Review Article

Medication related nausea and vomiting in palliative medicine

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Abstract: There are multiple potential states and/or symptoms that may occur in the palliative care population including: pain, nausea/vomiting, fatigue, anorexia, dyspnea, hiccups, cough, constipation, abdominal cramps/bloating, diarrhea, pruritis, depression/anxiety, dysphagia and sleep disturbances. Some of this may be the direct result of medications or drug-drug interactions from agents prescribed to treat the medical conditions that the patient has. Medication-related nausea and vomiting (MRNV) is a significant problem in palliative medicine that is reasonably common likely due to the multiple medications that these patients are often taking.

Key Words: Medication-related nausea; vomiting; palliative

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Introduction

Nausea is one of the most commonly reported side effects of medications. Clinical experience strongly suggests that both nausea and vomiting may occur with almost any medication in an individual patient. Indeed, nausea is listed as an adverse effect in FDA approved prescribing information (approved "package insert") for most medications. Medication related nausea and vomiting frequently interferes with successful drug therapy as well as patient quality of life. For the purposes of this review, medication related nausea and vomiting (MRNV) is defined as the development of nausea, vomiting, or both which occurs secondary to the use of a medication. Retching may accompany nausea and be a precursor to vomiting. Concurrent gastrointestinal symptoms of dyspepsia (indigestion) or symptoms of acid reflux may also occur with MRNV, but are not the focus of this review. Symptoms of MRNV may occur during initiation, continuation or discontinuation (due to withdrawal syndromes) of medications, and may occur continuously or intermittently. Typically, MRNV is temporally associated with drug administration (e.g., symptoms occur with, or are shortly after drug ingestion, then diminish). Symptom severity generally varies over time, and commonly decreases with continued use of a causative medication. Medication-related vomiting is less common than nausea, and may be dose related, with nausea occurring at lower doses, progressing to both nausea and vomiting at higher therapeutic, or toxic doses.

The exact mechanisms by which most medications produce nausea and/or vomiting are unknown. It is likely that drugs produce nausea and vomiting through direct and indirect actions, with more than one mechanism of action for some agents. Not surprisingly, as nausea and vomiting is thought to be a response to possibly noxious substances, medications may be perceived by the body's defense mechanisms as potentially toxic. Additionally, nausea and vomiting may signal a drug-related adverse effect or disease process involving the gastrointestinal or central nervous systems that secondarily results in stimulation of the pathways contributing to nausea and vomiting.

Given the frequency of MRNV, and potential of this side effect to interfere with therapy, successful management is necessary to attain optimal drug therapy outcomes. Prevention and management of medication related nausea and vomiting is highly dependent upon the clinical situation and medication(s) involved, however some general strategies can be applied to many agents. Consensus recommendations are available for management of two of the commonly encountered types of MRNV- chemotherapy induced nausea and vomiting (CINV) and post operative nausea and vomiting (PONV).

Medication related nausea and vomiting in palliative medicine is crucially important. The palliative all case population may be especially at risk for MRNV because they generally have advanced illness, advanced age, reduced renal and/or hepatic function and thus, reduced clearance; low proteins for drug binding, and multiple significant co-morbidities. Furthermore, the palliative care population tends to be on multiple medications and thus, tends to be at risk for multiple-drug drug-interaction.

Clark and colleagues studied all people referred to a community-based palliative care service over a period of 6.3 years had their bowel problem scores reported, using a numerical rating score at every clinical encounter until their death, at four discrete time points, namely, 90, 60, 30, and seven days before death (1). 3,248 (42.4%) people had disturbed bowel scores, at the time of referral; 548 to the Palliative Care Service, and (7.2%) described these as severe. Only 1,020 (13.1%) people never described disturbed bowel function over their time in palliative care. At each time point, approximately one-third were experiencing disturbed bowel function, with proportionally greater numbers of people experiencing more significant problems as death approached. Associations between bowel problem score and appetite problems, nausea, breathing problems, fatigue, and pain were explored. Although weak, there were statistically significant associations between all symptoms and bowel problem scores except for breathing problems (1). There were 22.06% experiencing nausea of any severity 90 days before death, 13.1% experiencing nausea of any severity 60 days before death, 24.8% experiencing nausea of any severity 30 days before death, and 24.07% of patients experiencing nausea of any sensitivity seven days before death (1).

Incidence of medication related nausea and vomiting

The incidence of MRNV varies widely based on the specific medication therapy involved, patient characteristics, and possibly the indication for use and treatment environment. Nausea is a common adverse drug event while emesis occurs much less frequently. Medication dose, dosage form, administration route, the rate and timing of administration and duration of use are known to influence occurrence of MRNV. Taking medication in a specific manner (such as with food) often reduces the frequency and severity of nausea. Certain medication classes are associated with high rates of MRNV, and incidence often varies between medications within the same class. Commonly, MRNV occurs early in drug therapy and wanes with continued use. Concurrent use of multiple medications, particularly if ingested at the same time, often increases MRNV. Additionally, measures of nausea used in trials are inconsistent, thus the reported frequency of MRNV will vary widely even for the same medication in the same treatment population.

The incidence of nausea and or vomiting has been reported to be as high as 70% for some drug therapies such as certain chemotherapeutics. Nausea is reported by 46% of HIV patients taking antiretrovirals. Some commonly chronically used medications such as opioid analgesics, glucose like protein 1 agonists (GLP-1) such as exenatide, and selective serotonin reuptake inhibitors such as fluoxetine produce nausea in 20-50% of patients, and rates of 20-30% are not uncommon for many medications. Note that nausea and vomiting also occur in placebo- treated groups such that the "background" incidence rate of nausea and vomiting depends on the population studied. Even in populations without underlying reasons or increased rates of nausea or vomiting, reported rates of 2-5% are common. Generally, some MRNV is an almost expected side effect with the use of multiple medications (often more than 5-10) agents so commonly used today.

