Palliative management of nausea and vomiting in advanced cancer

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Background
Patients with cancer often experience nausea. In some cases, a specific cause such as chemotherapeutic adverse effects, raised intracranial pressure or malignant bowel obstruction is identified. In other cases, no specific cause is apparent.

Objective
This article summarises the evidence-based management of nausea in advanced cancer. It includes the nausea of select, specific contexts such as raised intracranial pressure and bowel obstruction.

Discussion
It is not commonly appreciated that low-dose oral haloperidol is the standard of care arm for many trials looking to reduce nausea in advanced cancer. It is available cheaply through the Pharmaceutical Benefits Scheme. The relative merits of other medications are discussed, as are the merits of an empiric versus a mechanistic approach to treatment.

NAUSEA has been reported in 6–68% of patients with cancer.[1] A subset of these patients will have a specific cause identified, leading to treatment according to a relevant guideline. The remainder will be explained as multifactorial nausea and vomiting, to which their opioids, decreased peristaltic function, hypercalcaemia, subacute renal function decline and other factors might contribute.[2] One recent prospective study of 821 Danish cancer patients estimated the prevalence of such multifactorial nausea to be 46%.[3]

This article will describe how best to manage this multifactorial nausea and vomiting, which is referred to in the palliative care literature and throughout this paper as 'the nausea and vomiting of advanced cancer'.[3] The management of select, specific conditions with specific management approaches is discussed.

Aim

This article aims to demystify the treatment of nausea and vomiting in advanced cancer and provide a practical approach using medication formulations that are available and affordable in Australia.

Nausea and vomiting in advanced cancer

This section considers the treatment of multifactorial nausea in cancer patients (ie the nausea and vomiting of advanced cancer).

The traditional approach was to try and discern the main mechanism of the nausea (eg delayed gastric emptying or vestibular impairment) and use this mechanism to guide management (eg metoclopramide or cyclizine). Whether this was superior to an empiric approach was the subject of a recent Australian randomised controlled trial (RCT).[4] This RCT was adequately powered for the primary outcome, which was response rate (not magnitude) at day 3, where response was defined as a two or more (out of 10) point drop in the nausea score (0–10) and an average nausea score <3 out of 10 for the preceding 24 hours, measured at 72 hours. There was no difference in response rate (53% for the empiric arm) nor was there a significant difference in the secondary outcome of response magnitude.

A subsequent RCT of haloperidol versus methotrimeprazine (levomepromazine; Nozinan, GL Pharma, Vienna, Austria) showed a response rate of 74% and a complete response rate of 55.9%, with no significant difference between the two arms.[5] In both trials, metoclopramide was used as the rescue antiemetic. No increase in bradykinesia or similar adverse effects was observed.

Based on the above, use of haloperidol for the nausea and vomiting of advanced cancer is accepted as evidence based.[6] Levomepromazine is non-inferior but caused more sedation. Both can be used in conjunction with metoclopramide for

breakthrough nausea. Table 1 shows our recommended doses, which differ slightly from the trial doses. Haloperidol does come in a 0.5-mg tablet, although this dose is probably too low to serve as a routine starting dose in the absence of extenuating circumstances such as marked patient concern regarding adverse effects.

There has been no rigorous trial to evaluate metoclopramide in this setting. Such trials are difficult to recruit for as metoclopramide is often used empirically by primary care or emergency clinicians prior to reaching a palliative care specialist conducting a trial. One such trial found no difference between ondansetron, metoclopramide and placebo for opioid-induced nausea and emesis, although the inference is limited by the small sample size.[7] Other small trials have shown a benefit. Some guidelines give a consensus recommendation for metoclopramide as the first-line medication.[8]

Some practitioners use ondansetron. Certainly, it has good evidence for chemotherapy-induced nausea and vomiting. The few trials that consider its use for advanced cancer are at significant risk of bias due to lack of blinding.[9–11] They are not powered for their primary outcome. The measurement of nausea is hours of nausea rather than intensity. This is atypical and limits comparison to most other trials, which measure magnitude at a fixed time point. There are no blinded placebo-controlled, adequately powered trials evaluating ondansetron of which we are aware.

It is also known to be quite constipating, a problem to which palliative patients are uniquely vulnerable. It is more expensive than haloperidol (Table 1). Like ondansetron, cyclizine can be an option for patients with Parkinson's disease.[6]

As a practical matter, it is worth noting that the primary outcome in these trials is response rate. Thus, if someone has responded to metoclopramide, then it would be an incorrect application of the available evidence to switch them to haloperidol. Rather, the evidence helps guide medication choice for a patient whose nausea is uncontrolled.

