

**The Utilization of Amisulpride as a Rescue Drug for Postop Patients Compared to  
Promethazine for the Treatment of Postoperative Nausea and Vomiting:  
An Educational Module**

A DNP Project Presented to the Faculty of the  
Nicole Wertheim College of Nursing and Health Sciences  
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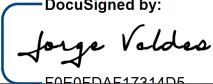
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By

Sharon Britton, MSN, RN

Supervised By

Dr. Yasmine Campbell, DNP, CRNA, APRN  
Dr. Carmen Chan, DNP, CRNA

Approval Acknowledged:  \_\_\_\_\_, DNA Program Chair  
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Approval Acknowledged:  \_\_\_\_\_, DNA Program Director  
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## Abstract

**Background:** Postoperative nausea and vomiting (PONV) persist as one of the most common adverse effects experienced by patients undergoing general anesthesia, as it can prolong a patient's stay in the hospital, increase hospital costs, and lead to further complications delaying the recovery process.<sup>1,3,7</sup> Despite prophylactic treatment with a combination of drugs, some patients still experience PONV. Despite its adverse side effects, Promethazine is still utilized as a rescue drug for PONV after failed prophylaxis.

**Objective:** This quality improvement project aims to increase anesthesia providers' knowledge of the current literature on Amisulpride's efficacy and safety profile for treating PONV after failed prophylaxis compared to Promethazine.

**Methods:** An in-depth analysis was conducted by using CINAHL, PubMed, Google Scholar, and the Cochrane Library database to obtain research studies discussing the use of Amisulpride and Promethazine as rescue treatments for failed PONV prophylaxis. CRNAs were invited to participate by completing an online pre-test survey, followed by viewing an online educational module, and a post-survey questionnaire to assess their acquired knowledge.

**Results:** There was an increase in knowledge among anesthesia providers on using Amisulpride as a rescue treatment for failed prevention of PONV compared to Promethazine. Amisulpride has a safer profile and is less likely to cause any side effects, unlike Promethazine, which has the potential for multiple adverse effects.

**Discussion:** Data collected from the surveys showed that anesthesia providers had increased their knowledge of the use, mechanism of action, and minimal potential for side effects of Amisulpride when used to treat PONV. A small sample size of 7 people and the online distribution were limitations for this project.

**Conclusion:** Evidence-based research shows Amisulpride has a safer profile for treating PONV when prophylaxis fails compared to Promethazine. Results from this quality improvement project showed an increase in anesthesia providers' knowledge regarding the benefits and adverse effects of both antiemetics. Introduction of Amisulpride to clinical practice can lead to improvements in patient outcomes by decreasing the occurrence of PONV and further complications.

**Keywords:** Postoperative nausea and vomiting, prophylaxis, rescue, antiemetic, Amisulpride, Barhemsys, Promethazine, Phenergan

## **The utilization of Amisulpride as rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea vomiting: An Educational Module**

### **Problem Identification**

Every year, millions of surgical procedures are performed under general anesthesia. Although numerous complications may transpire after surgery, postoperative nausea and vomiting (PONV) continue to be the most common adverse effects patients experience after anesthesia.<sup>1</sup> If not prophylactically treated before surgery, there is a probability that patients can develop PONV even if they do not have any known risk factors.<sup>1,2,3</sup> Patients with existing risk factors should be pre-medicated, as they are at a higher risk of experiencing PONV postoperatively.<sup>1,2,3</sup> This is a highly stressful experience for patients and a cause for potentially severe postoperative complications.

The gold standard for the treatment of PONV is prevention.<sup>1</sup> Various antiemetic drugs are available to be administered preoperatively as a prophylactic treatment, but common practice entails the administration of multiple antiemetic medications rather than one medication alone.<sup>1,3,4</sup> Some of these medications used for antiemetic therapy were initially made to target different problems, but over time were found to be effective as an antiemetic.<sup>4</sup> As healthcare providers, a careful and thorough evaluation of the patient's medical history must be done before prophylactic treatment of PONV to prevent any adverse effects from occurring after the administration of antiemetic drugs.<sup>2</sup> Extensive research exists on multimodal treatment for PONV and the different strategies developed for PONV prevention, but no optimal antiemetic regimen has been established as a solution to this problem.<sup>5</sup> Unfortunately, even after treatment with multiple antiemetic medications, some patients still suffer from PONV.<sup>1</sup>

## Background

The occurrence of postoperative nausea and vomiting dates back to the 1800s when volatile anesthetics, such as ether and chloroform, were first utilized during general anesthesia.<sup>6</sup> Since then, efforts to find the appropriate pharmacological treatment for patients became significant as the use of volatile anesthetics was widely used for numerous surgical procedures. Different risk factors must be considered when determining what patient is at potential risk of developing PONV. Gan et al.<sup>2</sup> identified that the main risk factors that place patients at risk for developing PONV include female sex, non-smoker, young age, history of previous PONV/motion sickness, use of volatile anesthetic agents or nitrous oxide, opioids, type of surgery and the duration of administered anesthesia. The Koivuranta and Apfel scores are evidence-based tools that are commonly used in the hospital setting to assess if a patient is at risk of developing PONV.<sup>2</sup> These tools provide a simplified risk score composed of 4 to 5 of the previously mentioned patient risk factors. Identifying these risk factors has been shown to help reduce the occurrence of PONV and helps guide the pharmacological treatment for patients undergoing surgery.<sup>2</sup>

Understanding the physiology of nausea and vomiting plays an essential role in understanding the pharmacodynamics of antiemetic drugs and choosing the treatment of choice for surgical patients. Although nausea is less understood, it is defined as a sensation that involves cortical structures within the brain.<sup>4</sup> On the other hand, vomiting consists of a combination of emetic afferents along with the incorporation of respiratory, abdominal, and gastrointestinal muscles.<sup>4</sup> The whole process is primarily controlled by the vomiting center, found in the medulla oblongata.<sup>4,5</sup> Five pathways are involved in the development of PONV: the chemoreceptor trigger zone (CTZ), reflex afferent pathways in the cerebral cortex, the vagal afferent pathway

within the gastrointestinal system, the vestibular system, and midbrain afferents.<sup>4,5,7</sup> Any stimulation of these pathways will cause the vomiting center to become activated through different receptors like the dopaminergic, cholinergic (muscarinic), serotonergic and histaminergic receptors.<sup>4,5,7</sup> Various antiemetic medications have been developed to target these specific receptors for the prevention and treatment of PONV, and are classified as 5-HT<sub>3</sub> antagonists, glucocorticoid steroids, NK-1 receptor antagonists, dopamine antagonists, antihistamines, and anticholinergics.<sup>2,4,5</sup> Promethazine and Amisulpride are two examples of the many antiemetic medications used to treat PONV.

In 1956, the Food and Drug Administration (FDA) approved the use of Promethazine as an antiemetic.<sup>8</sup> Promethazine is derived from a phenothiazine compound and functions as a histamine H<sub>1</sub>-receptor antagonist with anticholinergic and antidopaminergic properties.<sup>8</sup> In 2006, despite its practical use as an antiemetic, the Institute of Safe Medicine Practices labeled intravenous Promethazine as a highly caustic vesicant, followed by a black box warning issued by the FDA 3 years later.<sup>2,8</sup> Cases were reported in which the intravenous injection caused gangrene/necrosis at the infusion site from unintentional intra-arterial injection or extravasation.<sup>8</sup> Major adverse side effects reported from the administration of Promethazine include cardiovascular symptoms (e.g., tachycardia/bradycardia, hypotension/ hypertension, QT prolongation), central nervous system symptoms (e.g., sedation, extrapyramidal reactions, delirium, tardive dyskinesia, neuroleptic malignant syndrome), gastrointestinal symptoms (e.g., diarrhea), hematologic symptoms (e.g., thrombocytopenia), and dermatologic symptoms.<sup>9</sup> Regardless of the adverse effects reported from the administration of Promethazine, some providers refuse to cease its administration from their institution.<sup>8</sup> Safer antiemetic drugs have been found for the prophylaxis and treatment of PONV.

## **Scope of the Problem**

Without prophylactic treatment, approximately 30% of the population undergoing surgery will experience PONV, while in high-risk populations the incidence can increase up to about 80%.<sup>1,2,3</sup> Patients report significant dissatisfaction after experiencing PONV and often fear it as much or even worse than the pain from their surgical procedure. Gan et al.<sup>2</sup> published various evidence-based guidelines as recommendations on clinically managing PONV in the adult and pediatric populations. Despite these guidelines and the existence of anesthesia information management systems (AIMS), adherence to PONV guidelines remains poor.<sup>10</sup>

Failure to provide prophylaxis and improper pharmacological management of PONV in the post-anesthesia care unit (PACU) can lead to detrimental postoperative patient outcomes. Gillman et al.<sup>10</sup> concluded that from the 589 patients studied, 16% required up to 4 different antiemetic medications to treat PONV. From this group, some received a second dose of a previously administered medication that should not have been utilized again.<sup>10</sup> Regardless of the multiple drug administration, some patients did not have total relief from PONV.<sup>10</sup> While some patients end up requiring a prolonged stay in the hospital, others are discharged home with insufficient prophylaxis of PONV.<sup>10</sup> Unfortunately, this may cause patients to be readmitted into the hospital to be treated for complications related to PONV.

## **Consequences of the Problem**

Failure to properly medicate against PONV can prolong a patient's stay in the hospital, increase hospital costs, and lead to further complications delaying the recovery process.<sup>1,3,7</sup> Some of these complications can include dehydration, pulmonary aspiration, cardiac dysrhythmias due to electrolyte imbalances, increases in intracranial pressure, tearing of the esophagus, dehiscence of abdominal incisions, and bleeding from the surgical site.<sup>1,5,11</sup> Increases in hospital costs occur

due to the additional number of days that patients must remain admitted in the hospital and the cost of multiple antiemetic drug administration needed for PONV.<sup>12</sup> There is an estimated incremental cost \$75 for each patient that experiences PONV.<sup>2,12</sup> Surprisingly, patients are willing to pay that same amount just to avoid the PONV experience.<sup>2,12</sup>

### **Knowledge Gaps**

The administration of multiple antiemetic drugs has become the standard of care for preventing PONV in patients at risk.<sup>3</sup> Guidelines have been set in place to help providers determine the prophylactic treatment patients will require based on the number of risk factors. Unfortunately, lack of adherence to these guidelines remains one of the reasons why there is a persistent occurrence of PONV.<sup>2</sup> With constant updates in technology and the current use of electronic medical records, the addition of electronic automated reminders can improve clinician adherence to PONV guidelines.<sup>2,13</sup>

With the ongoing incidence of PONV, there is still no specific combination of antiemetic medications designated for optimal treatment. However, different combinations of antiemetic medications have been recommended as prophylactic treatment of PONV.<sup>2,5</sup> When these combinations of medications fail to prevent PONV, a drug with a different mechanism of action working on a different neuroreceptor must be administered.<sup>2,5</sup> Research projects have recently introduced the use of new antiemetic medications for the treatment of PONV.<sup>2</sup> One of these medications, named Amisulpride, has been recently approved by the FDA as a rescue drug for failed PONV prophylaxis.

