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# Historical perspectives supporting the ambitious anesthetist aiming for zero nausea/vomiting: should one trust every consensus statement every time?

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Within the domain of perioperative prophylaxis against postoperative nausea and/or vomiting (PONV), there seems to be (i) a consensus-guided "hard stop" recommendation after four prophylactic anti-emetic medications are utilized, and (ii) an assumption that each of the four "usual" PONV medications/categories produces 25% risk reduction from the "previous baseline", representing a "law of diminishing returns." Meanwhile, recently-described 5-medication PONV prophylaxis (palonosetron, perphenazine, aprepitant, dexamethasone, diphenhydramine) has been observed to achieve 90%–95% prophylaxis success, particularly in patients receiving intrathecal morphine (a known, potent emetogenic stimulus). This ***meaningful*** prevention thematically differs from the ***scholarly*** prevention benchmark that may be over-reliant on patient-specific preoperative risk factors, described in the 1990s and before, dictating prophylaxis strategies. Meaningful prevention with 5-medication PONV prophylaxis (which we recommend before entry into the operating theater) (i) may serve as a surprisingly effective antecedent to further avoid postoperative opioids, (ii) may be augmented throughout hospitalization and convalescence with daily "booster dosing", and (iii) may (in combination with booster dosing) mitigate possible "rebound nausea" that has been reported by esteemed PONV thought leaders in the context of post-***discharge*** nausea and/or vomiting. The described processes (pan-prophylaxis before emetic stimuli are incurred, antiemetic booster dosing, and potential downstream opioid reduction by enhancing adherence to postoperative oral/enteral non-opioid analgesic formulations) would seem to create a win-win scenario for patients and hospitals alike. The described antiemetic techniques remain compatible with available opioid-free anesthetic techniques [lidocaine, acetaminophen, N-methyl-D-aspartate (NMDA) antagonists, etc.]. Some perspectives shared herein may further inform as to how and why.

KEYWORDS

**palonosetron, perphenazine, aprepitant, diphenhydramine, dexamethasone, intrathecal morphine, postoperative nausea and vomiting**

# 1 Introduction

Macario et al. addressed patient-willingness-to-pay for common post-anesthesia symptoms [1999 (1)], describing patients given US$100 to spend to avoid unwanted outcomes: US $30 was allocated to avoid postoperative nausea/vomiting (PONV), US$18 to avoid gagging on the endotracheal tube, and US$17 to avoid pain. Currently, 5 off-patent antiemetics (2) of differing mechanisms are available for prophylaxis at a total cost which is lower than this US$30 threshold. This cost is also (i) half that of 200 mg sugammadex, a cost deemed as justified (3) for routine reversal of rocuronium neuromuscular blockade, and (ii) less than the cost difference between ~US$65 sugammadex (200 mg) and US$25 for 5 mg neostigmine and 0.6 mg glycopyrrolate for neuromuscular blockade reversal. Therefore, one could revisit patient-centered fiscally responsible multimodal antiemetic prophylaxis (MM-AEPPx), leading "closer to zero PONV" and to post-discharge nausea/vomiting (PDNV), irrespective of anesthetic technique. This is based on recent observations (2) when utilizing 5-medication MM-AEPPx in tandem with intrathecal morphine (ITM, which is by nature emetogenic), including in bariatric patients undergoing the especially-emetogenic sleeve gastrectomy surgery (4), irrespective of PONV risk factors. This (2) report described (with 5-medication prophylaxis) an ***~85% risk reduction*** when compared with case-matched historical controls following standard practice/consensus-guidance. Further noted is other external frustration with PONV Consensus Guidelines (PONVCG) (5–8) posted by, for example, bariatric surgery societies (International Society for the Perioperative Care of the Patient with Obesity, and the American Society for Metabolic and Bariatric Surgery) (4), motivating this perspective, and the following reflections from past and present.

# 2 Subsections of interwoven statements and perspectives

## 2.1 What was the impetus toward MM-AEPPx (irrespective of risk factors) starting in 1996–1998, years before the inaugural 2003 PONVCG?

