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SPECIAL ARTICLE

2016 Updated MASCC/ESMO consensus recommendations: Management of nausea and vomiting in advanced cancer

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Abstract
Purpose The aim of this paper is to review the existing literature related to the management of nausea and vomiting (N & V) in advanced cancer and derive clinical evidence-based recommendations for its management.
Methods Available systematic reviews on antiemetic drug effectiveness were used. One generic systematic review of antiemetics in advanced cancer (to 2009) was updated to February 2016. Agreement on recommendations was reached between panel members, and these were voted in favor unanimously by the larger antiemetic committee membership ($n = 37$).
Results The evidence base in this field is minimal with largely poor quality trials or uncontrolled trials and case studies. The level of evidence in most studies is low. The drug of choice for managing N & V in advanced cancer is metoclopramide titrated to effect. Alternative options include haloperidol, levomepromazine, or olanzapine. For bowel obstruction, the recommendation is to use octreotide given alongside an antiemetic (haloperidol) and where octreotide is not an option to use an anticholinergic antisecretory agent. For opioid-induced N & V, no recommendation could be made.
Conclusion These new guidelines, based on the existing (but poor) evidence, could help clinicians manage more effectively the complex and challenging symptoms of N & V in advanced cancer.

Keywords Cancer · Nausea · Vomiting · Symptoms · Antiemetics · Palliative care

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Introduction

In advanced cancer, nausea and vomiting (N & V) are both common and severely affect quality of life [1]. They may be both treatment and non-treatment related. About 20–30 % suffer from nausea—70 % in the last week of life—and this symptom can be more problematic particularly in women [2, 3]. Nausea may occur without vomiting or retching and vomiting without nausea. Both are multifactorial in origin [3]. The causes of N & V in advanced disease can be multifaceted and include elevated intracranial pressure due to brain tumors, cerebral secondaries, or meningeal disease; biochemical syndromes such as hypercalcemia, hyponatremia and hyperthyroidism, or due to infections or opioid use; vestibular dysfunction (i.e., motion sickness); and gastric stasis-related, such as with ascites, hepatomegaly, paraneoplastic neuropathy, opioid-induced, dyspepsia or gastritis, or malignant bowel

obstruction [1]. Constipation may cause N & V due to a sense of fullness. Psychological problems like anxiety can too.

Hence, a careful assessment is paramount in the management of N & V in advanced cancer. Assessment includes a detailed history, physical examination, and investigations for reversible causes. Assessment and management can further be influenced by goals of care, performance status, and prognosis. Assessment should include sentinel questions which can assist in the identification of the cause of N & V [1]. For example, infrequent large-volume vomiting (which relieves nausea) is consistent with impaired gastric emptying or a partial/complete bowel obstruction. Intermittent nausea alongside abdominal cramps and changes in bowel habit can also suggest bowel obstruction. Movement-related N & V occurs with vestibular dysfunction or mesenteric traction. Vertigo distinguishes the former. Intracranial pressure is linked with morning N & V and headaches. Nausea associated with hyperglycaemia and hypercalcemia can co-occur with polyuria and polydipsia. Uremia and hyponatremia both produce nausea and mental health changes which mimic brain secondaries.

Of those with a reversible cause, about half are drug-related, mostly from opioid drugs [4]. Other commonly prescribed drugs (antibiotics, anticonvulsants, digoxin, iron, and nonsteroidal anti-inflammatory drugs) may cause nausea and should be discontinued if they are suspected to cause nausea. Radiation, particularly to the abdomen and lumbosacral spine, is emetogenic too. Psychogenic N & V produces low volume vomitus and is triggered by anxiety. Adrenal insufficiency—due to inadvertent discontinuation of corticosteroid medications—is often missed and associated with abdominal pain, hypotension, and N & V.

The same management principles apply to both nausea and vomiting. Treatment is often effective, but many patients still suffer unnecessarily [5]. Success lies with effective treatment of the underlying cause. For example, N & V from hypercalcemia of malignancy is best treated with calcium-reducing agents (bisphosphonates, denosumab) and hydration. Limited data suggests a role for complementary and alternative therapies, although good quality studies in palliative care are lacking. Around-the-clock antiemetic regimens are usually better than intermittent. Opioid rotation or dose reduction is worth a trial if the cause of N & V is suspected to be the opioid drug used. In those who do not have a bowel obstruction, nausea may be more difficult to manage.

