RESEARCH
Review

Chemotherapy-Induced Nausea and Vomiting: A Narrative Review to Inform Dietetics Practice

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ABSTRACT

Chemotherapy-induced nausea and vomiting (CINV) are common symptoms experienced by patients with cancer that influence nutrition. They exert a detrimental effect on dietary intake, risk of malnutrition, and quality of life. Whereas CINV are primarily managed with medication, nutrition and dietetics practitioners play an important role in the management of CINV-related complications such as reduced dietary intake. This review discusses the burden of nausea and vomiting that patients with cancer can experience, including the effect on quality of life, nutritional status, and treatment outcomes. Implications for dietetics practice include the need to explore the nature of reported symptoms, identify predisposing risk factors, and to consider the use of a variety of interventions that are individualized to a patient's symptoms. There are little clinical data regarding effective dietetic interventions for nausea and vomiting. In summary, this review discusses dietetics-related issues surrounding CINV, including the pathophysiology, risk factors, prevalence, and both pharmacologic and dietetic treatment options.
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THERE ARE MULTIPLE CHEMOTHERAPY AGENTS THAT can induce nausea and vomiting. However, with the advent of modern antiemetic agents, there has been a significant reduction in the prevalence of vomiting, with a current estimated incidence of <20%.[1,2]

Efforts to control nausea in this setting have been less effective, with up to 60% of patients reporting nausea despite the use of antiemetic medication.[1] Consequently, nausea remains one of the most distressing side effects experienced by cancer patients, whereas vomiting is now of less concern.[3-5] In addition, research has consistently associated chemotherapy-induced nausea and vomiting (CINV) with adverse effects on dietary intake, risk of malnutrition, and quality of life (QOL).[6,7]

Nutrition and dietetics practitioners routinely consult with patients with cancer who are experiencing CINV and related symptoms. Our aim is to inform dietetics practice by providing a general overview of CINV, as well as CINV-specific issues related to clinical nutrition. These include the pathophysiology and management options for CINV, including current medications and potential dietetic treatment options.

METHODS

A literature search was undertaken between January and July 2015 using the following databases: Medline, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Library. Search terms were not limited by timeframe; instead, all searches were from the date of each database's inception until July 2015. The bibliographies of relevant articles were scanned to identify additional articles of interest. The evidence-based guidelines of the Academy of Nutrition and Dietetics, Dietetics Association of Australia, and the Practice-Based Evidence in Nutrition Knowledge Pathway were reviewed for additional references. The following search terms were used: (*Chemotherapy* AND (*nausea* OR *vomiting* OR *CINV*)) AND ((*Risk factors* OR *prognostic* OR *predictor*) OR (*Mechanism* OR *pathophysiology* OR *physiopathology*) OR (*Nutrition* OR *malnutrition* OR *weight*) OR *Quality of life* OR *guidelines* OR *ginger* OR *protein* OR (*CAM* OR *Complementary* OR *Alternative*)). Only studies published in English with human subjects were included. The results of this search strategy are detailed in Figure 1.[1-67] The results of the literature search were sorted based on the headings included in this review and were used to inform the discussion of each topic.

Defining CINV

CINV is a collective term used to describe the presentation of nausea, vomiting, or a combination of both symptoms associated with the administration of cytotoxic chemotherapy. Although nausea and vomiting are related concepts, they involve distinct physiologic mechanisms and are therefore defined separately in Figure 2.[68]

