Drug Class Review
On
Newer Antiemetics

Preliminary Scan Report

May 2014

Last Report: Update #1 January 2009

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Scan conducted by:
Kim Peterson, MS
Ryan Stoner, MA

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report

Update #1 Final Report: January 2009 (searches through October 2008)

Date of Last Preliminary Update Scan Report

The last preliminary update scan was conducted in April 2013.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for nausea and vomiting. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of newer antiemetics in treating or preventing nausea and/or vomiting?

2. What are the comparative tolerability and safety of newer antiemetics when used to treat or prevent nausea and/or vomiting?

3. Are there subgroups of patients based on demographics (age, race, and gender), pregnancy, other medications, or comorbidities for which 1 newer antiemetic is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

Adults or children at risk for or with nausea, vomiting (including retching), or both related to the following therapies and conditions:

- Chemotherapy of various emetogenicity
- Radiation therapy
- Surgical procedure
- Pregnancy

In this report, we use the emetogenicity classification scale that Hesketh defined in 1997 and modified in 1999(1, 2) to clarify the level of emetogenicity of the chemotherapeutic regimen with which the cancer population of the study is being treated. This scale rates the emetic potential of the chemotherapeutic agent (or combination of agents) given to a cancer patient as if the patient would not be receiving any antiemetic drugs; that is, it classifies the chemotherapeutic agents by the likelihood that the patient will experience emesis. Chemotherapeutic agents rated as "1" on this scale have a low emetic potential, while agents rated as "5" are considered to be severely emetic (a >90% chance of emesis in patients).

Interventions

Included interventions are listed in Table 1.

Table 1. Included interventions

Drug	Trade name	Formulations
Aprepitant/fosaprepitant	Emend®	injectable, oral
Doxylamine Succinate; Pyridoxine Hydrochloride	Diclegis	Tablet, oral, delayed release
Dolasetron	Anzemet®	injectable, oral
Granisetron	Generics, Sancuso®	injectable, oral, transdermal patch
Ondansetron	Zofran®, generics Zuplenz®	injectable, oral, orally disintegrating tablet, oral film
Palonosetron[a]	Aloxi®	injectable

Shading = new since last full report update

Effectiveness outcomes

Treatment of established postoperative nausea and/or vomiting

- Success: Absence of vomiting and/or retching in a nauseated or vomiting and/or retching patient
    - Early: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure
- Success: Absence of any emetic event (nausea, vomiting, retching)
    - Early: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure

- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of postoperative nausea and/or vomiting

- Success: Absence of vomiting and/or retching in the postoperative period
    - Acute: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure
- Success: Absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching) in the postoperative period
    - Acute: Within or close to 6 hours after surgical procedure
    - Late: Within or close to 24 hours after surgical procedure
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of nausea and/or vomiting related to chemotherapy

- Success: Absence of vomiting and/or retching
    - Acute: During the first 24 hours of chemotherapy administration
        - Vomiting and/or retching induced by highly emetic chemotherapy
        - Vomiting and/or retching induced by moderately emetic chemotherapy
    - Late: After the first 24 hours of chemotherapy administration
        - Vomiting and/or retching induced by highly emetic chemotherapy
        - Vomiting and/or retching induced by moderately emetic chemotherapy
- Success: Absence of any emetic event (nausea, vomiting, retching)
    - Acute: During the first 24 hours of chemotherapy administration
        - Emetic event induced by highly emetic chemotherapy
        - Emetic event induced by moderately emetic chemotherapy
    - Late: After the first 24 hours of chemotherapy administration
        - Emetic event induced by highly emetic chemotherapy
        - Emetic event induced by moderately emetic chemotherapy
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, worst day nausea/vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Prevention of radiation-induced nausea and/or vomiting

- Success: Absence of vomiting and/or retching
    - Acute: During the first 24 hours of onset of radiation therapy
    - Delayed: After the first 24 hours of onset of radiation therapy or after consecutive radiation therapy doses given during several days
- Success: Absence of any emetic event (nausea, vomiting, retching)
    - Acute: During the first 24 hours of onset of radiation therapy
    - Delayed: After the first 24 hours of onset of radiation therapy or after consecutive radiation therapy doses given during several days

- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, or need for rescue medications, serious emetic sequelae, worst day nausea/vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Treatment of nausea and/or vomiting associated with pregnancy (including hyperemesis gravidarum)

- Success: Absence of vomiting and/or retching in a nauseated or vomiting and/or retching pregnant woman
- Success: Absence of any emetic event (nausea, vomiting, retching)
- Change in Rhodes index or visual analog scale assessments of symptom severity
- Fetal outcome
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes per period of time, need for rescue medications, serious emetic sequelae, number of emesis-free days, number of episodes and duration of hospitalization

  Wherever possible, data on effective dose range, dose response, and duration of therapy (time to success) will be evaluated within the context of comparative effectiveness.ert text

Harms

- Overall adverse events
- Specific adverse events (headache, constipation, dizziness, sedation, etc)
- Withdrawals due to adverse events
- Serious adverse events reported

Study designs

- For effectiveness, controlled clinical trials and good-quality systematic reviews.
- For safety, controlled clinical trials and observational studies.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE from January 2013 to May 2014. We used terms for included drugs and limits for humans, English and controlled clinical trials. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) (http://www.effectivehealthcare.ahrq.gov/), the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm). We also

searched FDA websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X4) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

New drugs identified in this Preliminary Update Scan

No new drugs were identified.

New drugs identified in previous Preliminary Update Scan(s)

Doxylamine succinate/pyridoxine hydrochloride (Diclegis®) – FDA-approved April 2013 for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.
Granisetron transdermal patch (Sancuso®) – FDA-approved on 9/12/2008
Ondansetron oral film (Zuplenz®) – FDA-approved on 7/2/2010

New Indications

Identified in this Preliminary Update Scan
No new indications were identified.

Identified in previous Preliminary Update Scan(s)
None.

New Safety Alerts

Identified in this Preliminary Update Scan

No new safety alerts were identified.

Identified in previous Preliminary Update Scan(s)

On 12/17/2010, FDA notified healthcare professionals that the injection form of dolasetron should no longer be used to prevent nausea and vomiting associated with chemotherapy in pediatric and adult patients, due to risk of developing torsade de pointes, which in some cases can be fatal (Appendix A).

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

No new comparative effectiveness reviews were identified.

Reviews identified in previous Preliminary Update Scan(s)

On 12/4/2012 the FDA notified health care professionals that the 32 mg, single intravenous (IV) dose of the anti-nausea drug Zofran (ondansetron hydrochloride) will no longer be marketed because of a specific type of irregular heart rhythm called QT interval prolongation, which can lead to Torsades de Pointes, an abnormal, potentially fatal heart rhythm (Appendix A).

In September of 2011 the FDA approved a safety labeling change warning for Anzemet (dolasetron mesylate) tablet and injection indicating that it has been shown to cause dose dependent prolongation of the PR and QRS interval and reports of second or third degree atrioventricular block, cardiac arrest and serious ventricular arrhythmias including fatalities in both adult and pediatric patients for which it should be used with caution certain patients (Appendix A).

An updated practice guideline for antiemetics in Oncology was published by the American Society of Clinical Oncology in November 2011. Abstract is included in Appendix B. A rapid response review on Ondansetron for the management of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients was produced by CADTH in February 2013. See appendix B for the research questions on this topic.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Medline searches conducted for this scan resulted in 73 citations. Of those, there were 13 potentially relevant new trials, including 5 head-to-head trials and 8 placebo-controlled trials (see Appendix C for abstracts). We found no new trials of the fixed dose combination product doxylamine succinate and pyridoxine hydrochloride.

Including the 18 head-to-head trials and 13 placebo-controlled trials identified in the previous scans from April 2013, March 2011 and December 2009 (Appendix D), there are now cumulative totals of 23 head-to-head trials and 21 placebo-controlled trials. Characteristics of the head to head trials are shown in Table 2, below. Shading indicates trials identified in this scan; others were identified in previous scans. Placebo controlled trials are listed in Table 3. There are two placebo controlled trials on the new fixed dose combination product doxylamine succinate and pyridoxine hydrochloride.

Table 2. New head-to-head trials

Trial	Drugs	Indication
Habib 2011	Ondansetron vs aprepitant	PONV in adults
Grover 2009	Ondansetron orally disintegrating tablet vs IV ondansetron	PONV in adults
Kim 2004	Dolasetron vs ondansetron	Chemotherapy in adults

Mandanas 2005	Dolasetron vs ondansetron	Chemotherapy in adults
Maru 2013	Fosaprepitant vs aprepitant	Chemotherapy in adults
Boccia 2011	Granisetron transdermal vs Granisetron oral	Chemotherapy in adults
Metaxari 2011	Granisetron vs ondansetron	PONV in adults
Siddique 2011	Granisetron vs ondansetron	Chemotherapy in children
Dabbous 2010	Granisetron vs ondansetron	PONV in adults
Jain 2009	Granisetron vs ondansetron	PONV in adults
Tan 2010	Granisetron vs ondansetron	PONV in adults
Basu 2011	Palonosetron vs ondansetron vs granisetron	PONV in adults
Moon 2012	Palonosetron vs ondansetron	PONV in adults
Park 2011	Palonosetron vs ondansetron	PONV in adults
Kim 2013	Palonosetron vs ondansetron	PONV in adults
Kim 2013	Palonosetron vs ondansetron	PONV in adults
Laha 2013	Palonosetron vs ondansetron	PONV in adults
Kaushal 2010	Palonosetron vs ondansetron	Chemotherapy in adults
Mattiuzzi 2010	Palonosetron vs ondansetron	Chemotherapy in adults
Wenzell 2013	Palonosetron vs ondansetron	Chemotherapy in adults
Saito 2009	Palonosetron vs granisetron	Chemotherapy in adults
Tian 2011	Palonosetron vs granisetron	Chemotherapy in Chinese adults
Yu 2009	Palonosetron vs granisetron	Chemotherapy in adults

*Shading indicates trials identified in this scan; others were identified in previous scans.

Table 3. Placebo-Controlled Trials

Placebo-controlled trials of 5-HT3 antagonists		
Albany 2012	Aprepitant	PONV in adults
Jung 2013	Aprepitant	PONV in adults
Lim 2013	Aprepitant	PONV in adults
Sinha 2014	Aprepitant	PONV in adults
Tanioka 2013	Aprepitant	Chemotherapy in adults
Saito 2013	Fosaprepitant	Chemotherapy in adults
Barrett 2011	Ondansetron	PONV in adults
de Orange 2012	Ondansetron	PONV in children
Ebrahim Soltani, 2011	Ondansetron	PONV in adults
Zhang 2013	Ondansetron	PONV in adults
Chun 2014	Palonosetron	PONV in adults
Hesketh, 2012	Palonosetron	PONV in adults
Wagner 2007	Ondansetron orally disintegrating tablet	PONV in children
Vallejo 2012	aprepitant	PONV in adults
Trials of Aprepitant triple-therapy (aprepitant + 5-HT3 antagonist + corticosteroid) vs 5-HT3		

antagonist + corticosteroid		
Hu 2014	Granisetron	Chemotherapy in Chinese adults
Takahashi 2010	Granisetron	Chemotherapy in Japanese adults
Gore 2009	Ondansetron	Chemotherapy in adolescents
Rapoport 2010	Ondansetron	Chemotherapy in adults
Yeo 2009	Ondansetron	Chemotherapy in Chinese adults
Other		
Koren, 2010	Doxylamine succinate and pyridoxine hydrochloride	PONV in pregnancy
Reeve, 2005	Doxylamine succinate and pyridoxine hydrochloride	PONV in women undergoing laparoscopic tubal ligation

*Shading indicates trials identified in this scan; others were identified in previous scans.

PONV=post-operative nausea and vomiting, 5-HT3 Antagonists = ondansetron, granisetron, dolasetron and palonosetron

1. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. Journal of Clinical Oncology. [C]. 1997;15(1):103-9.
2. Hesketh PJ. Defining the emetogenicity of cancer chemotherapy regimens: Relevance to clinical practice. Oncologist. 1999;4(3):191-6.

