An Old Dog with New Tricks? Olanzapine’s Role in Chemotherapy Induced Nausea and Vomiting

Pharmacotherapy Rounds
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Learning Objectives:
1. Describe the epidemiology and pathophysiology of chemotherapy induced nausea and vomiting (CINV)
2. Discuss current pharmacotherapy options for the prevention and treatment of CINV
3. Evaluate the role of olanzapine for CINV
4. Recommend appropriate therapy for a patient suffering from CINV
I. Introduction
   A. CINV is a common and debilitating toxicity from chemotherapy
   B. Significant impact on quality of life (QOL)
      i. A distressing side effect that may discourage continuation of therapy
      ii. May lead to chemotherapy dose reductions
   C. CINV has a significant economic impact
      i. Unplanned office visits
      ii. Calls to the office
      iii. Hydration therapy
      iv. Hospitalizations
      v. Opportunity costs
   D. Patient ranking of most concerning side effects of chemotherapy

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Vomiting</td>
<td>Nausea</td>
<td>Nausea</td>
<td>Nausea</td>
<td>Fatigue</td>
</tr>
<tr>
<td>2</td>
<td>Nausea</td>
<td>Constantly tired</td>
<td>Loss of hair</td>
<td>Loss of hair</td>
<td>Nausea</td>
</tr>
<tr>
<td>3</td>
<td>Loss of hair</td>
<td>Loss of hair</td>
<td>Vomiting</td>
<td>Constantly tired</td>
<td>Sleep disturbances</td>
</tr>
<tr>
<td>4</td>
<td>Thought of coming for treatment</td>
<td>Effect on family</td>
<td>Constantly tired</td>
<td>Vomiting</td>
<td>Weight loss</td>
</tr>
<tr>
<td>5</td>
<td>Length of time treatment takes</td>
<td>Vomiting</td>
<td>Having to have an injection</td>
<td>Changes in the way things taste</td>
<td>Hair loss</td>
</tr>
</tbody>
</table>

E. CINV was first described in 1981 in patients receiving high dose cisplatin
   i. Metoclopramide used as prophylaxis with high dose cisplatin
      a) High dose metoclopramide resulted in one (range 0-9) emetic episode in a 24 hour period compared with 10.5 (range 5-25) in the placebo group.
      b) Demonstrated the need for prophylactic therapy in patients receiving chemotherapy
F. Since then, the pharmacotherapy of CINV has dramatically improved

II. Definitions
   A. Five categories of CINV
      i. Acute – nausea and vomiting that occurs within 24 hours of chemotherapy administration
      ii. Delayed – nausea and vomiting that occurs after 24 hours of chemotherapy administration
      iii. Anticipatory – nausea and vomiting that occurs prior to receiving chemotherapy (Abbreviated ANV)
      iv. Breakthrough – nausea and vomiting that occurs despite prophylactic administration of antiemetics and requiring the use of rescue antiemetic.
      v. Refractory – nausea and vomiting when there is poor response to multiple anti-emetic regimens

III. Epidemiology
   A. Nausea and vomiting is a significant problem in patients receiving chemotherapy
      i. Cisplatin is one of the most highly emetogenic agents resulting in 99% incidence of emesis without proper antiemetics
      ii. Historically, breakthrough emesis has occurred in 10-40% of patients treated with modern-day anti-emetics
   B. Prophylaxis
      i. Without appropriate prophylaxis, 70-80% of all cancer patients receiving chemotherapy experience nausea and vomiting
      ii. Administering a 5-HT3 antagonist plus dexamethasone prior to chemotherapy decreases incidence of vomiting (20-75%)
iii. Nausea is more resistant to treatment with incidence reaching 96% with prophylaxis
iv. Epidemiological data suggests that following guidelines results in 90.8% overall emesis control and 53.5% nausea control
v. Despite numerous prophylactic agents and robust studies, CINV remains a significant problem

**IV. Risk Factors**

<table>
<thead>
<tr>
<th>Treatment Related</th>
<th>Patient Related</th>
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<tbody>
<tr>
<td>Chemotherapy agents (<a href="#">Appendix A</a>)</td>
<td>Age (younger patients or those &lt;50 years)</td>
</tr>
<tr>
<td>Poor control of nausea and vomiting with previous chemotherapy cycles</td>
<td>Female sex</td>
</tr>
<tr>
<td>Infusion rate (bolus &gt; continuous infusion)</td>
<td>History of motion sickness</td>
</tr>
<tr>
<td>Circadian cycle with cisplatin (morning administration &gt; evening)</td>
<td>History of nausea and vomiting during pregnancy</td>
</tr>
<tr>
<td>Inadequate prophylaxis</td>
<td>Increased tumor burden</td>
</tr>
<tr>
<td>Lack of maintenance antiemetics after chemotherapy</td>
<td>Concomitant medications (opiates, antibiotics, antifungals)- Fluid electrolyte abnormalities, GI obstruction, Metastases to brain, meninges, liver, infections (septicemia, local infection) Anxiety</td>
</tr>
<tr>
<td>Administration of multiple agents on the same day</td>
<td>History of minimal chronic alcoholism</td>
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<td></td>
<td>Inadequate hydration</td>
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<td>Poor performance status</td>
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<tr>
<td></td>
<td>Enhanced CYP2D6 activity – Results in ultra-rapid metabolism of 5-HT₃ antagonists except granisetron</td>
</tr>
</tbody>
</table>

A. Eastern Cooperative Oncology Group (ECOG) Performance Status
   i. Used by clinicians to assess how patient’s disease state is progressing and affecting daily living abilities
   ii. Used to determine appropriate treatment prognosis

