
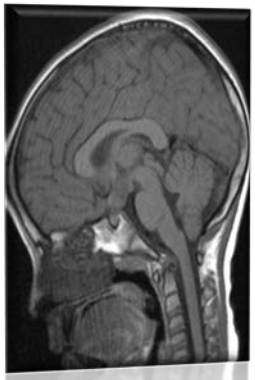


# Chemotherapy Induced-Nausea/Vomiting (CINV)

## *in Pediatric Practice*

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Pediatric Cancer & Hematologic Disorder
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# Outlines

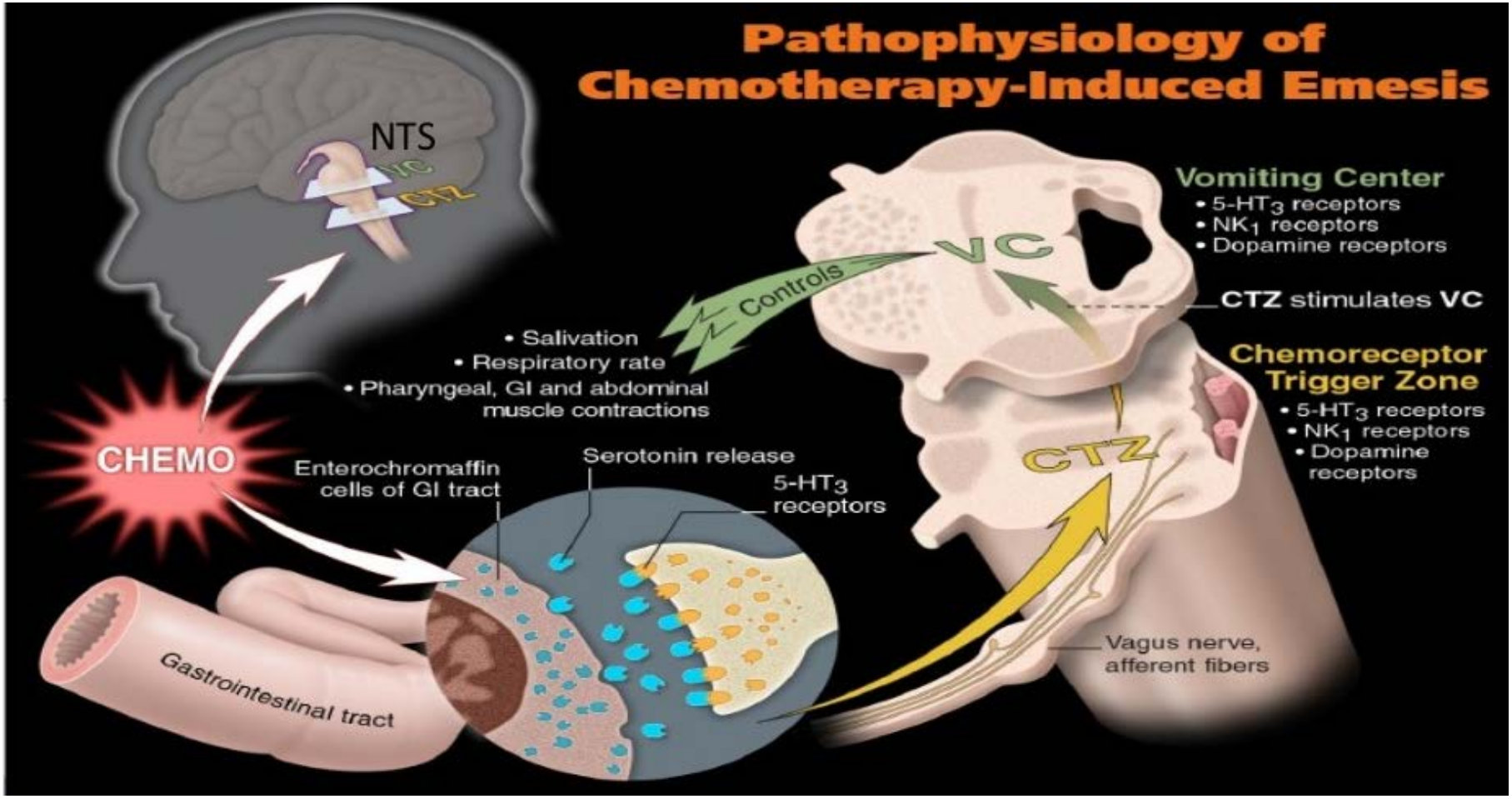
- Introduction
- Mechanism of CINV
- Causes of CINV
- Consequence of CINV
- Definitions
- Risk factors
- Treatment Guideline