An important caveat is that there is no toxicity data for long-term, low-dose haloperidol use. This would be more relevant

Table 1. Dosing, adverse effects and cost of commonly used antiemetics in advanced cancer[A]

Drug	Recommended daily dosing	Adverse effects	Cost ($) per day
Metoclopramide	• 10 mg TDS PO PRN, to a maximum of 30 mg in 24 h • 5–10 mg TDS IM/SC PRN, to a maximum of 30 mg in 24 h	• Diarrhoea, dizziness, drowsiness, akathisia, increased serum prolactin, galactorrhoea, extrapyramidal side effects, neuroleptic malignant syndrome, arrythmias	• 0.40–1.20 • 3.23–9.69
Haloperidol	• 1.5–3 mg PO BD PRN or 1 mg SC BD PRN. The maximum dose we would use for the indication of nausea is 6 mg PO per day, or 5 mg SC per day • The dose in the RCT was 1.5 mg orally once daily, increased to 1.5 mg twice daily if nausea continued[5]	• Sedation, extrapyramidal side effects, hypotension, dystonia, neuroleptic malignant syndrome, parkinsonism, tardive dyskinesia, stroke, VTE, QT prolongation, arrythmias	• 0.07–0.22 • 1.56–4.70
Cyclizine	• 25 mg TDS PRN PO, to a maximum of 150 mg in 24 h	• Sedation, dizziness, constipation, urinary retention, dry eyes/mouth, dyskinesia, hallucinations, agranulocytosis, hepatic dysfunction	• 1.16–3.49
Ondansetron	• 4–8 mg TDS PO PRN, up to 24 mg in 24 h • Most trials used tropisetron.[9,10,11] One trial used ondansetron 24 mg per day[7]	• Constipation, extrapyramidal side effects, QT prolongation, arrythmias	• 1.2–5.10
Levomepromazine	• Not AMH/PBS listed • Start at 3.125–6.25 mg PO BD, to a maximum of 12.5 mg per day orally. Or 3.125 mg SC once daily, to a maximum of 3.125 mg SC twice daily • The trial dose was 6.25 mg PO OD, increased to 6.25 mg PO BD if nausea continued[5]	• Sedation, extrapyramidal side effects, dry mouth, postural hypotension	• Not readily available in community but is available through hospital pharmacies

[A]Prices are for Pharmaceutical Benefits Scheme (PBS)-recommended formulations listed by a prominent Australian pharmacy chain. Dosages and prices are listed for PO, IM and SC preparations where relevant. Maximum doses are specific to the indication of nausea in advanced cancer

AMH, Australian Medicines Handbook; BD, twice per day; IM, intramuscular; OD, once a day; PO, oral; PRN, as required; RCT, randomised controlled trial; SC, subcutaneous; TDS, three times a day; VTE, venous thromboembolism.

for patients with metastatic disease but who seem to have achieved remission on – say – immunotherapy, which can sometimes go on indefinitely. There is appropriate concern regarding the risk of cerebrovascular accident from long-term antipsychotic use in the elderly and non-elderly alike.[12,13]

Another relevant factor that might affect the prescription of these medications is cost. The palliative patient cohort is socioeconomically heterogeneous. While the Pharmaceutical Benefits Scheme (PBS) subsidises the cost of most of these medications in Australia, it does not remove cost as an issue. Certain medications have an additional 'safety net' reduced cost, available via Medicare through a Health Care Card. As such, this might be an important issue for patients of lower financial means. A summary of these medications, as well as their relevant dosing regimens, adverse effects and cost, is presented in Table 1. Some dosing recommendations include practical considerations such as the fact that haloperidol comes in a 1.5 mg tablet. We have included trial doses along with our recommendations so that any differences are clear, although in our opinion, they are quite minor.

Some common, specific causes of nausea

Cancer patients can have a myriad of causes for their nausea. To cover them all in one article would be difficult. We have somewhat arbitrarily decided to highlight two important causes of nausea: raised intracranial pressure (ICP) and malignant bowel obstruction (MBO). We discuss these causes before outlining an approach to managing the nausea and vomiting of advanced cancer. Chemotherapy-induced nausea and vomiting are usually obvious and managed by the medical oncologist prescribing the chemotherapy, so a detailed discussion is omitted for brevity.

Raised intracranial pressure

Practitioners will often consider raised ICP in a palliative cancer patient who complains of a new or different headache but might not consider it for the complaint of nausea alone. Similarly, nausea alone would not trigger an immediate referral for cerebral imaging by palliative specialists. So when should imaging be pursued?

In our view, if the nausea is paired with a new or different headache, then brain imaging is warranted. Computed tomography (CT) of the brain without contrast performs poorly and should only be considered in patients who cannot tolerate any form of contrast enhancement. Contrast-enhanced magnetic resonance imaging (MRI) is the gold standard, as it has the highest sensitivity for brain metastases and outperforms the alternatives in excluding intracranial leptomeningeal disease.[14] MRI might not be readily available in rural and remote areas. A strategy of contrast-enhanced CT and then, if negative, a trial of empiric therapy (see below) can be justified on practical grounds.

