2 Course Meal
Past, Present & Future for CINV
FDA Approval Process / Primer

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Financial Disclosures

- Nothing to disclose
- Use of non-FDA approved labeling will be discussed

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Objectives

- Articulate the rationale for current chemotherapy induced nausea / vomiting (CIN/V) guideline drug selections
- Design an individualized anti-emetic regimen for pediatric patients receiving chemotherapy
- Identify evidence gaps and opportunities for future research for pediatric CIN/V
- Describe the current FDA drug approval pathways and implications for drug distribution channels

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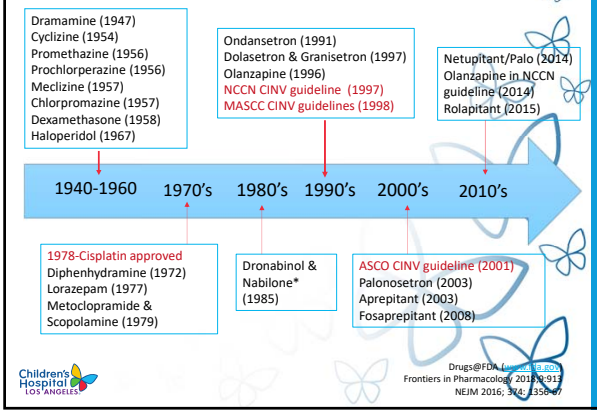
Key Milestones in CIN/V



Drugs@FDA [accessed 8.2021]
Frontiers in Pharmacology 2018; 9:913
NEJM 2016; 374: 1356-67

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The tale of two symptoms: Vomiting and Nausea

Nausea (subjective experience)

- Sensation accompanying the urge [to vomit] but not always leading to vomiting

Vomiting

- Forcible voluntary or involuntary emptying of the stomach contents through the mouth

Mosby's Medical Dictionary. 9th edition. Elsevier; 2013
https://www.cancer.gov/publications/dictionaries/cancer-terms

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Primary causes of nausea & vomiting

Disease (organic or functional)	Drug or therapies (incl PONV	Motion sickness

PONV: Post-operative nausea / vomiting
Front Pharmacol 2018; 9:913

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Potential Causes of N/V in Cancer Patients

- Tumor Invasion (GI tract, Liver, or CNS)
- Neurologic
- Non-antineoplastic medications
- Gastrointestinal
- Infection or Sepsis
- Psycho-physiologic
- **Therapy Related**

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CINV Types

Anticipatory — PRIOR to Chemotherapy
- Conditioned response to an emetic experience

Acute — Less than 24 hours
- following chemotherapy administration

Delayed — Greater than 24 hours to </=120 hours
- following chemotherapy administration (drug specific)
- 3 days for HEC and 2 days for MEC*

Breakthrough — N/V despite prophylaxis

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Antiemesis NCCN Guidelines version2.2022
https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf

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Measures of Success

- Emesis
  - Count
  - Breakthrough medications
- Nausea
  - Pediatric Nausea Assessment Tool (PeNAT) 4-18 yrs
  - Baxter Animated Retching Faces Scale (BARF) ≥6yrs
  - Edmonton Symptom Assessment Scale
  - Nausea Severity Scale (NSS) ≥ 11-17 yrs

Pediatrics (2011) 127 (6): e1542–e1549
Children 2018, 5(6), 68
Pharmacotherapy 2006;26(9):1221–1231
Pediatr Oncol Nurs. 2020 May/Jun;37(3):195-203
Cancer. 2000 May 1;88(9):2154-71

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Risk Factors for CINV

- Increased Risk
  - Younger age (<60 yrs)
  - Female Sex
  - History of CINV
  - History of Motion sickness
  - History of morning sickness w/pregnancy
  - Anxiety / high treatment expectation of Nausea
  - *Hours of sleep the night before**
- Decreased Risk
  - History of alcohol use