The lead author and clinical colleagues were charged with converting a "same-day admission" orthopaedic sports medicine surgical procedure [arthroscopic anterior cruciate ligament reconstruction (AACLR)] to "same-day discharge home." This preceded landmark PONV manuscripts by Dr. Christian Apfel and colleagues in 1999 [addressing predictive risk factors (9)] and 2004 [addressing multimodal therapeutic efficacy (10)]. Same-day discharge after AACLR was newly required (by market forces) in the mid-1990s, since third-party payers in the United States were no longer reimbursing hospitals for admission, instead only providing a capitated payment. The previous hospital culture of "all general anesthesia (GA) all the time" was soon transformed to primarily regional anesthesia (RA), or less commonly to combined RA-GA. One objective was to have patients emerge from anesthesia sufficiently quickly and symptom-free to reliably and safely fast-track through the traditional Phase 1 post-anaesthesia care unit (PACU) (11). Patients could then be reunited with their families sooner, *en route* to earlier discharge home. We learned (before any available PONVCG) that routine MM-AEPPx was central to minimizing both patient symptoms and postoperative nursing workload, *en route* to same-day discharge. We did this by (i) avoiding volatile agent GA (long before documented carbon footprint concerns), (ii) using propofol sedation, (iii) providing routine nerve blocks instead of opioids for analgesia, and (iv) using perphenazine and dexamethasone (and propofol sedation when GA was not used) as low-cost, off-patent MM-AEPPx, irrespective of risk factors. Phase 1 PACU Bypass fast-track criteria that were used [now called the WAKE Score (11)] emphasized multimodal prevention of pain/hyperalgesia, PONV, itching, and shivering. WAKE criteria called for routine MM-AEPPx (instead of rescue), since the postoperative routing goal of such patients was Phase 1 PACU Bypass (fast-tracking). This practice pattern of fast-tracking preceded international publications and professional societies addressing enhanced recovery after surgery (ERAS). Meanwhile, most every antiemetic study cited by the serial PONVCG publications (5–7), including the most recent (8), entailed a forced admission to the PACU Phase 1 recovery room after surgery, with no apparent option (or motivation) for PACU Bypass/fast-tracking. Meanwhile, our pre-ERAS observational data entailed ~50% Phase 1 fast-tracking after GA including femoral nerve block, vs. ~80% Phase 1 fast-tracking after RA (without GA) including femoral nerve block (12).

## 2.2 Are there other historical contexts that can inform MM-AEPPx ERAS today?

Outcomes involving shoulder surgery under RA without GA have been published (13). This population benefitted from "more than consensus-guided" MM-AEPPx (in its era), showing 94% fast-tracking of ~450 shoulder arthroscopy patients. Those that received perphenazine-dexamethasone-propofol had a <10% PONV rate, vs. a 16% PONV rate with one or fewer antiemetics co-administered with propofol ($P < 0.005$) (13).

## 2.3 Bariatric societies' 2021 frustration with PONVCG, their recommendations, and aftermath

Apparent frustration shared by aforementioned bariatric surgery societies (4), regarding the lack of success of PONVCG to date, is pertinent. Their response included recommendations to "Administer at least 2 or 3 antiemetics from different pharmacologic categories even in the absence of patient-related

risk factors." One of these bariatric-recommended AEPPx categories is anticholinergics (specifically transdermal scopolamine), for which a recent contemporaneous Cochrane review (14) provided data that contradicted the bariatric societies' position. Specifically, adding usually-efficacious aprepitant to scopolamine has not been shown to yield a beneficial effect on PONV (14), which directly contradicts the bariatric societies' guidance statement "NK-1 antagonists and an anticholinergic transdermal scopolamine patch should be considered prior to the patient's arrival at the facility." (4).

## 2.4 PONV specifically related to ITM

Most research addressing ITM-induced PONV originates in the obstetrical population. However, recent ERAS-related and other work in joint replacement and colorectal surgery populations are sufficiently illustrative on their own merits. For joint replacement, a recent prospective study (15) showed a 77% (27/35) PONV rate (on POD#0) after 0.2 mg ITM, and a 51% (18/35) PONV rate after 0.1 mg ITM, in the absence of any PONVCG AEPPx having been used. In GA-ITM for colorectal surgery, retrospective matched-cohort data review of ERAS patients showed a 44% PONV rate (POD#0–1) after ITM and GA with either aprepitant-ondansetron-dexamethasone or perphenazine-ondansetron-dexamethasone (16). No PONVCG ever specifically addressed ITM as its own, separately-quantifiable, emetogenic entity; it seems that 77% with no AEPPx, and 44% with consensus-guided AEPPx, are still unacceptably high PONV rates.

