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Chemotherapy-induced nausea and vomiting: A narrative review to inform dietetics practice

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Published in:
Journal of the Academy of Nutrition and Dietetics

DOI:
[10.1016/j.jand.2015.10.020](https://doi.org/10.1016/j.jand.2015.10.020)

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Recommended citation(APA):
Marx, W., Kiss, N., McCarthy, A. L., McKavanagh, D., & Isenring, L. (2016). Chemotherapy-induced nausea and vomiting: A narrative review to inform dietetics practice. *Journal of the Academy of Nutrition and Dietetics*, 116(5), 819-827. <https://doi.org/10.1016/j.jand.2015.10.020>

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1 Chemotherapy-induced nausea and vomiting: an overview to inform dietetic practice

2

3 Abstract

4 Chemotherapy-induced nausea and vomiting (CINV) are common nutrition-impact symptoms
5 experienced by cancer patients. They exert a detrimental effect on dietary intake, risk of
6 malnutrition and quality of life. While CINV are primarily managed with medication,
7 dietitians play an important role in the management of CINV-related complications such as
8 reduced dietary intake. This review discusses the burden of nausea and vomiting which
9 cancer patients can experience, including its effect on quality of life, nutrition status, and
10 treatment outcomes. Implications for dietetic practice include the need to explore the nature
11 of reported symptoms, identify predisposing risk factors, and to consider the use of a variety
12 of interventions that are individualised to the patient's symptoms. There are little clinical data
13 regarding effective dietetic interventions for nausea and vomiting. In summary, this review
14 discusses dietetic-related issues surrounding CINV including the pathophysiology, risk
15 factors, prevalence, and both pharmacological and dietetic treatment options.

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25 Introduction

26 There are multiple chemotherapy agents that can induce nausea and vomiting. However, with
27 the advent of modern anti-emetics, there has been a significant reduction in the prevalence of
28 vomiting, with a current estimated incidence of less than 20%.^{1, 2} Efforts to control nausea in
29 this setting have been less effective, with up to 60% of patients reporting nausea despite the
30 use of anti-emetic medication.¹ Consequently, nausea remains one of the most distressing
31 side effects experienced by cancer patients, while vomiting is now of less concern.³⁻⁵ In
32 addition, research has consistently associated chemotherapy-induced nausea and vomiting
33 (CINV) with adverse effects on dietary intake, risk of malnutrition and quality of life (QoL).^{6,}
34 ⁷

35 Dietitians routinely consult with cancer patients experiencing CINV and related symptoms.
36 The aim of this manuscript is to inform dietetic practice by providing a general overview of
37 CINV, as well as CINV-specific issues related to clinical nutrition. These include the
38 pathophysiology, and management options for CINV, including current medications and
39 potential dietetic treatment options.

40 Methods

41 A literature search was undertaken between January and July 2015 using the following
42 databases: Medline, Cumulative Index to Nursing and Allied Health Literature, and the
43 Cochrane Library. Search terms were not limited by timeframe; instead, all searches were
44 from the date of each database's inception until July 2015. The bibliographies of relevant
45 articles were scanned to identify additional articles of interest. The evidence-based guidelines
46 of the Academy of Nutrition and Dietetics, Dietetics Association of Australia and the
47 Practice-based Evidence in Nutrition Knowledge Pathway were reviewed for additional

48 references. The following search terms were used: (Chemotherapy AND (nausea OR
49 vomiting OR CINV)) AND ((Risk factors OR prognostic OR predictor) OR (Mechanism OR
50 pathophysiology OR physiopathology) OR (Nutrition OR malnutrition OR weight) OR
51 “Quality of life” OR guidelines OR ginger OR protein OR (CAM OR Complementary OR
52 Alternative)). Only studies published in English with human subjects were included. The
53 results of this search strategy are detailed in Figure 1 and include the following citations:¹⁻⁶⁷.
54 The results of the literature search were sorted based on the headings included in this review
55 and were used to inform the discussion of each topic.

56 Defining chemotherapy-induced nausea and vomiting

57 CINV is a collective term used to describe the presentation of nausea, vomiting or a
58 combination of both symptoms associated with the administration of cytotoxic chemotherapy.
59 While nausea and vomiting are related concepts, they involve distinct physiological
60 mechanisms and are therefore defined separately in Table 1.⁶⁸

61 Nausea is a subjective sensation of discomfort, typically associated with the epigastrium,
62 which might result in vomiting. Due to this subjective nature, the sensation, location, duration
63 and intensity of nausea reported by patients can vary.³⁰ In addition, multiple nutrition impact
64 symptoms interlink with nausea such as appetite loss, lack of energy, taste changes and
65 pain.³¹ Hence, if a patient experiences nausea, it is prudent to investigate the individual’s
66 sensations in order to effectively target treatment towards those symptoms.

