Tripplet regimen for CINV in HEC

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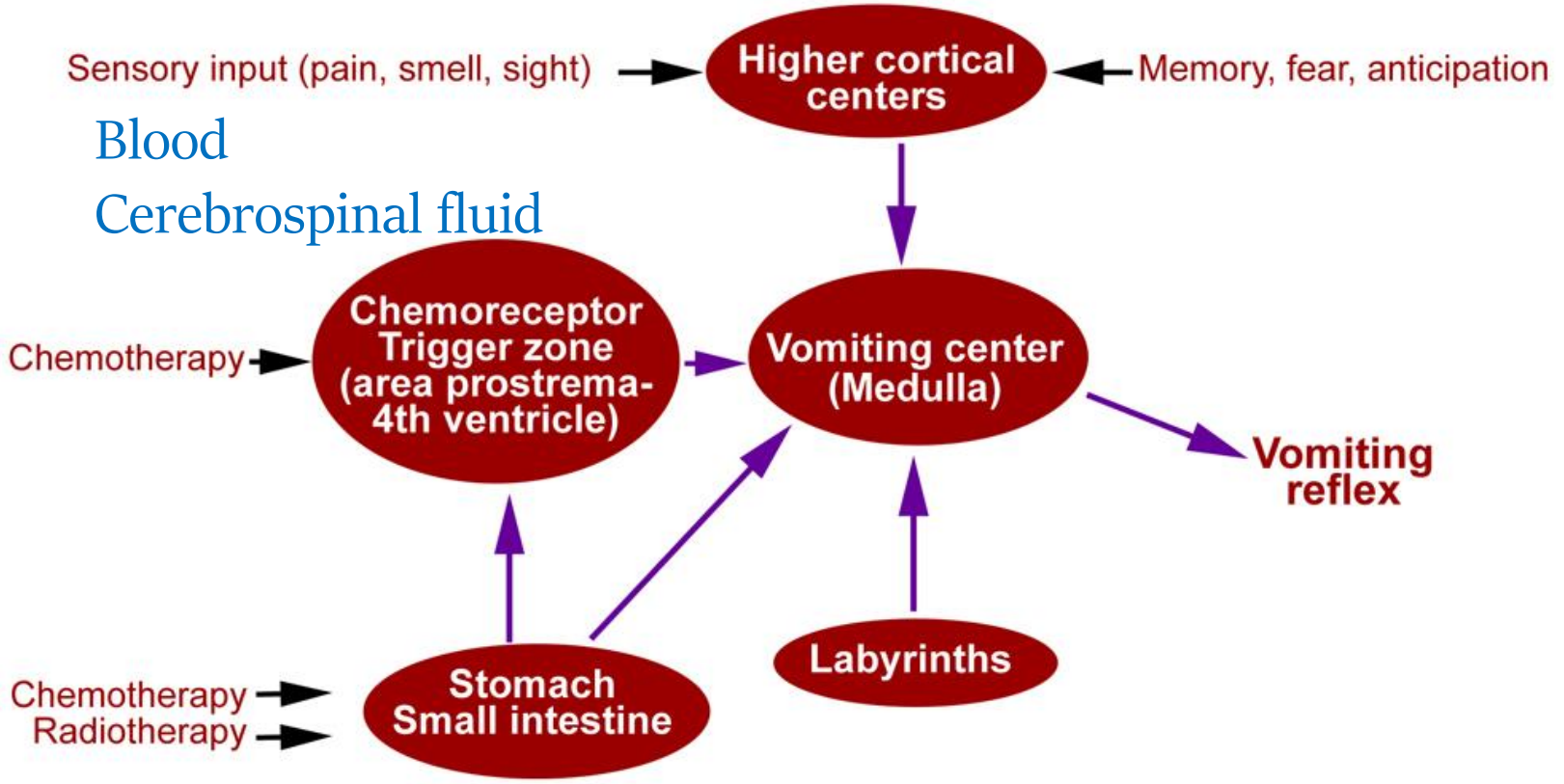
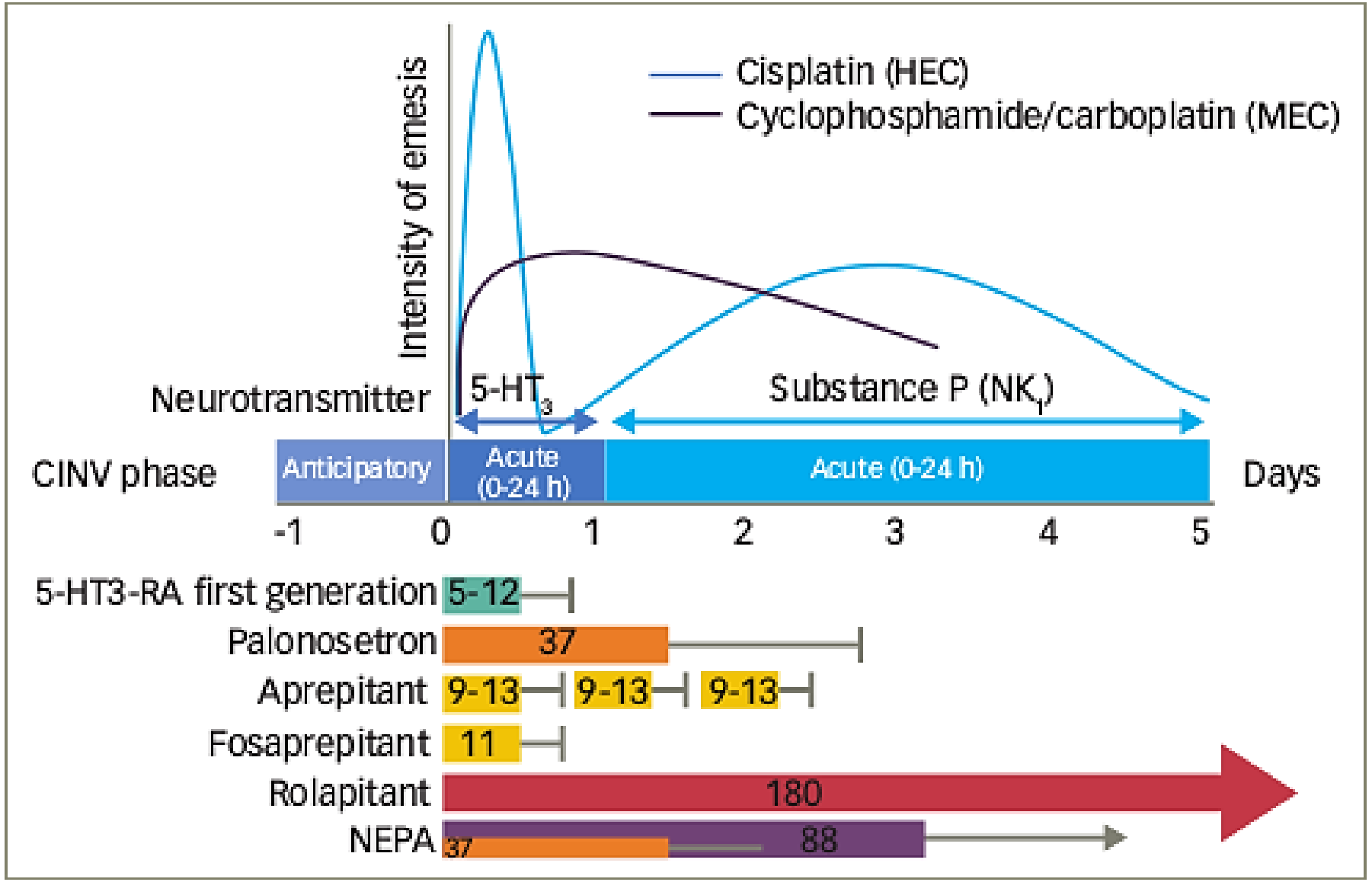
Vomiting Pathway





