



Evidence Summary SMG-2

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Guidelines on Management of Nausea and Vomiting and on Loss of Appetite, Anorexia, and Cachexia in Cancer

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Table of Contents

List of Tables	i
Evidence Summary	1
THE PROGRAM IN EVIDENCE-BASED CARE	1
INTRODUCTION.....	1
RESEARCH QUESTION	1
TARGET POPULATION.....	1
INTENDED PURPOSE	1
INTENDED USERS.....	2
METHODS	2
Literature Search Strategy.....	2
Study Selection Criteria and Process	3
Guideline Assessment.....	3
RESULTS AND DISCUSSION	4
Overview	4
SUGGESTIONS FOR USE OF THIS REVIEW.....	7
INTERNAL REVIEW	7
APPROVAL BY SPONSORS.....	7
ACKNOWLEDGEMENTS	7
References	14
Appendices.....	22
Appendix A: Members of the Working Group and their COI declarations.....	22
Appendix B: Websites Searched.....	23
Appendix C: Literature Search Strategy.....	26
Appendix D: AGREE II Rigour of Development Scores.....	27

List of Tables

Table 1. Guidelines Relevant to Nausea and Vomiting.....	8
Table 2. Treatment-Induced Nausea and Vomiting	10
Table 3. Guidelines on Loss of Appetite, Anorexia, and Cachexia	12

Guidelines on Management of Nausea and Vomiting or on Loss of Appetite/Anorexia/Cachexia in Cancer

Evidence Summary

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC and any associated programs is editorially independent from the OMHLTC.

INTRODUCTION

CCO developed a series of symptom treatment algorithms in the period 2009-2012 based on corresponding Guide-To-Practice documents consisting of reviews of then-current clinical practice guidelines (<https://www.cancercareontario.ca/en/symptom-management>). These covered the topics of constipation and diarrhea, delirium, loss of appetite, nausea and vomiting, oral care, and pain. Three additional algorithms on sleep disturbances, anxiety and depression, and fatigue were based on joint guidelines by Canadian Partnership Against Cancer (CPAC) and the Canadian Association of Psychosocial Oncology (CAPO). These CAPC/CAPO guidelines considered a broader evidence base as they included guidelines, systematic reviews, and other guidance documents; randomized controlled trials (RCTs) were included in the sleep document.

RESEARCH QUESTION

The research question was developed to direct the search for clinical practice guidelines:

- What are the most appropriate treatments for alleviation of nausea and vomiting or anorexia/cachexia in patients with cancer?

TARGET POPULATION

The target population is adult patients with cancer experiencing symptoms of nausea, vomiting, anorexia, or cachexia. Acute symptoms induced by the current cancer treatment (chemotherapy, radiotherapy) were not the primary focus but major guidelines on this topic have also been included.

INTENDED PURPOSE

This evidence summary was developed to assist the Patient Reported Outcomes and Symptom Management Program of CCO in revising the algorithms on nausea and vomiting [1] and on loss of appetite [2]. The 2010 nausea and vomiting algorithm is based on guidelines by

Fraser Health Hospice Palliative Care Program, Cancer Care Nova Scotia, Association of Comprehensive Cancer Centres, and the National Comprehensive Cancer Network (NCCN), as summarized in the Cancer Care Ontario's Symptom Management Guides-To-Practice: Nausea and Vomiting [3]. The final literature search was conducted in January 2009.

The 2012 loss of appetite algorithm is based on eight guidelines on anorexia, cachexia, appetite stimulants, and nutrition in cancer as summarized in Cancer Care Ontario's Symptom Management Guides-To-Practice: Loss of Appetite [4]. The latest literature search was conducted in January 2009; the National Guideline Clearinghouse, CPAC's Cancer Guidelines Resource Centre, and Google were consulted in September 2010.

INTENDED USERS

The intended users of this evidence summary are staff of the Patient Reported Outcomes and Symptom Management Program. This evidence summary may also be of interest to physicians and nurses dealing with cancer or palliative care symptom management.

METHODS

This evidence summary was developed by a Working Group at the request of the Patient Reported Outcomes and Symptom Management Program of CCO. The Working Group (see [Appendix A](#)) consisted of a health research methodologist, a palliative care physician/medical oncologist, and a nurse practitioner with expertise in oncology and palliative care. The Working Group was responsible for reviewing the identified guidelines and drafting the summary. Conflict of interest declarations for all authors are summarized in [Appendix A](#), and were managed in accordance with the [PEBC Conflict of Interest Policy](#).