# Patient Perceptions of the Most Severe Side Effects of Cancer Chemotherapy

| Rank | 1983[1] | 1993[2] | 1995[3] | 1999[4] |
|---|---|---|---|---|
| 1. | Vomiting | Nausea | Nausea | Nausea |
| 2. | Nausea | Constantly tired | Loss of hair | Loss of hair |
| 3. | Loss of hair | Loss of hair | Vomiting | Constantly tired |
| 4. | Thought of coming for treatment | Effect on family | Constantly tired | Vomiting |
| 5. | Length of time treatment takes | Vomiting | Having to have an injection | Changes in the way things taste |



Adapted from:
[1]Coates A et al. *Eur J Cancer Clin Oncol.* 1983;19:203-8.
[2]Griffin AM et al. *Ann Oncol.* 1996;7:189-95.
[3]De Boer-Dennert M et al. *Br J Cancer.* 1997;76:1055-61.
[4] Lindley C et al. *Cancer Pract* 1999;7:59-65.

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*Hesketch, PJ. et al. N Engl J Med 2008;358:2482-94*

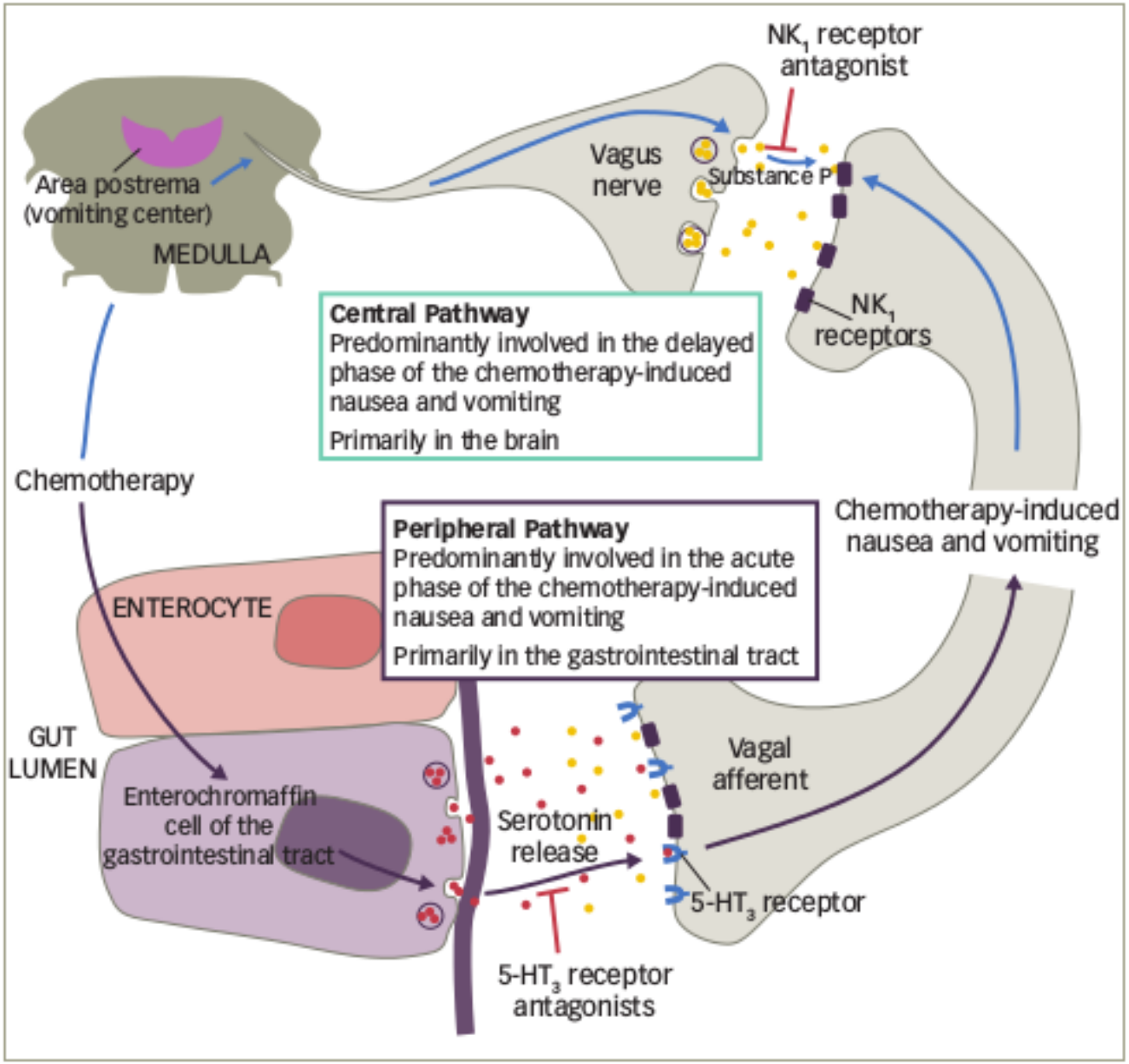
# Mechanisms of CINV

- Central mechanism:
  - Chemotherapeutic agent activates the chemoreceptor trigger zone (CTZ).
  - Activated CTZ invokes release of various neurotransmitters, which stimulate vomiting center.

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



Adapted from: Berger AM et al. In: *Cancer: Principles and Practice of Oncology.* 6th ed. Lippincott Williams & Wilkins; 2001:2869–2880.



# Causes of CINV

**In addition to emesis induced by chemotherapy, CINV can be caused by:**

- Partial or complete bowel obstruction
- Vestibular Dysfunction
- Brain Metastases
- Electrolyte imbalance: hypercalcemia, hyperglycemia, hyponatremia, uremia
- Concomitant drugs, including opiates
- Radiation
- Gastroparesis induced by a tumor or chemotherapy (such as vincristine)