Numbers are shown as mean half-life (h). 5-HT3 RA = 5-hydroxytryptamine type 3 receptor antagonist; CINV = chemotherapy-induced nausea and vomiting; HEC = highly emetic chemotherapy; MEC = moderate emetic chemotherapy; NEPA = netupitant/palonosetron; NK-1 = neurokinin 1.

Principles for the Prevention and Management of CINV

- Evaluate each patient individually
- Evaluate the emetogenic potential and pattern of the chemotherapeutic regimen to be given
- Antiemetics are most effective when given prophylactically
  - Begin therapy at least 30 minutes prior to chemotherapy
  - Administer around-the-clock until chemotherapy is complete and provide PRN agents for breakthrough N/V
  - Provide patients with additional PRN anti-emetics to take home after chemotherapy. Generally an agent with a different mechanism of action should be provided. Some patients may require multiple mechanisms of action for control.
  - Nausea is more challenging to control than emesis

Management: Highly emetogenic chemotherapy

- **ASCO**
- **Cisplatin and other agents**
  - To prevent ACUTE CINV: all patients should be offered a 4-drug combination of a NK1 antagonist plus serotonin antagonist plus dexamethasone and olanzapine.
  - To prevent DELAYED CINV: olanzapine should be continued on days 2-4 along with dexamethasone.
- **Anthracycline combined with cyclophosphamide**
  - To prevent ACUTE CINV: all patients should be offered a 4-drug combination of a NK1 antagonist plus serotonin antagonist plus dexamethasone and olanzapine.
  - To prevent DELAYED CINV: olanzapine should be continued on days 2-4 alone.

