

Nausea and Vomiting- what, when and why?

Dr Paul Paes

Consultant/ Reader in Palliative Medicine

Declaration of Interests

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

Content

- Treating the cause v empirical treatment
- Evidence base-
 - advanced cancer
 - opiate induced nausea
 - malignant bowel obstruction
- Summary

Nausea and vomiting in advanced cancer

- Reported to be present in over 60% of patients with advanced cancer
- Cause multifactorial:
 - medications such as opioids
 - delayed gastric emptying
 - mechanical bowel obstruction
 - increased intracranial pressure
 - vestibular dysfunction
 - metabolic issues
 - and/or cortical effects such as anxiety and/or depression
 - Delayed gastric emptying and partial bowel obstruction
 - secondary to a patient's treatment such as chemotherapy/and/or radiation therapy

Navari, R.M. Nausea and Vomiting in Advanced Cancer. *Curr. Treat. Options in Oncol.* 21, 14 (2020)

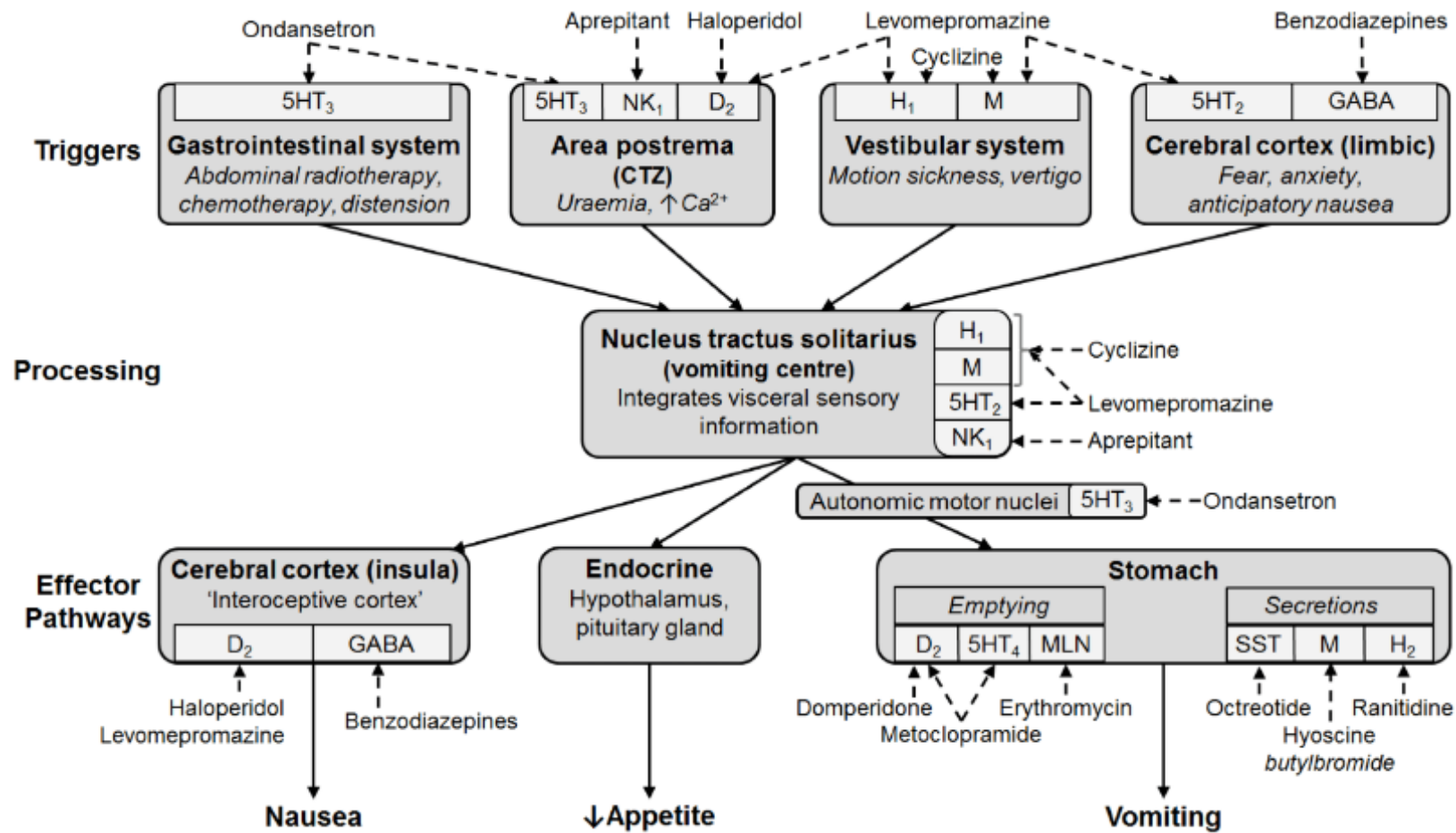
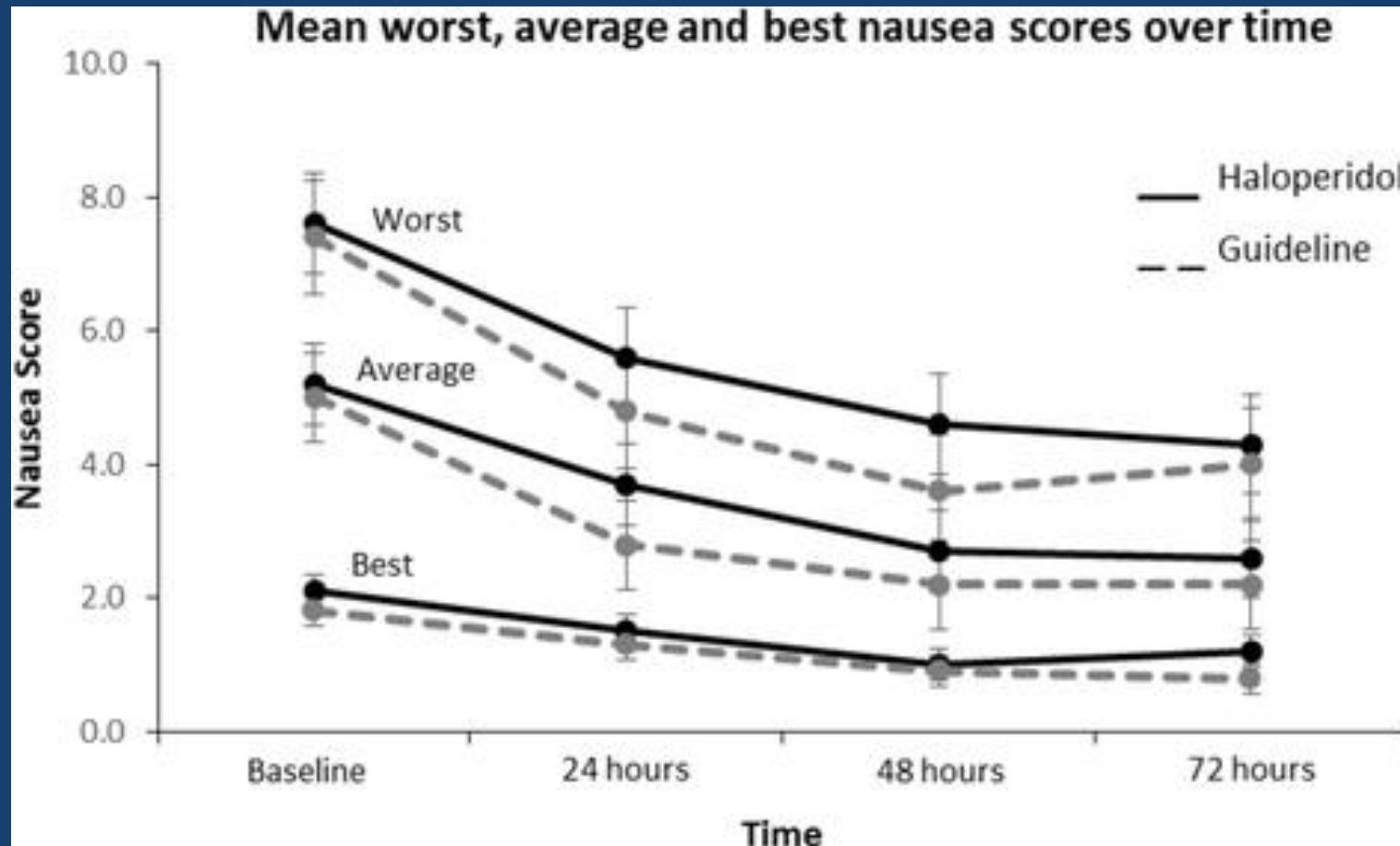


Figure 1 Putative peripheral and central sites of action of selected anti-emetics. Also see individual drug monographs. ⁷⁻¹²
 Abbreviations: Ca^{2+} = calcium, CTZ = chemoreceptor trigger zone. Other abbreviations refer to receptor types: D_2 = dopamine type 2; $5HT_2$, $5HT_3$ = 5-hydroxytryptamine (serotonin) type 2, type 3; H_1, H_2 = histamine type 1, type 2; M = muscarinic cholinergic; NK_1 = neurokinin 1. Note. Anti-emetics act as antagonists at these receptors, whereas the effects on $5HT_4$ (5-hydroxytryptamine type 4), MLN (motilin), SST (somatostatin) and GABA (gamma-aminobutyric acid) are agonistic.

