

Class Review: Conventional Antiemetics

Date of Review: January 2017

Purpose for Class Review:

The purpose of this class review is to evaluate the evidence for the safety and efficacy of conventional antiemetics in reducing nausea and vomiting (n/v) associated with gastroenteritis, motion sickness, migraine headache, pregnancy, surgery, and chemotherapy. This review will also help determine the role of these agents compared to newer antiemetics. In addition, an evaluation of use of conventional antiemetics for unfunded conditions will be completed.

Research Questions:

1. What is the comparative efficacy and effectiveness of conventional antiemetic treatments (dimenhydrinate, dronabinol, meclizine, metoclopramide, nabilone, prochlorperazine, promethazine, scopolamine and trimethobenzamide) in reducing n/v associated with pregnancy, chemotherapy, surgeries, gastroenteritis, migraine headaches or motion sickness?
2. What are the comparative harms of conventional antiemetic treatments used in patients with n/v?
3. Are there subpopulations of patients in which a particular antiemetic treatment would be more effective or associated with less harm?
4. What diagnoses in Oregon Health Plan (OHP) patients are most commonly associated with conventional antiemetic claims?

Conclusions:

- For adults experiencing n/v due to gastroenteritis, there is insufficient evidence to support the superiority of any one antiemetic over another, or the superiority of any drug over placebo.
- There is moderate quality evidence that scopolamine is effective in preventing motion sickness compared to placebo. No conclusions or recommendations can be made on the comparative effectiveness of scopolamine and other agents such as meclizine or dimenhydrinate.
- Pyridoxine is recommended as first-line therapy for pregnant women with nausea. Retrospective studies have evaluated the risks to the fetus of the use ondansetron in pregnant women and it appears to be safe for use in pregnancy based on this low quality evidence.
- There is moderate quality evidence that 5HT-3 receptor antagonists are superior to conventional antiemetics in managing post-operative nausea and vomiting (PONV). Moderate quality evidence also shows that transdermal scopolamine is effective in reducing PONV.
- There is moderate quality evidence that metoclopramide is an effective adjunct in combination with aspirin in managing nausea associated with migraine headaches.
- Management of chemotherapy induced nausea and vomiting (CINV) should include an assessment of the emetogenicity of the chemotherapy. High quality evidence demonstrates 5-HT3 receptor antagonists and neurokinin-1 receptor antagonists are effective at reducing CINV.
- Low quality evidence demonstrates that cannabinoids may be effective in controlling refractory CINV, however their use may be limited by adverse effects.

- Approximately 12% of the conventional antiemetic utilization in the state of Oregon's fee-for-service (FFS) Medicaid population is for unfunded conditions including vertigo, motion sickness, GERD, and noninfectious gastroenteritis.

Recommendations:

- Add conventional antiemetics to the Oregon Health Plan (OHP) fee-for-service practitioner-managed prescription plan.
- Designate scopolamine, dimenhydrinate, and meclizine as non-preferred since these drugs are primarily prescribed for nonfunded conditions.
- PDL status for other conventional antiemetics may be informed after comparative drug costs of conventional antiemetics in the executive session.
- Nonpreferred antiemetics and select preferred antiemetics that exceed specific quantity limits are already subject to the current clinical prior authorization (PA) criteria in **Appendix 5**. Consolidation of clinical PA criteria for newer antiemetics and dronabinol into one policy requires approval by the Committee (see **Appendix 4**). Non-preferred conventional antiemetics will also be subject to this policy.

Background:

A class update of newer antiemetics was presented at the January 2016 Pharmacy and Therapeutics Committee meeting and primarily focused on comparative efficacy and effectiveness of 5-hydroxytryptamine-3 (5-HT₃) and P/neurokinin 1 (NK1) receptor antagonists. Conventional antiemetics including dimenhydrinate, trimethobenzamide, scopolamine, meclizine, metoclopramide, prochlorperazine and promethazine have not previously been reviewed by the P&T Committee yet there is significant use of these agents in the fee-for-service population. The cannabinoids nabilone and dronabinol will also be reviewed with the conventional antiemetics.

Vomiting associated with pregnancy (line 1), complications associated with migraine headaches (line 415) or enteric infections and other bacterial food poisoning (line 150) are funded diagnoses on the OHP List of Prioritized Services.¹ Vertigo (line 515), gastroparesis (line 531) and noninfectious gastroenteritis (line 555) are not funded by OHP. A complete list of list of antiemetic indications and their associated OHP funding line is included in table 5 of **Appendix 3**.

A retrospective report of conventional antiemetic claims was generated to assess use of these agents over 1 year from October 2014 through September 2015. During this time frame, there were 7,364 claims for 4,330 separate patients which were associated with a total cost of \$134,500 to the OHP. Dronabinol is the only medication from this class that requires prior authorization (PA). Dronabinol comprised approximately 1% of the conventional antiemetic use but was associated with 32% of total claim costs during this time frame. Sixty-two percent of all antiemetic claims were for promethazine. The second most utilized agent was metoclopramide with 13% of total claims. A review of the antiemetic indications reveals that more patients received therapy for funded (30.4%) conditions than unfunded (11.8%) conditions. Most of the claims for funded indications were for PONV (24.8%). For unfunded diagnoses, vertigo (5.7%) was the primary associated diagnosis with antiemetic therapy. One of the limitations of this report is that diagnoses information is separate from prescription claims. Over half of the patients (57.8%) did not have a diagnosis associated with the antiemetic claims. The complete report can be reviewed in tables 6 and 7 of **Appendix 3**.

Promethazine abuse has been reported in several sources.^{2,3} Promethazine may be misused by itself or in conjunction with opioids. In an 11 year retrospective review by the Maryland Poison Center 354 single product abuse or misuse exposures of promethazine were documented in the National Poison Data System.³ A report was compiled from Oregon Medicaid Fee claims processed January 2016 through June 2016 to evaluate the possible correlation between antiemetic use and substance abuse. Fifty five percent of the patients receiving an antiemetic also had a claim for an opioid. Seventeen percent of this population also had a recent history (within the past 18 months) of substance abuse. Nine percent of the patients identified in this cohort had at least one antiemetic, but no opioids in the past six months and a history of substance abuse. This data reveals a possible connection between antiemetic utilization and substance abuse, however more evidence should be compiled to provide an accurate assessment of this potential issue. The details of the report can be reviewed in table 8 of **Appendix 3**.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Conventional Antiemetic Indications and Dosing.^{4,5}

Drug Name (Trade Name)	Indication(s)	Rx/OTC	Strength/Route	Dose and Frequency (Adults)
Dimenhydrinate (Dramamine, Draminate, Motion Sickness)	Motion sickness N/V Vertigo	OTC (tablets) Rx (injection)	50 mg tablet 50 mg chewable tablet 50 mg/mL IV solution	50-100 mg po q4-6h 50-100 mg IM/IV q4-6h Maximum 400 mg/day
Dronabinol (Marinol)	AIDS ; loss of appetite CINV	Rx – Schedule III	2.5 mg, 5 mg, 10 mg capsule	2.5 mg po BID 5 mg/m ² po q2-4 prn Maximum 20 mg per day
Meclizine (Antivert, Motion Relief)	Motion sickness RINV Vertigo	OTC	12.5 mg and 25 mg tablet 25 mg chewable tablet	25-50 mg po x1 prn 50 mg po 2-12 hour prior to imaging 25-100 mg per day in divided doses
Metoclopramide (Reglan)	CINV PONV GERD Diabetic gastroparesis	Rx	5 mg and 10mg tablet 5 mg and 10 mg rapid dissolve tablet 5 mg/mL IV solution 1 mg/mL oral solution	1-2 mg/kg/dose IV prn 10-20 mg IV q4-6h 10-15 mg po q6h (max 12 weeks) 10 mg po q6h (max 12 weeks)
Nabilone (Cesamet)	CINV	Rx –Schedule II	1 mg capsule	1-2 mg po BID Maximum 6 mg per day
Phosphoric Acid/Dextrose/Fructose (Formula EM, Emetrol)	Nausea	OTC	120 mL oral solution (fructose 1.87 gm, dextrose 1.87 gm, and phosphoric acid 21.5 mg/5 mL)	15-30 mL po q15 min Maximum 5 doses/hour
Prochlorperazine (Compazine)	Severe N/V	Rx	5 mg and 10 mg tablet 5 mg/mL vial 25 mg suppository	5-10mg po TID-QID 2.5 mg – 10mg IV q6h prn 5-10mg IM q6h prn 25 mg PR BID Maximum 40 mg per day
Promethazine (Phenergan)	Nausea/Vomiting Motion Sickness Vertigo	Rx	25 mg/mL and 50 mg/mL vial 6.25 mg/5 mL oral solution 12.5 mg, 25 mg, 50 mg tablet 12.5 mg, 25 mg, 50 mg suppository	<i>Dose varies by indication</i> 12.5 – 25 mg IM/IV q4-6h prn 12.5-25 mg po q4-6h prn 12.5-25 mg PR q4-6h prn 25 mg po BID 25 mg PR BID
Scopolamine (Transderm-Scop)	Motion Sickness PONV	Rx	1.5 mg extended release patch	1 patch every 3 days
Trimethobenzamide (Tigan)	Gastroenteritis PONV	Rx	250 mg and 300 mg capsule 100 mg/mL vial	300 mg po TID-QID 200 mg IM TID-QID