APPENDIX A. NEW FDA WARNINGS AND PRECAUTIONS

Ondansetron (Zofran) 32 mg, Single Intravenous (IV) Dose: Updated Safety Communication – Product Removal due to Potential For Serious Cardiac Risks
[Posted: 12/4/2012]
ISSUE: FDA is notifying health care professionals that the 32 mg, single intravenous (IV) dose of the anti-nausea drug Zofran (ondansetron hydrochloride) will no longer be marketed because of the potential for serious cardiac risks.
BACKGROUND: The 32 mg, single IV dose of Zofran had been used to prevent chemotherapy-induced nausea and vomiting. A previous Drug Safety Communication (DSC), issued on June 29, 2012, communicated that the 32 mg, single IV dose should be avoided due to the risk of a specific type of irregular heart rhythm called QT interval prolongation, which can lead to Torsades de Pointes, an abnormal, potentially fatal heart rhythm. These drugs are sold pre-mixed in solutions of either dextrose or sodium chloride in plastic containers.
FDA anticipates these products will be removed from the market through early 2013. FDA does not anticipate that removal of the 32 mg intravenous dose of ondansetron currently sold as pre-mixed injections will contribute to a drug shortage of IV ondansetron, as the 32 mg dose makes up a very small percentage of the current market
RECOMMENDATION: FDA continues to recommend the intravenous regimen of 0.15 mg/kg administered every 4 hours for three doses to prevent chemotherapy-induced nausea and vomiting. Oral dosing of Ondansetron remains effective for the prevention of chemotherapy-induced nausea and vomiting. At this time, there is not enough information available for FDA to recommend an alternative single IV dose regimen.
Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program:

Anzemet (dolasetron mesylate) tablet and injection-labeling revision
September 2011
Anzemet prolongs the QT interval in a dose dependent fashion. Torsade de Pointes has been reported during post-marketing experience. Avoid Anzemet in patients with congenital long QT syndrome, hypomagnesemia, or hypokalemia. Hypokalemia and hypomagnesemia must be corrected prior to Anzemet administration. Monitor these electrolytes after administration as clinically indicated. Use ECG monitoring in patients with congestive heart failure, bradycardia, renal impairment, and elderly patients.
PR and QRS Interval Prolongation
Anzemet has been shown to cause dose dependent prolongation of the PR and QRS interval and reports of second or third degree atrioventricular block, cardiac arrest and serious ventricular arrhythmias including fatalities in both adult and pediatric patients. At particular risk are patients with underlying structural heart disease and preexisting conduction system abnormalities, elderly, patients with sick sinus syndrome, patients with atrial fibrillation with slow ventricular response, patients with myocardial ischemia or patients receiving drugs known to prolong the PR interval (such as verapamil) and QRS interval (e.g., flecainide or quinidine). Anzemet should be used with caution and with ECG monitoring in these patients. Anzemet should be avoided in patients with complete heart block or at risk for complete heart block, unless they have an implanted pacemaker.

Anzemet (dolasetron mesylate): Drug Safety Communication - Reports of Abnormal Heart Rhythms
[Posted 12/17/2010]
AUDIENCE: Oncology, Cardiology

ISSUE: FDA notified healthcare professionals that a contraindication is being added to the prescribing information advising that the injection form of Anzemet (dolasetron mesylate) should no longer be used to prevent nausea and vomiting associated with cancer chemotherapy (CINV) in pediatric and adult patients. New data demonstrate that Anzemet injection can increase the risk of developing torsade de pointes, an abnormal heart rhythm, which in some cases can be fatal. Patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems. Anzemet causes a dose-dependant prolongation in the QT, PR, and QRS intervals on an electrocardiogram.

BACKGROUND: FDA previously noted cardiovascular safety concerns which suggested Anzemet could cause QT prolongation. However, limitations of the previous data did not clearly establish the degree to which Anzemet may cause QT prolongation. FDA recommended that the drug sponsor conduct a thorough QT study in adults in order to determine the degree of the prolongation. A pediatric study was not recommended due to the wide variability in heart rate and, thus, QTc interval in the pediatric population. See the Data Summary section of the Drug Safety Communication (DSC) for information that supports this change in the prescribing information.

RECOMMENDATION: Anzemet should not be used in patients with congenital long-QT syndrome. Hypokalemia and hypomagnesemia should be corrected before administering Anzemet. These electrolytes should be monitored after administration as clinically indicated. Use electrocardiogram monitoring in patients with congestive heart failure, patients with bradycardia, patients with underlying heart disease, the elderly and in patients who are renally impaired who are taking Anzemet. Anzemet injection may still be used for the prevention and treatment of postoperative nausea and vomiting because the lower doses used are less likely to affect the electrical activity of the heart and result in abnormal heart rhythms.

Anzemet tablets may still be used to prevent CINV because the risk of developing an abnormal heart rhythm with the oral form of this drug is less than that seen with the injection form. However, a stronger warning about this potential risk is being added to the Warnings and Precautions sections of the Anzemet tablet label.

See the DSC for additional recommendations for healthcare professionals and for patients.

APPENDIX B. NEW COMPARATIVE EFFECTIVENESS REVIEWS AND GUIDELINES

Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update

Purpose
To update the American Society of Clinical Oncology (ASCO) guideline for antiemetics in oncology.
Methods
A systematic review of the medical literature was completed to inform this update. MEDLINE, the Cochrane Collaboration Library, and meeting materials from ASCO and the Multinational Association for Supportive Care in Cancer were all searched. Primary outcomes of interest were complete response and rates of any vomiting or nausea.
Results
Thirty-seven trials met prespecified inclusion and exclusion criteria for this systematic review. Two systematic reviews from the Cochrane Collaboration were identified; one surveyed the pediatric literature. The other compared the relative efficacy of the 5-hydroxytryptamine-3 (5-HT3) receptor antagonists.
Recommendations
Combined anthracycline and cyclophosphamide regimens were reclassified as highly emetic. Patients who receive this combination or any highly emetic agents should receive a 5-HT3 receptor antagonist, dexamethasone, and a neurokinin 1 (NK1) receptor antagonist. A large trial validated the equivalency of fosaprepitant, a single-day intravenous formulation, with aprepitant; either therapy is appropriate. Preferential use of palonosetron is recommended for moderate emetic risk regimens, combined with dexamethasone. For low-risk agents, patients can be offered dexamethasone before the first dose of chemotherapy. Patients undergoing high emetic risk radiation therapy should receive a 5-HT3 receptor antagonist before each fraction and for 24 hours after treatment and may receive a 5-day course of dexamethasone during fractions 1 to 5. The Update Committee noted the importance of continued symptom monitoring throughout therapy. Clinicians underestimate the incidence of nausea, which is not as well controlled as emesis.

J Clin Oncol 29:4189-4198.

Ondansetron for the Management of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients: A Review of the Clinical Effectiveness, Safety and Guidelines
http://www.cadth.ca/media/pdf/htis/apr-2013/RC0424-Ondansetron-Final.pdf

RESEARCH QUESTIONS

1. What is the clinical effectiveness of ondansetron for the management of chemotherapy-induced nausea and vomiting (CINV) in pediatric patients?

2. What is the clinical evidence on the safety and harms of ondansetron for the management of CINV in pediatric patients?

3. What are the evidence-based guidelines regarding the use of ondansetron for the management of CINV in pediatric patients?

Appendix C. Abstracts of new randomized controlled trials from current scan

Head-to-head trials

Kim, S.-H., J.-Y. Hong, et al. (2013). "Palonosetron has superior prophylactic antiemetic efficacy compared with ondansetron or ramosetron in high-risk patients undergoing laparoscopic surgery: a prospective, randomized, double-blinded study." Korean Journal of Anesthesiology **64**(6): 517-523.

BACKGROUND: Postoperative nausea and vomiting (PONV) continues to be a major problem, because PONV is associated with delayed recovery and prolonged hospital stay. Although the PONV guidelines recommended the use of 5-hydroxy-tryptamine (5-HT3) receptor antagonists as the first-line prophylactic agents in patients categorized as high-risk, there are few studies comparing the efficacies of ondansetron, ramosetron, and palonosetron. The aim of present study was to compare the prophylactic antiemetic efficacies of three 5HT3 receptor antagonists in high-risk patients after laparoscopic surgery.

METHODS: In this prospective, randomized, double-blinded trial, 109 female nonsmokers scheduled for elective laparoscopic surgery were randomized to receive intravenous 4 mg ondansetron (n = 35), 0.3 mg ramosetron (n = 38), or 75 g palonosetron (n = 36) before anesthesia. Fentanyl-based intravenous patient-controlled analgesia was administered for 48 h after surgery. Primary antiemetic efficacy variables were the incidence and severity of nausea, the frequency of emetic episodes during the first 48 h after surgery, and the need to use a rescue antiemetic medication.

RESULTS: The overall incidence of nausea/retching/vomiting was lower in the palonosetron (22.2%/11.1%/5.6%) than in the ondansetron (77.1%/48.6%/28.6%) and ramosetron (60.5%/28.9%/18.4%) groups. The rescue antiemetic therapy was required less frequently in the palonosetron group than the other groups ($P < 0.001$). Kaplan-Meier analysis showed that the order of prophylactic efficacy in delaying the interval to use of a rescue emetic was palonosetron, ramosetron, and ondansetron.

CONCLUSIONS: Single-dose palonosetron is the prophylactic antiemetics of choice in high-risk patients undergoing laparoscopic surgery.

Kim, Y. Y., S. Y. Moon, et al. (2013). "Comparison of palonosetron with ondansetron in prevention of postoperative nausea and vomiting in patients receiving intravenous patient-controlled analgesia after gynecological laparoscopic surgery." Korean Journal of Anesthesiology **64**(2): 122-126.

BACKGROUND: Postoperative nausea and vomiting (PONV) are common complications after anesthesia and surgery. This study was designed to compare the effects of palonosetron and ondansetron in preventing PONV in high-risk patients receiving intravenous opioid-based patient-controlled analgesia (IV-PCA) after gynecological laparoscopic surgery.

METHODS: One hundred non-smoking female patients scheduled for gynecological laparoscopic surgery were randomly assigned into the palonosetron group (n = 50) or the ondansetron group (n = 50). Palonosetron 0.075 mg was injected as a bolus in the palonosetron group. Ondansetron 8 mg was injected as a bolus and 16 mg was added to

the IV-PCA in the ondansetron group. The incidences of nausea, vomiting and side effects was recorded at 2 h, 24 h, 48 h and 72 h, postoperatively.

RESULTS: There were no significant differences between the groups in the incidence of PONV during 72 h after operation. However, the incidence of vomiting was lower in the palonosetron group than in the ondansetron group (18% vs. 4%, P = 0.025). No differences were observed in use of antiemetics and the side effects between the groups.

CONCLUSIONS: The effects of palonosetron and ondansetron in preventing PONV were similar in high-risk patients undergoing gynecological laparoscopic surgery and receiving opioid-based IV-PCA.

Laha, B., A. Hazra, et al. (2013). "Evaluation of antiemetic effect of intravenous palonosetron versus intravenous ondansetron in laparoscopic cholecystectomy: a randomized controlled trial." Indian Journal of Pharmacology **45**(1): 24-29.

OBJECTIVES: Incidence of postoperative nausea and vomiting (PONV), without active intervention, following laparoscopic cholecystectomy is unacceptably high. We evaluated the effectiveness of intravenous (IV) palonosetron in counteracting PONV during the first 24 hrs following laparoscopic cholecystectomy, using ondansetron as the comparator drug.

MATERIALS AND METHODS: In a randomized, controlled, single blind, parallel group trial, single pre-induction IV doses of palonosetron (75 mcg) or ondansetron (4 mg) were administered to adult patients of either sex undergoing elective laparoscopic cholecystectomy. There were 49 subjects per group. The pre-anesthetic regimen, anesthesia procedure and laparoscopic technique were uniform. The primary effectiveness measure was total number of PONV episodes in the 24 hrs period following end of surgery. The frequencies of individual nausea, retching and vomiting episodes, visual analog scale (VAS) score for nausea at 2, 6 and 24 hrs, use of rescue antiemetic (metoclopramide), number of complete responders (no PONV or use of rescue in 24 hrs) and adverse events were secondary measures.

RESULTS: There was no statistically significant difference between the groups in primary outcome. Similarly, the frequencies of nausea, retching and vomiting episodes, when considered individually, did not show significant difference. Nausea score was comparable at all time points. With palonosetron, 14 subjects (28.6%) required rescue medication while 13 (26.5%) did so with ondansetron. The number of complete responders was 14 (28.6%) and 16 (32.7%), respectively. Adverse events were few and mild. QTc prolongation was not encountered.

CONCLUSION: Palonosetron is comparable to ondansetron for PONV prophylaxis in elective laparoscopic cholecystectomy when administered as single pre-induction dose.

