Chemotherapy-Induced Nausea and Vomiting (CINV): General Principles and Current Standard of Care

Paul J. Hesketh, MD, FASCO

Lahey Cancer Institute
Beth Israel Lahey Health

Disclosures

- None

Overview

- Background
  - Significance for the patient
  - Predictive factors
  - Physiology
- Evidence – Based Guidelines
  - ASCO 2020 update
- Expanding role of olanzapine

Chemotherapy-induced Nausea and Vomiting (CINV) in the Cancer Patient

- Among the most feared side effects of chemotherapy among patients
- Inadequately controlled, adds to the morbidity and cost of therapy and impairs quality of life
- Incidence often under reported
- Three CINV syndromes
  - acute (≤ 24 hours)
  - delayed (> 24 hours)
  - anticipatory

Predictive Factors for Emesis

- Patient related
  - age
  - gender
  - emesis with prior chemotherapy
  - alcohol consumption
  - polymorphisms in metabolism of antiemetics and neurotransmitter receptors
- Treatment related
  - chemotherapy dose, route, schedule, combination
  - chemotherapy emetogenicity

High Risk Profile for Chemotherapy-induced Nausea and Vomiting

- Female gender
- Age less than 50
- Light/non consumer of ethanol
- Diagnosis of breast cancer
- Scheduled to receive a combination of doxorubicin and cyclophosphamide

Chemotherapy Emetogenicity (IV)

Level	Emetic Risk (%)	Agent
5	>90	cisplatin(>50mg/m^2)
4	60-90	carboplatin
3	30-60	cyclophosphamide (>600 mg/m^2)
2	10-30	gemcitabine
1	<10	vinorelbine

