Chemotherapy-Induced Nausea and Vomiting (CINV): Perceptions, Mechanisms, and Treatment Guidelines

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Mayo Clinic College of Medicine

Chemotherapy-Induced Emesis Classification

- **Acute** (0-24 hr after chemotherapy)
- **Delayed** (24-120 hr after chemotherapy)
  - May last up to 6 days
  - Incidence without treatment 20%-90%
- **Anticipatory** (prior to chemotherapy)
Chemotherapy-Induced Emesis: Risk Factors

• Patient-related risk factors1:
  – Younger age (<50 years)
  – Female gender
  – No/minimal prior history of alcohol use
  – Prior CINV
  – Anxiety
  – Hx of morning sickness or motion sickness
  – Other medical conditions (e.g. intest. obstr., brain mets)

• Treatment-related risk factors1,2:
  – High emetogenicity of chemotherapy agents/regimens
  – High drug dose, rapid infusion rate

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The Four Emetic Risk Groups of Chemotherapeutic Drugs (ASCO/MASCC/NCCN)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>Risk in nearly all patients (&gt; 90%)</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Risk in 30% to 90% of patients</td>
</tr>
<tr>
<td>LOW</td>
<td>Risk in 10% to 30% of patients</td>
</tr>
<tr>
<td>MINIMAL</td>
<td>Fewer than 10% at risk</td>
</tr>
</tbody>
</table>

Patient Perceptions of the Most Severe Side Effects of Cancer Chemotherapy

<table>
<thead>
<tr>
<th>Rank</th>
<th>1983¹</th>
<th>1993²</th>
<th>1995³</th>
<th>1999⁴</th>
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<tbody>
<tr>
<td>1.</td>
<td>Vomiting</td>
<td>Nausea</td>
<td>Nausea</td>
<td>Nausea</td>
</tr>
<tr>
<td>2.</td>
<td>Nausea</td>
<td>Constantly tired</td>
<td>Loss of hair</td>
<td>Loss of hair</td>
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<tr>
<td>3.</td>
<td>Loss of hair</td>
<td>Loss of hair</td>
<td>Vomiting</td>
<td>Constantly tired</td>
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<tr>
<td>4.</td>
<td>Thought of coming for treatment</td>
<td>Effect on family</td>
<td>Vomiting</td>
<td>Vomiting</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>
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</tbody>
</table>


Moderately Emetogenic Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Patient Experience</th>
<th>MD/RN Prediction</th>
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<tbody>
<tr>
<td>Acute Nausea</td>
<td>24</td>
<td>37</td>
</tr>
<tr>
<td>Acute Vomiting</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Delayed Nausea</td>
<td>24</td>
<td>52</td>
</tr>
<tr>
<td>Delayed Vomiting</td>
<td>15</td>
<td>28</td>
</tr>
</tbody>
</table>

International observational study 298 pts, 14 practices.

Highly Emetogenic Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Patient Experience</th>
<th>MD/RN Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Nausea</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Acute Vomiting</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Delayed Nausea</td>
<td>39</td>
<td>60</td>
</tr>
<tr>
<td>Delayed Vomiting</td>
<td>22</td>
<td>50</td>
</tr>
</tbody>
</table>

International observational study 298 pts, 14 practices.

Evolution of Anti-emetic Agents Reflects Advances in Neuropharmacology of Emesis

First NK₁ receptor antagonist (Substance P)
First 5-HT₃ receptor antagonist (serotonin)
Further understanding of delayed emesis
Combination of Dex and 5-HT₃ receptor antagonist
High-dose metoclopramide (serotonin)
Combination regimens
Predictive variables identified

Phenothiazines (Dopamine,D₂)

1960s 1970s 1980s 1990s 2000s

Dex=dxamethasone.
Proposed Pathophysiology of CINV

- **Central** mechanism
  - Chemotherapeutic agent activates the CTZ.

- **Peripheral** mechanism
  - Chemotherapeutic agent causes irritation and damage to GI mucosa, resulting in the release of neurotransmitters.