## 2.5 Advancing recent and historical MM-AEPPx perspectives into new enhanced recovery guidance: A New MM-AEPPx paradigm predicated on phase 1 PACU bypass fast-tracking success

Anesthetists are in a unique position to provide benefit for inpatients (e.g., such as those routed through ERAS programs) and outpatients. First, avoiding GA (when feasible) no longer binds the clinician to subscribe to nearly 20 years of questionably-successful iterations of GA-based (5–8) PONVCG. Similarly, ITM use (in GA or RA-only contexts) absolves clinicians from using the same GA-based PONVCG, because ITM is an otherwise unstudied (i.e., by PONVCG) high-risk emetogenic entity. The 2003–2020 evolved GA-PONVCG (5–8) may have pre-ordained a "70% PONV prevention success" rate as "acceptable," in the possible guise of "first do no harm." This "acceptability" threshold seems predicated on 65%–70% predictive value of applying PONVCG AEPPx strictly based on traditional risk factors (8). Why the PONVCG authors seem "accepting" of "70% success" may be related to possible apprehension of being judged as "not cost effective", "too costly", or perhaps "conflicted" (in a conflict-of-interest financial context).

In 2003 (5), the industry-sponsored PONV consensus panel cited 84 references addressing prophylaxis/treatment. This was followed by a 2007 (6) update (166 references), this time originating from the Society for Ambulatory Anesthesia (without industry sponsorship expressed or implied in its listing). Another from the Society for Ambulatory Anesthesia followed in 2014 [335 references (7)], followed by the 2020 (8) combined statement from the American Society of Enhanced Recovery and the Society for Ambulatory Anesthesia (430 references). The 2007 guidelines were released just before ondansetron lost patent protection (leading to a cost decrease from US$15–20/dose to <$1/dose), rendering the "new" guidelines "already" (seemingly) no longer current with respect to fiscal responsibility. The initial draft of the 2014 (7) guidelines proposed to remove the anti-dopaminergic antiemetic perphenazine from the recommendation list that had been in place in both 2003 (5) and 2007 (6) (see Supplementary Materials Item 1). Later, the 2020 Guidelines (8) featured at least 10 of its 22 authors who also authored contemporaneous (2013–2019) industry-sponsored studies of the now patent-protected amisulpride.

Our perspective is that authors from the described PONV consensus conferences (5–8) may not have appropriately relaxed their original 2003 (5) position of universal multimodal PONV prophylaxis as not being cost-effective, in light of newly inexpensive multimodal options (particularly aprepitant and palonosetron, in 2020). We propose, and have recently (2) demonstrated an alternative position, achieving ≤~10% PONV the day-of and day-after surgery through the routine use of 5-medication MM-AEPPx (aprepitant, palonosetron, perphenazine, dexamethasone, and diphenhydramine), achieving this associated success rate amidst care plans involving emetogenic ITM.

We invite stakeholders to consider value in reducing PONV by ~85% (2) compared to PONVCG, while not creating other frequent side effects. One does not want the side effect to be more of a nuisance (e.g., dry mouth with scopolamine) than the primary symptoms being prevented (PONV). It is conceivable that PONVCG to date have not endorsed a multimodal plan due to concerns about dysrhythmogenicity of medications in combination, or because of sparse evidence of medication interactions that is both counterintuitive and contradictory to antiemetic goals [such as the aforementioned efficacy-reducing aprepitant-scopolamine interactions (14)]. Whatever the origin, we describe low-cost clinical routines which included ITM use that have been associated with a ≤~10% incidence of PONV and ≤11% pruritus (2) at any point throughout postoperative days zero-to-one (POD#0–1), with no apparent adverse effects.

## 2.6 With oral aprepitant no longer patent-protected, patients can benefit from low-cost routine oral multimodal premedication carrying ~24+ h of benefit, via neurokinin-1 antagonism

As a frame of reference, our (2) institutional costs for aprepitant went from US$85/dose to US$10/dose (40 mg orally).

Preoperative pill dosing "workload" with "one pill" encourages concurrent multiple pill dosing that can also include the non-sedating anti-dopaminergic perphenazine (most commonly 8 mg) in the absence of contraindications, even though oral premedication may be a cultural change in many centers (17). Such centers could also confidently implement the premedication concept for an antihistamine [either the long-generic oral dimenhydrinate (see below), or the inexpensive generic IV preparation diphenhydramine], along with non-sedating oral analgesics such as dextromethorphan and type-2 inhibitors of cyclo-oxygenase (such as celecoxib or meloxicam). When oral aprepitant is used in women with child-bearing potential, alternative contraceptive methods in addition to any baseline hormonal-based measures are recommended for 30 days after aprepitant use.

