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Nausea and Vomiting in Palliative Care: Antipsychotics as Antiemetics

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Advanced Practice Selective
in Palliative Care

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Objectives

- Overview of Nausea and Vomiting in Palliative Care
  - » Definitions
  - » Epidemiology
  - » Etiology
- Overview of Management
  - » General strategy
  - » Neurotransmitters and the Emesis Pathway
  - » Receptor profiles of common antiemetics
- Antipsychotics as antiemetics
  - » Evidence for Haloperidol as an antiemetic
  - » Haloperidol as antiemetic in Palliative Care

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Nausea and Vomiting in Palliative Care

- Nausea
  - Unpleasant sensation (or sensations) immediately preceding vomiting
  - Can occur alone or can accompany vomiting
  - Entirely subjective experience

- Vomiting
  - Rapid, forceful evacuation of gastric contents in retrograde fashion
  - Usually preceded by nausea (but not always)
  - Highly specific physical event

SOURCES:
Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. Clin Interv Aging. 2011;6:243-59.

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Nausea and Vomiting in Palliative Care

- Epidemiology
  - » Generally considered a common symptom in palliative care population
    - 62% of terminally ill cancer patients[1]
    - 71% of patients admitted to palliative care unit reported nausea during last week of life[2]
  - » Study by Solano, et. al suggests nausea and vomiting is less common than pain, breathlessness, fatigue[3]

Sources:
1. Reuben DB, Mor V. Nausea and vomiting in terminal cancer patients. Arch Intern Med. 1986;146(10):2021-2023
2. Fainsinger R, Miller MJ, Bruera E, Hanson J, Maceachern T. Symptom control during the last week of life on a palliative care unit. J Palliat Care. 1991;7(1):5-11
3. Solano JP, Gomes B, Higginson IJ**. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease.** J Pain Symptom Manage. 2006 Jan;31(1):58-69.

Nausea and Vomiting in Palliative Care

- Common Causes
  - Toxic/metabolic disturbances
    - Drugs
    - Organ failure
    - Metabolic
  - Disorders of viscera
    - Obstruction
    - Gastroparesis
    - Inflammation / irritation
  - CNS Causes
    - Increased intracranial pressure
    - Vestibular dysfunction
    - Anxiety

SOURCES:
Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. Clin Interv Aging. 2011;6:243-59.
Flake ZA, Scalley RD, Bailey AG. Practical selection of antiemetics.. Am Fam Physician. 2004 Mar 1;69(5):1169-74.
Baines MJ. ABC of palliative care: Nausea, vomiting, and intestinal obstruction. BMJ. 1997 Nov 1;315(7116):1148-50.

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Management Approach

- Three basic steps
  - » Clarify what patient is experiencing and identify etiology
  - » Identify and correct consequences of nausea and vomiting
    - Fluid depletion
    - Electrolyte imbalances (hypokalemia)
    - Metabolic alkalosis
  - » Treat nausea and vomiting
    - Correct underlying cause (if possible)
    - Symptom management
      - » Non-pharmacologic methods
      - » antiemetics