67 CINV is further classified as *acute*, *delayed*, *anticipatory*, *breakthrough*, and *refractory*.

68 Exact definitions of *acute CINV* vary but it is generally considered to be nausea and/or
69 vomiting that occurs within 24 hours of chemotherapy administration.³² *Delayed CINV* is
70 defined as nausea and/or vomiting that occurs after the first 24 hours post-chemotherapy.⁶⁸

71 While this distinction might appear arbitrary, research suggests that differing physiological
72 processes are involved in the acute phase when compared to the delayed phase.⁶⁹

73 *Anticipatory CINV* is a conditioned response that occurs after previous cycles of
74 chemotherapy in which nausea and/or vomiting were not adequately controlled. The current
75 understanding of anticipatory CINV is explained in Pavlovian terms. According to this
76 framework, a neutral stimulus (e.g. the smell of the hospital, the sight of treating staff) is
77 coupled with an unconditioned response (CINV), caused by the unconditioned stimuli
78 (chemotherapy). Once this occurs, a conditioned response develops wherein the formerly
79 neutral stimulus elicits the same response as the unconditioned stimulus.³³ While a
80 conditioning period is required for this coupling to occur, the length of this period varies
81 according to the individual and can occur as soon as the second cycle of chemotherapy.
82 Anticipatory CINV may also cause of certain food aversions, as food eaten during the days
83 surrounding chemotherapy can be mentally paired with the sensation of nausea.

84 *Breakthrough CINV* is nausea and/or vomiting that occurs despite adherence to optimal anti-
85 emetic protocols and is treated by administering additional “rescue” anti-emetic medication.³⁴

86 *Refractory CINV* comprises symptoms that occur in subsequent cycles despite delivery of
87 optimal anti-emetic control in previous cycles.³⁴ If this occurs, additional medication is likely
88 to be required.

89 Risk factors

90 An individual’s risk of developing CINV is influenced by numerous factors (Table 2), which
91 can be categorised into four broad categories: previous experience with nauseating stimuli
92 (e.g. previous history of motion or morning sickness); genetic and trait factors (e.g. age and
93 gender); psychosocial factors (e.g. anxiety); and finally, medical and treatment-related factors
94 (e.g. dose, type of chemotherapy). The primary determinant of a patient’s risk of

95 experiencing CINV is the emetogenic potential of the chemotherapy regimen. In order to
96 guide anti-emetic therapy, chemotherapy regimens are stratified into the following
97 classifications based on their emetogenic potential: minimally, fewer than 10% at risk; low ,
98 10% to 30% of patients at risk; moderately, 30% to 90% of patients at risk; and highly
99 emetogenic chemotherapy regimens, nearly all patients (> 90%) at risk.^{34, 71}

100 Individual risk factors are associated with different levels of risk. For example, Molassiotis et
101 al.³⁵ reported that patients with a history of nausea and vomiting (e.g. morning or motion
102 sickness) were three times more likely to experience CINV (OR 3.2 , 95% CI: 1.29–7.95),
103 while the odds of experiencing CINV increased by 69% for each incremental increase in
104 reported pain (OR 1.69, 95% CI: 1.03–2.77). Patients with a greater number of these risk
105 factors are more likely to experience CINV compared to patients with fewer traits. This has
106 led to the development of multiple tools designed to predict the risk of CINV by assessing the
107 cumulative effect of risk factors. For example, Bouganim et al.'s³⁶ tool to predict CINV risk
108 demonstrated that patients categorized as at high-risk of CINV were three times more likely
109 to experience symptoms than patients who were considered to be low risk. Predictive tools
110 such as this are currently being refined and validated in larger populations, but with further
111 studies these tools could improve symptom control by helping to identify high-risk patients
112 before chemotherapy begins.