B. Grade toxicities definitions
   i. Common Terminology Criteria for Adverse Events (CTCAE) rates and defines toxicities based on Grades 1-5
   ii. General grade definitions
      a) Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life-threatening, Grade 5 = death

V. Mechanisms of CINV
   A. Nausea and vomiting serve as important protective mechanisms against toxins
      i. Much redundancy and plasticity in emetic pathway = difficult control
   B. Gastrointestinal tract
      i. Chemotherapy induces neurotransmitter release from enterochromaffin cells of the gastrointestinal tract
      ii. Visceral afferents project to the brain stem
   C. Central Nervous System
      i. Emetic center (emetic central pattern generator or “vomiting center”)
      ii. Area postrema
      iii. Limbic System
         a) Various neurotransmitters (NT) travel to the chemoreceptor trigger zone (CTZ)-an area known to cause emesis
D. Most common NTs involved in nausea and vomiting
   i. **Dopamine (D₂)*, serotonin (5HT₃) *, Substance P*, acetylcholine, histamine, endorphins, GABA
      *most common pharmacologic targets for CINV

Figure 1: Pathophysiology of CINV

E. Conceptual Model of Acute and Delayed CINV
   i. Time periods for NT antagonist affect

Figure 2: Anti-emetic Sensitive Phases

VI. Treatment Strategies
A. Principles of Care
   i. Primary goal for CINV is prevention of acute nausea and vomiting
      a) Positively impacts incidence and control of delayed and anticipatory nausea and vomiting
   ii. Maintain therapy for duration of emetic risk
      a) Two days for patients receiving moderate emetogenic chemotherapy (MEC)
      b) Three days for patients receiving highly emetogenic chemotherapy (HEC)
   iii. Factors influencing antiemetic selection
      a) Degree of emetic potential for chemotherapy
      b) Prior emetic experience and treatment successes/failures
      c) Patient specific factors
d) Toxicities of antiemetics

B. Guidelines
i. Despite the existence of published guidelines, patients may have unique nausea and vomiting risk factors
ii. Individualization of antiemetic regimens is necessary to provide optimal control – Refer to Appendices B-E for each of the treatment guidelines
   a) American Society of Clinical Oncology (ASCO)
   b) Multinational Association of Supportive Care in Cancer (MASCC)
   c) National Comprehensive Cancer Network (NCCN)
      1) Consensus-based recommendations based on expert opinion
iii. All guidelines have same recommendations for HEC
   a) Refer to Appendices B-E for treatment guidelines

VII. Antiemetic Agents
A. Serotonin (5-HT₃) receptor antagonists
i. Examples: dolasetron, granisetron, ondasetron, palonosetron
ii. Mechanism of action: Blocks serotonin receptors peripherally in the gastrointestinal tract and centrally in the medulla
iii. Adverse effects
   a) Headache, constipation, malaise, may increase liver function tests (LFT’s), may cause QT prolongation
iv. Palonosetron is a preferred agent
   a) Palonosetron vs. ondansetron (both without dexamethasone)¹⁶
      1) Efficacy (no emesis and no rescue medication required) of palonosetron over ondansetron (p<0.01):
         • During first day (81% vs. 69%)
         • Days 2 to 5 (74% vs. 55%)
         • Over entire period of 1 to 5 days (69% vs. 50%)
   b) Patients free of nausea was similar between the groups on days 1 to 2, while palonosetron-treated patients had significantly less nausea on days 3 to 5
   c) NCCN and ASCO guidelines recommend palonosetron as the preferred 5-HT₃-antagonist for patients who receive HEC or MEC

B. Neurokinin-1 (NK-1) receptor antagonists
i. Examples: aprepitant, fosaprepitant
ii. Mechanism of Action: Blocks substance P from binding to NK-1 receptors in the chemoreceptor trigger zone
iii. Adverse Effects: Asthenia/fatigue, constipation, diarrhea, headache, dizziness, hiccups
iv. Aprepitant
   a) In cisplatin based treatment, aprepitant, ondansetron, and dexamethasone was more effective than ondansetron and dexamethasone¹⁷
      1) In days 1 to 5 after cisplatin 73% of aprepitant recipients vs. 52% of patients in the control group and a complete response (CR)-defined as no emesis and no rescue medications required (p<0.001)
      2) No difference in nausea incidence between the groups for acute, delayed, or overall period
   b) Three-drug antiemetic regimens including NK-1 antagonists superior to two drug regimen in both HEC and MEC
   c) Pharmacokinetics
      1) Metabolized primarily by CYP3A4, minor metabolism by CYP1A2 and CYP2C19
      2) Drug Interaction
         • Oral contraceptive interaction – reduced effectiveness – secondary form of birth control needed
         • Warfarin – may have a clinically significant decrease in INR
o Recheck levels 7-10 days after completing 3 day course
• Dexamethasone – may increase the area under the curve (AUC)
o Decrease dose by 40% on days 2-3 if given orally
o Not necessary if dexamethasone is given IV

d) Netupitant/Palonosetron combination (NEPA)
1) Novel fixed oral dose: 300 mg of netupitant (a highly selective NK-1 antagonist) and 0.5 mg of palonosetron – approved 2014
2) CR of single dose NEPA on day 1 with dexamethasone for acute and delayed CINV vs. aprepitant for 3 days plus a palonosetron and dexamethasone (81 vs. 76%) 18

C. Corticosteroids
i. Examples: Dexamethasone (most studied and used), methylprednisone, prednisone
ii. Mechanism of action: Unknown; thought to act by inhibiting prostaglandin synthesis in the cortex

iii. Adverse effects with short courses or single doses are rare but may include: Insomnia, jitters, hyperglycemia, euphoria, increased appetite, fluid retention