Amisulpride was introduced in the 1980s as an antipsychotic agent, but current research has shown that it is a safe and effective antiemetic when administered intravenously at low

doses.<sup>14,15</sup> It is a substituted benzamide that potently and selectively blocks D2/D3 receptors, which are both involved in the development of nausea and vomiting.<sup>14,15</sup> Unlike other D2 receptor antagonists, Amisulpride preferentially inhibits dopamine receptors in the limbic system at very low doses rather than at the D2 receptors in the striatum.<sup>16</sup> The advantage of working in the limbic system is that it prevents the possibility of causing any extrapyramidal side effects.<sup>16</sup> Other advantages of Amisulpride include no prolongation of QT interval, no active metabolites, 80% renally excreted in its parent form, and a very low risk of drug-drug interactions.<sup>16,17</sup> A combination of all these advantages makes Amisulpride the medication of choice for the treatment of unresolved PONV in surgical patients.

### **PROPOSAL SOLUTION**

Although several antiemetic drugs are clinically used for the prevention of PONV, there is still a significant failure rate after prophylactic administration.<sup>14</sup> There is currently no designated antiemetic medication used in cases of failed PONV prophylaxis. Administration of medications that work on different receptors is the best practice for treating persistent PONV. Amisulpride, a dopamine D2/D3 antagonist, has been approved as a rescue treatment of PONV in patients who failed prophylactic treatment.<sup>14</sup> Promethazine, known for its antidopaminergic and antihistamine properties, is another antiemetic medication that has been used to treat failed PONV prophylaxis.<sup>11</sup> Habib et al.<sup>14</sup> found that the administration of Amisulpride provided complete relief of PONV after failed prophylaxis without a need for further antiemetic administration. On the other hand, Promethazine has been found effective as a rescue medication, but along with its many adverse side effects it has a secondary sedative effect that can cause a delay in discharge from PACU.<sup>11</sup> Therefore, the administration of Amisulpride as a

rescue drug compared to the administration of Promethazine, can lead to a decrease in the incidence of PONV.

## **SUMMARY OF THE LITERATURE**

### **Search Strategy**

A thorough search was performed to find the research studies required to complete a literature review. Different search engines were utilized such as the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed, the Cochrane Library database, and Google Scholar. To obtain the most recent data, the timeline was narrowed to the last 10 years, starting from 2011 to 2021. Research articles that resulted in systematic reviews, literature reviews or analyses, or meta-analyses were excluded, and only randomized controlled trials were obtained from the search. A variety of keywords and phrases were used, with the assistance of Boolean operators (AND/OR) that included postoperative nausea and vomiting, PONV, failed PONV prophylaxis, rescue treatment for PONV, Amisulpride, Promethazine, and Phenergan. After narrowing down the search results, 8 research studies were chosen to generate a literature review.

### **Study Characteristics**

Eight research articles were selected for this literature review to analyze the topic of interest regarding treatment for postoperative nausea and vomiting. Habib et al.<sup>14</sup> introduced a newly FDA-approved drug, Amisulpride, for the rescue treatment of PONV when prophylaxis fails. Candiotti et al.<sup>15</sup> studied the effect of Amisulpride in patients with PONV who have not been previously treated with any prophylactic antiemetic drugs. Taubel et al.<sup>17</sup> studied the effect of intravenous Amisulpride on the QT interval, while Kranke et al.<sup>18</sup> focused on the effect of Amisulpride administered at different doses. Deitrick et al.<sup>19</sup> provided insight into Promethazine for treating PONV at varying doses, while Talebpour et al.<sup>20</sup> studied the effect of Promethazine

combined with dexamethasone for PONV treatment. In another study, Owczuk et al.<sup>21</sup> studied the effect of Promethazine on the QT interval, while Habib et al.<sup>22</sup> discussed the efficacy of Promethazine as a rescue drug for failed prophylaxis of PONV. All studies include randomized control trials that were performed on the adult population.

## **Results of Individual Studies**

### ***Amisulpride for the Rescue Treatment of Postoperative Nausea or Vomiting in Patients***

#### ***Failing Prophylaxis; A Randomized, Placebo-controlled Phase III Trial***

Currently, no medication has been designated as the drug of choice for the treatment of PONV when prophylaxis does not work. However, Habib et al.<sup>14</sup> recently published that Amisulpride, one of the newest FDA-approved antiemetic medications, successfully worked as a rescue treatment of failed PONV prophylaxis. Habib et al.<sup>14</sup> research study was an experimental, randomized control trial, categorized as level I evidence research. The study was conducted in 23 different centers in the United States, Germany, Canada, and France in patients older than 18 years of age. Patients enrolled in the study included those undergoing a broad range of surgeries, open and laparoscopic, that were exposed to inhalational anesthesia, also allowing participation of patients who had total intravenous anesthesia and still experienced PONV. The majority of the patients had 3 or 4 of the major risk factors for developing PONV based on the Apfel risk score.

With statistics showing that approximately 25% to 30% of patients develop PONV, Habib et al.<sup>14</sup> attempted to enroll around 2,500 people to obtain a good sample size. Quantitative data was collected and analyzed to produce results. A total of 2,285 patients were enrolled in the study, with 702 patients experiencing a PONV event, which were then medicated and monitored for the desired response. The group was then divided into 3 different groups, 2 with differing Amisulpride doses and 1 serving as the placebo group. The primary efficacy analysis compared

the total response between the Amisulpride and the placebo groups using Pearson's  $X^2$  test, showing a 5% significance level after utilizing Hommel's method. Next, the Cochran-Mantel-Haenszel test was used to analyze the strength of the primary analysis and the complete response of treatment by taking into consideration the number of risk factors, surgery type, and pharmacological treatment. Finally, the Pearson  $X^2$  test was used to assess secondary efficacy variables such as the occurrence of nausea and vomiting, and the use of rescue medication in the different groups.

After signs of failed prophylaxis, patients were medicated with Amisulpride. If emesis occurred within the first 30 minutes of administration time, it was not considered to be a failure of treatment as a thirty-minute window was designated for the drug to become effective. Results showed that the 10 mg dose of Amisulpride had a more significant effect in treating PONV in patients that were previously medicated for prophylaxis with one or more antiemetic medications of different pharmacological classes. In the group that received 10 mg of Amisulpride, 41.7% of the people showed a complete response to the medication with no further episodes of PONV within a 24-hour observation period after rescue treatment, making this a safe and effective drug for the treatment of failed PONV prophylaxis.

Habib et al.<sup>14</sup> made an important observation, stating that it is still common practice to re-dose antiemetic medications given for prophylaxis of PONV as a treatment of PONV, despite their ineffectiveness. The reason for this has been linked to the cardiac and extrapyramidal toxic effects of some dopamine antagonists, the risk of tissue damage with extravasation of Promethazine, and the sedative effects of some antihistamines and dopamine antagonists, like Promethazine.<sup>14</sup> It is crucial to remember that doses administered for the prevention of PONV may not be effective as a breakthrough treatment of PONV, as the drug could have a slow onset

of action or lack the potency to resolve active PONV.<sup>14</sup> Therefore, in the Habib et al.<sup>14</sup> study, two doses of Amisulpride are tested to assess the effects of each dose in the prevention versus treatment of PONV.

One of the limitations in Habib et al.<sup>14</sup> was that although the inclusion of patients undergoing a broad range of surgeries was useful regarding validity, the large population limited their ability to recognize whether the response towards treatment varied throughout different surgical groups. Another limitation encountered in this study was the lack of patients' electrocardiograph (ECG) data to assess for possible QT interval prolongation in response to the administration of Amisulpride.<sup>14</sup> However, an in-depth study by Taubel et al.<sup>16</sup> analyzed the effects of Amisulpride on the QT interval.

***Randomized, Double-Blind, Placebo-Controlled Study of Intravenous Amisulpride as Treatment of Established Postoperative Nausea and Vomiting in Patients Who Have Had No Prior Prophylaxis***

Candiotti et al.<sup>15</sup> studied whether different dosing of Amisulpride would provide a complete response (signifying no emesis after drug administration) in patients who experienced PONV without previous prophylaxis. Candiotti et al.<sup>15</sup> was an experimental study, and a randomized control trial classified as level I evidence. The criteria to enroll patients in the study included being older than 18, receiving inhalational general anesthesia, surgical procedures expected to be over an hour long, and having a low to moderate risk of developing PONV as per the risk factor scoring system. Patients were excluded if they were to receive regional anesthesia, if they had received Amisulpride within 2 weeks of the study, if they were pregnant or breastfeeding, if they had any significant arrhythmias or prolonged QT syndrome, and if they

were receiving antiemetic treatment prior to surgery. A 24-hour assessment of the drug's efficacy was monitored for all patients to evaluate the effect of the drug over a more extended time range.

Quantitative data was collected and Pearson's  $X^2$  test was utilized to analyze the primary and secondary efficacy of the drug like in Habib et al.<sup>14</sup> previous study. A sample group of 1,988 people were initially enrolled for this study. Only 568 participants were officially randomized to receive treatment. Within the three groups, findings showed that 21.5% of 181 patients showed a complete response in the placebo group, 31.4% of 191 patients in the 5 mg Amisulpride group and 31.4% of 188 patients in the 10 mg Amisulpride group showed a complete response to treatment of PONV without prior prophylaxis. For further analysis, a logistic regression model was done analyzing the correlation between risk factors, treatment, and type of surgery showing that both doses provided more benefits in patients than the placebo. More significant benefits were evident within the first 2 hours of receiving Amisulpride, with a statistically significant difference in percentage between the placebo and Amisulpride groups.

Results showed that 74.6% of the placebo group required administration of more rescue medication within the 24-hour period after treatment, compared to only 63% in both Amisulpride groups. Significant decreases in PONV were seen within the first 3 hours of treatment in the Amisulpride group. Some of the adverse effects seen to occur in 5% of any of the groups from the administration of Amisulpride included flatulence, constipation, nausea after 24 hours post-treatment, and some pain in the site of infusion. Candiotti et al.<sup>15</sup> reported no symptoms of toxicity with Amisulpride administration, compared to some of the other detrimental effects of other antiemetics causing cardiac and extrapyramidal effects (i.e. dopamine antagonists), sedative effects (Promethazine), or diabetogenesis and infection risk (dexamethasone).<sup>15</sup>

Candiotti et al.<sup>15</sup> have a significant limitation within the study involving the inclusion of only patients that did not receive any PONV prophylaxis. This is also important to analyze because there is a large population of patients with low to moderate risk factors that are not routinely treated with prophylactic medications, and still manage to experience PONV.<sup>15</sup> This is one of the reasons for this study, as it is of great value to analyze the effectiveness of Amisulpride in groups who haven't been previously medicated.<sup>15</sup> Another limitation was that children were not included as part of the study group. The efficacy of Amisulpride in treating PONV in the pediatric population is yet to be determined. Overall, the use of Amisulpride has shown to have a significant effect in the treatment of PONV with or without previous prophylaxis with antiemetic drugs.

