenazine [4–8 mg *per os* (PO), with dose selection based on age and body mass index (BMI), assuming no Parkinson's disease and/or past extrapyramidal reactions to drugs of a similar class]. After palonosetron-perphenazine, aprepitant 40 mg PO,

diphenhydramine 20 mg IV, *and* dexamethasone 8 mg IV, are incorporated, with all 5-MMAEPPx medications administered before operating room entry (1). We also confidently propose booster dosing postoperatively for future hypothesis testing (and compassionate care, within or outside the ITM ± Mg$^+$ context), entailing daily perphenazine PO, 4–8 mg (based on age and BMI), daily aprepitant 40 mg PO, and every 40 h IV palonosetron, dose to be determined, likely 150–250 µg, with the latter already accepted and approved as a chemotherapy dose.

4.1.2 The non-opioid analgesic "bundle (v)," and the NMDA-based "bundles (i and v)," and their boosters

To restate herein the recommended non-opioid analgesic bundle for hypothesis testing and/or compassionate care, we suggest (a) pre-, intra- and post-operative acetaminophen, (b) pre- and daily post-operative celecoxib (400 then 200–400 mg) or instead meloxicam (15 then 7.5–15 mg), assuming no renal dysfunction, and (c) 60 mg PO sustained-release dextromethorphan, before surgery and every 12 h thereafter; all of these within or outside the ITM ± Mg$^+$ context). The NMDA focus entails the described dextromethorphan (bundle [v]), and the 25 mg dose of IT Mg$^+$ (bundle [i]) to be routinely used in conjunction with ITM. Intraoperative ketamine would be another likely beneficial NMDA-based strategy.

4.1.3 The HALO-avoiding bundle (ii)

To restate herein the recommended HALO-avoiding bundle for confident hypothesis testing and/or compassionate care, we suggest (a) IT Mg$^+$ enhancing ITM (bundle [i]), (b) ITM (bundle [i]) starting at doses of 250 µg for women and 300 µg for men, with further mathematical adjustments, previously reported (2), and (c) avoided pre-/intra-operative fentanyl/remifentanil/hydromorphone (bundle [ii]). Future hypothesis testing (not based on our data) could further entail postoperative buprenorphine (25) (and the aforementioned non-opioids in Section 4.1.2 above and bundle [v]) replacing usual postoperative hydromorphone/oxycodone/hydrocodone sequences (and reflexive discharge prescriptions thereof).

4.2 Raw data regarding downstream opioid avoidance with ITM + Mg$^+$; forecasting the value of methadone and/or buprenorphine intra-/peri-operatively based on ITM + Mg$^+$ outcomes herein

4.2.1 Phase out the HALO?

The following data-informed opinion likely serves as a centerpiece to downstream opioid avoidance after surgery (in patients not taking opioids at baseline). Strategic avoidance of intraoperative usual HALO (fentanyl/remifentanil/hydromorphone, Panel 2c, bundle [ii]), and avoidance of usual HALO immediately postoperatively (hydromorphone/oxycodone/hydrocodone) appears to be a logical starting point. This can then logically incorporate bundles (i, ii, and v), with likely

further facilitation by bundles (iii, iv, and vi), to promote associated postoperative HALO downstream avoidance, based on recommended enhanced recovery QI tracking/research, with the ITM + Mg$^+$ being the "opioid of choice" instead of HALO. Our confidence in these statements is further based on (a) similarities to clinical observational findings of Curry et al. (23), and (b) similar basic science mechanistic findings in rodent models (24) by Chen et al. In the first of these, Curry et al. (23) reported that during joint replacement, increasing doses of intraoperative hydromorphone in an enhanced recovery pathway was associated with paradoxically higher pain scores and opioid requirements, which these authors attributed to intraoperative acute tolerance and/or opioid-induced hyperalgesia. Rephrased, any brief exposure to HALO opioids, be it intraoperatively (23), or in a rodent model (2022) (24), produces hyperalgesia and early tolerance. *Hyperalgesia and early tolerance* from fentanyl/remifentanil/hydromorphone/oxycodone, likely hydrocodone, and perhaps tramadol (26), etc., *should be generally expected and accepted as likely to occur*.