Palliative Care Formulary:
<https://www.medicinescomplete.com/#/content/palliative/anti-emetics>



- Open Label
- 185 patients: 86 (74 completed) haloperidol
95 (72) guideline
- 24 hrs: greater response rate in guideline arm than single agent arm 49% vs 32%; $p = 0.02$
- 72 hrs: 49% v 53%; $p = 0.59$

Hardy J, Skerman H, Glare P, Philip J, Hudson P, Mitchell G, Martin P, Spruyt O, Currow D, Yates P (2018).

A randomized open-label study of guideline-driven antiemetic therapy versus single agent antiemetic therapy in patients with advanced cancer and nausea not related to anticancer treatment. BMC Cancer May 2;18(1):510 18(1):510

Evidence Base- Systematic Reviews

- Davis MP, Hallerberg G (2010) Palliative Medicine Study Group of the Multinational Association of Supportive Care in C. A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation. *J Pain Symptom Manag* 39(4):756–767
- Walsh D, Davis M, Ripamonti C et al.(2017) 2016 Updated MASCC/ESMO consensus recommendations: management of nausea and vomiting in advanced cancer. *Support Care Cancer* 25(1):333–340
- Davis, M, Hui, D, Davies, A et al. (2021) MASCC antiemetics in advanced cancer updated guideline. *Support Care Cancer* 29, 8097–8107:
 - Covers chronic generalized nausea and vomiting in advanced cancer and nausea and vomiting associated with opioid therapy
 - Update includes all new randomised trials from 2015-2021

What is the evidence for therapeutic benefit of common anti-emetics in advanced cancer?

No high-quality randomized trial evidence as to benefit

- Cyclizine
- Ondansetron
- Palonosetron
- Prochlorperazine
- Promethazine
- Antihistamines
- Scopolamine

Haloperidol

- Incomplete evidence from published RCTs to determine the effectiveness of haloperidol for nausea and vomiting in palliative care
- Evidence largely derived from post-surgery, radiotherapy and chemotherapy

Murray-Brown F, Dorman S.

Haloperidol for the treatment of nausea and vomiting in palliative care patients.

Cochrane Database Syst Rev. 2015 Nov 2;2015(11):CD006271

- 2 randomised haloperidol trials:
- Haloperidol v methotrimeprazine: both effective antiemetics (75% v 63% 2 point reduction in nausea score) in patients with advanced cancer and nausea
- Haloperidol v antiemetics based on aetiology: no difference in effectiveness (53% v 49% 2 point reduction in nausea score and to <3/10

Hardy JR, Skerman H, Philip J, Good P, Currow DC, Mitchell G, Yates P (2019) Methotrimeprazine versus haloperidol in palliative care patients with cancer-related nausea: a randomised, double-blind controlled trial. BMJ Open 9(9):e029942

Hardy JR, O'Shea A, White C, Gilshenan K, Welch L, Douglas C (2010) The efficacy of haloperidol in the management of nausea and vomiting in patients with cancer. J Pain Symptom Manag 40(1):111–116

Metoclopramide- good evidence of efficacy

- 1 randomised placebo controlled trial:

Bruera E, Belzile M, Neumann C, Harsanyi Z, Babul N, Darke A (2000) A double-blind, crossover study of controlled-release metoclopramide and placebo for the chronic nausea and dyspepsia of advanced cancer. J Pain Symptom Manag 19(6):427–435

- 4 randomised controlled trials:

Bruera ED, MacEachern TJ, Spachynski KA et al (1994) Comparison of the efficacy, safety, and pharmacokinetics of controlled release and immediate release metoclopramide for the management of chronic nausea in patients with advanced cancer. Cancer 74(12):3204–3211

Bruera E, Moyano JR, Sala R et al (2004) Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. J Pain Symptom Manag 28(4):381–388

Corli O, Cozzolino A, Battaiotto L (1995) Effectiveness of levosulpiride versus metoclopramide for nausea and vomiting in advanced cancer patients: a double-blind, randomized, crossover study. J Pain Symptom Manag 10(7):521–526