D. Adjunctive Agents

Table 3: Adjunctive Agents used in CINV

<table>
<thead>
<tr>
<th>Class</th>
<th>Medications</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
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</table>
| Benzamide analogs      | Metoclopramide                   | Blocks dopamine receptors in the chemoreceptor trigger zone; stimulation of cholinergic activity in the gut, increasing gut motility; antagonism of peripheral serotonin receptors in the intestines. Effects are dose related | Mild sedation and diarrhea
Extrapyramidal reactions (dystonia, akathisia) |
| Phenothiazines         | Prochlorperazine                 | Blocks dopamine receptors in the chemoreceptor trigger zone                          | Drowsiness
Hypotension
Akathisia
Dystonia |
|                        | Chlorpromazine                   |                                                                                     |                                      |
|                        | Promethazine                     |                                                                                     |                                      |
| Butyrophenones         | Haloperidol                      | Similar to phenothiazines – blocks dopamine receptors in the chemoreceptor trigger zone | Sedation
Hypotension – not as common as phenothiazine
Extrapyramidal side effects |
|                        | Droperidol                       |                                                                                     |                                      |
| Benzodiazepines        | Lorazepam                        | Minimal antiemetic properties. Has action at the higher central nervous system centers. Has anxiolytic, sedative, amnesic properties | Sedation*
Antegrade amnesia*
Hypotension
Perceptual disturbances
Urinary incontinence
*may be desirable side effects for nausea and vomiting |
| Cannabinoids           | Dronabinol                       | Unknown; thought to be through cannabinoid receptors exhibiting antiemetic properties. Other proposed mechanisms include inhibition of prostaglandin and blockade of adrenergic activity | Drowsiness
Dizziness
Euphoria
Orthostatic hypotension
Ataxia
Hallucinations
Time disorientation |
E. Non-pharmacological strategies$^{19,20,21}$
   a) If nausea develops patients can be advised to
      1) Eat smaller meals
      2) Choose bland foods (crackers, flat soda, etc.)
      3) Avoid fatty, fried, very spicy, or sweet foods
   b) To prevent nausea patients should be encouraged to
      1) Eat foods that are cold or at room temperature (aroma of warm or hot foods can increase nausea)
c) Ginger has shown some efficacy is doses of 0.5 to 1 gram for 6 days$^{19}$

VIII. Olanzapine$^{22}$
   A. Second generation atypical antipsychotic
   B. Mechanism of action: blocks dopamine (D$_1$-D$_4$ receptors), serotonin (5-HT$_{2a}$, 5-HT$_{2c}$, 5-HT$_3$, 5-HT$_6$), muscarinic (acetylcholine), histamine (H$_1$), and catecholamines (alpha 1) receptors
      i. Has five times the affinity for 5-HT$_{2}$ than D$_2$
         a) Less extrapyramidal side effects
   C. Mechanism in CINV – largely unknown
      i. Thought to be mainly through serotonin and dopamine blockade
      ii. Animal model blockade of 5-HT$_{2c}$ has shown antiemetic potential
   D. FDA approved indications since 1996 – generically approved in 2011
      i. Schizophrenia, bipolar disorders, delirium, major depressive disorder (treatment resistant)
   E. Pharmacokinetics
      i. Metabolized primarily by
         a) Glucuronidation
         b) Some CYP1A2 and CYP2D6
      ii. Long half-life: 20-50 hrs
   F. Common toxicities
      i. Dizziness, sedation, and extra-pyramidal symptoms (e.g. akathisia)
      ii. Long term use increases risk of: Weight gain, dyslipidemia, and onset of diabetes
   G. Antiemetic option
      i. Currently endorsed by NCCN guidelines
      ii. No CYP450 inhibition – few drug interactions
   H. Acute and delayed CINV
      i. First demonstrated potential in a few case reports and retrospective trials between years 2003-2011$^{23,24,25}$
      ii. Led to early Phase I and Phase II single-arm trials$^{26,27,28}$

IX. Challenges Remain
   A. Prevention of nausea
   B. Guideline adherence is poor due to many reasons
      i. Lack of knowledge
      ii. Differing recommendations
      iii. Cost/financial issues
      iv. Institutional enforcement
      v. Inadequate measurement of quality of care and outcomes

X. Clinical Question
   A. Current NCCN guidelines recommend olanzapine as first line option for HEC without preference to commonly used agents
   B. Review of the literature was performed to determine olanzapine’s role in the treatment of CINV and its current place in therapy
      i. Should olanzapine be used first line over standard of care?
      ii. Can olanzapine be used in addition to standard of care?
      iii. Should olanzapine be used as the initial choice for breakthrough nausea and vomiting?

### Objective
To compare the effectiveness of olanzapine to aprepitant for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy

### Study Design
Un-blinded, randomized, phase III trial

### Population
Inclusion/Exclusion
- ≥18 years of age with confirmed malignant disease
- Chemotherapy-naïve and scheduled to receive highly emetogenic chemotherapy (HEC) – i.e. cisplatin ≥ 70 mg/m², cyclophosphamide ≥ 600-1000 mg/m² and doxorubicin ≥ 50-60 mg/m²).
- No nausea in the 24 hrs prior to beginning chemotherapy, serum creatinine ≤ 2.0 mg/dL, serum bilirubin ≥2.0 mg/dL, serum glutamic-pyruvic transaminase (SGPT) or serum glutamic-oxaloacetic transaminase (SGOT) ≤ 3x upper limits of normal (ULN), absolute neutrophil count (ANC) ≥1500 mm³
- Patients of childbearing potential (male and female) had to consent to use adequate contraception throughout protocol

### Primary Outcome
- Complete response (CR) = no emetic episodes and no use of rescue medications from the 0-120 hrs post chemotherapy in either treatment arm