The scourge of oxycodone on society at large goes without saying (27, 28). Any HALO drug given to patients that are awake/conscious *should be generally expected, and accepted*, to be euphoria-producing (29), adding to baseline psychological and other behavioral factors that may contribute ultimately to conditions up to and including opioid use disorder (OUD), and colloquially stigmatized as "addiction."

4.2.2 Is it more important to avoid all opioids, or instead to specifically avoid HALO?

Extending these principles from above leads to necessary re-interpretation of *opioid-avoidance* literature (30) (Santa Cruz Mercado, et al., 2023) in recent years. Specifically, their reported outcomes were *converse* to those in the above joint replacement case series (23) (upon superficial evaluation). This context now, *in retrospect*, may have since generated worrisome misinterpretations (and likely HALO use exacerbation). Specifically, they (30) reported less chronic persistent surgical pain (CPSP) and less new persistent opioid use (NPOU) with intraoperative fentanyl (as opposed to *non-opioid* techniques), but they excluded from their analyses cases that involved regional anesthesia, methadone use, and/or buprenorphine use. If academic dialogue entails "meeting in the middle" for important public health considerations, we opine that (i) fentanyl/hydromorphone/oxycodone/hydrocodone/tramadol avoidance of initial exposure is likely more important than the mitigation of chronic persistent surgical pain from non-opioid anesthesia techniques, and (ii) replacement of HALO with ITM + Mg$^+$, methadone, and/or buprenorphine may better mitigate outcomes related to CPSP and NPOU than do the described HALO agents. These (30) authors considered only two opioids that we define as HALO (fentanyl and hydromorphone), this research having occurred during an earlier era (2016–2020, i.e., just after declaration of the opioid epidemic) where anesthesia QI/research was considering (briefly) "all-opioid avoidance," or *opioid-free anesthesia*. Specifically, data (30) analyzed over 11 months concluding in

October 2022 not only may have missed the Curry et al. institutional case series (23), but also likely pre-dated the basic science (24) demonstration of short-duration exposure to opioids mechanistically creating both tolerance and hyperalgesia in rodents. To their credit, these (30) authors used elegant institutional data harvesting of over 61,000 patients, and propensity-based data modeling, that unfortunately included *only* HALO *while specifically excluding* (a) non-HALO, and (b) interventions such as regional anesthesia use. Then these (30) authors, in good faith, reported that *absence of fentanyl/hydromorphone* had *worse hospital outcomes* and *worse 3-month chronic pain* reports, than did patients receiving fentanyl and/or hydromorphone. The methodological difference between our work (1–3) including herein, and the good-faith methodological advance (30) ("big data" and propensity scoring, but exclusively HALO use vs. no opioids) is that our protocol herein was *not* "opioid free." Rather, our protocol was *HALO-free*, and showed important, logical, interacting associated bundles, factors, and trends that can confidently allow us to safely and reasonably remove fentanyl, hydromorphone, and remifentanil HALO opioids from ITM + Mg$^+$-applicable cases. Further, HALO avoidance can urgently compel new enhanced recovery QI/research necessity for similar non-HALO characteristics, such as perineural (31–34) or other routes of buprenorphine delivery, and/or methadone via front-loaded IV bolus (35–46) or before surgery oral-enterally (47) (as recently shown in contexts of IV methadone drug shortage). In other words, *we are confident that perioperative HALO avoidance is feasible in the opioid-naïve*, when replaced by (i) non-HALO opioids, (ii) appropriate MMAEPPx "bundles" as outlined herein and elsewhere (1–3), and (iii) non-opioid analgesic bundles encompassing acetaminophen, nonsteroidals or COX-2 inhibitors, *and* N-methyl-D-aspartate agents (IV ketamine intraoperatively, and oral sustained-release dextromethorphan *both* pre- *and* post-operatively). The authors herein are not claiming an "*easy button*" process, but, rather, we are outlining a *complex but feasible* process, entailing all integrated facets, after needed re-education distinguishing HALO from the proposed non-HALO [ITM + Mg$^+$, likely methadone, and likely buprenorphine, as described further below (Sections 4.2.3 through 4.2.6)], strengthened observationally by the multivariable logistic regression model and outcomes described herein.