There are two therapeutic approaches [6]. One is empirical; starting with one drug and if unsuccessful adding or rotating to another. The second is etiological; that is management tailored to the suspected cause and/or likely receptors involved in generating nausea and/or vomiting. If antiemetics are ineffective, decompression by nasogastric tube or (preferably) a venting percutaneous endoscopic gastrostomy tube can help many with bowel obstruction. In the case of bowel obstruction, surgical resection of an obstructing lesion or diverting ostomies may be needed. Corticosteroids can also reduce nausea from brain metastasis, cranial radiation and/or surgery, or stereotactic radiation. Paracentesis is effective at reducing nausea from massive ascites. Rectal suppositories and/or enemas reduce nausea from rectal impaction.

Aim

The aim of this paper is to develop a set of evidence-based guidelines for the management of different syndromes related to nausea and vomiting in advanced cancer. This is part of the update of the MASCC/ESMO antiemetic guidelines 2015, although advanced cancer is a new specialty area of the said guidelines.

Methods

Existing systematic reviews [7] served as main sources of data for discussion. A systematic review from January 1, 2009 to May 2015 was completed by the authors of this paper, updating the review by Davis [7], following the same process. The search terms for the latter review are shown in Table 1. Studies were included if they met the following criteria:

(1) antiemetic trials in active cancer
(2) adults (age 18 years or older)
(3) nausea and/or vomiting from cancer or as a complication
(4) systematic reviews and meta-analysis, randomized controlled trials, prospective single arm trials, prospective

Table 1 Antiemetic systematic review—search terms

	Index terms (MeSH vocabulary)	"keywords" (article title, abstract, or indexing)
Nausea	Nausea Vomiting Any antiemetics (exploded: long list of drug names)	"nausea…" "vomit…" emesis "antiemet…" "antiemes…"
Cancer	Any neoplasms (exploded: long list of specific names)	"neoplasm…" "cancer…" "malignan…"
Palliative care/hospice	Palliative care Palliative medicine Hospice and palliative care nursing Hospice care	"palliate…" "hospice…"
Terminal care	Terminal care Terminally ill	"terminal…"
Chemotherapy	Any antineoplastic agents (exploded: long list of drug names) Any neoplasms/drug therapy	

trials that used antiemetics based on the presumed etiology, cohort studies, case series, and single case reports.

Trials focusing on chemotherapy-induced and postoperative nausea and vomiting were excluded. PubMed and Ovid Medline were searched and yielded 411 articles in English. Exclusion of chemotherapy trials reduced this to 219. Twelve articles and two abstracts met the inclusion criteria. A further extension to February 2016 yielded four additional articles. Those specifically about antiemetics in malignant bowel obstruction yielded another 11 articles.

Review findings were discussed by the committee members, and recommendations were agreed upon. These were presented in a face-to-face meeting with the wider antiemetic guidelines panel in Copenhagen, in June 2015, and recommendations underwent voting from all committee members. Recommendations achieved unanimous agreement from the panel. Minor alterations in terms of phrasing and for consistency with the remaining guidelines were followed. Then, the current paper was formed, summarizing the key data that led to the development of the recommendations.

Results

Antiemetic trials (excluding malignant bowel obstruction)

Many antiemetics (largely phenothiazines) were studied in various reports and designs, but there were no randomized trials [7]. A systematic review of droperidol for N & V in 2010 identified 1664 abstracts (and 827 duplicates) [8]. Twenty-three studies were obtained in full and potentially met inclusion criteria. On review of the full papers, none did. A second systematic review from 1950 to November 2013 was limited to randomized control trials in adults [9], and again, no relevant trials were available. A systematic review of haloperidol for N & V involved literature up to 2007 [10]. No randomized controlled trials were available or published too [10]. The Cochrane Database was updated in 2015 [11]. There were 27 non-randomized trials from the 2007 search. A further 38 studies (up to and including 2013) and two in 2014 were found. There was one randomized placebo-controlled study of moderate quality (and low risk of bias) which compared "ABH" topical gel (diphenhydramine, haloperidol, and lorazepam) with placebo for nausea in 22 patients [12]. The mean changes in nausea score from baseline to 60 min after treatment in the ABH gel group were 1.7 ± 2.05 and 0.9 ± 2.45 for the placebo group ($P = 0.42$), and hence, it was shown that the gel was comparable to placebo [12]. Haloperidol has further been used in an open label uncontrolled trial [13]. Response was measured after 1 day. Out of 33 evaluable participants, 20 responded and 8 had complete response. The overall response rates at days 2 and 5 were 47 and 40 %, respectively [13]. One trial (in abstract form only) suggested that haloperidol was effective in 65 % of patients given systemically.

