Evidence-Based Antiemetic Decision Tool for Management of Postoperative Nausea and Vomiting in Patients at High Risk of QT Prolongation and Patients Receiving Neurotransmitter-Modulating Medications

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Anesthesia providers have a myriad of medication options when developing and implementing a plan for the management of postoperative nausea and vomiting (PONV). However, anesthetists must be aware of the potential side effects, complications, and interactions of those medications, especially when managing high-risk populations. Although guidelines exist for the management of PONV in the general population, an evidence-based antiemetic decision support tool has not been developed for patients at risk of prolonged QT interval or for patients who are routinely receiving neurotransmitter-modulating medications. Safe practice recommendations exist but are scattered throughout the literature. The goal of this project was to develop a tool for anesthetists that concentrates the evidence and provides practice guidelines in these 2 selected populations. The methods for developing this tool were to perform a thorough literature search to gather evidence-based guidelines, organize findings in a convenient easy-to-read format, and validate guidelines by consultation with an expert panel. The product is a quickly accessible clinical tool listing guidelines for 8 commonly used antiemetic agents to assist anesthetists in PONV management.

Keywords: Antiemetic decision tool, nurse anesthesia, postoperative nausea and vomiting,

Approximately 48 million patients undergo anesthesia annually in the United States,[1] and about one-third of these patients will present with cardiac disease.[2] Additionally, many patients presenting for surgery are currently on a home drug regimen that includes neurotransmitter-modulating medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs). Use of neurotransmitter-modulating medications increased from 7.7% in 1999 to 12.7% in 2014.[3] Medications commonly used during the perioperative period may place vulnerable patients at higher risk of drug interactions such as QT prolongation and serotonin syndrome. Arming anesthetists with evidence-based guidelines that are consistent with best practices supports them in confidently making decisions under high-stress, fast-paced conditions. Anesthetists may not have access to multiple resources in the short time they care for surgical patients. Standardized protocols and checklists not only help clarify decisions but also have been shown to improve safety.[4] Checklists help with memory recall and to establish both the minimum necessary steps in a process and a higher standard of baseline performance.[5] Checklists, algorithms, protocols, and guidelines are tools that may help decrease mental burden, allow the anesthetist to focus on higher-order tasks,[6] contribute to higher standards of care, and facilitate better outcomes.[4]

Postoperative nausea and vomiting (PONV) affects between 20% and 40% of surgical patients and as many as 80% of patients in high-risk groups.[7-9] Nausea and vomiting pose a real threat to quality and safety outcomes in the postoperative period. Many patients state PONV as their most pressing concern when they are deciding whether to have a medically beneficial surgery. In addition to being uncomfortable, PONV can also contribute to detrimental consequences such as increased length of stay, inadvertent hospitalization, aspiration, dehydration, electrolyte imbalance, wound dehiscence,[10] bleeding, neck hematoma, and airway compromise.[9,11-13] Although clinical practice tools are currently available to determine the incidence of PONV risk according to the number of risk factors[14] and interventions (Figure)[15] and to guide prophylactic management (Table 1),[16] a tool that is concise and provides guidelines for high-risk patients is not currently available, to the authors' knowledge.

The baseline risk of PONV can be determined by assessing patient demographics. Patient demographics

Estimated Incidence of Postoperative Nausea and Vomiting as a Function of Baseline Risk, on the Basis of the Assumption That Each Intervention Reduces the Relative Risk by 26 Percent.

Baseline Risk (No Intervention)*	Estimated Incidence of Postoperative Nausea and Vomiting			
	One Intervention	Two Interventions	Three Interventions	Four Interventions
	percent			
10%	7	5	4	3
20%	15	11	8	6
40%	29	22	16	12
60%	44	33	24	18
80%	59	44	32	24

* The baseline risk levels of 10 percent, 20 percent, 40 percent, 60 percent, and 80 percent reflect the presence of 0, 1, 2, 3, and 4 risk factors, respectively, according to a simplified risk score.