Mystakidou K, Befon S, Trifyllis J, Lioffi C, Papadimitriou J (1997) Tropisetron versus metoclopramide in the control of emesis in far-advanced cancer. Oncologist 2(5):319–323

Mystakidou K, Befon S, Lioffi C, Vlachos L (1998) Comparison of the efficacy and safety of tropisetron, metoclopramide, and chlorpromazine in the treatment of emesis associated with far advanced cancer. Cancer 83(6):1214–1223

- 2 randomised trials where metoclopramide used as rescue medication:

Hardy JR, Skerman H, Philip J, Good P, Currow DC, Mitchell G, Yates P (2019) Methotrimeprazine versus haloperidol in palliative care patients with cancer-related nausea: a randomised, double-blind controlled trial. BMJ Open 9(9):e029942

Hardy JR, O'Shea A, White C, Gilshenan K, Welch L, Douglas C (2010) The efficacy of haloperidol in the management of nausea and vomiting in patients with cancer. J Pain Symptom Manag 40(1):111–116

Olanzapine

- Theoretically interesting because of receptor and tolerance profile
- Studies scarce with low statistical power: limited evidence

Saudemont G, Prod'Homme C, Da Silva A, Villet S, Reich M, Penel N, Gamblin V.

The use of olanzapine as an antiemetic in palliative medicine: a systematic review of the literature.

BMC Palliat Care. 2020 Apr 22;19(1):56

- Moderate-quality evidence that oral olanzapine probably increases the likelihood of not being nauseous or vomiting during chemotherapy from 25% to 50% in adults with solid tumours

Sutherland A, Naessens K, Plugge E, Ware L, Head K, Burton MJ, Wee B.

Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults.

Cochrane Database Syst Rev. 2018 Sep 21;9(9):CD012555

- Randomised placebo controlled trial: olanzapine better than placebo. At 7 days, olanzapine nausea: 9/10 to 1/10 v placebo 9/10 to 8/10

Navari RM, Pywell CM, Le-Rademacher JG et al (2020)

Olanzapine for the treatment of advanced cancer-related chronic nausea and/or vomiting: a randomized pilot trial.

JAMA Oncol 6(6):895–899

Levomepromazine/ methotrimeprazine

- Further studies of levomepromazine and other antiemetic agents are needed to provide better evidence for their use in this setting

Cox L, Darvill E, Dorman S.

Levomepromazine for nausea and vomiting in palliative care.

Cochrane Database Syst Rev. 2015 Nov 2;2015(11):CD009420

- Randomised controlled trial:

- Haloperidol v methotrimeprazine: both effective antiemetics (75% v 63% 2 point reduction in nausea score) in patients with advanced cancer and nausea

Hardy JR, Skerman H, Philip J, Good P, Currow DC, Mitchell G, Yates P (2019) Methotrimeprazine versus haloperidol in palliative care patients with cancer-related nausea: a randomised, double-blind controlled trial. BMJ Open 9(9):e029942

Other key data

- Levosulpiride (75mg/day) found to be a better antiemetic than metoclopramide (30mg) in a small randomized double-blind pilot study

Corli O, Cozzolino A, Battaiotto L (1995) Effectiveness of levosulpiride versus metoclopramide for nausea and vomiting in advanced cancer patients: a double-blind, randomized, crossover study. *J Pain Symptom Manag* 10(7):521–526

- Large randomized open-label (not powered and method of randomisation unclear) trial compared tropisetron to metoclopramide, chlorpromazine, and dexamethasone in combinations. Tropisetron (5HT3 antagonist) more active antiemetic with little benefits to combinations and no benefit to the addition of dexamethasone

Mystakidou K, Befon S, Lioffi C, Vlachos L (1998) Comparison of the efficacy and safety of tropisetron, metoclopramide, and chlorpromazine in the treatment of emesis associated with far advanced cancer. *Cancer*. 83(6):1214–1223

- Dexamethasone is an ineffective adjuvant to other antiemetics found in 2 RCT. May have a role in nausea due to brain metastases or malignant bowel obstruction

Bruera E, Moyano JR, Sala R, Rico MA, Bosnjak S, Bertolino M, Willey J, Strasser F, Palmer JL (2004) Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. *J Pain Symptom Manag* 28(4):381–388

Mystakidou K, Befon S, Lioffi C, Vlachos L (1998) Comparison of the efficacy and safety of tropisetron, metoclopramide, and chlorpromazine in the treatment of emesis associated with far advanced cancer. *Cancer*. 83(6):1214–1223

- NEPA (netupitant/palonosetron) in a small randomized phase II trial demonstrated that both placebo and NEPA improved nausea but there were no between group differences.