A systematic review of levomepromazine from 1946 to April 2012 and peer review journals from 1980 to 2001 found seven prospective and nine retrospective studies, six case reports, and two surveys [14]. There were no randomized controlled trials. However, in one open label study, 60 of 70 patients (86 %) responded well to levomepromazine but there was no dose–response association [14]. Two other prospective quasi-experimental studies reported in this review also supported the effectiveness of levomepromazine [14]. Darvill et al. [15] also undertook a review of levomepromazine and found no related trials. An update of the latter Cochrane review identified 35 abstracts but no randomized controlled trials or additional data [16].

The Canadian Agency for Drugs and Technologies in Health reviewed the evidence available in nabilone for N & V unrelated to chemotherapy. The search was from January 1982 to August 2014. There was one randomized trial in postoperative nausea and vomiting, a case series (two patients) with nausea in AIDS, but none in advanced cancer [17]. A retrospective review from 2008 suggested benefit in 47 patients [18] as did two case studies of dronabinol [19, 20].

Our systematic review of antiemetics for N & V (unrelated to chemotherapy or radiation) found 93 articles but only nine randomized trials (of moderate to poor quality) [7]. Sustained release metoclopramide was of similar efficacy to immediate release in a 3-day trial [21]. Continuous release (sustained) metoclopramide was better than placebo [22]. Dexamethasone did not improve the antiemetic effect of metoclopramide [23]. Levosulpiride was superior to metoclopramide [24]. Metoclopramide plus tropisetron was superior to metoclopramide alone, but dexamethasone did not add to the combination [25]. Tropisetron alone was similar to tropisetron plus metoclopramide, and again dexamethasone did not enhance antiemesis. It was superior to metoclopramide and chlorpromazine as single agents [26, 27], but trial quality was low in both studies. Study duration in all of the randomized trials was 15 days or less.

Sublingual scopolamine 0.15 mg was evaluated in a prospective single arm study [28]. At 30 min, 25 of 26 participants had at least a 1-point NRS decrease in N & V and all participants had a reduction at 60 min. Toxicity (drowsiness) occurred in four (15 %) [28]. A three-patient case series also reported improved nausea with scopolamine [29].

One report described the use of olanzapine from 2013–2015 in 108 patients [30]. Doses were 2.5–5 mg daily, and treatment duration was 39 days [30]. In a case series of 14 patients, olanzapine controlled "difficult to control nausea and vomiting" in 13 patients with an acceptable adverse effect profile [31]. Similar results were described elsewhere [32].

Summary of evidence

There are no randomized trials for droperidol, haloperidol, and nabilone. Case series of levomepromazine favor improvements. A cohort study favors haloperidol. While not documented, experience suggests that clinicians favor metoclopramide as first-line therapy due to randomized trials; however, a quarter use haloperidol. Haloperidol is often used as a second line. Agents used after haloperidol are multiple; metoclopramide is used only in a minority as a second-line agent. Unlike chemotherapy-induced nausea and vomiting, there is no evidence that combining antiemetics improves responses over monotherapy, although this needs formal research confirmation. Of second-line antiemetics, only levomepromazine has evidence of benefit in prospective studies. Haloperidol has weak evidence as first line. There is no evidence for benefit with nabilone or cannabis in prospective studies.

Trials in malignant bowel obstruction

Based on the review of the literature, those unresponsive to specific oncologic therapy (and unfit for surgery), can be managed medically through two pharmacological approaches [33, 34]:

(1) Antisecretory drugs like anticholinergics (hyoscine hydrobromide, hyoscine butylbromide HB, glycopyrrolate) and/or somatostatin analogs octreotide ± glucocorticoids
(2) Antiemetics alone or combined with antisecretory drugs.