Maru, A., V. P. Gangadharan, et al. (2013). "A Phase 3, randomized, double-blind study of single-dose fosaprepitant for prevention of cisplatin-induced nausea and vomiting: Results of an Indian population subanalysis." Indian Journal of Cancer **50**(4): 285-291.

Context: Currently, there is limited data on the prevention of chemotherapy-induced nausea and vomiting (CINV) in Indian patients. Aims: This post hoc study assessed the efficacy and safety of fosaprepitant compared with aprepitant for prevention of CINV in the Indian population. A subgroup analysis was performed from data collected in a phase 3 study of intravenous (IV) fosaprepitant or oral aprepitant, plus the 5-HT 3 antagonist ondansetron and the

corticosteroid dexamethasone, in cisplatin-nave patients with solid malignancies. Materials and Methods: Patients scheduled to receive cisplatin (>70 mg/m 2) were administered a single IV dose of fosaprepitant dimeglumine (150 mg) on day 1 or a 3-day dosing regimen of oral aprepitant (day 1:125 mg, days 2 and 3:80 mg) with standard doses of ondansetron and dexamethasone. Patients recorded nausea and/or vomiting episodes and their use of rescue medication and were monitored for adverse events (AEs) and tolerability. Statistical Analysis Used: Differences in response rates between fosaprepitant and aprepitant were calculated using the Miettinen and Nurminen method. Results: In the Indian subpopulation (n = 372), efficacy was similar for patients in both the fosaprepitant or aprepitant groups; complete response in the overall, acute, and delayed phases and no vomiting in all phases were approximately 4 percentage points higher in the fosaprepitant group compared with the aprepitant group. Fosaprepitant was generally well-tolerated; common AEs were similar to oral aprepitant. Conclusions: IV fosaprepitant is as safe and effective as oral aprepitant in the Indian subpopulation and offers an alternative to the oral formulation.

Wenzell, C. M., M. J. Berger, et al. (2013). "Pilot study on the efficacy of an ondansetron- versus palonosetron-containing antiemetic regimen prior to highly emetogenic chemotherapy." Supportive Care in Cancer **21**(10): 2845-2851.

PURPOSE: Nausea and vomiting are among the most feared complications of chemotherapy reported by patients. The objective of this study was to establish the overall complete response (CR; no emesis or use of rescue medication 0-120 h after chemotherapy) with either ondansetron- or palonosetron-containing antiemetic regimens in patients receiving highly emetogenic chemotherapy (HEC).

METHODS: This was a prospective, open-label, randomized, single-center, pilot study that enrolled patients receiving their first cycle of HEC. Patients were randomized to receive either palonosetron 0.25 mg IV (PAD) or ondansetron 24 mg orally (OAD) on day 1 prior to HEC. All patients received oral aprepitant 125 mg on day 1, then 80 mg on days 2 and 3, and oral dexamethasone 12 mg on day 1, then 8 mg on days 2, 3, and 4. Descriptive statistics were used to summarize the data.

RESULTS: A total of 40 patients were enrolled, 20 in each arm. All patients were female, and 39 received doxorubicin/cyclophosphamide chemotherapy for breast cancer. For the primary endpoint, 65 % (95 % CI, 40.8-84.6 %) of patients in the PAD arm and 40 % (95 % CI, 19.1-63.9 %) of patients in the OAD arm achieved an overall CR.

CONCLUSIONS: While CR rates for aprepitant and dexamethasone plus palonosetron or ondansetron-containing regimens have been published previously, this is the first documentation of CR rates with these regimens in the same patient population. These results may be used to design a larger, adequately powered, prospective study comparing these regimens.

Placebo-controlled trials

Chun, H. R., I. S. Jeon, et al. (2014). "Efficacy of palonosetron for the prevention of postoperative nausea and vomiting: a randomized, double-blinded, placebo-controlled trial." British Journal of Anaesthesia **112**(3): 485-490.

BACKGROUND: The aim of this study was to evaluate the efficacy of palonosetron, the latest 5-HT3 receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) during the first 72 h after operation.

METHODS: In this randomized, double-blinded, placebo-controlled study, 204 healthy inpatients who were undergoing elective surgery with general anaesthesia were enrolled. Patients were divided into two groups: the palonosetron group (palonosetron 0.075 mg i.v.; n=102) and the placebo group (normal saline i.v.; n=102). The treatments were given after the induction of anaesthesia. The incidence of nausea, vomiting, severity of nausea, and the use of rescue anti-emetics during the first 72 h after surgery were evaluated.
RESULTS: The incidence of PONV was lower in the palonosetron group compared with the placebo group during the 0-24 h (33% vs 47%) and 0-72 h period (33% vs 52%) ($P<0.05$), but not during the 24-72 h postoperative period (6% vs 11%). The incidence of nausea was also significantly lower in the palonosetron group than in the placebo group during the 0-24 and 0-72 h period ($P<0.05$), but not during the 24-72 h postoperative period. However, there were no significant differences in the incidence of vomiting, and the use of rescue anti-emetics between the groups.
CONCLUSIONS: Palonosetron 0.075 mg i.v. effectively reduced the incidence of PONV during the first 72 h after operation, with most of the reduction occurring in the first 24 h.

Hu, Z., Y. Cheng, et al. (2014). "Aprepitant triple therapy for the prevention of chemotherapy-induced nausea and vomiting following high-dose cisplatin in Chinese patients: a randomized, double-blind, placebo-controlled phase III trial." Supportive Care in Cancer **22**(4): 979-987.
PURPOSE: Aprepitant, an oral neurokinin-1 receptor antagonist, has demonstrated improved control of chemotherapy-induced nausea and vomiting (CINV) in previous studies. This is the first phase III study to evaluate the efficacy and tolerability of aprepitant in patients receiving highly emetogenic chemotherapy (HEC) in Asian countries.
METHODS: This multicenter, double-blind, placebo-controlled trial assessed the prevention of CINV during the acute phase (AP), delayed phase (DP), and overall phase (OP). Patients receiving HEC were randomized to either an aprepitant group (day 1, aprepitant 125 mg; days 2-3, aprepitant 80 mg) or a standard therapy group (days 1-3, placebo). Both groups received intravenous granisetron and oral dexamethasone. The primary end point was complete response (CR; no emesis and no use of rescue therapy) during the OP.
RESULTS: Of the 421 randomized patients, 411 (98%) were assessable for efficacy; 69.6% (142/204) and 57.0% (118/207) of patients reported CR during the OP in the aprepitant and standard therapy groups, respectively ($P = 0.007$). CR rates in the aprepitant group were higher during the DP (74.0% vs. 59.4%, $P = 0.001$) but were similar during the AP (79.4% vs. 79.3%, $P = 0.942$). Toxicity and adverse events were comparable in both groups.
CONCLUSIONS: The addition of aprepitant to standard antiemetic treatment regimens for Chinese patients undergoing HEC provided superior CINV prevention and was well tolerated.

Jung, W. S., Y. B. Kim, et al. (2013). "Oral administration of aprepitant to prevent postoperative nausea in highly susceptible patients after gynecological laparoscopy." Journal of Anesthesia **27**(3): 396-401.
PURPOSE: The use of opioids following surgery is associated with a high incidence of postoperative nausea and vomiting (PONV). We conducted a prospective, randomized, double-blind, placebo-controlled study to investigate the effect of orally administered

aprepitant, a neurokinin-1 receptor antagonist, for reducing PONV in patients with fentanyl-based, patient-controlled analgesia (PCA) given intravenously after gynecological laparoscopy.

METHODS: One hundred and twenty female patients (ages 21-60) undergoing laparoscopic hysterectomy were randomly allocated to receive 80 mg (A80 group, n = 40) or 125 mg aprepitant (A125 group, n = 40) or placebo (control group, n = 40) orally 2 h before anesthesia induction. Anesthesia was maintained with isoflurane and remifentanil, and PCA IV using fentanyl and ketorolac were provided for 48 h after surgery. Incidences of nausea, vomiting/retching, and use of rescue antiemetics were recorded at 2, 24, and 48 h after surgery. Complete response was defined as no PONV and no need for rescue treatment.

RESULTS: The incidence of complete response was significantly lower in the A80 and A125 groups than in controls, 56 % and 63 %, vs. 28 %, respectively, P = 0.007 and P = 0.003, respectively, during the first 48 h, and 65 % and 65 % vs. 38 %, respectively, both P = 0.025, during the first 2 h. However, there were no statistically significant differences between A80 and A125 groups in the incidences of complete response and PONV during the study period.

CONCLUSIONS: Aprepitant 80 mg orally was effective in lowering the incidence of PONV in the first 48 h after anesthesia in patients receiving fentanyl-based PCA after gynecological laparoscopy.

Lim, C. S., Y.-K. Ko, et al. (2013). "Efficacy of the oral neurokinin-1 receptor antagonist aprepitant administered with ondansetron for the prevention of postoperative nausea and vomiting." Korean Journal of Anesthesiology **64**(3): 212-217.

BACKGROUND: 5-HT3 receptor antagonist, dexamethasone and droperidol were used for the prevention of postoperative nausea and vomiting (PONV). Recently, neurokinin-1 (NK1) antagonist has been used for PONV. We evaluated the effect of oral aprepitant premedication in addition to ondansetron.

METHODS: A total 90 patients scheduled for elective rhinolaryngological surgery were allocated to three groups (Control, Ap80, Ap125), each of 30 at random. Ondansetron 4 mg was injected intravenously to all patients just before the end of surgery. On the morning of surgery, 80 mg and 125 mg aprepitant were additionally administered into the Ap80 group and Ap125 group, respectively. The rhodes index of nausea, vomiting and retching (RINVR) was checked at 6 hr and 24 hr after surgery.

RESULTS: Twelve patients who used steroids unexpectedly were excluded. Finally 78 patients (control : Ap80 : Ap125 = 24 : 28 : 26) were enrolled. Overall PONV occurrence rate of Ap125 group (1/26, 3.9%) was lower (P = 0.015) than the control group (7/24, 29.2%) at 6 hr after surgery. The nausea distress score of Ap125 group (0.04 + 0.20) was lower (P = 0.032) than the control group (0.67 + 1.24) at 6 hr after surgery. No evident side effect of aprepitant was observed.

CONCLUSIONS: Oral aprepitant 125 mg can be used as combination therapy for the prevention of PONV.

Saito, H., H. Yoshizawa, et al. (2013). "Efficacy and safety of single-dose fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving high-dose

cisplatin: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial." Annals of Oncology **24**(4): 1067-1073.

BACKGROUND: We evaluated the efficacy and safety of single-dose fosaprepitant in combination with intravenous granisetron and dexamethasone.

PATIENTS AND METHODS: Patients receiving chemotherapy including cisplatin (>70 mg/m(2)) were eligible. A total of 347 patients (21% had received cisplatin with vomiting) were enrolled in this trial to receive the fosaprepitant regimen (fosaprepitant 150 mg, intravenous, on day 1 in combination with granisetron, 40 mug/kg, intravenous, on day 1 and dexamethasone, intravenous, on days 1-3) or the control regimen (placebo plus intravenous granisetron and dexamethasone). The primary end point was the percentage of patients who had a complete response (no emesis and no rescue therapy) over the entire treatment course (0-120 h).

RESULTS: The percentage of patients with a complete response was significantly higher in the fosaprepitant group than in the control group (64% versus 47%, P = 0.0015). The fosaprepitant regimen was more effective than the control regimen in both the acute (0-24 h postchemotherapy) phase (94% versus 81%, P = 0.0006) and the delayed (24-120 h postchemotherapy) phase (65% versus 49%, P = 0.0025).

CONCLUSIONS: Single-dose fosaprepitant used in combination with granisetron and dexamethasone was well-tolerated and effective in preventing chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic cancer chemotherapy, including high-dose cisplatin.

Sinha, A. C., P. M. Singh, et al. (2014). "Aprepitant's prophylactic efficacy in decreasing postoperative nausea and vomiting in morbidly obese patients undergoing bariatric surgery." Obesity Surgery **24**(2): 225-231.

BACKGROUND: Postoperative nausea and vomiting is a major cause of patient dissatisfaction towards surgery. For bariatric surgery, increased vomiting/retching is detrimental to surgical anastomosis. The present study evaluated the efficacy of aprepitant (neurokinin-1 inhibitor) as a prophylactic antiemetic in morbidly obese patients for laparoscopic bariatric surgery.