Figure. Apfel PONV Risk Stratification Chart
Abbreviation: PONV, postoperative nausea and vomiting.
(From Apfel et al.[15] Copyright 2004 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

that increase the risk of a patient experiencing PONV are female gender, history of PONV or motion sickness, being a nonsmoker, age younger than 50 years, general anesthesia (vs regional), duration of anesthesia, use of volatile anesthetics and nitrous oxide, use of postoperative opioids, and type of surgery.[8,14] One point is awarded for each positive risk factor. Then points are totaled to determine PONV risk score.

The impetus for development of our antiemetic decision support tool stemmed from clinically practicing Certified Registered Nurse Anesthetists (CRNAs) who had concerns about potential drug interactions due to antiemetics' mechanism of action. The questions that guided the methods of tool development were as follows: (1) Do any of the commonly administered antiemetic medications actually pose a clinically significant risk to patients susceptible to QT prolongation or those receiving neurotransmitter-modulating agents? (2) What preexisting factors may potentiate QT prolongation in patients who are given antiemetics?

Review of Literature

Eight commonly used medications were examined in the literature for safety of use in each of the high-risk project groups. Those medications are ondansetron, dexamethasone, metoclopramide, promethazine, prochlorperazine, diphenhydramine, scopolamine, and fosaprepitant.[7,14]

• ***Ondansetron.*** Hydroxytryptamine-3 receptor antagonists medications are one of the most commonly used antiemetics during the perioperative period.[7] They are nonsedating, generally well tolerated, and highly effective when used for prophylaxis and treatment of PONV.[17] Patients receiving ondansetron may experience side effects such as headache, dizziness, diarrhea, constipation,[17] and, most notably, QT prolongation. Factors that place a patient at higher risk of QT prolongation include female gender, hypothyroidism, hypothermia, pheochromocytoma, hemodialysis, electrocardiographic (ECG) abnormality, and electrolyte imbalance (Table 2).[18]

Several studies have been undertaken to assess the safety of 5-hydroxytryptamine-3 receptor antagonists in patients undergoing anesthesia who also have cardiac disease, and in patients receiving multiple QT-prolonging medications. A meta-analysis of 10 studies including 2,099 patients who received ondansetron reported only insignificant electrocardiogram (ECG) changes (2 cases of atrial fibrillation), with the risk being more likely with 32-mg doses of ondansetron.[18] A prospective single-blind study comparing corrected QT interval (QTc) changes in patients receiving either ondansetron or granisetron found transient prolonged QTc with both, which corrected within a few hours.[19] A retrospective chart review examining the charts of 2,451 patients (1,429 who received ondansetron and 1,022 who did not) failed to find a significant increase in QT interval in patients who had received ondansetron during the perioperative period.[20] The risk of QT prolongation is minimized or diminished if there is adherence to the recommended maximum dose of 16 mg.[21]

A few sources link concurrent use of ondansetron and other serotonin-modulating agents to an increased risk of serotonin syndrome.[22-24] Serotonin syndrome is an adverse drug reaction caused by excessive activation of postsynaptic serotonin receptors presenting a host of symptoms that range from mild to life-threatening.[23] This complex interplay of neurotransmitters may cause symptoms such as mental status changes, agitation, myoclonus and hyperreflexia (especially in the legs), diaphoresis, shivering, tremor, diarrhea, incoordination, and fever.[25,26] Differential diagnosis for serotonin syndrome includes malignant hyperthermia, neuroleptic malignant syndrome (NMS) and side effects of anticholinergics and vasopressors since these conditions have similar clinical presentations.[25] The diagnosis of serotonin syndrome is made based on symptoms and patient exposure to proserotonergic medications since no diagnostic test is available.[27]

• ***Dexamethasone.*** Dexamethasone is a corticosteroid that is one of the most commonly used antiemetics[7] and has a large safety profile. The use of dexamethasone perioperatively has been shown to significantly decrease PONV, pain and pain medication use, and the use of rescue antiemetics with low toxicity.[12,13,28,29] Due to the systemic effects of altered glucose levels and immunosuppression, concerns about the risk of increased blood glucose levels, increased wound infection, and delayed wound healing are potential limitations for the use of dexamethasone.[30] Those considerations are beyond the scope of this project. No articles were identified that link dexamethasone use with QT prolongation or drug interactions with neurotransmitter-modulating agents.