More specifically, few studies have assessed efficacy while there are no comparative studies on different approaches. From 2009 to 2015, four randomized trials (three double-blind) were published [35–38]. Results related to octreotide (OCT) are fairly consistent across studies. One trial [35] compared OCT 600 mcg to placebo for 3 days in 87 inoperable patients and found no reduction in vomit-free days in the two groups. There was a significant reduction in vomiting episodes with OCT but not nausea or number of days free from vomiting (which was the primary outcome measure). The study had several limitations: the bowel obstruction diagnosis was clinical, and the obstruction level and presence or not of carcinomatosis was unclear. It also included H2 blockers, corticosteroids (dexamethasone), and antiemetics; their use may have hidden some OCT benefits evident in a single arm design. Furthermore, ranitidine use was unique to this study also and its use was based on a previous study demonstrating reduced gastric secretions.

In another trial, OCT 300 mcg/24 h was more effective than scopolamine butylbromide (SB) 60 mg/24 h for nausea, secretions, and vomiting in 96 patients [36]. This trial precluded antiemetics, corticosteroids, and H2 blockers for the first 72 h. Another trial [37] demonstrated that 12 of 32 patients (38 %) treated with OCT LAR 30 mg on days 1, 29, and 57 plus OCT immediate release 600 mcg (+3 to 4 mg/Kg/day methylprednisolone on days 1–6) improved their N & V as opposed to 9 of 32 patients (28 %) in the placebo group. This study had imbalances and significant drop out rates which make the results difficult to interpret.

A study of 30 mg lanreotide versus placebo in 80 patients with peritoneal carcinomatosis showed that the treatment group had one or less episodes of vomiting/day (or no vomiting recurrence) [38]. This was not statistically significant in intention to treat analysis, but was for the supportive PP and ITT analysis of the investigators' assessment ($p < 0.05$). Sense of well-being was significantly greater with lanreotide [38]. Furthermore, in a small randomized trial of 18 patients [39], octreotide was linked with more favorable results related to N & V compared to hyoscine butylbromide. It was also interesting that lower levels of hydration in this group of patients resulted to more nausea irrespective of treatment [39].

From 2009 until 2015, an additional four [40–43] prospective studies were published. One study [40] assessed granisetron 3 mg IV plus 8 mg dexamethasone plus 2.5 mg SC haloperidol (as rescue therapy) in 24 patients refractory to previous antiemetics. After 4 days, abdominal pain, nausea, and vomiting episodes decreased. N & V control was achieved in 87 %, and 71 % did not require rescue medications. As granisetron was given with corticosteroids, it may be the combination rather than the single drug which was effective.

OCT 300–600 mcg/day was studied together with haloperidol (or prochlorperazine) for nausea and opioids for pain [41]. Fatigue, nausea, thirst, and vomiting were improved, and daily nasogastric drainage was decreased. Another prospective trial used 300 mcg/day for 7 days and then up to 600 mcg/day in women with gynaecologic cancer refractory to conventional therapy [42]. Overall response rate was 82 % on vomiting severity. In urologic cancers (bladder, kidney, prostate, ureter), OCT was given early (once bowel obstruction was diagnosed) in 14 patients [43]. The mean time to symptom improvement (WHO toxicity grading system) was 1.6 days, and the use of OCT was deemed safe and effective.

From 2009–2015, one retrospective study and two case series were also published [44–46]. A retrospective study [44] assessed olanzapine activity against nausea and vomiting in incomplete bowel obstruction unresponsive to chlorpromazine, corticosteroids, domperidone, haloperidol, metoclopramide, or prochlorperazine. The average olanzapine dose was 4.9 ± 1.2 mg, and the treatment duration was 23 ± 16 days. Olanzapine significantly decreased the average nausea score in 90 % of the patients as well as the vomiting frequency ($p < 0.001$) [44]. A retrospective case series [45]

evaluated 12 patients treated with dexamethasone, metoclopramide, and OCT. Nausea resolved in all patients at day one; the median time to resumption of oral intake was 2 days (range 1–6) in eight evaluable patients. As olanzapine was given in the above studies with corticosteroids, it may be that there were synergistic effects in the outcome. In four case reports, patients received OCT plus corticosteroids; 3 of the 4 remained without tube drainage at death and survival was 51–64 days [46].