METHODS: After institutional review board approval, 125 morbidly obese patients were recruited into this double-blind placebo-controlled trial. On random division, the patients received a tablet of aprepitant (80 mg) in group A, or a similar-appearing placebo in group P, an hour prior to surgery. All patients received intravenous ondansetron (4 mg) intraoperatively. Postoperatively, the patients were evaluated for nausea and vomiting by a blinded evaluator at 30 min, 1, 2, 6, 24, 48, and 72 h.

RESULTS: Both groups were evenly distributed for age, body mass index, type, and length of surgery. Cumulative incidence of vomiting at 72 h was significantly lower in group A (3%) compared to group P (15%; p=0.021). Odds ratio for vomiting in group P compared to group A was 5.47 times. On Kaplan-Meier plot, time to first vomiting was also significantly delayed in group A (p=0.019). A higher number of patients showed complete absence of nausea or vomiting in group A compared to group P (42.18 vs. 36.67%). On the other hand, nausea scores were unaffected by aprepitant, and no significant difference between groups was found at any of the measured time points.

CONCLUSIONS: In morbidly obese patients undergoing laparoscopic bariatric surgery, addition of aprepitant to ondansetron can significantly delay vomiting episodes simultaneously lowering the incidence of postoperative vomiting.

Tanioka, M., A. Kitao, et al. (2013). "A randomised, placebo-controlled, double-blind study of aprepitant in nondrinking women younger than 70 years receiving moderately emetogenic chemotherapy." British Journal of Cancer **109**(4): 859-865.

BACKGROUND: We evaluated the efficacy of aprepitant plus granisetron and an increased dose of dexamethasone in selected patients undergoing moderately emetogenic chemotherapy (MEC).

METHODS: Nondrinking women <70 years undergoing MEC were randomly assigned to aprepitant (day 1, 125 mg; days 2 and 3, 80 mg) or placebo. Dexamethasone on days 1-3 was 12, 4, and 4 mg with aprepitant and 20, 8, and 8 mg with placebo. The primary end point was complete response (CR; no emesis or rescue therapy) during 120 h of the first cycle. Logistic regression analysis was performed to identify predictors of overall CR.

RESULTS: Of the 94 patients enrolled, 91 were assessable. Most received carboplatin-based chemotherapy. In the aprepitant (n=45) and placebo (n=46) groups, the overall, acute (day 1), and delayed (days 2-5) CR rates were 62% and 52%, 98% and 96%, and 62% and 52%, respectively. Although not statistically significant, the overall CR rate was 10% higher in the aprepitant group. Both regimens were well tolerated. On multivariate analysis, advanced ovarian cancer (OR, 0.26 (0.10-0.72)) was independently associated with a lower CR.

CONCLUSION: Even with an increased dose of dexamethasone, aprepitant seemed more effective than placebo in these selected patients undergoing MEC; however, delayed phase management remains a significant problem.

Zhang, D., Z. Shen, et al. (2013). "Effect of ondansetron in preventing postoperative nausea and vomiting under different conditions of general anesthesia: a preliminary, randomized, controlled study." Upsala Journal of Medical Sciences **118**(2): 87-90.

METHODS: Two hundred and forty patients were randomly allocated into six groups: Group I, anesthesia was maintained with sevoflurane; Group II, anesthesia was maintained with sevoflurane and 8 mg of ondansetron; Group III, anesthesia was maintained with propofol; Group IV, anesthesia was maintained with propofol and 8 mg of ondansetron; Group V, anesthesia was maintained with sevoflurane and propofol; Group VI, anesthesia was maintained with sevoflurane combined with propofol and 8 mg of ondansetron.

RESULTS: We found that the incidence of vomiting was lower in group II (17.5%), group IV (7.5%), and group VI (10%) compared with group I (55%), group III (27.5%), and group V (30%), respectively ($P < 0.05$). The incidence of vomiting was also lower in group III (27.5%) and group V (30%) when compared with group I (55%) ($P < 0.05$). The incidence of nausea was 55% in group I, 42.5% in group II, 30% in group III, 27.5% in group IV, 30% in group V, and 30% in group VI. Groups III and V had a lower incidence of nausea than group I ($P < 0.05$).

CONCLUSIONS: We conclude that compared with sevoflurane anesthesia alone, anesthesia with either propofol alone or propofol combined with sevoflurane resulted in a reduced incidence of vomiting and nausea during the first 24 h after surgery. Administration of

ondansetron effectively reduced the incidence of vomiting but not that of nausea for all three types of general anesthesia.

Wenzell, C. M., M. J. Berger, et al. (2013). "Pilot study on the efficacy of an ondansetron- versus palonosetron-containing antiemetic regimen prior to highly emetogenic chemotherapy." Supportive Care in Cancer **21**(10): 2845-2851.

PURPOSE: Nausea and vomiting are among the most feared complications of chemotherapy reported by patients. The objective of this study was to establish the overall complete response (CR; no emesis or use of rescue medication 0-120 h after chemotherapy) with either ondansetron- or palonosetron-containing antiemetic regimens in patients receiving highly emetogenic chemotherapy (HEC).

METHODS: This was a prospective, open-label, randomized, single-center, pilot study that enrolled patients receiving their first cycle of HEC. Patients were randomized to receive either palonosetron 0.25 mg IV (PAD) or ondansetron 24 mg orally (OAD) on day 1 prior to HEC. All patients received oral aprepitant 125 mg on day 1, then 80 mg on days 2 and 3, and oral dexamethasone 12 mg on day 1, then 8 mg on days 2, 3, and 4. Descriptive statistics were used to summarize the data.

RESULTS: A total of 40 patients were enrolled, 20 in each arm. All patients were female, and 39 received doxorubicin/cyclophosphamide chemotherapy for breast cancer. For the primary endpoint, 65 % (95 % CI, 40.8-84.6 %) of patients in the PAD arm and 40 % (95 % CI, 19.1-63.9 %) of patients in the OAD arm achieved an overall CR.

CONCLUSIONS: While CR rates for aprepitant and dexamethasone plus palonosetron or ondansetron-containing regimens have been published previously, this is the first documentation of CR rates with these regimens in the same patient population. These results may be used to design a larger, adequately powered, prospective study comparing these regimens.

APPENDIX D. ABSTRACTS OF POTENTIALLY RELEVANT TRIALS FOUND IN PREVIOUS SCANS

Head to head trials

Basu, A., D. Saha, et al. (2011). "Comparison of palanosetron, granisetron and ondansetron as anti-emetics for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery." Journal of the Indian Medical Association 109(5): 327-329.

The objective of the study was to compare the efficacy of palanosetron (0.25 mg), granisetron (3.0 mg) and ondansetron (8.0 mg) used as anti-emetics for the prevention of postoperative nausea/vomiting in patients undergoing middle ear surgery. The study was done among 75 adult patients (age group 30-45 years) of which 50 were males and rest (25) females, all of ASA I and ASA II. The patients were randomly allocated into 3 equal groups: Group I (n = 25) received injection palanosetron (0.25 mg) IV, group II (n = 25) received injection granisetron (3 mg) IV and group III (n = 25) received injection ondansetron (8.0 mg) IV at the end of the surgical procedure. A standard general anaesthesia technique was employed. Emetic episodes and safety assessments were performed during two periods of 0-6 hours in the postanaesthesia care unit and 6-24 hours in the ward after anaesthesia. The incidence of emesis-free patients during the 0-6 hours period was 100% for group I; 72% for group II and 56% for group III. During the 6-24 hours period incidence of emesis-free patients were 96% for group I; 56% for group II and 32% for group III. So to conclude, a single dose of palanosetron (0.25 mg) is a superior anti-emetic to granisetron (3.0 mg) or ondansetron (8.0 mg) in complete prevention of postoperative nausea and vomiting after middle ear surgery during the first 24 hours period.

Boccia, R. V., L. N. Gordan, et al. (2011). "Efficacy and tolerability of transdermal granisetron for the control of chemotherapy-induced nausea and vomiting associated with moderately and highly emetogenic multi-day chemotherapy: a randomized, double-blind, phase III study." Supportive Care in Cancer 19(10): 1609-1617.

PURPOSE: A novel transdermal formulation of granisetron (the granisetron transdermal delivery system (GTDS)) has been developed to deliver granisetron continuously over 7 days. This double-blind, phase III, non-inferiority study compared the efficacy and tolerability of the GTDS to daily oral granisetron for the control of chemotherapy-induced nausea and vomiting (CINV).

PATIENTS AND METHODS: Six hundred forty-one patients were randomized to oral (2 mg/day, 3-5 days) or transdermal granisetron (one GTDS patch, 7 days), before receiving multi-day chemotherapy. The primary endpoint was complete control of CINV (no vomiting/retching, no more than mild nausea, no rescue medication) from chemotherapy initiation until 24 h after final administration. The prespecified non-inferiority margin was 15%.

RESULTS: Five hundred eighty-two patients were included in the per protocol analysis. The GTDS displayed non-inferiority to oral granisetron: complete control was achieved by 60% of patients in the GTDS group, and 65% in the oral granisetron group (treatment

difference, -5%; 95% confidence interval, -13-3). Both treatments were well tolerated, the most common adverse event being constipation.
CONCLUSIONS: The GTDS provides effective, well-tolerated control of CINV associated with moderately or highly emetogenic multi-day chemotherapy. It offers a convenient alternative route for delivering granisetron for up to 7 days that is as effective as oral granisetron.

Dabbous, A. S., S. I. Jabbour-Khoury, et al. (2010). "Dexamethasone with either granisetron or ondansetron for postoperative nausea and vomiting in laparoscopic surgery." Middle East Journal of Anesthesiology **20**(4): 565-70.

In a prospective randomized double-blind study, we compared the effectiveness of dexamethasone 8 mg with either granisetron 1 mg or ondansetron 4 mg in the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgery. Hundred ASA I and II patients scheduled for laparoscopic surgery were enrolled in the study and 84 patients completed it. Following induction of anesthesia, group I (n=42) received granisetron 1 mg and dexamethasone 8 mg, group II (n=42) received ondansetron 4 mg and dexamethasone 8 mg. Nausea and vomiting episodes, pain scores as well as side effects were recorded during the first hour and subsequently during the first 6 and 24 hours postoperatively. Satisfaction scores were obtained at discharge. There was no statistically significant difference between the 2 groups during the 1st 24 hours following surgery in regards to pain scores, satisfaction and side effects manifestations. At 0-1 hour interval, 100% of patients in group I and 97.6% in group II had no vomiting. Total response (no moderate or severe nausea and no rescue antiemetics) was 83.3% in group I and 80.95% in group II, and metoclopramide was used in 7.1% of patients in both groups. At 1-6 hours interval, 97.6% of patients in group I and 100% in group II had no vomiting. Total response was 92.8% in group I and 90.9% in group II, and metoclopramide was used in 4.76% of patients in group I and 2.38% in group II. At 6-24 hours no vomiting occurred in 97.6% of patients in group I and 100% in group II. Total response was 95.2% in both groups, and metoclopramide was used in 2.38% of patients in both groups. In conclusion, the combination of dexamethasone 8 mg with either granisetron 1 mg or ondansetron 4 mg following induction of anesthesia in patients undergoing laparoscopic surgery showed no statistically significant difference in antiemetic efficacy with minimal side effects and excellent patient satisfaction.

Grover, V. K., P. J. Mathew, et al. (2009). "Efficacy of orally disintegrating ondansetron in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy: a randomised, double-blind placebo controlled study." Anaesthesia **64**(6): 595-600.

Peri-operative prophylactic anti-emetics are commonly used parenterally. Orally disintegrating ondansetron is efficacious during chemotherapy. Therefore, we aimed to study the efficacy of orally disintegrating ondansetron for postoperative nausea and vomiting. In a randomised, double-blind, placebo controlled trial on 109 patients scheduled for laparoscopic cholecystectomy, oral ondansetron was compared to intravenous ondansetron and placebo. The anaesthetic technique was standardised. Mean time (SD) to tolerating oral intake was delayed in the placebo group to 366.1 (77.6) min compared to oral 322.9 (63.7) min and intravenous 322.4 (65.2) min groups. This is corroborated by a higher incidence of nausea and vomiting in the control group during the first 6 h

postoperatively (control 44.4%, oral 17.7%, intravenous 18.2%). There was no significant difference between oral and intravenous groups. In conclusion, orally disintegrating ondansetron was as efficacious as intravenous ondansetron in the peri-operative phase and may be a viable option for prophylaxis of emesis in day care surgery

Habib, A. S., J. C. Keifer, et al. (2011). "A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy." Anesthesia & Analgesia 112(4): 813-818.