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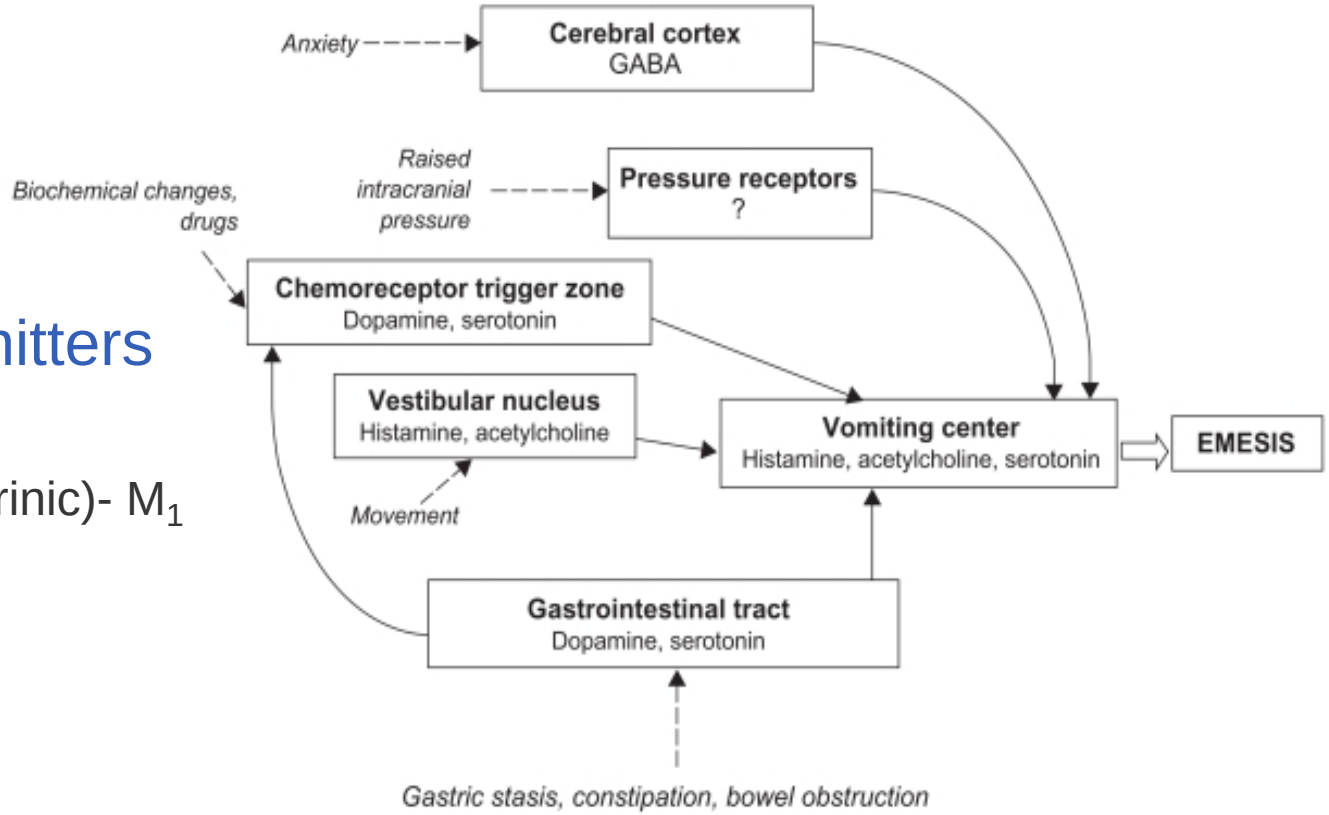
Neurotransmitters and the Emetic Pathway

Major Neurotransmitters and Receptors:

- Acetylcholine (muscarinic)- M_1
- Dopamine - D_2
- Histamine - H_1
- Serotonin - $5HT_{2\text{-}4}$



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Receptor Profiles of Common Antiemetics

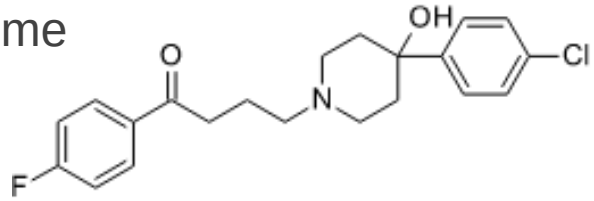
Drug	D2	H1	M1	5HT
Anti-cholinergic:				
Hyoscine (Scopolamine)				
Antii-histamine:				
Promethatzine (Phenergan)				
Selective 5HT antagonists:				
Ondansetron (Zofran)				
Dopamine Receptor Antagonists:				
Prochlorperazine (Compazine)				
Chlorpromazine (Thorazine)				
Metoclopramide (Reglan)				
Haloperidol (Haldol)				
Olanzapine (Zyprexa)				

High affinity
Moderate affinity
Low affinity
Minimal / No known affinity

SOURCES:
Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. Clin Interv Aging. 2011;6:243-59.
Prommer E. Olanzapine: palliative medicine update. Am J Hosp Palliat Care. 2013 Feb;30(1):75-82
Pommer E. Role of Haloperidol in Palliative Medicine: An Update. Am J Hosp Palliat Care. 2012 Jun;29(4):295-301

Haloperidol

- Butyrophenone derivative
  - Discovered in 1958
  - FDA approved in 1967 as antipsychotic
- Dopamine (D2) receptor antagonist[1,2]
  - Chemorecptor trigger zone (CTZ)
- Adverse effects[1]
  - Extrapyramidal side effects
  - QT Interval Prolongation
  - Seizures
  - Neuroleptic Malignant Syndrome