- Psychophysiologic factors, including anxiety as well as anticipatory nausea and vomiting



*Adapted from NCCN Practice Guidelines in Oncology–Version 3. 2008. Antiemesis.*

# Consequence of Unresolved CINV

**Adverse sequelae of nausea and vomiting in the cancer patient.**

- **Discontinuation of therapy**
- Serious metabolic derangements
- Nutritional depletion and anorexia
- Esophageal tears
- Wound dehiscence
- Deterioration of patients' physical, mental status and quality of life
- Degeneration of self-care and functional ability



*Adapted from NCCN Practice Guidelines in Oncology–Version 3. 2008. Antiemesis.*

# Definitions

- **Nausea** urge to vomit
- **Vomiting** forceful expulsion of gastric contents
- **Retching** contractions without expulsion

# Definitions

- Acute < 24 hours
- Delayed > 24 hours (2-5 days later)
  - May last up to 6 days
  - It commonly occurs with cisplatin, carboplatin, cyclophosphamide and/or anthracyclines.
- Anticipatory – nausea and/or vomiting before patients receive their chemotherapy, after a prior negative experience with chemotherapy
- Breakthrough – occurs despite prophylactic treatment and/or requires rescue.
- Refractory – nausea and emesis during subsequent cycles when antiemetic prophylaxis and/or rescue have failed in earlier cycles



Adapted from:
1. ASHP *Am J Health Syst Pharm* 1999;56:729-764
2. NCCN Practice Guidelines in Oncology–Version 3. 2008. *Antiemesis*

# Risk factors

- Treatment factors
  - Agent-specific emetogenic potential
    - Intensity
    - Time to onset
    - Acute vs Delayed
  - Combinations more emetogenic
  - Higher dosages usually more emetogenic
  - Longer infusion duration less emetogenic