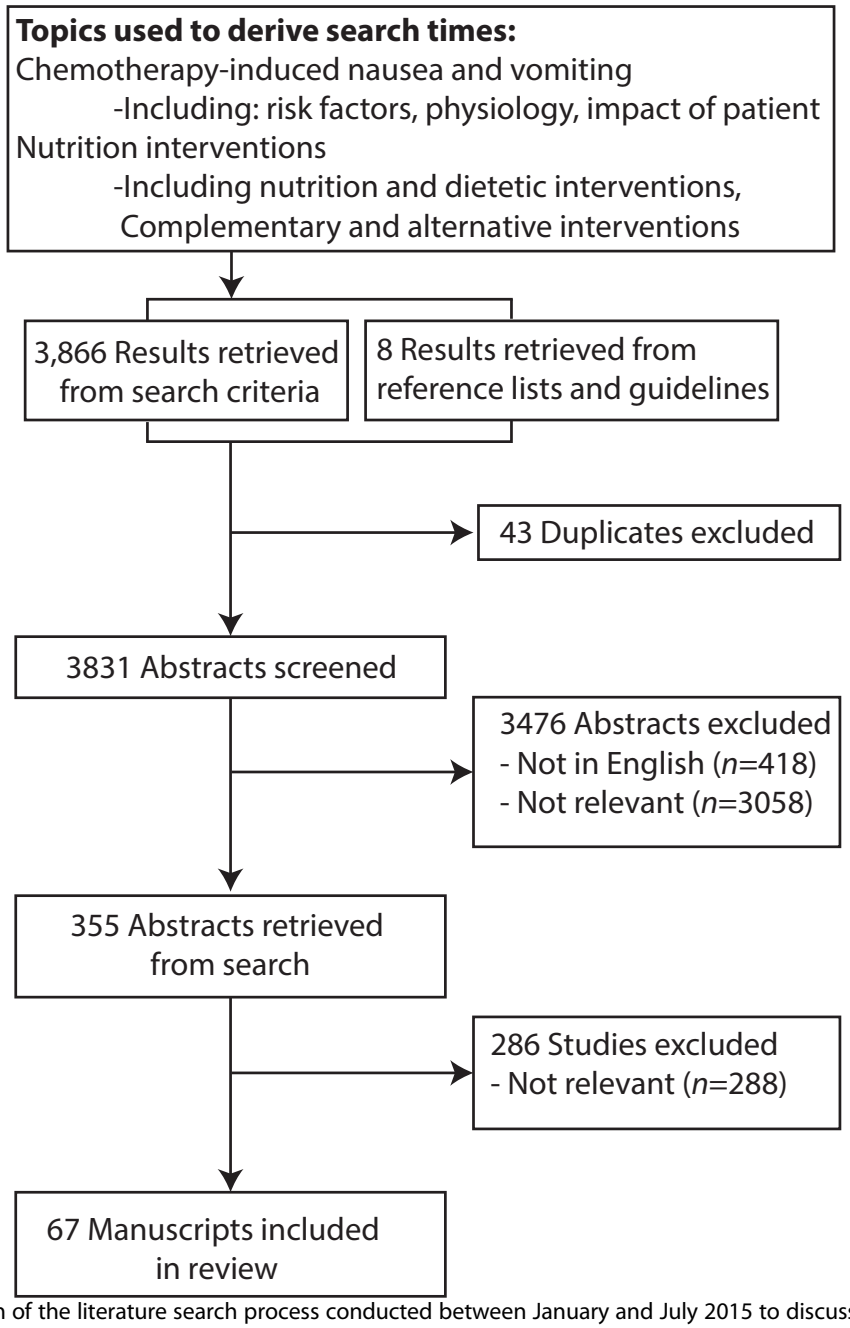

Figure 1. Flow diagram of the literature search process conducted between January and July 2015 to discuss the burden of nausea and vomiting that patients with cancer can experience.

Nausea is a subjective sensation of discomfort, typically associated with the epigastrium, which might result in vomiting. Due to this subjective nature, the sensation, location, duration, and intensity of nausea reported by patients can vary.[30] In addition, multiple symptoms that influence nutrition interlink with nausea, such as appetite loss, lack of energy, taste changes, and pain.[31] Hence, in cases where a patient experiences nausea, it is prudent to investigate an individual's sensations to effectively target treatment toward those symptoms.