SOURCES:
1. Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. Clin Interv Aging. 2011;6:243-59.
2. Pommer E. Role of Haloperidol in Palliative Medicine: An Update. Am J Hosp Palliat Care. 2012 Jun;29(4):295-301

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Haloperidol as an Antiemetic

- Widely used as antiemetic despite limited data

- 2004 Meta-analysis by Büttner, et. al evaluated data in three general areas
  - » Chemotherapy and Radiotherapy
  - » Nausea and Vomiting related to Gastrointestinal diseases
  - » Postoperative Nausea and Vomiting

Source:
Büttner M, Walder B, von Elm E, Tramèr MR. Is low-dose haloperidol a useful antiemetic?: A meta-analysis of published and unpublished randomized trials. Anesthesiology. 2004 Dec;101(6):1454-63.

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Haloperidol as an Antiemetic

- Chemotherapy and Radiation Therapy
  - » No conclusions drawn from meta-analysis[1]
    - Neidhart et. al. (1981) comparing Haloperidol vs. Benzquinamide[2]
      - » Patients preferred haloperidol for control of emesis induced by cis-platinum (78 vs. 22%) and nitrogen mustard (67 vs. 16%)
    - Cole et. al (1974) Radiation therapy trial comparing Haloperidol to placebo[3]
      - » 96% of patients taking haloperidol reported reduced vomiting compared to 20% of placebo
- Gastrointestinal Diseases
  - » Meta-analysis demonstrated efficacy for both 1mg and 2 mg doses at controlling nausea and vomiting[1]
    - 12 hrs post haloperidol therapy:
      - » 1 mg IM haloperidol vs. placebo RB 2.59 (CI 95% 1.74-3.91) NNT 2.5 (CI 95% 1.9 – 3,.8)
      - » 2 mg IM haloperidol vs. placebo RB 3.84 (CI 95% 1.93 – 7.65) NNT 2.1 (CI 95% 1.5-3.5)

Source:
1. Büttner M, Walder B, von Elm E, Tramèr MR. Is low-dose haloperidol a useful antiemetic?: A meta-analysis of published and unpublished randomized trials. Anesthesiology. 2004 Dec;101(6):1454-63.
2. Neidhart JA, Gagen M, Young D, Wilson HE. Specific antiemetics for specific cancer chemotherapeutic agents: haloperidol versus benzquinamide. Cancer. 1981 Mar 15;47(6):1439-43.
3. Cole DR, Duffy DF. Haloperidol for radiation sickness: Control of associated nausea, vomiting, and anorexia. N Y State J Med. 1974 Aug;74(9):1558-62.

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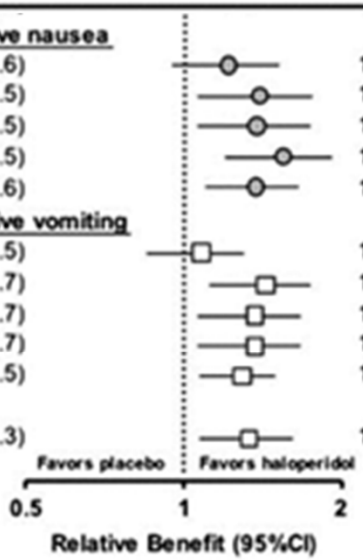
Haloperidol as an Antiemetic

- Prevention of postoperative Nausea and Vomiting (PONV)
  - » Meta-analysis revealed efficacy for prevention of PONV at doses between 0.5 – 4 mg haloperidol (but not for 0.25 mg)[1] - no evidence of dose responsiveness