*”Challenges in multiple-day chemotherapy regimens”*

# Emetogenic potential: Acute

| High | Moderate | Low | Minimal |
|---|---|---|---|
| > 90% | 30-90% | 10-30% | < 10% |

If absence of prophylaxis



*Adapted from COG Guidelines on Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients, Dec 2016*

# Emetogenic potential: Acute

| High | Moderate | Low | Minimal |
|---|---|---|---|
| Cisplatin/ carboplatin | Busulfan | Etoposide | Vincristine |
| Nitrogen mustard | LD CTX | 5-FU | VBL |
| MTX ≥ 12g/m$^2$ | LD Ara-C | Mitoxantrone | L-asp |
| Dacarbazine | Antracyclins | Topotecan | LD MTX |
| Actinomycin | HD MTX | Taxol | 6-MP |
| HD Ara-C | IT MHA | | Bleomycin |
| HD CPM/Ifos | Irinotecan | | -nib |
| | | | -mab |

*Delay: Cisplatin 80%*

*HD CTX/Ifos 50-60%*

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*Adapted from COG Guidelines on Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients, July 2019*

# Acute Emetogenic Potential of Specific Antineoplastic Given in Combination

- High emetic risk
  - Cyclophosphamide + doxorubicin
  - Cyclophosphamide + etoposide
  - Cytarabine 300 mg/$m^2$ + etoposide
  - Doxorubicin + ifosfamide
  - Doxorubicin + methotrexate 5 g/$m^2$
  - Etoposide + ifosfamide
- Acute AND delayed nausea and vomiting



*Adapted from COG Guidelines on Chemotherapy-induced Nausea and Vomiting in Pediatric Cancer Patients, July 2019*

# Risk factors

- Patient factors (adult data)
  - Prior chemotherapy
  - Anxiety
  - Female sex
  - Age <50 years
  - No/minimal prior history of alcohol use
  - Prior CINV
  - High pretreatment expectation of severe nausea



Adapted from:
1.Gregory RE et al. *Drugs*. 1998.; 2. Hesketh PJ et al. *J Clin Oncol*. 1997.
2.Roscoe JA, et al. Cancer 2004;101:2701-2708

# Prognostic Factors for Delayed CINV

- Strongest predictor of delayed nausea and vomiting was the occurrence of acute nausea and vomiting.
- Patients aged ≤ 52 years and women were more likely to have delayed nausea than were those > 52 years and men.
- A high expectation of nausea was a significant predictor of more severe nausea.



*Adapted from The Lancet Oncology October 2005;Vol(6):Issue(10):765-72.*

# Principles of therapy

| | Prophylaxis | Breakthrough treatment |
|---|---|---|
| Acute | √ | √ |
| Delayed | √ | √ |
| Anticipatory | √ | √ |

*"Prevention more effective than treatment of breakthrough symptoms!"*

# Treatment

- True antiemetics
- Anxiolytics
- Sedatives
- Non-pharmacologic approaches

# Antiemetics

- Serotonin and 5-$HT_3$ Receptor Antagonist
- Substance P and Neurokinin1 ($NK_1$) Receptor Antagonist
- Dopamine receptor antagonist: metoclopramide
- Steroid

| GENERIC NAME | BRAND NAME | DOSAGE FORMS |
|---|---|---|
| **5-HT$_3$ RECEPTOR ANTAGONISTS** | | |
| Dolasetron | Anzemet® (sanofis-aventis, U.S.) | PO, IV |
| Granisetron | Kytril®, Sancuso® (Pro-Straken Inc.) | PO, IV, transder-mal |
| Ondansetron | Zofran® (GlaxoSmithKline) | PO, IV, IM |
| Palonosetron | Aloxi® (Eisai Inc.) | PO, IV |
| **NEUROKININ-1 RECEPTOR ANTAGONISTS** | | |
| Aprepitant | Emend® (Merck & Co., Inc.) | PO |
| Fosaprepitant | Emend for Injection (Merck & Co., Inc.) | IV |
| **CORTICOSTEROIDS** | | |
| Dexamethasone | Decadron® (Merck & Co., Inc.) | PO, IV, IM |
| Methylprednisolone | Medrol® (Pfizer, Inc.) | PO, IV, IM |
| **CANNABINOIDS** | | |
| Dronabinol | Marinol® (Solvay Pharma-ceuticals, Inc.) | PO |
| Nabilone | Cesamet® (Valent Pharma-ceuticals International) | PO |
| **DOPAMINE RECEPTOR ANTAGONISTS** | | |
| **Substituted benzamides** | | |
| Metoclopramide | Reglan® (Baxter Pharma-ceuticals) | PO, IV, IM |
| **Phenothiazines** | | |
| Perphenazine | Trilafon® (Schering Corp.) | PO |
| Prochlorperazine | Compazine® (GlaxoSmith-Kline) | PO, IV, IM, PR |
| Thiethylperazine | Torecan® (Novartis) | PO, IV, IM |
| **Butyrophenones** | | |
| Haloperidol | Haldol® (Ortho-McNeil Pharmaceuticals) | PO, IM |