BACKGROUND: Postoperative nausea and vomiting (PONV) occur commonly after craniotomy. In patients receiving prophylaxis with ondansetron and dexamethasone, vomiting occurred in 45% of patients at 48 hours. In addition to causing patient discomfort, the physical act of vomiting may increase intracranial pressure or cerebral intravascular pressure, jeopardizing hemostasis and cerebral perfusion. Aprepitant is a neurokin-1 receptor antagonist with a long duration of action and no sedative side effect. In a large multicenter study in patients undergoing abdominal surgery, aprepitant was significantly more effective than was ondansetron in preventing vomiting at 24 and 48 hours postoperatively. We hypothesized that the combination of aprepitant with dexamethasone will decrease the incidence of postoperative vomiting when compared with the combination of ondansetron and dexamethasone in patients undergoing craniotomy under general anesthesia.

METHODS: Patients scheduled to undergo craniotomy under general anesthesia were enrolled in this prospective, double-blind, randomized study. Patients were randomized to receive oral aprepitant 40 mg (or matching placebo) 1 to 3 hours before induction of anesthesia or ondansetron 4 mg IV (or placebo) within 30 minutes of the end of surgery. All patients received dexamethasone 10 mg after induction of anesthesia. The anesthetic technique was standardized. Data were collected at regular intervals by blinded personnel for 48 hours after surgery. Statistical analysis was performed using Wilcoxon's ranked sum test and (2) test. $P < 0.05$ was considered statistically significant.

RESULTS: One hundred four patients completed the study. The cumulative incidence of vomiting at 48 hours was 16% in the aprepitant group and 38% in the ondansetron group ($P = 0.0149$). The incidence of vomiting was also decreased in the aprepitant group at 2 hours (6% vs. 21%, $P = 0.0419$) and 24 hours (14% vs. 36%, $P = 0.0124$). From 0 to 48 hours, there was no difference between the aprepitant and ondansetron groups in the incidence of nausea (69% vs. 60%), nausea scores, need for rescue antiemetics (65% vs. 60%), complete response (no PONV and no rescue, 22% vs. 36%), or patient satisfaction with the management of PONV.

CONCLUSION: The combination of aprepitant and dexamethasone was more effective than was the combination of ondansetron and dexamethasone for prophylaxis against postoperative vomiting in adult patients undergoing craniotomy under general anesthesia. However, there was no difference between the groups in the incidence or severity of nausea, need for rescue antiemetics, or in complete response between the groups.

Jain, V., J. K. Mitra, et al. (2009). "A randomized, double-blinded comparison of ondansetron, granisetron, and placebo for prevention of postoperative nausea and vomiting after supratentorial craniotomy." Journal of Neurosurgical Anesthesiology **21**(3): 226-30.

Postoperative nausea and vomiting (PONV) are frequent and distressing complications after neurosurgical procedures. We evaluated the efficacy of ondansetron and granisetron to prevent PONV after supratentorial craniotomy. In a randomized double-blind, placebo controlled trial, 90 adult American Society of Anesthesiologists I, II patients were included in the study. A standard anesthesia technique was followed. Patients were divided into 3 groups to receive either placebo (saline), ondansetron 4 mg, or granisetron 1 mg intravenously at the time of dural closure. After extubation, episodes of nausea and vomiting were noted for 24 hours postoperatively. Statistical analysis was performed using chi2 test and 1-way analysis of variance. Demographic data, duration of surgery, intraoperative fluids and analgesic requirement, and postoperative pain (visual analog scale) scores were comparable in all 3 groups. It was observed that the incidence of vomiting in 24 hours, severe emetic episodes, and requirement of rescue antiemetics were less in ondansetron and granisetron groups as compared with placebo ($P<0.001$). Both the study drugs had comparable effect on vomiting. However, the incidence of nausea was comparable in all 3 groups ($P=0.46$). A favorable influence on the patient satisfaction scores, and number needed to prevent emesis was seen in the 2 drug groups. No significant correlation was found between neurosurgical factors (presence of midline shift, mass effect, pathologic diagnosis of tumor, site of tumor) and the occurrence of PONV. We conclude that ondansetron 4 mg and granisetron 1 mg are comparably effective at preventing emesis after supratentorial craniotomy. However, neither drugs prevented nausea effectively.

Kaushal, J., M. C. Gupta, et al. (2010). "Clinical evaluation of two antiemetic combinations palonosetron dexamethasone versus ondansetron dexamethasone in chemotherapy of head and neck cancer." Singapore Medical Journal **51**(11): 871-5.

INTRODUCTION: Palonosetron and ondansetron are two selective 5-hydroxytryptamine (5-HT3) receptor antagonists that have shown remarkable efficacy in controlling nausea and vomiting following administration of moderately emetic anticancer chemotherapy. Their efficacy is enhanced by the concurrent administration of dexamethasone. In the present study, we aimed to compare the antiemetic efficacy of a palonosetron plus dexamethasone (PD) schedule versus an ondansetron plus dexamethasone (OD) schedule. METHODS: A randomised, crossover trial was conducted in 30 patients with head and neck cancer who were receiving moderately emetogenic chemotherapy. The patients were divided into two groups. In the first cycle, one group was given a PD schedule and the other, an OD schedule. For the subsequent cycle, crossover of the antiemetic schedules was done. The antiemetic effects were evaluated by recording the intensity of nausea and the frequency of vomiting in the acute and delayed phases. RESULTS: Complete response in the acute phase was observed in 83.3 percent of the patients on the PD schedule and in 80 percent of those on the OD schedule. In the delayed phase, complete response was observed in 76.7 percent and 66.7 percent of the patients on the PD schedule and OD schedule, respectively. The overall rate of complete response was 66.7 percent in the PD group and 46.7 percent in the OD group. In the PD group, there were 73.3 percent of nausea-free patients as opposed to 66.7 percent in the OD group.

CONCLUSION: The results suggest that the PD schedule was superior to the OD schedule in controlling emesis in cancer chemotherapy, although this difference was not statistically significant.

Kim, J.-S., J. Y. Baek, et al. (2004). "Open-label, randomized comparison of the efficacy of intravenous dolasetron mesylate and ondansetron in the prevention of acute and delayed cisplatin-induced emesis in cancer patients." Cancer Research & Treatment **36**(6): 372-6.

PURPOSE: The aim of this study is to compare the antiemetic efficacy and tolerability of intravenous dolasetron mesylate and ondansetron in the prevention of acute and delayed emesis. MATERIAL AND METHODS: From April 2002 through October 2002, a total of 112 patients receiving cisplatin- based combination chemotherapy were randomized to receive a single i.v. dose of dolasetron 100 mg or ondansetron 8 mg, 30 minutes before the initiation of chemotherapy. In the ondansetron group, two additional doses of ondansetron 8 mg were given at intervals of 2 to 4 hours. To prevent delayed emesis, dolasetron 200 mg p.o. daily or ondansetron 8 mg p.o. bid was administered from the 2(nd) days to a maximum of 5 days. The primary end point was the proportion of patients that experienced no emetic episodes and required no rescue medication (complete response, CR) during the 24 hours (acute period) and during Day 2 to Day 5+/-2 days (delayed period), after chemotherapy. The secondary end points included the incidence and severity of emesis. RESULTS: 105 patients were evaluable for efficacy. CR rates during the acute period were 36.0% for a single dose of dolasetron 100 mg, and 43.6% for three doses of ondansetron 8 mg. CR rates during the delayed period were 8.0% and 10.9%, respectively. There was no significant difference in the efficacy between the two groups. Adverse effects were mostly mild to moderate and not related to study medication. CONCLUSIONS: A single i.v. dose of dolasetron 100 mg is as effective as three i.v. doses of ondansetron 8 mg in preventing acute and delayed emesis after cisplatin-based chemotherapy, with a comparable safety profile.

Mandanas, R. A., R. Beveridge, et al. (2005). "A randomized, multicenter, open-label comparison of the antiemetic efficacy of dolasetron versus ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy." Supportive Cancer Therapy **2**(2): 114-21.

This study assessed the efficacy and safety of dolasetron compared with ondansetron for the prevention of nausea and vomiting during high-dose myeloablative chemotherapy followed by peripheral blood stem cell support. Twenty centers randomized 197 patients to receive dolasetron 100 mg intravenously (I.V.) followed 8-12 hours later by a single oral dose of dolasetron 100 mg or ondansetron 32 mg I.V., followed 8-12 hours later by a single oral dose of ondansetron 8 mg during high-dose chemotherapy (HDC) regimens for breast cancer (n = 96; 48.7%), non-Hodgkin's lymphoma (n = 83; 42.1%), or Hodgkin's disease (n = 18; 9.1%). All patients received a daily I.V. bolus of dexamethasone 10 mg with study antiemetic agents and a continuous infusion of diphenhydramine, lorazepam, and dexamethasone (ie, BAD pump) throughout the course of the study, with patient-controlled on-demand bolus doses as needed. After completing a daily diary of emetic episodes and rescue medication use, 164 of 197 patients were evaluable. Total plus complete responses (no emesis, no nausea, no rescue) over the entire study period were achieved in 45.7% and 46.9% of patients on the dolasetron and

ondansetron arms, respectively. Dolasetron and ondansetron were well-tolerated. This study demonstrates that dolasetron and ondansetron are equally safe and effective in the prevention of nausea and vomiting associated with HDC (P = 0.955).

Mattiuzzi, G. N., J. E. Cortes, et al. (2010). "Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia." Cancer **116**(24): 5659-66.

BACKGROUND: Nausea and vomiting in patients with acute myelogenous leukemia (AML) can be from various causes, including the use of high-dose cytarabine.
METHODS: The authors compared 2 schedules of palonosetron versus ondansetron in the treatment of chemotherapy-induced nausea and vomiting (CINV) in patients with AML receiving high-dose cytarabine. Patients were randomized to: 1) ondansetron, 8 mg intravenously (IV), followed by 24 mg continuous infusion 30 minutes before high-dose cytarabine and until 12 hours after the high-dose cytarabine infusion ended; 2) palonosetron, 0.25 mg IV 30 minutes before chemotherapy, daily from Day 1 of high-dose cytarabine up to Day 5; or 3) palonosetron, 0.25 mg IV 30 minutes before high-dose cytarabine on Days 1, 3, and 5. RESULTS: Forty-seven patients on ondansetron and 48 patients on each of the palonosetron arms were evaluable for efficacy. Patients in the palonosetron arms achieved higher complete response rates (no emetic episodes plus no rescue medication), but the difference was not statistically significant (ondansetron, 21%; palonosetron on Days 1-5, 31%; palonosetron on Days 1, 3, and 5, 35%; P = .32). Greater than 77% of patients in each arm were free of nausea on Day 1; however, on Days 2 through 5, the proportion of patients without nausea declined similarly in all 3 groups. On Days 6 and 7, significantly more patients receiving palonosetron on Days 1 to 5 were free of nausea (P = .001 and P = .0247, respectively). CONCLUSIONS: The daily assessments of emesis did not show significant differences between the study arms. Patients receiving palonosetron on Days 1 to 5 had significantly less severe nausea and experienced significantly less impact of CINV on daily activities on Days 6 and 7. Cancer 2010. Copyright 2010 American Cancer Society.

Metaxari, M., A. Papaioannou, et al. (2011). "Antiemetic prophylaxis in thyroid surgery: a randomized, double-blind comparison of three 5-HT3 agents." Journal of Anesthesia 25(3): 356-362.