## 2.7 IV palonosetron, primarily acting at the 5-hydroxytryptamine subtype-3 (5-HT3) receptor, before induction of anesthesia, is no longer patent-protected, allowing for inexpensive ~40 h sustained multi-modal antiemetic effect, when compared to ondansetron's every 4–6 h redosing requirement

A palonosetron dose of 75 μg is consensus-recommended (8) in adults, and was shown to be superior for ITM-related late-onset vomiting prevention [when compared to ondansetron 4 mg (18)]. Understanding that most monotherapy PONV outcomes did not differ (53% after ondansetron, 43% after palonosetron) in this ITM study in women, it is important to note that late vomiting differences were present, favoring palonosetron (11% vs. 27%, $P = 0.018$) (18). Our (2) institutional cost is US$10 per single-patient 250 μg palonosetron syringe (down from US$90), vs. <US$1 for 4 mg IV ondansetron. In meta-analyses, palonosetron (75 μg) monotherapy has been more effective for general anesthesia (GA)-related PONV than ondansetron (4–8 mg) plus dexamethasone (5–8 mg) (8). We cannot imagine clinical situations favoring ondansetron over palonosetron, but inpatient hospital controls may wish to avoid any rescue 5-HT3-antagonist dosing for the first 40 h after palonosetron is given, to avoid theoretical risk of QT prolongation (for patients carrying any such risks). We assume that palonosetron is preferred over ondansetron for ITM-induced pruritus based on duration of action; the 5-HT3 antagonist drug class is accepted as efficacious for prophylaxis against ITM-related itching (19). We have since cautiously escalated this 75 μg "base dose" to 150–250 μg, in non-ITM and ITM contexts respectively, based on early internal quality improvement data (improvements in next-day PONV prevention) that we hope to report in the near future, understanding that the 250 μg palonosetron dose is already approved for chemotherapy-induced nausea and/or vomiting without apparent dysrhythmogenic risk.

## 2.8 Perphenazine (5 mg IV dose) was accepted by 2003–07 consensus guidelines, but these PONVCGs and subsequent iterations (and associated industry-sponsored randomized clinical trials) have not addressed off-patent oral perphenazine/multimodal outcomes, despite ample observational efficacy/safety data (see Supplementary Materials Item 1)

Injectable perphenazine (5 mg) is non-sedating, and was reported in systematic review (20) to be in evidence-category "A1" in 2003–07 PONV guidelines (5, 6). However, injectable perphenazine has not been available in the United States, for example, since 2001. Oral perphenazine is ~20%–40% bioavailable (21). No industry sponsor, to our knowledge, has underwritten the prospective study costs of non-sedating, off-patent oral perphenazine (US$0.39 for 8 mg) as antiemetic. If the under-70-year patient is not diagnosed with Parkinson's disease, is not taking a simultaneous antidopaminergic psychotropic medication, and has had no past extrapyramidal adverse reactions to popular antidopaminergic legacy antiemetics such as prochlorperazine, we consider the screening process as ~99.97% successful for the avoidance of possible extrapyramidal complications after 8 mg single-dose po perphenazine (22). Additional safety research could entail similar study of patients over 70–75 years with a single 4 mg oral dose [instead of 8 mg as in (22)]. We assume similar contraindications and risks for off-patent perphenazine as those for patent-protected amisulpride. The lead author does not use perphenazine in patients with Parkinson's disease, but has used lower-dose (e.g., 4 mg PO) perphenazine uneventfully and confidently in non-Parkinsonian patients with conditions such as essential tremor and/or restless legs syndrome, without any observed sequelae to date. In patients with co-existing antidopaminergic therapy (in psychiatric contexts) that includes routine benztropine for offsetting known extrapyramidal symptoms, the lead author will not administer perphenazine. Stakeholders are reminded that for patients on other anti-dopaminergic agents (e.g., taken the day before surgery, but not yet on the day of surgery upon hospital presentation), one further recommended antiemetic (below in section 2.11) is an antihistamine, which is also successful in offsetting or preventing unwanted extrapyramidal effects (22).

## 2.9 An antipruritic effect against ITM would be valuable; in the absence of prophylaxis, recent reports indicate a 37% pruritus risk after 0.1 mg ITM, and 57% risk after 0.2 mg ITM (15)

We are not aware of literature addressing benzamides or derivatives (drug class of amisulpride) as having any efficacy against itching/pruritus (warranting its patent-protected higher cost).