***Thorough QT study of the effect of intravenous Amisulpride on QTc interval in Caucasian and Japanese healthy subjects***

Taubel et al.<sup>17</sup> investigated whether the administration of intravenous Amisulpride has any effect on the QTc interval. Taubel et al.<sup>17</sup> was an experimental, randomized, double-blind controlled study, categorized as level I evidence. A total of 102 people were screened for eligibility to participate in the study. These included both healthy female and male subjects, non-smokers, between 20 and 40 years of age, Japanese or Caucasian, and with a body mass index between 18 to 25 kg/m<sup>2</sup>. Exclusion criteria consisted of previous history (or family history) of prolonged QT syndrome, significantly abnormal ECG (120 ms > PR > 230ms; QRS ≥ 120 ms; QTc > 450ms for females and >430ms for males; 45 > HR > 100 beats/min), use of medications that impaired drug metabolism or prolonged QT interval, and intolerance to Amisulpride or Moxifloxacin (antibiotic that can prolong QT interval).<sup>17</sup>

After the screening process, 40 subjects were chosen to participate and were randomly divided into four groups. First group was given 400 mg of oral Moxifloxacin, second group 5 mg of intravenous Amisulpride, third group 40 mg of intravenous Amisulpride, and the fourth group normal saline as the placebo.<sup>16</sup> Intravenous medications were delivered through syringe drivers, with the 5 mg of Amisulpride delivered as 2.5 mL over 2 minutes, the 40 mg delivered as 20 mL over 8 minutes, and the Moxifloxacin as a 400mg oral tablet. Baseline ECGs and blood samples were drawn one day before starting treatment and at the same time on the start date. A 12-lead ECG was recorded with a MAC1200 ECG recorder, and electronically stored during various times including pre-dose, 2 minutes, 8 minutes, 30 minutes, 1 hour, 1.5 hours, 2 through 6 hours, 8 hours, 12 hours, and 24 hours after treatment in each group.<sup>16</sup> The ECGs were analyzed by experienced cardiologists with extensive training on interpreting ECGs. Subjects in each group were provided with breakfast before medication administration, lunch, and dinner of similar nutritional content at around 6 and 12 hours, respectively, after administration.<sup>17</sup>

A linear graph model was used to plot the results at different time points, and to validate study sensitivity the Hochberg procedure was utilized at the 2-, 3- and 4-hour periods to analyze the difference between the positive control (Moxifloxacin) and the placebo.<sup>17</sup> The effect of the Moxifloxacin on the QTc demonstrates the sensitivity of the study in detecting a relevant increase of the QTc. Blood samples were drawn at the exact times designated for ECG assessment.<sup>17</sup> The concentration of Amisulpride in the plasma samples was analyzed by Quotient BioAnalytical Sciences, using a liquid chromatography/tandem mass spectrometry method.<sup>17</sup> The analytical software SAS version 9.2 was used to perform the pharmacokinetic analyses.

Results showed that the change in QT duration caused by the 5 mg dose of Amisulpride was both small and short lived, returning to baseline levels within thirty minutes of drug

administration.<sup>17</sup> Rapid infusion of the 40 mg supratherapeutic dose of Amisulpride did show to cause a significant prolongation, with an increase from the baseline in QTc > 30 ms.<sup>17</sup> However, the plasma concentration of Amisulpride measured for the 40 mg dose was nowhere near the toxic levels reported to cause torsade de pointes. Amisulpride doses ranging from 4,000 to 80,000 milligrams have been found to cause the toxic plasma concentration levels that can lead to lethal cardiac arrhythmias, like torsade de pointes.<sup>17</sup> Taubel et al.<sup>17</sup> reported that both doses of Amisulpride tested in the study were tolerated well by both Japanese and Caucasian participants, and that ethnicity did not have any influence on the QT response. This study's most frequent reported adverse event was pain on infusion, which could be avoided by reducing the infusion rate.<sup>17</sup> Overall, Taubel et al.<sup>17</sup> concluded that the administration of 5mg to 40 mg of Amisulpride did not show significant blood pressure variations, or cause any arrhythmias, making this a cardiovascular safe medication for the treatment of PONV.

***I.V. APD421 (Amisulpride) prevents postoperative nausea and vomiting: a randomized, double-blind, placebo-controlled, multicentre trial***

Kranke et al.<sup>18</sup> research study analyzes the effect of three different doses of Amisulpride on the prevention of PONV. This study is an experimental, randomized, double-blind control trial classified as level I evidence. It was conducted in various sites including university hospitals in France, Germany, and the United States. Subjects were chosen to participate if they were scheduled to have surgery that lasted a minimum of one hour under general anesthesia and had at least two risk factors for developing PONV. Subjects were also required to have a normal renal, hepatic, and hematological function to be part of the study. Exclusion criteria included subjects requiring postoperative ventilation, need for oro-gastric or nasogastric tubes post-surgery, history

of Parkinson's disease or alcohol abuse, any pre-existing vestibular disease, or any cardiac arrhythmias.

After the screening process, 215 people participated in the study and were then divided into four groups. First group received 1mg of Amisulpride, the second group 5 mg, the third group 20 mg, and the fourth group received a placebo. Subjects were randomized according to the amount of risk factors intending to give each group as homogenous as possible a risk of PONV due to the limited sample size.<sup>18</sup> Each group was administered their respective test dose slowly over two minutes during induction of anesthesia. Any vomiting episodes, the need to use a rescue medication, the severity of nausea, and the amount of time taken to develop PONV were monitored throughout the study during a 24-period starting after the end of wound closure.<sup>18</sup> A verbal rating scale ranging from 0 (having no nausea) to 10 (worst possible nausea) was utilized to assess the severity of any nausea episode, in addition to individual assessments evaluating for nausea at 30 minutes, 1 hour, 1.5 hours, 2 hours, 6 hours, and 24 hours after end of surgery.

To analyze and compare the efficacy of different doses of Amisulpride in each of the groups, Pearson's  $X^2$  test was used along with Yates's continuity correction. Kaplan-Meier estimations were arranged for the amount of time taken for patients to experience PONV, excluding data in which no PONV event occurred within 24 hours after surgery. The analysis software SAS version 8.2 was used to perform all calculations necessary for the study. To analyze the safety profile of Amisulpride, Kranke et al.<sup>18</sup> monitored and documented any occurrence of adverse events, changes in patient's vital signs and blood work, and changes from the baseline electrocardiogram obtained from patients.

Results showed that the 5 mg dose of Amisulpride had the most significant efficacy at reducing PONV, or requirement of rescue medication, with only a 40% incidence of PONV in

the 5mg group, while a 69% was seen with the placebo group.<sup>18</sup> The 1 and 20 milligram doses of Amisulpride seemed to be less effective as an antiemetic, although the 1 mg dose showed to have some potential as the results overlapped with those of the 5 mg up until the tenth hour.<sup>18</sup> Kranke et al.<sup>18</sup> found that 5 mg Amisulpride has a 42% relative risk reduction, and referenced a Cochrane Collaboration meta-analysis of 737 research studies which reported that eight different effective antiemetic medications only showed a 20% to 40% reduction. Few patients reported experiencing one or more adverse events, which commonly included insomnia but until after 48 hours after drug administration (considering that the half-life of Amisulpride is 7.5 hours).<sup>18</sup> No extrapyramidal or cardio-toxic side effects were seen with any of the three doses, making 5mg Amisulpride an ideal dose for PONV prophylaxis.

### ***A Comparison of Two Differing Doses of Promethazine for the Treatment of Postoperative Nausea and Vomiting***

Promethazine, a dopaminergic antagonist and histamine-1 blocker, has been widely used for its effect as an antiemetic drug.<sup>19</sup> Deitrick et al.<sup>19</sup> study compares two doses of intravenous Promethazine to provide relief in patients experiencing PONV. It is a double-blind, randomized control trial that can be categorized as level I evidence. It was conducted in a teaching hospital setting with a capacity of 750 beds. Participants were selected between the ages of 18 years of age to 75, undergoing various types of surgeries, and English speakers. Exclusions included patients younger than 18 and older than 75, non-English speakers, pregnant or breastfeeding women, or anyone with a previous allergic reaction to Promethazine.

A total of 352 females and 271 males were enrolled as part of the study, but only 120 participants complaining of PONV were given either dose of Promethazine for treatment. With the assistance of a computer-generated program, participants were randomized to receive either a

6.25 mg intravenous dose of Promethazine, while the other group was to receive a 12.5 mg intravenous dose. To maintain randomization, pharmacists provided nurses with the desired dose with a safety measure in place for them to determine the given dosage if necessary, yet nurses were not made aware of the dose they were administering. To assess the degree of PONV, a verbal descriptive scale (VDS) was developed to facilitate the process of gathering information. For patients who suffered from PONV, treatment with Promethazine was offered to help relieve symptoms. Sedation, a well-known side effect of Promethazine, was another factor that was monitored in the post-anesthesia care unit (PACU) as it is one of the reasons patients can spend longer periods in recovery. The IBM Statistical Package for Social Sciences (IBM-SPSS) was used to help thoroughly analyze the data by using the t-test and chi-square as two comparison techniques.<sup>19</sup>

Results showed that many of the patients who experienced PONV reported having complete relief of symptoms after a single dose of Promethazine.<sup>19</sup> However, there was a high incidence of patients experiencing sedation effects from the medication. After thirty minutes after administration of medication, sedation effects were significantly greater in the group of patients receiving the 12.5 mg dose of Promethazine.<sup>19</sup> Deitrick et al.<sup>19</sup> reported that sedation effects after treatment of PONV appeared to be significantly higher in females compared to men. Type of surgery also determined the level of PONV incidence, with plastic surgery being reported as the highest incidence of nausea after discharge from the hospital.<sup>19</sup>

Deitrick et al.<sup>19</sup> did not expand the research to other facilities; instead, this study was limited to data collection within one hospital where all patients underwent ambulatory surgery. Also, with a higher population of women in the study group, a disparity in the results was seen, limiting the ability to report generalized findings. No assessment tools were utilized to assess the

actual level of nausea; instead, it was obtained by patients' self-reporting. Deitrick et al.<sup>19</sup> stated their most significant limitation was the size of the sample group, in which from the total number of participants, only 120 patients experienced PONV. Overall, results showed that administration of a lower dose of Promethazine does not cause a significant level of sedation when treated for PONV. However, sedation effects could not be avoided entirely.

***Comparison Effect of Promethazine/Dexamethasone and Metoclopramide /Dexamethasone on Postoperative Nausea and Vomiting after Laparoscopic Gastric Plication: A Randomized Clinical Trial***

Postoperative nausea and vomiting have a 40% chance of occurring in bariatric surgery due to the type of surgical technique and a reduction in the size of the remaining gastric lumen, regardless of PONV prophylaxis.<sup>20</sup> Talebpour et al.<sup>20</sup> studied a group of 80 bariatric patients undergoing laparoscopic gastric plication (LGP) and their response to different combinations of antiemetic drugs. The study was an experimental, double-blinded randomized controlled trial that was classified as level I evidence. Patients were excluded from the study if they had received any of the antiemetic drugs within the last 24 hours of the study, and the presence of uncontrolled hypertension and/or diabetes.<sup>20</sup>

A computer-generated program randomly separated patients into two groups: the promethazine group, and the metoclopramide group. Patients in their assigned groups received the assigned antiemetic drug combined with a dose of dexamethasone during their recovery phase and were monitored for a total of 48 hours. A nausea scale was used to score the patients' severity and a visual analog scale to assess epigastric pain. To compare the occurrence of PONV

at different times, a Fisher's exact test, a repeated measure test, and a chi-2 were used for data analysis.<sup>20</sup>

Results showed that the group treated with promethazine/dexamethasone had significantly lower episodes of PONV within 24 hours than those treated with metoclopramide/dexamethasone. However, the patients in the group taking Promethazine/dexamethasone were unable to walk for long periods after surgery due to the medication's sedative effects. Talebpour et al.<sup>20</sup> reported that the use of Promethazine combined with an antiemetic drug of a different mechanism of action was more effective for PONV treatment than the use of Promethazine alone. Although Promethazine appears to have positive outcomes in the treatment of PONV, its use is limited due to the sedative effects, which can prolong patient recovery and time in the PACU.<sup>20</sup>

***Influence of Promethazine on cardiac repolarisation: a double-blind, midazolam-controlled study***

Owczuk et al.<sup>21</sup> research study analyzes the effect of Promethazine on the transmural dispersion of repolarization and the QTc interval. This study is an experimental, randomized, control trial classified as level I evidence. A total of forty subjects were selected to participate in the study, all between the ages of 20 to 60 years old. All participants were scheduled for elective surgery, having an American Society of Anesthesiologists (ASA) grade of 1 or 2, with a baseline QT and QTc less than 440 ms.<sup>21</sup> Exclusion criteria included patients with cardiac arrhythmias, those receiving treatment with drugs that could prolong QT interval, history of coronary artery disease or heart failure, history of any congenital heart defect, electrolyte imbalances, and any history of allergic reactions to Promethazine or Midazolam.<sup>21</sup>

Participants were randomized by using a pseudo-random number generator by Wichmann and Hill, and then separated into two groups of 20.<sup>21</sup> Throughout the study, patients were to be continuously monitored with an ECG, non-invasive blood pressure readings, and pulse oximetry. Once a standard 12-lead ECG was placed on the patient, monitoring began, and random administration of either 2.5 mg of Midazolam or 25 mg of Promethazine intravenously was given in the operating room. Syringes were prepared and assigned a randomized number, so the person administering the medication was blind to the solution in the syringe. Baseline ECG parameters and blood pressure were obtained before drug administration, and then at the 5-minute, 10-minute, 15-minute, and 20-minute marks after administration. To obtain a value for the QTc, the QT and RR intervals were measured from lead II of the ECG reading. All ECG parameters were measured without the knowledge of the medication administered to the patient, and once complete all results were decoded to analyze drug effects.