This evidence summary is based on a systematic review on the topics of nausea and vomiting or anorexia/cachexia in cancer in adults, limited to clinical practice guidelines that are based on systematic reviews of the literature.

Literature Search Strategy

The systematic search for guidelines was conducted in two stages. In the first stage, websites of organizations known to have produced cancer-related guidelines were reviewed in February to March 2018. As it was anticipated that all the symptom management algorithms listed in the Introduction would eventually be updated, guidelines with management of any symptoms of interest were noted, along with the symptom(s) covered; only those guidelines relevant to the current evidence summary were added to the Endnote database and summarized in this document. Organizations included those identified from guideline databases (Cancer Guidelines Database,¹ Canadian Partnership Against Cancer; National Guidelines Clearing House; Canadian Medical Association CPG Infobase), those with cancer-related guidelines identified in the pain evidence summary in this series [5], and those known to be major cancer guideline developers (e.g., CCO, American Society of Clinical Oncology [ASCO], Alberta Health Services, Cancer Australia, National Institute for Health and Care Excellence [NICE], Scottish Intercollegiate Guidelines Network [SIGN]). A list of organizations is provided in [Appendix B](#). For guidelines that appeared to have several versions, the latest

¹ The Cancer Guidelines Database (CGD) was released in 2018; it updates and replaces the Standards and Guidelines Evidence directory (SAGE). SAGE was used in the initial search, but is no longer available.

version was used and earlier versions excluded. Guidelines based primarily on outdated versions of guidelines by other organizations were also excluded.

The second stage of the systematic search was conducted using MEDLINE, Embase, Allied and Complementary Medicine (AMED), and Emcare on March 28, 2018. The search included terms for a) cancer, b) nausea and vomiting, or loss of appetite, weight loss, anorexia or cachexia, and c) guidelines. The search strategy is reported in [Appendix C](#). Results were limited to publications since January 2009.

Study Selection Criteria and Process

For inclusion, publications needed to include recommendations regarding assessment or management of nausea and vomiting or of loss of appetite/anorexia/cachexia in adult patients with cancer. Only guidelines in English were included; guidelines with English summaries including the recommendations were considered if other details were also given and quality could be assessed. A systematic literature review had to be conducted and, where evidence was found, be the basis of the recommendations. Guidelines without a systematic review were excluded. In determining whether a systematic review was conducted, criteria such as an explicit statement of a systematic review along with databases searched, or databases searched plus time period, search terms, and results had to be reported. Some evidence-based guidelines included a literature search but it was unclear whether a systematic review was conducted.

It was considered outside the scope of the evidence summary to address *in detail* the management of patients experiencing acute adverse effects secondary to systemic therapy or radiation therapy; however, chronic symptoms as a result of treatment were considered within scope. As chemotherapy- or radiotherapy-induced nausea and vomiting were included in the algorithms on nausea and vomiting [1], guidelines focused on this topic were retained; the search did not include guidelines on other topics such as use of specific chemotherapy agents or management of specific cancers that peripherally mentioned nausea and vomiting.

Guidelines dealing only with control or treatment of the disease were excluded. Also excluded were publications of clinical trials, case reports, non-systematic reviews, reviews without recommendations, or guidelines focused only on children. Guidelines focused on low/middle income countries or other resource-limited applications were also excluded. Guidelines only available to paying members of the development organization were also excluded. A review of the titles and abstracts that resulted from the search was conducted by one reviewer (GGF). For items that warranted full-text review, one reviewer (GGF) reviewed each item.

NCCN guidelines are regularly updated, comprehensive, frequently used, and evidence-based consensus guidelines. Most do not have an explicit systematic review and the linkage between recommendations and evidence is poor. They do not generally meet criteria for inclusion or endorsement by the PEBC. It was decided that NCCN guidelines specifically on symptom management would be listed (with the above limitations noted); guidelines on treatment or management of cancer itself would not be looked at.