Mechanisms of medication related nausea and vomiting

Despite the fact that nausea and/or vomiting (N/V) are commonly side effects, of many pharmacotherapies, the specific mechanisms involved in MRNV for most drugs are not fully understood. It is likely there are numerous direct and indirect mechanisms by which drugs produce N/V, and that medication may act through more than one of these mechanisms. The physiology of vomiting is fairly well described while nausea, the more physiologically complex symptom, and more commonly encountered adverse drug

effect, is somewhat less well understood. It is probable that MRNV is the result of medications acting through the main types of stimuli known to induce nausea and vomiting from any cause:

(I) Direct or indirect stimulation of abdominal vagal and abdominal splanchic nerve afferents that project to the chemoreceptor trigger zone (CTZ), nucleus tractus sloitarius (NTS) of the vagal nerve, and directly to the vomiting (or emesis) center (VC). Stimulation of vagal and splanchic nerve afferents can result from direct activation of mucosal receptors, or indirectly through other effects such as altered gastrointestinal motility, distension, and toxic damage to G.I. tissues (2). Serotonin (5HT) release from mucosal enteroendocrine cells is thought to be the primary mediator of vagal and splanchic nerve stimulation, though Substance P and cholecystokinin may also play a role. Serotonin release is enhanced by acetylcholine (M_3), norepinephrine (beta), 5HT ($5HT_3$) and histamine (H_1) receptors. Activation of these pathways can also result from medication related toxicity producing pathologic effects on the visceral organs or dysmotility.

(II) Direct stimulation of the chemoreceptor trigger zone (CTZ) in the area postrema of the fourth ventricle. Drugs could also produce CTZ activation indirectly by releasing substances from the gastrointestinal tract. The CTZ contains dopamine (D_2), histamine (H_1), and acetylcholine (M_1) neurokinin-1, mu opiate, gaba-aminobutyric acid (GABA), N-methyl d-aspartate (NMDA), and serotonin ($5HT_3$) receptors (3).

(III) Activation of the vomiting center through the poorly understood central nervous system stimuli. The role of the central nervous system is likely predominant when MRNV is due to unpleasant medication taste or smell as well as anticipatory N/V (4).

(IV) Activation of vestibular inputs to the VC resulting in nausea and emesis. These stimuli are thought to be primarily mediated through H1 and M1 receptors.

(V) Direct effects of medications on the NTS and/or VC through activation of 5-HT_3, H_1 and M_1 receptors or mediated through other neurotransmitters such as Substance P (5).

The pathophysiologic mechanisms of nausea are less well understood. Nausea may be a low intesity activation of the same systems as vomiting resulting in CNS perception of nausea. Understanding of the mechanisms of MRNV can assist clinicians in management of patients experencing these symptoms. Because of the many and complex aspects of MRNV prevention and treatment, individual strategies are often insufficient, requiring additional, and often multiple therapeutic approaches to manage this common side effect.

Management of medication related nausea and vomiting

Since MRNV is most likely to be more frequent and severe upon initiation of therapy, a number of steps should be taken when patients are starting a medication. Medications should be started at the lowest appropriate dose. Some medications have specific recommendations for upward titration of dosage in order to improve initial tolerance. Close patient-provider communication and patient education can be critical during this phase of therapy (6). Medications should generally be taken with food unless specifically contraindicated. Mechanisms by which this simple strategy likely reduces MRNV through diluting drug in the upper GI tract thereby reducing local drug concentrations, improving motility, and reducing tthe rate of absorption (although for aa number of drugs food increases rate and amount absorbed), thus decreasing rate of rise and peak blood drug concentrations. Care providers should always refer to appropriate drug information resources for guidance on administration on medications. Some medication regimens are specifically designed based on timing of medication dose in trelation to food and even types of food and such recommendations should be followed.

When patients experience significant N/V when using medications, a systematic investigation into causes should be undertaken. Possible non-medication related causes and contributors should be evaluated. The relationship of symptoms to initiation of drug therapy, and to dose administration method and times, should be determined. Factors reducing or increasing the patients symptoms should be sought (7). A comprehensive review of the patient's current medications and use of alternative medications and dietary supplements may provide useful information. Dietary habits that may exacerbate MRNV should be considered. Changing the type of food eaten (e.g., using bland foods), size and frequency of meals when taking a medication may also improve tolerance. Using enteric coated and controlled release dosage forms may aalso reduce MRNV by reducing local drug concentrations in the G.I tract or controlling the site of dosage form dissolution. Other recommendations include eating high-carbohydrate foods or drinking ginger ale, herbal or ice tea, and getting

fresh cool air when feeling nauseous (8).

When taking multiple medications, tolerance may be improved by seperating the time of dose administration (when clinically appropriate) to reduce the numder of medications taken at one time. Reducing the dose frequency (e.g., taking smaller doses more often) or use controlled release dosage forms, both which reduce local GI drug conentrations and the rate of rise and peak blood drug levels. If medications are associated with dizzines or appear to produce N/V through vestibular stimulation, administration prior to sleep may be helpful. Giving in the evening or at bedtime may also improve tolerance as side effects occurring with increasing drug levels or peak blood levels will then occur while the patient is sleeping. Advise the patient that they can "experiment" to determine when and how medications are best tolerated, given this does not interfere with therapeutic efficacy.