What if there is nausea but no headache? In the aforementioned Danish study, six of 378 (1.6%) patients with nausea were diagnosed with raised ICP.[3] There is no comment as to what other symptoms these patients had.

For palliative care patients, it seems prudent to restrict imaging for nausea without headache until antiemetic therapy has been trialled or some other sign of raised ICP has appeared.

The management of raised ICP will be guided by the aetiology. Symptomatic brain metastasis (nausea and headache) is managed initially with high-dose dexamethasone (8 mg orally twice a day) and a discussion with a radiation oncologist and/or a neurosurgeon, if so desired by the patient.

If radiotherapy and/or neurosurgery are not indicated or desired, the lowest dose of dexamethasone that relieves the nausea and other symptoms should be used. There is no hard evidence to guide dose reduction, but our practice is to reduce the starting dose of 16 mg by 4 mg orally every second day and use the lowest dose that maintains the clinical improvement. There is some evidence to suggest a lower dose is equally effective.[15]

Malignant bowel obstruction

MBO is a common occurrence in gynaecological and colorectal malignancies. Surgery is not always indicated nor beneficial in this condition (although a discussion with a surgeon is always valuable); conservative management of MBO is well established.

Conservative (medical) management involves dexamethasone (8–16 mg per day), antiemetics (typically haloperidol 2 mg per day subcutaneously), consideration of intravenous or subcutaneous rehydration and consideration of nasogastric tube (NGT) insertion. MBO in gynaecological cancers is frequently managed without the need for NGT insertion.

Octreotide is advocated in some guidelines, although we agree with the lead authors of one of the RCTs, which led to it being recommended that its routine use is not justified by the available evidence.[16]

Oral water-soluble contrast (eg Gastrografin, Bracco, Geneva, Switzerland) is thought by some to hasten MBO resolution. Trials to test this hypothesis have struggled with recruitment. One of the authors of the present study was involved in a pilot study that demonstrated a benefit, although it was open label and was not adequately powered.[17] The trial used 100 mL of oral Gastrografin per day for patients who did not improve with conservative management of their MBO. Conservative management was defined as ceasing oral intake, parenteral fluid replacement, parenteral dexamethasone (8 mg per day) and parenteral ranitidine (200 mg per day). Ranitidine is no longer available in Australia in this formulation.

In our clinical practice, if patients struggle with the taste, we often use 25–50 mL orally once or twice daily. An abdominal X-ray could be performed 24 hours following administration to see if it passes through to the rectum. If it does pass through to the rectum, the interpretation is not necessarily that the MBO has resolved. In fact, defining resolution for MBO trials is quite difficult. We would more cautiously interpret it as evidence that the patient might tolerate an upgrade to a small amount of clear fluid diet, if this is concordant with clinical findings (less or no nausea, passing flatus or stool, and less or no abdominal pain). Similarly, it is difficult to say whether recurrence of these symptoms after Gastrografin has been imaged in the rectum means a new MBO has occurred or reflects the fact that MBO is a dynamic process. We feel this is not a purely academic matter: appreciating how hazy the definition of MBO resolution is helps us set the expectations of our patients for the days and weeks following discharge.

The most common adverse effects in this trial were diarrhoea, nausea and

vomiting, and abdominal pain. Severe pneumonitis has been reported when oral water-soluble contrast has been aspirated, so it should not be given where the patient has difficulties swallowing or an altered level of consciousness.

Most clinicians avoid metoclopramide in MBO to avoid worsening pain, although a minority advocate using it to hasten resolution, particularly in partial MBO.[18] Neither recommendation is evidence based. Whatever antiemetic is chosen, it will need to be given subcutaneously, intravenously or sublingually. Therefore, ondansetron would seem appealing, although the high rate of associated constipation and lack of evidence-based benefit compared to haloperidol discourages its use in this context.

Conclusion

Nausea is a common problem in advanced cancer. When caused by raised ICP due to cerebral metastases, dexamethasone and consideration of radiotherapy or neurosurgical intervention are the mainstays of management. MBO can be managed without the need for surgery or an NGT. Where no cause can be identified, there is no evidence to suggest that trying to treat mechanistically is superior to treating with haloperidol with rescue metoclopramide. Levomepromazine is as effective as haloperidol but seems to be more sedating. Metoclopramide and ondansetron are often used, although rigorous evidence is lacking on their efficacy. The latter commonly causes constipation and is expensive.

Key points

- Nausea is common in advanced cancer.
- Some specific causes of nausea have specific treatments.
- Where no specific, treatable cause is found, the nausea can be treated empirically.
- Haloperidol is an effective, evidence-based first-line treatment for nausea and vomiting in advanced cancer.