Guideline Assessment

The AGREE II is a tool to assess the quality and reporting of practice guidelines [6,7], and consists of 23 questions in six domains. The Rigour of Development (RoD) domain is sometimes used for an initial screening; for example, Walton et al. [8] used this domain and selected a threshold score of 50 for inclusion. This domain includes a set of questions related to the guideline development process (see headings in [Appendix D](#)) and was used in the current evidence summary. Lower marks may reflect that an item was not included in the

guideline process, or that the publication(s) did not report sufficient details. When guidelines referred to other documents as part of the methods, such as separately published systematic reviews or guideline development procedures, these were considered in the evaluation. Domain scores were calculated as a percentage of the maximum possible score for that subset of questions: (obtained score - minimum possible score)/(maximum possible score - minimum possible score).

Because of the large number of guidelines, only one rater from PEBC evaluated each guideline. For guidelines included in the pain evidence summary [5], ratings (RC) have been copied from that document. The remaining guidelines were rated for this summary (GGF). Some of the guidelines were also rated by CGD and these additional RoD scores have been included in Tables 1-3.

Ratings for each question are subjective and scores may vary according to who is conducting the rating. The scores reported, therefore, may be useful in giving a general grouping (e.g., high vs. low quality) but not an absolute ranking. Ratings were not used as a method of including or excluding guidelines from this literature review.

RESULTS AND DISCUSSION

Overview

From the search of organization websites, 20 guidelines were identified (12 relevant to nausea and vomiting, 5 relevant to anorexia and cachexia, and 3 relevant to both topics). The search of MEDLINE, Embase, AMED, and Emcare located 2850 publications. After removal of duplicate publications and guidelines already found in the website search, there were 2787 results; of these, two guidelines on anorexia/cachexia were considered relevant.

The applicable guidelines fell into three major groups: (1) focused on management of either nausea/vomiting or on anorexia/cachexia; (2) management of symptoms (including nausea/vomiting and/or anorexia/cachexia; and (3) management of specific cancers, with a section on management of the relevant symptoms. Characteristics of each guideline including the organization that created or approved the guideline, citation, and the general topic have been extracted and included in tables. Notes include more details of the topic and major concepts covered, details of the systematic review including databases (an indication of how comprehensive the search was), and time period searched (indicating how recent the evidence is). These guidelines are discussed in the following sections. Results of the guideline assessment RoD are given in [Appendix D](#).

Guidelines Relevant to Nausea and Vomiting (other than treatment-induced)

Nine guidelines relevant to nausea and vomiting outside the period of active chemotherapy or radiotherapy treatment are summarized in Table 1 [9-17]. The 2016 guideline by the Multinational Association of Supportive Care in Cancer/ European Society for Medical Oncology (MASCC/ESMO) [9] is the most comprehensive. The MASCC/ESMO guideline is the only one found that has a full review and publication specifically on nausea and vomiting in cancer outside of active treatment. It includes a subsection on nausea and vomiting due to malignant bowel obstruction and a paragraph on opioid-induced nausea and vomiting. In preparation of this guideline, 10 committees [18] were formed to conduct systematic reviews and prepare draft recommendations, followed by discussion and voting to reach consensus by the entire antiemetic guidelines panel. Most topics had their own separate publication [19-25], with these combined to give the full guideline [9]. Most topics were updates of those in previous versions and were related to chemotherapy or

radiotherapy-induced nausea and vomiting; these are discussed in the next section. A new topic, managing nausea and vomiting in advanced cancer [25], is of most relevance to this evidence summary.

The other eight guidelines included in Table 1 deal more generally with symptom management [10-12], specific cancers [13,14], or adverse effects of opioids [15-17] and include a small section on nausea and vomiting. The information in these additional guidelines may be useful to supplement the information in the MASCC/ESMO guideline. The NICE guideline [12] deals with care in the last days of life and is not specific to patients with cancer; however, patients with cancer comprise a large portion of this patient population. The NCCN guideline on palliative care [11] contains a chart (two pages) on nausea and vomiting, and refers the reader to their guideline on antiemesis for chemotherapy/radiation therapy-induced symptoms (see Table 2). As indicated early, NCCN guidelines do not meet the strict inclusion criteria but are listed due to widespread use. The SIGN guideline on ovarian cancer includes a section on nausea and vomiting due to malignant bowel obstruction [14] and can be compared to that in the MASCC/ESMO guideline.