*Hawkins, et al. Clinical Journal of Oncology Nursing, Vol 13. 2009. P54-64.*

# Dosage

- Ondansetron: 0.15 mg/kg/dose q 8 hours (max 8 mg/dose)
  0.45 mg/kg/dose single dose (max 24 mg/dose)
- Dexamethasone: 10 mg/m$^2$/dose D1 then 5 mg/m$^2$/dose IV/PO q 12 hr (Max 20mg/day)
- Metoclopramide: 0.5-1 mg/kg IV/PO q 6 hr prn or scheduled (Usual starting max 25-50 mg/dose) Give w/ diphenhydramine 0.5-1 mg/kg/dose IV/PO q6hr PRN or scheduled for dystonia prophylaxis
- Lorazepam: 0.025-0.05 mg/kg/dose q 6 hrs (max 2 mg/dose)
- Alprazolam: 0.5-2 mg qid
- Aprepitant: ≥ 20 kg: 125 mg PO on day 1, then 80 mg PO daily x 2 days
  10-20 kg: 80 mg PO on day 1, then 40 mg PO daily x 2 days
  <10 kg: 40 mg PO on day 1, then 20 mg PO daily x 2 days



*Adapted from Oncology Drug Reference Card, Boston Children's Hospital, July 2016.*

# 2011 NCCN Guidelines for CINV

| Emetogenic | Day 1 | Day 2-4 |
|---|---|---|
| High | Ondansetron<br>Dexamethasone<br>Aprepitant (125)<br>± Lorazepam | Ondansetron<br>Dexamethasone<br>Aprepitant (80)x2<br>± Lorazepam |
| Moderate | Ondansetron<br>Dexamethasone<br>± Aprepitant (125)<br>± Lorazepam | Ondansetron or<br>Dexamethasone or<br>± Aprepitant (80)x2<br>± Lorazepam |
| Low | Dexamethasone or<br>Metoclopramide or<br>Ondansetron<br>± Lorazepam | As needed |
| Minimal | - | Metoclopramide |

# Management of Breakthrough N/V

- Breakthrough:
  - Lorazepam OR
  - Ondansetron OR
  - Dexamethasone OR
  - Metoclopramide
  - If patient has dyspepsia, consider antacid therapy