Abbreviations: BID = twice daily; CINV = chemotherapy-induced nausea and vomiting; IM = intramuscularly; IV = intravenously; n/v = nausea and vomiting; OTC = over-the-counter; PONV = post-operative nausea and vomiting; PO = by mouth; PR = per rectum; PRN = as needed; RINV = radiation-induced nausea and vomiting; RX = prescription only; TID = three times daily.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Gastroenteritis in Children

Acute enteric illness resulting in emesis is most prevalent in children younger than 3 years, then decreases in prevalence throughout childhood and becomes more common between ages 20 and 29 years.⁶ Viral gastroenteritis may be caused by the Hawaii agent, rotaviruses, and adenoviruses as well as the Snow Mountain and Norwalk agents.⁷ Bacterial infections with *Staphylococcus aureus*, *Salmonella*, *Bacillus cereus*, and *Clostridium perfringens* also produce nausea and vomiting, in many cases via toxins that act on the brainstem.⁷ Vomiting is usually accompanied by diarrhea, and each year in the United States more than 200,000 children aged less than 5 years require hospitalization for treatment of dehydration secondary to gastroenteritis.⁶ In a report published in 2003, the CDC recommended avoiding the use of antiemetics in children for treatment of gastroenteritis due to potential side effects.⁶ Prochlorperazine and promethazine have a high incidence of side effects and should be avoided in patients less than 2 years.⁸ The safety and efficacy of antiemetics in children with gastroenteritis has been evaluated in 3 systematic reviews.

A 2008 systematic review and meta-analysis of antiemetic agents in children with vomiting due to acute gastroenteritis evaluated emesis cessation, use of intravenous fluid for rehydration, hospital admission, and medication adverse effects.⁹ Thirty articles were identified and 11 RCTs met inclusion criteria for the analysis. Antiemetics that were studied included ondansetron (n = 6), domperidone suppositories (n = 2), trimethobenzamide suppositories (n = 2), pyrilamine-pentobarbital (n = 2), metoclopramide (n = 2), dexamethasone (n = 1), and promethazine (n = 1).⁹ Of note, pyrilamine-pentobarbital is no longer available in the United States and trimethobenzamide suppositories have been removed from the market due to lack of demonstrated efficacy. The authors noted the quality of studies were highly variable due to small sample sizes, low methodological quality, and inconsistent results. Data from 6 randomized, double-blind, placebo-controlled ondansetron studies including 745 subjects were robust enough to pool for a meta-analysis. The analysis of the ondansetron studies demonstrated decreased risk of further vomiting (RR 0.45; 95% CI, 0.33-0.62), reduced need for intravenous fluid (RR 0.41; 95% CI, 0.28-0.62), and decreased risk of immediate hospital admission (RR 0.52; 95% CI, 0.27-0.95).⁹ Three studies noted increased diarrhea in ondansetron-treated patients. The authors concluded ondansetron decreases the risk of persistent vomiting, the use of intravenous fluids, and hospital admissions in children with vomiting due to gastroenteritis.⁹ It was difficult to draw conclusions about the safety and efficacy of metoclopramide, dexamethasone, and promethazine in treating children with n/v secondary to

gastroenteritis due to poor study design. This systematic review provides moderate evidence to support the efficacy and safety of ondansetron in children with vomiting due to gastroenteritis.

A Cochrane review completed in 2009 evaluated the effectiveness and safety of antiemetics used in children for vomiting due to gastroenteritis.¹⁰ The authors found limited data and significant heterogeneity amongst the studies. Consequently, they were not able to complete a meta-analysis of the extracted data. Four RCTs were deemed acceptable for review and provided limited evidence regarding safety and effectiveness of ondansetron and metoclopramide compared to placebo. The total population was 501 children under the age of 18 years. The primary outcome selected by the reviewers was precise time to cessation of vomiting after being administered study medication. However, none of the studies selected for inclusion assessed this outcome, so the authors provided descriptive data on the measured outcomes. Oral ondansetron in one trial demonstrated cessation of emesis for 8/12 (67%) patients within the first 4 hours and 7/12 (58%) patients in the first 24-hour period.¹⁰ In one trial 14% of patients who received oral ondansetron vomited during oral rehydration compared to 35% in the placebo group.¹⁰ In another trial, intravenous rehydration was required in 21.6% (ondansetron group) versus 54.5% (placebo group) which was a statistically significant difference ($p < 0.001$).¹⁰ The authors concluded that ondansetron may have reduced the amount of acute vomiting and may have reduced the number of children who required intravenous rehydration.¹⁰ Because the evidence was weak and unreliable, the authors advocated for more research focused on the safety and efficacy of antiemetics in children with n/v secondary to gastroenteritis.

A Cochrane review compiled in 2010 updated an assessment originally published in 2005.¹¹ The purpose was to evaluate the efficacy and safety of antiemetics in reducing vomiting related to gastroenteritis in children and adolescents. The review included 7 RCTs and involved 1,020 patients. Four studies compared ondansetron to placebo, while 2 studies evaluated intravenous (IV) ondansetron with IV metoclopramide. One study compared rectal administration of dimenhydrinate to placebo. The authors rated the evidence as low to moderate quality with unclear to high risk of bias. There was significant heterogeneity between the trials with limited useful data. Data were pooled from 3 placebo-controlled ondansetron studies to complete a meta-analysis. The primary outcome measure was the time taken from the administration of the medication or placebo until cessation of vomiting. This primary outcome was only reported in one study. Pooled data from 3 studies comparing oral ondansetron with placebo showed a reduction in the immediate hospital admission rate (RR 0.40, 95% CI 10 to 100) and an increase in the proportion of patients with cessation of vomiting (RR 1.34, 95% CI 3 to 7).¹¹ Mean time to cessation of vomiting in one study was 0.34 days less with dimenhydrinate suppository compared to placebo ($p = 0.036$).¹¹ In one study the proportion of patients with cessation of vomiting in 24 hours was 58% with IV ondansetron, 17% with placebo and 33% in the metoclopramide group ($p = 0.039$).¹¹ No significant differences were noted in the rate of adverse events, although diarrhea was reported as a side effect in 4 of the ondansetron studies. The authors concluded IV ondansetron and metoclopramide reduced the number of episodes of vomiting and dimenhydrinate as a suppository reduced the duration of vomiting.¹¹ Oral ondansetron increased the proportion of patients who ceased vomiting and reduced the number needing IV hydration.¹¹ This systematic review provides moderate evidence to support the safety and efficacy of ondansetron and metoclopramide and in addition to oral rehydration therapy in pediatric gastroenteritis for patients experiencing mild to moderate dehydration.