### Secondary Outcomes
- CR in the acute phase (0-24 hours post-chemotherapy)
- CR in the delayed phase (days 2-5 post-chemotherapy)
- Incidence of no nausea in the acute, delayed, and overall periods determined by M.D. Anderson Symptom Inventory (MDASI) score – validated test for assessing nausea and vomiting

### Methods
- Patients randomly assigned to either of two therapies:
  - Olanzapine, palonosetron, and dexamethasone (OPD)
  - Aprepitant, palonosetron, and dexamethasone (APD)
- Patients furthered stratified by gender and chemotherapy regimen

![Figure 3: Treatment Protocol]

<table>
<thead>
<tr>
<th>OPD group (n=121)</th>
<th>APD group (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone 20 mg IV</td>
<td>Dexamethasone 12 mg IV</td>
</tr>
<tr>
<td>Palonosetron 0.25 mg IV</td>
<td>Palonosetron 0.25 mg IV</td>
</tr>
<tr>
<td>Olanzapine 10 mg PO</td>
<td>Aprepitant 125 mg PO</td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td></td>
</tr>
<tr>
<td>Olanzapine 10 mg PO</td>
<td>Aprepitant 80 mg PO</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 4 mg PO twice daily</td>
</tr>
<tr>
<td><strong>Day 3</strong></td>
<td></td>
</tr>
<tr>
<td>Olanzapine 10 mg PO</td>
<td>Aprepitant 80 mg PO</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 4 mg PO twice daily</td>
</tr>
<tr>
<td><strong>Day 4</strong></td>
<td></td>
</tr>
<tr>
<td>Olanzapine 10 mg PO</td>
<td>Dexamethasone 4 mg PO twice daily</td>
</tr>
</tbody>
</table>

### Statistics
- Powered to detect a 15% difference between the two anti-emetic regimens. With a tolerance of 15%, a total of 111 subjects were needed in each arm to obtain 0.80 power at a α=0.05
Enrollment
- 251 patients were assessed for eligibility
- 4 were excluded due to nausea within 24 hours of treatment
- 247 were randomized to treatment
  - 121 in the OPD group
  - 120 in the APD group

Baseline
- No significant difference between baseline characteristics
- Females (81%) in OPD arm and (83%) in APD arm
- Majority of patients had ECOG score of 0: (77% OPD, 78% APD)
- Majority of patients were breast cancer patients (60% OPD, 66% APD), with next highest cancer being lung (non-small cell): (42% OPD, 40% APD)

Results

**Primary Outcome**

Figure 4: OPD vs. APD Complete Response

<table>
<thead>
<tr>
<th></th>
<th>OPD CR</th>
<th>APD CR</th>
</tr>
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<tbody>
<tr>
<td>Acute (0-24 hrs)</td>
<td>97</td>
<td>87</td>
</tr>
<tr>
<td>Delayed (24-120 hrs)</td>
<td>77</td>
<td>73</td>
</tr>
<tr>
<td>Overall (0-120 hrs)</td>
<td>77</td>
<td>73</td>
</tr>
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</table>

**Secondary Outcome**

Figure 5: OPD vs. APD Nausea Comparison

<table>
<thead>
<tr>
<th></th>
<th>OPD No Nausea</th>
<th>APD No Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (0-24 hrs)</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>Delayed (24-120 hrs)</td>
<td>69</td>
<td>38</td>
</tr>
<tr>
<td>Overall (0-120 hrs)</td>
<td>69</td>
<td>38</td>
</tr>
</tbody>
</table>

**Adverse effects**
- No Grade 3 or 4 toxicities were attributed to the study drug
- No major severity of 17 symptoms measured by MDASI score
- CR and control of nausea in patients receiving subsequent cycles was not significantly different between the groups

**Conclusions**
- OPD regimen was superior to APD in controlling nausea in the delayed and overall periods
- Olanzapine combined with a single dose of dexamethasone and single dose of palonosetron was very effective at controlling acute and delayed CINV in patients receiving HEC
- Olanzapine use was not associated with significant sedation, weight gain or induction of significant hyperglycemia
- The four-day treatment with olanzapine is approximately 10-20% of the cost of the three-day aprepitant treatment
## Discussion

### Strengths
- Randomized controlled trial comparing standard of care regimen for HEC
- Adequately powered to show difference in CR with emesis
- Demonstrate efficacy of a dexamethasone sparing regimen
- Demonstrated efficacy in chemotherapy naïve patients

### Limitations
- Majority female population
- Mostly ECOG score 0
- Majority of cancers were breast and non-small cell lung cancer - difficult to generalize
- No account for co-morbid conditions
- No account of compliance with medication regimen
- No actual economic analysis to determine olanzapine cost effectiveness
- Not blinded or placebo controlled

### Take Home Points
- OPD was non-inferior to APD in HEC patients for the primary outcome of CR
- Olanzapine containing anti-emetic regimen (OPD) is superior to APD in controlling delayed and overall nausea and appears to be as effective as APD for complete response

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#### Objective
Determine if olanzapine can reduce frequency of CINV and improves QOL during chemotherapy

#### Study Design
Double-blind, randomized, placebo-controlled trial

#### Population
**Inclusion**
- ECOG score 0-2
- Hospital inpatients scheduled to receive MEC or HEC

**Exclusion**
- Experienced significant vomiting, retching , or nausea in 24 hrs before the start of the trial
- Scheduled to receive concurrent abdominal radiation
- History of diabetes mellitus
- Other antipsychotic treatment

#### Primary Outcome
- “Total control” time 0-120 hrs – no vomiting, no acute use of rescue medications, and maximum nausea of 5 mm on a 100 mm visual analogue scale (VAS)