PURPOSE: The aim of this double-blind randomized study was to compare the antiemetic efficacy of three 5-hydroxytryptamine type 3 antagonists in terms of the incidence and intensity of postoperative nausea and vomiting (PONV) in a homogenous group of female patients undergoing thyroidectomy.
METHODS: The study cohort consisted of 203 American Society of Anesthesiologists PS I-II female patients randomized into four groups to receive at induction of anesthesia an intravenous (IV) bolus of 5 ml solution of one of the following: normal saline (placebo), granisetron 3 mg, ondansetron 4 mg, or tropisetron 5 mg. Nausea and vomiting were evaluated at five time points: during the first hour in the postanesthesia care unit (PACU) and 6, 12, 18, and 24 h postoperatively. Nausea intensity was measured using a visual analogue scale score (0-10).
RESULTS: Patients in the placebo group displayed a high incidence of nausea in the PACU and at 6, 12, and 18 h postoperatively (44, 60, 50, and 34%, respectively) and of

vomiting (26, 42, 30 and 10%). The administration of granisetron reduced significantly the incidence of nausea at 6, 12, and 18 h (26, 18, and 2%, respectively) and vomiting at 6 and 12 h (10 and 6%, respectively). Ondansetron reduced significantly the incidence of nausea and vomiting only at 6 h postoperatively (28 and 12%, respectively). The administration of tropisetron did not affect the incidence of PONV compared to placebo. CONCLUSION: Among the female patients of this study undergoing thyroid surgery, granisetron 3 mg provided the best prophylaxis from PONV. Ondansetron 4 mg was equally effective, but its action lasted only 6 h, whereas tropisetron 5 mg was found ineffective.

Moon, Y. E., J. Joo, et al. (2012). "Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study.[Erratum appears in Br J Anaesth. 2012 Jun;108(6):1047-8]." British Journal of Anaesthesia 108(3): 417-422.

BACKGROUND: Palonosetron is a new potent 5-hydroxytryptamine 3 antagonist. Although this drug is thought to be more effective in patients receiving opioid-based patient-controlled analgesia (PCA), clinical data are lacking. This study compared the effects of i.v. ondansetron and palonosetron administered at the end of surgery in preventing postoperative nausea and vomiting (PONV) in high-risk patients receiving i.v. PCA after thyroidectomy.
METHODS: A total of 100 female non-smoking subjects were randomly assigned into a palonosetron group or an ondansetron group. Ondansetron was given as an 8 mg bolus and 16 mg was added to the i.v. PCA mixture. In the palonosetron group, 0.075 mg was injected as a bolus only. Fentanyl-based PCA was provided for 24 h after operation. The incidence of nausea and vomiting, severity of nausea, requirement for rescue anti-emetics, and adverse effects were evaluated during 0-2 and 2-24 h.
RESULTS: The incidence of PONV during the 24 h postoperative period was lower in the palonosetron group than in the ondansetron group (42% vs 62%, P=0.045). No differences were observed between the groups during the first 2 h. However, the incidence of nausea and vomiting and nausea severity were significantly lower in the palonosetron group than in the ondansetron group during 2-24 h. The only difference in the use of rescue anti-emetics was at 2-24 h (10% with palonosetron compared with 28% with ondansetron, P=0.02).
CONCLUSIONS: Palonosetron is more effective than ondansetron for high-risk patients receiving fentanyl-based PCA after thyroidectomy, especially 2-24 h after surgery.

Park, S. K. and E. J. Cho (2011). "A randomized, double-blind trial of palonosetron compared with ondansetron in preventing postoperative nausea and vomiting after gynaecological laparoscopic surgery." Journal of International Medical Research 39(2): 399-407.

This randomized, double-blind study evaluated the relative efficacy of palonosetron (a new, selective 5-hydroxytryptamine type 3 [5-HT(3)] receptor antagonist) and ondansetron in preventing postoperative nausea and vomiting (PONV) in patients undergoing gynaecological laparoscopic surgery. Patients received either palonosetron 0.075 mg (n = 45) or ondansetron 8 mg (n = 45), intravenously, immediately before induction of general anaesthesia. The occurrence of nausea and vomiting and the severity of nausea according to a visual analogue scale were monitored immediately after the end of surgery and during the following 24 h. The incidence of PONV was significantly

lower in the palonosetron group compared with the ondansetron group (42.2% vs 66.7%, respectively). There were no significant statistical differences in the visual analogue scale for nausea. In conclusion, palonosetron 0.075 mg was more effective than ondansetron 8 mg in preventing PONV.

Saito, M., K. Aogi, et al. (2009). "Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial.[see comment]." Lancet Oncology **10**(2): 115-24.

BACKGROUND: Palonosetron is a second-generation 5-hydroxytryptamine 3 (5-HT(3))-receptor antagonist that has shown better efficacy than ondansetron and dolasetron in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy, and similar efficacy to ondansetron in preventing CINV in patients receiving highly emetogenic chemotherapy. In this phase III, multicentre, randomised, double-blind, double-dummy, stratified, parallel-group, active-comparator trial, we assessed the efficacy and safety of palonosetron versus granisetron for chemotherapy-induced nausea and vomiting, both of which were administered with dexamethasone in patients receiving highly emetogenic chemotherapy. METHODS: Between July 5, 2006, and May 31, 2007, 1143 patients with cancer who were receiving highly emetogenic chemotherapy (ie, cisplatin, or an anthracycline and cyclophosphamide combination [AC/EC]) were recruited from 75 institutions in Japan, and randomly assigned to either single-dose palonosetron (0.75 mg), or granisetron (40 microg/kg) 30 min before chemotherapy on day 1, both with dexamethasone (16 mg intravenously) on day 1 followed by additional doses (8 mg intravenously for patients receiving cisplatin or 4 mg orally for patients receiving AC/EC) on days 2 and 3. A non-deterministic minimisation method with a stochastic-biased coin was applied to the randomisation of patients. Covariates known to effect emetic risk, such as sex, age, and type of highly emetogenic chemotherapy, were used as stratification factors of minimisation to ensure balance between the treatment groups. Primary endpoints were the proportion of patients with a complete response (defined as no emetic episodes and no rescue medication) during the acute phase (0-24 h postchemotherapy; non-inferiority comparison with granisetron) and the proportion of patients with a complete response during the delayed phase (24-120 h postchemotherapy; superiority comparison with granisetron). The non-inferiority margin was predefined in the study protocol as a 10% difference between groups in the proportion of patients with complete response. The palonosetron dose of 0.75 mg was chosen on the basis of two dose-determining trials in Japanese patients. All patients who received study treatment and highly emetogenic chemotherapy were included in the efficacy analyses (modified intention to treat). This trial is registered with ClinicalTrials.gov, number NCT00359567. FINDINGS: 1114 patients were included in the efficacy analyses: 555 patients in the palonosetron group and 559 patients in the granisetron group. 418 of 555 patients (75.3%) in the palonosetron group had complete response during the acute phase compared with 410 of 559 patients (73.3%) in the granisetron group (mean difference 2.9% [95% CI -2.70 to 7.27]). During the delayed phase, 315 of 555 patients (56.8%) had complete response in the palonosetron group compared with 249 of 559 patients (44.5%) in the granisetron group ($p<0.0001$). The main treatment-related adverse events were constipation (97 of 557

patients [17.4%] in the palonosetron group vs 88 of 562 [15.7%] in the granisetron group) and raised concentrations of serum aminotransferases (aspartate aminotransferase: 24 of 557 [4.3%] vs 34 of 562 [6.0%]; alanine aminotransferase: 16 of 557 [2.9%] vs 33 of 562 [5.9%]); no grade 4 main treatment-related adverse events were reported. INTERPRETATION: When administered with dexamethasone before highly emetogenic chemotherapy, palonosetron exerts efficacy against chemotherapy-induced nausea and vomiting which is non-inferior to that of granisetron in the acute phase and better than that of granisetron in the delayed phase, with a comparable safety profile for the two treatments. FUNDING: Taiho Pharmaceutical (Tokyo, Japan).

Siddique, R., M. G. Hafiz, et al. (2011). "Ondansetron versus granisetron in the prevention of chemotherapy induced nausea and vomiting in children with acute lymphoblastic leukemia." Mymensingh Medical Journal: MMJ 20(4): 680-688.

Effect of ondansetron and granisetron were evaluated in sixty (60) children (age 4-11 years) irrespective of sex, diagnosed case of acute lymphoblastic leukemia (ALL) who received high dose methotrexate and did not receive any antiemetic 24 hours prior to HDMTX. This was a prospective, randomized, double-blind, single center study. Of 60 children, 30 received oral ondansetron (4mg) and rest 30 granisetron (1mg) half an hour before therapy. Drugs were randomly allocated with appropriate code. The patients were followed up from day 1 to day 5 of therapy. Episodes of nausea and vomiting were recorded and scorings was done every 24 hours following chemotherapy. No significant difference was found between two groups according to acute emesis (Day-1) ($p=0.053$). In day two and day three it was significant ($p<0.05$). In day four it was significant ($p=0.002$). Early chemotherapy induced nausea and vomiting (CINV) were controlled 90% in children who received granisetron and 70% in children who received ondansetron. Delayed (Day 2-4) CINV were controlled in 80% of children who received granisetron and 43.4% who received ondansetron ($p<0.05$). Granisetron group required additional doses only 3.3% cases and ondanseton group 30% cases on the second day ($p<0.05$). Result was significant between two groups. About 36.7% patients had episodes of nausea on day four of chemotherapy in ondansetron group and it was only 3.3% in granisetron group due to adverse effects of antiemetic drug itself ($p=0.001$). Maximum episodes of vomiting were found on the second day in ondansetron group 33.3% and in granisetron group 3.3% ($p=0.003$). Though adverse effects like headache, constipation, abdominal pain and loose motion were common in both group of children but their number was much less in children who received granisetron. On second day of therapy score of nausea and vomiting was maximum in ondansetron and minimum in granisetron treated on day 4 and the result was significant. So, to prevent acute and delayed CINV in children with ALL, oral graniseteron can be considered as more effective and well tolerated with minimum adverse effects compared with ondansetrons.

Tan, T., R. Ojo, et al. (2010). "Reduction of severity of pruritus after elective caesarean section under spinal anaesthesia with subarachnoid morphine: a randomised comparison of prophylactic granisetron and ondansetron." International Journal of Obstetric Anesthesia **19**(1): 56-60.

BACKGROUND: The incidence of pruritus after elective caesarean section under spinal anaesthesia with subarachnoid morphine may be 60-100%, and is a common cause of maternal dissatisfaction. Ondansetron has been shown to reduce pruritus but the effect is

short-lived. The objective of this randomized double-blind trial was to evaluate the anti-pruritic efficacy of granisetron compared with ondansetron. METHODS: Eighty ASA I or II women undergoing elective caesarean section received spinal anaesthesia with 0.5% hyperbaric bupivacaine 10 mg, fentanyl 25 microg and preservative-free morphine 150 microg. After delivery of the baby and clamping of the umbilical cord, they were randomised to receive granisetron 3mg i.v. (group G) or ondansetron 8 mg i.v. (group O). RESULTS: The two groups were similar for age, gestational age, height and weight. According to visual analogue pruritus scores, patients in group G experienced less pruritus at 8h (P=0.003) and 24h (P=0.01). Fewer patients in group G (n=8) than group O (n=18) required rescue anti-pruritic medication (P=0.03). Satisfaction scores were also higher in group G than in group O (P=0.03). There was no difference in overall incidence of pruritus, nausea and vomiting, and visual analogue pain scores between the two groups. CONCLUSIONS: Administration of granisetron 3mg i.v. reduces the severity of pruritus and the use of rescue anti-pruritic medication, and improves satisfaction but does not reduce the overall incidence of pruritus in women who have received subarachnoid morphine 150 microg compared to ondansetron 8 mg i.v. Copyright 2009 Elsevier Ltd. All rights reserved.

Tian, W., Z. Wang, et al. (2011). "Randomized, double-blind, crossover study of palonosetron compared with granisetron for the prevention of chemotherapy-induced nausea and vomiting in a Chinese population." Medical Oncology **28**(1): 71-8.

The objective of this study was to compare the efficacy and tolerability of palonosetron and granisetron in a Chinese population receiving highly emetogenic cisplatin-based chemotherapy or moderately emetogenic chemotherapy. Patients were stratified by chemotherapy with cisplatin (yes/no) and then randomly assigned to receive either palonosetron (0.25mg i.v.) in the first cycle followed by granisetron (3mg i.v.) in the second cycle or vice versa. The primary efficacy endpoint was the proportion of patients with complete response 0-24h post-chemotherapy administration. The proportions of patients with complete response 24-120 and 0-120h following chemotherapy were also compared. Of the 144 patients randomized, 36 (25%) received 60-80mg/m(2) cisplatin; 66 of 72 patients in the palonosetron to granisetron group and 56 of 72 patients in the granisetron to palonosetron group completed treatment with both antiemetics. The efficacy and safety analyses included 128 palonosetron treatments and 138 granisetron treatments. Palonosetron consistently produced numerically higher complete response rates than granisetron in the acute phase (0-24h, 71.09 vs. 65.22%), the delayed phase (24-120h, 60.16 vs. 55.80%), and overall (0-120h, 53.13 vs. 50.00%) though the differences were not significant. Both palonosetron and granisetron were well tolerated. Palonosetron was well tolerated and effective in preventing acute and delayed chemotherapy-induced nausea and vomiting in a Chinese population. When used as monotherapy, 0.25-mg palonosetron was not inferior to 3-mg granisetron for preventing vomiting following highly or moderately emetogenic chemotherapy.