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References

1. 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;31(1):58–69. doi: 10.1016/j.jpainsymman.2005.06.007.
2. Wickham RJ. Nausea and vomiting: A palliative care imperative. Curr Oncol Rep 2020;22(1):1. doi: 10.1007/s11912-020-0871-6.
3. Harder S, Herrstedt J, Isaksen J, et al. The nature of nausea: Prevalence, etiology, and treatment in patients with advanced cancer not receiving antineoplastic treatment. Support Care Cancer 2019;27(8):3071–80. doi: 10.1007/s00520-018-4623-1.
4. Hardy J, Skerman H, Glare P, et al. 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 2018;18(1):510. doi: 10.1186/s12885-018-4404-8.
5. Hardy JR, Skerman H, Philip J, et al. Methotrimeprazine versus haloperidol in palliative care patients with cancer-related nausea: A randomised, double-blind controlled trial. BMJ Open 2019;9(9):e029942. doi: 10.1136/bmjopen-2019-029942.
6. Hardy J, Davis MP. The management of nausea and vomiting not related to anticancer therapy in patients with cancer. Curr Treat Options Oncol 2021;22(2):17. doi: 10.1007/s11864-020-00813-0.
7. Hardy J, Daly S, McQuade B, et al. A double-blind, randomised, parallel group, multinational, multicentre study comparing a single dose of ondansetron 24 mg p.o. with placebo and metoclopramide 10 mg t.d.s. p.o. in the treatment of opioid-induced nausea and emesis in cancer patients. Support Care Cancer 2002;10(3):231–36. doi: 10.1007/s00520-001-0332-1.
8. Davis M, Hui D, Davies A, et al. MASCC antiemetics in advanced cancer updated guideline. Support Care Cancer 2021;29(12):8097–107. doi: 10.1007/s00520-021-06437-w.
9. Mystakidou K, Befon S, Liossi C, Vlachos L. Comparison of the efficacy and safety of tropisetron, metoclopramide, and chlorpromazine in the treatment of emesis associated with far advanced cancer. Cancer 1998;83(6):1214–23. doi: 10.1002/(SICI)1097-0142(19980915)83:6<1214::AID-CNCR22>3.0.CO;2-7.
10. Mystakidou K, Befon S, Liossi C, Vlachos L. Comparison of tropisetron and chlorpromazine combinations in the control of nausea and vomiting of patients with advanced cancer. J Pain Symptom Manage 1998;15(3):176–84. doi: 10.1016/S0885-3924(97)00349-7.
11. Mystakidou K, Befon S, Trifyllis J, Liossi C, Papadimitriou J. Tropisetron versus metoclopramide in the control of emesis in far- advanced cancer. The Oncologist (Dayton, Ohio) 1997;2(5):319–23. doi: 10.1634/theoncologist.2-5-319.
12. Shin JY, Choi NK, Lee J, Park MJ, Lee SH, Park BJ. A comparison of risperidone and haloperidol for the risk of ischemic stroke in the elderly: A propensity score-matched cohort analysis. J Psychopharmacol 2015;29(8):903–09. doi: 10.1177/0269881115578162.
13. Fife D, Blacketer C, Knight K, Weaver J. Stroke risk among non-elderly users of haloperidol or first-generation antipsychotics vs second-generation antipsychotics: A cohort study from a US health insurance claims database. Drugs Real World Outcomes 2021;8(4):481–96. doi: 10.1007/s40801-021-00267-2.
14. Kaufmann TJ, Smits M, Boxerman J, et al. Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases. Neuro Oncol 2020;22(6):757–72. doi: 10.1093/neuonc/noaa030.
15. Vecht CJ, Hovestadt A, Verbiest HBC, van Vliet JJ, van Putten WLJ. Dose–effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: A randomized study of doses of 4, 8, and 16 mg per day. Neurology 1994;44(4):675–80. doi: 10.1212/WNL.44.4.675.
16. Boland JW, Boland EG, Currow DC. High-quality phase 3 studies do not support the use of somatostatin analogues to reduce vomiting in malignant bowel obstruction. Support Care Cancer 2023;31(4):211. doi: 10.1007/s00520-023-07669-8.
17. Wan Bahrum WFIB, Hardy J, Foster K, Good P. Oral water-soluble contrast (Gastrografin) for malignant bowel obstruction: Open label pilot study. BMJ Support Palliat Care 2022;bmjspcare–2021–003444. doi: 10.1136/bmjspcare-2021-003444.
18. Mercadante S, Ferrera P, Villari P, Marrazzo A. Aggressive pharmacological treatment for reversing malignant bowel obstruction. J Pain Symptom Manage 2004;28(4):412–16. doi: 10.1016/j.jpainsymman.2004.01.007.

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