NCCN Antiemesis Guidelines v2.2022
Annals of Oncology 2017; 28: 1280-1267

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Patient Case

- MJ is a 12 yo male with newly diagnosed Ewings sarcoma to begin VDC (vincristine + doxorubicin (75mg/m^2/cycle) + cyclophosphamide 1.2gm/m^2). Based on COG/POGO emetogenicity which best described this regimen?
  A. Minimally emetogenic
  B. Low emetogenicity
  C. Moderate emetogenicity
  D. High Emetogenicity

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Emetogenicity of Chemotherapy

IV Chemotherapy Emetogenic Risk	Incidence of Acute Emesis
Minimal	<10%
Low	10-30%
Moderate	>30-90%
HIgh	>90%

CHILDREN'S ONCOLOGY GROUP

POGO
PEDIATRIC ONCOLOGY GROUP OF ONTARIO

PO Chemotherapy Emetogenic Risk	Incidence of Acute Emesis
Minimal to Low	< 30%
Moderate to High	≥30%

- Checkpoint inhibitors are considered minimally emetogenic
- Biosimilars are same emetogenicity as parent compound

Pediatr Blood Cancer 2019;66:e27646
COG supportive Care Guidelines
https://childrensoncologygroup.org/downloads/COG_SC_CINV_Guidelines_Document.pdf

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Emetogenicity

Antineoplastic Agents with HIGH Emetic Risk
90% frequency of emesis in absence of prophylaxis

Single agent antineoplastic therapy

Altretamine	Dactinomycin
Carboplatin	Mechlorethamine
Carmustine > 250 mg/m²	Methotrexate ≥ 12 g/m²
Cisplatin	Procarbazine (oral)
Cyclophosphamide ≥1 g/m²	Streptozocin
Cytarabine 3 g/m²/dose	Thiotepa > 300 mg/m²
Dacarbazine	

Multiple agent antineoplastic therapy

With the exceptions listed below, emetogenicity is classified based on the most highly emetogenic agent.

The following are also classified as high emetic risk:

Cyclophosphamide + anthracycline
Cyclophosphamide + doxorubicin
Cyclophosphamide + epirubicin
Cyclophosphamide + etoposide
Cytarabine 150-200 mg/m² + daunorubicin
Cytarabine 300 mg/m² + etoposide
Cytarabine 300 mg/m² + teniposide
Doxorubicin + ifosfamide
Doxorubicin + methotrexate 5 g/m²
Etoposide + ifosfamide

Multi-day antineoplastic therapy

Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.

Antineoplastic Agents with MODERATE Emetic Risk
30-90% frequency of emesis in absence of prophylaxis

Single agent antineoplastic therapy

Aldesleukin > 12 to 15 million units/m²
Amifostine > 300 mg/m²
Arsenic trioxide
Azacitidine
Bendamustine
Busulfan
Carmustine ≤ 250 mg/m²
Clofarabine
Cyclophosphamide < 1 g/m²
Cyclophosphamide (oral)
Cytarabine > 200 mg to < 3 g/m²
Daunorubicin
Doxorubicin
Epirubicin
Etoposide (oral)
Idarubicin
Ifosfamide
Imatinib (oral)
Intrathecal therapy (methotrexate, hydrocortisone & cytarabine)
Irinotecan
Lomustine
Melphalan > 50 mg/m²
Methotrexate ≥ 250 mg to < 12 g/m²
Oxaliplatin > 75 mg/m²
Temozolomide (oral)
Vinorelbine (oral)

Multiple agent antineoplastic therapy

With the exceptions listed under high emetic risk, emetogenicity is classified based on the most highly emetogenic agent.

Multi-day antineoplastic therapy

Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.

Antineoplastic Agents with LOW Emetic Risk
10% to <30% frequency of emesis in absence of prophylaxis

Single agent antineoplastic therapy

Amifostine ≤300 mg/m²	Methotrexate >50 mg/m² to <250mg/m²
Amsacrine	Mitomycin
Bexarotene	Mitoxantrone
Busulfan (oral)	Nilotinib
Capecitabine	Paclitaxel
Cytarabine ≤200 mg/m²	Paclitaxel-albumin
Docetaxel	Pemetrexed
Doxorubicin (liposomal)	Temsirolimus
Etoposide	Teniposide
Fludarabine (oral)	Thiotepa <300 mg/m²
5-Fluorouracil	Topotecan
Gemcitabine	Vinorelbine
Ixabepilone	Vorinostat

Multiple agent antineoplastic therapy

With the exceptions listed under high emetic risk, emetogenicity is classified based on the most highly emetogenic agent.