Hesketh et al: J Clin Oncol 15:103-9, 1997

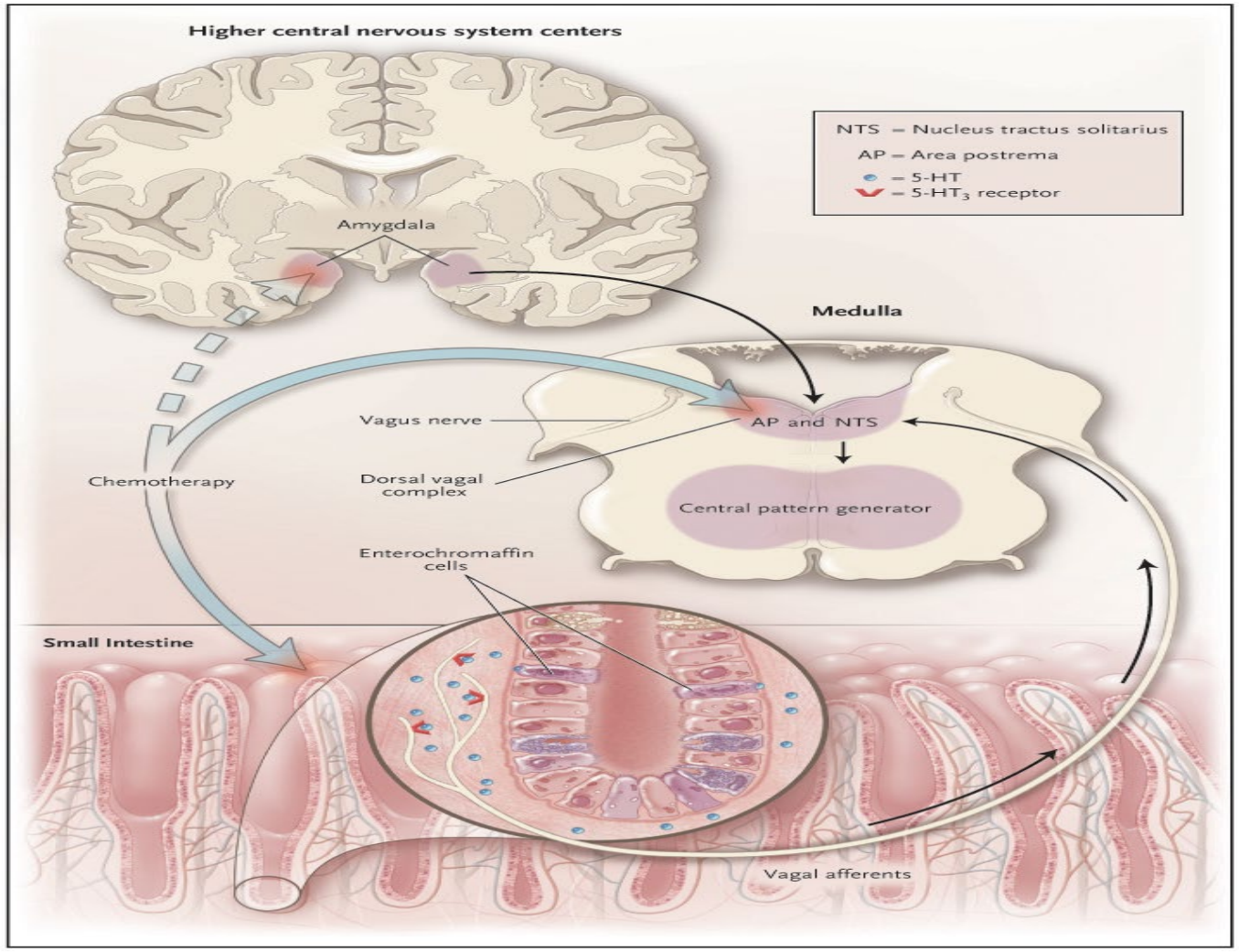
Physiology of Nausea and Vomiting

Nausea and vomiting
serve as important defense mechanisms to protect an animal from ingested toxins.

Key Components of the Emetic Reflex in CINV

- Central Nervous System
  - Emetic center (emetic central pattern generator)
  - Area postrema (chemoreceptor trigger zone)
  - Limbic system
- Gastrointestinal tract
  - Enterochromaffin cells
  - Visceral afferents projecting to the brainstem