113 Pathophysiology

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

116 The trigger site for CINV is thought to be within the gastrointestinal tract. Chemotherapy
117 agents can directly interact with enterochromaffin cells located within the gastric epithelium,
118 resulting in the release of the neurotransmitters serotonin and substance *P*.⁷⁵ The released

119 neurotransmitters then interact with receptors located upon the vagus nerve, which
120 subsequently transmits afferent signals to the chemoreceptor receptor zone (CTZ), a section
121 of the brain within the area postrema, via the nucleus tractus solitarius. It is thought that
122 modern 5-HT₃ antagonist medications (e.g. ondansetron) interact with the 5-HT₃ receptors
123 involved in this process, which then mitigates the degree of afferent vagal signalling. Another
124 neurotransmitter, substance *P*, is also implicated in the generation of CINV primarily by
125 binding to NK₁ receptors located centrally within the brain. Stimuli transmitted using these
126 two neuropeptides, as well as stimuli from other neurotransmitters (e.g. dopamine, histamine)
127 and other regions of the brain (e.g. the amygdala), are processed by the CTZ and vomiting
128 centre, which then coordinate the relevant musculature to induce a nausea and/or vomiting
129 response.⁷⁶

130 An additional source of afferent signalling is suggested to be via direct interaction with the
131 area postrema, as this part of the brain has a semi-permeable membrane that enables direct
132 interaction with emetic stimuli within the blood or cerebrospinal fluid.

133 Impact on patient

134 Nutrition status

135 Malnutrition is both a serious and prevalent concern within the oncology setting.⁴⁴ Estimates
136 vary but between 30-50% of the general oncology population experience malnutrition and has
137 been reported to be as high as 88% in certain populations (i.e. head and neck cancer
138 patients).⁴⁵⁻⁴⁷ Malnutrition is considered an independent risk factor for mortality, increased
139 length of stay, secondary infections, and healthcare costs.^{44, 48, 49} Patients who experience
140 CINV are particularly susceptible to malnutrition due to the direct effect of nausea and
141 vomiting (e.g. the expulsion of food) or through behavioural factors (such as avoiding certain
142 foods in an effort to prevent future bouts of CINV). Furthermore, vomiting can impede
143 accurate nutrition diagnoses as it can reduce the validity of recorded dietary intake. Both

144 nausea and vomiting are considered nutrition impact symptoms that can result in
145 malnutrition.⁵⁰⁻⁵³ Cross-sectional and prospective studies investigating the effect of CINV on
146 a patient's risk of malnutrition have reported a significant link.^{7, 54}

147 For example, in a cross-sectional study of cancer patients undergoing chemotherapy (N=121),
148 CINV was associated with malnutrition, as assessed using the Patient Generated-Subjective
149 Global Assessment, demonstrating that the majority of patients with severe CINV were
150 malnourished.⁷ Similarly, in a prospective study including 104 chemotherapy patients,
151 patients that experienced severe acute (mean: 5 vs 8; $p=0.003$) and delayed nausea (mean: 5.1
152 vs 8; $p=0.017$) were associated with higher PG-SGA scores compared to patients who
153 experienced less severe or no nausea. ⁵⁴ However, the authors of this study noted that the
154 anti-emetic regimens prescribed to patients within this study were not congruent with current
155 guidelines. Therefore, while the observed prevalence might reflect typical clinical practice,
156 the incidence and severity of CINV within this cohort could be higher than what might be
157 observed if current anti-emetic recommendations were implemented.

158 When weight loss was measured instead of malnutrition, similar associations were identified.
159 In a retrospective analysis of cachectic patients with pancreatic cancer (N=107), the absence
160 of nausea and vomiting was an independent determinant of weight stabilisation (OR 6.5, 95%
161 CI: 1.6-27.2; $p=0.010$).²⁹ Another study in a mixed oncology population (N=254) found that
162 the prevalence of vomiting was higher in patients that experienced significant weight loss
163 (>5% usual body weight) compared to patients that experienced minimal weight loss(32% vs
164 14%, respectively; $p=0.005$).⁵⁵

165 In summary, while few studies have purposely investigated the association between CINV
166 and malnutrition, the existing literature is consistent in its support of this association. In

167 particular, these studies suggest that in patients who experience CINV, nutritional status
168 should be actively monitored and managed in order to reduce the risk of malnutrition.