4.2.3 Are there any non-HALO down-sides?

We acknowledge room for improvement on ITM-induced opioid complications, particularly itching, and perhaps urinary retention (pending necessary study), understanding that any route-of-delivery of methadone and/or buprenorphine may also cause, perhaps less-frequently, similar itching or urinary concerns as ITM ± Mg$^+$. Logic may dictate that nuisance itching in ~20% of patients (until further discovery of better prevention) might be an acceptable interim "trade-off" alternative if downstream HALO avoidance approaches or surpasses a 50% opioid-sparing avoidance outcome, as reported in our observational data.

4.2.4 Is postoperative oxycodone (as prescribed by our surgical colleagues) the real problem? Or is the problem truly *any* exposure to *any* HALO, sufficiently before *any* oxycodone exposure?

Taking the position above further (from Sections 4.2.2 and 4.2.3), health care professionals not appreciating these nuances (23, 24) may be unknowingly steering their patients via *initial* or *any* HALO exposure (23, 30) to both "part of the numerator and denominator" of the opioid epidemic, *even with brief* (24) *exposure, involving now-documented mechanisms of action*. It is generally accepted that 6% of surgical patients go on to develop new persistent opioid use (NPOU) (48). Regarding *opioid overdose events* within 1 year after surgery, Veterans are ascribed a 0.68%–0.8% risk, vs. propensity-matched non-surgical controls (0.1%) (49). Much of the work from these authors (48, 49) has entailed a well-intended effort, targeting surgeons' postoperative prescriptions of oxycodone as the basis of analysis (i.e., number of pills), for what seems to be a *secondary* prevention focus. Neither of these citations (48, 49) seems to have considered the specific type of opioid exposure intraoperatively, as a "gateway" to subsequent oxycodone homegoing prescription "craving", presumably related to such datasets not disclosing or analyzing intraoperative opioid used. We recommend reconsidering the definitions of *primary* vs. *secondary prevention*, by assuming that even brief intraoperative HALO exposure (23, 24, 30) may be just as "guilty of a culprit" as postoperative oxycodone prescriptions by our surgical colleagues, and therefore may be a more logical (and simultaneous) target of "*primary prevention.*"

Regarding *primary* prevention, we now have literature basis (35–46) to supplant all intraoperative HALO with either ITM + Mg$^+$ (herein), or intraoperative methadone (while patients are on continuous telemetry, and esmolol/magnesium therapy is available), and we have early literature basis to replace HALO/oxycodone default with an option such as transdermal (25) or buccal buprenorphine, as recently reported, for patients that present to surgery not on baseline full-agonist HALO opioids.

4.2.5 Can we trust *every* consensus guidance or government statement *every* time?

Continuing the theme of agency guidance regarding "opioid safety," we are grateful for the 2022 United States Veterans Administration and Department of Defense Clinical Practice Guidelines (USVADODCPG) (50) incorporating buprenorphine for the treatment of *chronic* pain. It seems that similar refinement of the guidance for the *acute* pain realm, also incorporating preoperative ITM + Mg$^+$ and/or pre-/intra-operative methadone, would be similarly central to both adequate pain relief and primary prevention of NPOU. As background, since the release of the original US Centers for Disease Control (CDC) Guidelines for Prescribing Opioids for Chronic Pain (2016) (51), before USVADODCPG), medical providers, including in surgery, have better acknowledged abuse liability after any HALO exposure, and some have steered patients to incrementally shorter courses of HALO for acute, post-surgical pain (51–53). This change in practice has had some impact on