Pathways by Which Chemotherapy May Produce Emesis

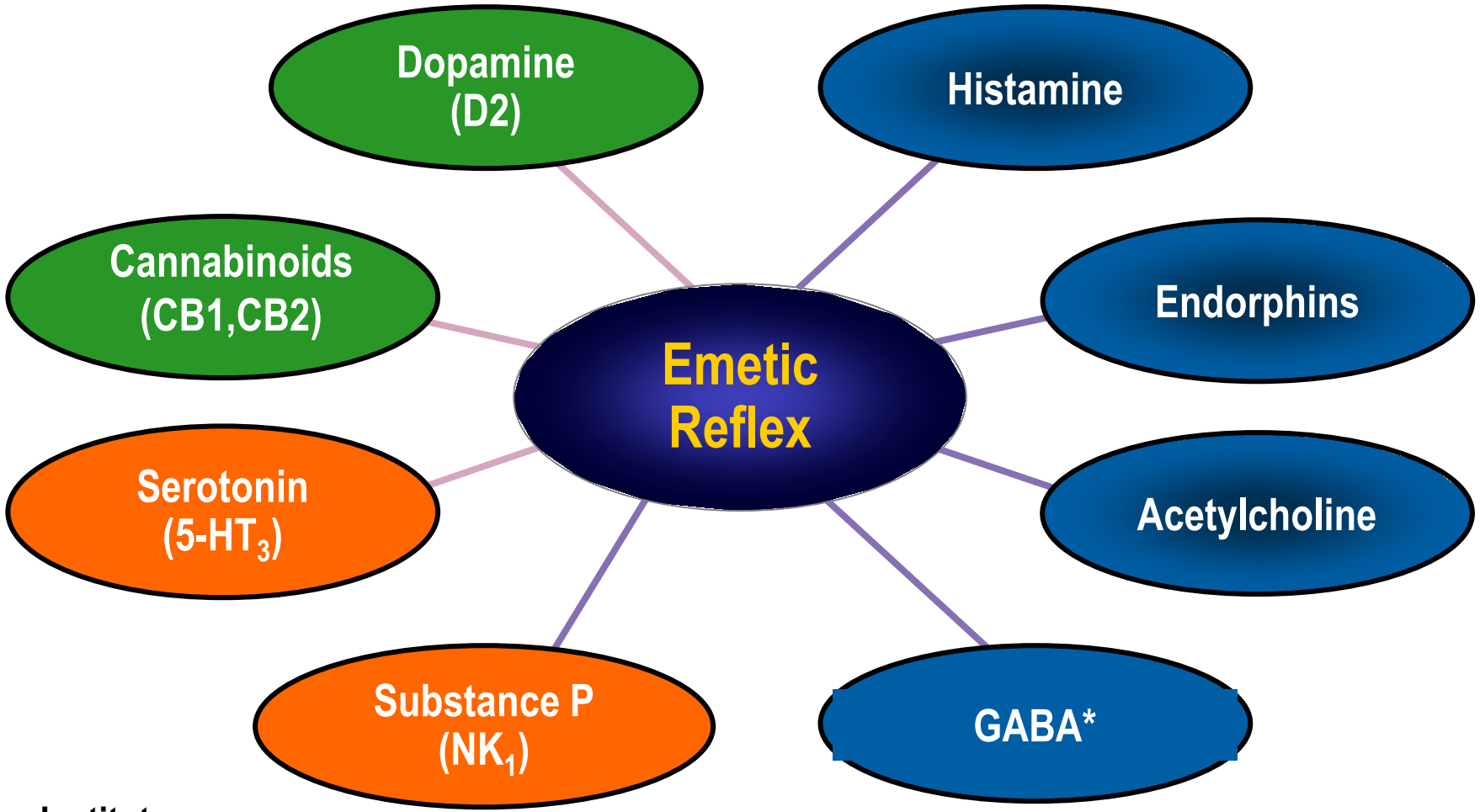


Hesketh PJ NEJM 2008;358:2482-94

Evidence-based Antiemetic Guidelines

- ASCO
- MASCC/ESMO
- NCCN
- Cancer Care Ontario

Neurotransmitters in Emesis

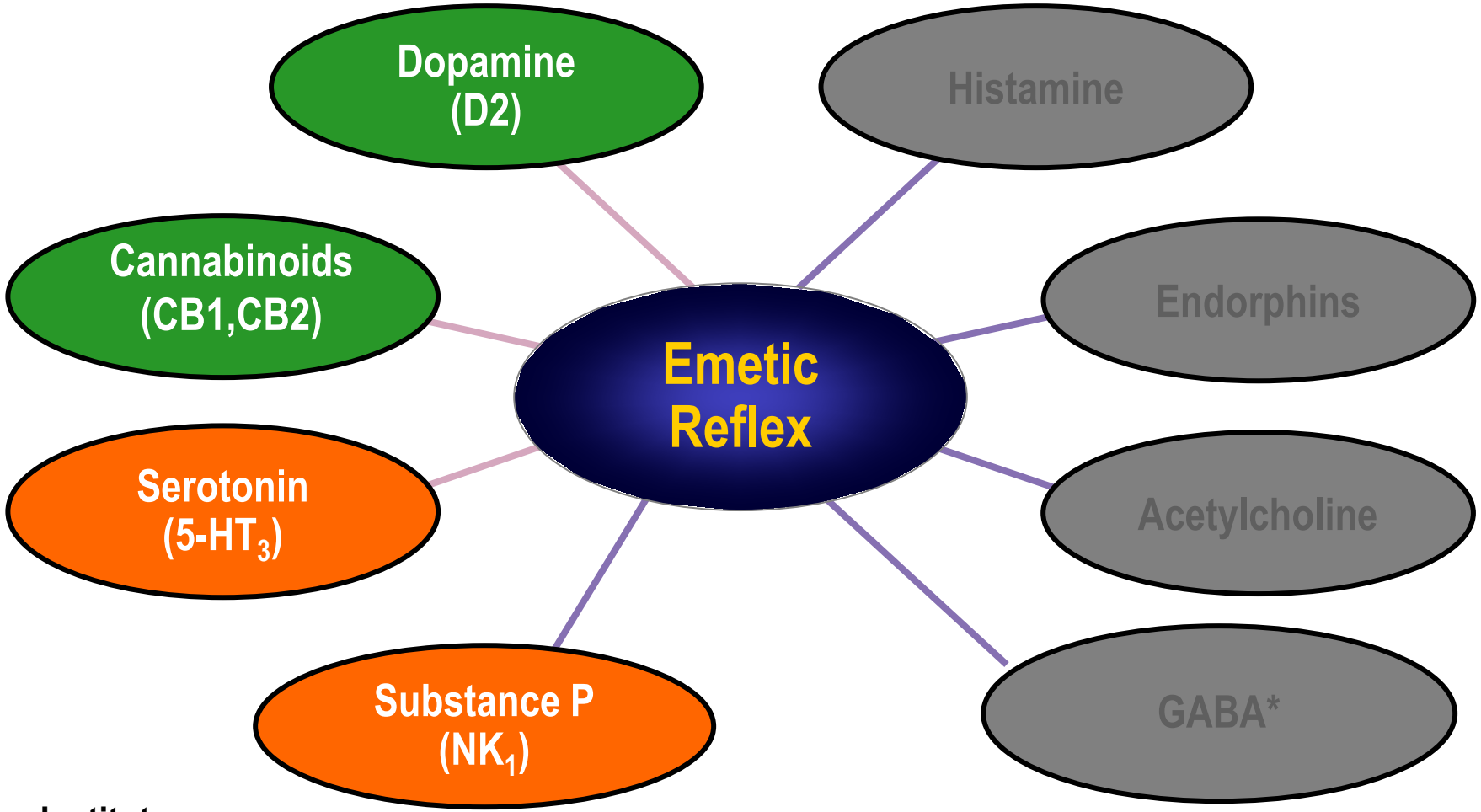


*GABA= Gamma-aminobutyric acid.

General Principles of Antiemetic Treatment

- Prevention is the best policy: always use agents prophylactically
- Assess need for both acute (first 24 hours) and delayed (> 24 hours) prophylaxis
- Choose antiemetic agents to match emetogenic potential of chemotherapy
- Prescribe antiemetics for breakthrough emesis

Neurotransmitters in Chemotherapy-induced Emesis (CINV)



*GABA= Gamma-aminobutyric acid.

Antiemetic Guidelines for Oral Antineoplastic Agents

- Evidence-based guidelines lacking for oral antineoplastic agents
- Limiting factors
  - Lack of antiemetic trials
  - Difficulty evaluating antiemetic efficacy in the setting of antineoplastics often administered on an extended daily basis