- **Combined** mechanism
  - Some chemotherapeutic agents activate both the central and peripheral mechanisms.

Proposed Pathophysiology of CINV

- **Central** mechanism
  - Chemotherapeutic agent activates the CTZ.
  - Activated CTZ invokes release of various neurotransmitters, which stimulates vomiting center.

- **Peripheral** mechanism
  - Chemotherapeutic agent causes irritation and damage to GI mucosa, resulting in the release of neurotransmitters.
  - Activated receptors send signals to vomiting center via vagal afferents.

- **Combined** mechanism
  - Some chemotherapeutic agents activate both the central and peripheral mechanisms.

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Emesis and Cancer Treatment

Approach to the Problem

In controlling emesis, the strategy is prevention rather than treatment
Neurotransmitters/Treatments Associated With Emesis

Emetic reflex

Dopamine/DA RAs
Histamine
Endorphins
Acetylcholine
GABA
Cannabinoids

Substance P/NK-1 RAs
Serotonin/5-HT3 RAs

DA = dopamine; GABA = gamma-aminobutyric acid; NK = neurokinin; RAs = receptor antagonists.

Antiemetic Arsenal

- **5-HT3-RA**
  - Ondansetron PO 8-24 mg, IV 8 mg
  - Granisetron PO 1-2 mg, IV 1 mg
  - Dolasetron PO 100-200 mg, IV 100 mg
  - Palonosetron IV 0.25 mg

- **Corticosteroids**
  - Dexamethasone PO/IV 10-20 mg
  - Delayed emesis: 8 mg BID

- **NK1-RA**
  - Aprepitant PO 125 mg d1, 80 mg d2,3

- **Dopamin-RA**
  - Prochlorperazine PO/IV 5-20 mg q6h
  - Metoclopramide Acute E: 2-3 mg/kg
  - Delayed E: 20-40 mg BID-QID

- **Benzodiazepines**
  - Lorazepam PO/IV 1-2 mg

- **Cannabinoid**
  - Dronabinol PO 5-20 mg q3-6h
Antiemetic Arsenal

- **5-HT\textsubscript{3}-RA**
  - Ondansetron
  - Granisetron
  - Dolasetron
  - Palonosetron
- **Corticosteroids**
  - Dexamethasone
- **NK1-RA**
  - Aprepitant
  - Fosaprepitant
- **Dopamin-RA**
  - Prochlorperazine
  - Metoclopramide
- **Benzodiazepines**
- **Cannabinoid**

Serotonin and 5-HT\textsubscript{3} Receptors
Serotonin and 5-HT$_3$ Receptor Pathway

- First recognized with high-dose metoclopramide.$^1$
- Introduction of 5-HT$_3$ antagonists offered an improved treatment option.
  - Effective in acute vomiting, variable efficacy for delayed events.$^2$
  - Usually used with dexamethasone.$^2$
- Primary mechanism of action appears to be peripheral.$^3,^4$


Half-Life and Binding Affinities of 5-HT$_3$ Receptor Antagonists

<table>
<thead>
<tr>
<th>5-HT$_3$ Antagonist</th>
<th>Half-Life (h)</th>
<th>Binding Affinity (pKi)*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palonosetron (Aloxi®)</td>
<td>40.0$^1$</td>
<td>10.45$^5$</td>
</tr>
<tr>
<td>Ondansetron (Zofran®)</td>
<td>4.0$^2$</td>
<td>8.39$^5$</td>
</tr>
<tr>
<td>Dolasetron (Anzemet®)</td>
<td>7.3$^3$</td>
<td>7.60$^6$</td>
</tr>
<tr>
<td>Granisetron (Kytril®)</td>
<td>9.0$^4$</td>
<td>8.91$^5$</td>
</tr>
<tr>
<td>Tropisetron (Navoban®)</td>
<td>8.0$^5$</td>
<td>8.7$^5$</td>
</tr>
</tbody>
</table>

*Log-scale.
†In vitro data; clinical significance has not been established.