Treatment of nausea and vomiting in adults in the emergency department setting

A Cochrane review published in 2015 sought to provide evidence of the efficacy and safety of antiemetic medications in the management of n/v in adults admitted to the emergency department (ED).¹² The review included 8 RCTs and involved 952 participants aged 16 years and older. Selected trials were generally of adequate quality, with 6 trials at low risk of bias, and 2 trials at high risk of bias. The trials evaluated 6 different IV antiemetics: metoclopramide (n=5), ondansetron (n=4), prochlorperazine (n=3), promethazine (n=3), tropisetron (n=1) and droperidol (n=1). Three studies compared 5 antiemetics to placebo with the same primary outcome: mean change in visual analogue scale (VAS) (0 to 100) for nausea severity from baseline to 30 minutes. Differences in mean VAS change from baseline to 30 minutes between placebo and the study drugs were noted as: metoclopramide (mean difference (MD) -5.27, 95% CI -11.33 to 0.80),

ondansetron (MD -4.32, 95% CI -11.20 to 2.56), prochlorperazine (MD -1.80, 95% CI -14.40 to 10.80), promethazine (MD -8.47, 95% CI -19.79 to 2.85) and droperidol (MD -15.8, 95% CI -26.98 to -4.62).¹² The only statistically significant change in baseline VAS to 30 minutes was for droperidol, in a single trial of 48 participants. No other drug was statistically significantly superior to placebo. The other 5 trials compared one drug to an alternative antiemetic. The evidence reported in these trials did not demonstrate superiority of any particular drug over another agent. Adverse events were generally mild and there were no reported serious adverse events. The authors concluded there is no definitive evidence to support the superiority of any one antiemetic over another or the superiority of any drug over placebo for adults admitted to the ED with n/v.¹² If a drug is considered necessary to manage n/v, choice of antiemetic may be directed by other considerations such as a patient preference and adverse-effect profile. One of the limitations of the review was the small number of clinical trials in adults treated for nausea in the ED environment.

Motion Sickness

A Cochrane review published in 2011 focused on evaluating scopolamine for preventing and treating motion sickness. This was an update of a review initially published in 2004. The authors set out to assess the effectiveness of scopolamine versus no therapy, placebo, other drugs, behavioral and complementary therapy or 2 or more therapies in combination for prevention of motion sickness.¹³ Thirty-five studies were identified and 14 RCTs met inclusion criteria for the analysis. The studies were generally small in size and variable in quality with unclear risks of bias. Most of the participants had a history of motion sickness and were recruited from naval personnel on training exercises. Scopolamine was administered transdermally, orally, or intravenously. It was compared to placebo, cinnarizine, meclizine, dimenhydrinate, methscopolamine or ephedrine. The primary outcomes were prevention of onset and treatment of clinically defined motion sickness symptoms. When the data were pooled, 5 studies showed transdermal scopolamine to be superior over placebo for preventing motion sickness symptoms (risk ratio [RR] 0.48; 95% CI 0.32-0.73).¹³ When compared to meclizine, scopolamine showed a decrease in the mean motion sickness score: 89% with scopolamine versus 59% with meclizine. The mean delay in onset of symptoms with scopolamine was 4.32 minutes with a (32.47% increase from baseline compared to a mean delay in symptoms of 0.58 seconds with meclizine and an 8.66% increase from baseline.¹³ Adverse effects with scopolamine included drowsiness, blurred vision, dry mouth and dizziness. The small sample sizes and poor study design of the trials limited the ability to compare scopolamine to other agents. However, there was reasonable evidence to support the effectiveness of scopolamine over placebo in preventing motion sickness.

Nausea Associated with Migraine Headaches

Headache is listed among the World Health Organization's (WHO) major causes of disability with a global prevalence of 47%.¹⁴ Migraine headaches are characterized by enhanced sensitivity of the nervous system and additional symptoms may include n/v.¹⁵ The National Institute of Health and Care Excellence (NICE) guidelines recommend initial treatment of migraine with an oral triptan and an NSAID or an oral triptan in combination with acetaminophen.¹⁶ If these treatments are ineffective or not tolerated, the next step is to offer an injectable or rectal preparation of metoclopramide or prochlorperazine and add an injectable NSAID such as ketorolac or nasal/injectable triptan such as sumatriptan if those therapies have not yet been tried.¹⁶ The American Academy of Neurology (AAN) supports these recommendations and advocates for utilization of injectable, rectal or nasal routes of antiemetic administration to mitigate nausea that often accompanies migraine.¹⁷ AAN guidelines state that nausea is one of the most aversive and disabling symptoms of migraine attack and should be treated appropriately with antiemetics.¹⁷ Antiemetics recommended by the AAN as adjuncts in treatment of migraine include metoclopramide, prochlorperazine and 5HT3 antagonists.¹⁷

A Cochrane review completed in 2013 set out to determine the efficacy and tolerability of aspirin alone or in combination with an antiemetic compared to placebo or other medications in the treatment of acute migraine headaches in adults.¹⁸ Thirteen studies with 4222 participants were included in the overall assessment.¹⁸ The primary outcome was reduction in headache pain or pain free at 2 hours. A secondary outcome was relief of headache-associated symptoms including n/v. The studies were evaluated by the authors as medium to high quality. Aspirin 900-1000 mg with or without metoclopramide 10 mg was compared

to placebo or sumatriptan 50-100 mg in 2 studies with small numbers of patients. All medications were administered once via the oral route. The addition of metoclopramide 10 mg to aspirin 900 mg reduced nausea (RR 7.53 95% CI 4.2-13.5) and vomiting (RR 16.14 95% CI 2.3-113.05) compared with aspirin alone plus placebo in 2 studies with 417 subjects experiencing nausea and 59 subjects that vomited.¹⁸ When metoclopramide 10mg plus aspirin 900 mg was compared to sumatriptan 100mg alone nausea was slightly reduced (RR 1.10 95% CI 0.83-1.46) in 2 studies with 410 patients. The effect on decreasing vomiting was significant in the metoclopramide/aspirin arm as compared to sumatriptan (RR 10.59 95% CI 1.43-78.64) in 67 patients. Adding metoclopramide was also effective in alleviating n/v associated with migraine headache but did not make a difference on pain relief.

Nausea Associated with Pregnancy

About 50% of women have n/v in early pregnancy, and an additional 25% have nausea alone.¹⁹ The reported incidence of hyperemesis gravidarum is 0.3 to 1.0%.¹⁹ This condition is characterized by persistent vomiting, weight loss of more than 5%, ketonuria, electrolyte abnormalities, and dehydration.¹⁹ Approximately 10% of women with n/v in pregnancy require medication.¹⁹ According to the American College of Obstetricians and Gynecologists (ACOG), treatment of n/v during pregnancy with pyridoxine or pyridoxine plus doxylamine is safe and effective and should be considered first-line therapy.²⁰ Several case-control and cohort studies involving more than 170,000 exposures have found this combination to be safe with regard to fetal effects.²¹

The risks of conventional antiemetics used to alleviate n/v in pregnancy have been evaluated in numerous studies. Table 4 in **Appendix 1** outlines conventional antiemetics and their safety in pregnancy as categorized by the Food and Drug Administration (FDA). A retrospective review was recently published that evaluated the risks of birth defects in children born to women who used ondansetron early in pregnancy for n/v of pregnancy or hyperemesis gravidarum.²² Eight studies met criteria for inclusion for this analysis although data from the various studies were inconsistent and conflicting. The 3 studies of highest quality showed no increased risk of birth defects (36 malformations, 1,233 exposed compared with 141 malformations and 4,932 unexposed; with odds ratios [OR] of 1.12 [95% confidence interval [CI] 0.69–1.82], 1.3 [95% CI 1.0–1.7], and 0.95 [95% CI 0.72–1.26], respectively).²² Two of these studies demonstrated a slightly increased risk of cardiac defects (OR 2.0 [95% CI 1.3–3.1] and 1.62 [95% CI 1.04–2.14]), but this finding was not replicated in other studies.²² The overall risk of birth defects associated with ondansetron exposure appears to be low though there may be a small increase in the incidence of cardiac abnormalities in ondansetron-exposed babies. The authors concluded ondansetron use for n/v of pregnancy should be reserved for those women whose symptoms have not been adequately controlled by other methods.²²

Another recent review analyzed fetal outcomes in pregnancies exposed to ondansetron to treat hyperemesis gravidarum (HG).²³ In this retrospective cohort study, data were collected on 1070 pregnancies exposed to ondansetron and compared to outcomes in 2 control groups: 771 pregnancies in women with a history of HG and no ondansetron exposure and 1555 pregnancies in women with neither a history of HG nor ondansetron exposure.²³ Ventricular septal defects were reported in 2/952 infants in the group with history of HG exposed to ondansetron and 4/1286 infants in the group with no history of HG and no exposure to ondansetron.²³ Cleft palate was reported in 1/952 live births in the group with history of HG exposed to ondansetron and 2/1286 live births in the group with no history of HG and no exposure to ondansetron.²³ Women with a history of HG who took ondansetron reported less miscarriages and terminations and higher live birth rates.²³ The overall results of this report do not support evidence of teratogenicity of ondansetron.