If intolerance to the medication is still unacceptable, dose adjustment, change in dosage form or switching to alternative agent within or outside the class of medication not being tolerated. should be considered. Patients often report dramatically different tolerance to medications within the same therapeutic class and rarely even different manufacturers.. If available, feasible, and clinically appropriate, changing the route of administration (e.g., transdermal patch instead of oral) may reduce MRNV. Review the patient's entire medication profile to determine if other medications can be contributing to the N/V, and if such therapies should be modified or discontinued.

Failing the above strategies, pharmacologic treatments may be effective in controlling MRNV. Obviously, use of any agent to treat MRNV brings further risk of adverse events.Anti-emetics are available with a number of mechanisms of action, and some are thought to work through more than one mechanism. Antiemetic agents with dopamine$_1$ and 5HT$_3$ blocking properties are often effective when MRNV is due to effects on the GI tract or CTZ, however antihistamines and anticholinergics may also work. When MRNV is due to GI dysmotility, a prokinetic agent as metoclopramide may be effective when other agents are not. Both dopamine blocking agents and metoclopramide carry risks for tardive dyskinesia when used long term and alternative therapy should be sought when ongoing therapy is needed. Of note is that small doses of anti-emetics are often as effective as higher doses such that antiemetic dose minimization is an appropriate approach to reducing side effects. When MRNV is due to GI dysmotility, a prokinetic agent as metoclopramide may be effective when other agents are not. Both dopamine blocking agents and metoclopramide carry risks for tardive dyskinesia when used long term. When MRNV is accompanied by vertigo or exacerbated by movement, using agents that suppress signals from the vestibular apparatus such as antihistamines and anticholinergics may be useful. Corticosteroids may be effective in MRNV due to a number of drugs (see CINV and PONV sections below), and neurokinin-1 inhhibitor is be effective in CINV and PONV. Benzodiazepine are often useful for reducing anticipatory N/V to drugs. Since MRNV may be caused by multiple mechanisms, or a patient is taking multiple medications, more than one pharmacologic agent may be needed.

Medications that commonly cause nausea and vomiting

Cancer chemotherapy

Almost all medications can cause nausea and vomiting, perhaps the most well-known cause is chemotherapy agents. There are three classifications of chemotherapy induced nausea and omitting (CINV). Acute CINV occurs within the first 24 hours after the completion of the chemotherapy infusion. Delayed CINV typically begins at least 24 hours after and can last up to several days after following the chemotherapy infusion completion. Anticipatory CINV usually occurs within 12 hours prior to treatment administration. Anticipatory CINV is usually due to a previous episode of uncontrolled vomiting with previous chemotherapy administrations (9).

The pathophysiology of CINV is not entirely understood. The two pathways though to be involved in CINV are the CTZ and the gastrointestinal (GI) tract. The CTZ is a highly vascular and is directly exposed to the chemotherapy agents in the blood and in the cerebral spinal fluid. When the enterochromoffin cells, most rapidly dividing cells in the GI tract, are damaged by the chemotherapeutic agent, serotonin is released. Serotonin binds to the vagal afferent receptors that stimulate emesis through CTZ or directly through the vomiting center.

Although the incidence of nausea correlates with the incidence of vomiting; vomiting generally occurs less frequently. There are several guidelines that exist that clearly define the prevention and treatment of chemotherapy induced nausea and vomiting. The American Society of Clinical Oncology (ASCO) (10,11) and the National Comprehensive Cancer Network (NCCN) (12)

Table 1 Chemotherapy emetogenicity risk categories

Highly emetogenic (>90%)	Cisplatin
	Cyclophosphamide (>1.5 g/m^2)
	Mechlorethamine
	Streptozocin
Moderately ematogenic (30-90%)	Carboplatin
	Cytarabine (>1 g/m^2)
	Daunorubicin
	Doxorubicin
	Epirubicin
	Idarubicin
	Ifosfamide
	Ironotecan
	Oxaliplatin
Low risk (10-30%)	Bortezomib
	Cetuximab
	Cytarabine (<100 mg/m^2)
	Docetaxil
	Etoposide
	Gemcitabine
	Methotrexate
	Mitomycin
	Mitoxantrone
	Paclitaxel
	Pemetrexed
	Trastuzumab
	5-fluorouracil
Minimal risk (<10%)	Bevacizumab
	Bleomycin
	Busulfan
	Cladribine
	Fludarabine
	Vinblastine
	Vincristine
	Vinorelbine

are two commonly referred to guidelines. There are slight differences between the guidelines.

There are several risk factors that make patients more predisposed to development of CINV. Patient factors include age since younger patients are more likely to experience CINV and female gender. Treatment related factors include the chemotherapy emetogenicity and the chemotherapy dose. *Table 1* lists the emetogenicity of several chemotherapy agents.

Prevention of chemotherapy induced nausea and vomiting depends on the chemotherapy regimen that the patient is receiving. Prophylactic antiemetics are selected based on the classification of CINV and the emetogenicity of the chemotherapeutic agent (*Table 2*). Dexamethasone is a well established antiemetic for patients who receive highly emetogenic agents. More detailed explanations can be found in the NCCN and ASCO guidelines.

Table 2 Recommended treatment regimens for prevention of chemotherapy induced nausea and vomiting

Emetic risk category	Antiemetic regimen
Highly emetogenic	Dexamethasone
	5HT$_3$ receptor antagonist
	Aprepitant
Moderately emetogenic	Dexamethasone
	5HT$_3$ receptor antagonist
Low risk	Dexamethasone
Minimal risk	No routine prophylaxis recommended

For patients who are experiencing anticipatory CINV, lorazepam or alprazolam can be recommended. These agents have both amnesic and anti-anxiety properties that would be beneficial.