Multi-day antineoplastic therapy

Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.

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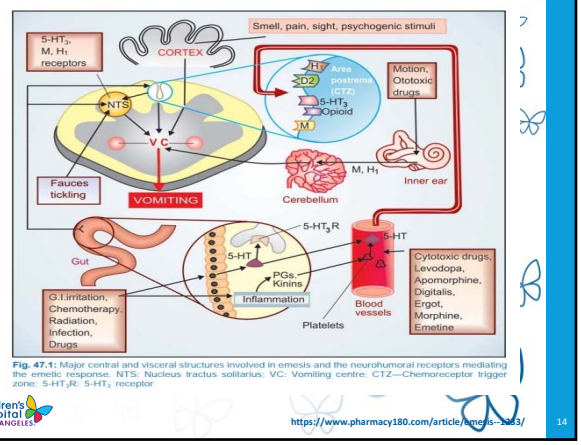

Fig. 47.1: Major central and visceral structures involved in emesis and the neurohumoral receptors mediating the emetic response. NTS: Nucleus tractus solitarius; VC: Vomiting centre; CTZ—Chemoreceptor trigger zone; 5-HT$_3$R: 5-HT$_3$ receptor

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https://www.pharmacy180.com/article/emesis--2083/

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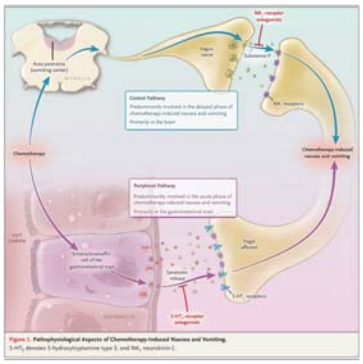
NK-1 & 5HT$_3$ Receptor Antagonists



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NEJM 2016; 374: 1356-67

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What's on the CINV Menu?

- Serotonin Receptor Antagonists (5-HT_3-RA)
  - Effective for acute N/V w/ maximal effective dose
    - Ondansetron (Zofran®)
    - Granisetron (Kytril ®)
    - Palonosetron (Aloxi ®)
    - Dolansetron (Anzemet®)
- Substance P/NK-1 Receptor Antagonists (NK-1)
  - In combination w/5-HT3-RA & dexamethasone for acute and delayed N/V
  - Drug Interaction checking (CYP34A inhibitor)
    - Aprepitant (Emend ®), Fosaprepitant (Emend ®)
- Corticosteroids (Dexamethasone) (DEX)
  - In combination (but can be monotherapy)- primarily delayed N/V
- *Olanzapine (atypical antipsychotic) (OLZ)*
  - *Multi-receptor blockade (serotonergic, dopaminergic, muscarinic)*

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Guidelines for HEC Regimens

	Acute Phase	Delayed Phase
COG	≥ 6 months 1. 5-HT_3 RA+NK1+DEX 2. 5-HT_3 RA+DEX 3. 5-HT_3 RA+ NK1 < 6months 1. 5-HT_3 RA+DEX 2. Palo	NK1 +/- DEX
POGO	1. 5-HT_3 RA+NK1+DEX 2. Palo +/- NK1	NK1 +/- DEX NK1
ASCO (Peds)	1. 5-HT_3 RA+NK1+DEX 2 5-HT_3 RA+DEX 3. Palo + NK1	
ASCO	5-HT_3 RA+NK1+DEX+OLA	OLA+DEX
NCCN (2022)	1. OLZ+NK1+5-HT3 RA+DEX 2. OLZ+Palo+DEX 3. NK1+5-HT3 RA+DEX	1. OLA+NK1+DEX 2. OLZ 3. NK1+DEX
MASCC/ESMO	NK1+5-HT3 RA+DEX +/- OLZ	NK1+DEX