- Intrinsic emetogenicity of oral antineoplastics poorly characterized
- 2020 ASCO guideline divides emetogenicity for oral agents into two categories
  - Moderate or high (emetic risk $\geq$ 30%)
  - Minimal or low (emetic risk < 30%)
- With short course moderate/high risk emetogenic agents (e.g. 5 day course of temozolomide), a daily antiemetic such as ondansetron is typically prescribed
- In most cases of protracted course minimal/low risk emetogenic agents prn, agents such as prochlorperazine prescribed

ASCO special articles

Antiemetics: ASCO Guideline Update

Paul J. Hesketh, MD[1]; Mark G. Kris, MD[2]; Ethan Basch, MD, MSc[3]; Kari Bohlke, ScD[4]; Sally Y. Barbour, PharmD[5]; Rebecca Anne Clark-Snow, BSN, RN[6]; Michael A. Danso, MD[7]; Kristopher Dennis, MD, PhD[8,9]; L. Lee Dupuis, PhD, RPh[10]; Stacie B. Dusetzina, PhD[11,12]; Cathy Eng, MD[12]; Petra C. Feyer, MD, PhD[13]; Karin Jordan, MD[14]; Kimberly Noonan, MS, RN[15]; Dee Sparacio, MS[16]; and Gary H. Lyman, MD, MPH[17]