Medications used in peri-operative care

Post-operative nausea and vomiting (PONV) continues to be an unfavorable consequence of surgery and anesthesia. Nausea and vomiting should be considered individual entities and therefore should be assessed independently. The frequency of PONV ranges from 10-80%. In the ambulatory care setting, PONV rates range from 30-50%.

The exact etiology of PONV is unknown. The major receptors involved in the development of PONV are dopaminergic, cholinergic, histaminergic, serotonergic and neurokinin (NK-1). Stimulation of the vestibular system during surgery, increased vestibular sensitivity due to opiod administration and movement following surgery can lead to PONV. Using morphine to manage post-operative pain has been associated with an increase the frequency of PONV. Opioids on their own can cause nausea and vomiting by direct stimulation of the CTZ, delaying gastric emptying, reducing gastrointestinal motility and sensitizing the vestibular system to motion.

It is suggested that there are a number of patient-specific, surgical and anesthetic factors that can lead to the development of PONV (*Tables 3,4*). Nitrous oxide is known to cause N/V when administered as the sole anesthetic

Table 3 Factors which increase risk of PONV

Medication related
Use of post-operative opioids
Use of nitrous oxide
Use of physostigmine
Other risk factors
Female sex
History of post-operative nausea and vomiting
History of motion sickness
Non-smoker
Surgical duration >60 min

Table 4 Procedures with highest risk of PONV

Procedures with highest risk of PONV
Laparoscopy
Laparotomy gynecologic surgery
Breast surgery
Craniotomy
ENT surgery

agent. Other predictors include the use of peri-operative opioids and dehydration prior to surgery. Aggressive hydration prior to surgery has been shown to reduce the risk of post-operative nausea.

Female sex , non-smoking status and general anesthesia are factors which of both post-operative nausea and post-operative vomiting while history of migraine and the type of surgery are more predictive for post-operative nausea alone. Inhaled anesthetic agents are the strongest risk factor in the development of post-operative vomiting.

PONV frequency is highly dependent on the number of risk factors that a patient has. Patient with only one risk factor have lower tendency to develop PONV, 20-30%; conversely patients with two or more risk factors have the highest risk of developing PONV, 60-80%.

Patients should be assessed prior to surgery for their risk of PONV. In patients who are high risk, administration of a prophylactic antiemetic should be considered. The agent should block at least one for the receptors thought to be involved PONV (dopaminergic, cholinergic, histaminergic, serotonergic and neurokinin). None of the available agents are entirely effective for the prevention of PONV, especially in patients who are considered high risk (13). Thus, it is recommended that clinicians administer combinations of antiemetic treatments from different drug classes (with different mechanisms of action) (14,15).

Opioid analgesics

Opioid analgesics are a well recognized cause of N/V both during acute and chronic use. Nausea and vomiting is often cited by patients as an "allergy" to opioids, and a good medication history to explore the patients symptoms should be performed. Opioids contibute considerably to the problem of PONV and N/V in cancer patients. (see sections on PONV and CINV above). Nausea and vomiting is a major reason for treatment discontinuation in long-term opioid use. In acute use of opioids post operatively, nausea is reported in up to 70% of patients and and vomiting in up to 40%. Chronic opioid use is associated with nausea in 10-40% of patients, with vomiting occurring in 7-12% (16). In general the incidence and severity of N/V decreases with continued use, but a significant minority of patients will have continuing symptoms. Orally administered opioids appear to produce more N/V than parenterally administered drug. Transdermal fentanyl generally elicits N/V at the same rate as other chronic opioids, but may be better tolerated in an individual patient (16).

The opioids produce N/V through activation of opioid receptors (mu, delta and kappa).in the central nervous system and periphery (17). Peripherally, opioids alter gut motility (mu and kappa receptors) (18,19), direct activation of the CTZ (mu and delta receptors) and activation or sensitization of the vestibular apparatus (mu and possibly delta and kappa receptors). Cortical inputs may also play a role in opioid nausea and vomiting. Note that at higher doses, opioids may act as an anti-emetic. The role of any specific mechanism possibly varies by patient, specific agent, clinical situation, route of administration, and duration of use.

All opioids may be associated with nausea and vomiting, and controlled trials typically demonstrate a similar frequency for compared agents. There is wide interpatient variability in tolerance of opioids with patients experiencing significant N/V with one agent, but tolerating other opioids. This variability most likely results in differences in drug action at opioid receptors and interpatient variability in drug metabolism and opioid receptor expression. Some clinicians consider codeine and morphine to be more likely to produce N/V. However controlled trials have note born out this "clinical lore". Chang *et al*. found morphine and hydromorphone to be equally effective and to produce N/V at the same rates when given as a bolus dose in emergency

room patients (20) and Hong *et al*. found the two agents equivalent when administered as patient controlled analgesia (21). The agonist antagonist opioids (e.g., butorphanol and nalbuphine) may produce less N/V, but have limited clinical utility in many settings.

The important point is that reponse varies from drug to drug and patient to patient. Tapentadol, a new "non-opioid" analgesic agent with mu opioid agonist effects as well as norepinephrine reuptake blocking activity, produces less nausea and vomiting than pure mu agonists, however with rates of nausea as high as 50% (compared to 70% for oxycodone) and vomiting frequency of 17% (compared to 40% for oxycodone) during post operative use, MRNV remains highly problematic (22).