Risk score	Prevalence PONV, %	Prophylaxis: No. of antiemetics	Examples[a]
0	9	0-1	± Ondansetron 4 mg
1	20	1	Ondansetron 4 mg ± Dexamethasone 4 mg
2	39	2	Ondansetron 4 mg +Dexamethasone 4 mg ± Propofol infusion
3	60	3	Ondansetron 4 mg + Dexamethasone 4 mg + Propofol infusion ± Scopolamine patch
4	78	4	Ondansetron 4 mg + Dexamethasone 4 mg + Propofol infusion + Scopolamine patch

Table 1. Stanford University Anesthesia Department PONV Guidelines Chart
Abbreviations: PONV, postoperative nausea and vomiting; +, plus.
[a]Combinations should be with drugs that have a different mechanism of action.
(From Base Prophylaxis on Risk Score table. Reproduced by permission of Ether, Stanford Department of Anesthesiology, Perioperative and Pain Medicine.[16])

• ***Diphenhydramine.*** The antihistamine diphenhydramine may increase the risk of prolonged QT interval,[30,31] especially when excessive doses are given.[31] Diphenhydramine should be avoided in patients with congenital long QT syndrome (LQTS).[31] The critical dose limit for diphenhydramine is 1 g.[32] Perioperatively, patients may receive doses ranging from 6.25 to 50 mg once or every 4 hours as needed if PONV recurs. Anesthetists should administer minimal effective doses of diphenhydramine to patients with positive risk factors for prolonged QT interval (Table 2).

A case report of a 55-year-old dialysis recipient who received 50-mg doses of diphenhydramine as needed over 2 consecutive days showed that she experienced a prolonged QTc. Her QTc interval returned to baseline after the passing of 4 half-lives, with no clinical sequalae.[32] No studies reviewed indicated potential drug interactions when diphenhydramine was administered in conjunction with an SSRI, SNRI, or MAOI.

• ***Scopolamine.*** Scopolamine is an anticholinergic drug applied as a transdermal patch that may be worn for up to 72 hours. No studies reviewed, nor the CredibleMeds website,[31] identified QT prolongation as a potential risk in conjunction with scopolamine administration. The use of scopolamine may be inappropriate for patients over the age of 65 years.[17,33]

Although no studies link a drug interaction between scopolamine and SSRI, SNRI, or MAOI medications, the provider should take special note of the patient receiving centrally acting medications and scopolamine. Considering the centrally acting nature of both antidepressants and scopolamine, this medication combination comes with a warning of an increased risk of mental status changes. The administration of scopolamine may increase the risk of development of central anticholinergic syndrome.[34]

Cardiac risk factor	Other risk factor
Bradycardia	Pheochromocytoma
Atrioventricular block	Hypokalemia
Cardiac pauses	Hypomagnesemia
Takotsubo cardiomyopathy	Hypocalcemia
Heart disease	Female gender
Congenital long QT syndrome	Hypothyroidism
	Hypothermia
	Hemodialysis

Table 2. Factors That May Increase Risk of QT Prolongation[12,28]

• ***Metoclopramide.*** Metoclopramide is a dopamine antagonist and gastrokinetic agent.[34] Patients who receive metoclopramide may be at increased risk of experiencing tardive dyskinesia and extrapyramidal effects, especially patients with Parkinson's disease.[33] Metoclopramide has a black box warning for the risk of tardive dyskinesia.[30,35] Concurrent use of metoclopramide and SSRIs, SNRIs, and MAOIs places patients at increased risk of side effects and a broader spectrum of potential side effects. For instance, the combination of metoclopramide and serotonin-modulating agents can result in extrapyramidal effects, serotonin syndrome, and NMS.[30,36,37]

CredibleMeds assigns a conditional risk of QT prolongation to the use of metoclopramide.[31] Based on these findings, metoclopramide should be avoided in patients with Parkinson's disease, congenital LQTS, or LQTS.