## 2.10 Dexamethasone for multimodal PONV prophylaxis is consensus-supported and does not adversely influence surgical site infections after non-urgent non-cardiac surgery

Dexamethasone given intraoperatively, in a 4 mg IV dose (10) is long-supported; furthermore, an 8 mg IV dose does not adversely influence surgical site infections after non-urgent non-cardiac surgery (23). Although traditional dose-limited studies of dexamethasone (i.e., 4 mg) guided the primary practice pattern for the lead author for many years, this latter study (23) showing safe dose escalation to a popular standard dose entailing 8 mg (or 0.1 mg/kg) in adults appears to confer both confident antiemetic effects and meaningful non-opioid analgesic effects.

## 2.11 Antihistamines, commonly sedating in higher doses, are consensus-recommended as antiemetics, but their effects on ITM-related itching have not been well-studied

Dimenhydrinate is PONV-consensus-recommended (8), but with unknown effects on ITM-induced pruritus. If one were to reduce other concomitant sedatives during surgery, we forecast that inexpensive 25–50 mg oral dimenhydrinate would be unlikely to harm. Instead, we forecast that oral dimenhydrinate, co-administered with aprepitant/perphenazine above, and being part of the described (2) 5-medication MM-AEPPx plan will prove helpful for both PONV and pruritus. Similarly simple and inexpensive (instead of oral dimenhydrinate) would be IV diphenhydramine 12.5–20 mg, given before any emetogenic stimuli (such as ITM) are incurred [see (2)]. Even with a low-dose antihistamine and its potential sedative properties, one may wish to be cautious with usual customary dosing of typical non-opioid analgesic strategies (with unwanted sedative potential) such as dexmedetomidine or high-dose lidocaine infusions, at least until more multimodal research addressing sedation outcome data are available. Antihistamine use as part of 5-drug MM-AEPPx should not hinder dosing of other non-sedating non-opioid co-analgesics such as acetaminophen, non-steroidal anti-inflammatory drugs, cyclo-oxygenase (type 2) inhibitors, or NMDA-antagonists such as ketamine or magnesium; these co-analgesics seem to be logical and successful opioid-sparing techniques to sustain, in efforts to aim for "opioid-free". In either case, the lead author is anecdotally (based on institutional quality data review) far more confident in the 24-h anti-emetic (and anti-itching) benefit of the described fronted-dose of antihistamine, when compared with far less incremental confidence with respect to sustained analgesia from an intraoperative dexmedetomidine infusion, for example, which is turned off typically before the end of surgery.

## 2.12 Antiemetic momentum, PONV risk factors, and regional anesthesia (RA)

Recently, an enhanced recovery joint replacement study (24) reported on a complementary advance with respect to both establishing and sustaining antiemetic prophylaxis benefit. This was a retrospective case-control study achieving 50% reduction of PONV on postoperative days 1–3 (24). This study did NOT involve GA (rather, spinal anesthesia with local anesthetics, but not ITM). Consensus guidelines [2003–2020 (5–8)] have directed their attention toward GA (±opioids), not necessarily toward RA, nor toward spinal anesthesia replacing GA. The last-known systematic review of PONV in RA [2003 (25)] did not cite (as problematic for RA) then-known GA PONV risk factors of female gender, non-smoker, and/or past history of PONV (8, 10). However, PONV was not the primary outcome in most of the RA studies of this (25) systematic review. A few years later, the lead author's group analyzed secondary outcomes from a prospective randomized trial (2001–2005) of patients undergoing spinal anesthesia with femoral nerve block and propofol sedation; in the parent study, only 4% of patients (10/233) had PONV on the day of surgery before hospital discharge after 4 antiemetic drugs (perphenazine, ondansetron, dexamethasone, and propofol), irrespective of risk factors (26). More detailed secondary review (27) of PONV outcomes at home [after the parent (26) study's day-of-surgery] similarly showed "antiemetic momentum" to be valuable. Specifically, PONV on the day of surgery was predictive of PONV on postoperative day (POD)#1 [odds ratio (OR) = 16, $P = 0.001$], while PONV on POD#1–3 were each individually and respectively predictive of PONV on POD#2–4 (OR = 10–14, $P \leq 0.001$). In other words, the previous day's PONV outcome was the only predictor of PONV outcomes on all 4 subsequent postoperative days, while usually-expected factors such as opioid consumption and female gender were each only predictive for two of the four postoperative days, with much lower odds ratios (14). Our group's recent ITM and 5-medication MM-AEPPx work also demonstrated the value of antiemetic momentum (OR = 9, $P < 0.001$) (2), for which we now (for our inpatients) provide daily oral doses of both aprepitant (40 mg) and perphenazine (4–8 mg), serving a multimodal "booster" function.