Data analysis was completed with the help of the STATISTICA 7.1 PL software. A Student's t-test or the chi-squared test was used for independent samples to compare data between groups. Two-sided ANOVA tests were used to analyze interval data for any existing repeated measurements, and further analysis of any significant differences was performed using the post-hoc method. Also, Pearson's correlation method was used to analyze the relationship between the changes in the QTc value and the transmural dispersion of repolarization. In order to correct the QT interval and obtain a QTc value, Fridericia's correction ( $QT_{cf} = QT RR^{-1/3}$ ) and Bazett's formula ( $QT_{cb} = QT RR^{-1/2}$ ) were used.<sup>21</sup>

Results showed that the group of patients given 25 mg of Promethazine significantly increased their QTc interval at the fifth minute and all the measurement that followed. In the Midazolam group, no significant changes were seen in the QTc value. The measured transmural

dispersion of repolarization showed no significant change in either of the groups. Data showed that there was no significant correlation between the maximum time of transmural dispersion of repolarization and the maximum QTc value in either group. This is an important finding because a significant prolongation of the QT interval accompanied by an increase in the transmural dispersion of repolarization can cause torsadogenesis.<sup>21</sup> There were no changes in heart rate seen between either group, although a significant decrease in the mean arterial pressure (MAP) was observed. Owczuk et al.<sup>21</sup> research study concluded that Promethazine causes a significant prolongation of the QTc interval in people without a history of cardiovascular disease and should therefore be used with caution, and avoided in people with cardiac disorders.

***A Comparison of Ondansetron with Promethazine for Treating Postoperative Nausea and Vomiting in Patients Who Received Prophylaxis with Ondansetron: A Retrospective Database Analysis***

With little data available at the time on antiemetic treatment for failed PONV prophylaxis, Habib et al.<sup>22</sup> focused on studying the efficacy of Promethazine as a rescue drug for PONV in patients who failed prophylaxis with Ondansetron. This study is a non-experimental database analysis, categorized as level II evidence. After receiving IRB approval, Habib et al.<sup>22</sup> retrieved data from the Duke Perioperative Anesthesia Database analyzing data between April 2001 to June 2005. Subjects chosen for this analysis were greater than 18 years of age, exposed to anesthetic gases during surgical procedures lasting from 30 to 240 minutes, who received Ondansetron for PONV prophylaxis. In addition, patients who received Promethazine or Ondansetron as a rescue drug for active PONV treatment were also included in the study.

Habib et al.<sup>22</sup> retrieved patient data from documented Ramsay scores upon their admission to the post-anesthesia care unit (PACU) to assess patient sedation. Information was

also gathered to analyze the length of stay in PACU, and opioid consumption during surgery and in PACU. Habib et al.<sup>22</sup> utilized the Wilcoxon's ranked sum test and the t-test for continuous data analysis, and the  $X^2$  test to analyze categorical data. Changes in sedation levels, represented by the Ramsay score, were assessed by using the Mantel-Haenszel  $X^2$  test.

Of all the patients who received preoperative PONV prophylaxis with Ondansetron, 18,209 patients met all eligibility criteria, with 4,391 of them requiring rescue drugs for PONV after surgery. Habib et al.<sup>22</sup> found that 72% of the patients received Ondansetron as a rescue drug and 17% received Promethazine. A complete response (meaning no further nausea, vomiting, or need for additional antiemetic) was observed in 68% of the patients in the Promethazine group and 50% in the Ondansetron group. Patients who were given Promethazine received different doses, including 6.25 mg, 12.5 mg and 25 mg, showing no difference in efficacy between the lower and higher doses. Habib et al.<sup>22</sup> concluded that Promethazine was more efficient than Ondansetron in treating patients who failed prophylaxis of PONV.

The Habib et al.<sup>22</sup> research study was faced with limitations due to data being retrospectively collected. The data quality depends on operator entry, leading to inaccuracies due to the under-reporting of information or lack of experience in electronic charting. Also, the rescue antiemetic was chosen by an anesthesiologist rather than being randomized. Some of the data evaluating patients' risk for PONV was not included in the history, making it difficult to compare both groups in terms of number of pre-existing PONV risk factors. The Habib et al.<sup>22</sup> research study was done to provide some insight on managing patients experiencing PONV in the PACU.

## DISCUSSION

### Summary of the Evidence

The incidence of PONV continues to be a common researchable topic as there is no current optimal treatment to entirely prevent it. Recently Habib et al.<sup>14</sup> and Candiotti et al.<sup>15</sup> published a study on the efficacy of Amisulpride, a newly approved FDA dopamine antagonist, in the treatment of failed PONV prophylaxis. The studies analyze the effect of different doses of Amisulpride on patients ranging from low risk to a high risk of experiencing PONV, despite previous administration of antiemetic drugs. Both studies found that the ideal dose for the prevention of PONV is 5 mg of Amisulpride, while a 10 mg rescue dose was found to have a complete response in 41.7% of patients with active PONV. Kranke et al.<sup>18</sup> studied 3 doses of Amisulpride, with results also showing that 5 mg of Amisulpride was the ideal dose to use for PONV prophylaxis. In addition, results showed that Amisulpride did not cause any cardio-toxic or extrapyramidal side effects at 1 mg, 5 mg, or 20 mg. Finally, Taubel et al.<sup>17</sup> studied the effects of Amisulpride on the QT interval, with results showing that the effect was minimal and short lived, and that even higher doses administered for the treatment of PONV showed no significant changes.

Deitrick et al.<sup>19</sup> and Talebpour et al.<sup>20</sup> focused on the effects of Promethazine in treating PONV. Deitrick et al.<sup>18</sup> study analyzes the effect of different doses of Promethazine for PONV treatment and concludes that a sedative effect is still seen within both groups of differing doses of the medication. Talebpour et al.<sup>20</sup> studied a group of bariatric patients at high risk for developing PONV, and results also showed that Promethazine can effectively relieve PONV causing an unfortunate sedative effect delaying patients' recovery and discharge from PACU. Owczuk et al.<sup>21</sup> studied the effect of Promethazine on the parameters of cardiac repolarization

and found that Promethazine causes a significant prolongation of the QTc interval in patients who have no prior history of cardiovascular disease. To study the efficacy of antiemetic medications in patients with failed PONV prophylaxis, Habib et al.<sup>22</sup> published a retrospective database analysis studying the effect of Promethazine as a rescue drug. Results showed that 68% of patients had a complete response with Promethazine compared to Ondansetron but were found to have higher number of patients with Ramsay score greater than two.

### **Conclusion**

Studies have shown that PONV remains one of the most common adverse effects experienced by patients after surgery. Although many antiemetic medications exist to treat PONV prophylactically, a significant number will fail prophylaxis. To date, there is no one antiemetic, or combination of antiemetic medications that is considered to be optimal in treating PONV. Multimodal therapy for PONV prevention is considered the standard of care, while guidelines have been established to assess and properly manage patients who have been identified as moderate to high risk for developing PONV. Recent studies show that a single dose of 10 mg of Amisulpride was found to have a 41.7% complete response in patients experiencing PONV after failed prophylaxis, while prophylaxis with 5 mg causes a significant reduction in episodes of PONV. Promethazine, another antiemetic found to be effective as a rescue drug for treating PONV, has been found to cause undesirable side effects such as QT interval prolongation, sedation and occasional akathisia. These side effects can limit the use of Promethazine in patients who suffer from cardiac disorders, the elderly, or those receiving multiple narcotics. However, several research studies found that Amisulpride has no cardiovascular, sedative, or extrapyramidal side effects at the doses administered to treat PONV, making this a very safe drug for the treatment of PONV.

Author(s)	Purpose	Methodology/ Research Design	Intervention(s)/ Measures	Sampling/Settin g	Primary Results	Relevant Conclusions
<b>Habib et al.,<sup>14</sup> 2019</b>	To investigate the effect of Amisulpride as the rescue medication for the treatment of PONV in patients who have failed prophylaxis	Randomized control trial  Level I	Subjects were divided into 3 groups: 5 mg Amisulpride, 10 mg of Amisulpride, and placebo  Patients with active PONV were given Amisulpride as a rescue drug. Emesis in the first 30 min of administration was not considered treatment failure to allow medication to take effect.	A total of 2,500 people were enrolled in the study.  Only 2,285 met eligibility criteria, with 702 experiencing a PONV event.	The 10 mg of Amisulpride had a more significant effect in treating PONV for patients who failed previous PONV prophylaxis.  Patients that received 10 mg Amisulpride had a 41.7% complete response to the medication with no further episodes of PONV.	Habib et al. <sup>14</sup> compared this result to their previous study where Promethazine is used as a rescue drug for PONV yielding higher success rate, stating that in that study the response of Promethazine administration was only monitored for 2 hours in comparison to 24 hours in this study. <sup>18</sup>
<b>Candiotti et al.,<sup>15</sup> 2019</b>	To investigate the use of Amisulpride as treatment of PONV for patients who had no prior prophylaxis before surgery	Randomized control trial  Level I	Sample size was divided into three different groups.  One group was the placebo group, the second group was given a 5mg dose of Amisulpride to treat PONV with no prior prophylaxis and the third group a 10mg dose of Amisulpride as treatment.	A sample group of 1,988 people was initially enrolled for this study, in which only 568 participants were officially randomized to receive treatment.	Results showed that 21.5% of 181 patients showed a complete response in the placebo group;  31.4% of 191 patients in the 5 mg Amisulpride group and 31.4% of 188 patients in the 10 mg Amisulpride group showed a complete response to treatment of PONV without prior prophylaxis	Results showed that 74.6% of placebo group required administration of more rescue medication within the 24 hour period after treatment, compared to only a 63% in both Amisulpride groups.  No symptoms of toxicity with Amisulpride administration, compared to other antiemetics that cause cardiac and extrapyramidal effects (i.e. dopamine antagonists), sedative effects (Promethazine), or diabetogenesis and infection risk (dexamethasone)