Management: Highly emetogenic chemotherapy

- MASCC guidelines
  - Patients receiving highly emetogenic chemotherapy (outside of AC)
    - Acute ; a three-drug regimen including a NK1 antagonist, serotonin antagonist and dexamethasone.
    - Delay ; Dexamethasone should be given on days 2-4. If aprepitant 125 mg was given on day 1, either aprepitant and dexamethasone or metoclopramide and dexamethasone
  - AC for breast cancer was reclassified as a special category within highly emetogenic due to a differing delayed phase.
    - Acute: NK1 antagonist plus a serotonin antagonist plus a corticosteroid
      - 1. DO NOT reduce dose or change schedules of any corticosteroids that are part of the treatment regimen (such as prednisone in CHOP)
    - Delayed: aprepitant alone (if given aprepitant 125 mg on day 1)

Management: Highly emetogenic chemotherapy

- NCCN
  - NK1 antagonist plus serotonin antagonist plus dexamethasone for acute CINV with continuation of dexamethasone on days 2-4 for delayed CINV
  - Olanzapine plus serotonin antagonist plus dexamethasone for acute CINV with continuation of olanzapine on days 2-4
  - 4-drug combination with NK1 antagonist plus serotonin antagonist plus dexamethasone plus olanzapine for acute CINV with continuation of dexamethasone and olanzapine on days 2-4 for delayed CINV

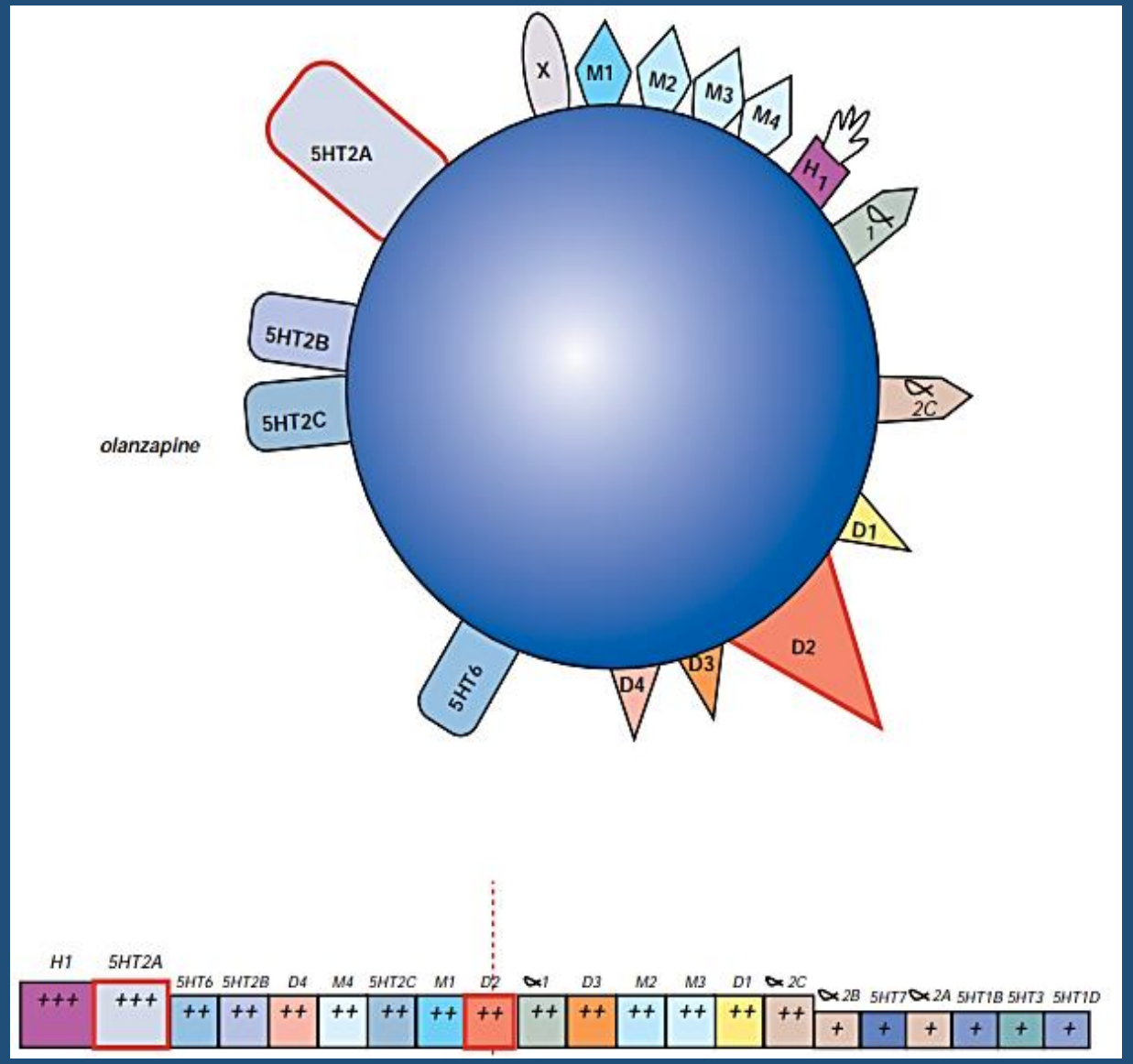
HIGH EMETIC RISK PARENTERAL CHEMOTHERAPY — ACUTE AND DELAYED EMESIS PREVENTION[h,i,j,k,l]