# 3 Discussion

A robust and fiscally responsible 5-drug MM-AEPPx plan, used in preferential tandem with propofol sedation or propofol GA, is presented (including rescue and "booster/momentum" considerations in Supplementary Table 2). Unlike PONVCG past and present (5–8) which have prioritized a "risk factor" basis of AEPPx, stakeholders can prioritize patient-centered multimodal "Aim for Zero" PONV outcomes over "GA-specific PONVCG risk factors," especially since PONVCG have not addressed PONV risk after RA, and/or with ITM use. Our opening statement cited patient-preference research from the late 1990s related to the humane [and economic (1)] value of avoiding PONV, but stakeholders should also prudently consider the extreme value of avoided PONV in (i) complex surgery involving the upper gastrointestinal tract, (ii) eye surgery risking the loss of intraocular contents if vomiting or retching were to occur, or (iii) neurosurgical or traumatic emetogenic contexts where

intracranial pressure is already at risk (such as in a context of intracranial bleed, pending the clipping of an aneurysm).

Our having used ITM successfully as a "PONV stress test," we have observed low ITM-associated [and sleeve gastrectomy-associated (4)] PONV rates with this 5-medication plan (2), and there appears to be no evidence of adverse drug interactions (i.e., with 5-drug MM-AEPPx described) such as those seen with scopolamine (14). Transdermal scopolamine should likely be excluded from future 5-drug MM-AEPPx considerations based on the 2020 Cochrane review (14) showing lower efficacy of both antidopaminergics (specifically perphenazine) and NK-1-antagonists (specifically aprepitant) when scopolamine is co-administered as prophylaxis. With a ≤~10% PONV incidence on POD#0–1 combined (and ≤11% pruritus during the same time period) (2), it seems unlikely that palonosetron-aprepitant-perphenazine-dexamethasone-diphenhydramine-propofol adversely interact, and can seemingly be confidently recommended as a fair and reasonable "do no harm" clinical routine with few contraindications to finally resolve the PONV problem identified decades ago (28) and recently reaffirmed (29) as "the big little problem", with observed ~90+% success, pending confirmatory prospective research.

We endorse these low-cost, fiscally-responsible MM-AEPPx strategies for routine PONV prevention with off-patent aprepitant, palonosetron, perphenazine, dexamethasone, and diphenhydramine. Future research should explore whether high-success PONV prevention can favorably benefit analgesic aspects of postoperative care, particularly whether the absence of PONV better facilitates postoperative patient success adhering to a non-opioid regimen [e.g., paracetamol, celecoxib (30), and dextromethorphan (31)] that may be completely oral/enteral, including after discharge home, thus creating a potential "positive domino" effect of meaningful opioid avoidance as well. The sedative properties of dexmedetomidine and/or higher-dose lidocaine infusions might lead to their reconsideration in the setting of an antiemetic antihistamine with sedative properties (diphenhydramine or dimenhydrinate), but antinociceptive properties of esmolol (32) infusions could be logically considered, to continue due attention to the desired "domino effect." The "positive domino" effect desired, including described daily antiemetic booster dosing, may also represent a meaningful act of mitigation against ondansetron-mediated "rebound post-discharge nausea/vomiting" effect first described by Apfel et al. (33), regarding which there unfortunately does not yet appear to be much follow-up research to address, other than palonosetron likely being more promising than ondansetron due to its 40-h half life, and palonosetron not being associated with any QTc interval dysrhythmogenic effect (34).

## 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.

## Author contributions

BW: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. CS: Data curation, Investigation, Writing – review & editing. RC: Data curation, Investigation, Writing – review & editing. KG: Investigation, Methodology, Writing – review & editing. JL: Investigation, Methodology, Writing – review & editing. DH: Investigation, Methodology, 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.

## Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fanes.2024.1525030/full#supplementary-material

# References


1. Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg*. (1999) 89:652–8. doi: 10.1097/00000539-199909000-00022

2. Williams BA, Holder-Murray JM, Nettrour JF, Ibinson JW, DeRenzo JS, Dalessandro C, et al. Aim for zero: prevention of postoperative nausea and vomiting using an off-patent five-drug multimodal approach. *Br J Anaesth*. (2023) 131(1):e1–4. doi: 10.1016/j.bja.2023.01.005

3. Kheterpal S, Vaughn MT, Dubovoy TZ, Shah NJ, Bash LD, Colquhoun DA, et al. Sugammadex versus neostigmine for reversal of neuromuscular blockade and postoperative pulmonary complications (STRONGER): a multicenter matched cohort analysis. *Anesthesiology*. (2020) 1326:1371–81. doi: 10.1097/ALN.0000000000003256

4. Schumann R, Ziemann-Gimmel P, Sultana A, Eldawlatly AA, Kothari SN, Shah S, et al. Postoperative nausea and vomiting in bariatric surgery: a position statement endorsed by the ASMBS and the ISPCOP. *Surg Obes Relat Dis*. (2021) 17:1829–33. doi: 10.1016/j.soard.2021.08.005

5. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, et al. Consensus guidelines for managing postoperative nausea and vomiting. *Anesth Analg*. (2003) 97:62–71. doi: 10.1213/01.ane.0000068580.00245.95

6. Gan TJ, Meyer TA, Apfel CC, Chung F, Davis PJ, Habib AS, et al. Society for ambulatory anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. (2007) 105:1615–28. doi: 10.1213/01.ane.0000295230.55439.f4

7. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. (2014) 118:85–113. doi: 10.1213/ANE.0000000000000002

8. Gan TJ, Belani KG, Bergese S, Chung F, Diemunsch P, Habib AS, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. (2020) 131:411–48. doi: 10.1213/ANE.0000000000004833

9. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology*. (1999) 91:693–700. doi: 10.1097/00000542-199909000-00022

10. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med*. (2004) 350:2441–51. doi: 10.1056/NEJMoa032196

11. Williams BA, Kentor ML. The WAKE© score: patient-centered ambulatory anesthesia and fast-tracking outcomes criteria. *Int Anesthesiol Clin*. (2011) 49:33–43. doi: 10.1097/AIA.0b013e3182183d05

12. Williams BA, Kentor ML, Vogt MT, Vogt WB, Coley KC, Williams JP, et al. The economics of nerve block pain management after anterior cruciate ligament reconstruction: significant hospital cost savings via associated PACU bypass and same-day discharge. *Anesthesiology*. (2004) 100:697–706. doi: 10.1097/00000542-200403000-00034

13. Williams BA, Kentor ML. Fast-track ambulatory anesthesia: impact on nursing workload when analgesia and antiemetic prophylaxis are near-optimal. *Can J Anaesth*. (2007) 54:243–4. doi: 10.1007/BF03022649

14. Weibel S, Rücker G, Eberhart LH, Pace NL, Hartl HM, Jordan OL, et al. Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: a network meta-analysis. *Cochrane Database Syst Rev*. (2020) 10(10):Cd012859. doi: 10.1002/14651858.CD012859.pub2

15. Pathonsamit C, Onklin I, Hongku N, Chaiyakit P. Randomized double-blind controlled trial comparing 0.2 mg, 0.1 mg, and no intrathecal morphine combined with periarticular injection for unilateral total knee arthroplasty. *Arthroplast Today*. (2020) 7:253–9. doi: 10.1016/j.artd.2020.11.008

16. Holder-Murray J, Esper SA, Boisen ML, Gealey J, Meister K, Medich DS, et al. Postoperative nausea and vomiting in patients undergoing colorectal surgery within an institutional enhanced recovery after surgery protocol: comparison of two prophylactic antiemetic regimens. *Korean J Anesthesiol*. (2019) 72:344–50. doi: 10.4097/kja.d.18.00355

17. Jin Z, Gan TJ, Belani KG, Bergese S, Chung F, Diemunsch P, et al. In response. *Anesth Analg*. (2021) 132:e31–3. doi: 10.1213/ANE.0000000000005280

18. Campos GO, de Jesus Martins M, Jesus GN, de Oliveira PRR, Lessa CN, de Oliveira Junior J, et al. Palonosetron versus ondansetron for prevention of nausea and vomiting after total abdominal hysterectomy under spinal anesthesia with intrathecal morphine: a double-blind, randomized controlled trial. *BMC Anesthesiol*. (2019) 19:159. doi: 10.1186/s12871-019-0830-7

19. Subramani Y, Nagappa M, Kumar K, Mortuza R, Fochesato LA, Chohan MBY, et al. Medications for the prevention of pruritus in women undergoing cesarean delivery with intrathecal morphine: a systematic review and Bayesian network meta-analysis of randomized controlled trials. *J Clin Anesth*. (2021) 68:110102. doi: 10.1016/j.jclinane.2020.110102