• ***Promethazine and Prochlorperazine.*** Promethazine and prochlorperazine are phenothiazines. Although the

pharmacodynamics of these 2 medications differs, resulting in variable desirable effects and undesirable side effects, they both may place patients at increased risk of experiencing extrapyramidal side effects. Phenothiazines are known to have antipsychotic, antiemetic, and sedative properties. Promethazine has antihistaminergic properties that may provide relief from nausea and vomiting. Prochlorperazine may be administered for its antipsychotic and antiemetic properties. Authors of a statistical analysis of drug interaction at serotonin receptors state that medications that act on any serotonin or monoamine oxidase receptors may play a role in serotonin syndrome.[25] Medications that affect more than 1 receptor also may increase this risk.[25] The concurrent use of phenothiazines with any of the following medications increases the risk of serotonin syndrome: cyclobenzaprine, meperidine, paroxetine, sertraline, methadone, tramadol, venlafaxine, fentanyl, and methylene blue.[14] Several sources confirm that administration of phenothiazines increases the risk of serotonin syndrome.[25,26]

Promethazine and prochlorperazine may also increase a patient's risk to experience NMS.[30] The US Food and Drug Administration (FDA) defines *NMS* as a "potentially fatal symptom complex" with symptoms such as hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).[38] The FDA reports increased risk of NMS with concurrent use of promethazine and antipsychotics, including prochlorperazine.[38]

CredibleMeds[31] assigns a possible risk of prolongation of the QT interval with promethazine administration and states that promethazine has been found to increase QT intervals in some patients and that it could theoretically be dangerous for patients with congenital LQTS. Use in this population should be reserved to those for whom the benefits outweigh the risks.

Of note, the FDA[38] has placed a black box warning on promethazine for the risk of tissue necrosis with administration by parenteral/superficial intramuscular injection and a black box warning on prochlorperazine for the risk of death in elderly individuals when prescribed as an antipsychotic.[39]

• ***Fosaprepitant.*** Approved for use in the United States in 2008, fosaprepitant is the parenteral formula of the neurokinin-1 receptor antagonist (NK1RA).[40] Because of its relatively recent introduction, there are few studies about the drug or its drug interactions. Fosaprepitant should be avoided in patients receiving cisapride or pimozide because of reports of life-threatening QT prolongation.[24] No studies reviewed to date list any serious drug interactions between an NK1RA and an SSRI, SNRI, or MAOI; nor do any mention QT prolongation as a potential side effect of fosaprepitant. A pooled analysis of 4 randomized controlled trials examined adverse effects of antiemetic regimens in 3,280 patients receiving chemotherapy.[33] The analysis examined the safety of 3 different antiemetic regimens all containing NK1RAs and found NK1RA drugs to be safe with very few cardiac side effects.[41] With simultaneous use of dexamethasone and fosaprepitant, the dose of dexamethasone should be decreased because of the risk of Cushing syndrome and immunosuppression developing.

Methods

The first draft of the antiemetic decision tool was developed by the lead author (N.H.) based on findings from the literature review. The 8 previously discussed medications are listed in the tool, and guidelines for use of each medication in the project's selected high-risk populations are provided.

After the initial tool was developed, validation was sought from an expert panel. Experts were identified during the literature review via reference lists in publications on the project topic and by recommendation from a project collaborator. Experts had to be anesthesiologists, CRNAs, or pharmacists. Ideally, expert panel members had published on the topic of antiemetics. Anesthesia school faculty status and having expertise in the field of anesthesia or pharmacology were also recognized as qualifying criteria. Initially, 5 potential experts were sent an invitation by email. Nine rounds of invitations were sent out, with a total of 19 experts being invited. Experts were given 2 weeks to accept or decline the invitation. If experts declined or did not respond within 2 weeks, additional experts were invited. The invitation process continued until feedback was received from 5 experts. Five experts is the minimum number required for obtaining an affirmation response (AR) of 0.78.[43] The expert panel consisted of 4 CRNAs and 1 pharmacist (expert panel member biographies are available on request). Institutional review board approval was not required for this project.