CINV is further classified as acute, delayed, anticipatory, breakthrough, and refractory. Exact definitions of acute CINV vary, but it is generally considered to be nausea and/or vomiting that occurs within 24 hours of chemotherapy administration.[32] Delayed CINV is defined as nausea and/or vomiting that occurs after the first 24 hours postchemotherapy.[68] Whereas this distinction might appear arbitrary, research suggests that differing physiologic processes are involved in the acute phase when compared with the delayed phase.[69]

Anticipatory CINV is a conditioned response that occurs after previous cycles of chemotherapy in which nausea and/or vomiting were not adequately controlled. The current understanding of anticipatory CINV is explained in Pavlovian terms. According to this framework, a neutral

Symptom	Definition
Vomiting	Reflexive, rapid, and forceful oral expulsion of upper gastrointestinal tract contents due to powerful and sustained contractions in the abdominal and thoracic musculature.[70]
Nausea	Unpleasant, subjective feeling of discomfort, typically associated with the epigastrium, that can result in vomiting. Although nausea can cause pain and/or stress, it is considered as a distinct concept.[69]

Figure 2. Definitions of chemotherapy-induced nausea and vomiting.

stimulus (eg, the smell of the hospital or the sight of treating staff) is coupled with an unconditioned response (eg, CINV), caused by the unconditioned stimuli (eg, chemotherapy). Once this occurs, a conditioned response develops wherein the formerly neutral stimulus elicits the same response as the unconditioned stimulus.[33] Whereas a conditioning period is required for this coupling to occur, the length of this period varies according to the individual and can occur as soon as the second cycle of chemotherapy. Anticipatory CINV may also cause certain food aversions, because food eaten during the days surrounding chemotherapy can be mentally paired with the sensation of nausea.

Breakthrough CINV is nausea and/or vomiting that occurs despite adherence to optimal antiemetic protocols and is treated by administering additional antiemetic medication.[34] Refractory CINV comprises symptoms that occur in subsequent cycles despite delivery of optimal antiemetic control in previous cycles.[34] If this occurs, additional medication is likely to be required.

Risk Factors

An individual's risk of developing CINV is influenced by numerous factors (Figure 3) that can be categorized into four broad categories: previous experience with nauseating stimuli (eg, previous history of motion or morning sickness), genetic and trait factors (eg, age and sex), psychosocial factors (eg, anxiety), and medical and treatment-related factors (eg, dose and type of chemotherapy). The primary determinant of a patient's risk of experiencing CINV is the emetogenic potential of the chemotherapy regimen. To guide antiemetic therapy, chemotherapy regimens are stratified into the following classifications based on their emetogenic potential: minimally risky, <10% at risk; low, 10% to 30% of patients at risk; moderately risky, 30% to 90% of patients at risk; and highly emetogenic chemotherapy regimens, nearly all patients (>90%) at risk.[34,71]

Individual risk factors are associated with different levels of risk. For example, Molassiotis and colleagues[35] reported that patients with a history of nausea and vomiting (eg, morning or motion sickness) were three times more likely to experience CINV (odds ratio [OR] 3.2, 95% CI 1.29 to 7.95), whereas the odds of experiencing CINV increased by 69% for each incremental increase in reported pain (OR 1.69, 95% CI 1.03 to 2.77). Patients with a greater number of these risk factors are more likely to experience CINV compared to patients with fewer traits. This has led to the development of multiple tools designed to predict the risk of CINV by assessing the cumulative effect of risk factors. For example, the tool developed by Bouganim and colleagues[36] to predict CINV risk demonstrated that patients categorized as at high-risk of CINV were three times more likely to experience symptoms than patients who were considered to be at low risk. Predictive tools such as this are currently being refined and validated in larger populations, but with further studies these tools could improve symptom control by helping to identify high-risk patients before chemotherapy begins.

Pathophysiology

The development of CINV is complex; this section briefly describes the pathophysiology in CINV development.