20. Schnabel A, Eberhart LH, Muellenbach R, Morin AM, Roewer N, Kranke P. Efficacy of perphenazine to prevent postoperative nausea and vomiting: a quantitative systematic review. *Eur J Anaesthesiol*. (2010) 27:1044–51. doi: 10.1097/EJA.0b013e32833b7969

21. Hansen CE, Christensen TR, Elley J, Hansen LB, Kragh-Sorensen P, Larsen NE, et al. Clinical pharmacokinetic studies of perphenazine. *Br J Clin Pharmacol*. (1976) 3(5):915–23. doi: 10.1111/j.1365-2125.1976.tb00647.x

22. Henao JP, Peperzak KA, Lichvar AB, Orebaugh SL, Skledar SJ, Pippi MA, et al. Extrapyramidal symptoms following administration of oral perphenazine 4 or 8 mg: an 11-year retrospective analysis. *Eur J Anaesthesiol*. (2014) 31:231–5. doi: 10.1097/EJA.0000000000000048

23. Corcoran TB, Myles PS, Forbes AB, Cheng AC, Bach LA, O'Loughlin E, et al. Dexamethasone and surgical-site infection. *N Eng J Med*. (2021) 384:1731–41. doi: 10.1056/NEJMoa2028982

24. Berg AR, Lakra A, Jennings EL, Cooper HJ, Shah RP, Geller JA. Transdermal scopolamine as an adjunct to multimodal pain management in patients undergoing total joint arthroplasty. *J Arthroplasty*. (2019) 34(7S):S159–63. doi: 10.1016/j.arth.2019.03.028

25. Borgeat A, Ekatodramis G, Schenker CA. Postoperative nausea and vomiting in regional anesthesia: a review. *Anesthesiology*. (2003) 98:530–47. doi: 10.1097/00000542-200302000-00036

26. Williams BA, Kentor ML, Vogt MT, Irrgang JJ, Bottegal MT, West RV, et al. Reduction of verbal pain scores after anterior cruciate ligament reconstruction with two-day continuous femoral nerve block: a randomized clinical trial. *Anesthesiology*. (2006) 104:315–27. doi: 10.1097/00000542-200602000-00018

27. Williams BA, Kentor ML, Irrgang JJ, Bottegal MT, Williams JP. Nausea, vomiting, sleep, and restfulness upon discharge home after outpatient anterior cruciate ligament reconstruction with regional anesthesia and multimodal analgesia/antiemesis. *Reg Anesth Pain Med*. (2007) 32:193–202. doi: 10.1016/j.rapm.2006.12.002

28. Kapur PA. The big "little problem". *Anesth Analg*. (1991) 73:243–5. doi: 10.1213/00000539-199109000-00001

29. Benhamou D. Postoperative nausea and vomiting: is the big little problem becoming a smaller little problem? *Br J Anaesth*. (2023) 131:22–5. doi: 10.1016/j.bja.2023.04.004

30. Khan JS, Margarido C, Devereaux PJ, Clarke H, McLellan A, Choi S. Preoperative celecoxib in noncardiac surgery: a systematic review and meta-analysis of randomised controlled trials. *Eur J Anaesthesiol*. (2016) 33:204–14. doi: 10.1097/EJA.0000000000000346

31. Chau-In W, Sukmuan B, Ngamsangsirisapt K, Jirarareungsak W. Efficacy of pre- and postoperative oral dextromethorphan for reduction of intra- and 24-hour postoperative morphine consumption for transabdominal hysterectomy. *Pain Med*. (2007) 8:462–7. doi: 10.1111/j.1526-4637.2006.00226.x

32. Bahr MP, Williams BA. Esmolol, antinociception, and its potential opioid-sparing role in routine anesthesia care. *Reg Anesth Pain Med*. (2018) 43:815–8. doi: 10.1097/AAP.0000000000000873

33. Apfel CC, Philip BK, Cakmakkaya OS, Shilling A, Shi Y-Y, Leslie JB, et al. Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? *Anesthesiology*. (2012) 117:475–86. doi: 10.1097/ALN.0b013e318267ef31

34. Apfel CC, Jukar-Rao S. Is palonosetron also effective for opioid-induced and post-discharge nausea and vomiting? *Br J Anaesth*. (2012) 108:371–3. doi: 10.1093/bja/aer516