Palonosetron has a binding affinity at least 30-fold higher than other 5-HT$_3$ RA.

Protection from cisplatin-induced emesis by various 5-HT3 antagonists. Reprinted, with permission, from Grunberg.

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**Palonosetron vs Ondansetron in MEC – Complete Response: Acute and Delayed Emesis**

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Complete Response (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute: 0-24 (Day 1)</td>
<td>Palonosetron 0.25 mg IV (n=189)</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 32 mg IV (n=185)</td>
</tr>
<tr>
<td>Delayed: 24-120 (Days 2-5)</td>
<td>Palonosetron 0.25 mg IV (n=189)</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 32 mg IV (n=185)</td>
</tr>
<tr>
<td>Overall: 0-120 (Days 1-5)</td>
<td>Palonosetron 0.25 mg IV (n=189)</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 32 mg IV (n=185)</td>
</tr>
</tbody>
</table>

- **p<0.025 (Fisher’s exact test)**

- 72% female; mean age 56 years
- 41% chemotherapy-naïve
- Majority receiving cyclophosphamide and/or doxorubicin combination MEC for breast cancer
- No concomitant dexamethasone pretreatment

Palonosetron vs Ondansetron in MEC – Complete Response: Acute and Delayed Emesis

Palonosetron 0.25 mg IV (n=189)

Ondansetron 32 mg IV (n=185)

Time (hr)
0
20
40
60
80
100

Acute: 0-24 (Day 1)

Delayed: 24-120 (Days 2-5)

Overall: 0-120 (Days 1-5)

Complete Response (No Emesis, No Rescue) (% of Patients)*

81.0
68.6
74.1
55.1
69.3
50.3

*p<0.025 (Fisher’s exact test)

• No concomitant dexamethasone pretreatment


Palonosetron vs Ondansetron in MEC – No Nausea: Daily

Palonosetron 0.25 mg IV (n=189)

Ondansetron 32 mg IV (n=185)

Nausea-Free (% of Patients)*

60.3
56.8
59.8
64.6
72.5
78.3

*p < 0.05 (Chi-Square test)

• 72% female; mean age 56 years
• 41% chemotherapy-naïve
• Majority receiving cyclophosphamide and/or doxorubicin combination MEC for breast cancer
• No concomitant dexamethasone pretreatment

Palonosetron vs Ondansetron in MEC – No Nausea: Daily

*No concomitant dexamethasone pretreatment

\[ p < 0.05 \text{ (Chi-Square test)} \]


PALO-99-03

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Palonosetron vs Ondansetron in MEC – Time to Treatment Failure

*\( p=0.0003 \)


PALO-99-03

---

72% female; mean age 56 years
41% chemotherapy-naïve
Majority receiving cyclophosphamide and/or doxorubicin combination MEC for breast cancer
No concomitant dexamethasone pretreatment

Time to Treatment Failure: time to first emetic episode or use of rescue medication.
Palonosetron vs Ondansetron in MEC – Time to Treatment Failure

Time to Treatment Failure: time to first emetic episode or use of rescue medication.

No concomitant dexamethasone pretreatment


Dexamethasone
Dexamethasone Meta-analysis

- Objective: Review efficacy of dexamethasone for acute and delayed CINV
- 1,200 literature citations screened
- 32 studies with 42 pertinent comparisons analyzed
- 5,613 patients total
- Conclusion: Dexamethasone is effective for acute and delayed emesis

Acute Emesis: Dexamethasone + 5-HT₃ Antagonist

<table>
<thead>
<tr>
<th>Study author</th>
<th>5-HT₃ + Dex</th>
<th>5-HT₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams</td>
<td>11%</td>
<td>25%</td>
</tr>
<tr>
<td>Carmichael</td>
<td>15%</td>
<td>24%</td>
</tr>
<tr>
<td>Heron</td>
<td>34%</td>
<td>44%</td>
</tr>
<tr>
<td>Hesketh</td>
<td>39%</td>
<td>54%</td>
</tr>
<tr>
<td>IGAR</td>
<td>7%</td>
<td>28%</td>
</tr>
<tr>
<td>Joss</td>
<td>24%</td>
<td>44%</td>
</tr>
<tr>
<td>Latrelle</td>
<td>36%</td>
<td>61%</td>
</tr>
<tr>
<td>Roila</td>
<td>9%</td>
<td>36%</td>
</tr>
<tr>
<td>Smith</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Smyth</td>
<td>42%</td>
<td>58%</td>
</tr>
<tr>
<td>Sorbe</td>
<td>25%</td>
<td>60%</td>
</tr>
</tbody>
</table>