Yu, Z., W. Liu, et al. (2009). "The efficacy and safety of palonosetron compared with granisetron in preventing highly emetogenic chemotherapy-induced vomiting in the Chinese cancer patients: a phase II, multicenter, randomized, double-blind, parallel, comparative clinical trial." Supportive Care in Cancer **17**(1): 99-102.

PURPOSE: This clinical trial was conducted to evaluate the efficacy and safety of Palonosetron in preventing chemotherapy-induced vomiting (CIV) among the Chinese cancer patients. PATIENTS AND METHODS: Two hundred and forty patients were scheduled to be enrolled and randomized to receive a single intravenous dose of palonosetron 0.25 mg, or granisetron 3 mg, 30 min before receiving highly emetogenic chemotherapy. The primary efficacy endpoint was the complete response (CR) rate for acute CIV (during the 0-24-h interval after chemotherapy). Secondary endpoints included the CR rates for delayed CIV (more than 24 h after chemotherapy). RESULTS: Two hundred and eight patients were accrued and received study medication. CR rates for acute CIV were 82.69% for palonosetron and 72.12% for granisetron, which demonstrated that palonosetron was not inferior to granisetron in preventing acute CIV. Comparisons of CR rates for delayed CIV yielded no statistical difference between palonosetron and granisetron groups and did not reveal non-inferiority of palonosetron to granisetron. Adverse events were mostly mild to moderate, with quite low rates among the two groups. CONCLUSIONS: A single dose (0.25 mg) of palonosetron is not inferior to a single dose (3 mg) of granisetron in preventing CIV and possesses an acceptable safety profile in the Chinese population.

Placebo-controlled trials

Albany, C., M. J. Brames, et al. (2012). "Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: a hoosier oncology group study." Journal of Clinical Oncology 30(32): 3998-4003.

PURPOSE: Aprepitant, a 5-HT3 receptor antagonist (5HT3-RA), and dexamethasone are standard antiemetic therapy for prevention of single-day, cisplatin-induced nausea and vomiting. We conducted a double-blind, placebo-controlled phase III cross-over study that compared aprepitant to placebo combined with standard antiemetic prophylaxis (a 5HT3-RA and dexamethasone) in patients receiving 5 days of cisplatin combination chemotherapy for testicular cancer.

PATIENTS AND METHODS: Patients receiving two consecutive identical courses of a 5-day cisplatin-based chemotherapy were randomly assigned to aprepitant 125 mg on day 3 and 80 mg per day on days 4 through 7 or to placebo with the initial course and crossover to the opposite treatment with the second course. The primary objective was complete response (CR). Secondary end points were emetic episodes (acute and delayed), nausea measurement based on a visual analog scale (VAS), and patient-stated preference after the second study cycle.

RESULTS: In all, 71 patients were screened for the study and 69 were evaluable. Thirty-five patients were randomly assigned to receive aprepitant and 34 to receive placebo for the first course. Forty-two percent achieved CR with aprepitant compared with 13% with placebo ($P < .001$). Eleven patients (16.2%) had at least one emetic episode during the aprepitant cycle versus 32 patients (47.1%) with placebo. Thirty-eight patients preferred the aprepitant cycle whereas 11 preferred placebo ($P < .001$). There was no statistical difference in VAS for nausea, but it was numerically superior with aprepitant. There was no toxicity with aprepitant compared with placebo.

CONCLUSION: There was a significant improvement in CR rate with aprepitant combined with a 5HT3-RA and dexamethasone. Patient preference strongly favored the aprepitant cycle.

Barrett, T. W., D. M. DiPersio, et al. (2011). "A randomized, placebo-controlled trial of ondansetron, metoclopramide, and promethazine in adults." American Journal of Emergency Medicine 29(3): 247-255.

OBJECTIVES: The objective of the study was to assess whether ondansetron has superior nausea reduction compared with metoclopramide, promethazine, or saline placebo in emergency department (ED) adults.

METHODS: This randomized, placebo-controlled, double-blinded superiority trial was intended to enroll a convenience sample of 600 patients. Nausea was evaluated on a 100-mm visual analog scale (VAS) at baseline and 30 minutes after treatment. Patients with a minimum preenrollment VAS of 40 mm were randomized to intravenous ondansetron 4 mg, metoclopramide 10 mg, promethazine 12.5 mg, or saline placebo. A 12-mm VAS improvement in nausea severity was deemed clinically important. We measured potential drug adverse effects at baseline and 30 minutes. Patients received approximately 500 mL of saline hydration during the initial 30 minutes.

RESULTS: Of 180 subjects who consented, 163 completed the study. The median age was 32 years (interquartile range, 23-47), and 68% were female. The median 30-minute VAS reductions (95% confidence intervals) and saline volume given for ondansetron, metoclopramide, promethazine, and saline were -22 (-32 to -15), -30 (-38 to -25.5), -29 (-40 to -21), and -16 (-25 to -3), and 500, 500, 500, and 450, respectively. The median 30-minute VAS differences (95% confidence intervals) between ondansetron and metoclopramide, promethazine, and saline were -8 (-18.5 to 3), -7 (-21 to -5.5), and 6 (-7 to 20), respectively. We compared the antiemetic efficacy across all treatments with the Kruskal-Wallis test (P = .16).
CONCLUSIONS: Our study shows no evidence that ondansetron is superior to metoclopramide and promethazine in reducing nausea in ED adults. Early study termination may have limited detection of ondansetron's superior nausea reduction over saline.

de Orange, F. A., J. Marques, et al. (2012). "Dexamethasone versus ondansetron in combination with dexamethasone for the prophylaxis of postoperative vomiting in pediatric outpatients: a double-blind, randomized, placebo-controlled clinical trial." Paediatric Anaesthesia 22(9): 890-896.

OBJECTIVES: To determine the frequency of postoperative vomiting (POV) in children submitted to outpatient surgery and to compare the efficacy of antiemetic drugs in preventing this complication.
BACKGROUND: Nausea and vomiting are common in the immediate postoperative period following anesthetic and surgical procedures. Compared to adults, pediatric patients are more likely to develop postoperative nausea and vomiting, the incidence of which ranges from 8.9% to 42%.
METHODS: This double-blind, randomized, placebo-controlled clinical trial included 129 children. The participants were randomized into three prophylactic treatment groups: dexamethasone (n = 43), ondansetron in combination with dexamethasone (n = 44), and placebo (n = 42). The variables studied were the frequency of POV and the incidence of vomiting after the patient had been discharged from hospital, the need for antiemetic rescue therapy in the postanesthesia care unit (PACU), need for hospitalization, and the time the patient remained in the PACU. A significance level of 5% was adopted.
RESULTS: Postoperative vomiting occurred in 12.4% of the children, with no statistically significant difference between the groups: 6.8% in the group receiving ondansetron combined with dexamethasone, 14.3% in the placebo group, and 14% in the group that received dexamethasone alone (P = 0.47). Furthermore, no significant difference was found between the groups with respect to the time the children remained in the PACU, and only five patients reported having vomited following discharge from hospital.
CONCLUSIONS: The prophylactic use of antiemetic drugs failed to reduce the incidence of POV in pediatric outpatient surgery with a low emetic potential; therefore, routine prophylaxis may be unnecessary.

Ebrahim Soltani, A. R., H. Mohammadinasab, et al. (2011). "Comparing the efficacy of prophylactic p6 acupressure, ondansetron, metoclopramide and placebo in the prevention of vomiting and nausea after strabismus surgery." Acta Medica Iranica 49(4): 208-212.

To compare the efficacy of acupressure wrist bands, ondansetron, metoclopramide and placebo in the prevention of vomiting and nausea after strabismus surgery. Two hundred patients, ASA physical status I or II, aged between 10 and 60 years, undergoing strabismus surgery in Farabi Hospital in 2007-2008 years, were included in this randomized, prospective, double-blind and placebo-controlled study. Group I was the Control, group II received metoclopramide 0.2 mg/kg, group III received ondansetron 0.15 mg/kg iv just before induction, in Group IV acupressure wristbands were applied at the P6 points. Acupressure wrist bands were placed inappropriately in Groups I, II and III. The acupressure wrist bands were applied 30 min prior to the induction of anesthesia and removed six hours after surgery. Postoperative nausea and vomiting (PONV) was evaluated within 0-2 hours and 2-24 hours after surgery by a blinded observer. Results were analyzed by X(2) test. A P value of < 0.05 was taken as significant. The incidence of PONV was not significantly different in acupressure, metoclopramide and ondansetron during the 24 hours. Acupressure at P6 causes a significant reduction in the incidence of PONV 24 hours after strabismus surgery as well as metoclopramide 0.2 mg/kg and ondansetron 0.15 mg/kg iv for patients aged 10 or more.

Gore, L., S. Chawla, et al. (2009). "Aprepitant in adolescent patients for prevention of chemotherapy-induced nausea and vomiting: a randomized, double-blind, placebo-controlled study of efficacy and tolerability." Pediatric Blood & Cancer **52**(2): 242-7.

BACKGROUND: The neurokinin-1 receptor antagonist aprepitant, plus a 5HT3 antagonist and corticosteroid is well-tolerated and effective in preventing chemotherapy-induced nausea and vomiting in adults but has not been formally assessed in adolescents. PROCEDURE: Patients age 11-19 years old receiving emetogenic chemotherapy were randomized 2:1 to aprepitant triple therapy (aprepitant [A] 125 mg p.o., dexamethasone [D] 8 mg p.o., and ondansetron [O] 0.15 mg/kg i.v. t.i.d. day 1; A 80 mg, D 4 mg, and O 0.15 mg/kg t.i.d. day 2; A 80 mg and D 4 mg day 3; and D 4 mg day 4) or a control regimen (D 16 mg and O 0.15 mg/kg t.i.d. day 1; D 8 mg and O 0.15 mg/kg t.i.d. day 2; and D 8 mg days 3 and 4). The primary endpoint was the difference in drug-related adverse events during and for 14 days following treatment. Efficacy and aprepitant pharmacokinetics were assessed. RESULTS: Baseline characteristics were similar between aprepitant (N = 28) and control (N = 18) groups. Febrile neutropenia was more frequent in the aprepitant group (25% vs. 11.1%). Complete response (CR) rates were 35.7% for aprepitant triple therapy versus 5.6% for the control group. Mean plasma aprepitant AUC(0-24 hr) and C(max) on day 1 and mean trough concentrations on days 2 and 3 were consistently lower compared to historical data obtained from healthy adults; however, the differences were not clinically significant. CONCLUSION: Aprepitant triple therapy was generally well tolerated; CR were greater with aprepitant, although not statistically significant. Pharmacokinetics suggest that the adult dosing regimen is appropriate for adolescents. (c) 2008 Wiley-Liss, Inc.

Hesketh, P. J., G. Morrow, et al. (2012). "Efficacy and safety of palonosetron as salvage treatment in the prevention of chemotherapy-induced nausea and vomiting in patients receiving low emetogenic chemotherapy (LEC)." Supportive Care in Cancer **20**(10): 2633-2637.

PURPOSE: The purpose of this study is to evaluate the efficacy and safety of intravenous (IV) palonosetron in preventing chemotherapy-induced nausea and vomiting (CINV) in patients with cancer who had incomplete control of CINV during their previous cycle of low emetogenic chemotherapy (LEC).

METHODS: Patients with histologically or cytologically confirmed cancer, >=18 years of age, with a Karnofsky Performance Scale score of >=50% who had received LEC that induced vomiting and/or at least moderate nausea during their previous treatment cycle received palonosetron 0.25 mg IV 30 min before chemotherapy. Outcomes were recorded in patient diaries over 120 h and at an end-of-study visit on days 6, 7, or 8 after LEC administration. The primary efficacy variable was the complete response rate, defined as no emetic episodes and no rescue medication at 0-24 h (acute post-chemotherapy phase), 24-120 h (delayed phase), and 0-120 h (overall).