DAY 1: Select option A, B, or C (order does not imply preference) All are category 1, start before chemotherapy:[j]	DAYS 2, 3, 4:
A • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[m] ▸ Fosaprepitant 150 mg IV once ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[n] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[n] ▸ Rolapitant 180 mg PO once[o] • 5-HT3 RA (choose one):[p,q] ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once,[r] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of chemotherapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[s,t]	A • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • Dexamethasone 8 mg[s,t] PO/IV daily on days 2, 3, 4
B • Olanzapine 5–10 mg PO once[u] • Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[s,t]	B • Olanzapine 5–10 mg PO daily on days 2, 3, 4[u]
C • Olanzapine 5–10 mg PO once[u,v,w] • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[m] ▸ Fosaprepitant 150 mg IV once ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[n] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[n] ▸ Rolapitant 180 mg PO once[o] • 5-HT3 RA (choose one):[p,q] ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once,[r] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of chemotherapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[s,t]	C • Olanzapine 5–10 mg PO daily on days 2, 3, 4[u] • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • Dexamethasone 8 mg[s,t] PO/IV daily on days 2, 3, 4

Olanzapine

- Potently blocks many subtypes of dopaminergic, serotonergic, histaminergic and muscarinic receptors, some of which play roles in CINV, albeit to a lesser extent than well-known subtypes dopamine2 and 5-HT3

- Common side effect
  - Fatigue
  - Drowsiness
  - Sleep disturbance
- Caution with Elderly
  - Data suggest 5 mg dose



Supportive Care in Cancer
https://doi.org/10.1007/s00520-018-4400-1

ORIGINAL ARTICLE

Cost-effectiveness analysis of olanzapine-containing antiemetic therapy for managing highly emetogenic chemotherapy in Southeast Asia: a multinational study

Results Compared to doublet antiemetic regimen, addition of olanzapine resulted in incremental QALY of 0.0022–0.0026 with cost saving of USD 2.98, USD 27.71, and USD 52.20 in Thailand, Malaysia, and Indonesia, respectively. Compared to triplet antiemetic regimen, switching aprepitant to olanzapine yields additional 0.0005 QALY with cost saving of USD 60.91 in Singapore. The probability of being cost-effective at a cost-effectiveness threshold of 1 GDP/capita varies from 14.7 to 85.2% across countries.

Conclusion The use of olanzapine as part of standard antiemetic regimen is cost-effective for the prevention of CINV in patients receiving HEC in multiple SEA countries.

Chanthawong S, et al. Support Care Cancer. 2019;27(3):1109-1119.

ด่วนที่สุด

ที่ กค ๐๔๑๖.๒/ว ๔๒๔

กรมบัญชีกลาง
ถนนพระรามที่ ๖ กทม. ๑๐๔๐๐

๒๐ กันยายน ๒๕๖๑

เรื่อง หลักเกณฑ์การเบิกจ่ายค่ารักษาพยาบาลสำหรับผู้ป่วยโรคมะเร็งและโลหิตวิทยาซึ่งจำเป็นต้องใช้ยาที่มีค่าใช้จ่ายสูง (เพิ่มเติม)

เรียน ผู้อำนวยการสถานพยาบาลของทางราชการ

อ้างถึง ๑. หนังสือกรมบัญชีกลาง ด่วนที่สุด ที่ กค ๐๔๑๖.๒/ว ๓๔ ลงวันที่ ๑๙ มกราคม ๒๕๖๑
๒. หนังสือกรมบัญชีกลาง ที่ กค ๐๔๑๖.๒/ว ๑๕๖ ลงวันที่ ๒๓ มีนาคม ๒๕๖๑

สิ่งที่ส่งมาด้วย ๑. แนวทางกำกับการเบิกจ่ายค่ายา Imatinib, Nilotinib, Dasatinib, Bortezomib, Rituximab และ Bevacizumab ที่ปรับปรุงแก้ไข
๒. แนวทางกำกับการเบิกจ่ายค่ายาในระบบ OCPA ที่กำหนดเพิ่มเติม
๓. แนวทางกำกับการเบิกจ่ายค่ายาแก้อาเจียน Aprepitant หรือ Palonosetron

ตามหนังสือที่อ้างถึง ๑ กรมบัญชีกลางได้กำหนดหลักเกณฑ์การเบิกจ่ายค่ารักษาพยาบาลสำหรับผู้ป่วยโรคมะเร็งและโลหิตวิทยาซึ่งจำเป็นต้องใช้ยาที่มีค่าใช้จ่ายสูง โดยได้กำหนด

๑. หลักเกณฑ์และแนวทางการปฏิบัติในการเบิกจ่ายเงินสวัสดิการเกี่ยวกับการรักษาพยาบาลตามโครงการเบิกจ่ายตรงสำหรับผู้ป่วยโรคมะเร็งและโลหิตวิทยา (ระบบ OCPA) สำหรับยา ๙ รายการ ได้แก่ Imatinib, Nilotinib, Dasatinib, Rituximab, Bortezomib, Sunitinib, Trastuzumab, Gefitinib และ Bevacizumab

๒. รายการยา ซึ่งกรณีการรักษาพยาบาลประเภทผู้ป่วยนอก มิให้เบิกในระบบเบิกจ่ายตรง ส่วนกรณีการรักษาพยาบาลประเภทผู้ป่วยใน มิให้เบิกแยกต่างหากจากกลุ่มวินิจฉัยโรคร่วม (DRGs)