In trials where corticosteroids were not part of treatment [36, 41–43], there appeared to be a robust improvement in nausea and vomiting with improvements in secondary outcomes as opposed to trials that included corticosteroids and antiemetics [35, 37]. Adverse outcomes were minimal, and only in one randomized trial abdominal colic was increased necessitating an anticholinergic.

Cyclizine, an antihistamine H_1 receptor antagonist, is commonly used as antiemetic in patients with advanced cancer, especially in cases of mechanical bowel obstruction, movement-related N & V, and intracranial pressure. A review of the evidence in cyclizine [1] found only one clinical audit where cyclizine has been used as part of a local N & V management guideline in advanced cancer, showing 82 % improvement in nausea and 84 % improvement in vomiting from the use of the guidelines. Nevertheless, clinical consensus and current practice indicate that this class of drugs have a place in the management of N & V in advanced cancer, despite the lack of robust evidence.

Trials in opioid-induced nausea and vomiting

N & V are two of the most common side effects of opioid analgesics [47] with up to 19 % incidence of moderate/severe nausea and 40 % vomiting [48]. In some, opioid-induced nausea and vomiting (OINV) seems an initiation side-effect, with tolerance after 5–7-day therapy [49]. In others, it may be chronic [1].

There are no randomized controlled trials of prophylactic antiemetics for those starting opioids. There is no good evidence to support/refute any antiemetic in OINV prophylaxis. We found one, underpowered, placebo-controlled randomized trial of the therapeutic use of metoclopramide and ondansetron in established OINV [50]. In this trial, there were no significant differences between the ondansetron, metoclopramide, or placebo groups. Hence, overall, there is no good evidence to support/refute specific antiemetics in OINV treatment.

Several antiemetics appear active in managing OINV. The choice may be empirical or based on the pathophysiology e.g., a prokinetic for impaired gastric emptying; an antihistamine with vestibular apparatus sensitization. There is limited evidence to support opioid-switching i.e., changing the opioid or the route [51].

Discussion

Our findings support metoclopramide as the drug of choice (Table 2) and some other antidopaminergic agents (haloperidol, levomepromazine, or olanzapine) as alternatives for N & V in advanced cancer. It is notable that all these agents continue to have an important role for chronic nausea in cancer, although largely replaced by 5HT3 or NK1 receptor antagonists in chemotherapy-induced N & V. In bowel obstruction, octreotide with an antiemetic (such as haloperidol) is recommended but may be expensive. In these situations, other antisecretory agents like scopolamine butylbromide and glycopyrronium bromide may be useful and less costly. Unfortunately, a common and potentially distressing problem like opioid-induced emesis has been studied insufficiently to allow specific recommendations to be made. However, clinicians should be aware that emesis is frequently associated with initiation and/or of significant opioid dose increases [52]. Education and antiemetic prescriptions should help ensure adherence to opioids, since they will be needed by the vast majority.

There are several challenges to clinical research on N & V in advanced cancer. Significant issues include that this syndrome is frequently multicausal. Another major barrier is the variable onset. Contrary to N & V, from medical interventions like anesthesia, chemotherapy etc., that of advanced cancer occurs at variable points in the illness. This suggests that the methodology of clinical trials in N & V in advanced disease should differ from that of, for example, chemotherapy agents.

Our findings also suggest several opportunities to improve research:

Define the patient population

The statement “nausea and vomiting associated with advanced cancer” is vague and likely includes multiple etiologies. Clinical trials should thoroughly assess the major contributors. In a minority, there will be a major specific mechanism like mechanical bowel obstruction, most will not. Efforts to weigh their relative contributions to the severity of emesis will allow a better understanding of the possible role of different pharmacological interventions.