A retrospective cohort study to evaluate the safety of metoclopramide during the first trimester of pregnancy was published in 2009 before ondansetron became widely utilized.²⁴ There were 113,612 singleton births during the study period. A total of 81,703 of the infants (71.9%) were born to women in the registry, 3458 of them (4.2%) were exposed to metoclopramide during the first trimester of pregnancy.²⁴ Exposure to metoclopramide, as compared with no exposure to the drug, was not associated with significantly increased risks of major congenital formations (5.3% and 4.9%, respectively; odds ratio, 1.04; 95% CI,

0.89 to 1.21).²⁴ In this large cohort of patients, exposure to metoclopramide in the first trimester was not associated with significantly increased risks of any of several adverse outcomes.

A recent Cochrane review assessed the effectiveness and safety of all interventions for hyperemesis gravidarum (HG) in pregnancy up to 20 weeks gestation.²⁵ Twenty-five trials involving 2052 participants met the inclusion criteria for 18 different types of interventions including acupressure, acupuncture, ginger, IV fluids, and pharmaceutical interventions. The quality of the evidence was rated as low to very low by the authors. There was insufficient evidence to note a difference between acupuncture and metoclopramide. When metoclopramide was compared to ondansetron, no clear differences in severity of nausea measured on 10 point visual analog scale (VAS) or number of episodes of vomiting (MD 1.70; 95% CI -0.15 to 3.55 and MD -0.10; 95% CI -1.63 to 1.43, respectively) were observed.²⁵ However, more women taking metoclopramide complained of drowsiness and dry mouth (RR 2.40, 95% CI 1.23 to 4.69 and RR 2.38, 95% CI 1.10 to 5.11, respectively).²⁵ In another study, which compared promethazine to metoclopramide, promethazine appeared to cause more drowsiness (RR 0.70, 95% CI 0.56 to 0.87) and dizziness (RR 0.48, 95% CI 0.34-0.69) than metoclopramide.²⁵ No clear differences in quality of life were noted with promethazine compared to metoclopramide. The authors concluded there is very little high quality evidence to support one intervention over another. They recommended more research in larger controlled studies to compare efficacy and safety of the different interventions.

Postoperative Nausea and Vomiting

Nausea and vomiting can complicate 11%–73% of surgical procedures.²⁶ PONV is more prevalent in women, non-smokers, and younger patients.²⁶ PONV is also more likely in patients with a history of PONV or motion sickness.²⁶ Type of anesthesia administered, use of postoperative opioids, and type of surgery may also affect the risk of PONV. Conventional antiemetics recommended by the Society for Ambulatory Anesthesia for managing PONV include droperidol, scopolamine, meclizine, dimenhydrinate, and promethazine.²⁷ 5HT₃ receptor antagonists (ondansetron, dolasetron, granisetron, palonosetron) and NK-1 antagonists (aprepitant, casopitant, and rolapitant) or corticosteroids (dexamethasone and methylprednisolone) are also recommended in some cases.²⁷ Nabilone and dronabinol do not have proven efficacy in PONV.²⁷ The evidence for the safety and efficacy of conventional antiemetics in PONV has been evaluated in several systematic reviews.

A Cochrane review in 2006 assessed the efficacy of drugs in preventing PONV.²⁸ Seven hundred thirty-seven studies met the inclusion criteria. Sixty medications were included in the analysis and included 103,237 children and adults. Over half of the studies had some risk of bias due to unclear concealment of allocation or unclear randomization. The studies were stratified into several subgroups in order to assess if outcomes were impacted by route of administration, timing of drug administration, or administered dose. Patient demographics such as age, sex, and type of surgery were highly variable amongst all the studies. Comparisons in the studies included head-to-head studies, placebo-controlled studies and non-controlled studies. Post-operative durations studied varied from 6 to 72 hours which added more complexity to the analysis. The risk for PONV was decreased compared to placebo with cyclizine 0.67 (95% CI 0.56 to 0.79); dimenhydrinate 0.71 (95% CI 0.59 to 0.86); dolasetron 0.72 (95% CI 0.62 to 0.83); droperidol 0.62 (95% CI 0.58 to 0.67); granisetron 0.39 (95% CI 0.31 to 0.48); metoclopramide 0.76 (95% CI 0.70 to 0.82); ondansetron 0.56 (95% CI 0.50 to 0.62); prochlorperazine 0.68 (95% CI 0.55 to 0.86); promethazine 0.46 (95% CI 0.25 to 0.82); ramosetron 0.51 (95% CI 0.39 to 0.68); and tropisetron 0.72 (95% CI 0.63 to 0.82).²⁸ The authors concluded there is convincing evidence that cyclizine, droperidol, granisetron, metoclopramide, ondansetron, tropisetron, dolasetron and dexamethasone reduce PONV by similar amounts.²⁸ The authors theorized that evidence for differences in the efficacy of these 8 drugs was not convincing due to publication bias.

A meta-analysis was compiled to evaluate the efficacy and tolerability of transdermal scopolamine (TDS) in preventing PONV in adults.²⁹ Data from 25 randomized, placebo controlled trials were analyzed in 3298 subjects. The reviewers evaluated the following outcomes: PONV in the post-anesthesia care unit (PACU), PONV up to 48 hours after surgery, use of rescue treatment, and the prevalence of adverse effects. Study heterogeneity was reported as not significant

for nausea in the PACU. In the PACU, TDS was associated with a significantly reduced risk for PONV compared with placebo (RR = 0.77; 95% CI, 0.61–0.98; p = 0.03).²⁹ Significant results were also noted 24 hours after surgery as TDS application resulted in reduced risk for postoperative nausea (RR = 0.59; 95% CI, 0.48–0.73; p < 0.001), postoperative vomiting (RR = 0.68; 95% CI, 0.61–0.76; p < 0.001), and combined post-operative n/v (RR = 0.73; 95% CI, 0.60–0.88; p = 0.001).²⁹ Adverse effects reported with TDS therapy included dry mouth, visual disturbances, dizziness, somnolence, confusion, skin irritation, urinary retention and headache. TDS was associated with a higher prevalence of visual disturbances at 24 to 48 hours compared with placebo (RR = 3.35; 95% CI, 1.78–6.32).²⁹ Other adverse effects (AEs) did not show a significant association with TDS. The authors concluded TDS was associated with significant reductions in PONV but patients may also experience visual disturbances 24 to 48 hours after applying the patch.²⁹ This meta-analysis provides evidence for the efficacy of TDS in PONV, although some adverse effects may be experienced by patients.

A systematic review and meta-analysis compared the effectiveness of 5HT3 receptor antagonists (ondansetron, dolasetron, granisetron, and tropisetron) with traditional antiemetics (metoclopramide, perphenazine, prochlorperazine, cyclizine and droperidol) for the prevention of PONV in adults.³⁰ A total of 32 RCTs met the inclusion criteria and were included in the meta-analysis. Trials were stratified by surgery type, antiemetic, and induction anesthetic. The authors did not note significant heterogeneity amongst the different subgroups. Pooled data indicated a 46% reduction in the odds of PONV in the 5-HT3-treated group (OR 0.54; 95% CI 0.42-0.71; p < 0.001).³⁰ There was not enough evidence to pool data for the other traditional antiemetics besides metoclopramide and droperidol. 5HT3 receptor antagonists demonstrated a beneficial effect over droperidol (OR 0.61; 95% CI 0.42-0.89; p < 0.001) and metoclopramide (OR 0.44; 95% CI 0.31-0.62; p < 0.001).³⁰ Results in the 34 studies examining vomiting indicated a 38% reduction in the odds of vomiting in the 5-HT3-treated group (OR 0.62; 95% CI 0.48-0.81; p < 0.001).³⁰ The authors concluded the 5-HT3 receptor antagonists are superior to traditional antiemetic agents for the prevention of PONV.