RESULTS: Complete responses among the intent-to-treat study population (n = 34) were recorded for 88.2 % of patients in the acute phase, 67.6% in the delayed phase, and 67.6% overall. No emetic episodes occurred in 91.2 and 79.4% of patients during the acute and delayed phases, respectively, and no nausea in 73.5 and 52.9%, respectively. Palonosetron was well tolerated; only two patients experienced treatment-related adverse events.

CONCLUSIONS: Among the patients with cancer who had a history of CINV with LEC, palonosetron was effective in preventing CINV in both the acute and delayed post-chemotherapy phases, and was well tolerated. Randomized comparative studies in larger populations of patients receiving LEC are needed to confirm these findings.

Koren, G., S. Clark, et al. (2010). "Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial." American Journal of Obstetrics & Gynecology 203(6): 571.e571-577.

OBJECTIVE: To evaluate the effectiveness of Diclectin (doxylamine succinate 10 mg-pyridoxine hydrochloride 10 mg, delayed-release preparation) as compared with placebo for nausea and vomiting of pregnancy.

STUDY DESIGN: A randomized, double-blind, multicenter placebo controlled trial studying pregnant women suffering from nausea and vomiting of pregnancy, analyzed by intention to treat. Women received Diclectin (n = 131) or placebo (n = 125) for 14 days. Nausea and vomiting of pregnancy symptoms were evaluated daily using the pregnancy unique quantification of emesis scale.

RESULTS: Diclectin use resulted in a significantly larger improvement in symptoms of nausea and vomiting of pregnancy compared with placebo based on both the pregnancy unique quantification of emesis score (-4.8 +/- 2.7 vs -3.9 +/- 2.6; P = .006) and quality of life. After the trial, 64 (48.9%) women receiving Diclectin asked to continue compassionate use of their medication, as compared with 41 (32.8%) of placebo-treated women (P = .009).

CONCLUSION: Diclectin delayed release formulation of doxylamine succinate and pyridoxine hydrochloride is effective and well tolerated in treating nausea and vomiting of pregnancy.

Rapoport, B. L., K. Jordan, et al. (2010). "Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study." Supportive Care in Cancer **18**(4): 423-31.

PURPOSE: Aprepitant was shown previously to be effective for prevention of chemotherapy-induced nausea and vomiting (CINV) with moderately emetogenic chemotherapy (MEC) in breast cancer patients receiving an anthracycline and cyclophosphamide (AC)-based regimen. This study assessed aprepitant in patients receiving a broad range of MEC regimens with a variety of tumor types. METHODS: This phase III, randomized, gender-stratified, double-blind trial enrolled patients with confirmed malignancies, naive to MEC or highly emetogenic chemotherapy, who were scheduled to receive a single dose of at least one MEC agent. Patients received an aprepitant triple-therapy regimen (aprepitant, ondansetron, and dexamethasone) or a control regimen (ondansetron and dexamethasone) administered orally. Primary and key secondary efficacy endpoints were proportions of patients with no vomiting and complete response (no vomiting and no rescue medication), respectively, during the 120 h post-chemotherapy. RESULTS: Of 848 randomized patients, 77% were female, and 52% received non-AC-based antineoplastic regimens. Significantly, more patients in the aprepitant group achieved no vomiting and complete response, regardless of whether they received AC or non-AC regimens, in the 120 h after chemotherapy. Overall, the incidences of adverse events were generally similar in the aprepitant (62.8%) and control groups (67.2%). CONCLUSIONS: The aprepitant regimen provided superior efficacy in the treatment of CINV in a broad range of patients receiving MEC (non-AC or AC) in both no vomiting and complete response endpoints. Aprepitant was generally well tolerated. These results show the benefit of including aprepitant as part of the standard antiemetic regimen for cancer patients receiving MEC.

Reeve, B. K., D. J. Cook, et al. (2005). "Prophylactic Diclectin reduces the incidence of postoperative vomiting." Canadian Journal of Anaesthesia 52(1): 55-61.

BACKGROUND: Diclectin(R) (DCL) is an effective antiemetic used for relief of nausea and vomiting in pregnancy. It is unknown whether DCL is effective in the prevention of postoperative nausea and vomiting (PONV).

METHODS: We conducted a randomized, stratified, double-blind placebo-controlled trial to examine the incidence of PONV in women undergoing elective laparoscopic tubal ligation in the day surgery setting. DCL (doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg) was administered orally the night before surgery, the morning of surgery, and upon hospital discharge.

RESULTS: We enrolled 146 women in the trial, 127 of whom were included in the effectiveness analysis and 102 of whom were included in the efficacy analysis. We did not detect a difference in the incidence of nausea and vomiting in the first six hours postoperatively after adjusting for additional antiemetics administered. Patients receiving DCL as compared with placebo were significantly less likely to experience vomiting six to 24 hr

postoperatively [5/59 (8.5%) vs 14/55 (25.4%), P < 0.017]. Treated patients tended to return to work earlier than those who received placebo (1.74 vs 3.7 days P = NS). CONCLUSION: Perioperative oral DCL reduces the incidence of postoperative vomiting in women undergoing elective laparoscopic tubal ligation, and may accelerate return to work.

Takahashi, T., E. Hoshi, et al. (2010). "Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin." Cancer Science **101**(11): 2455-61.

Aprepitant is a new neurokinin-1 (NK(1)) receptor antagonist developed as a treatment for chemotherapy-induced nausea and vomiting (CINV). To evaluate the efficacy and safety of aprepitant used in combination with standard therapy (granisetron and dexamethasone), we conducted a multicenter, phase II, placebo-controlled, double-blind, randomized study in Japanese cancer patients who received cancer chemotherapy including cisplatin (>=70mg/m(2)). Aprepitant was administered for 5days. A total of 453 patients were enrolled. In the three study groups, (i) standard therapy, (ii) aprepitant 40/25mg (40mg on day 1 and 25mg on days 2-5) and (iii) aprepitant 125/80mg (125mg on day 1 and 80mg on days 2-5), the percentage of patients with complete response (no emesis and no rescue therapy) was 50.3% (75/149 subjects), 66.4% (95/143 subjects) and 70.5% (103/146 subjects), respectively. This shows that efficacy was significantly higher in the aprepitant 40/25mg and 125/80mg groups than in the standard therapy group ((2) test [closed testing procedure]: P=0.0053 and P=0.0004, respectively) and highest in the aprepitant 125/80mg group. The delayed phase efficacy (days 2-5) was similar to the overall phase efficacy (days 1-5), indicating that aprepitant is effective in the delayed phase when standard therapy is not very effective. In terms of safety, aprepitant was generally well tolerated in Japanese cancer patients. (ClinicalTrials.gov number, NCT00212602.) Copyright 2010 Japanese Cancer Association.

Vallejo, M. C., A. L. Phelps, et al. (2012). "Aprepitant plus ondansetron compared with ondansetron alone in reducing postoperative nausea and vomiting in ambulatory patients undergoing plastic surgery." Plastic & Reconstructive Surgery 129(2): 519-526.

BACKGROUND: Postoperative nausea and vomiting is a major challenge in the perioperative setting. The incidence can be as high as 80 percent, and the majority of the symptoms among outpatients occur after discharge. This study evaluated the efficacy of a neurokinin-1 receptor antagonist (aprepitant) in reducing postoperative symptoms for up to 48 hours in patients undergoing outpatient plastic surgery.
METHODS: A prospective, double-blinded, randomized, two-arm evaluation of 150 ambulatory plastic surgery patients receiving a standardized general anesthetic, including postoperative nausea and vomiting prophylaxis with ondansetron and either aprepitant or placebo, was performed. The main outcome measures were the occurrence of vomiting and the severity of nausea for up to 48 hours postoperatively.
RESULTS: Overall, 9.3 percent of patients who received aprepitant versus 29.7 percent in group B had vomiting, with the majority of vomiting episodes occurring after hospital discharge. The Kaplan-Meier plot of the hazards of vomiting revealed an increased incidence of emesis in patients receiving ondansetron alone compared with the combination of ondansetron and aprepitant (p = 0.006). The incidence of nausea was not significantly different in the two groups. Severity of nausea, however, was significantly higher in those receiving ondansetron alone compared with those receiving ondansetron

and aprepitant, as measured by a peak nausea score (p = 0.014) and by multivariate analysis of variance results comparing repeated verbal rating scale scores over 48 hours after surgery (p = 0.024).
CONCLUSION: In patients undergoing plastic surgery, the addition of aprepitant to ondansetron significantly decreases postoperative vomiting rates and nausea severity for up to 48 hours postoperatively.
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

Wagner, D. S., V. Gauger, et al. (2007). "Ondansetron oral disintegrating tablets for the prevention of postoperative vomiting in children undergoing strabismus surgery." Therapeutics & Clinical Risk Management **3**(4): 691-4.

Strabismus surgery in pediatric patients is associated with a high incidence of postoperative nausea and vomiting (PONV). Ondansetron disintegrating tablets (ODT), an oral freeze-dried formulation of the 5-HT(3) antagonist, are well-tolerated and have been shown to reduce chemotherapy-induced vomiting. The purpose of this study was to assess the efficacy of the ODT in preventing postoperative vomiting (POV) in children undergoing strabismus repair. Healthy children aged 4-12 years of age were administered a 4 mg ODT 30 minutes prior to the induction of general anesthesia. Induction and maintenance of anesthesia were standardized; each child received acetaminophen and ketorolac pre-emptively for analgesia. This study group was compared with a historical control group who received a placebo in previously conducted identical trials of POV. The 35 children included in this study were compared with 31 controls. The incidence and severity of POV and use of rescue antiemetics were significantly lower in children who received ODT compared with placebo (p </= 0.001). The acute complete response (ie, no emesis and no rescue antiemetics in 24 hours) was 76% in the ODT group compared with 16% in the controls (p </= 0.001). Results suggest that ODT given preoperatively reduces the incidence and severity of POV in children undergoing strabismus surgery.

Yeo, W., F. K. F. Mo, et al. (2009). "A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy." Breast Cancer Research & Treatment **113**(3): 529-35.

OBJECTIVES: This is a single center, randomized, double-blind placebo-controlled study to evaluate the NK(1)-receptor antagonist, aprepitant, in Chinese breast cancer patients. The primary objective was to compare the efficacy of aprepitant-based antiemetic regimen and standard antiemetic regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients who received moderately emetogenic chemotherapy. The secondary objective was to compare the patient-reported quality of life in these two groups of patients. PATIENTS AND METHODS: Eligible breast cancer patients were chemotherapy-naive and treated with adjuvant AC chemotherapy (i.e. doxorubicin 60 mg/m(2) and cyclophosphamide 600 mg/m(2)). Patients were randomly assigned to either an aprepitant-based regimen (day 1, aprepitant 125 mg, ondansetron 8 mg, and dexamethasone 12 mg before chemotherapy and ondansetron 8 mg 8 h later; days 2 through 3, aprepitant 80 qd) or a control arm which consisted of standard regimen (day 1, ondansetron 8 mg and dexamethasone 20 mg before chemotherapy and

ondansetron 8 mg 8 h later; days 2 through 3, ondansetron 8 mg bid). Data on nausea, vomiting, and use of rescue medication were collected with a self-report diary, patients quality of life were assessed by self-administered Functional Living Index-Emesis (FLIE). RESULTS: Of 127 patients randomized, 124 were assessable. For CINV in Cycle 1 AC, there was no significant difference in the proportion of patients with reported complete response, complete protection, total control, 'no vomiting', 'no significant nausea' and 'no nausea'. The requirement of rescue medication appears to be lesser in patients treated with the aprepitant-based regimen compared to those with the standard regimen (11% vs. 20%; P = 0.06). Assessment of FLIE revealed that while there was no difference in the nausea domain and the total score between the two groups; however, patients receiving standard antiemetic regimen had significantly worse quality of life in the vomiting domain (mean score [SD] = 23.99 [30.79]) when compared with those who received the aprepitant-based regimen (mean score [SD] = 3.40 [13.18]) (P = 0.0002). Both treatments were generally well tolerated. Patients treated with the aprepitant-based regimen had a significantly lower incidence of neutropenia (53.2% vs. 35.5%, P = 0.0468), grade >or= 3 neutropenia (21.0% vs. 45.2, P = 0.0042) and delay in subsequent cycle of chemotherapy (8.1% vs. 27.4%, P = 0.0048). CONCLUSION: The aprepitant regimen appears to reduce the requirement of rescue medication when compared with the control regimen for prevention of CINV in patients receiving both an anthracycline and cyclophosphamide, and is associated with a better quality of life during adjuvant AC chemotherapy.