	N° with endpoint/tot N° (%) Haloperidol	Placebo	RB (95% CI)	NNT (95% CI)
Prevention of late (0-24 h) postoperative nausea				
0.25 mg IM	41/50 (82.0)	35/51 (68.6)	1.19 (0.95 to 1.50)	7.5 (3 to -31)
0.5 mg IM	41/50 (82.0)	30/48 (62.5)	1.36 (1.06 to 1.74)	4.5 (3 to 18)
1 mg IM	45/53 (84.9)	30/48 (62.5)	1.35 (1.06 to 1.73)	4.5 (3 to 19)
2 mg IM	49/52 (94.2)	30/48 (62.5)	1.51 (1.20 to 1.90)	3.2 (2 to 6)
4 mg IM	47/51 (92.2)	35/51 (68.6)	1.34 (1.10 to 1.64)	4.3 (3 to 11)
Prevention of late (0-24 h) postoperative vomiting				
0.25 mg IM	40/50 (80.0)	39/51 (76.5)	1.05 (0.85 to 1.29)	28 (5 to -8)
0.5 mg IM	49/53 (92.5)	32/48 (66.7)	1.39 (1.12 to 1.72)	3.9 (2 to 9)
1 mg IM	46/52 (88.5)	32/48 (66.7)	1.33 (1.06 to 1.66)	4.6 (3 to 17)
2 mg IM	46/52 (88.5)	32/48 (66.7)	1.33 (1.06 to 1.66)	4.6 (3 to 17)
4 mg IM	49/51 (96.1)	39/51 (76.5)	1.26 (1.07 to 1.48)	5.1 (3 to 15)
4 mg IV	59/70 (84.3)	45/70 (64.3)	1.31 (1.07 to 1.60)	5.0 (3 to 17)



  - » Two more recent RCTs comparing haloperidol to ondansetron in PONV
    - Lee et. al. 2 mg haloperidol vs. 4 mg ondansetron demonstrated low incidence of PONV (<30% incidence, no significant difference; expected incidence of 60%)[2]
    - Roswo et. al. 1 mg haloperidol vs. 4 mg ondansetron demonstrated complete resolution of PONV (78.2% vs. 76.8% respectively, no significant difference) [3]

Source:
1. Büttner M, Walder B, von Elm E, Tramèr MR. Is low-dose haloperidol a useful antiemetic?: A meta-analysis of published and unpublished randomized trials. Anesthesiology. 2004 Dec;101(6):1454-63.
2. Lee Y, Wang PK, Lai HY, Yang YL, Chu CC, Wang JJ. Haloperidol is as effective as ondansetron for preventing post operative nausea and vomiting. Can JAnesth. 2007; 54:349-354
3. Rosow CE, Haspel KL, Smith SE, Grecu L, Bittner EA. Haloperidol versus ondansetron for prophylaxis of postoperative nausea and vomiting. Anesth Analg..2008;106:1407-1409.

Haloperidol in Palliative Care

- Haloperidol considered one of the 20 essential drugs in palliative care[1]
- Evidence for haloperidol as antiemetic in palliative care patients?
  - » No RCTs studying haloperidol in palliative care patients
  - » 2010 Cochrane Review[2]: "*There is not enough evidence to be able to recommend haloperidol for the treatment of nausea and vomiting in adult patients suffering from incurable progressive medical conditions*"
  - » Observational study on efficacy of haloperidol in management of nausea and vomiting in palliative care cancer patients
    - 61 % patients reported response (complete or partial) ((CI 95% 44-77%) after treatment with haloperidol
    - 24% of patient reported complete response (CI 95% 10-39%) after treatment with haloperidol
  - » Consensus, based largely on case series, that haloperidol is an effective antiemetic for chemical and metabolic causes of nausea and vomiting[4]

Source:
1. De Lima L. Doyle D. The International Association for Hospice and Palliative Care list of essential medicines for palliative care. J Pain Palliat Care Pharmacother. 2007;21(3):29-36.
2. Perkins P, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006271
3. Hardy JR, O'Shea A,, White C,, Gilshenan K,, Welch L, Douglas C. The efficacy of haloperidol in the management of nausea and vomiting in patients with cancer.. J Pain Symptom Manage. 2010 Jul;40(1):111-6
4. Keeley PW. Nausea and vomiting in people with cancer and other chronic diseases. Clin Evid (Online). 2009 Jan 13;2009.

Conclusions

- Nausea and vomiting are common symptoms encountered in palliative care patient population
- Treatment is often complex and requires thoughtful evaluation of the patient s' symptoms
- Evidence behind use of haloperidol as antiemetic in palliative care patients is limited
  - » Recommended dose: 0.5 mg IV q4-6 hours[1]

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.Source:
1. Pommer E. Role of Haloperidol in Palliative Medicine: An Update. Am J Hosp Palliat Care. 2012 Jun;29(4):295-301.