Management of opioid related N/V involves both general and targeted strategies. General strategies include modification of drug, dose, route, dosage form or dose regimen. Providing an appropriate bowel regimen to avoid constipation may reduce N/V. Non-pharmacologic strategies include use of relaxation techniques, dietary alteration (avoiding spicy and salty foods or heavy sweets) and environmental changes (cool fresh air, lower lights, limit moving objects) (23). No pharmacologic class has been shown to be superior in the treatment of opioid N/V (24). Dopamine blockers, $5HT_3$ blockers, antihistamines, anticholinergics and steroids all appear to be equally effective (or equally ineffective) as single agents (25). Dopamine antagonists, and 5HT3 inhibitors are often effective when opioid N/V is due to direct and indirect CTZ stimultion. When opioid N/V is associated with early satiety, bloating, constipation or early post-meal vomiting, treatment with metoclopramide to increase gut motility may help somewhat in conjunction with other strategies. When N/V occurs with vertigo, use of an antihistamine or anticholinergic should be considered. Combination therapy having antiemetics with different mechanisms of action is often more effective than single agent therapy. Other pharmacologic agents with evidence of effect on opioid N/V include using low dose opioid antagonists (naloxone, naltrexone) and agonist-antagonist opiates. Due to the incomplete blood-brain barrier of the area postrema (CTZ), peripheral mu antagonists block opioid induced N/V without reducing pain control. However the clinical use of such agents (e.g., methylnaltrexone) has not been fully evaluated for the treatment of opoioid for the treatment of opioid-induced nausea (26). Benzodiazeines may be efective for anticipatory N/V associated with opioids. Corticosteroids and the neurokinin-1 antagonists are effective in control of PONV. However there is no data available demonstrating effectiveness of neurokinin-1 antagonists when opioid use alone is the cause of N/V. The atypical antipsychotic agent risperidone may be effective when other agents are not. Given the multiple mechanisms of opioid N/V, more than one therapy may be required to manage same patients..

Antiretrovirals

Nausea and vomiting is an extremely common and bothersome symptom reported by HIV patients. Nausea in HIV is often caused or exacerbated by antiretrovirals, reducing quality of life and adherence to therapy (27). Note that HIV patient often concurrently receive other medications that produce N/V frequenly including opioids, SSRI and antimicrobials.

In patients treated with antiretrovirals or occupational and non-occupational HIV exposure prohylaxis (zidovudine, lamivudine together, with indinavir, nelfinavir or tenofovir), 42-53% experienced nausea and 14-16% vomited (28). Combination antiretroviral therapy given to treatment naive asymptomatic HIV postive patients treated with indinavir/zidovudine/lamivudine 69% reported nausea ans\d 42% vomiting (29). In general, nausea occurs in 25% of patients taking initial antiretroviral therapies, is the most common cause of drug discontinuation and is correlated with treatment failure (30). Patients with advanced disease requiring complex regimens are more likely to experience N/V (31). Overall, 25% of highly active antiretroviral therapy discontinuations are a result of nausea and vomiting (32). Symptoms are typically worse upon therapy initiation, however ongoing nausea and vomiting are not uncommon. The frequency of N/V varies between available antiretroviral regimens (33).

Antiretroviral agents most commonly associated with nausea and vomiting are the non-nuceoside reverse transcriptase inhibitors and protease inhibitors, in particular nevirapine, ritonavir, amprenavir, abacavir and efavirenz. Nausea and vomiting from antiretrovirals likely results from both effects on the gastrointestinal tract and through activation of the CTZ. In patients with previous severe nausea and vomiting from antiretrovirals, anticipatory nausea and vomiting may possibly contribute. Management of antiretroviral induced nausea and vomiting includes administration with food or meals, changing foods eaten prior to taking doses, taking smaller but more frequent meals, relaxation techniques, altering timing of doses and switching of medications and dosage forms. A number of

Table 5 Suggestions for non-pharmacologic management

Practical tips for managing preventing nausea and vomiting
• Keep dry crackers near the bed for morning nausea
• Try chamomile, peppermint, catnip, or ginger tea, and fresh, dried, or candied ginger
• Sniff a cut lemon
• Eat salty foods such as pretzels; carry a small packet of salt when going out
• Avoid trigger foods known to cause nausea
• Avoid strong odors
• Avoid stomach irritants (e.g., tobacco, aspirin)
• If there is a pattern to nausea, eat more during periods with less nausea
• Do not eat and drink at the same time; drink liquids an hour before or after eating
• Eat meals sitting up rather than lying down
• Avoid lying down for at least an hour after eating; rest with your head higher than your feet
• Keep the room temperature cool
• Avoid eating in a room that is hot, stuffy, or filled with cooking odors
Dietary measures for relieving nausea, vomiting, and diarrhea
• Drink clear beverages such as fruit juices, broth, ginger ale, energy drinks, or herbal teas
• Eat small amounts of food every few hours rather than 2-3 large meals per day
• Eat slowly and sip beverages slowly
• Suck on popsicles or frozen fruit juice
• Try the BRAT diet: bananas, white rice, applesauce, and white bread toast
• Eat bland, soft foods (e.g., pasta, mashed potatoes, jello)
• Eat dry foods like unbuttered toast, saltine crackers, and dry cereal without milk
• Avoid greasy foods, fried foods, margarine, butter, and oils
• Avoid spicy foods
• Avoid dairy products
• Avoid caffeine (in coffee, tea, soft drinks, chocolate, some pain medications)
• Avoid alcoholic beverages
• Avoid acidic foods and juices (e.g., citrus fruits, tomatoes)
• Eat foods high in soluble fiber
• Avoid foods high in insoluble fiber

suggestions for non-pharmacologic management have been recommended (*Table 5*) (34). Providers need to be aware of recommendations for administration of each agent the patient is taking and to provide effective education on proper use.