Chemotherapy Induced Nausea and Vomiting (CINV)

Chemotherapy-induced n/v is a common treatment-related side effect that has a detrimental effect on the quality of life of patients with cancer and may lead to dose reductions in or discontinuation of chemotherapy.³¹ Guidelines on antiemetic therapy in CINV that have been developed by different cancer societies show broad agreement on key principles, including: prophylaxis should be the primary goal of antiemetic therapy and should be implemented for groups of patients who have a 10% or greater risk of chemotherapy-induced emesis; the duration of prophylaxis should cover the entire risk period; oral and intravenous administration routes have the same efficacy; and the most effective antiemetic treatment is determined on the basis of chemotherapy emetogenicity, a patient's history of chemotherapy-induced emesis, and additional patient-related factors.³¹

The American Society of Clinical Oncology (ASCO) guidelines assist practitioners in determining the optimal antiemetic regimen for different clinical situations.³² Key recommendations state:

- All patients who receive highly emetogenic chemotherapy regimens (including anthracycline plus cyclophosphamide) should be offered a 3-drug combination of a neurokinin 1 receptor antagonist, a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist, and dexamethasone. The oral combination of netupitant and palonosetron (NEPA) plus dexamethasone is an additional treatment option in this setting.
- The preferred 5-HT3 receptor antagonist for patients who receive moderately emetogenic chemotherapy regimens is palonosetron; antiemetic treatment includes that agent combined with a corticosteroid.
- Both dexamethasone and a 5-HT3 receptor antagonist are recommended for patients receiving high-dose chemotherapy.
- Pediatric patients receiving either highly or moderately emetogenic chemotherapy should be treated with a 5-HT3 receptor antagonist and corticosteroids; higher weight-based dosing may be required.
- For those treated with highly emetogenic radiation therapy, a 5-HT3 receptor antagonist before each fraction and a 5-day course of dexamethasone are recommended.

-
- A 5-HT₃ receptor antagonist before each fraction is also recommended before moderately emetogenic radiation therapy; a 5-day course of dexamethasone is optional.
 - For patients who receive combination chemotherapy and radiotherapy, antiemetic therapy is dictated by the emetogenicity of chemotherapy, unless the emetic risk of radiation therapy is higher.

A Cochrane review to evaluate the effectiveness and tolerability of cannabis-based medications for CINV revealed limited evidence on this topic.³³ Twenty-three RCTs were included in the evaluation. The majority of studies were at risk of bias due to lack of allocation concealment or attrition and were rated as low to moderate quality. Most of the trials were conducted from 1975 to 1991; therefore comparisons with 5HT₃ receptor antagonists were not conducted. Primary outcomes included complete control of n/v, control of vomiting or control of nausea. Nine studies compared cannabinoids as monotherapy to placebo, prochlorperazine (n=11), metoclopramide (n=2), domperidone (n=1) or chlorpromazine (n=1). In 2 studies, cannabinoids were co-administered with another antiemetic and compared to an antiemetic alone. Nabilone was evaluated in 12 RCTS and dronabinol in 11 studies. When compared to placebo, cannabinoids were more likely to reduce vomiting (RR 5.7; 95% CI 2.6 to 12.6) or reduce n/v (RR 2.9; 95% CI 1.8 to 4.7).³³ There were no differences detected between prochlorperazine and cannabinoids for n/v (nausea: RR 1.5; 95% CI 0.67 to 3.2 vomiting: RR 1.1; 95% CI 0.86 to 1.4).³³ There was not enough information to assess differences between metoclopramide, domperidone, or chlorpromazine and the cannabinoids. The authors concluded that methodological limitations limited their ability to draw definitive conclusions and that nabilone and dronabinol may be useful for treating refractory CINV.

New Formulations:

Insys Therapeutics, Inc. received FDA approval to market a new liquid formulation of dronabinol, brand name Syndros® in early July, 2016. It is indicated for the treatment of anorexia associated with weight loss in patients with AIDS and for nausea and vomiting associated with cancer chemotherapy in patients who fail to respond adequately to conventional antiemetic treatments. The oral solution is available as a 5 mg/ml concentrate. The recommended starting dose is 2.1mg orally twice daily, one hour before lunch and one hour before dinner. The maximum recommended daily dose is 8.4mg twice daily.³⁴

References:

1. Health Evidence Review Commission Prioritized List of health services. <http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx>. Accessed April 27, 2016.
2. Shapiro BJ, Lynch KL, Toochinda T, Lutnick A, Cheng HY, Kral AH. Promethazine Misuse Among Methadone Maintenance Patients and Community-Based Injection Drug Users: *Journal of Addiction Medicine*. 2013;7(2):96-101. doi:10.1097/ADM.0b013e31827f9b43.
3. Tsay ME, Procopio G, Anderson BD, Klein-Schwartz W. Abuse and Intentional Misuse of Promethazine Reported to US Poison Centers: 2002 to 2012. *J Addict Med*. 2015;9(3):233-237. doi:10.1097/ADM.000000000000124.
4. Lexicomp Online. <http://online.lexi.com/lco/action/home>. Accessed May 9, 2016.
5. Micromedex Solutions | Evidence Clinical Decision Support. <http://micromedex.com/>. Accessed May 9, 2016.
6. Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. <http://www.cdc.gov/mmwr/PDF/rr/rr5216.pdf>. Accessed May 18, 2016.
7. Quigley EM, Hasler WL, Parkman HP. AGA technical review on nausea and vomiting. *Gastroenterology*. 2001;120(1):263-286.
8. Manteuffel J. Use of antiemetics in children with acute gastroenteritis: Are they safe and effective? *J Emerg Trauma Shock*. 2009;2(1):3-5. doi:10.4103/0974-2700.44674.
9. DeCamp LR, Byerley JS, Doshi N, Steiner MJ. Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med*. 2008;162(9):858-865. doi:10.1001/archpedi.162.9.858.
10. Alhashimi D, Al-Hashimi H, Fedorowicz Z. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. [Review] [20 refs][Update in Cochrane Database Syst Rev. 2011;(9):CD005506; PMID: 21901699], [Update of Cochrane Database Syst Rev. 2006;(4):CD005506; PMID: 17054262]. *Cochrane Database of Systematic Reviews*. 2009. doi:10.1002/14651858.CD005506.pub4.
11. Fedorowicz Z, Jagannath VA, Carter B. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. *Cochrane Database Syst Rev*. 2011;(9):CD005506. doi:10.1002/14651858.CD005506.pub5.
12. Furyk JS, Meek RA, Egerton-Warburton D. Drugs for the treatment of nausea and vomiting in adults in the emergency department setting. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2015. <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010106.pub2/abstract>. Accessed April 25, 2016.
13. Spinks A, Wasiak J. Scopolamine (hyoscine) for preventing and treating motion sickness. *Cochrane Database Syst Rev*. 2011;(6):CD002851. doi:10.1002/14651858.CD002851.pub4.
14. Kwon KT, Rudkin SE, Langdorf MI. Antiemetic use in pediatric gastroenteritis: a national survey of emergency physicians, pediatricians, and pediatric emergency physicians. *Clin Pediatr (Phila)*. 2002;41(9):641-652.
15. Patanwala AE, Amini R, Hays DP, Rosen P. Antiemetic therapy for nausea and vomiting in the emergency department. *J Emerg Med*. 2010;39(3):330-336. doi:10.1016/j.jemermed.2009.08.060.
16. Headaches in over 12s: diagnosis and management | Guidance and guidelines | NICE. <https://www.nice.org.uk/guidance/CG150>. Accessed May 6, 2016.
17. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.
18. Kirthi V, Derry S, Moore RA. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2013;4:CD008041. doi:10.1002/14651858.CD008041.pub3.
19. Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. *N Engl J Med*. 2010;363(16):1544-1550. doi:10.1056/NEJMcp1003896.
20. Anonymous. Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy. [Review]. *Obstetrics & Gynecology*. 2015;126(3). doi:10.1097/AOG.0000000000001048.

21. McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. *Teratology*. 1994;50(1):27-37. doi:10.1002/tera.1420500105.
22. Carstairs SD. Ondansetron Use in Pregnancy and Birth Defects: A Systematic Review. *Obstet Gynecol*. 2016;127(5):878-883. doi:10.1097/AOG.0000000000001388.
23. Fejzo MS, MacGibbon KW, Mullin PM. Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States. *Reproductive Toxicology*. 2016;62:87-91. doi:10.1016/j.reprotox.2016.04.027.
24. Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Levy A. The safety of metoclopramide use in the first trimester of pregnancy. *N Engl J Med*. 2009;360(24):2528-2535. doi:10.1056/NEJMoa0807154.
25. Boelig RC, Barton SJ, Saccone G, Kelly AJ, Edwards SJ, Berghella V. Interventions for treating hyperemesis gravidarum. *Cochrane Database Syst Rev*. 2016;5:CD010607. doi:10.1002/14651858.CD010607.pub2.
26. Quinn AC, Brown JH, Wallace PG, Asbury AJ. Studies in postoperative sequelae. Nausea and vomiting--still a problem. *Anaesthesia*. 1994;49(1):62-65.
27. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2014;118(1):85-113. doi:10.1213/ANE.0000000000000002.
28. Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. [Review] [896 refs]. *Cochrane Database of Systematic Reviews*. 2006.
29. Apfel CC, Zhang K, George E, et al. Transdermal scopolamine for the prevention of postoperative nausea and vomiting: a systematic review and meta-analysis. [Review][Erratum appears in Clin Ther. 2010 Dec;32(14):2502]. *Clinical Therapeutics*. 2010;32(12):1987-2002. doi:10.1016/j.clinthera.2010.11.014.
30. Loewen PS, Marra CA, Zed PJ. 5-HT3 receptor antagonists vs traditional agents for the prophylaxis of postoperative nausea and vomiting. *Journal of Anaesthesia*. 2000;47(10):1008-1018.
31. Navari RM, Aapro M. Antiemetic Prophylaxis for Chemotherapy-Induced Nausea and Vomiting. *N Engl J Med*. 2016;374(14):1356-1367. doi:10.1056/NEJMra1515442.
32. Hesketh PJ, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology Focused Guideline Update. *J Clin Oncol*. 2016;34(4):381-386. doi:10.1200/JCO.2015.64.3635.
33. Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. [Review]. *Cochrane Database of Systematic Reviews*. 2015. doi:10.1002/14651858.CD009464.pub2.
34. Syndros (dronabinol) Prescribing Information. Chandler, AZ: Insys Therapeutics, Inc.; July 2016.
35. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2015;63(11):2227-2246. doi:10.1111/jgs.13702.
36. Oregon Secretary of State Archives Division. http://arcweb.sos.state.or.us/pages/rules/oars_400/oar_410/410_121.html. Accessed May 16, 2016.

Appendix 1: Specific Drug Information

Table 2. Clinical Pharmacology and Pharmacokinetics.^{4,5}

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
ANTIHISTAMINES				
Dimenhydrinate	Antihistamine	Well absorbed after oral or parenteral administration	Extensive hepatic metabolism Renal excretion of metabolites	•Half-life: 5-8 hours •Vd: 3-4 L/kg
Meclizine	Antihistamine	Unknown	Hepatic: CYP2D6 dominant Renal excretion: unknown	•Half-life: 5- 6 hours
CANNABINOID AGONISTS				
Dronabinol	Cannabinoid Agonist	Oral bioavailability = 90-95% absorbed, only 10-20% reaches circulation due to extensive first pass metabolism	Extensive hepatic metabolism Renal excretion: 10-15%	•Half-life: 19-36 hours •Vd: 10 L/kg (highly lipid soluble)
Nabilone	Cannabinoid Agonist	Oral bioavailability = 95.6-100%	Extensive hepatic metabolism Renal excretion = 20-24%	•Half-life: 2 hours (parent) 35 hours (metabolites) •Vd: 12.5 L/kg
BENZAMIDES				
Metoclopramide	Benzamide <ul style="list-style-type: none"> • Cholinomimetic • Dopamine antagonist • Serotonin antagonist (at higher doses) 	Oral bioavailability = 80%	Minimal hepatic excretion Renal Excretion = 75-85%	•Half-life: 5-6 hours •Vd: 3.5 L/kg
Trimethobenzamide	Benzamide <ul style="list-style-type: none"> • Histamine Antagonist 	Oral bioavailability = 100%	Renal excretion: 30-50%	•Half-life: 7-9 hours
PHENOTHIAZINES				
Prochlorperazine	Phenothiazine <ul style="list-style-type: none"> • Anticholinergic • Dopamine antagonist 	Oral bioavailability = 12.5%	Extensive hepatic metabolism	•Half-life: 7-9 hours •Vd: 12.9-17.7 L/kg
Promethazine	Phenothiazine <ul style="list-style-type: none"> • Anticholinergic • Antihistamine • Dopamine antagonist 	Well absorbed orally	Hepatic	•Half-life: 9 hours
ANTICHOLINERGIC				
Scopolamine	Anticholinergic	Well absorbed percutaneously	Extensive hepatic metabolism Renal < 10%	•Half-life: 9.5 hours

Use in Specific Populations:

Potentially Inappropriate Medication in Older Adults (AGS Beers Criteria) ³⁵

Dimenhydrinate
Meclizine
Metoclopramide
Prochlorperazine
Promethazine
Scopolamine

Pediatric Warnings ^{4,5}

Dimenhydrinate: safety in children < 2 years of age not established – may cause excitation in young children

Meclizine: safety and efficacy not established in children < 12 years of age

Prochlorperazine: safety and efficacy not established in children < 2 years of age or < 9 kg

Promethazine: use is contraindicated in children < 2 years of age due to the risk of fatal respiratory depression

Drug Safety:

Black Boxed Warnings

Metoclopramide: May cause tardive dyskinesia a serious movement disorder that is often irreversible. Risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose. There is no known treatment for tardive dyskinesia, although symptoms may lessen or resolve after metoclopramide discontinuation. Prolonged treatment with metoclopramide (greater than 12 weeks) should be avoided in all but rare cases where therapeutic benefit outweighs the risks.⁵

Prochlorperazine injection: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared with placebo. Although the causes of death in the clinical trials were varied, most deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. It is unclear from these studies to what extent the mortality findings may be attributed to the antipsychotic drug as opposed to the patient characteristics. Prochlorperazine edisylate injection is not approved for the treatment of patients with dementia-related psychosis.⁵

Promethazine injection: Promethazine hydrochloride injection should not be used in pediatric patients less than 2 years old because of the potential for fatal respiratory depression. Respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years old in post-marketing experience. Exercise caution when administering promethazine hydrochloride injection to pediatric patients 2 years or older. Regardless of the administration route, promethazine hydrochloride injection can cause severe chemical irritation and damage to the tissue. Adverse reactions include burning, pain, thrombophlebitis, tissue necrosis, and gangrene, requiring surgical intervention, skin graft and/or amputation in some cases. Due to the risks of IV administration, the preferred route of administration is deep IM injection. Subcutaneous injection is contraindicated.⁵

Table 3. Summary of Warnings and Precautions.^{4,5}

Warning/Precaution	Dimenhydrinate	Meclizine	Dronabinol	Nabilone	Metoclopramide	Prochlorperazine	Promethazine	Trimethobenzamide	Scopolamine
Controlled substance due to abuse potential			X	X					
CV Disease	X		X	X	X	X	X		X
Seizures	X		X		X		X	X	X
Hepatic Impairment	X	X							
CNS depression	X	X	X	X	X	X	X		X
Glaucoma	X	X				X			X
Respiratory Disease	X	X							X
Prostatic Hypertrophy	X	X							X
Extrapyramidal reactions					X	X	X	X	
Neuroleptic Malignant Syndrome					X	X	X		
Dementia Related Psychosis						X			
Peptic Ulcer	X	X							X
Hyperthyroidism	X								
Renal Impairment					X			X	X
Psychiatric Disorders			X	X	X				
Hepatic Impairment								X	X