Pediatr Blood Cancer. 2017 Oct;64(10). doi: 10.1002/pbc.26421 (POGO)
NCCN Antiemesis guidelines version 2. 2022
www.asco.org/supportive-care-cancer-guidelines
Supportive Care in Cancer (2021) 29:3075–3107 (ASCO guidelines)
Children's Oncology Group Supportive Care Guidelines (CINV) www. childrensoncologygroup.org/

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Guidelines for MEC Regimens

	Acute Phase	Delayed Phase
COG	All ages 1. 5-HT_3 RA+DEX 2. 5-HT_3 RA+NK1 3. Palonosetron	NK1 or DEX
POGO	1. 5-HT_3 RA+DEX 2. 5-HT_3 RA+NK1 3. Palonosetron	NK1 or DEX
ASCO (Peds)	1. 5-HT_3 RA+DEX 2. 5-HT_3 RA+NK1	
ASCO (Adult)	1. 5-HT_3 RA+DEX 2. 5-HT_3 RA+DEX+ NK-1 (Carbo AUC≥4)	DEX
NCCN (2022)	1. 5-HT_3 RA+DEX 2. OLZ+Palo+DEX 3. NK1+5-HT3 RA+DEX	1. DEX or 5-HT3 RA 2. OLZ 3. NK1+DEX
MASCC/ESMO	NK1+5-HT3 RA+DEX +/- OLZ	NK1+DEX

Pediatr Blood Cancer. 2017 Oct;64(10). doi: 10.1002/pbc.26421 (POGO)
NCCN Antiemesis guidelines version 2. 2022
www.asco.org/supportive-care-cancer-guidelines
Supportive Care in Cancer (2021) 29:3075–3107 (ASCO guidelines)
Children's Oncology Group Supportive Care Guidelines (CINV) www. childrensoncologygroup.org/

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Guidelines for LEC Regimens

	IV LEC	ORAL Chemotherapy
COG	No recommendations	No recommendations
POGO	5-HT3 RA	Same as parenteral
ASCO	1. 5-HT3 RA 2. DEX	HEC/MEC- same as IV recs Low to minimal -same as IV recs
NCCN (2022)	1. DEX or Metoclopramide or Prochlorperazine or 5-HT3 RA	HEC/MEC - 5-HT3 RA Low to minimal –provide PRN medication
MASCC/ESMO	5-HT3 RA Haloperidol DEX	

Pediatr Blood Cancer. 2017 Oct;64(10):e26542 (POGO)
NCCN Antiemesis Guidelines version 2.2022
www.asco.org/supportive-care-guidelines
Supportive Care in Cancer (2021) 29:8097–8107 (MASCC guidelines)
Children's Oncology Group Supportive Care Guidelines (CINV) www. childrensoncologygroup.org/

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Fosaprepitant (MEC/HEC) in combination w/5HT$_3$ +/- Dexamethasone

Complete infusion 30min prior to chemo	Fosaprepitant (Emend®) (single day)	Fosaprepitant (Emend®) (Multi day)	Aprepitant emulsion (Cinvanti®) (single day)	Aprepitant emulsion (Cinvanti®) Multi day
6mths - < 2 yrs	5mg/kg (max: 150mg) IV over 60min	Day 1: 3mg/kg (max: 115mg) IV over 60min Days 2-3: 2mg/kg by mouth		
2 yrs to < 12 yrs	4mg/kg (max: 150mg) IV over 60min	Day 1: 3mg/kg (max: 115mg) IV over 60min Days 2-3: 2mg/kg by mouth		
12 to 17 yrs	150mg IV over 30min	115mg IV over 30min Days 2-3: 80mg PO or IV		
Adults Dex mandatory	150mg IV over 20-30 + DEX 12mg		130mg IV slow push+Dex 12mg Day 2: Dex 8mg Days 3-4: Dex 8mg BID	Day 1: 100mg IV slow push + Dex 12mg Days 2-3 aprepitant PO 80mg
Cost	150mg vial $400	125mg (cap) = $318 80mg (cap) = $200	130mg vial = $500	130mg vial = $500 80mg (cap) = $200

All prices listed as AWP

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5HT$_3$-RA: Are they the same?