The trigger site for CINV is thought to be within the gastrointestinal tract. Chemotherapy agents can directly interact with enterochromaffin cells located within the gastric epithelium, resulting in the release of the neurotransmitters serotonin and substance P.[75] The released neurotransmitters then interact with receptors located upon the vagus nerve, which subsequently transmits afferent signals to the chemoreceptor receptor zone (CTZ), a section of the brain within the area postrema, via the nucleus tractus solitarius. It is thought that modern 5-hydroxytryptamine type 3 (5-HT_3) antagonist medications (eg, ondansetron) interact with the 5-HT_3 receptors involved in this process, which then mitigates the degree of afferent vagal signaling. Another neurotransmitter, substance P, is also implicated in the generation of CINV primarily by binding to neurokinin 1 receptors located centrally within the brain. Stimuli transmitted using these two neuropeptides, as well as stimuli from other neurotransmitters (eg, dopamine and histamine) and other regions of the brain (eg, the amygdala), are processed by the CTZ and vomiting center, which then coordinate the relevant musculature to induce a nausea and/or vomiting response.[76]

An additional source of afferent signaling is suggested to be via direct interaction with the area postrema, because this part of the brain has a semipermeable membrane that enables direct interaction with emetic stimuli within the blood or cerebrospinal fluid.

Effects on Patients

Nutritional Status. Malnutrition is both a serious and prevalent concern within the oncology setting.[44] Estimates vary, but between 30% and 50% of the general oncology population experiences malnutrition and has been reported to be as high as 88% in certain populations (ie, patients with head and neck cancer).[45-47] Malnutrition is considered an independent risk factor for mortality, increased length of stay, secondary infections, and health care costs.[44,48,49] Patients who experience CINV are particularly susceptible to malnutrition due to the direct effect of nausea and vomiting (eg, the expulsion of food) or through behavior-related factors (such as avoiding certain foods in an effort to prevent future bouts of CINV). Furthermore, vomiting can impede accurate nutrition diagnoses because it can reduce the validity of recorded dietary intake. Both nausea and vomiting are considered

Medical or treatment-related factors
• Dose and emetogenicity of chemotherapy regimen[37] • History of inner ear infections[38] • Feeling of "warm or hot all over" or sweating during previous treatment cycles[39] • Feeling of generalized weakness during previous treatment cycles[39] • Lack of food consumption before chemotherapy session[40]
Psychosocial factors
• Anxiety (both trait and state)[41] • Negative expectations of chemotherapy[41]
Previous experience with nauseating stimuli
• History of poorly controlled chemotherapy[42] • History of motion sickness or morning sickness[25,26] • History of low alcohol intake[72]
Genetic and trait factors
• Female sex[3,25] • Younger age (younger than age 40 to 65 y)[2,43] • Genetic polymorphisms related to 5-HT_3 metabolism[73,74]

Figure 3. Individual risk factors of chemotherapy-induced nausea and vomiting.

symptoms that influence nutrition that can result in malnutrition.[50-53] Cross-sectional and prospective studies investigating the effect of CINV on a patient's risk of malnutrition have reported a substantial link.[7,54]

For example, in a cross-sectional study of cancer patients undergoing chemotherapy (N=121), CINV was associated with malnutrition, as assessed using the Patient Generated-Subjective Global Assessment, demonstrating that the majority of patients with severe CINV were malnourished.[7] Similarly, in a prospective study of 104 patients undergoing chemotherapy, patients who experienced severe acute (mean=5 vs 8; P=0.003) and delayed nausea (mean=5.1 vs 8; P=0.017) were associated with higher Patient Generated-Subjective Global Assessment scores compared with patients who experienced less severe or no nausea.[54] However, the authors of this study noted that the antiemetic regimens prescribed to patients within this study were not congruent with current guidelines. Therefore, although the observed prevalence might reflect typical clinical practice, the incidence and severity of CINV within this cohort could be higher than what might be observed if current antiemetic recommendations were implemented.