Optimal Dosing of Dexamethasone in Highly to Moderately Emetogenic Chemotherapy

All patients received ondansetron 8 mg IV in combination with dexamethasone.


Substance P and NK₁ Receptors
Substance P and NK$_1$ Receptor Pathway

- Relays noxious sensory information to the brain (ie, modulates nociception).\textsuperscript{1}
- High density of substance P/NK$_1$ receptors located in brain regions implicated in the emetic reflex.\textsuperscript{2,3}
- Primary mechanism of NK$_1$ receptor blockade action appears to be central.\textsuperscript{4}
  - Effective for both acute and \textbf{delayed} events.
  - Augments antiemetic activity of a 5-HT$_3$ receptor antagonist and corticosteroid.

\textsuperscript{1} DeVane CL. *Pharmacotherapy*. 2001;21:1061–1069.
\textsuperscript{3} Saria A. *Eur J Pharmacol*. 1999;375:51-60.
\textsuperscript{4} Hesketh PJ. *Support Care Cancer*. 2001;9:350-354.

Substance P and NK Receptors

- Substance P is one of three tachykinins identified to date
  - Substance P, NK\textsubscript{A}, NK\textsubscript{B}
- Binds to neurokinin (NK) receptors
  - Three subtypes isolated: NK\textsubscript{1}, NK\textsubscript{2} and NK\textsubscript{3/3B}
- Substance P has affinity for NK\textsubscript{1} receptors
  - Possibly implicated in emesis, depression, asthma, bladder irritability, inflammatory bowel disease, functional GI diseases
- Substance P induces emesis in ferrets and dogs
- Blocking NK1-receptor decreases acute + \textbf{delayed} emesis

Aprepitant in Patients Receiving Cisplatin ≥70 mg/m²: Phase III Trials 052 and 054

### Group Day 1
- **Aprepitant**
  - O = ondansetron IV
  - D = dexamethasone po
  - A = aprepitant po
  - Day 1:
    - 32 mg
    - 12 mg
    - 125 mg

### Days 2-3
- D = dexamethasone po
- A = aprepitant po
- 8 mg
- 80 mg

### Day 4
- D = dexamethasone po
- 8 mg

O = ondansetron IV
A = aprepitant po
D = dexamethasone po
P = placebo po


### Aprepitant in Patients Receiving Cisplatin: Trial 052 + 054 Complete Response Rates

- **Acute: 0-24 (Day 1)**
  - *p < 0.001.
  - Aprepitant (n=520): 86%
  - Standard (n=523): 73%

- **Delayed: 24-120 (Days 2-5)**
  - *p < 0.001.
  - Aprepitant (n=520): 72%
  - Standard (n=523): 52%

- **Overall: 0-120 (Days 1-5)**
  - *p < 0.001.
  - Aprepitant (n=520): 68%
  - Standard (n=523): 47%

Complete response (CR): no emesis and no rescue medication.

Time Course of Emesis Following Cisplatin With a 5-HT₃ Antagonist or Aprepitant


Do you need 3 days of aprepitant?
Phase III randomized double-blind study of single-dose fosaprepitant for prevention of cisplatin-induced nausea and vomiting.