<p><b>Taubel et al.,<sup>17</sup> 2017</b></p>	<p>To study the effect of Amisulpride on QTc interval in healthy Caucasian and Japanese patients</p>	<p>Randomized control trial  Level I</p>	<p>Sample group was divided into 4 groups: 1st group given 400 mg oral Moxifloxacin, 2nd group 5 mg IV Amisulpride, 3rd group 40 mg IV Amisulpride, 4th group normal saline as placebo.</p> <p>Baseline ECGs and blood samples taken.</p> <p>ECG recorded and stored during various times: pre-dose, 2, 8, and 30 minutes, 1 hour, 1.5, 2-6, 8, 12 and 24 hours after treatment for each group</p>	<p>A total of 102 patients were enrolled, with only 40 meeting the eligibility criteria</p>	<p>Changes in QT duration by 5 mg of the Amisulpride was small and short lived, returning to baseline within 30 min of administration</p> <p>Rapid infusion 40 mg of Amisulpride caused a significant prolongation, with an increase from the baseline in QTc &gt; 30 ms; however, plasma concentration levels were nowhere near toxic to cause torsade de pointes</p>	<p>Both doses of Amisulpride were tolerated well, meaning ethnicity does not have an effect on QT response.</p> <p>Most common adverse event was pain on infusion, alleviated by slowing infusion rate</p>
<p><b>Kranke et al.,<sup>18</sup> 2013</b></p>	<p>To study the effect of different doses of Amisulpride for PONV prevention</p>	<p>Randomized control trial  Level I</p>	<p>Sample size divided into four groups: 1<sup>st</sup> group given 1mg of Amisulpride, 2<sup>nd</sup> group 5 mg, 3<sup>rd</sup> group 20 mg, and the 4<sup>th</sup> group a placebo</p>	<p>Conducted in various sites: University hospitals, France, Germany and the U.S.</p> <p>215 people participated in the study</p>	<p>5 mg dose of Amisulpride had the most significant efficacy at reducing PONV, with only a 40% incidence of PONV, while a 69% was seen with the placebo group.</p>	<p>The 1 mg and 20 mg doses of Amisulpride seemed to be less effective as an antiemetic, although the 1 mg dose showed some antiemetic potential.</p> <p>No extrapyramidal or cardiotoxic side effects were seen with any of the three doses of Amisulpride.</p>
<p><b>Deitrick et al.,<sup>19</sup> 2015</b></p>	<p>To investigate the effect of different doses of</p>	<p>Randomized control trial</p>	<p>Compares 2 different doses of intravenous</p>	<p>Conducted in a teaching hospital setting with a</p>	<p>Patients who experienced PONV had full relief of</p>	<p>Sedation effects appeared to be significantly higher in females compared to men.</p>

	Promethazine for treatment of PONV	Level I	<p>Promethazine to treat PONV.</p> <p>Participants were randomized to receive either a 6.25 mg IV dose of Promethazine, while the other group was to receive a 12.5 mg IV dose</p>	<p>capacity of 750 beds.</p> <p>A total of 352 females and 271 males were enrolled, but only 120 complaining of PONV were given either dose of Promethazine for treatment</p>	<p>symptoms after single dose of Promethazine, but with a high incidence of sedation effects.</p> <p>After 30min of administration, sedation effects were significantly greater group receiving 12.5 mg dose of Promethazine.</p>	Type of surgery also determined level of PONV incidence, with plastic surgery reported as the highest incidence of nausea after discharge from the hospital
<b>Talebpour et al.,<sup>20</sup> 2017</b>	To compare the effect of Promethazine/Decadron and Reglan/Decadron on PONV after laparoscopic procedure	<p>Randomized control trial</p> <p>Level I</p>	<p>Patients randomly divided into 2 groups: the promethazine group and the metoclopramide group.</p> <p>Each group received the assigned antiemetic combined with a dose of dexamethasone during their recovery phase and were monitored for a total of 48 hrs.</p> <p>Severity of nausea was evaluated as well as epigastric pain.</p>	<p>Sample size consisted of 80 bariatric patients undergoing laparoscopic gastric plication (LGP)</p>	<p>Group given promethazine/dexamethasone had significantly lower episodes of PONV within 24 hr period, than group treated with metoclopramide/dexamethasone.</p> <p>However, the patients in the group taking Promethazine/dexamethasone were unable to walk for long periods of time after surgery due to the sedative effects</p>	<p>Promethazine combined with an antiemetic drug of different MOA was more effective for PONV than Promethazine alone.</p> <p>Sedative effects of Promethazine limit its use because it can prolong patient recovery and time in the PACU</p>

<p><b>Owczuk et al.,<sup>21</sup> 2009</b></p>	<p>To study effect of Promethazine on QT interval and transmural dispersion of re-polarization</p>	<p>Randomized control trial  Level I</p>	<p>Continuous monitoring of patients with an ECG, non-invasive BP readings, and pulse oximetry.</p> <p>12-lead ECG was collected during random administration of 2.5 mg of Midazolam or 25 mg of Promethazine</p> <p>Baseline ECG parameters and BP were obtained before drug administration, &amp; then at 5, 10, 15, &amp; 20 min marks after administration</p>	<p>A total of 40 subjects were selected, between the ages of 20 to 60 years old</p>	<p>Patients given 25 mg of Promethazine had significant increase in QTc interval at 5 min and all measurements that followed.</p> <p>The measured transmural dispersion of repolarization showed no significant change in either of the groups.</p> <p>No changes in HR seen in either group, although a significant decrease in MAP was observed</p>	<p>The Midazolam group showed no significant changes in the QTc value.</p>
<p><b>Habib et al.,<sup>22</sup> 2007</b></p>	<p>Study effect of Promethazine versus Ondansetron as rescue drugs for failed PONV prophylaxis</p>	<p>Retrospective Database Analysis  Level II</p>	<p>72% of the patients given Ondansetron as a rescue drug and 17% received Promethazine.</p>	<p>18,209 patients met all eligibility criteria, with 4,391 of them requiring rescue drugs for PONV after surgery.</p>	<p>A complete response (meaning no further nausea, vomit, or need for additional antiemetic) was observed in 68% of the patients in the Promethazine group and 50% in Ondansetron group.</p>	<p>Patients given Promethazine received different doses: 6.25 mg, 12.5 mg &amp; 25 mg showing no difference in efficacy between the lower and higher doses</p>

## PURPOSE AND PICO CLINICAL QUESTION

### Purpose

The purpose of this project was to increase anesthesia providers' knowledge on the utilization of Amisulpride as a rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea and vomiting through an educational module.

### PICO Clinical Question

In postoperative patients, what is the effect of intravenous Amisulpride administration compared to Promethazine on improving postoperative nausea and vomiting?

Population (P): Postoperative patients

Intervention (I): Intravenous Amisulpride

Comparison (C): Intravenous Promethazine

Outcomes (O): Improvement of postoperative nausea and vomiting

## CONCEPTUAL UNDERPINNING OF THE PROJECT

### DNP Project Goal

Research for prevention of PONV has been ongoing for years, and there is still no preferred, or designated, treatment for its prevention. Despite the multimodal approach to prevent PONV, there are still patients who are unresponsive to prophylaxis and experience it postoperatively. Different combinations of antiemetic medications are usually administered preoperatively to patients who qualify as high risk, or have previous history of PONV, yet sometimes prophylaxis still fails. PONV has been known as one of the many adverse events that patients define as one of the most unpleasant experiences post-surgery, and therefore research continues to find medications to treat it.

Recently, the FDA approved Amisulpride as the first rescue medication to treat PONV in patients who have failed prophylactic treatment. It was also found that it could treat PONV in patients who had not been previously administered any antiemetic medication preoperatively. With this project, an educational module will provide anesthesia providers with new knowledge on this new medication as treatment for PONV. Online questionnaires will be done to evaluate the current knowledge of PONV prophylaxis by anesthesia providers, and the current practice of treatment in situations of PONV prophylactic failure. The primary goal is to educate anesthesia providers on the importance of preventing PONV, and the use of Amisulpride in clinical practice to treat for PONV, and as a rescue medication for failed prophylaxis of PONV.

## **Goals and Outcomes**

### **Specific**

An educational module was presented to anesthesia providers to introduce Amisulpride as a recently discovered antiemetic that aids in resolving postoperative nausea and vomiting in patients in whom preoperative prophylaxis has failed.

### **Measurable**

A small questionnaire was provided before and after the educational module was presented so that one can analyze the knowledge of the anesthesia providers regarding the current treatment of failed preoperative prophylaxis of PONV with Amisulpride. Furthermore, after collection of all questionnaires, a qualitative analysis can be made about the current knowledge anesthesia providers have regarding the treatment for failed PONV with a recently new antiemetic, current approaches for treating PONV, and pharmacological choices for PONV prevention.

**Achievable**

A good sample size may be obtained by involving anesthesiologists, certified registered nursing assistants (CRNAs), and post-anesthesia care unit nurses. This group of healthcare providers in the perioperative setting can provide the necessary information regarding current practice in the treatment of failed prophylaxis of PONV.

**Realistic**

A group of anesthesia providers was selected to be educated on the new introduction of Amisulpride, as a medication with antiemetic properties that has been shown to provide relief in patients who have failed to be prophylactically treated for PONV. The education occurred through an online multimedia presentation, with methods to assess the provider's knowledge before and after the information has been presented.

**Timely**

Over a two-month time span, data were collected and analyzed, and results reported on the findings of the quality improvement project. A time was designated to start data collection after education had been provided to anesthesia providers, with an end date to be able to finalize data and put together significant findings.

**Project Structure**

Stakeholders are an essential key factor to help in facilitating change, or to improve the quality of care. To create change within practice, healthcare providers must understand how Amisulpride functions as an antiemetic medication that will serve as a rescue drug for failed PONV prophylaxis. An online educational presentation was offered to different anesthesia providers, and an evaluation was done before and after to assess providers' knowledge of the current methods and

pharmacological approaches to preventing and treating PONV. To adequately structure the development of a quality improvement project, it is vital to complete a strength, weaknesses, opportunities and threats (SWOT) analysis. A breakdown of this SWOT analysis can create an outline of the weaknesses that the researcher may face, further leading to opportunities that can help improve the project's outcome.

### **Strengths and Opportunities**

Although much research exists on PONV, it is still a significant research topic as it is one of the reasons as to why postoperative complications occur. Providing patients with the proper pharmacological treatment can improve patient recovery. Amisulpride has been found as an antiemetic that can help treat PONV when prophylactic administration of antiemetic medications has failed. Checklists and algorithms exist to aid in identifying patients who may be at risk of PONV.<sup>10, 12</sup> These have been found to help decrease the incidence of PONV, therefore decreasing the number of patients who experience PONV. Without a current combination of antiemetic medications as the designated treatment for PONV, the integration of Amisulpride as a new treatment for PONV should be considered and included in patients who experience PONV despite prophylactic treatment. This can lead to a more significant decrease in number of patients who remain inpatient due to PONV complications.

### **Weaknesses and Threats**

When weaknesses and threats exist, these can lead in failure to progress with a quality improvement project. Although PONV is well known in the world of anesthesia, anesthesia providers still exist who do not follow the algorithms within the system to prevent it. Guidelines have been published to aid anesthesia providers on how to approach the management of PONV, but some providers fail to follow them based on their own beliefs in clinical practice, or the lack of

understanding the new technology that provides them with these guidelines.<sup>2</sup> Failure to follow these guidelines to prevent PONV can lead to patient dissatisfaction and extended length of stay in the hospital. Therefore, anesthesia providers need to adhere to the guidelines and obtain training when unsure of how to identify patients at high risk of experiencing PONV.