Immune-related adverse effects from immunotherapy using immune checkpoint inhibitors that target PD-1 (e.g., pembrolizumab, nivolumab), PD-L1 (e.g., atezolizumab, avelumab, durvalumab), or CTLA-4 (e.g., ipilimumab) often appear within three months, but have been reported months, or sometimes years, after treatment is complete ([26,27]. While strictly these are treatment-related, the connection may be less apparent due to this potential delay in symptoms, and it is considered relevant to mention in this section. ASCO has a recent guideline [10] on immune-related adverse effects. This guideline is primarily based on consensus due to limited information being available. CCO also has a new (March 2018) guideline on Immune Checkpoint Inhibitor Toxicity Management (<https://www.cancercareontario.ca/en/content/immune-checkpoint-inhibitor-toxicity-management-clinical-practice-guideline>). It contains general principles, but does not mention nausea and vomiting.

Guidelines by the European Palliative Care Research Collaborative/European Association for Palliative Care (EPCRC/EAPC) [16] and by NICE [15] deal with use of opioids in cancer pain and in palliative care. These provide more detailed information than the MASCC/ESMO guideline for this topic. Opioids are used frequently for pain relief, and sometimes for cough suppression or other respiratory problems. Nausea and vomiting are among the common adverse effects of opioid use, reported in up to 40% of cancer patients [15,16]. The systematic review by Laugsand et al [28] was the basis of the section of the EPCRC/EAPC guideline on nausea and vomiting. The American College of Chest Physicians lung cancer guideline includes a chapter on symptom management and includes two recommendations on nausea and vomiting with opioids [17].

Guidelines on Treatment-Induced Nausea and Vomiting

Nausea and vomiting in patients with cancer occurs most frequently as a result of chemotherapy, and to a lesser extent due to radiotherapy. Most oncology-related guidelines on nausea and vomiting therefore deal with chemotherapy- and/or radiotherapy-induced nausea and vomiting. Seven guidelines are summarized in Table 2 [9,29-34]. This topic is mentioned in the CCO algorithm [1] and therefore found guidelines are reported; however, it is outside the direct scope of the evidence summary and thus the literature search was more limited than for the other topics.

Several reviews (e.g., [35-41] indicate that the most widely used guidelines are those by MASCC/ESMO [9] (see also the previous section), ASCO [29], and NCCN [30]. All three of these have been recently updated. The guideline by MASCC/ESMO [9] has several companion

publications [18-24]. Several other guidelines, including the [antiemetics guideline by CCO](#) in 2013 were based on older versions of these guidelines, and therefore not included in this evidence summary. As indicated earlier, NCCN guidelines do not meet the strict inclusion criteria but are listed due to widespread use.

The Oncology Nursing Society guideline on chemotherapy-induced nausea and vomiting (CINV) [32] is also recent. It lists agents by strength of evidence and recommendation, then citations to supporting evidence, but provides no further analysis. It is unique in that it lists agents for which there is insufficient evidence. Guidelines on integrative therapies in breast cancer [33] and lung cancer [34] are also available and note that they are likely applicable to other cancers as well. These are considered high quality and may supplement the other guidelines for non-pharmaceutical approaches. They recommend ginger and relaxation can be considered as additions to antiemetic drugs. The guideline by Toward Optimized Practice on medical cannabinoids [31] recommends consideration of medical cannabinoids for treatment of refractory CINV (i.e., persistent CINV after first- and second-line therapy) as adjunct to other prescribed therapies.

Many reviews (e.g., [39,42]) and studies of treatment effectiveness (e.g., [43]) have found that management of CINV is sub-optimal, due at least in part to poor adherence to guidelines. UpToDate has evidence-based clinical decision support resources on pathophysiology and prediction of CINV [44], on prevention and treatment of CINV [45], and prophylaxis and treatment of radiotherapy-induced nausea and vomiting [46].

Guidelines on Anorexia, Cachexia, and Nutrition

Eight guidelines relevant to anorexia and cachexia are summarized in Table 3 [11,13,34,47-53]. Many of the guidelines were evidence-based consensus documents. Evidence is limited in many areas and therefore supplemented by consensus of participants. ESMO has a guideline on cancer cachexia in development and future users may wish to look for this guideline. It is noted that most ESMO guidelines are not based on explicit systematic reviews and therefore do not meet the inclusion criteria for this summary.

The most recent guideline is by the Oncology Nursing Society on anorexia in cancer [49] with literature until December 2016. It is subject to the same limitations as for the nausea and vomiting guideline. It lists agents by strength of evidence and recommendation, then citations to supporting evidence, but provides no further analysis.