preventing NPOU, given that the baseline NPOU rate is estimated to be 6% after at least 1 day of HALO therapy, 13.5% NPOU after a first extended episode of exposure entailing ≥8 days, and ~30% NPOU when the first extended episode of exposure use was for ≥31 days (54) [this (54) citation not having addressed NPOU risk of methadone-as-first-opioid, or of buprenorphine-as-first-opioid]. Indeed, patients with even one day of HALO exposure can develop NPOU; the mandate for care process advances is evident. *In other words, standard perioperative opioid regimens incorporating HALO agents (before any exposure to surgeons' oxycodone prescriptions) may be inadvertently leading patients to NPOU, and so the anesthesia process "gateway" can now serve as a logical portal for primary prevention.* As a result, ITM + Mg$^+$ (in conjunction with other proposed changes such as an "NMDA bundle" [i and v], a non-opioid analgesic bundle [v], and the described 5- and 3-MMAEPPx bundles [iii and iv]) may ultimately provide "net-less-addictive" alternatives for pain management (directly, with bundles [i and v], and indirectly, with bundles [iii, iv, and vi]). Furthering this HALO avoidance concept, Morrissey et al. (25) recently advocated for a paradigm shift toward *buprenorphine for treating acute, post-surgical pain* for orthopedic surgery; we support this change in practice, and offer the additional hypothesis that buprenorphine seems likely to further reduce NPOU post-surgery by facilitating downstream avoidance of HALO analgesics. Together, these integrated innovative bundles may lower the otherwise unchanged potential for NPOU post-surgery. The available bundles can hopefully compel refinement of current clinical practice guidelines grounded in the aftermath of Oxycontin®, which assume (50) that all long-acting opioids (i.e., methadone and buprenorphine) resemble Oxycontin® in its hyperalgesic neuroplasticity (an assumption possibly warranting a re-phrase by the CDC and in subsequent USVADODCPG).

4.2.6 Moving forward by defining "HALO" vs. "non-HALO", and incorporating enhanced recovery bundles

We previously described our OVID Medline search failing to identify single-injection ITM as either euphoric, hyperalgesic, and/or creating worrisome acute tolerance effects. Our position is that methadone seems more likely to resemble the pharmacologic behavior of ITM + Mg$^+$ than of HALO (fentanyl, hydromorphone, etc.). Our position continues to extend favorable non-HALO attributes to buprenorphine, with lead author BAW having fairly extensive experience with perineural buprenorphine being both duration-extending (31–34) and opioid-sparing (33, 34). There may be value in abandoning HALO opioids for routine use in perioperative contexts in favor of a combination or series of ITM + Mg$^+$ (when anatomically appropriate), buprenorphine by any route, and/or methadone (IV and/or PO), along with esmolol infusions (55) as a "therapeutic substitution" for fentanyl/hydromorphone boluses and/or remifentanil infusions during surgery. Supplementation of all three *non*-HALO opioids by an NMDA antagonist bundle (e.g., IT Mg$^+$ before surgery, IV ketamine during surgery, PO dextromethorphan *both before and after* surgery) appears to be

rational. The work herein again (1–3) supports (a) the 5- and 3-MMAEPPx (bundle concepts [iii, iv], and (b) associated postoperative multimodal analgesic booster (bundle [v]) dosing daily, described above (Sections 4.1.1–4.1.3). After our having observed only a modest effect from just using booster perphenazine and aprepitant as non-sedating antiemetics, producing an associated antiemetic benefit on POD#1 in bariatric sleeve gastrectomy (2), but not for all ITM cases previously (2) evaluated, we have suggested (for bundle [iv] moving forward) booster palonosetron every 40 h for hypothesis testing and compassionate care, in addition to perphenazine/aprepitant boosters. Regarding other non-HALO options when ITM + Mg⁺ is anatomically inappropriate for the planned surgery, buprenorphine (inserted into bundles [ii and v] via the transdermal route was recently described by Morrissey et al. (25), steered in part by palliative care medicine expertise (see Section 4.1.3 above, while also incorporating Section 4.1.2 above). Perioperative methadone use has had a recent plethora of successful research, and a longstanding record of success for over 3 decades (35–46), with much of this perioperative methadone research unfortunately "contaminated," at least partially, by a routinely-used perioperative HALO opioid; methadone could be inserted into: (a) bundle (i) as both a non-HALO opioid, and an IT Mg⁺-analogous agent addressing NMDA, (b) bundle (ii) as differing from the enlisted HALO opioids, and (c) bundle (v) with its co-analgesic effects again addressing NMDA.