### **Organizational Factors**

An educational module provided new knowledge and information on the use of Amisulpride for failed prophylaxis for PONV and treatment of PONV without any prior prophylaxis. As the FDA has recently approved the drug as treatment of PONV, some anesthesia providers may benefit from an educational presentation, handouts, and/or an in-service that provides details of the new drug. Gathering information of the current knowledge of anesthesia providers of the importance of a multimodal approach to prevent PONV can give insight to the gaps of knowledge, or impediments in clinical practice. A thorough analysis of data, research methods, background information, educational tools and learning will allow for further improvement in prevention methods for PONV.

## **METHODOLOGY**

PONV is one of many adverse events that can cause many postoperative complications in patients. Being one of the most unwanted symptoms after surgery, we can apply the nursing Theory of Unpleasant Symptoms (TOUS) to the theory that builds on this quality improvement project. PONV alone is a highly unwanted symptom, but it comes with the risk of causing further complications like dehydration, electrolyte imbalances, aspiration, bleeding and dehiscence of wounds.<sup>1,5,11</sup> This theory is critical because it states that symptoms build on one another and can eventually lead to multiplicative effects.<sup>22</sup> The severity of the symptoms can cause deterioration in a patient's ability to function physically and mentally.<sup>22</sup> This theory is a significant representation of the purpose of this project, which focuses on decreasing the occurrence of PONV by incorporating

Amisulpride as part of the pharmacological multimodal treatment. Treatment of PONV and prevention of it will significantly impact the recovery process for postoperative patients, decreasing the unpleasant symptoms that follow.

### **Setting and Participants**

The quality improvement (QI) project took place in the perioperative setting of a large, private, not-for-profit teaching hospital in South Florida. This large hospital has numerous surgical procedures requiring general anesthesia, in which patients are usually administered antiemetic medications to prevent postoperative nausea and vomiting. The quality improvement project consisted of only a total of 7 certified registered nurse anesthetists (CRNAs).

### **Description of Approach and Project Procedures**

To participate in this QI project, anesthesia providers involved in the perioperative care of patients will be asked to take part in an online survey consisting of a pre- and post-test questionnaire. In addition, a virtual educational module was presented that reviews the current guidelines for prevention of PONV and introduces Amisulpride as a newly designated rescue medication for PONV, compared to Promethazine, when prophylaxis fails. Participants were tested through the online survey on their current knowledge of utilizing Promethazine and Amisulpride for the treatment of PONV in patients who are at high risk, as well as others who are not considered high risk.

### **Protection of Human Rights**

CRNAs who decide to partake in the QI project were asked to join through their work email. After approval of the proposed project by the Institutional Review Board, all participants were kept anonymous and consent was acquired by utilizing HIPAA protected software, like Qualtrics, to

gather data. Participants were aware that they may withdraw from participating in the survey at any point, as participation in the project is voluntary. By participating in this QI project, CRNAs can benefit from gaining new knowledge on the utilization of Amisulpride as a rescue drug for postoperative patients compared to Promethazine for the treatment of PONV. This can create a new practice in the perioperative setting that can greatly improve treatment of PONV and patient satisfaction, as well as decreasing the incidence of unresolved PONV.

### **Data Collection**

CRNAs at the hospital facility were asked to participate in an online survey, distributed via Qualtrics through their work email. An online pre-test questionnaire was given before presenting the virtual educational module to assess their current knowledge on the prevention and treatment of PONV. After the educational module was presented, participants completed a post-test questionnaire to assess their understanding of the utilization of Amisulpride as a rescue drug for PONV compared to Promethazine. The educational module provided evidence-based research information on Amisulpride and Promethazine, listing the drug classification, mechanism of action, and adverse effects reported from both antiemetics.

### **Data Management and Analysis Plan**

Data collected from participants were stored in an online database and was only accessed by the primary investigator of the QI project. Data collected from the pre- and post-test questionnaires was collected with all personal information from participants safely protected by the primary investigator. Each participant was assigned a random identifier number, which allowed all data to remain anonymous. It was kept and confidentially stored in a locked computer with a code, where data was compiled for further analysis.

## RESULTS

### Participant Demographics

A total of 7 participants completed the survey after launching the quality improvement project via Qualtrics. Participants consisted of all females, accounting for 100% of the data collected. The participants that completed the survey included a variety of ethnicities, which included 14.29% Hispanic, 28.57% Caucasian and 57.14% African American. All participants consisted of CRNAs; however, educational levels varied with 28.57% (n=2) having a Master's degree and 71.43% (n=5) having a doctoral degree. Also, the years of experience from all participants varied; those having less than 1 year consisted of 14.29% (n=1), 1 to 5 years consisted of 42.86% (n=3), no participants reported experience between 6 to 10 years, and those having over 10 years of experience consisted of 42.86% (n=3). A summary of the participants' demographics can be visualized in **Table 1**.

**Table 1.** Participant's Demographics

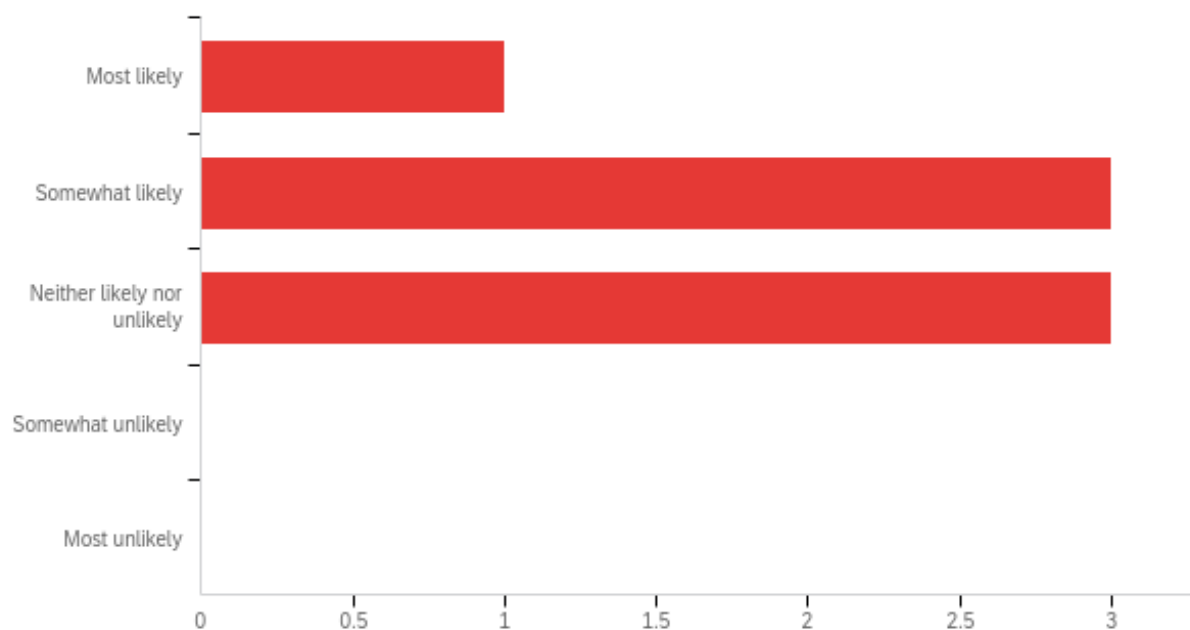
<b>Demographics</b>	<b>N (%)</b>
<b>Total Participants</b>	7 (100%)
<b>Gender</b>	
Female	7 (100%)
Male	0
Other	0
Prefer not to say	0
<b>Ethnicity</b>	
Hispanic	1 (14.29%)
Caucasian	2 (28.57%)
African American/Black	4 (57.14%)
Asian	0
Other	0
<b>Position/Title</b>	
CRNA	7 (100%)
MD	0
<b>Education Level</b>	
Master's	2 (28.57%)
Doctorate	5 (71.43%)
<b>Experience</b>	
Less than 1 year	1 (14.29%)
1 to 5 years	3 (42.86%)
6 to 10 years	0
Over 10 years	3 (42.86%)

### **Pre-Test: Assessment of Baseline Knowledge**

A pre-test questionnaire was administered to assess participants' baseline knowledge on PONV and its treatment before viewing an educational module. After viewing the educational module, a post-test questionnaire was administered to assess participants learning. The pre- and post-test questionnaires consisted of identical questions that were then compared to analyze if learning took place after viewing the educational module. The results for the pre-test can be seen in **Table 2**. The questions provided for both pre- and post-test consisted of the following:

1. PONV are adverse effects that occur during the postoperative period with an incidence as high as \_\_\_ in high-risk populations.
2. PONV can lead to an increased risk of postoperative complications like:
3. True or False. If prophylaxis of PONV fails, a higher dose of the antiemetic medication given for prophylaxis should be administered in order to treat active PONV effectively.
4. Promethazine is classified as what type of drug?
5. Promethazine is used as a rescue medication for failed PONV prophylaxis, but caution should be taken as it can cause which of the following adverse effects?
6. Amisulpride is classified as what type of antiemetic medication?
7. What dose of Amisulpride was approved by the FDA as safe and most efficacious for treating established PONV when patients fail PONV prophylaxis?
8. Research studies show that the antiemetic dose of Amisulpride is associated with:
9. Which of the following characteristics make the antiemetic doses of Amisulpride different when compared to other Dopamine D2 receptor antagonists?
10. The primary mode of elimination Amisulpride is:
11. After intravenous administration of Amisulpride, about \_\_\_\_ is excreted unchanged in the urine and feces.
12. How likely are you to implement Amisulpride over Promethazine for the treatment of PONV?

Participants were all asked on the last question how likely they were to implement Amisulpride over Promethazine for the treatment of PONV. Participant responses varied: 1 (14.29%) answered “most likely,” 3 (42.86%) answered “somewhat likely,” and 3 (42.86%) answered “neither likely nor unlikely.” The results can be seen in **Figure 1** below.

**Figure 1.** Pre-Test Question 11**Table 2.** Pre-Test Results

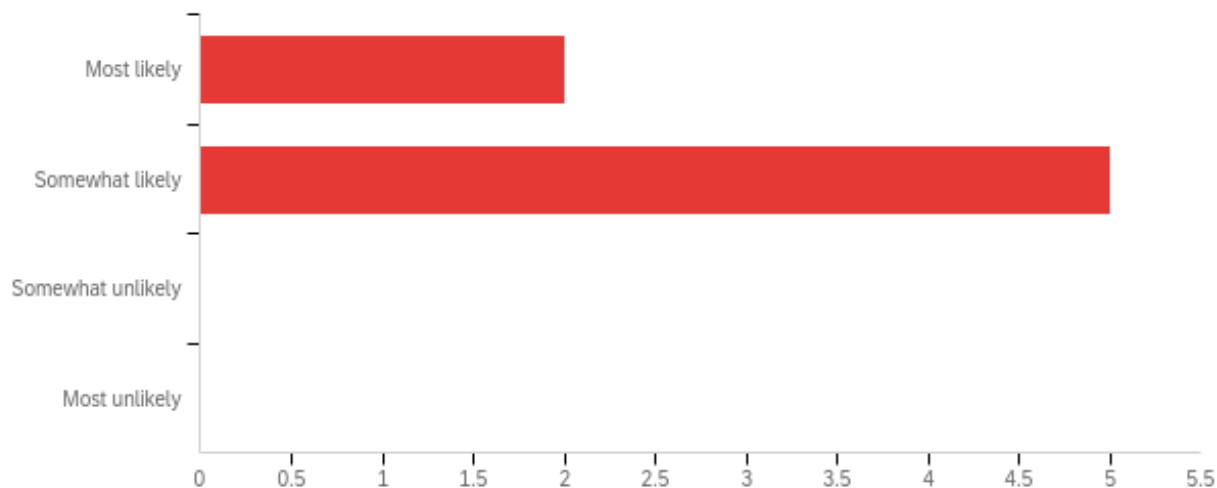
Question #	Number of Participants that answered correctly	Percentage of questions correctly answered
#1	1/7	14.29%
#2	4/7	57.14%
#3	5/7	71.43%
#4	1/7	14.29%
#5	3/7	42.86%
#6	5/7	71.43%
#7	2/7	28.57%
#8	2/7	28.57%
#9	0/7	0%
#10	5/7	71.43%
#11	1/7	14.29%

### Post-Test: Assessment of Learning

A post-test was administered after viewing the educational module to assess the knowledge gained by the participants and the likelihood of the utilizing Amisulpride over Promethazine as a rescue drug in the case PONV after failed prophylaxis. From the results, when asked how likely the participant was to use Amisulpride over Promethazine, 5 (71.43%) responded "somewhat likely," and 2 (28.57%) responded "most likely." The results are graphically represented in **Figure 2**. As

this is a new drug, more learning is still required to introduce Amisulpride in practice for the treatment of PONV. The responses for the post-test can be seen in **Table 3**.