A more comprehensive guideline is by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Partnership for Action Against Cancer (EPAAC) [47], although the literature search only covers until 2013. This guideline was also rated highly on the AGREE RoD scale. An ESPEN oncology expert group with many of the same participants also discussed the guideline and created a position paper the following year [48]. While the titles refer to nutrition and malnutrition, this appears to be a question of terminology, as the guidelines include catabolic metabolic derangements and loss of muscle mass.

The French Speaking Society of Clinical Nutrition and Metabolism (SFNEP) [50] covers literature until 2011. It is an English summary of a series of 12 publications in French, each with systematic reviews and expert opinion/consensus for areas without sufficient trial evidence for recommendations.

The other guideline often cited is by the EPCRC [51]. It focuses on cachexia in advanced cancer patients; however, it is based on a scoping review up until about 2008, and therefore less current than the previously mentioned guidelines.

ASCO guidelines on pancreatic cancer [52,53] indicate use of pancrelipase replacement in patients with exocrine pancreatic insufficiency, and use of appetite stimulants in severe cases.

Supportive care guidelines, as mentioned in the sections on nausea and vomiting, were also found. The NCCN guideline on palliative care [11] has a chart on anorexia/cachexia assessment and intervention. Information is subdivided by estimated life expectancy. Despite the limitations of NCCN guidelines discussed earlier, this may be of use due to the more recent literature review. The American College of Chest Physicians guideline on complementary therapies [34] suggests high calorie and protein supplements and omega-3 fatty acids; this topic is covered more comprehensively in other guidelines.

An international consensus group developed a definition and classification of cancer cachexia, as well as key features for assessment [54]. It was indicated that validation was required. A subsequent study that included the three organizers of the consensus group used a data set of 8160 patients with cancer and concluded that they had validated that “the severity of weight loss should be evaluated based on the rate of weight loss and the level of depletion of body reserves” [55]. A later review by one of the study authors noted that the data set had expanded to include more than 11,000 patients and had been used to develop and validate a new grading system for cancer-associated weight loss, based on risk stratification with survival as the outcome [56]. While not a guideline itself, the publication indicates it may aid in clinical trial design, development of guidelines, and clinical management.

SUGGESTIONS FOR USE OF THIS REVIEW

For purposes of updating the symptom management algorithms by the Patient Reported Outcomes and Symptom Management, it is suggested that the most recent comprehensive guidelines be considered first, with recommendations then supplemented or modified by recommendations in guidelines of narrower scope, but which may be more appropriate in specialized circumstances.

INTERNAL REVIEW

The evidence summary was reviewed by the Assistant Director of the PEBC. The Working Group was responsible for ensuring the necessary changes were made.

APPROVAL BY SPONSORS

After internal review, the report was approved by the Patient Reported Outcomes and Symptom Management Program of CCO.

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- Melissa Brouwers and Sheila McNair for providing feedback on draft versions.
- Ruth Chau for conducting an AGREE evaluation on some of the included guidelines.
- Sara Miller for copy editing.

Table 1. Guidelines Relevant to Nausea and Vomiting

Organization	Citation	Topic	Notes	AGREE RoD ²
Focus on nausea and vomiting				
Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO)	Roila, 2016 [9]; Molassiotos, 2017 [18]; Walsh, 2017 [25]	a) Chemotherapy- and radiotherapy-induced nausea and vomiting. b) Nausea and vomiting in advanced cancer	Used an available review for publications up to 2009 and updated the systematic review to February 2016 using PubMed and Medline; follows methodology of previous (2010) guideline [57,58]. Nausea and vomiting in advanced cancer is a new topic	71 (GGF)
Focus on symptom management, including nausea and vomiting				
American Society of Clinical Oncology (ASCO)	Brahmer, 2018 [10]	Immune checkpoint inhibitor adverse events	Systematic review: PubMed, Embase, Cochrane Register of Control Trials, 2000-2017 -onset of GI symptoms is most often 5-10 weeks after initiation but can occur or recur months after discontinuation of immunotherapy	40 (GGF)
National Comprehensive Cancer Network (NCCN)	Dans, 2017 [11]	Palliative care in cancer	Updated search using PubMed for June 2015-May 2017, but not explicit systematic review. Included here as current, widely used, and a main source in the previous algorithm	58 (RC) 69 (CGD, 2016 version)
National Clinical Guideline Centre, National Institute for Health and Care Excellence (NICE)	NICE, 2015 [12,59]	Care in last days of life	NICE NG31 -Systematic review using Medline, Embase, Cochrane Library until Nov 2014; PsychINFO and CINAHL for some questions	85 (RC)
Focus on management of specific cancer				
UK Myeloma Forum (UKMF) and the British Society for Haematology (BSH)	Snowden, 2017 [13]	Late effects of myeloma and its treatment	Indicates that ongoing nausea and emesis may occur due to anti-myeloma therapy, analgesics, renal failure and hypercalcaemia -systematic review, searched Cochrane database and Medline Apr 2006-March 2016	31 (GGF)
Scottish Intercollegiate	SIGN, 2013 [14]	Management of	SIGN 135	71 (RC)