When weight loss was measured instead of malnutrition, similar associations were identified. In a retrospective analysis of cachectic patients with pancreatic cancer (N=107), the absence of nausea and vomiting was an independent determinant of weight stabilization (OR 6.5, 95% CI 1.6 to 27.2; P=0.010).[29] Another study in a mixed oncology population (N=254) found that the prevalence of vomiting was higher in patients that experienced significant weight loss (>5% usual body weight) compared with patients who experienced minimal weight loss (32% vs 14%, respectively; P=0.005).[55]

In summary, whereas few studies have purposely investigated the association between CINV and malnutrition, the existing literature is consistent in its support of this association. In particular, these studies suggest that in patients who experience CINV, nutritional status should be actively monitored and managed to reduce the risk of malnutrition.

QOL. QOL is poorer among patients who experience CINV, either during the acute or delayed phase, compared with patients without these symptoms.[27,28] Highly emetogenic chemotherapy regimens are more likely to reduce QOL than moderately or low emetogenic regimens. This detrimental effect on QOL is exacerbated with each additional day of CINV and is often compounded as treatment progresses, because patients who experience CINV in their initial cycle of chemotherapy are more likely to report poorer CINV-related QOL in subsequent cycles.[27,56] This indicates that the burden of CINV might be cumulative and affects future chemotherapy cycles if not adequately controlled during the first cycle.[25,77] When nausea and vomiting are measured separately, the adverse effect of nausea on QOL has been reported to be greater than the effect of vomiting, which is particularly pertinent because the prevalence of nausea is higher when compared with vomiting.[57] This difference in effect on QOL is likely due to current antiemetic therapy being predominantly effective for controlling vomiting compared with nausea.

Physical Function. Uncontrolled CINV can lead to a number of potentially serious physical conditions and CINV-related hospital admissions. Due to the loss of potassium, sodium, chloride, and water resulting from frequent or severe vomiting, CINV might result in dehydration, electrolyte disturbances, and acid–base imbalances.[24] Another concern is the risk of aspiration pneumonia, a condition where vomitus enters the bronchial tree, resulting in pneumonitis. This can lead to further complications and, in some cases, is fatal.[24] In severe cases of vomiting, esophageal tearing and related bleeding and pain can occur. Nutritional deficiencies are also a potential issue due to inadequate dietary intake of nutrients secondary to nausea and the inability to digest consumed food due to vomiting. These conditions can be further exacerbated by additional comorbidities.[58] Finally, during the 1980s, CINV-related treatment termination was reported to occur in patients[23]; however, it is likely that the prevalence of CINV-related treatment termination has been significantly reduced due to the improvement in antiemetic medications.[22,59]

Pharmacotherapy of CINV

Multiple medications prevent and relieve the distressing symptoms of CINV. International evidence-based guidelines, such as those developed by the Multinational Association for Supportive Care in Cancer and the National Comprehensive Cancer Network, suggest the ideal combination and timing of the available antiemetic agents, according to the

emetogenicity of the chemotherapy treatment.[34,71] It is now common practice to include this standardized, combination approach to provide optimal control of CINV. Although these medications are effective in reducing CINV, there is no single medication that offers complete protection during highly or moderately emetogenic regimens; therefore, the medications discussed below are administered in combination.[34]

5-HT_3 antagonists such as ondansetron, granisetron, and palonosetron, are important components of modern antiemetic therapy. 5-HT_3 antagonists work by binding to the 5-HT_3 receptors within the gastrointestinal tract, which consequentially blocks afferent emetic signalling to the CTZ within the brain. Corticosteroids such as dexamethasone are used for their incidental antiemetic attributes and are commonly prescribed in combination with other antiemetic agents.[34] The mechanism of action for this class of drug is poorly understood but suggested mechanisms include the modulation of the capillary permeability of the CTZ, anti-inflammatory effects within the gastrointestinal tract, and the release of endorphins.[21] A relatively new class of antiemetic medication is neurokinin 1 antagonists such as aprepitant and fosaprepitant. These medications are believed to act centrally within the CTZ by inhibiting the actions of the neuropeptide known as substance P.[60] Neurokinin 1 antagonists are used in combination, usually with dexamethasone and a 5-HT_3 antagonist. They are most effective for moderate to highly emetogenic chemotherapy, especially where delayed CINV occurs. Until the introduction of 5-HT_3 antagonists, metoclopramide was one of the primary antiemetic medications used to treat CINV. It has been suggested that metoclopramide, as with other dopamine antagonists such as phenothiazine and butyrophenone, primarily interacts with dopamine D2 receptors within the central nervous system, eliciting a prokinetic effect on the gut and therefore regulating gut mobility. However, due to the superiority of the new generation of antiemetic therapy and the incidence of extrapyramidal reactions with high-dose metoclopramide, antiemetic guidelines only recommend metoclopramide for low emetogenic regimens and as a rescue antiemetic in breakthrough emesis.[34,71]