4.3 Dosing guidance for ITM + Mg⁺, methadone, and/or buprenorphine intra-/ peri-operatively

The recommended ITM dose has been reported by our group recently in this journal (2), and anticipated analgesic durations with ITM dosing (but without Mg⁺) were also presented as a potentially useful, statistically-driven formula/calculation (2). Anecdotally, our efforts to reduce ITM doses (below 250 µg in women and 300 µg in men) in the presence of IT Mg⁺ did not manifest as successful, after a limited number of cases required IV opioid in the post-anesthesia care unit; this could be an avenue for further study. As for other non-HALO, we (i) re-cite recommended IV methadone dosing as covered by Kharasch et al. both in outpatient same-day (45) and next-day (37) discharge, and (ii) reference perineural buprenorphine dosing from our center's work (31, 32), and associated precautions (56).

4.4 Central role of the 5-MMAEPPx bundle

Our described 5-MMAEPPx strategy (1–3) (bundle [iii]) appears to be a useful and *necessary* start point for the likely increase in nausea created with preferential use of ITM + Mg⁺, methadone, and/or buprenorphine. It is *unlikely sufficient*, however. Our models herein supported "double-booster" antiemetic dosing on POD#1 as a signal for our bariatric cases

(Panel 1a), including the highly-emetogenic sleeve gastrectomy procedure, but "antiemetic double booster" postoperatively was neither a predictor nor a signal in our overall ITM cohort (Panel 2a). Our guidance for enhanced recovery protocols is to now embrace every-40-hour palonosetron boosters in hypothesis testing and in compassionate care, in addition to perphenazine/aprepitant, to re-evaluate whether the third MMAEPPx booster dose (bundle [iv], Section 4.4) is associated with an improved longer-term antiemetic outcome that is more generalizable than just in bariatrics/sleeve gastrectomy. In such a situation, IV diphenhydramine could preferentially serve as a PONV *rescue* agent (as it is in our center) due to its sedation risk (as opposed to being used as a booster).

4.5 PONV predictors (bundle [vi]) on POD#0−1 having a differing profile than PONV predictor bundles on POD#2

Our bundles of predictors and signals for PONV differed on POD#2 vs. POD#0–1. We are not aware of such having been previously reported. The Mg⁺ adjunct to ITM seemed to create opioid-sparing and antiemetic benefits downstream, even into POD#2. POD#0–2 multimodal analgesics dextromethorphan (Panels 1b, 2b) and celecoxib (Panel 2b) contributing (unfavorably) toward POD#2 PONV risk reinforces the probable usefulness of enhancing the antiemetic booster regimen (bundle [iv], Section 4.4), as described above. Apfel et al. (57) are to be congratulated and thanked for their original predictors, for which "past PONV" was a predictor in our POD#0–1 model (Panel 2a) and a signal in our POD#2 model (Panel 2b). Two other 1999 (57) predictors (gender, smoking status) from Apfel et al. did not enter any of our POD#0–2 PONV models, perhaps because of ITM (with or without Mg⁺) being a dominant predictor in these equations. It is logical to consider inflammatory response dynamics, likely cumulative, as also contributing to POD#2 PONV predictors differing from those of POD#0–1.

Intraoperative *and* POD#0–1 postoperative IV opioids (Panel 2a) were another astute predictor of POD#0–1 PONV that originated from Apfel et al. (57), although in our data, no particular opioids or routes of delivery (including ITM dose-response) were predictive of POD#2 PONV (after encountering no PONV on POD#0–1).

4.6 Predictors of downstream HALO need/consumption

No opioid specifics were factors or signals in our limited-sample, all-endoscopic, bariatric surgery ITM cases (Panel 1c). However, for the entire ITM ± Mg⁺ cohort (Panel 2c), baseline opioid was a signal ($P = 0.159$) for later opioid need/consumption, while in-OR IV HALO (opposite of bundle [ii]) was a potent associated predictor of downstream opioid need/consumption. In short, these two variations of Apfel et al.