Define outcomes

There is a need for a consensus on appropriate and clinically meaningful outcomes to determine response of interventions for N & V in advanced cancer. Given the variable inception points and since N & V in advanced cancer is mainly a chronic syndrome, multiple follow-up time points will be required. People with advanced cancer often develop N & V with

Table 2 Antiemetic guidelines in advanced cancer

Recommendation	MASCC/ESMO level of evidence
Drugs of choice	
The antiemetic drug of choice in advanced cancer is metoclopramide (titrated to effect).	MASCC level of consensus: high MASCC level of confidence: moderate ESMO level of evidence: III ESMO grade of recommendation: C
Alternative options include haloperidol, levomepromazine, or olanzapine.	MASCC level of consensus: high MASCC level of confidence: low ESMO level of evidence: V ESMO grade of recommendation: D
The use of cyclizine* or 5-HT3 receptor antagonists is poorly defined to date and may be used where dopamine antagonists are contraindicated or ineffective.	MASCC level of consensus: low MASCC level of confidence: low ESMO level of evidence: V ESMO grade of recommendation: D
Bowel obstruction	
The drug recommended in a bowel obstruction is octreotide, dosed around the clock and given alongside an antiemetic (with the committee recommending haloperidol).	MASCC level of consensus: high MASCC level of confidence: high ESMO level of evidence: II ESMO grade of recommendation: A
If Octreotide plus antiemetic is ineffective, the use of anticholinergic antisecretory agents (e.g., scopolamine butylbromide, glycopyrronium bromide) and/or corticosteroids is recommended as either adjunct or alternative interventions.	MASCC level of consensus: high (moderate for corticosteroids) MASCC level of confidence: moderate (low for corticosteroids) ESMO level of evidence: IV ESMO grade of recommendation: D
The use of cyclizine* or 5-HT3 receptor is poorly defined in this setting**. Metoclopramide should be used with caution in partial bowel obstruction and should not be used in complete bowel obstruction.	MASCC level of consensus: low MASCC level of confidence: low ESMO level of evidence: V ESMO grade of recommendation: D
Opioid-induced nausea and vomiting	
No recommendation can be made for specific antiemetics, although various antiemetics may help. Opioid rotation and route switching may be effective approaches. There is no data to support prophylactic antiemetics in this situation.	MASCC level of consensus: high MASCC level of confidence: low ESMO level of evidence: V ESMO grade of recommendation: D

*Unavailable in some countries

**Caution should be exercised because of the risk of drug interactions

multiple other (moderate to severe) symptoms which include anorexia, anxiety, depression, fatigue, pain, and dyspnea. The relative contribution of these other symptom complexes to nausea (and the effect of antiemetics on these other symptoms) should be determined by assessment tools capable of evaluating multiple symptoms simultaneously.

Define the intervention

There is a need for well-done randomized trials that include haloperidol, atypical antipsychotics (levomepromazine, olanzapine), and 5-HT3 receptor antagonists. It will be important to explore the dose response relationships of different antiemetics in persons given multiple other medications for moderate to severe symptoms—thereby increasing the potential for drug interactions and side effects. There is also a need to determine the optimal dose of antiemetics. Due to the more chronic nature of most of these syndromes (compared to studies in chemotherapy-induced nausea and vomiting), these drugs will be required chronically, so toxicities should be measured at multiple endpoints.

Unlike the existing evidence for chemotherapy-induced nausea and vomiting, there are no studies on multiple antiemetic interventions for nausea in advanced cancer. This offers a unique opportunity to test agents not only with different side effects but also those with a potential to have beneficial effects on multiple other symptoms. Furthermore, randomized trials which compare single versus multiple antiemetics are needed.

Our results are encouraging since we have identified and recommended antiemetic interventions for the major

syndromes associated with N & V in advanced cancer albeit the level of evidence is low. Large randomized controlled trials with appropriate patient selection, more specific (and multiple) endpoints, longer follow-up, and the potential for single and multiple drug interventions, will improve the evidence base. There may be a role for non-pharmacological interventions, alone or as adjunct to pharmacological treatments, in the management of N & V in advanced disease, and this should also be the focus of future research.

Compliance with ethical standards

Conflict of interest AD, EB, MD declare no conflict of interest. AM declares honoraria or grants from MSD Merck; Helsinn; Tesaro; Norgine; Acacia Pharma. DW Advisory Role for Nualtra Ltd. & Tesaro; CR from Teva; Norgine; Otsuka; Amgen.

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