Medications useful in antiretrovirals include the commonly used anti-emetics, plus dronabinol and medical marijauna. Because of the frequency of MRNV with non-antiretroviral medications used in HIV patients, review and possible adjustment of other pharmacologic agents taken by the patient should be undertaken. Again, the complexity of HIV patients may require the use of multiple strategies aimed at reducing N/V to an acceptable level for the individual patient.

Other medications

Most medications are associated with nausea and less commonly, vomiting in a small minority of patients. However, MRNV may become a significant issue with some therapies. *Table 6* lists medications which are associated with N/V in 10% or more of patients compiled from standard drug information resources, primary and secondary medical literature and the FDA approved prescribing information. Factors that will influence reported rates of N/V include "background" rates of N/V in the treated population,

Table 6 Medications commonly associated with nausea and vomiting

Therapeutic use	Therapeutic class	Example medications	% Nausea	% Vomit	Recommendations/Comments
Amyotropic lateral sclerosis		Riluzole	12-21		
Analgesic	CCB N type	Ziccomitide	40	16	
Analgesics	Non-steroidal antinflammatory	Celecoxib Ibuprofen	7%	<6	Take with food
Analgesics	Non-steroidal antinflammatory	Ketorolac	12		Take with food
Analgesics	Novel	Tapentadol	50		
Analgesics	Novel	Tramadol	15-40	5-17	
Analgesics	Opiates	Mu agonists	20-60	10-30	
Anti gout	Urate oxidase	Rasburicase	50	27	
Anti- gout		Colchicine	>10		
Antidiabetics		Metformin	6-25		
Antidiabetics		Pramlintide	28-48	7-11	
Antidiabetics	GLP-1 agonists	Exanetide	44	13	Give with meals
Antidiabetics	GLP-1 agonists	Liraglutide	28	11	
Antimicrobial	Antibacterial	Tigecycline	25-30	20	
Antimicrobial	Antibiotics	Azithromycin	Up to 18		
Antimicrobial	Antibiotics	Clindamycin			
Antimicrobial	Antibiotics	Daptomycin	06-10	3-12	
Antimicrobial	Antibiotics	Erythromycins	????		
Antimicrobial	Antibiotics	Linezolid	10		
Antimicrobial	Antibiotics	Metronidazole			
Antimicrobial	Antibiotics	Minocycline			
Antimicrobial	Antibiotics	Quinolones			
Antimicrobial	Antibiotics	Tetracyclines			
Antimicrobial	Antibiotics	Tigecycline			
Antimicrobial	Antibiotics	Vancomycin	>10 NV		
Antimicrobial	Antifungals	Flucytosine			
Antimicrobial	Antifungals	Itraconazole	11	5	
Antimicrobial	Antifungals	Micafungin	22	22	
Antimicrobial	Antimalarial	Chloroquine			
Antimicrobial	Antimalarial	Hydroxychloroquine			
Antimicrobial	Antimalarial	Primaquin			Take with meals
Antimicrobial	Antimalarial	Quinine			
Antimicrobial	Antimycobactrial	Rifabutin	>10		
Antimicrobial	Antiretroviral	Abacavir	7-10		
Antimicrobial	Antiretroviral	Amprenavir	43-74	24-34	
Antimicrobial	Antiretroviral	Atazanavir	3-14	3-4	
Antimicrobial	Antiretroviral	Darunavir	18	2	
Antimicrobial	Antiretroviral	Delavirdine	20-25	3-11	

Table 6 *(continued)*

Table 6 *(continued)*

Therapeutic use	Therapeutic class	Example medications	% Nausea	% Vomit	Recommendations/Comments
Antimicrobial	Antiretroviral	Efavirenz	3-14 children 20-40	3-6	
Antimicrobial	Antiretroviral	Emtricitibine	13-18	9 children 13	
Antimicrobial	Antiretroviral	Enfuvirtide	23		
Antimicrobial	Antiretroviral	Fosamprenavir	3-7	2-6	
Antimicrobial	Antiretroviral	Indinivir	12	8	
Antimicrobial	Antiretroviral	Lamivudine	15-33	13-15	
Antimicrobial	Antiretroviral	Ritonavir	26-30	14-17	
Antimicrobial	Antiretroviral	Saquinavir	11	7	
Antimicrobial	Antiretroviral	Stavudine	43-53	18-30	
Antimicrobial	Antiretroviral	Tenofovir	11	4-7	
Antimicrobial	Antiretroviral	Zidovudine	51	17	
Antimicrobial	Antituberculars	Ethambutol	??		
Antimicrobial	Antituberculars	Isoniazid	??		
Antimicrobial	Antituberculars	Rifampin			
Antimicrobial	Antiviral	Acyclovir			
Antimicrobial	Antiviral	Cidofovir	>10		
Antimicrobial	Antiviral	Famciclovir	7-12	1-5	
Antimicrobial	Antiviral	Foscarnet	47	26	
Antimicrobial	Antiviral	Ganciclovir	25	13	
Antimicrobial	Antiviral	Oseltamivir	3-10	2-15	
Antimicrobial	Antiviral	Valacyclovir	5-15	1-6	
Antimicrobial	Antiviral	Valganciclovir	8-30	21	
Antimicrobial	Misc	Atovaquone	>10		
Antimicrobial	Misc	Dapsone	>10		
Antimicrobial	Misc	Pentamidine	>10		
Antimicrobial	Misc	Primaquine			
Antimicrobial	Misc	Pyrimethamine			Give with meals
Antimicrobials	Antifungals	Amphoterecin	16-40	10-30	
Antimicrobials	Antifungals	Caspofungin	6	4	
Biologic	Multiple sclerosis	Glatiramer	22	6	
Biologics		Anti Thymoglob	>10		
Biologics	Interferon	Interferon alfa	33-39	33-39	
Biologics	Monoclonal antibodies	Efalizumab	11		
Biologics	Monoclonal antibodies	Infliximab	21		
Biologics	Multiple sclerosis	Beta interferon	23		
Bisphosphanate		Pamidronate	50	35	
Bisphosphonate		Zoledronic acid	29-46	14-32	
Cancer therapies		Bicalutamide	15	6	