แนวทางกำกับการเบิกจ่ายค่ายาแก้อาเจียน Aprepitant หรือ Palonosetron

เงื่อนไข ใช้เป็นยาป้องกันอาการอาเจียนที่เกิดจากยาเคมีบำบัดชนิด high emetogenic chemotherapy เฉพาะในกรณีที่ได้รับยาแก้อาเจียนสูตรมาตรฐานที่ประกอบด้วยยา Olanzapine มาแล้ว และไม่สามารถควบคุมอาการอาเจียนได้ โดยมีรายละเอียด ดังต่อไปนี้

1. ได้ผ่านการใช้ยาในบัญชียาหลักแห่งชาติ ได้แก่ Ondansetron + Dexamethasone + Olanzapine ตามสูตรมาตรฐานของการใช้ยามาแล้ว และยังมีอาการอาเจียนหลังได้รับยาเคมีบำบัด

- Ondansetron 8 - 16 mg IV day1
- Olanzapine 5 - 10 mg/day, PO, day 1-4
- Dexamethasone 20 mg IV once หรือ Dexamethasone 12 mg PO/IV day1, 8 mg PO/IV day 2, 3, 4

2. กลุ่มยาที่เป็น high emetogenic chemotherapy ได้แก่ cisplatin ≥ 70 mg/m^2, doxorubicin ≥ 60 - 70 mg/m^2, cyclophosphamide ≥ 1,500 mg/m^2, Epirubicin ≥ 90 mg/m^2 หรือ combination ของยาดังกล่าวข้างต้น เช่น สูตร AC, CHOP เป็นต้น

3. กรณีของการรับเข้านอนโรงพยาบาลเป็นผู้ป่วยใน การใช้ยาแก้อาเจียนเป็นไปตามความเห็นของแพทย์ผู้รักษา

4. ไม่อนุญาตการเบิกค่ายา Fosaprepitant และการเบิกค่ายา Aprepitant ร่วมกับ Palonosetron