#### Secondary Outcomes
- Complete Response (CR) – no vomiting and no use of rescue medication
- Complete Protection (CP) – CR plus maximum nausea of 25 mm on a 100 mm (VAS)
- QOL assessed by
  - Functional Living Index – Emesis (FLI-E) – validated test
    - 18 questions (9 for nausea, 9 for vomiting) – specifically addressing effects of nausea on physical activities, social and emotional function, ability to enjoy meals
    - Score ranges from 18-126 – higher scores = ↓ QOL
    - Score >36 considered affecting QOL
  - Amount of dietary intake during chemotherapy
    - Measured by percent change in total daily intake
  - Satisfaction score
    - (1: Dislike, 2: Not satisfied, 3: Neither, 4: Satisfied, 5: Well-satisfied)
Methods

Figure 6: Study 2 Protocol

<table>
<thead>
<tr>
<th>Olanzapine group (n=22)</th>
<th>Control group (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 1</td>
</tr>
<tr>
<td>Olanzapine 5mg PO</td>
<td>Aprepitant 125 mg PO</td>
</tr>
<tr>
<td>Aprepitant 125 mg PO</td>
<td>5HT3 Antagonist*</td>
</tr>
<tr>
<td>5HT3 Antagonist*</td>
<td>Dexamethasone 10 mg IV</td>
</tr>
<tr>
<td>Dexamethasone 6.6 mg IV Days 2,3,4</td>
<td>Dexamethasone 10 mg IV</td>
</tr>
<tr>
<td>Olanzapine 5 mg PO Days 2,3,4</td>
<td>Aprepitant 80 mg PO Days 2,3</td>
</tr>
<tr>
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</tr>
<tr>
<td>Dexamethasone 6.6 mg IV Days 2,3,4</td>
<td>Dexamethasone 6.6 mg IV Days 2,3</td>
</tr>
</tbody>
</table>

*granisetron days 1-3, ondansetron days 1-2, ramosetron days 1-3, palonosetron day 1 only

Statistics
- Chi square test or Fischer exact test to detect statistical significance between groups
- Cochrane Mantel-Haenzel to adjust for stratification

Enrollment
- 22 patients in each treatment arm (50% male vs. female)
- Baseline characteristics were similar between the groups

Results

Primary Endpoint
- Total control of nausea and vomiting favoring olanzapine group 59% vs. 23%, p=0.031
- Difference greater in delayed phase (24-120 hrs) – 64% vs. 23%, p=0.014

Secondary Endpoints
- FLI-E score – (p<0.0004)
  - Olanzapine group: <36 – CINV did not affect daily activities
  - Control group: 36% of patients had daily life affected
- VAS
  - Acute and delayed phase favored olanzapine group (p=0.0211 and p=0.0036 respectively)
- Satisfaction level
  - 91% satisfied with olanzapine treatment
- Percent change in dietary intake during chemotherapy
  - Olanzapine – less change days two through six (p<0.05)

Conclusions
- Addition of olanzapine to standard anti-emetic therapy reduced CINV and improved QOL in patients receiving HEC and MEC – especially in the delayed phase
- Appetite stimulating side effect of olanzapine may improve appetite and mood during chemotherapy

Discussion

Strengths
- Robust controlled study design
- Validated QOL assessment tool
- First study to show that adding olanzapine to conventional three drug combination can improve CINV control

Limitations
- Palonosetron with longer half-life may have affected improvement of CINV in delayed phase
- Small study population
Take Home Points

- Study included both chemotherapy naïve and chemotherapy experienced patients
- Average age in olanzapine group was higher – lower risk of CINV
- Olanzapine as additive therapy to aprepitant, 5HT3 antagonist, and dexamethasone improves total control of CINV and QOL in patients undergoing chemotherapy


<table>
<thead>
<tr>
<th>Objective</th>
<th>To compare the use of olanzapine versus metoclopramide for the treatment of breakthrough CINV in chemotherapy-naïve patients receiving highly emetogenic chemotherapy (HEC) and guideline directed prophylactic antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>A double-blind, randomized phase III trial</td>
</tr>
</tbody>
</table>
| Population Inclusion/Exclusion | - Chemotherapy naïve receiving either cisplatin ≥ 70 mg/m² or AC (Doxorubicin + Cyclophosphamide)  
- Patients without nausea in 24 hrs prior to chemotherapy, creatinine of ≤ 2 mg/dl, serum bilirubin of ≤ 2 mg/dl, SGOT or SGPT ≤ 3x ULN, and ANC of ≥ 1,500 mm³  
- Patients of childbearing potential (men and women) must consent to use adequate contraception throughout protocol therapy  
- Women of childbearing potential must have a negative urine pregnancy test  
- Patients should have no severe cognitive compromise, no known history of CNS disease (e.g., brain metastases, seizure disorder), no use of other antipsychotics within 30 days  
- Could only receive prochlorperazine and other phenothiazines as rescue antiemetic therapy |
| Primary Outcome | Number of patients with no emetic episodes in the 72-hr observation period following the initiation of the treatment with either olanzapine or metoclopramide |
| Secondary Outcomes | Number of patients with no nausea in the 72-hr observation period |
| Methods | Patients were stratified based on gender and chemotherapy regimen  
**Figure 7: Study 3 Protocol**

**Olanzapine group**
- Olanzapine 10 mg PO every 24 hrs (for total of 72 hrs)

**Metoclopramide group**
- Metoclopramide 10 mg PO every 8 hrs (total of 24 hrs)

**All patients received:**
- Dexamethasone 12 mg IV*
- Palonosetron 0.25 mg IV
- Fosaprepitant 150 mg IV 30-60 minutes before chemo