	Ondansetron	Granisetron	Palonosetron**
Pediatric Dosing Guidelines	YES (CINV, RadTx N/V, PONV, CVS, Gastroenteritis)	YES (CINV, PONV)	YES (single dose only) (CINV, PONV)
Dosage Formulation	IV, PO tablet, PO-ODT, Oral Solution	IV, PO tablet *(adults only: patch, long acting SQ injection)*	IV ONLY (peds) *(adults only: combo PO capsule w/netupitant)*
QTc Prolongation	Doses > 16mg given IV push	Caution w/ pre-existing arrhythmia or QTc prolongation	None
Pharmacogenomics	CYP2D6 ultra rapid metabolizers	None	None
Cost	<$	$$	$$$
Combination products		Sustol SQ - $818 Sancuso (patch) $ 760	PO: Netupitant/Palo ($828/dose) IV: Fosnetupitant/palo ($820/dose)

**Dose 20mcg/kg-max: 1.5mg per PI guideline BUT 5mcg/kg (max: 0.25mg) and 20mcg/kg (max: 0.75mg) reported effectious

CINV-Chemotherapy Induced Nausea/Vomiting; RadTx – Radiation induced Nausea & Vomiting
PONV- Post-operative Nausea / vomiting; CVS= cyclic vomiting syndrome

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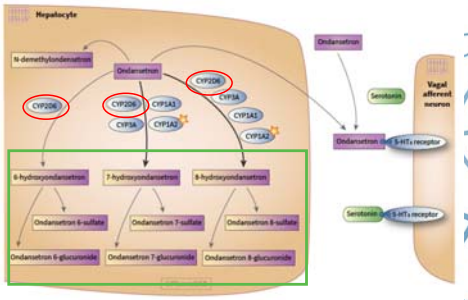
Pharmacogenomics (PGx) CYP2D6 and Ondansetron



https://www.pharmgkb.org/pathway/PA166179808

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What is CYP2D6 UltraRapid Metabolizer?

Table 2 Dosing recommendations for ondansetron and tropisetron based on CYP2D6 genotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]	Consideration for alternative 5-HT_3 receptor antagonists antiemetics[b]
CYP2D6 Ultrarapid Metabolizer	Increased metabolism to less active compounds when compared to NMs and is associated with decreased response to ondansetron and tropisetron (i.e., vomiting)	Select alternative drug not predominantly metabolized by CYP2D6 (i.e., granisetron).[c]	Moderate	Dolasetron, palonosetron, and ramosetron are also metabolized by CYP2D6. Limited evidence is available regarding the utilization of CYP2D6 genetic variation to guide use of these drugs.
CYP2D6 Normal Metabolizer	NM	Initiate therapy with recommended starting dose.[c]	Strong	
CYP2D6 Intermediate Metabolizer	Very limited data available for CYP2D6 IMs	Insufficient evidence demonstrating clinical impact based on CYP2D6 genotype. Initiate therapy with recommended starting dose.[c]	No recommendation	
CYP2D6 Poor Metabolizer	Very limited data available for CYP2D6 PMs	Insufficient evidence demonstrating clinical impact based on CYP2D6 genotype. Initiate therapy with recommended starting dose.[c]	No recommendation	

5-HT_3, 5-hydroxytryptamine type 3; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.
[a]Rating scheme described in the **Supplementary Material** online. [b]Clinical Pharmacogenetics Implementation Consortium strength of recommendation: no recommendation. See rating scheme described in the **Supplementary Material** online. [c]Drug-drug interactions and other patient characteristics (e.g., age, renal function, and liver function) should be considered when selecting alternative therapy.

https://cpicpgx.org/guidelines/guideline-for-ondansetron-and-tropisetron-and-cyp2d6-genotype/

Clinical Pharmacology & Therapeutics 2017 ; 102(2): 213-221

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Olanzapine- where's the data?