J Clin Oncol 2020 Aug;38(24):2782-2797

Corticosteroid Use with Checkpoint Inhibitors

- Concerns have been raised about the potential for concurrent corticosteroid use to adversely affect the therapeutic efficacy of CPIs through their immunosuppressive effects
- Dexamethasone is a potent corticosteroid that is a critical component of a number of antiemetic guideline–endorsed regimens for use in the prevention of nausea and vomiting caused by chemotherapy
- Non issue with CPI monotherapy; do not require antiemetic prophylaxis
- Ten RCTs compared the combination of chemotherapy and a CPI with chemotherapy alone
- Two trials (KEYNOTE- 189, KEYNOTE- 407) in stage 4 NSCLC evaluated the addition of pembrolizumab to chemotherapy and specified that standard corticosteroid containing antiemetic regimens be used
- In both trials, the addition of pembrolizumab to chemotherapy improved overall survival (OS) and progression-free survival (PFS).

Corticosteroid Use with Checkpoint Inhibitors

- There is no evidence from clinical trials in adults to warrant omitting dexamethasone from guideline-compliant prophylactic antiemetic regimens when CPIs are administered in combination with chemotherapy
- CPIs administered alone or in combination with another CPI are minimally emetogenic in adults and do not require routine use of a prophylactic antiemetic

ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee guideline process includes:

- a systematic literature review by ASCO guidelines staff
- an expert panel provides critical review and evidence interpretation to inform guideline recommendations
- final guideline approval by ASCO CPGC

The full ASCO Guideline methodology manual can be found at:
www.asco.org/guideline-methodology

ASCO Guidelines

High-emetic-risk antineoplastic agents (AC)

- Adults treated with an anthracycline combined with cyclophosphamide should be offered a four-drug combination of an NK1 receptor antagonist, a 5-HT_3 receptor antagonist, dexamethasone, and olanzapine (day 1)
- Olanzapine should be continued on days 2 to 4
- (Type: evidence based, benefits outweigh harms; Evidence quality:high;Strength of recommendation: strong)

ASCO Guideline Panel Members

Name	Affiliation/Institution	Role/Area of Expertise
Paul J. Hesketh, MD (co-chair)	Lahey Hospital and Medical Center, Burlington, MA	Hematology and oncology, supportive care, investigational therapeutics
Mark G. Kris, MD (co-chair)	Memorial Sloan Kettering Cancer Center, New York, NY	Medical oncology, thoracic oncology, supportive care, investigational therapeutics
Ethan Basch, MD, MSc	University of North Carolina at Chapel Hill, Chapel Hill, NC	Medical oncology, health services research, patient-reported outcomes, comparative effectiveness research
Gary H. Lyman, MD, MPH	Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA	Hematology and oncology, health economics, epidemiology and biostatistics
Sally Y. Barbour, PharmD, BCOP, CPP	Duke University Medical Center, Durham, NC	Oncology pharmacy
Rebecca Anne Clark-Snow, RN, BSN, OCN	Overland Park, KS	Oncology nursing, supportive care
Michael A. Danso, MD (PGIN representative)	Virginia Oncology Associates, Norfolk and Virginia Beach, VA	Medical oncology, community oncology, clinical trials
Kristopher Dennis, MD	The Ottawa Hospital and the University of Ottawa, Ottawa, Ontario, Canada	Radiation oncology, supportive care
L. Lee Dupuis, RPh, ACPR, MScPhm, PhD	The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada	Supportive care of children with cancer
Stacie B. Dusetzina, PhD	Vanderbilt University School of Medicine and Vanderbilt-Ingram Cancer Center, Nashville, TN	Health economics, pharmaceutical outcomes and policy
Cathy Eng, MD	Vanderbilt-Ingram Cancer Center, Nashville, TN	Gastrointestinal medical oncology
Petra C. Feyer, MD, PhD	Vivantes Clinics Neukoelln, Berlin, Germany	Radiation oncology, supportive care
Karin Jordan, MD	University of Heidelberg, Heidelberg, Germany	Medical oncology, supportive care
Kimberly Noonan, MS, RN, ANP, AOCN	Dana-Farber Cancer Institute, Boston, MA	Oncology nursing
Dee Sparacio (patient representative)	Hightstown, NJ	Patient representative
Kari Bohlke, ScD	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