Table 4. Antiemetics and their safety risk in pregnancy.¹⁵

Medication	FDA Category*
Vitamin B6 (Pyridoxine)	A
Vitamin B6-Doxylamine combination	A
Doxylamine	A
Diphenhydramine	B
Meclizine	B
Dimenhydrinate	B
Promethazine	C
Prochlorperazine	C
Trimethobenzamide	C
Metoclopramide	B
Droperidol	C
Ondansetron	B
Ginger	C

*FDA categories: A: controlled studies show no risk, B: no evidence of risk in humans, C: risk cannot be ruled out, D: positive evidence of risk, X: contraindicated in pregnancy

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 10, 2016

1 gastroenteritis {No Related Terms} 9320

2 nausea {No Related Terms} 11863

3 vertigo {No Related Terms} 7424

4 motion sickness {No Related Terms} 1281

5 post-operative nausea and vomiting 206

6 pregnancy and nausea {No Related Terms} 10977

7 chemotherapy induced nausea {No Related Terms} 10108

8 1 or 2 or 3 or 4 or 5 or 6 or 7 41050

9 8 no related terms 26609

10 limit 9 to humans 17818

11 dimenhydrinate {No Related Terms} 198

12 dronabinol {No Related Terms} 3027

13 meclizine {No Related Terms} 73

14 metoclopramide {No Related Terms} 2097

15 nabilone {No Related Terms} 112

16 prochlorperazine {No Related Terms} 322

17 promethazine {No Related Terms} 837

18 scopolamine patch {No Related Terms} 5645

19 trimethobenzamide {No Related Terms} 21

20 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 12024

21 limit 20 to (humans and (clinical study or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 2610

22 8 and 20 948

23 limit 22 to (full text and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 317

Appendix 3: Utilization of Conventional Antiemetics in the Medicaid Fee For Service Population

Table 5. Antiemetic Indications and OHP Funding.¹

Diagnosis	OHP Funded Line	Funding Status
Pregnancy-related N/V	1	Funded
Enteritis	32	Funded
Enteric Infection/Food Poisoning	150	Funded
Cancer	28, 116,117,137,161,195,204,205,213, 215, 219, 220, 222,243,263,264,266,267,275,280, 291,292,299,319, 320, 321, 334, 439, 440	Funded
Post-Operative N/V	75	Funded
Migraine Headache	415	Funded
Motion Sickness/Vertigo	515	Not Funded
Gastroesophageal Reflux	516	Not Funded
Persistent Vomiting	531	Not Funded
Gastroparesis*	531	Not Funded
Irritable Bowel Syndrome	531	Not Funded
Noninfectious Gastroenteritis	555	Not Funded

*If gastroparesis is due to diabetes, it is funded condition due to the comorbidity rule as described in Oregon Administrative Rule (OAR) 410-121-0040³⁶

Table 6. Fee For Service Pharmacy Claims for Conventional Antiemetics: October 2014 to September 2015.

Drug Name	Drug Form	Patient Count	Claim Count	Amount Paid
Compro	Supp.rect	2	7	\$624
Dimenhydrinate	Tablet	1	1	\$6
Driminate	Tablet	2	3	\$29
Dronabinol	Capsule	24	66	\$17,761
Formula EM	Solution	1	1	\$13
Marinol	Capsule	1	1	\$14
Meclizine	Tab chew	35	45	\$399
Meclizine	Tablet	372	630	\$9,315
Metoclopramide	Solution	31	143	\$1,492
Metoclopramide	Tablet	456	831	\$7,559
Metoclopramide	Vial	3	3	\$27
Motion sickness	Tablet	1	1	\$10
Phenadoz	Supp.rect	109	139	\$8,428
Prochlorperazine	Supp.rect	24	30	\$2,574
Prochlorperazine maleate	Tablet	381	580	\$5,287
Promethazine	Ampul	4	5	\$62
Promethazine	Supp.rect	21	29	\$2,264
Promethazine	Syrup	41	53	\$496
Promethazine	Tablet	2,486	4,259	\$41,976
Promethazine	Vial	10	13	\$191
Promethegan	Supp.rect	146	191	\$19,331
Transderm-scop	Patch td 3	107	193	\$15,318
Travel sickness	Tab chew	71	139	\$1,293
Trimethobenzamide	Capsule	1	1	\$29
Totals		4,330	7,364	\$134,500

Table 7. Number of patients started on antiemetic therapy from 10/1/14 to 9/30/15 in the Medicaid FFS population.

Total Patients Meeting Criteria		
	2,212	
Funded	Patient Count	%
Enteritis	3	0.1%
Enteric Infection/Food Poisoning	2	0.1%
Cancer	161	7.3%
Post Op N/V	548	24.8%
Total Unique Funded:	672	30.4%
Not Funded	Patient Count	%
Motion Sickness	5	0.2%
Vertigo	125	5.7%
Gastroesophageal Reflux	87	3.9%
Gastroparesis	11	0.5%
Irritable Bowel Syndrome	10	0.5%
Noninfectuous Gastroenteritis	37	1.7%
Total Unique Not Funded:	262	11.8%
Patients with none of the above:	1,278	57.8%

Table 8. Antiemetic claims in patients with concurrent claims for an opioid and a recent history (past 18 months) of substance abuse.

Category	#	%
Received at least one Antiemetic in the last 6 months (FFS or MCO - Jan-Jun 2016)	1,960	100%
Received at least one opioid and one antiemetic in the last 6 months (FFS or MCO - Jan-Jun 2016)	1,075	55%
Received at least one opioid and one antiemetic in the last 6 months and has a recent history (18 months Jan-15 through Jun-16) of substance abuse	336	17%
Received at least one antiemetic but no opioids in the last 6 months and has a recent history (18 months Jan-15 through Jun-16) of substance abuse	168	9%

Appendix 4: Proposed Prior Authorization Criteria

Antiemetics

Goal(s):

- Promote use of preferred antiemetics.
- Restrict use of antiemetics for OHP-funded conditions.
- Restrict inappropriate chronic use.
- For patients receiving chemotherapy or radiation, approve a quantity sufficient for 3 days beyond the duration of treatment.

Length of Authorization:

- Up to 6 months, or variable depending on chemotherapy

Requires PA:

- Non-preferred drugs
- Preferred drugs when quantity limit exceeded (Table 1)

Table 1. Quantity Limits for Antiemetic Drugs.

Drug	Trade Name	Dose Limits
5-HT3 Receptor Antagonists		
Ondansetron	Zofran, Zuplenz, generic formulations	12 doses/ 7 days
Dolasetron	Anzemet	1 dose/ 7 days
Granisetron	Sancuso transdermal Generic oral	1 patch / 7 days 1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists		
Aprepitant	Emend	3 doses/ 7 days
Rolapitant	Varubi	1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists and 5-HT3 Receptor Antagonists Combinations		
Netupitant/palonosetron	Akynzeo	1 dose/ 7 days
Cannabinoid Receptor Agonist		
Dronabinol	Marinol	2.5 mg and 5 mg = 3 doses/day 10 mg = 2 doses/day