² AGREE II Rigor of Development sub-scale score (see Methods section and Appendix D). Reviewer initials or source are next to RoD score; CGD, Cancer Guidelines Database (Canadian Partnership Against Cancer).

Evidence Summary SMG-2

Organization	Citation	Topic	Notes	AGREE RoD ²
Guidelines Network, Healthcare Improvement Scotland (SIGN)		epithelial ovarian cancer	Management. Version modified May 2014 Systematic review: MEDLINE, Embase, CINAHL, PsycINFO, Cochrane, 2003-2012 -addresses nausea and vomiting due to malignant bowel obstruction	87 (CGD)
Adverse effects of opioids				
National Institute for Health and Care Excellence (NICE)	NICE, 2012 [15] (evaluated 2016)	Opioids for pain in palliative care	NICE CG140 Systematic Review: Cochrane reviews and RCTs, DARE, HTA, CINAHL, Embase, MEDLINE, PsycINFO, Web of Science 1950-2011; search strategy reported	71 (RC)
European Palliative Care Research Collaborative (EPCRC), on behalf of the European Association for Palliative Care (EAPC)	Caraceni, 2012 [16]	Opioid analgesics in cancer pain	Is based on 22 systematic reviews; the one by Laugsand et al [28] is on opioid-induced nausea and vomiting in cancer patients -Systematic search for guidelines: MEDLINE, CINAHL, Cochrane reviews, Embase, Google 2001-2008; English only -Systematic reviews for each question include evidence up to 2009-2010 (depending on question): MEDLINE; Embase also for most, some also used CINAHL, Cochrane	67 (RC)
American College of Chest Physicians	Simoff, 2013 [17]	Symptom management in lung cancer	Symptom management -Systematic review (more detailed methodology published separately [60]: MEDLINE, CINAHL, PsycINFO, Cochrane, Embase, Web of Science, Google Scholar; searches until 2012 (based on date of included articles) and extended back more than 10 years (stated in methodology) -section on pain control, and 2 recommendations on nausea and vomiting with opioids	73 (RC) 59 (CGD); 68 for methodology document)

Abbreviations: RCTs, randomized controlled trials; RoD, Rigour of Development

[Back to Results](#)

Table 2. Treatment-Induced Nausea and Vomiting

[Back to Results](#)