High-emetic-risk antineoplastic agents (single agents)

- Adults treated with cisplatin and other high-emetic-risk single agents should be offered a four-drug combination of an NK1 receptor antagonist, a serotonin (5-HT_3) receptor antagonist, dexamethasone, and olanzapine (day 1)
- Dexamethasone and olanzapine should be continued on days 2 to 4
- (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)

Moderate-emetic-risk antineoplastic agents (carboplatin)

- Adults treated with carboplatin area under the curve (AUC) ≥ 4 mg/mL/min should be offered a three-drug combination of an NK1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone (day 1)
- (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)

Moderate-emetic-risk antineoplastic agents (excluding carboplatin AUC ≥ 4)

- Adults treated with moderate-emetic-risk antineoplastic agents (excluding carboplatin AUC ≥ 4 mg/mL/min) should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone (day 1)
- (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)
- Adults treated with cyclophosphamide, doxorubicin, oxaliplatin and other moderate-emetic-risk antineoplastic agents known to cause delayed nausea and vomiting may be offered dexamethasone on days 2 to 3
- (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)

Low-emetic-risk antineoplastic agents

- Adults treated with low-emetic-risk antineoplastic agents should be offered a single dose of a 5-HT_3 receptor antagonist or a single 8-mg dose of dexamethasone before antineoplastic treatment
- (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)

Minimal-emetic-risk antineoplastic agents

- Adults treated with minimal emetic risk antineoplastic agents should not be offered routine antiemetic prophylaxis
- (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)

Antineoplastic Combinations and Multi-day therapy

- Adults treated with antineoplastic combinations should be offered antiemetics appropriate for the component antineoplastic agent of greatest emetic risk
- (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)
- Adults treated with multi-day antineoplastic agents should be offered antiemetics before treatment that are appropriate for the emetic risk of the antineoplastic agent given on each day of the antineoplastic treatment and for 2 days after antineoplastic regimen completion
- (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)
- Adults treated with 4 - or 5 - day cisplatin regimens should be offered a three-drug combination of an NK1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone
- (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)

Cannabinoids, Complementary, Alternative and Adjunctive therapies

- Evidence remains insufficient for a recommendation regarding medical marijuana for the prevention of nausea and vomiting in patients with cancer receiving chemotherapy or radiation therapy
- Evidence is also insufficient for a recommendation regarding the use of medical marijuana in place of the tested and US Food and Drug Administration-approved cannabinoids dronabinol and nabilone
- Evidence remains insufficient for a recommendation for or against the use of ginger, acupuncture/acupressure, and other complementary or alternative therapies for the *prevention* of nausea and vomiting in patients with cancer.
- Lorazepam is a useful adjunct to antiemetic drugs, but is not recommended as a single-agent antiemetic

Breakthrough Nausea and Vomiting

- For patients with breakthrough nausea or vomiting, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications; and ascertain that the best regimen is being administered for the emetic risk
- (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).
- Adults who experience nausea or vomiting despite optimal prophylaxis, and who did not receive olanzapine prophylactically, should be offered olanzapine in addition to continuing the standard antiemetic regimen
- (Type: evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).
- Adults who experience nausea or vomiting despite optimal prophylaxis, and who have already received olanzapine, may be offered a drug of a different class (e.g. an NK1 receptor antagonist, lorazepam or alprazolam, a dopamine receptor antagonist, dronabinol, or nabilone) in addition to continuing the standard antiemetic regimen
- (Type: informal consensus; benefits outweigh harms; Evidence quality: intermediate for dronabinol and nabilone, low otherwise; Strength of recommendation: moderate).