Hui D, Puac V, Shelal Z, Liu D, Maddi R, Kaseb A, Javle M, Overman M, Yennurajalingam S, Gallagher C, Bruera E (2021) Fixed-dose netupitant and palonosetron for chronic nausea in cancer patients: a double-blind, placebo run-in pilot randomized clinical trial. *J Pain Symptom Manag* 62:223–232.e1

Table 5 MASCC guideline statement

From: [MASCC antiemetics in advanced cancer updated guideline](#)

Guideline statements	LOE	GOE	Guideline
Metoclopramide is first-line antiemetic	II	A	Recommendation
Haloperidol is a first-line antiemetic	II	A	Recommendation
Methotrimeprazine is a second-line antiemetic	II	B	Recommendation
Olanzapine is a second-line antiemetic	II	B	Recommendation
Levosulpiride is a third-line antiemetic	III	B	Suggested use
Tropisetron is a third-line antiemetic	II	B	Suggested use

Table 4 MASCC categories of guidelines

From: [MASCC antiemetics in advanced cancer updated guideline](#)

Recommendation Reserved for guidelines that are based on level I or level II evidence.

Suggestion Used for guidelines that are based on level III, level IV, and level V evidence: this implies panel consensus on the interpretation of this evidence.

No guideline possible: Used when there is insufficient evidence on which to base a guideline. This implies (1) that there is little or no evidence regarding the practice in question, or (2) that the panel lacks consensus on the interpretation of existing evidence.

D Little or no systematic empirical evidence

Specific situations

Opioid induced nausea

- Currently no good evidence to support the use of any anti-emetic in the prevention or treatment
- Choice of anti-emetic should be either empirical or based on the underlying mechanism causing nausea

Davis, M, Hui, D, Davies, A et al. (2021) MASCC antiemetics in advanced cancer updated guideline. Support Care Cancer 29, 8097–8107

- Opioid rotation: systematic review made weak recommendation supporting switching opiates eg. morphine to oxycodone

Sande TA, Laird BJA, Fallon MT (2019) The management of opioid-induced nausea and vomiting in patients with cancer: a systematic review. J Palliat Med 22(1):90–97

Nausea and vomiting in malignant bowel obstruction

Table 4 MASCC guideline statement

From: [Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update](#)

Guideline statements	LOE	GOE	Guideline
Octreotide should be considered as a front-line treatment for inoperable MBO	I	A	Recommend
Metoclopramide is an active antiemetic in the management of MBO	III	B	Suggestion used
Olanzapine is an active antiemetic in the management of MBO	III	B	Suggestion used
Haloperidol is an active antiemetic in the management of MBO	III–IV	B	Suggestion used
Dexamethasone may be considered in the treatment of MBO	III	B	Suggestion used
Ranitidine may be active in reducing symptoms from MBO	III	B	More evidence is needed

Davis, M., Hui, D., Davies, A. et al. Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update. Support Care Cancer 29, 8089–8096 (2021)

Remember side effects

Classification of medications according to QT prolongation risk

Drug class	Of concern: known risk of QT prolongation	Conditional (under certain conditions or in presence of risk factors) or possible risk of QT prolongation	Drugs less likely to cause QT prolongation
ANTI-EMETICS	HALOPERIDOL DOMPERIDONE ONDANSETRON LEVOMEPRMAZINE CHLORPROMAZINE	METOCLOPRAMIDE OLANZAPINE PROCHLORPERAZINE MIRTAZAPINE PROMETHIAZINE	CYCLIZINE

Crediblemeds.org

Extra-pyramidal side effects

Quetiapine
Clozapine

Olanzapine

Risperidone

Phenothiazine
eg. levomepromazine

Haloperidol

Increasing
risk of extra-
pyramidal
side effects

Rummel-Kluge C, Komossa K, Schwarz S, et al.

Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons.

Schizophrenia Bulletin. 2012 Jan;38(1):167-177

Summary

Take home messages

- Treating nausea in advanced cancer on the basis of cause of nausea is no more effective than empirical use of haloperidol (and metoclopramide)
- Metoclopramide and haloperidol are recommended 1st line anti-emetics
- Methotrimeprazine and olanzapine are recommended 2nd line anti-emetics
- Role of dexamethasone, opioid rotation and dexamethasone in specific situations
- Above evidence needs to be individualised to the patient