Table 6 *(continued)*

Table 6 *(continued)*

Therapeutic use	Therapeutic class	Example medications	% Nausea	% Vomit	Recommendations/Comments
Cancer therapies		Denilleukin difitox	64 NV		Premedicate/antiemetics
Cancer therapies	Antiandrogen	Flutamide	12		
Cancer therapies	Antiestrogens	Fulvestrant	26	13	
Cancer therapies	Aromatase inhibitor	Exemestane	9-18	7	
Cancer therapies	Aromatase inhibitor	Letrazol	9-17	3-7	
Cancer therapies	Biologic response modifier	Aldesleukin	20-50 NV	--	
Cancer therapies	Estrogen receptor antagonist	Fulvestrant	25	13	
Cancer therapies	LHRH antagonists	Leuprolide	<25 NV		
Cancer therapies	Monoclonal antibody	Alemtuzumab	40-50	3-40	
Cancer therapies	Monoclonal antibody	Bevacizumab	-	47-50	
Cancer therapies	Monoclonal antibody	Bortezomib	44-57	27-35	
Cancer therapies	Monoclonal antibody	Cetuximab	29		
Cancer therapies	Monoclonal antibody	Gemtuzumab	68	58	
Cancer therapies	Monoclonal antibody	Rituximab	8-23	10	
Cancer therapies	SERM	Raloxifen			
Cancer therapies	TNF blocker	Lenalidomide	22-24	10	
Cancer therapies	Tyrosine kinase inhibitor	Erlotinib	11-33	23-42	Take on empty stomach
Cancer therapies	Tyrosine kinase inhibitor	Geftinib	13-18	9-12	
Cancer therapies	Tyrosine kinase inhibitor	Imatinib	42-74	23-58	Take with food
Cancer therapies	Tyrosine kinase inhibitor	Lapatinib	44	26	Take on empty stomach Taken as single daily dose
Cancer therapies	Tyrosine kinase inhibitor	Nilotinib	18-31	10-21	
Cancer therapies	Tyrosine kinase inhibitor	Soratinib	24	15-16	Administer on an empty stomach
Cancer therapy		Tretenoin	57 NV		
Cancer therapy	Monoclonal antibody	Trastuzumab	6-33	4-23	
Cancer therapy	MTOR kinase inhibitor	Temsirolimus	37	19	
Cancer therapy	SERM	Tamoxifen	5-26		
Cancer therapy	TNF blocker	Thalidomide	4-24		
Cancer therapy	Tyrosine kinase inhibitor	Sunitinib	31-49	24-28	
Cardiovascular		Digoxin			Suspect OD
Cardiovascular	Antiarrhythmic	Quinidine	>10		
Cardiovascular	Antiarrhythmics	Amiodarone	10-35	10-20	
Cardiovascular	Antiarrhythmics	Mexilitine	40 NV		
Cardiovascular	Antiarrhythmics	Propafenone	2-11		

Table 6 *(continued)*

Table 6 *(continued)*

Therapeutic use	Therapeutic class	Example medications	% Nausea	% Vomit	Recommendations/Comments
Cardiovascular	Antiplatelet	Clopidogrel	???		
Cardiovascular	CCB	Nifedipine	11		
Cardiovascular	Prostaglandin	Epoprostenol	67 NV		
Cardiovascular	Prostaglandin	Treprostenil	22		
Cholinesterase inhibitor		Neostigmine			
Cholinesterase inhibitor		Pyridostigmine			
CNS	Alzhiemer's	Donepezil	5-10	3-8	
CNS	Alzhiemer's	Galantamine	4-24	4-13	
CNS	Alzhiemer's	Rivastigmine	7-47	6-31	Give with meals
CNS	Alzhiemer's	Tacrine	>10 NV		
CNS	Anti manic	Lithium			
CNS	Anti OCD	Clomipramine	33	7	Titrate, Food, divide doses
CNS	Anticonvulsant	Carbamazepine	15-25	15-18	
CNS	Anticonvulsant	Ethosuximide			
CNS	Anticonvulsant	Felbamate			
CNS	Anticonvulsant	Lamotrigine	7-14	5-9	
CNS	Anticonvulsant	Levetirecetam		15	
CNS	Anticonvulsant	Oxcarbazine	15-29	7-36	
CNS	Anticonvulsant	Phenytoin			
CNS	Anticonvulsant	Primidone			
CNS	Anticonvulsant	Tiagibine	>10		
CNS	Anticonvulsant	Topiramate	6-12	1-3	
CNS	Anticonvulsant	Valproic acid	26-34	15-23	
CNS	Anticonvulssnts	Valproic acid	26-34	15-23	
CNS	Antidepresant	Citalopram	>10		
CNS	Antidepresant	Duloxetine	4-22	1-6	
CNS	Antidepresant	Escitaloopram	15		
CNS	Antidepresant	Fluoxetine	12-29	3	
CNS	Antidepresant	Fluvoxamine	>10		
CNS	Antidepresant	Milnacipran	37	7	
CNS	Antidepresant	Sertraline	>10		
CNS	Antidepressant	Dexvenlafaxine	22-26	<4	
CNS	Antidepressant	Paroxetine	19-26	2-3	
CNS	Antidepressant	Trazodone	>10		
CNS	Antidepressant	Venlafaxine	21-58	3-6	Take with food
CNS	Antimanic	Lithium	???		
CNS	Antiparkinsonian	Apomorphine	30 NV		
CNS	Antiparkinsonian	Bromocriptine	>10		
CNS	Antiparkinsonian	Entacapone	14	4	