(57) opioid-related PONV predictors were associated in our data with postoperative HALO requirement/consumption. Enhanced recovery QI/research priorities should, hence, entail total HALO avoidance in the OR [reiterating esmolol infusion (55) as a therapeutic substitution], along with further testing of methadone and/or buprenorphine intra-/peri-operatively, to specifically detect patterns of downstream HALO avoidance, and associated satisfactory analgesia (conferred by the described multimodal non-opioid analgesics, and if insufficient, preferential rescue doses of methadone or of buprenorphine (25), as opposed to hydromorphone (58) or oxycodone (27, 28).

4.7 The pruritus dilemma

In our sample, women had more frequent ITM-associated pruritus (Table 2 Panel 2d) than did men. The ITM dose was an associated predictor across all ITM cases (Panel 2d), but we do not rule out the possibility that the spinal Mg^+ effect may have been underpowered, with 16/60 $ITM + Mg^+$ patients (27%) encountering pruritus, and not differing (in incidence) between 25 and 50 mg Mg^+ doses. Anecdotally, the 50 mg-associated pruritus may have been more intense and bothersome than was itching after 25 mg Mg^+. Future research may best start with 25 mg Mg^+ (not 50–100 mg) as the intrathecal dose, and consider a visual analog scale for itching to better quantify this otherwise subjective response related to $ITM \pm Mg^+$. Also surprising, in bariatric surgery, the primary nonsteroidal class of drug used was celecoxib (technically, a type-2 cyclo-oxygenase inhibitor), and the "nonsteroidal drug class" was an itching predictor (Panel 1d). We later learned of anti-itching benefits of higher doses of palonosetron [than the 75 µg dose recommended for consensus-guided (59) PONV prophylaxis]; we then increased routine palonosetron doses from 75 to 150 µg, only to learn even later that 250 µg was the ED_{50}-associated dose (60) of palonosetron required to meaningfully address itching. It may make sense to hereafter "supersize" palonosetron ITM-MMAEPPx dosing to 250 µg (an already-approved dose for nausea from chemotherapy) for both anti-itching and antiemetic purposes, particularly since Apfel et al. (20) have declared *palonosetron as non-concerning* for QT-interval prolongation on the electrocardiogram.

As far as other interventions with which better anti-itching may be achievable, IV opioids on POD#0–1 was a logical predictor of associated pruritus in bariatrics (Panel 1d). Another pruritus signal in both bariatrics (Panel 1d) and across the entire ITM sample (Panel 2d) entailed volatile agents enhancing itching risk, while baseline consumption of other substances [tetrahydrocannabinol/cannabidiol (THC/CBD), or ethanol] may have desensitizing effects with respect to ITM-related pruritus (Panel 2d). Higher BMI signaled an incremental (step) function of higher itching risk, while surgical duration signaled an incrementally lower itching risk (both Panel 2d) across the entire ITM sample, with or without Mg^+-specific effects statistically apparent, in an acknowledged small sample.

4.8 Limitations

As previously reported recently in this journal (2), Veterans may be a lower-risk population for PONV than others, so future validation in diverse cohorts is indicated. As a result, forecasts of 5-MMAEPPx success in ITM cases (with or without Mg^+) may differ in the non-Veteran population. To offset this, we again allowed for signals (with $P \geq 0.05$ but <0.2) in our bundles for the final regression equations (Panels 1a–d, 2a–d), representing potentially interacting factors manifested, perhaps, by the further inclusion of Mg^+ with ITM, but heretofore remaining possibly underpowered. Further, there may have been uncontrolled confounders such as surgical technique variations and patient adherence to the recommended regimen (such as not following the orders as written, and/or opting instead to skip a step in the recommended sequence of booster doses, and related).

For the next limitation, postoperative bladder catheters were near-ubiquitous in this ITM/major abdominal surgery patient population; issues regarding postoperative urinary retention will need to be separately addressed, related to Mg^+ specifically. Importantly, our data did not entail co-administered local anesthetics such as bupivacaine, and their independent effects on recovery of bladder function.

Further, we acknowledge [as we did previously (2)] our inability to derive sample sizes and power analyses: our observations remain limited to a single-center Veterans population, which may not generalize to broader, diverse patient populations. Again, we could only "case match" the cases that were performed with ITM (with or without Mg^+), from a smaller pool of historical control cases performed at the same institution, as was previously described (2). Future work by research teams internationally can certainly expand the cohort and include non-Veteran populations, to enhance generalizability. Accordingly, we cannot rule out the problematic potential of selection bias.