*Post-chemotherapy – oral dexamethasone 4 mg twice daily Days 2-4

**Validated MDASI score was used to assess symptoms daily**

| Statistics | Powered with a sample size to detect a 15% difference between the two treatment regimens  
133 subjects were needed in each arm to obtain a 0.80 power level at type 1 error level at 0.05  
19 analyses of variance were performed, the level of significance was lowered to 0.01 as an adjustment for multiple comparisons |

---

12 | *M al a m a k a l*
Enrollment

- 280 patients assessed for eligibility; 276 patients underwent randomization
  - 56 patients in the olanzapine treatment arm
  - 52 patients in the metoclopramide treatment arm
- No difference between baseline characteristics of two groups

Results

**Primary and Secondary Endpoints**

**Figures: Olanzapine vs. Metoclopramide (No Emesis and No Nausea)**

- Majority of patients in both groups developed nausea and emesis on days 2 or 3 of chemotherapy
- Despite following guidelines for HEC, approximately 39% of the patients developed breakthrough emesis and/or nausea
- No Grade 3 or 4 toxicities attributed to the olanzapine group

**Author’s Conclusions**

- Olanzapine was significantly more effective in the treatment of breakthrough nausea and vomiting compared to metoclopramide without significant toxicities of sedation, weight gain, or hyperglycemia
- Olanzapine offers an economic benefit (one 10 mg tablet costs ~$40.48)

Discussion

**Strengths**

- Results add important information to an area where there no comparative trials in breakthrough nausea and vomiting medication options
- First study to show superiority of a breakthrough agent

**Limitations**

- Small sample size
- Inconsistent dosing of metoclopramide – doses can range from 10-40 mg
- Lack of comparison amongst other commonly used agents prohibits claim of overall superiority of olanzapine as breakthrough agent of choice

**Take Home Points**

- Olanzapine is a superior choice to metoclopramide for breakthrough nausea and vomiting
- Only existing comparative trial between breakthrough agents
- Inconsistent dosing comparison diminishes overall value of results

I. Additional Evidence

a. Recent meta-analysis shows overall superiority of olanzapine containing regimens over non-olanzapine containing regimens
b. Limitations
  i. Many trials conducted in Chinese population
  ii. Many studies do not follow standard of care using medications available in United States
COSTS & CONSIDERATIONS

I. Cost Effective Analysis (CEA) in CINV
   A. No current data to show olanzapine is a more cost effective option
   B. Data is needed to make fair comparison between regimens
   C. 5HT3 CEA comparison
      i. Palonosetron has higher acquisition costs compared to other agents
      ii. Palonosetron has lower use of rescue medications and outpatient services

II. Wholesale Acquisition Cost (WAC) Comparison
   A. Cost estimates via Lexicomp© – prices may vary

Table 4: Total Cost (WAC) of Standard of Care Therapy

<table>
<thead>
<tr>
<th>Standard of Care</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone (20 mg/5 mL)</td>
<td>$2.34</td>
</tr>
<tr>
<td>Dexamethasone Oral 4 mg (Bottle of 100)</td>
<td>$64.25</td>
</tr>
<tr>
<td>Palonosetron 0.25 mg IV</td>
<td>$481.20</td>
</tr>
<tr>
<td>Ondansetron 4mg/2mL Injection (x2)</td>
<td>$1.44</td>
</tr>
<tr>
<td>Fosaprepitant 150 mg</td>
<td>$308.35</td>
</tr>
<tr>
<td>Aprepitant (80mg and 125 mg [3 tablets])</td>
<td>$545.00</td>
</tr>
</tbody>
</table>
| **Total**                                    | **$1092.79** (using Aprepitant and Palonosetron)**

Table 5: Total Cost (WAC) of Olanzapine Containing Regimen

<table>
<thead>
<tr>
<th>Olanzapine Containing Regimen</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone (20 mg/5 mL)</td>
<td>$2.34</td>
</tr>
<tr>
<td>Olanzapine 10 mg (x 4)</td>
<td>$93.20</td>
</tr>
<tr>
<td>Palonosetron 0.25 mg IV</td>
<td>$481.20</td>
</tr>
</tbody>
</table>
| **Total**                                     | **$576.74**

CONCLUSIONS

I. CINV Anti-Emetic Overview
   A. There are many effective options available for patients undergoing chemotherapy
   B. Prevention is the best management strategy for CINV
   C. Choice of specific treatment
   D. Following available guidelines has shown to reduce incidence of relapse
   E. Pharmacist intervention
      i. Can play a significant role in education and management of patients
      ii. Education for continued antiemetic home regimen even if feeling okay
      iii. Maintenance of effective communication

II. Future Directions
   A. Clinicaltrials.gov - 4 relevant studies in progress pertaining to olanzapine use in CINV
      i. Two studies in pediatric population
   B. Cost effective analysis of olanzapine use compared to conventional regimens are needed
   C. Newer agents
      i. NEPA – time will show its worth

III. Final Recommendations
   A. Without more robust evidence, olanzapine should not be used first line for acute CINV over current first line recommendations accepted by all three major guidelines
      i. More cost-effective analysis data is needed to determine economic advantage over conventional regimen
B. Olanzapine has shown efficacy in CINV especially in delayed and breakthrough nausea and vomiting
   i. Potential niche in therapy
      1. Need for improved nausea control
      2. Patients who dislike or are intolerant to dexamethasone
      3. Patients who experience infusion reactions to fosaprepitant
      4. Palliative setting, chronic nausea, or refractory patients
      5. Potentially for cost saving purposes
C. Until further data is available, olanzapine should not be started initially in patients receiving HEC or MEC
   i. Reserve use for specific patient populations or failure of standard regimen

REFERENCES

35. Gralla RJ, et. al. Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology Antiemetic Guideline. 2013.
### APPENDIX