- Efficacy
  - Single Institution randomized (non blinded) patients 5-18 receiving HEC. (New Dehli, India) [Naik et al 2020]
  - Ondansetron + Dexamethasone + aprepitant +/- Olanzapine (0.15mg/kg/DAY – rounded to nearest 2.5mg with max dose 10mg
  - CR in acute period 78% vs. 59%, CR in Delayed period 74% vs. 47% and overall 64% vs. 38%
  - Grade 1 or 2 somnolence noted in olanzapine group (0% in control group) and no grade 3 or 4 somnolence noted in either group
- Safety
  - Retrospective multi-institutional pediatric review of 60 pts receiving HEC/MEC (99% of patients) [Flank et al 2015]
    - –Started day 1 = 65% with 100% control (regardless of olanzapine dose)
    - –"Sedation" in 7%, 0% weight gain, LFT changes <20%, no EPS or QTc reported
    - –Authors specifically comment = well tolerated with no severe adverse effects
- Guidelines
  - POGO guidelines for Treatment of Breakthrough and the prevention of refractory chemotherapy-induced Nausea and Vomiting in Children with Cancer [0.1mg/kg/dose – max: 10mg]

J Clin Oncol 2020;38:3785-3793
Pediatr Blood Cancer 2015;62:796–801
Pediatr Blood Cancer 2016;63:1144–1151

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Anticipatory or Breakthrough

- Anticipatory [2021 guidelines / COG endorsed]
  - Maximize combination anti-emetics
  - Consider non-pharmacologic interventions
    - Hypnosis, relaxation techniques, desensitization
  - Lorazepam
- Breakthrough Nausea / Vomiting [POGO 2016/NCCN]
  - Increase prophylaxis to next higher regimen (change $5HT_3$)
  - Add agent from different class
    - Metoclopramide, Prochlorperazine/promethazine, olanzapine, lorazepam, dronabinol, scopolamine (motion induced)

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Pediatr Blood Cancer. 2021;68:e28947
Pediatric Blood Cancer 2016;63:1144–1151

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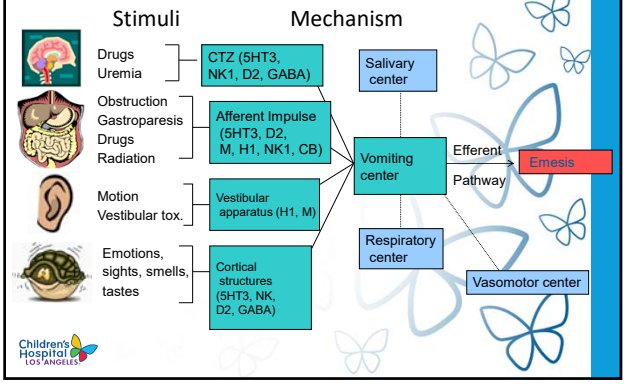
Pathophysiology of Emesis



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Neurotransmitters, Receptors and Drugs

- Histamine (H1)
  - Diphenhydramine (++++)
  - Promethazine (++++)
  - Prochlorperazine (++)
- Muscarinic acetylcholine receptors (M)
  - Scopolamaine (++++)
  - Diphenhydramine (++)
  - Promethazine (++)
- Dopamine (D2)
  - Haloperidol (++++)
  - Metoclopramide (+++)
  - Olanzapine (++++)
  - Prochlorperazine (++++)
  - Promethazine (++)
- Cannabinoid (CB)
  - Dronabinol
  - Nabilone
- GABA
  - Lorazepam

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Future Directions for CINV

- FDA Guidance for future CIN/V
  - To achieve a delayed N/V indication MUST include HEC with documented delayed N/V (per ASCO guidelines)
  - IF documented benefit in HEC FDA may consider MEC without additional trials
  - Patient with brain metastases should be included in early-stage drug development trials
  - Patients must receive antiemetics per ASCO guidelines
  - Patients must receive active comparator
  - Primary endpoints included emetic episodes and use of breakthrough medication AND secondary endpoints SHOULD include nausea scale / metric