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria

1. What is the diagnosis being treated?	Record ICD10 Code.	
2. Is the diagnosis funded by OHP?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP
3. Is the requested drug preferred?	Yes: Go to #5	No: Go to #4
4. Will the prescriber consider a change to the preferred product? Note: <ul style="list-style-type: none"> Preferred products do not require a PA unless they exceed dose limits in Table 1. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee. 	Yes: Inform prescriber of covered alternatives in class and dose limits. If dose exceeds limits, go to #5.	No: Go to #5
5. Is the request for doxylamine/pyridoxine (Diclegis®) for pregnancy-related nausea or vomiting?	Yes: Go to #6	No: Go to #7
6. Has the patient failed a trial of pyridoxine? Note: <ul style="list-style-type: none"> Preferred pyridoxine products do not require a PA and are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee. 	Yes: Approve for up to 3 months	No: Pass to RPh; deny and recommend a trial of pyridoxine.
7. Is the request for dronabinol?	Yes: Go to #8	No: Go to #9
8. Does the patient have anorexia associated with HIV/AIDS?	Yes: Approve for up to 6 months. Apply quantity limit for drugs listed in Table 1 .	No: Go to #9
9. Does the patient have a cancer diagnosis AND receiving chemotherapy or radiation?	Yes: Approve for 3 days beyond length of chemotherapy regimen or radiation (not subject to quantity limits)	No: Go to #10

10. Does patient have refractory nausea/vomiting that has resulted in hospitalizations or ED visits in the past 6 months?	Yes: Approve for up to 6 months (not subject to quantity limits)	No: Go to #11
11. Has the patient tried and failed, or have contraindications, to at least 2 preferred antiemetics?	Yes: Approve for up to 6 months. Apply quantity limit for drugs listed in Table 1 .	No: Pass to RPh. Deny; medical appropriateness. Must trial at least 2 preferred antiemetics

P&T/DUR Review: 1/17 (DM); 1/16; 11/14; 9/09; 2/06; 2/04; 11/03; 9/03; 5/03; 2/03
Implementation: TBD; 2/12/16; 1/1/15; 1/1/14; 1/1/10; 7/1/06; 3/20/06; 6/30/04; 3/1/04; 6/19/03; 4/1/03

Appendix 5: Current Prior Authorization Criteria

Antiemetics

Goal(s):

- Promote use of preferred drugs.
- Restrict use of costly antiemetic agents for appropriate indications.
- Restrict inappropriate chronic use (>3 days per week).
- For patients receiving chemotherapy or radiation, approve a quantity sufficient for 3 days beyond the duration of treatment.

Length of Authorization:

- Up to 6 months, or variable depending on chemotherapy (criteria specific)

Requires PA:

- Non-preferred drugs will be subject to PA criteria and quantity limits (Table 1)
- Preferred drugs will deny only when quantity limit exceeded

Table 1. Quantity Limits for Antiemetic Drugs.

Drug	Trade Name	Dose Limits
5-HT3 Receptor Antagonists		
Ondansetron	Zofran, Zuplenz, generic formulations	12 doses/ 7 days
Dolasetron	Anzemet	1 dose/ 7 days
Granisetron	Sancuso transdermal	1 patch / 7 days
	Generic oral	1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists		
Aprepitant	Emend	3 doses/ 7 days
Rolapitant	Varubi	1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists and 5-HT3 Receptor Antagonists Combinations		
Netupitant/palonosetron	Akynzeo	1 dose/ 7 days

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria

1. What is the diagnosis being treated?	Record ICD10 Code.	
2. Is the requested drug preferred?	Yes: Go to #4	No: Go to #3
3. Will the prescriber consider a change to the preferred product? Message: <ul style="list-style-type: none"> Preferred products do not require a PA unless they exceed dose limits in table 1. Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. 	Yes: Inform prescriber of covered alternatives in class and dose limits. If dose exceeds limits, continue to #4.	No: Go to #4
4. Is the request for doxylamine/pyridoxine (Diclegis®) for pregnancy-related nausea or vomiting?	Yes: Go to #5	No: Go to #6
5. Has the patient failed a trial of pyridoxine? Message: <ul style="list-style-type: none"> Preferred vitamin B products do not require a PA and are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. 	Yes: Approve for up to 3 months	No: Pass to RPh; deny and recommend a trial of pyridoxine.
6. Does the patient have a cancer diagnosis and receiving chemotherapy or radiation?	Yes: Approve for 3 days beyond length of chemotherapy regimen or radiation (not subject to dose limits above)	No: Go to #7
7. Does patient have refractory nausea that has resulted in hospitalizations or ED visits?	Yes: Approve for up to 6 months	No: Go to #8
8. RPh only: All other indications need to be evaluated as to whether they are funded under the Oregon Health Plan. <input type="checkbox"/> Funded: Deny for medical appropriateness <input type="checkbox"/> Non-funded: Deny; not funded by the OHP		

P&T / DUR Review: 1/16 (KS); 11/14; 9/09; 2/06; 2/04; 11/03; 9/03; 5/03; 2/03
Implementation: 2/12/16; 1/1/15; 1/1/14; 1/1/10; 7/1/06; 3/20/06; 6/30/04; 3/1/04; 6/19/03; 4/1/03

Dronabinol (Marinol®)

Goal(s):

- Cover drugs only when used for covered OHP diagnoses, and restrict use to instances where medical evidence supports use (e.g. Nausea associated with chemotherapy). There is limited medical evidence supporting the use of dronabinol for many conditions.

Length of Authorization:

6 months to lifetime (criteria specific)

Requires PA:

- Dronabinol (Marinol®)

Quantity Limits:

- 2.5mg & 5 mg = 3 units per day
- 10mg = 2 units per day

Apply ONLY to HIV/AIDS related anorexia and Non-Oncology related antiemetic use. No quantity limits apply for Oncology (cancer) related antiemetic use.

Covered Alternatives:

- Preferred alternatives listed at www.orpd.org
- Metoclopramide (Reglan®)
- Prochlorperazine (Compazine®)
- Promethazine (Phenergan®)
- 5 HT3 antagonists (Zofran®, Anzemet®, or Kytril®) – authorized for >3 days

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does client have diagnosis of anorexia associated with AIDS? HIV?	Yes: Approve for lifetime (until 12-31-2036). Apply quantity limit (Anorexia associated with AIDS/HIV)	No: Go to #3.

Approval Criteria

<p>3. Does client have current diagnosis of cancer AND receiving chemotherapy or radiation therapy?</p>	<p>Yes: Approve for length of chemo or radiation therapy. No quantity limit. (Chemotherapy or Radiation, whichever is applicable)</p>	<p>No: Go to #4.</p>								
<p>4. Does client have refractory nausea that would require hospitalization or ER visits?</p>	<p>Yes: Go to #5.</p>	<p>No: Go to #7.</p>								
<p>5. Has client tried two medications listed below?</p> <table border="1" data-bbox="159 573 833 727"> <thead> <tr> <th>Generic Name</th> <th>Brand Name</th> </tr> </thead> <tbody> <tr> <td>Metoclopramide</td> <td>Reglan®</td> </tr> <tr> <td>Prochlorperazine</td> <td>Compazine®</td> </tr> <tr> <td>Promethazine</td> <td>Phenergan®</td> </tr> </tbody> </table> <p>5 HT3 drugs - Zofran®, Anzemet®, Kytril®</p>	Generic Name	Brand Name	Metoclopramide	Reglan®	Prochlorperazine	Compazine®	Promethazine	Phenergan®	<p>Yes: Approve for up to six months. Apply quantity limit (Refractory Nausea With Failure of Alternative Meds)</p>	<p>No: Go to #6.</p>
Generic Name	Brand Name									
Metoclopramide	Reglan®									
Prochlorperazine	Compazine®									
Promethazine	Phenergan®									
<p>6. Does client have contraindications, such as allergies, or other reasons they CANNOT use these anti-emetics? Document reason.</p>	<p>Yes: Approve for up to six months. Apply quantity limit (Refractory Nausea With Contraindication of Alternative Meds)</p>	<p>No: Go to #7.</p>								
<p>7. Does client have ONE of more of following diagnosis? Cancer associated anorexia, dystonic disorders, glaucoma, migraine, multiple sclerosis, pain.</p>	<p>Yes: Pass to RPH; Deny, (Medical Appropriateness)</p>	<p>No: Pass to RPH; Go to #8.</p>								
<p>8. RPH only All other indications need to be evaluated to see if they are above or below the line</p>	<p>Above: Deny, (Medical Appropriateness)</p>	<p>Below: Deny, (Not-Covered by the OHP)</p>								

P&T / DUR Review: 2/23/06, 2/24/04, 2/11/03
Implementation: 10/15, 7/1/06, 5/31/05