**Appendix A: Emetogenic Potential of IV Chemotherapy Agents**

<table>
<thead>
<tr>
<th>High Emetic Risk (&gt;90% frequency of emesis)</th>
<th>Moderate Emetic Risk (30% - 90% frequency of emesis)</th>
<th>Low Emetic Risk (10% – 30% frequency of emesis)</th>
<th>Minimal Emetic Risk (&lt;10% frequency of emesis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC (combination defined as either doxorubicin or epirubicin with cyclophosphamide) Dacarbazine</td>
<td>Carmustine &gt; 250 mg/m²</td>
<td>Amifostine ≤ 300 mg</td>
<td>Alemtuzumab</td>
</tr>
<tr>
<td>Carmustine &gt; 250 mg/m²</td>
<td>Doxorubicin &gt; 60 mg/m²</td>
<td>Methotrexate ≤ 50 mg/m²</td>
<td>Asparaginase</td>
</tr>
<tr>
<td>Epirubicin &gt; 90 mg/m²</td>
<td>Ifosfamide ≥ 10 g/m²</td>
<td>Methotrexate &gt; 10 million IU/m²</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Mechlorethamine</td>
<td>Dactinomycin</td>
<td>Bleomycin</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide ≥ 10 g/m²</td>
<td>Daunorubicin</td>
<td>Bleomycin</td>
</tr>
<tr>
<td></td>
<td>Cisplatin &gt; 50 mg/m²</td>
<td>Doxorubicin &lt; 60 mg/m²</td>
<td>Ofatumumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carmustine &gt; 250 mg/m²</td>
<td>Denileukin diftitox</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate ≥ 250 mg/m²</td>
<td>Bortezomib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clofarabine</td>
<td>Docetaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate &lt; 250 mg/m²</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclophosphamide ≤ 1500 mg/m²</td>
<td>Mitomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytarabine &gt; 200 mg/m²</td>
<td>Cladribine (2-chlorodeoxyadenosine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cytarabine &lt; 100 mg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cladribine (2-chlorodeoxyadenosine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Denileukin diftitox</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Dexamethone</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Fludarabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ifosfamide ≥ 10 g/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Methotrexate &gt; 10 million IU/m²</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Vinblastine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vinorelbine</td>
</tr>
</tbody>
</table>

*Causes delayed emesis*
### Appendix B: Multinational Association of Supportive Care in Cancer (MASCC) Antiemetic Guidelines 2013 – Summary of Acute Nausea and Vomiting Recommendations

<table>
<thead>
<tr>
<th>Emetic Risk Group</th>
<th>Antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>5HT₃ + DEX + [APR or FOS]</td>
</tr>
<tr>
<td>Anthracyline + Cyclophosphamide (AC)</td>
<td>5HT₃ + DEX + [APR or FOS]</td>
</tr>
<tr>
<td>Moderate (other than AC)</td>
<td>PALO + DEX</td>
</tr>
<tr>
<td>Low</td>
<td>DEX OR 5HT₃ OR DRA</td>
</tr>
<tr>
<td>Minimal</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>

*Note: If the NK1 receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT₃ receptor antagonist*

### Appendix C: Multinational Association of Supportive Care in Cancer (MASCC) Guidelines 2013 – Summary of Delayed Nausea and Vomiting Recommendations

<table>
<thead>
<tr>
<th>Emetic Risk Group</th>
<th>Antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>DEX + APR</td>
</tr>
<tr>
<td>Anthracyline + Cyclophosphamide (AC)</td>
<td>APR OR none</td>
</tr>
<tr>
<td>Moderate (other than AC)</td>
<td>DEX</td>
</tr>
<tr>
<td>Low</td>
<td>No routine prophylaxis</td>
</tr>
<tr>
<td>Minimal</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>

### Appendix D: The American Society of Clinical Oncology (ASCO) Antiemetic Guidelines 2011 update

#### Summary of Recommendations

**Highly emetogenic agents**

- The three-drug combination of:
  - NK1 receptor antagonist (days 1-3 for aprepitant; day 1 only for fosaprepitant)
  - 5-HT3 receptor antagonist (day 1 only),
  - dexamethasone (days 1-3 or 1-4)

**Moderately emetogenic agents**

- The two-drug combination of:
  - palonosetron (day 1 only)
  - dexamethasone (days 1-3)

  If palonosetron is not available, clinicians may substitute a first-generation 5-HT3 serotonin receptor antagonist:
  - Preferably granisetron or ondansetron. Limited evidence also supports adding aprepitant to the combination.

  Should clinicians opt to add aprepitant in patients receiving moderate-risk chemotherapy, any one of the 5-HT3 antagonists is appropriate.

**Low emetogenic agents**

- A single 8-mg dose of dexamethasone before chemotherapy is suggested.

**Minimally emetogenic**

- No antiemetic should be administered routinely before or after chemotherapy

**Adjunctive Medications**

- Lorazepam or diphenhydramine
  - NOT recommended as single-agent anti-emetic

**Complementary Therapy**

- No published randomized controlled trial data that met inclusion criteria are currently available to support a recommendation about such therapies

**High dose chemotherapy with stem-cell or bone marrow transplantation**

- A 5-HT₃ receptor antagonist combined with dexamethasone is suggested. Aprepitant should be considered, although evidence to support its use is limited
| Emesis or Nausea despite optimal prophylaxis | Clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; ascertain that the best regimen is being administered for the emetic risk; consider adding lorazepam or alprazolam to the regimen; and consider adding olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT3 antagonist or adding a dopamine antagonist to the regimen. |

| Anticipatory nausea and vomiting | Use of the most active antiemetic regimens appropriate for the chemotherapy being administered to prevent acute or delayed emesis is suggested. Such regimens should be used with initial chemotherapy, rather than assessing the patient’s emetic response with less effective treatment. If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and suggested. No change since the original guideline. |