Dietetic and Lifestyle Interventions

Dietetic Interventions. Nutrition and dietetics practitioners regularly recommend a number of strategies to help patients manage their nausea and vomiting during chemotherapy. Broadly, these are categorized as strategies that involve modification to meal types and/or composition, behavior-related strategies that target the way food is consumed, and lifestyle or environment-related strategies (Figure 4).[78-80] Whereas many of these strategies appear intuitive, there are currently no clinical trials that have specifically investigated the efficacy of these strategies in reducing measures of CINV. Furthermore, although there are guidelines for the dietetic management of CINV,[80,81] the lack of clinical trials means that these guidelines largely rely on expert opinion. However, medical nutrition therapy (MNT) is an intervention delivered by a registered dietitian nutritionist that is tailored to an individual's need and circumstances and utilizes the strategies outlined in Figure 4. Therefore, despite the lack of studies specifically investigating dietary interventions for CINV, studies investigating MNT as an intervention may provide some evidence for the use of these strategies in the management of CINV.[44,82]

The oncology guidelines of the Academy of Nutrition and Dietetics state that there is currently strong evidence that MNT improves multiple treatment outcomes in patients undergoing chemotherapy, radiation, or chemoradiotherapy in ambulatory or outpatient and inpatient oncology settings.[82] However, when studies that have investigated the use of MNT in chemotherapy have been analyzed separately from studies that have investigated MNT during radiotherapy, the evidence remains strong to suggest that MNT improves clinical and patient-centered outcomes (eg, QOL) in patients receiving radiotherapy but less so in patients receiving chemotherapy. Updated evidence-based practice guidelines endorsed by the Dietetic Association of Australia state that evidence that MNT during chemotherapy results in similar improvements in clinical or patient-centered outcomes is currently insufficient.[44] The authors of these guidelines found that although dietary supplements or simple dietary interventions (eg, provision of handouts detailing food high in protein and energy or basic nutrition counseling) were able to improve nutrition-related outcomes such as dietary intake

Meal-modification strategies

- Avoid overly spicy, fatty, and sweet foods
- Flavor cold or warm drinks and foods
- Drink cold clear fluids between meals such as cordial,[a] lemonade, dry ginger ale, or fruit juice
- Use well-tolerated foods with neutral odors
- Avoid unpleasant food textures
- Choose dry foods such as toasts, crackers, and cereals

Behavior-related strategies

- Eat slowly
- Small and frequent meals
- Avoid skipping meals
- Eat before feeling hungry, because hunger can increase nausea
- Avoid overeating

Lifestyle or environment-related strategies

- Stay away from the kitchen during food preparation.
- Eat in a pleasant, cool environment with fresh air
- Avoid strong odors such as perfumes and cleaning products
- Undertake activities that might distract from nausea (eg, exercise and hobbies)

[a]A nonalcoholic fruit drink concentrate common in Australia.

Figure 4. Common diet-related interventions to relieve chemotherapy-induced nausea and vomiting. Interventions were obtained from references.[78-80]

and weight status, they did not find an improvement in QOL or survival.