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

- Adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation should be offered a three-drug combination of an NK1receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone
- (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)
- A four-drug combination of an NK1 receptor antagonist, a 5-HT_3 receptor antagonist, dexamethasone, and olanzapine may be offered to adults treated with high-dose chemotherapy and stem-cell or bone marrow transplantation
- (Type: evidence based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak)

Anticipatory Nausea and Vomiting

- All patients should receive the most active antiemetic regimen appropriate for the antineoplastic agents being administered
- Clinicians should use such regimens with initial antineoplastic treatment, rather than assessing the patient's emetic response with less effective antiemetic treatment
- If a patient experiences anticipatory emesis, clinicians may offer behavioral therapy with systematic desensitization
- (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate)

Olanzapine: Expanding Role in Chemotherapy-induced Nausea and Vomiting

- Olanzapine is an second generation antipsychotic used for schizophrenia and bipolar disorder
- Multi –receptor binding (serontonergic 5-HT_{2a},5-HT_{2c},5-HT_3, 5-HT_6, and dopamine D_1,D_2; D_3, and D_4 receptors)
- Unlike 5-HT_3 and NK_1 receptor antagonists which were specifically developed for use in CINV with major pharma support, studies evaluating olanzapine's potential value in CINV have been primarily investigator – initiated
- Early phase I-II trials showed promising antiemetic activity
- Four phase III trials support efficacy in three settings
  - Highly emetogenic standard- dose chemotherapy
  - Highly emetogenic chemotherapy in HSCT
  - Breakthrough nausea and vomiting

Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting

- NCI sponsored trial by the Alliance cooperative group
- 380 chemotherapy-naïve patients
- Receiving either cisplatin $\geq$ 70 mg/m^2 or doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2
- Randomized to 5HT$_3$ RA day 1, dexamethasone days 1-4, NK1 RA day1 and olanzapine 10 mg or placebo days 1 -4
- Endpoints
  - Primary – no nausea
  - Secondary – complete response (no emesis or use of rescue medication)

Additional Resources

More information, including a Data Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/supportive-care-guidelines

Patient information is available at www.cancer.net

ASCO Guidelines

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting

Rudolph M. Navari, M.D., Rui Qin, Ph.D., Kathryn J. Ruddy, M.D., Heshan Liu, Ph.D., Steven F. Powell, M.D., Madhuri Bajaj, M.D., Leah Dietrich, M.D., David Biggs, M.D., Jacqueline M. Lafky, M.S., and Charles L. Loprinzi, M.D.

Navari RM: N Engl J Med 2016; 375:134 -142

Table 2. Primary End Point According to Study Group.

Variable	Olanzapine (N = 192)	Placebo (N = 188)	Total (N = 380)	P Value*	Adjusted P Value†
	number/total number (percent)				
0–24 hr after chemotherapy					
No nausea	135/183 (73.8)	82/181 (45.3)	217/364 (59.6)	<0.001	0.002
Nausea	48/183 (26.2)	99/181 (54.7)	147/364 (40.4)		
25–120 hr after chemotherapy					
No nausea	75/177 (42.4)	45/177 (25.4)	120/354 (33.9)	0.001	0.002
Nausea	102/177 (57.6)	132/177 (74.6)	234/354 (66.1)		
0–120 hr after chemotherapy					
No nausea	66/177 (37.3)	39/178 (21.9)	105/355 (29.6)	0.002	0.002
Nausea	111/177 (62.7)	139/178 (78.1)	250/355 (70.4)		

* P values were calculated with the use of the chi-square test.
† P values were calculated according to the Simes gatekeeping procedure.