The experts were provided with the project tool (final version shown in Table 3) and an evaluation form as well as the Apfel Risk Stratification Chart (Figure) and the Stanford PONV Guidelines Chart (Table 2). Experts were asked to complete the evaluation form by circling a "yes" response if they believed the guideline in the tool was accurate or a "no" response if they thought the guideline was inaccurate. Blank space was provided after the series of questions for each medication with the request to place any additional comments in the space.

Results

During the expert panel's review of the antiemetic decision support tool, 2 experts had clarification questions about the tool, which were discussed via phone calls. Additional feedback was provided via email by 1 expert (evaluation form and expert panel feedback analyzation form available on request).

Antiemetic agent	QT prolongation risk	Use with SSRI/SNRI	Use with MAOI	Cost[a]
Ondansetron	⚠	⚠	⚠	$
Comments: Avoid in CLQTS. Use caution in patients with hypokalemia/hypomagnesemia/other electrolyte disturbances, bradycardia/bradyarrhythmias/patients receiving medications that cause bradycardia, underlying heart disease/CHF, and patients receiving other QT-prolonging medications (especially chemotherapeutic agents). Ondansetron plus promethazine may increase the risk of prolonged QT interval; consider obtaining baseline ECG and monitor for ECG changes during use.				
Dexamethasone	✓	✓	✓	$
Comments: Reduce dose of dexamethasone in concomitant use of NK1 agents due to risk of high serum dexamethasone levels (apparent for 8 d after NK1 use).				
Diphenhydramine	✓	✓	✓	$
Comments: Avoid in CLQTS. Avoid excessive dose.				
Scopolamine	✓	⚠	⚠	$$
Comments: Scopolamine plus SSRI/SNRI/MAOI may increase patient's risk of development of central anticholinergic syndrome, especially in patients receiving multiple agents that affect neurotransmitters or in patients over age 65 y. Observe for mental status changes and central anticholinergic syndrome when scopolamine is given with antidepressants. Avoid use in patients with narrow angle glaucoma and patients receiving aclidinium, azelastine, cimetropium, eluxadoline, glucagon, glycopyrrolate, ipratropium, levosulpiride, orphenadrine, paraldehyde, potassium chloride, thalidomide, tiotropium, and umeclidinium.				
Promethazine	⚠	⚠	⚠	$
Comments: Avoid in CLQTS. Best to avoid concomitant use of metoclopramide and promethazine. This combination may increase risk of QT prolongation. Consider obtaining baseline ECG and monitor for ECG changes during coadministration. Coadministration of promethazine and metoclopramide may increase the risk of CNS depression and extrapyramidal effects. Best to avoid use with other potentially QT-prolonging medications.				
Prochlorperazine	⚠	⚠	⚠	$$
Comments: Combination of metoclopramide and prochlorperazine can result in extrapyramidal effects and neuroleptic malignant syndrome. Prochlorperazine may increase the risk of QT interval prolongation. Best to avoid use with other potentially QT-prolonging medications. Combination of prochlorperazine with SSRI/SNRI, ondansetron, metoclopramide, promethazine, isoflurane, and sevoflurane may increase the risk of QT prolongation.				
Metoclopramide	⚠	✗	✗	$
Comments: Avoid in CLQTS, avoid in patients with low/high serum potassium ions or magnesium or other electrolyte disturbances. Use with caution in elderly, patients with cardiac conduction disturbances/bradycardia, or patients receiving other QT-prolonging drugs. Avoid in any serotonin-modulating agents, including tramadol, due to risk of extrapyramidal activity and neuroleptic malignant syndrome. Combination of metoclopramide and prochlorperazine can result in extrapyramidal effects and neuroleptic malignant syndrome.				
Fosaprepitan	✓	✓	✓	$$$$
Comments: Reduce dose of dexamethasone in concomitant use of NK1 agents due to risk of high serum dexamethasone levels (apparent for 8 d after NK1 use).				