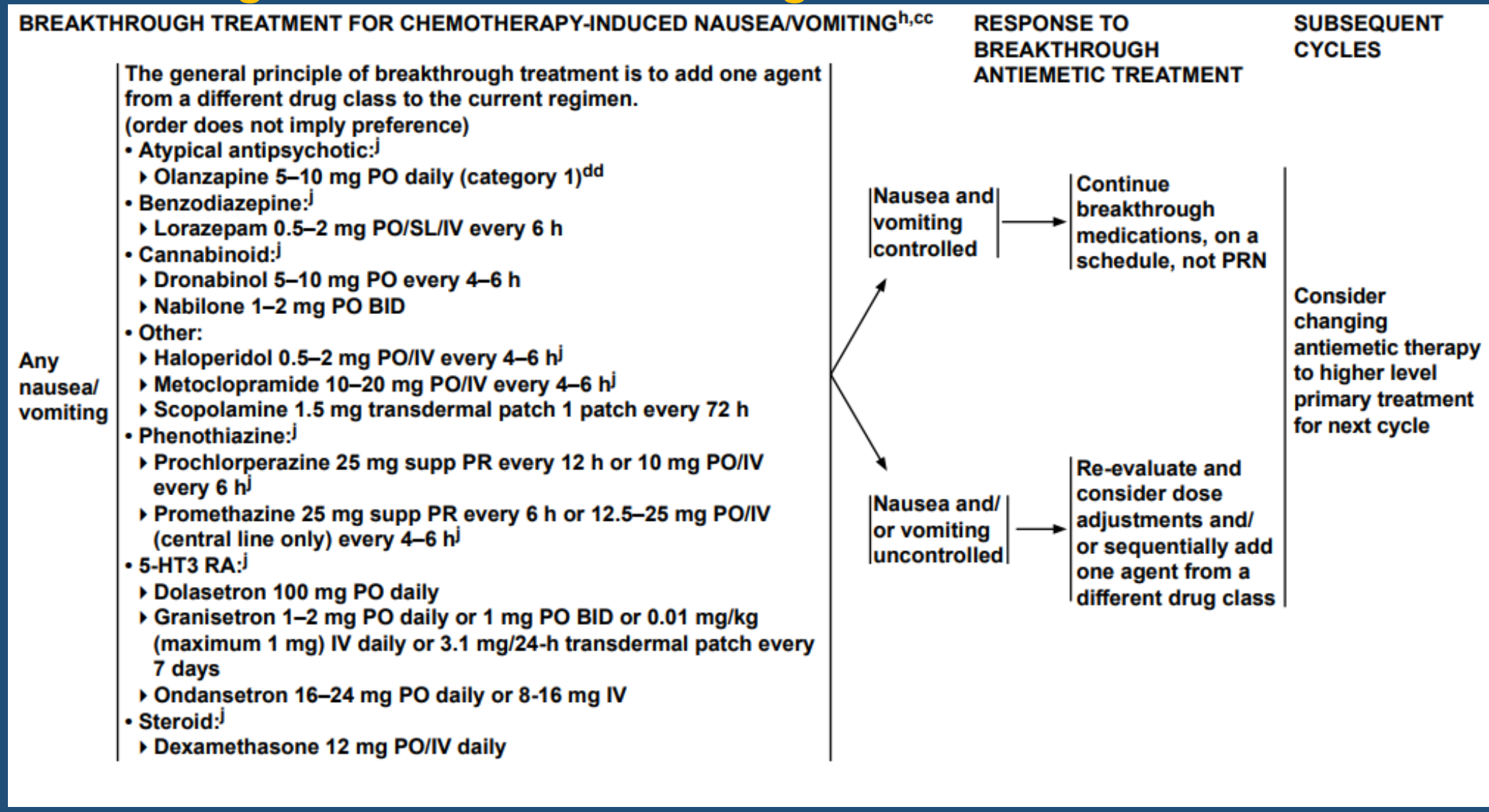
สูตรการใช้ยา Aprepitant

- Aprepitant 125 mg PO day 1, 80 mg PO day 2-3
- Ondansetron 8 - 16 mg IV once,
- Dexamethasone 12 mg PO/IV day 1, 8 mg PO/IV day 2, 3, 4
- Olanzapine 5 - 10 mg/day, PO, day 1 - 4

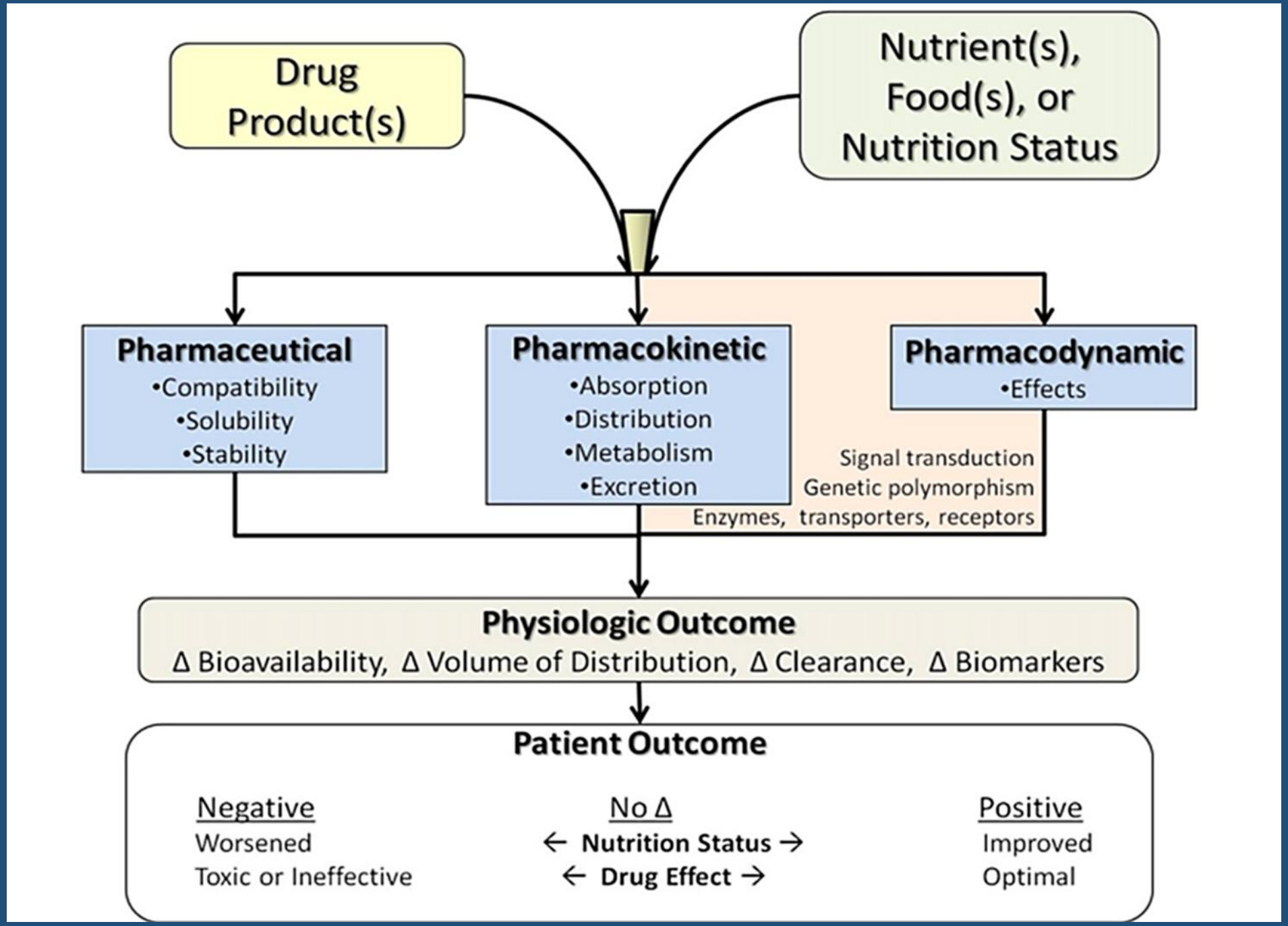
สูตรการใช้ยา Palonosetron

- Palonosetron 0.25 mg IV day 1,
- Dexamethasone 12 mg PO/IV day1, 8 mg PO/IV day 2, 3, 4
- Olanzapine 5 - 10 mg/day, PO, day 1-4