Next, we acknowledge the 27% pruritus incidence, regarding which our mitigation strategies were to first pre-empt with diphenhydramine (which was already part of the 5-MMAEPPx strategy, bundle [iii]), and next increase our 5-MMAEPPx palonosetron dose to a standardized 150 µg dose, with rescue diphenhydramine followed by transnasal butorphanol (based on repeated shortages of IV butorphanol/nalbuphine). We observed a possible reticence of healthcare professional support staff to use the ordered butorphanol for reasons unclear to the authors, opting instead for "easy button" repeated diphenhydramine doses and verbal reassurance. This may be related to requirements with butorphanol for two-person unused opioid discard practice, with pruritus often occurring during overnight shifts with possibly less nurse staffing, having been a potential contributor to this local cultural factor. Future antipruritic prophylaxis [beyond increasing palonosetron from 150 to 250 µg per dose, an approved dose for chemotherapy, and not (20) affecting QTc interval matters] would seem to be on the immediate forefront of pruritus prevention research, along with any other pruritus-related interventions. Future antipruritic research should also include clinical data collection of pruritus severity scales (for which a visual analog score should be sufficient), that would be easily

incorporated into routine care for QI analysis when also ensuring comparability of groups including factors such as age and type of surgery, evaluating administered ITM with vs. without intrathecal Mg^+.

Finally, incorporating all described multimodal processes and bundles (i–vi) into an overarching enhanced recovery protocol [including 5-MMAEPPx, and otherwise complete opioid avoidance (other than $ITM + Mg^+$) until after extubation with the patient being physically stationed in PACU] may be a suitable start-point for prospective evaluations, for example, evaluating another type-2 cyclo-oxygenase inhibitor (e.g., meloxicam instead of celecoxib), or evaluating palonosetron-perphenazine-aprepitant boosters (instead of only perphenazine/aprepitant, to date).

5 Conclusions

We can confidently hypothesize for future enhanced recovery "bundle" research addressing HALO avoidance pre- and intraoperatively. First (a), $ITM + Mg^+$ (supported by 5-MMAEPPx and the recommended 3-drug booster dosing enhancements, while limiting Mg^+ to a 25 mg dose) will likely yield significant outcome improvements, including a potential "quantum leap" in downstream HALO opioid avoidance after surgery. Next (b), intraoperative and immediate postoperative avoidance of all described HALO opioids seems likely to facilitate downstream HALO avoidance success, with such intraoperative HALO opioids being easily substituted out and replaced by intraoperative esmolol infusions (55), knowing that analgesia would be confidently covered by preoperative intrathecal Mg^+ added to a sufficient, previously reported (2), formula-based ITM dose. Further (c), PONV on POD#0–1 vs. POD#2 appears to have differing predictor bundle patterns, warranting *maintained* 5-MMAEPPx preoperatively, *while further upgrading* daily booster prophylaxis (perphenazine-aprepitant) to include every 40-hour palonosetron as the logical next step in booster PONV prophylaxis. Finally (d), ITM-related pruritus requires further study regarding prophylaxis and treatment, for $ITM + Mg^+$ to seemingly achieve its full enhanced recovery potential in trying to avoid HALO exposure.

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 Institutional approval (approval/exemption 1670098, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Quality Improvement query of clinical routine is not deemed to be research.

Author contributions

BW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. RC: Conceptualization, Data curation, Methodology, Resources, Software, Writing – review & editing. CS: Conceptualization, Data curation, Methodology, Resources, Software, Writing – review & editing. KG: Conceptualization, Data curation, Methodology, Resources, Writing – review & editing. CE: Data curation, Formal analysis, Investigation, Resources, Writing – review & editing. MB-K: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Writing – review & editing. LL: Conceptualization, Investigation, Resources, Writing – review & editing. JL: Conceptualization, Investigation, Methodology, Project administration, Resources, Writing – review & editing.

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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.2025.1592643/full#supplementary-material

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