**Figure 2.** Post-Test Question 11



**Table 3.** Post-Test Results

Question #	Number of Participants that answered correctly	Percentage of questions correctly answered
#1	3/7	42.86%
#2	3/7	42.86%
#3	4/7	57.14%
#4	5/7	71.43%
#5	5/7	71.43%
#6	5/7	71.43%
#7	4/7	57.14%
#8	4/7	57.14%
#9	5/7	71.43%
#10	4/7	57.14%
#11	4/7	57.14%

**Table 4.** Pre-Test vs. Post-Test Results

Question	Pre-Test Score Percentage	Post-Test Score Percentage	% Change
#1	14.29%	42.86%	2.00%
#2	57.14%	42.86%	-0.25%
#3	71.43%	57.14%	-0.20%
#4	14.29%	71.43%	4.00%
#5	42.86%	71.43%	0.67%
#6	71.43%	71.43%	0%
#7	28.57%	57.14%	1%
#8	28.57%	57.14%	1%
#9	0%	71.43%	714%
#10	71.43%	57.14%	-0.20%
#11	14.29%	57.14%	3%

## DISCUSSION

After analyzing the results, data showed that there was an increase in the knowledge regarding the use and properties of Amisulpride as a new rescue drug for the treatment of PONV when prophylaxis fails. In addition, there was an increase of knowledge in identifying what type of drug Promethazine is and its adverse effects, where 5 (71.43%) participants answered these questions correctly after watching the educational module.

### Limitations

The quality improvement project had its limitations mainly due to the small sample size of participants. The survey was distributed to 34 CRNAs in a large hospital facility in South Florida via Qualtrics and one email bounced back, therefore reducing the number to 33 participants. After the initial launching of the survey and a reminder email was sent out, only a total of 7 participants completed the survey. Another limitation was that the project was completed entirely online, rather than being able to provide a live presentation of the project with immediate surveys collected post presentation to assess learning. A significant disadvantage of utilizing email for delivery is that

these may be overlooked, some participants may not constantly check their emails, and there is no method to ensure that participants will complete the survey in a timely manner.

### **IMPLICATIONS FOR ADVANCED NURSING PRACTICE**

Several research studies exist on PONV and the attempt to prevent patients from experiencing it after surgery. Algorithms and guidelines have been set in place as a way to help anesthesia providers identify the patients who may be at high risk of developing PONV after surgical procedures. Despite the many combinations of antiemetic medications administered to patients before surgery, there still exist patients who fail prophylaxis and still develop PONV post-surgery. The FDA has recently approved Amisulpride as the first rescue drug to treat failed PONV prophylaxis. Exposure and education about this drug to anesthesia providers can create a new practice that can improve patient satisfaction. Promethazine is another antiemetic that is still used as a rescue drug for PONV, but has been found to cause sedation in patients, which causes prolonged stay in recovery. By educating providers about the advantages of Amisulpride, changes in clinical practice can occur and will help to introduce the medication as another available treatment for PONV.

### **CONCLUSION**

After launching of the educational module, a total of 7 participants completed the survey. After all data was collected and analyzed, results showed an increase in knowledge in the utilization of Amisulpride versus Promethazine, as a new FDA-approved rescue drug for the treatment of PONV when prophylactic treatment fails. In addition, results showed that participants increased their knowledge of what type of drug Promethazine is and some of the potential adverse effects that can be seen from its use for treating PONV. On the other hand, Amisulpride shows promising qualities for its use in PONV treatment as prophylaxis, and as a rescue drug. Results show that

participants increased their knowledge in identifying what type of drug Amisulpride is, the dosage for treatment of PONV, and the lack of adverse effects from its use.

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## Appendix A. Facility Support Letter



# Miami Beach Anesthesiology Associates, Inc.

*Mount Sinai Medical Center • Division of Anesthesia*

S. Howard Wittels MD  
Chairman

Hector Davila MSS, MD  
Executive Director

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Co-Assistant Director

Flor Marin MD

Gerald Rosen MD  
Residency Program  
Director

Jason Wigley MD  
Residency Program  
Co-Assistant Director

Alexander Volsky MD

Jennifer Wright MD

J.P. Mato DNP, CRNA  
CRNA Director & SRNA  
Coordinator

Paula Schultz DNP, CRNA  
OB-Chief CRNA

February 1, 2022

Dr. Yasmine Campbell, DNP, CRNA, APRN  
Assistant Professor  
Department of Nurse Anesthesiology  
Florida International University

Dr. Campbell,

Thank you for inviting Mount Sinai Medical Center to participate in Doctor of Nursing Practice (DNP) project conducted by Sharon Britton entitled "The Utilization of Amisulpride as Rescue Drug for Postoperative Patients Compared to Promethazine for Treatment of Post Operative Nausea Vomiting: An Educational Module" in the Nicole Wertheim College of Nursing and Health Sciences, Department of Nurse Anesthesiology at Florida International University. I have given the student permission to conduct the project using our providers.

Evidence-based practice's primary aim is to yield the best outcomes for patients by selecting interventions supported by the evidence. This proposed quality improvement project seeks to investigate and synthesize the latest evidence.

We understand that participation in the study is voluntary and carries no overt risk. All Division of Anesthesia providers are free to participate or withdraw from the study at any time. The educational intervention will be conveyed by a 15-minute virtual PowerPoint presentation, with a pretest and posttest questionnaire delivered by a URL link electronically via Qualtrics, an online survey product. Responses to pretest and posttest surveys are not linked to any participant. The collected information is reported as an aggregate, and there is no monetary compensation for participation. All collected material will be kept confidential, stored in a password encrypted digital cloud, and only be accessible to the investigators of this study: Sharon Britton and Dr. Campbell.

Once the Institutional Review Board's approval is achieved, this scholarly project's execution will occur over two weeks. Sharon Britton will behave professionally, follow standards of care, and not impede hospital performance. We support the participation of our Division of Anesthesia providers in this project and look forward to working with you.

Respectfully,

Jampierre (J.P.) Mato, DNP, CRNA, APRN  
Executive CRNA Director  
SRNA Coordinator/Supervisor  
Electronic Mail: [Jampierre@bellsouth.net](mailto:Jampierre@bellsouth.net)  
Mobile Phone: 954-668-6080

## Appendix B. IRB Approval



Office of Research Integrity  
Research Compliance, MARC 414

### MEMORANDUM

**To:** Dr. Yasmine Campbell  
**CC:** File  
**From:** Chris Grayson, MBA, CIM, CIP, Director, Research Integrity *CG*  
**Date:** March 25, 2022  
**Protocol Title:** The utilization of Amisulpride as a rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea and vomiting: An Educational Module.

---

The Florida International University Office of Research Integrity has reviewed your research study for the use of human subjects and deemed it Exempt via the **Exempt Review** process.

**IRB Protocol Exemption #:** IRB-22-0110      **IRB Exemption Date:** 03/25/22  
**TOPAZ Reference #:** 111558

As a requirement of IRB Exemption you are required to:

- 1) Submit an IRB Exempt Amendment Form for all proposed additions or changes in the procedures involving human subjects. All additions and changes must be reviewed and approved prior to implementation.
- 2) Promptly submit an IRB Exempt Event Report Form for every serious or unusual or unanticipated adverse event, problems with the rights or welfare of the human subjects, and/or deviations from the approved protocol.
- 3) Submit an IRB Exempt Project Completion Report Form when the study is finished or discontinued.

*Special Conditions:* N/A

For further information, you may visit the IRB website at <http://research.fiu.edu/irb>.

**Appendix C. Participant Recruitment Letter****Nicole Wertheim College of  
Nursing & Health Sciences****Dear Mt. Sinai Anesthesia Provider:**

My name is Sharon Britton and I'm a Student Registered Nurse Anesthetist at Florida International University conducting a DNP project on the utilization of Amisulpride as a rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea and vomiting. You are invited to participate in a survey regarding your current knowledge on the use of both, Promethazine and Amisulpride via the Qualtrics platform. The survey is expected to take you approximately 15 to 20 minutes. You will not be asked to reveal any personal identifying information. The results will be reported in aggregate and may be presented in advocacy communications, journal articles, poster presentations, and/or as lectures. Short narrative quotes may also be included, but no identifying information will be revealed during the reporting of the results.

**Purpose:** Educational module to improve knowledge on the utilization of Amisulpride as a rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea and vomiting.

**Participation:** You are being invited to participate in this study because you are a Mt. Sinai anesthesia provider. Participation is voluntary and if you choose to participate, you may stop at any time without any penalty. You may also choose not to answer questions that are asked in the survey.

**Risks and discomforts:** Any risks related to participation in this study are minimal. You may opt to skip and question, and you may stop the survey at any time. Best practices will be utilized to protect the confidentiality of survey data.

**Benefits to you and others:** The following benefits may be associated with your participation in this project: An increased understanding of the administration of Ondansetron and Amisulpride as prophylaxis of postoperative nausea and vomiting. The overall objective of the program is to increase the quality of healthcare delivery and improve healthcare outcomes for our patients. Thank you for your continued dedication to the anesthesia practice.

This project was approved by the Florida International University's IRB and Mount Sinai IRB. If you would like to talk with someone about your rights pertaining to being a subject in this project or about ethical issues with this project, you may contact the FIU Office of Research Integrity by phone at (305) 348-2494 or email [ori@fiu.edu](mailto:ori@fiu.edu). If you have any questions about this study, feel free to contact me.

Thanks again,

**Sharon Britton BSN, RN**

[sbrit003@fiu.edu](mailto:sbrit003@fiu.edu)

(786) 351-0034

## Appendix D. Informed Consent



## Nicole Wertheim College of Nursing & Health Sciences

### CONSENT TO PARTICIPATE IN A QUALITY IMPROVEMENT PROJECT

“The utilization of Amisulpride as a rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea vomiting: An Educational Module”

#### SUMMARY INFORMATION

Things you should know about this project:

- **Purpose:** Educational module to increase anesthesia provider’s knowledge on the utilization of Amisulpride as a rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea and vomiting.
- **Procedures:** If you choose to participate, you will be asked to complete a virtual pre-test, watch a voice PowerPoint, and then a virtual post-test.
- **Duration:** This will take about a total of 20 minutes.
- **Risks:** The main risks for this quality improvement project are minimal. As with any educational module, potential minimal risks for participants may include mild emotional stress or physical discomfort from sitting on a chair for an extended period of time.
- **Benefits:** The main benefit to you from this educational module is an increase in the participant’s knowledge on the advantages of utilizing Amisulpride as a rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea and vomiting.
- **Alternatives:** There are no known alternatives available to you other than not taking part in this project.
- **Participation:** Taking part in this quality improvement project is voluntary.