Modifying antiemetics for next cycle of chemotherapy due to breakthrough nausea and vomiting



PART 2


Drug Product(s)
Nutrient(s), Food(s), or Nutrition Status
Pharmaceutical
•Compatibility
•Solubility
•Stability
Pharmacokinetic
•Absorption
•Distribution
•Metabolism
•Excretion
Pharmacodynamic
•Effects
Signal transduction
Genetic polymorphism
Enzymes, transporters, receptors
Physiologic Outcome
Δ Bioavailability, Δ Volume of Distribution, Δ Clearance, Δ Biomarkers
Patient Outcome
Negative
Worsened
Toxic or Ineffective
No Δ
← Nutrition Status →
← Drug Effect →
Positive
Improved
Optimal

Drug interaction ;Incid

- van Leeuwen et al
  - A prospective intervention pts.
  - 603 DI are identified by sof
    - 120 DI (81 pts) are clinic intervention

Annals of Oncology 26: 992–997, 2015

Table 2. Identified drug–drug interactions (DDIs) and drug–drug interactions with an intervention

	N	%
DDIs		
Total no.	603	100
Drug interaction mechanism		
Pharmacodynamic	407	67.5
CNS interaction	187	31.0
QT interaction	110	18.2
GI interaction	81	13.5
Other pharmacodynamic interactions	29	4.8
Pharmacokinetic	126	20.9
Unknown	70	11.6
DDIs with an intervention		
Total no.	120	19.9[a]
Drug interaction mechanism		
Pharmacodynamic	52	8.6
QT interval prolongation	10	1.7
GI interaction	26	4.3
Other pharmacodynamic interactions	16	2.6
Pharmacokinetic	34	5.6
Unknown	34	5.6

Antiemetics:NK1 receptor antagonists

Drug	Interaction	Precaution
Drugs affected by aprepitant		
Dexamethasone	2.2-fold ↑ in AUC on D 1 and 5 of treatment	Reduce oral dose by 50%
Methylprednisolone	1.34-fold ↑ in AUC on D 1 of oral treatment; 2.5-fold ↑ in AUC on D 3 of i.v. treatment	Reduce oral dose by 50% and i.v. dose by 25%
Midazolam	2.3–3.3-fold ↑ in AUC	Caution when co-administering
Warfarin	34% ↓ in trough concentration of S-warfarin; 14% ↓ in prothrombin time after 5 days	Careful monitoring of patients on chronic warfarin therapy
Drugs affecting aprepitant		
Ketoconazole	5-fold ↑ in AUC, 3-fold ↑ in plasma terminal half-life	Caution when co-administering
Rifampin	11-fold ↓ in AUC, 3-fold ↓ in plasma terminal half-life	May decrease aprepitant efficacy
Paroxetine	25% ↓ in AUC of both aprepitant and paroxetine	Interaction noted; no warning given

Critical Reviews in Oncology/Hematology.2005:55;117–142

Antiemetics:5-HT3-receptor antagonists

Agents	CYP1A2	CYP2D6	CYP3A3/4/5
Granisetron			√ No induction or inhibition
Ondansetron	√ Moderate inhibition	√ Moderate inhibition	√
Dolasetron		√ Weak inhibition	√
Palonosetron	√	√	√

Critical Reviews in Oncology/Hematology.2005:55;117–142

Caution should be used when administering aprepitant with any drug metabolized by CYP3A4

- **Oral contraceptives** – decreases efficacy, therefore women of child-bearing years should use another form of birth control when using aprepitant

- **Warfarin** – patients being treated with therapeutic warfarin will need to have their INR checked 7-10 days after the completion of their 3-day regimen as there may be clinically significant decrease in INR.

- **Dexamethasone / Methylprednisolone** – increased AUCs of dexamethasone were seen in clinical trials; reduced doses should be used.225 Most significant for PO administration.

Drug-Drug interaction between antiemetic

Summary of drug interactions from Micromedex.

Drug combinations	Severity of interactions	Documentation	Onset	Summary
Olanzapine – Metoclopramide	Contraindicated	Fair	Not specified	Increased extrapyramidal reactions and NMS risk
Olanzapine – ondansetron	Major	Fair	Not specified	Increased QT prolongation risk
Ondansetron – granisetron	Major	Fair	Not specified	Increased QT prolongation risk
Netupitant – ondansetron	Major	Fair	Rapid	Increased ondansetron exposure as netupitant inhibits CYP3A4
Dexamethasone – Aprepitant and Fosaprepitant	Moderate	Excellent	Rapid	Increased dexamethasone exposure
Dexamethasone – Neputant		Good		

Drug-Drug interaction between antiemetic

Summary of drug interactions from Lexicomp.