There is preliminary support for the use of MNT as part of CINV management. In a small study (N=35) of ambulatory cancer patients, nausea modestly improved after a 2-month multidisciplinary intervention involving a dietitian as well as a physical therapist, social worker, nurse, and a physician (no *P* value reported).[20] Furthermore, two randomized controlled trials that investigated the use of dietary counseling or nutrition supplements in colorectal and patients with head and neck cancer undergoing radiotherapy found that the severity and incidence of CINV was reduced within participants who received dietary counseling.[19,61] Whereas this was in a population undergoing radiotherapy, the pathways involved in the generation of nausea and vomiting are thought to be similar to CINV. These studies, therefore, provide preliminary support for the use of dietary counseling for these symptoms. Further studies are required to investigate the use of MNT during chemotherapy to manage CINV and assess the effect on clinical outcomes such as survival, length of stay and QOL.

There is limited evidence that CINV is associated with taste changes. One study found that patients who reported experiencing CINV also reported greater levels of taste changes and metallic taste.[18] The nature of this relationship has not been elucidated, so it is unclear whether the use of MNT to manage taste changes may also provide relief to nausea and vomiting symptoms.

Protein-Rich Meal Consumption. Preliminary clinical data suggest the consumption of a mixed meal and, in particular, a protein-rich meal, might improve nausea and vomiting symptoms from a variety of nauseating stimuli, including chemotherapy. For example, a prospective study (N=143) reported that patients who did not consume food before chemotherapy were 6.8 times more likely to experience CINV compared with patients who reported eating meals before chemotherapy.[57] Jednak and colleagues[62] examined this effect further in a clinical trial that investigated the effect of different macronutrients on nausea during pregnancy. The results indicated that a protein-rich meal significantly reduced nausea symptoms compared with both equicaloric carbohydrate and fat meals, and noncaloric meals. Subsequently, Levine and colleagues[17] explored this in 28 cancer patients undergoing chemotherapy and reported that a combination of ginger and protein supplementation resulted in a significant reduction in CINV. This effect was more pronounced in the group receiving the highest dose of protein, which indicates that protein supplementation might have been primarily responsible for the reduction in CINV.

The exact mechanism for this is unclear, but it has been observed that during exposure to nauseating stimuli, the electrical rhythm of the stomach becomes dysregulated.[17] The ingestion of a meal maintains the normal physiologic rhythm of the stomach, which might in turn reduce symptoms of nausea and vomiting. The observed superiority of protein in reducing nausea symptoms is attributed to its effect on gastrin secretion, which is believed to normalize gastric activity.[16] However, while the current evidence is supportive, further studies that include larger sample sizes are required, particularly in the chemotherapy setting.

Ginger Supplementation. In vitro and animal research indicate that compounds within ginger might exert several effects on pathways relevant to CINV. These include 5-HT_3 receptor antagonism and the modulation of gastrointestinal motility and gastric emptying rate.[14] In a recent systematic literature review, seven clinical trials were included that tested doses between 0.5 and 2 g ginger capsules.[15] The results provide equivocal evidence, with two studies reporting no effect,[13,63] three finding some effect,[12,64,83] and two studies in favor but with caveats that reduce the real-world application of the results.[10,65] Our review also identified multiple limitations within the literature such as a lack of control for anticipatory nausea and prognostic factors that might influence individual CINV response, inconsistent use of standardized ginger formulations and validated questionnaires, and the use of potentially suboptimal dosing regimens. Hence, whereas some evidence supports ginger as an adjuvant anti-CINV therapy, existing limitations must be addressed before firm recommendations for its use can be made.

Additional Complementary Therapies. Several additional complementary therapies have demonstrated varying degrees of efficacy. These include yoga, progressive muscle relaxation, massage, aromatherapy, hypnosis, exercise, education programs, and acupuncture-point stimulation.[8,9,66,67] However, although many of these therapies are likely to be low in cost and have minimal side effects, further trials are required to address limitations within the literature such as small sample sizes and inconsistent results.

CONCLUSIONS

CINV poses a significant burden to patients undergoing chemotherapy with the potential to result in further medical complications, reduce QOL, and increase the risk of malnutrition. Although some evidence of a benefit from dietary intervention using MNT or protein-rich meals exists, further research is required.

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