169 Quality of life (QoL)

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

183 Physical function

184 Uncontrolled CINV can lead to a number of potentially serious physical conditions and
185 CINV-related hospital admissions. Due to the loss of potassium, sodium, chloride and water
186 resulting from frequent or severe vomiting, CINV might result in dehydration, electrolyte
187 disturbances, and acid-base imbalances.²⁴ Another concern is the risk of aspiration
188 pneumonia, a condition where vomitus enters the bronchial tree, resulting in pneumonitis.
189 This can lead to further complications and in some cases is fatal.²⁴ In severe cases of
190 vomiting, oesophageal tearing and related bleeding and pain can occur. Nutritional
191 deficiencies are also a potential issue due to inadequate dietary intake of nutrients secondary

192 to nausea and the inability to digest consumed food due to vomiting. These conditions can be
193 further exacerbated by additional comorbidities.⁵⁸ Finally, during the 1980s, CINV-related
194 treatment termination was reported to occur in patients;²³ however, it is likely that the
195 prevalence of CINV-related treatment termination has been significantly reduced due to the
196 improvement in anti-emetic medications.^{22, 59}

197 Pharmacotherapy of CINV

198 Multiple medications prevent and relieve the distressing symptoms of CINV. International
199 evidence-based guidelines, such as those developed by the Multinational Association for
200 Supportive Care in Cancer and the National Comprehensive Cancer Network, suggest the
201 ideal combination and timing of the available anti-emetics, according to the emetogenicity of
202 the chemotherapy treatment.^{34, 71} It is now common practice to include this standardised,
203 combination approach to provide optimal control of CINV. While these medications are
204 effective in reducing CINV, there is no single medication that offers complete protection
205 during highly or moderately emetogenic regimens and therefore, the medications discussed
206 below are administered in combination.³⁴

207 5-HT₃ antagonists such as ondansetron, granisetron and palonosetron are important
208 components of modern anti-emetic therapy. 5-HT₃ antagonists work by binding to the 5-HT₃
209 receptors within the gastrointestinal tract, which consequentially blocks afferent emetic
210 signalling to the CTZ within the brain. Corticosteroids such as dexamethasone are used for
211 their incidental anti-emetic attributes and are commonly prescribed in combination with other
212 anti-emetics.³⁴ The mechanism of action for this class of drug is poorly understood but
213 suggested mechanisms include the modulation of the capillary permeability of the CTZ, anti-
214 inflammatory effects within the gastrointestinal tract, and the release of endorphins.²¹ A
215 relatively new class of anti-emetic medication is NK₁ antagonists such as aprepitant and
216 fosaprepitant. These medications are believed to act centrally within the CTZ by inhibiting

217 the actions of the neuropeptide, substance *P*.⁶⁰ NK₁ antagonists are used in combination,
218 usually with dexamethasone and a 5-HT₃ antagonist. They are most effective for moderate to
219 highly emetogenic chemotherapy, especially where delayed CINV occurs. Until the
220 introduction of 5-HT₃ antagonists, metoclopramide was one of the primary anti-emetic
221 medications used to treat CINV. It has been suggested that metoclopramide, as with other
222 dopamine antagonists such as phenothiazine and butyrophenone, primarily interacts with
223 dopamine D₂ receptors within the central nervous system, eliciting a prokinetic effect on the
224 gut and therefore regulating gut mobility. However, due to the superiority of the new
225 generation of anti-emetic therapy and the incidence of extrapyramidal reactions with high-
226 dose metoclopramide, anti-emetic guidelines only recommend metoclopramide for low
227 emetogenic regimens and as a rescue anti-emetic in breakthrough emesis.^{34, 71}

228 Dietetic and lifestyle interventions

229 Dietetic-related interventions

230 Dietitians regularly recommend a number of strategies to help patients manage their nausea
231 and vomiting during chemotherapy. Broadly, these are categorised as strategies that involve
232 modification to meal types and/or composition, behavioural strategies that target the way
233 food is consumed, and lifestyle or environmental strategies (Table 3).⁷⁸⁻⁸⁰ While many of
234 these strategies appear intuitive, there are currently no clinical trials that have specifically
235 investigated the efficacy of these strategies in reducing measures of CINV. Furthermore,
236 while there are guidelines for the dietetic management of CINV,^{80, 81} the lack of clinical trials
237 means that these guidelines largely rely on expert opinion. However, medical nutrition
238 therapy (MNT) is an intervention delivered by a dietitian that is tailored to the individual's
239 need and circumstances and utilises the strategies outlined in table 3. Therefore, despite the
240 lack of studies specifically investigating dietary interventions for CINV, studies investigating