Please carefully read the entire document before agreeing to participate.

#### PURPOSE OF THE PROJECT

You are being asked to be in a quality improvement project. The goal of this project is to increase anesthesia provider’s knowledge on the utilization of Amisulpride as a rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea and vomiting.

#### NUMBER OF PARTICIPANTS

If you decide to participate, you will be one of approximately 10 people in this project.

#### DURATION OF THE PROJECT

Your participation will require about 20 minutes of your time.

#### PROCEDURES

If you agree to be in the project, we will ask you to do the following things:

1. Complete an online 10 question pre-test survey via Qualtrics, an Online survey product for which the URL link is provided
2. Review the educational PowerPoint Module lasting 15 minutes.

3. Complete the online 10 question post-test survey via Qualtrics, an Online survey product for which the URL link is provided.

**RISKS AND/OR DISCOMFORTS**

The main risks for this quality improvement project are minimal. As with any educational module, potential minimal risks for participants may include mild emotional stress or physical discomfort from sitting on a chair for an extended period of time.

**BENEFITS**

The following benefits may be associated with your participation in this project: An increased understanding of the advantages of utilizing Amisulpride as a rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea and vomiting (PONV). The overall objective of the program is to improve patients' postoperative experience by decreasing the incidence of PONV.

**ALTERNATIVES**

There are no known alternatives available to you other than not taking part in this project. However, if you would like to receive the educational material given to the participants in this project, it will be provided to you at no cost.

**CONFIDENTIALITY**

The records of this project will be kept private and will be protected to the fullest extent provided by law. If, in any sort of report, we might publish, we will not include any information that will make it possible to identify you as a participant. Records will be stored securely, and only the project team will have access to the records.

**PARTICIPATION:** Taking part in this research project is voluntary.

**COMPENSATION & COSTS**

There is no cost or payment to you for receiving the health education and/or for participating in this project.

**RIGHT TO DECLINE OR WITHDRAW**

Your participation in this project is voluntary. You are free to participate in the project or withdraw your consent at any time during the project. Your withdrawal or lack of participation will not affect any benefits to which you are otherwise entitled. The investigator reserves the right to remove you without your consent at such time that they feel it is in the best interest.

**RESEARCHER CONTACT INFORMATION**

If you have any questions about the purpose, procedures, or any other issues relating to this research project, you may contact Sharon Britton at 786-351-0034 or at [sbrit003@fiu.edu](mailto:sbrit003@fiu.edu) and **Yasmine Campbell** at 305-348-9894 or [ycampbel@fiu.edu](mailto:ycampbel@fiu.edu).

**IRB CONTACT INFORMATION**

If you would like to talk with someone about your rights pertaining to being a subject in this project or about ethical issues with this project, you may contact the FIU Office of Research Integrity by phone at 305-348-2494 or by email at [ori@fiu.edu](mailto:ori@fiu.edu).

**PARTICIPANT AGREEMENT**

I have read the information in this consent form and agree to participate in this project. I have had a chance to ask any questions I have about this project, and they have been answered for me. By clicking on the "consent to participate" button below I am providing my informed consent.

## Appendix E. Pre- and Post- Test Questionnaire



# Nicole Wertheim College of Nursing & Health Sciences

### Pretest and Posttest Questionnaire:

#### The utilization of Amisulpride as rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea and vomiting: An Educational Module

### INTRODUCTION

The primary aim of this QI project is to increase anesthesia provider's knowledge on the utilization of Amisulpride as a rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea and vomiting.

Please answer the questions below to the best of your ability. Questions include demographic information and knowledge of Amisulpride and Promethazine use in postoperative patients. The questions are either in multiple choice or true/false format and are meant to measure anesthesia providers' knowledge of the efficacy of Amisulpride as a rescue drug compared to Promethazine for the treatment of PONV.

### PERSONAL INFORMATION

1. **Gender:** Male          Female          Other\_\_\_\_\_
2. **Age:** \_\_\_\_\_
3. **Ethnicity:**  
Hispanic    Caucasian    African American    Asian    Other\_\_\_\_\_
4. **Position/Title:** \_\_\_\_\_
5. **Level of Education:** Bachelors    Masters    Doctorate    Other \_\_\_\_\_

6. **Years of experience:**    Less than 1 year    1 to 5    6 to 10    greater than 10 years

## QUESTIONNAIRE

1. **PONV are adverse effects that occur during the postoperative period with an incidence as high as \_\_\_ in high-risk populations.**
  - a. 40%
  - b. 60%
  - c. 80%
  - d. 20%
  
2. **PONV can lead to an increased risk of postoperative complications like:**
  - a. Aspiration
  - b. Dehydration
  - c. Wound dehiscence
  - d. Esophageal rupture
  - e. All of the above
  
3. **If prophylaxis of PONV fails, a higher dose of the antiemetic medication given for prophylaxis should be administered in order to effectively treat active PONV.**
  - a. True
  - b. False
  
4. **Promethazine is classified as what type of drug?**
  - a. Dopamine antagonist
  - b. H1-receptor antagonist
  - c. Anticholinergic
  - d. All of the above

**5. Promethazine is used as a rescue medication for failed PONV prophylaxis, but caution should be taken as it can cause which of the following adverse effects?**

- a. QT prolongation
- b. Delirium
- c. Tardive dyskinesia
- d. Gangrene
- e. All of the above

**6. Amisulpride is classified as what type of antiemetic medication?**

- a. 5-HT<sub>3</sub> receptor antagonist
- b. Dopamine D<sub>2</sub>/D<sub>3</sub> receptor antagonist
- c. H<sub>1</sub>-receptor antagonist
- d. NK<sub>1</sub> receptor antagonist

**7. What dose of Amisulpride was approved by the FDA as safe and most efficacious for the treatment of established PONV when patients fail PONV prophylaxis?**

- a. 1 mg
- b. 5 mg
- c. 10 mg
- d. 20 mg

**8. Research studies show that the antiemetic dose of Amisulpride is associated with:**

- a. Sedation
- b. QT prolongation
- c. Extrapiramidal side effects
- d. None of the above

**9. Which of the following characteristics make the antiemetic doses of Amisulpride different when compared to other Dopamine D2 receptor antagonists?**

- a. Inhibits dopamine receptors in the limbic system
- b. Inhibits dopamine receptors in the striatum
- c. Lower affinity for presynaptic dopamine receptors
- d. Higher affinity for postsynaptic dopamine receptors

**10. The primary mode of elimination Amisulpride is:**

- a. Renal excretion
- b. Fecal excretion
- c. Redistribution
- d. None of the above

**11. After intravenous administration of Amisulpride, about \_\_\_\_ is excreted unchanged in the urine and feces.**

- a. 25%
- b. 50%
- c. 60%
- d. 80%

**12. How likely are you to implement Amisulpride over Promethazine for the treatment of PONV?**

- a. Most likely
- b. Somewhat likely
- c. Somewhat unlikely
- d. Most unlike

Appendix E. Educational Module

**FIU**

The utilization of Amisulpride as a rescue drug for postop patients compared to Promethazine for the treatment of postoperative nausea and vomiting: An Educational Module

SHARON BRITTON, BSN, RN  
YASMINE CAMPBELL, DNP, CRNA, APRN

FLORIDA INTERNATIONAL UNIVERSITY

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**Learning Objectives**

- Review of the physiology of postoperative nausea and vomiting (PONV)
- Identifying risk factors of PONV
- Standard guidelines for treatment of PONV
- Review the mechanism of action of Promethazine, its uses and side effects
- Review the mechanism of action of Amisulpride, its uses and side effects

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**Background**

PONV dates back to the 1800s when volatile anesthetics were first used during general anesthesia.

A variety of antiemetic medications have been developed to treat against PONV.

Failure to provide any prophylaxis can lead to postoperative complications and delay recovery.

Despite prophylactic treatment for PONV with combinations of antiemetic medications, failure rate exceeds 30%.

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**Physiology of PONV**

- Five pathways in the development of PONV:
  1. Chemoreceptor trigger zone (CTZ)
  2. Reflex afferent pathways in the central cortex
  3. Vagal pathway within the gastrointestinal system
  4. Vestibular system
  5. Midbrain afferents
- Stimulation of any of these pathways will activate the vomiting center through different receptors.
  1. Dopamine
  2. Serotonin
  3. Muscarinic
  4. Histamine
  5. NK-1

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**Factors Influencing PONV**

Risk factors for PONV in adults

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**Standard Guidelines for Management of PONV**

**Adult PONV Management**

1. RISK FACTORS
2. RISK MITIGATION
3. RISK STRATIFICATION
4. PROPHYLAXIS
5. RESCUE TREATMENT

↕ Complications caused by unrelieved PONV:

1. Dehydration
2. Pulmonary aspiration
3. Cardiac dysrhythmias
4. Esophageal tear
5. Wound dehiscence
6. Bleeding

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### Rescue Treatment

Antiemetics currently used as a rescue drug for the treatment of PONV


- Promethazine
- Amisulpride

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### Promethazine

- Approved by the FDA in 1956
- Phenothiazine derivative that targets multiple receptors:
  - H<sub>1</sub>-receptor antagonist
  - Dopamine antagonist
  - Anticholinergic
- Black box warning issued by FDA in 2009



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### Promethazine

**Adverse Effects**


- QT prolongation
- Gangrene/Necrosis
- Tardive dyskinesia, delirium, EPS, Seizures
- Diarrhea
- Thrombocytopenia

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### Amisulpride

- First introduced as an antipsychotic agent, currently being used as an effective antiemetic for the treatment of PONV.
- A substituted benzamide
  - Selective antagonist for D<sub>2</sub>/D<sub>3</sub> receptors
- Approved by the FDA for prevention and rescue treatment of PONV
  - Prevention – 5 mg IV Amisulpride
  - Rescue treatment – 10 mg IV Amisulpride



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### Amisulpride: Pharmacodynamics

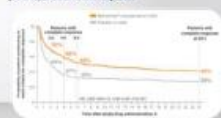
- Preferentially inhibits dopamine receptors in the limbic system, with very low potency at the D<sub>2</sub> receptors in the striatum.
- NO significant effect on QT interval
- Renally excreted 80% excreted unchanged in the urine and feces
- No metabolites
- Reduced risk of drug-drug interactions

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### Summary of Literature Review

- Eight randomized control trials were analyzed on the utilization of Promethazine and Amisulpride as rescue drugs for the treatment of PONV after failed prophylaxis.
- Research shows that while Promethazine may provide relief as a rescue drug for PONV, its sedative effects, significant prolongation of the QT interval and other possible adverse effects make it an unfavorable drug as it may prolong patients' recovery and hospital stay.
- Research studies found that Amisulpride is not only safe, but also has the most significant efficacy at reducing PONV. In a research study from 2010, Habib and colleagues reported that 42% of patients who received 10 mg of Amisulpride had a complete response at 24 hours, meaning no emesis or the need for additional rescue medications. The most common adverse effects reported in less than 5% were infusion-site pain, increased serum prolactin, headache and constipation.



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### References

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Thank You

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Appendix G: DNP Symposium Presentation



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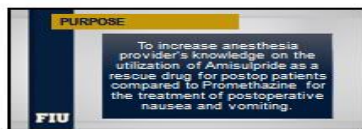
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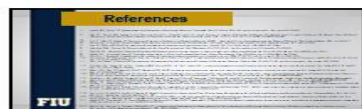
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