Grunberg S et al. JCO 2011;29:1495-1501

<table>
<thead>
<tr>
<th>Study Drug Schedule</th>
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<tbody>
<tr>
<td><strong>Fosaprepitant regimen</strong></td>
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<tr>
<td>Day 1</td>
</tr>
<tr>
<td>Fosaprepitant 150 mg IV</td>
</tr>
<tr>
<td>Dexamethasone 12 mg PO</td>
</tr>
<tr>
<td>Ondansetron 32 mg IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aprepitant regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
</tr>
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</tr>
<tr>
<td>Dexamethasone 12 mg PO</td>
</tr>
<tr>
<td>Ondansetron 32 mg IV</td>
</tr>
</tbody>
</table>
Complete response (CR) and no vomiting (NV) by phase.

Grunberg S et al. JCO 2011;29:1495-1501

Phase III randomized double-blind study of single-dose fosaprepitant for prevention of cisplatin-induced nausea and vomiting.

Steven M. Grunberg, MD, et al

Grunberg S et al. JCO 2011;29:1495-1501
**Venous toxicity**

Infusion site adverse events such as pain, erythema, induration, and thrombophlebitis

- Noted to be infrequent
- More frequently with fosaprepitant, compared to aprepitant (2.7% vs. 0.3%, respectively)

Grunberg S et al. JCO 2011;29:1495-1501

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**Fosaprepitant-induced Phlebitis**

**Mayo Experience with AC**

- 148 patients analyzed
  - 98 patients initially received fosaprepitant
  - 44 received aprepitant
- Venous toxicity
  - 33.7% with fosaprepitant
  - 2.3% with aprepitant
  - All with peripheral IV access

Leal et al
### Guidelines

ASCO 2006 Antiemetic Consensus Guidelines

<table>
<thead>
<tr>
<th>Emetic Risk Group</th>
<th>Risk (% of Patients)</th>
<th>Acute Prevention</th>
<th>Delayed Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (+AC)</td>
<td>&gt;90%</td>
<td>5-HT₃ + DEX + aprepitant</td>
<td>DEX + aprepitant</td>
</tr>
<tr>
<td>Moderate (excluding AC combinations)</td>
<td>30-90%</td>
<td>5-HT₃ + DEX</td>
<td>Oral DEX (preferred) 5-HT₃ (alternate)</td>
</tr>
<tr>
<td>Low</td>
<td>10-30%</td>
<td>DEX (20 mg)</td>
<td>No preventive measures</td>
</tr>
<tr>
<td>Minimal</td>
<td>&lt; 10%</td>
<td>No preventive measures</td>
<td>No preventive measures</td>
</tr>
</tbody>
</table>

DEX, dexamethasone; AC, anthracycline-cyclophosphamide.

Adapted from Kris et al, JCO 2006.
ASCO 2011 Antiemetic Consensus Guidelines –Highly Emetogenic

- Recommendation is similar to the 2006 update
- Reclassification of AC as highly emetogenic
  - NK1 receptor antagonist
    - Days 1-3 for aprepitant
    - Day 1 only for fosaprepitant
  - A 5-HT3 receptor antagonist (day 1 only)
  - Dexamethasone (days 1-3 or 1-4)

Adapted from Basch et al, JCO Nov 1 2011: 4189-4198..

ASCO 2011 Antiemetic Consensus Guidelines –Moderately Emetogenic

- Palonosetron (day 1 only)
- Dexamethasone (days 1-3)
  - If no palonosetron available, substitute first-generation 5-HT3RA (granisetron or ondansetron)
  - Limited evidence supports adding aprepitant
    - If aprepitant used, any 5-HT3 antagonist is OK.

Adapted from Basch et al, JCO Nov 1 2011: 4189-4198.
ASCO 2011 Antiemetic Consensus Guidelines –Low Emetogenic

• Single 8-mg dose of dexamethasone before chemotherapy

• Similar to 2006 recommendation

ASCO 2011 Antiemetic Consensus Guidelines –Minimally Emetogenic

• No routine antiemetic before or after chemotherapy

• Same as 2006 guideline
**SUMMARY ACUTE NAUSEA AND VOMITING**

<table>
<thead>
<tr>
<th>EMETIC RISK GROUP</th>
<th>ANTIEMETICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>5HT3 + DEX + APR</td>
</tr>
<tr>
<td>Anthracycline + Cyclophosphamide (AC)</td>
<td>5HT3 + DEX + APR</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 5HT3 receptor antagonist.*