Drug Combinations	Severity/risk rating	Reliability Rating	Summary
Olanzapine – Metoclopramide	Major/Avoid combination	Fair	Increased risk of extrapyramidal reactions and NMS
Aprepitant – Netupitant	Major/Avoid combination	Fair	Decrease in aprepitant clearance by CYP3A4 Inhibition
Dexamethasone – Aprepitant and Fosaprepitant	Major/Consider therapy modification	Fair	Increase in serum concentrations of dexamethasone
Dexamethasone – Neputant		Good	
Granisetron – Ondansetron	Major/Consider therapy modification	Fair	Increased QT prolongation risk
Olanzapine –Ondansetron and Granisetron	Moderate/Monitor therapy	Fair	Increased QT prolongation risk
Olanzapine – Tropisetron	No action		
Olanzapine – Ramosetron	Moderate/Monitor therapy	Fair	Increase in constipation risk of ramosetron by Anticholinergic activity
NK_1 Receptor Antagonists	Moderate/Monitor therapy	Excellent	All are CYP3A4 substrates, they may increase the serum concentration of each other.
Metoclopramide - 5-HT_3 Receptor Antagonists Except Palonosetron and Ramosetron	Moderate/Monitor therapy	Fair	Increased QT prolongation risk
Granisetron – Tropisetron	Moderate/Monitor therapy	Fair	Increased risk of QT interval prolongation
Ondansetron – Tropisetron	Moderate/Monitor therapy	Fair	Increased risk of QT interval prolongation

Olanzapine/Lorazepam interaction

Case report

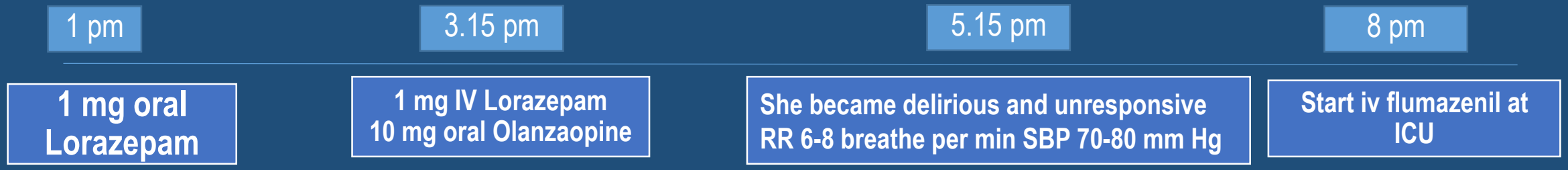
Parenteral olanzapine and a benzodiazepine

- Single case report has been published detailing the potential for serious adverse effects with concomitant use of parenteral olanzapine and a benzodiazepine
  - Patient developed severe hypotension (66/30 mm Hg) after receiving intramuscular olanzapine and intramuscular lorazepam within 30 minutes of each other.
  - The patient's blood pressure recovered to baseline after 12 hours of intravenous fluid therapy.
  - The patient was later rechallenged with intramuscular olanzapine alone on several occasions with no further incident.
  - This probable adverse drug reaction prompted a call for statements that would warn practitioners to avoid the combined intramuscular administration of olanzapine and benzodiazepines until further studies are conducted

Hypotension secondary to the combination of intramuscular olanzapine and intramuscular lorazepam. J Clin Psychiatry. 2005; 66:1614–5. Letter.

Acute benzodiazepine toxicity exacerbated by olanzapine; Case report

- 61-year-old woman scheduled to receive dose-attenuated oxaliplatin with fluorouracil and folinic acid (FOLFOX) chemotherapy pancreatic cancer
- She experienced persistent nausea that had not been responsive to multiple prior interventions
  - the patient began a prescription of oral olanzapine 10 mg daily for 10 days for the prevention of chemotherapy-induced delayed nausea and vomiting.



- Her laboratory indicating a lack of other clear explanations for her acute hypotension.
- She was diagnosed with acute benzodiazepine toxicity exacerbated by olanzapine and discharged in stable condition.

Hofmann et al THE JOURNAL OF COMMUNITY AND SUPPORTIVE ONCOLOGY. 2016

Olanzapine/Lorazepam interaction

- This case of acute benzodiazepine toxicity exacerbated by olanzapine when given in the oral formulation confirms the potential for severe toxicity with oral formulations in both the psychiatric and supportive care settings.

- The mechanism for this interaction remains unknown.
  - Features of olanzapine toxicity (somnolence, hypotension) overlap with benzodiazepine toxicity
  - Metabolic interactions; not seem to be significant
  - olanzapine is metabolized by CYP1A2 and CYP2A6
  - Lorazepam undergoes extensive hepatic metabolism independent of the cytochrome system then excreted in the urine

Hofmann et al THE JOURNAL OF COMMUNITY AND SUPPORTIVE ONCOLOGY. 2016

Olanzapine and other dopamine antagonist

- To avoid excessive dopamine blockade caution is recommended when giving olanzapine concurrently with metoclopramide or haloperidol