241 MNT as an intervention may provide some evidence for the use of these strategies in the
242 management of CINV.

243 ^{44, 82}The oncology guidelines of the Academy of Nutrition and Dietetics state that there is
244 currently strong evidence that MNT improves multiple treatment outcomes in patients
245 undergoing chemotherapy, radiation or chemoradiotherapy in ambulatory or outpatient and
246 inpatient oncology settings.⁸² However, when studies that have investigated the use of MNT
247 in chemotherapy have been analysed separately from studies that have investigated MNT
248 during radiotherapy, the evidence remains strong to suggest that MNT improves clinical and
249 patient-centred outcomes (e.g. quality of life) in patients receiving radiotherapy but less so in
250 patients receiving chemotherapy. Updated evidence-based practice guidelines endorsed by
251 the Dietetic Association of Australia, state that evidence that MNT during chemotherapy
252 results in similar improvements in clinical or patient-centred outcomes is currently
253 insufficient.⁴⁴ The authors of these guidelines found that while dietary supplements or simple
254 dietary interventions (e.g. provision of handouts detailing food high protein and energy or
255 basic nutrition counselling) were able to improve nutritional outcomes such as dietary intake
256 and weight status, they did not find an improvement in quality of life or survival.

257 There is preliminary support for the use of MNT as part of CINV management. In a small
258 study (N=35) of ambulatory cancer patients, nausea modestly improved after a two month
259 multidisciplinary intervention involving a dietitian as well as a physical therapist, social
260 worker, nurse, and a physician (no *p* value reported).²⁰ Furthermore, two randomized
261 controlled trials that investigated the use of dietary counselling or nutrition supplements in
262 colorectal and head and neck cancer patients undergoing radiotherapy found that the severity
263 and incidence of CINV was reduced within participants who received dietary counselling.¹⁹

264 ⁶¹ While this was in a population undergoing radiotherapy, the pathways involved in the
265 generation of nausea and vomiting are thought to be similar to CINV. These studies therefore

266 provide preliminary support for the use of dietary counselling for these symptoms. Further
267 studies are required to investigate the use of MNT during chemotherapy to manage CINV and
268 assess the effect on clinical outcomes such as survival, length of stay and QoL.

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

274 Protein-rich meal consumption

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

288 The exact mechanism for this is unclear but it has been observed that during exposure to
289 nauseating stimuli, the electrical rhythm of the stomach becomes dysregulated.¹⁷ The

290 ingestion of a meal maintains the normal physiological rhythm of the stomach, which might
291 in turn reduce symptoms of nausea and vomiting. The observed superiority of protein in
292 reducing nausea symptoms is attributed to its effect on gastrin secretion, which is believed to
293 normalise gastric activity.¹⁶ However, while the current evidence is supportive, further
294 studies that include larger sample sizes are required, particularly in the chemotherapy setting.

295 Ginger supplementation

296 *In vitro* and animal research indicate that compounds within ginger might exert several
297 effects on pathways relevant to CINV. These include 5-HT₃ receptor antagonism and the
298 modulation of gastrointestinal motility and gastric emptying rate.¹⁴ In a recent systematic
299 literature review, seven clinical trials were included that tested doses between 0.5-2g of
300 ginger capsules.¹⁵ The results provide equivocal evidence, with two studies reporting no
301 effect,^{13, 63} three finding some effect,^{12, 64, 83} and two studies in favour but with caveats that
302 reduce the real world application of these results.^{10, 65} Our review also identified multiple
303 limitations within the literature such as a lack of control for anticipatory nausea and
304 prognostic factors that might influence individual CINV response, inconsistent use of
305 standardized ginger formulations and validated questionnaires, and the use of potentially
306 suboptimal dosing regimens. Hence, while some evidence supports ginger as an adjuvant
307 anti-CINV therapy, existing limitations must be addressed before firm recommendations for
308 its use can be made.

309 Additional complementary therapies

310 Several additional complementary therapies have demonstrated varying degrees of efficacy.
311 These include yoga, progressive muscle relaxation, massage, aromatherapy, hypnosis,
312 exercise, education programs, and acupuncture-point stimulation.^{8, 9, 66, 67} However, while
313 many of these therapies are likely to be low-cost and have minimal side effects, further trials

314 are required to address limitations within the literature such as small sample sizes and
315 inconsistent results.

316 Conclusion

317 In summary, CINV poses a significant burden to patients undergoing chemotherapy with the
318 potential to result in further medical complications, reduce QoL, and increase the risk of
319 malnutrition. While some evidence of a benefit from dietary intervention using MNT or
320 protein rich meals exists further research is required.

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