Table 3. Antiemetic Decision Tool for High-Risk Anesthesia Patients

Abbreviations: CHF, congestive heart failure; CLQTS, congenital long QT syndrome; CNS, central nervous system; ECG, electrocardiogram; MAOI, monoamine oxidase inhibitor; NK, neurokinin; SSRI/SNRI, selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor.

Symbols key: Green check mark, literature finds no clinically significant risk; yellow yield mark, literature finds potential risks, and additional monitoring or observation for interactions may be beneficial; red X mark, literature reports known or observed drug interactions or side effects or a higher risk of drug interactions or side effects, so it is optimal to choose an alternative therapy.

[a]$ indicates $0.10-$5; $$, $5.01-$49.99; and $$$$, $400.01-$499.99. None listed here cost $50.01 to $400, the third cost category.

Of 21 items, 17 garnered full consensus (yes responses) among all experts. The exceptions were the combination of ondansetron with SSRI/SNRIs (AR = 0.6), ondansetron with MAOIs (AR = 0.8), dexamethasone with SSRI/SNRIs (AR = 0.8), and dexamethasone with MAOIs (AR = 0.8). An AR of less than 0.78 required tool revision.

The expert panel recommended several changes to the project tool. One expert recommended removing metoclopramide because of declining clinical use, and another recommended the addition of propofol to the tool. Tool

adjustment such as these required a second review process.

The original guideline in the tool regarding ondansetron use by patients receiving SSRI/SNRI and MAOI drugs contained a green check mark, indicating no clinical concerns for this combination of medications. However, after analyzing expert panel feedback, the AR of this guideline was only 0.6. Additional literature searches confirmed the expert panel feedback, which resulted in this guideline receiving a yellow yield mark, indicating caution and increased observation for this patient population.

A tool development collaborator recommended that a cost valuation also be assigned to each medication. Table 3 denotes the associated cost of medication at the time of publication.[44]

Discussion

The goals of this project were to answer questions regarding the safe use of antiemetics in at-risk populations and to provide evidence-based guidelines in a quickly accessible format to anesthetists working in the fast-paced perioperative environment. Access to decision support tools that can help decrease mental burden can be especially helpful in fast-paced, stressful environments.

Anesthetists unfamiliar with the most up-to-date research on this topic may find this antiemetic decision tool helpful during clinical practice. Student registered nurse anesthetists and anesthesia residents may find it quite assistive as they are learning a high volume of material in a short period. Perioperative nurses may find the tool helpful while checking the safety of administering a newly prescribed medication to patients before and after surgery. Last, clinicians prescribing antiemetics to obstetric, oncologic, and neurologic patients may find it helpful since they also manage patients who commonly fall into the examined populations.

Conclusion

Anesthetists have many factors to consider when developing a PONV regimen for patients. The medical history, operative and anesthetic details, and the entire pharmacologic regimen play a role in patient outcomes. When considering the risk of side effects, drug interactions, and adverse drug events, the provider must keep the role of polypharmacy in mind. This project highlights the importance of an anesthetist's pharmacologic knowledge, recognition of medications that may increase the risk of serotonin syndrome, and prevention of other adverse drug events.

The perioperative course is brief and fast paced. Tools and guidelines that can be quickly accessed can be helpful to anesthetists during this time. This antiemetic decision support tool can provide anesthetists with evidence-based information to help guide their clinical decisions regarding PONV management, resulting in the safest and most cost-effective care.

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DISCLOSURES

The authors have declared no financial relationships with any commercial entity related to the content of this article. The authors did not discuss off-label use within the article.

ACKNOWLEDGMENTS

The first author would like to acknowledge her coauthor, Dr Davies, for coaching her through the research and article writing process; her mentor, Chuck Biddle, PhD, CRNA, for being an invaluable resource; the expert panel members for offering enlightening recommendations; and her DNP cohort for providing encouraging support when needed most.