Table 6 *(continued)*

Table 6 *(continued)*

Therapeutic use	Therapeutic class	Example medications	% Nausea	% Vomit	Recommendations/Comments
CNS	Antiparkinsonian	Levodopa/carbidopa	???		
CNS	Antiparkinsonian	Pramipexole	RLS 5 PD 28		Titrate dose
CNS	Antiparkinsonian	Rasagiline	10-12		
CNS	Antiparkinsonian	Ropinrole	40-69	12	Titrate dose
CNS	Antiparkinsonian	Rotigitine	34-48	10-20	
CNS	Antiparkinsonian	Selegiline	11	1-3	
CNS	Antipsychotic	Bupropion	Up to 18	2-4	
CNS	Antipsychotic	Clozapine	3-17 nV		
CNS	Antipsychotic	Risperidone	Ch- 8-16 A- 4-9		
CNS	Antipsychotic	Ziprasidone	4-12	3-5	
CNS	Antipsychotics	Aripiprazole	16	11	
CNS	Sedative	Dexmedetomidine	11		
CNS	Sedative	Etomidate	>10 NV		
CNS	Sedative-hypnotics	Chloral hydrate			
CNS	Stimulants	Amphetamines			
CNS	Stimulants	Methylphenedate	12		
CNS	Stimulants	Modafinil	11		
Corticosteroids		Prednisone			
Gastrointestinal		Octreatide	5-61	4-21	
Gastrointestinal	Inflammatory bowel	Mesalamine	13		
Gastrointestinal	Inflammatory bowel	Sulfasalazine	33 NV		
Gastrointestinal	Pancreatic Enzymes	Pancrelipase			
Gastrointetinal	Laxative	PEG bowel prep	14-47	7-12	
Glaucoma	Carbonic anhydrase inhibitprs	Acetazolamide			
Hematologic	Anticoagulant	Fondaparinux	11	6	
Hematologic	Antiplatelet	Abciximab	14%		
Hematologic	Colony stimulating factor	Sargramostim	58-70	46-70	
Hematologic	Erythropoetin stimulating	EPO darbepoetin	15-58	8-29	
Hematologic	Thrombopoetin	Oprelvekin	77 nv		
Hormonal		Testosterone			
Hormonal	androgen	Danazol	???		
Hormonal	Contraceptive	Levonorgestrel	23	18	tabs
Hormonal	Corticosteroids	Prednisone	<10		Give with food
Hormonal	Estrogens	Estradiol	9-18	7	
Hormonal	FSH	Follitropin	>10		
Migraine		Dihydroergotamine			
Misc		Acetylcysteine	5-10	-	
Misc		Azathioprine	---	-	

Table 6 *(continued)*

Table 6 *(continued)*

Therapeutic use	Therapeutic class	Example medications	% Nausea	% Vomit	Recommendations/Comments
Misc		Dantrolene	>10		
Misc		Defoxamine	???		
Misc		Demeclocycline	???		
Misc	Antidote	Fomepizole	11		
Misc	Rheumatoid arthritis	Abatacept	>10%		
Nutritional		Levocarnitine			
Oxytocic		Methergine			
Prostaglandin		Epoprostenol	67 NV		
Prostaglandin analogs		Misoprostol			
Respiratory		Theophyllines			Suspect OD
Rheumatoid arthritis		Methotrexate			
Smoking cessation		Varenecline	16-40	1-5	Take with food
Transplant	Immune suppressants	Basiliximab	>10		
Transplant	Immune suppressants	Cyclosporine	23	02/10/10	
Transplant	Immune suppressants	Daclizumab	???		
Transplant	Immune suppressants	Mycophenolate	20-55	34	Give on empty stomach
Transplant	Immune suppressants	Sirolimus	25-36	19-25	
Transplant	Immunosupresant	Mycophenolate	20-54	33-34	
Vitamins, minerals and electrolytes		Cinecalcet	31	27	
Vitamins, minerals and electrolytes		Deferasirox	11	10	Take on empty stomach
Vitamins, minerals and electrolytes		Niacin			
Vitamins, minerals and electrolytes	Minerals and electrolytes	Iron salts	PO IV 1-15		
Vitamins, minerals and electrolytes	Minerals and electrolytes	Potassium salts			
Vitamins, minerals and electrolytes	Minerals and electrolytes	Zinc salts			
Vitamins, minerals and electrolytes	Phosphate binders	Lanthanum	11	9	
Vitamins, minerals and electrolytes	Phosphate binders	Sevelamer	7-20	22	
Vitamins, minerals and electrolytes	Vitamin D analog	Paricalcitol	6-13	6-8	

asessment tools and measurment of MRNV, timing of MRNV assesment, and concurrent therapies. Because of the variablliity of study populations and methods of adverse event detection and assessment, comparing the frequency of N/V associated with different therapeutic options using available drug information resources is of limited value unless very large differences in reported rates exist.

Summary

Medication-related nausea and vomiting (MRNV) is a significant clinical issue in the palliative care population

likely due to the multiple medications that these patients are often taking. A greater appreciation of the etiologies contributing to; and associated with MRNV may help lead to optimal outcomes for the palliative care population.

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