*Adapted from 2011 NCCN Guidelines for CINV*

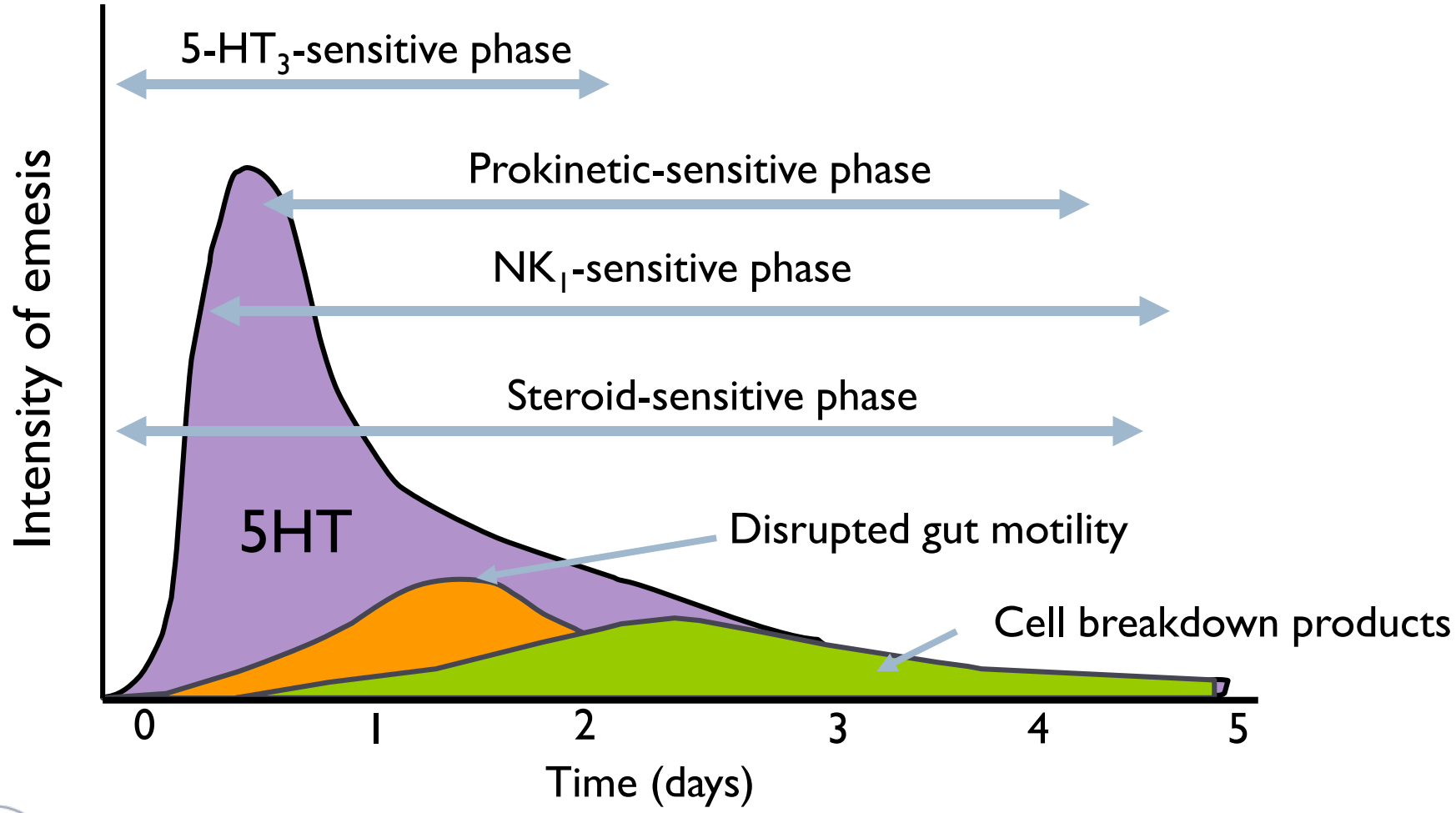
# Management of Anticipatory N/V

- Anticipatory
  - The most effective way to treat is to prevent CINV by using optimal antiemetics during every cycle of therapy.
  - Younger patients may be more susceptible as they generally receive more aggressive therapy and have poorer emesis control than older patients
  - Lorazepam OR
  - Alprazolam
  - Others: behavioral therapy, acupuncture



*Adapted from 2011 NCCN Guidelines for CINV*

# Conceptual Model of Acute & Delayed CINV

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*Adapted from Andrews & Davis. In: Andrews PLR & Sanger GJ (Eds). Emesis in Anti-Cancer Therapy: Mechanisms and Treatment. London: Arnold; 1993:147.*

# Conclusion

- Chemotherapy-induced nausea/vomiting (CINV) is a common side effect despite antiemetic therapy.
- Health care professionals need to ensure patients are being treated according to current antiemetic guidelines.
- 'It is always better and easier to PREVENT than to treat nausea/vomiting associated with chemotherapy.'
- Optimal antiemetic management with EVERY cycle!
  - If lots of prn last time, add more scheduled this time


for

children with cancer

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