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/chemotherapy-induced-nausea-and-vomiting-developing-drugs-prevention-guidance-industry

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Patient Case Con't

- MJ received cycle 1 and received a 5HT3 +DEX + NK-1. He reported a median BARF nausea score of 2, had 1 emesis on Day 1 and continued his oral intake (continued to eat and drink) throughout his stay.
- What would you do for his next cycle of VDC?
  A. Continue with same 3 drug combination
  B. Continue 3 drug combination and add scopolamine
  C. Change to different 5HT3 + DEX + NK-1
  D. Continue 3 drug combination and add olanzapine

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Principles of Therapy

- Use prophylactically
- Schedule doses
- Provide breakthrough coverage
- Base decisions on emetogenic potential
- Know patient history
- Allow for individualization
- Anticipate combination therapy

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Future Study Opportunities

- ACCL2121 (Aprepitant emulsion (Cinvanti®) in pediatric patients)
- Symptom management- [patient related outcomes] / tracking with mobile application
  - https://www.cancer.net/navigating-cancer-care/managing-your-care/cancernet-mobile
  - Cerner Application: carevive
  - Epic application eSyM
- Reporting / sharing data collectively

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FDA Approval Process Is there one path to the market?

Pre-clinical

- Animal trials – not reported to FDA. Looking for hint of benefit and prospect of benefit in humans. If things look good -> submit IND.

Phase 1 (~ 70% move to Phase 2) n= 20-80 pts

- Investigational New Drug Application submitted to FDA
- FDA decides of proposal from sponsor is reasonably and should more forward
- SAFETY / Pharmacokinetics / Pharmacodynamics /Dose Limiting toxicity (DLT) / Maximum tolerated dose (MTD) Recommended Dose Phase 2 (RDP2)
- Common 3 x 3 design

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FDA Approval Process Is there one path to the market?

Phase 2 (n < 100) (see accelerated approval process)

- Expanded safety, confirmation of dose / schedule, preliminary efficacy in targeted population
- Umbrella vs. basket
- Common open label / non-controlled
- Alternative endpoints

Phase 3

- Randomized controlled trial
- Testing efficacy potentially thousands of patients

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FDA Approval Process

	Fast Track	Priority Review	Accelerated Approval	Breakthrough Therapy
Established	1988	1992	1992	2012
Definition	Drugs that treat serious conditions and fill an unmet medical need	Drugs with major advances in treatment with no existing adequate treatment	Drugs that fill unmet need for serious conditions	Drug to treat serious or life-threatening conditions with better data than existing options
Approval Considerations	Can approve after single phase 2 study	None	Can approve off surrogate endpoint	None
Benefit	Expedites development and review. Rolling review	Expedites NDA review (6 months vs. standard 10 month)	Approval based on surrogate endpoint. Expedites data	Guidance from FDA. Rolling review
Post Approval Requirement			Studies to confirm clinical benefit	

Adapted from J Pers Med. 2021;11(1):45

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How to manage risk

- Black Box warning
  - May be assigned during or post approval process
  - Alert the public and health care providers of serious side effects (injury or death)
    - Manufacturer must create a medication guide that describes how the patient can take medication safely
- Risk Evaluation and Mitigation Strategy (REMS)
  - FDA requires if serious safety concerns to help ensure benefits of the medication outweigh the risks
  - Can vary from 3rd party managed programs, attestations by prescribers, registration with drug company,

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Limited Distribution Drugs

- Limited distribution drugs (LDD) (aka specialty pharmacy distribution only)
  - Drug manufacturer will choose (often already established relationships)
  - Allows for closer patient relationship most specifically impacting patient adherence and side effect management
  - Allow for robust data capture
  - Nationally accredited specialty pharmacies -> increase drug inclusion listing
  - Oncology and neurology comprise most of LDD

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