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**Appendix E: National Comprehensive Cancer Network Guidelines (NCCN) 2014 High Emetic Risk Treatment Recommendation**

<table>
<thead>
<tr>
<th>HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY - ACUTE AND DELAYED EMESIS PREVENTION&lt;sup&gt;a,b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurokinin 1 antagonist containing regimen consisting of the following:</td>
</tr>
<tr>
<td>• Serotonin (5-HT3) antagonist (Choose one):&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Dolasetron 100 mg PO&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Granisetron 2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (max 1 mg) IV day 1&lt;sup&gt;f&lt;/sup&gt; or transdermal patch as 3.1 mg/24 h patch (containing 34.3 mg granisetron total dose) applied approximately 24-48 h prior to first dose of chemotherapy; maximum duration of patch is 7 days&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Ondansetron 16-24 mg PO or 8-16 mg IV day 1&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Palonosetron 0.25 mg IV day 1 (preferred)&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td>• Steroid (Choose one):&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Dexamethasone 12 mg PO or IV day 1, 8 mg PO daily days 2-4 (with aprepitant 125 mg)</td>
</tr>
<tr>
<td>• Dexamethasone 12 mg PO or IV day 1, 8 mg PO day 2, then 8 mg PO BID days 3 and 4 (with fosaprepitant 150 mg IV day 1)</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td>• Neurokinin 1 antagonist (Choose one):</td>
</tr>
<tr>
<td>• Aprepitant 125 mg PO day 1, 80 mg PO daily days 2-3</td>
</tr>
<tr>
<td>• Fosaprepitant 150 mg IV day 1 only</td>
</tr>
<tr>
<td>• ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 hours or every 6 hours days 1-4</td>
</tr>
<tr>
<td>• ± H2 blocker or proton pump inhibitor</td>
</tr>
</tbody>
</table>

**OR**

• Olanzapine-containing regimen<sup>k</sup>

• Olanzapine 10 mg PO days 1-4
• Palonosetron 0.25 mg IV day 1
• Dexamethasone 20 mg IV day 1
• ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 hours or every 6 hours days 1-4
• ± H2 blocker or proton pump inhibitor
### Appendix F: National Comprehensive Cancer Network Guidelines (NCCN) 2014 Moderate Emetic Risk Treatment Recommendation

#### Moderate Emetic Risk Intravenous Chemotherapy - Emesis Prevention\(^{d,o}\)

**DAY 1**

- Start before chemotherapy\(^{c,d}\)
- 5HT3 antagonist + steroid ± NK1 antagonist regimen consisting of the following:
  - Serotonin (5-HT3) antagonist (category 1) (Choose one)\(^{5,7}\)
    - Dolasetron 100 mg PO
    - Granisetron 2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (max 1 mg) IV daily or
      transferd patch as 3.1 mg/24 h patch (containing 34.3 mg granisetron total dose) applied approximately 24 to 48 h prior to first dose of chemotherapy; maximum duration of patch is 7 days
    - Ondansetron 8-16 mg PO daily or 8-16 mg IV\(^n\)
    - Palonosetron 0.25 mg IV (preferred)\(^{7}\)
  - Steroid\(^{1}\)
    - Dexamethasone 12 mg PO or IV
  - Neurokinin 1 antagonist (Choose one; for selected patients, where appropriate)\(^{7}\)
    - Aprepitant 125 mg PO
    - Fosaprepitant 150 mg IV
- ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN
- ± H2 blocker or proton pump inhibitor

**OR**

- Olanzapine-containing regimen\(^k\)
  - Olanzapine 10 mg PO
  - Palonosetron 0.25 mg IV
  - Dexamethasone 20 mg IV
- ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN
- ± H2 blocker or proton pump inhibitor

**DAYS 2 and 3**

- Serotonin (5-HT3) antagonist monotherapy (unless palonosetron used on Day 1) (Choose one)\(^{5,7}\)
  - Dolasetron 100 mg PO daily
  - Granisetron 1-2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (max 1 mg) IV
  - Ondansetron 8 mg PO BID or 16 mg PO daily or 8-16 mg IV\(^n\)
- Steroid monotherapy\(^{1}\)
  - Dexamethasone 8 mg PO or IV daily
- Aprepitant used day 1: Aprepitant 80 mg PO ± dexamethasone 8 mg PO or IV daily
- Fosaprepitant used day 1: ± dexamethasone 8 mg PO or IV daily
- ± Lorazepam 0.5-2 mg PO or IV or sublingual either every 4 or every 6 h PRN
- ± H2 blocker or proton pump inhibitor


#### Low and Minimal Emetic Risk Intravenous Chemotherapy - Emesis Prevention\(^{d,o}\)

**Low**

- Start before chemotherapy\(^{c,d}\)
  - Repeat daily for multiday doses of chemotherapy\(^{d,e}\)
  - Dexamethasone 12 mg PO or IV daily\(^i\)
  - Metoclopramide 10-40 mg PO or IV and then either every 4 or every 6 h PRN\(^n\)
  - Prochlorperazine 10 mg PO or IV and then every 6 h PRN (maximum 40 mg/d day)\(^n\)
  - Serotonin (5-HT3) antagonist (Choose one)\(^{5,6,7}\)
    - Dolasetron 100 mg PO daily
    - Granisetron 2 mg PO daily or 1 mg PO BID
    - Ondansetron 16-24 mg PO daily
- ± Lorazepam, 0.5-2 mg PO or IV either every 4 or every 6 h PRN
- ± H2 blocker or proton pump inhibitor

**Minimal**

- No routine prophylaxis