## SUMMARY DELAYED NAUSEA AND VOMITING

<table>
<thead>
<tr>
<th>EMETIC RISK GROUP</th>
<th>ANTIEMETICS</th>
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</thead>
<tbody>
<tr>
<td>High</td>
<td>DEX + APR</td>
</tr>
<tr>
<td>Anthracycline + Cyclophosphamide (AC)</td>
<td>APR</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>
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### How Well Do Anti-emetics Work for Treatment of CINV?
Can Something Else be Used Instead of Aprepitant?

Olanzapine

Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting (CINV): A randomized phase III trial.

Rudy Navari, et al
South Bend, IN

ASCO 2010, Abstract # 9020
Study design basics

- Sixty-one chemotherapy naïve patients randomized to the OLN or APR regimen
- Out-patient clinic

<table>
<thead>
<tr>
<th>Antiemetic Regimens</th>
<th>OLN</th>
<th>APR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin (&gt;70 mg/m²):</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Doxorubicin (&gt;50 mg/m²):</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatments

**OLANZAPINE:**
- Day 1:
  - Olanzapine, 10 mg oral
  - Palonosetron, 0.25 mg, IV
  - Dexamethasone 20 mg, IV
- Days 2-4:
  - Olanzapine, 10 mg/day, oral

**APREPITANT**
- Day 1:
  - Aprepitant, 125 mg oral
  - Palonosetron, 0.25 mg, IV
  - Dexamethasone 12 mg, IV
- Days 2-4:
  - Aprepitant, 80 mg/day, oral, days 2-3
  - Dexamethasone, 4 mg BID, oral, days 2-4
## No Nausea (%)

<table>
<thead>
<tr>
<th>Time Period (hours)</th>
<th>OLN (n=31)</th>
<th>APR (n=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (0 – 24):</td>
<td>90%</td>
<td>87%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Delayed (24 – 120):</td>
<td>68%</td>
<td>37%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Overall (0 – 120):</td>
<td>68%</td>
<td>37%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

## Why olanzapine might perform well against nausea

- Impact on multiple receptors
- Anxiolytic effects as well as anti-emetic
Megestrol Acetate

Antiemetic activity of megestrol acetate in patients receiving chemotherapy

Zang, et al
Sichuan Province, 610041, China.

PATIENTS AND METHODS

• Patients receiving chemotherapy
• Randomized to receive, days -1 to 4
  – Megestrol acetate 320 mg PO
  – Placebo
• All also received, on day 1
  – Granisetron 3 mg IV
  – Metoclopramide 20 mg IM
• Crossover design during two consecutive cycles

RESULTS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Megestrol</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Protection</td>
<td>45%</td>
<td>17%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CP, acute phase</td>
<td>85%</td>
<td>72%</td>
<td>0.011</td>
</tr>
<tr>
<td>CP, delayed emesis</td>
<td>49%</td>
<td>18%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
### The Cost of Progress

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Non-Medicare</th>
<th>Medicare</th>
<th>Medicare Pt responsibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granisetron 1 mg Tab</td>
<td>$8</td>
<td>$0.77</td>
<td>$0.15</td>
</tr>
<tr>
<td>Dexamethasone 4 mg Tab</td>
<td>$1</td>
<td>$1</td>
<td>$0.2</td>
</tr>
<tr>
<td>Palonosetron 0.25 mg IV</td>
<td>$389 + $93 admin fee</td>
<td>$189 + $24 admin fee</td>
<td>$43</td>
</tr>
<tr>
<td>Aprepitant Tri-Pack</td>
<td>$684</td>
<td>$341</td>
<td>$68</td>
</tr>
<tr>
<td>Fosaprepitant 150 mg IV</td>
<td>$450 + $93 admin fee</td>
<td>$258 + $24 admin fee</td>
<td>$56</td>
</tr>
</tbody>
</table>