Navari RM: N Engl J Med 2016; 375:134 -142

Table 3. Complete Response According to Study Group.*

Complete Response	Olanzapine (N=192)	Placebo (N=188)	Total (N=380)	Odds Ratio†	P Value‡	Adjusted P Value§
	number/total number (percent)					
0–24 hr after chemotherapy				0.30		
No	26/182 (14.3)	64/181(35.4)	90/363 (24.8)			
Yes	156/182 (85.7)	117/181 (64.6)	273/363 (75.2)		<0.001	<0.001
25–120 hr after chemotherapy				0.55		
No	54/163 (33.1)	80/168 (47.6)	134/331 (40.5)			
Yes	109/163 (66.9)	88/168 (52.4)	197/331 (59.5)		0.007	0.007
0–120 hr after chemotherapy				0.39		
No	59/162 (36.4)	101/170 (59.4)	160/332 (48.2)			
Yes	103/162 (63.6)	69/170 (40.6)	172/332 (51.8)		<0.001	<0.001

* A complete response (a secondary end point) was defined as no emesis and no use of rescue medication.
† Odds ratios are for emesis or the use of rescue medication (i.e., lack of complete response) in the olanzapine group as compared with the placebo group.
‡ P values were calculated with the use of the chi-square test.
§ P values were calculated according to the Simes gatekeeping procedure.

Navari RM: N Engl J Med 2016; 375:134-142

Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Hironobu Hashimoto, Masakazu Abe, Osamu Tokuyama, Hideaki Mizutani, Yosuke Uchitomi, Takuhiro Yamaguchi, Yukari Hoshina, Yasuhiko Sakata, Takako Yanai Takahashi, Kazuhisa Nakashima, Masahiko Nakao, Daisuke Takei, Sadamoto Zenda, Koki Mizukami, Satoru Iwasa, Michiru Sakurai, Noboru Yamamoto, Yuichiro Ohe

- Initial cycle cisplatin ≥ 50 mg/m2
- 710 patients
- Aprepitant/palonosetron/dexamethasone ± olanzapine 5 mg po days 1-4
- Endpoints
  - Primary – complete response in delayed phase
  - Secondary – complete response in acute and overall study periods
- Delayed complete response (no emesis/no rescue) 79% vs 66 % favoring the olanzapine arm
- Good tolerance

Lancet Oncol 2020;21:242-249

Biol Blood Marrow Transplant 24 (2018) 2065–2071

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Supportive Care

Randomized, Placebo-Controlled, Phase III Trial of Fosaprepitant, Ondansetron, Dexamethasone (FOND) Versus FOND Plus Olanzapine (FOND-O) for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients with Hematologic Malignancies Receiving Highly Emetogenic Chemotherapy and Hematopoietic Cell Transplantation Regimens: The FOND-O Trial

Amber B. Clemmons[1,2,*,§], Julianne Orr[3,§], Benjamin Andrick[4], Arpita Gandhi[2], Claude Sportes[5], David DeRemer[6]

- 101 patients undergoing HCT with variety of preparative regimens
- Fosaprepitant/ondansetron/dexamethasone ± 10 mg olanzapine po
- Overall complete response 55% vs 26% in favor of olanzapine p = 0.003
- Delayed complete response 60.8% vs 30% in favor of olanzapine p= 0.001

Support Care Cancer (2013) 21:1655–1663
DOI 10.1007/s00520-012-1710-6

ORIGINAL ARTICLE

The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy

Rudolph M. Navari · Cindy K. Nagy · Sarah E. Gray

- 276 patients receiving highly emetic chemotherapy
- Initial prophylaxis fosaprepitant/palonosetron/dexamethasone
- 110 patients (108 evaluable) with breakthrough emesis
- Randomized at breakthrough to olanzapine 10 mg po qd X 3 days or metoclopramide 10 mg tid po X 3 days
- Complete response:39/56 (70%) with olanzapine vs 16/52 (31%) with metoclopramide $p < 0.01$

Thank you!

Questions ??