Organization	Citation	Topic	Notes	AGREE RoD ³
Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO)	Roila, 2016 [9]; Molassiotos, 2017 [18]	a) Chemotherapy- and radiotherapy-induced nausea and vomiting. b) Nausea and vomiting in advanced cancer	2016 update of 2010 recommendations [57,58], and follows same methodology -Guideline also included in Table 1 Several publications cover various subsets of recommendations [19-24,61,62]; systematic reviews with searches on Medline and/or PubMed until early to mid-2015 (dates vary slightly depending on topic)	71 (GGF)
American Society of Clinical Oncology (ASCO)	Hesketh, 2017 [29]	Antiemetics in oncology	Prevention or management of nausea and vomiting due to antineoplastic agents or radiotherapy Systematic review using PubMed and Cochrane Library Nov 2009-Jun 2016	73 (GGF) 68 (CGD for 2015 version)
National Comprehensive Cancer Network (NCCN)	Ettinger, 2018 [30]	Therapy-related antiemesis in patients with cancer	For use of antiemetics for nausea/vomiting that are not related to radiation and/or chemotherapy, see NCCN Guidelines for Palliative Care. Literature search using PubMed to find key literature (results not reported)	50 (GGF) 63 (CGD for 2016 version)
Prescribing Guideline Committee of PEER (Patients, Experience, Evidence, Research) at University of Alberta; Toward Optimized Practice (Alberta)	Allan, 2018 [63]; Toward Optimized Practice, 2018 [31]	Medical cannabinoids in primary care for nausea and vomiting, pain, or spasticity	Cannabinoids in primary care, includes recommendation on CINV -Targeted systematic review of systematic reviews on cannabinoids to treat chronic pain, nausea/vomiting, and spasticity; searched Medline and Cochrane [64] April 2017 Conclusion: consider for refractory CINV; recommends nabilone for this purpose	33 (GGF)
Oncology Nursing Society	Lee, 2017 [32]	CINV	Systematic review: searched PubMed, CINAHL, Cochrane Collaboration, NCCN Jan 2009 to Jan 2017. Guideline process described in separate paper [65]	52 (GGF)
Society for Integrative Oncology	Greenlee, 2017 [33]	Integrative therapies in breast cancer	Previous (2014) version included a systematic review for 1990-2013. This update searched Embase, MEDLINE, PsycINFO, CINAHL Jan 2014-Dec 31 2015	69 (GGF) 75 (CGD for 2014 version)

³ AGREE II Rigor of Development sub-scale score (see Methods section and Appendix D). Reviewer initials or source are next to RoD score; CDG, Cancer Guidelines Database (Canadian Partnership Against Cancer).

Evidence Summary SMG-2

Organization	Citation	Topic	Notes	AGREE RoD ³
American College of Chest Physicians	Deng, 2013 [34]	Complementary therapies and integrative medicine in lung cancer	Complementary therapies and integrative medicine in lung cancer, though mostly applicable to all cancers -Systematic review: MEDLINE, PubMed, Web of Science 2000-2011 for mind-body modalities; searched further back for exercise and for acupuncture	88 (RC) 77 (CGD)

Abbreviations: CINV, chemotherapy-induced nausea and vomiting; PDQ, Physician Data Query; RoD, Rigour of Development

[Back to Results](#)

Table 3. Guidelines on Loss of Appetite, Anorexia, and Cachexia

[Back to Results](#)

Organization	Citation	Topic	Notes	AGREE RoD ⁴
Focus on anorexia, cachexia				
European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Partnership for Action Against Cancer (EPAAC)	Arends, 2017 [47]	Nutrition in cancer patients	PubMed and Cochrane Library for systematic reviews and meta-analyses 2006-June 2013; if none found then looked for comparative studies; cites ESPEN guideline framework [66]. Reported search terms, evidence tables	98 (GGF) 79 (CGD)
ESPEN oncology expert group which met for a Cancer and Nutrition Workshop in Berlin Oct 2016	Arends, 2017 [48]	Cancer-related malnutrition	Discussed ESPEN/EPAAC guideline [47] at a workshop and created a position paper. Stressed the importance of putting the guidelines into practice and offered recommendations for improving nutrition care	
Oncology Nursing Society	Thorpe, 2017 [49]	Anorexia in cancer	Systematic review: PubMed, CINAHL, Cochrane Collaboration, NCCN 2009-Dec 2016. Guideline process described in separate paper [65]	52 (GGF)
French Speaking Society of Clinical Nutrition and Metabolism (SFNEP)	Senesse, 2014 [50]	Nutrition in non-surgical cancer treatment	Position paper/guideline. English version of recommendations. The original guideline is a series of 12 publications in French [67-78]. Medline/PubMed 2000-2011, with previous years searched if there was no relevant data found. Cites guideline method development procedure of HAS (Haute Autorité de Santé) It is based on systematic reviews for each chapter, with expert opinion/consensus for areas with insufficient evidence	67 (GGF)
European Palliative Care Research Collaborative (EPCRC)	Radbruch, 2010 [51]	Cachexia in advanced cancer patients	Consensus and evidence-based guideline on cachexia in advanced cancer patients, with a focus on refractory cachexia -based on scoping review; evidence base up to about 2008 (closed two years before publication) with systematic review for 2 recommendations for which there was inadequate consensus -Systematic review for topic of fish oil for treatment of cachexia in advanced cancer was published separately [79]; it include Medline/PubMed 1966-June 2010	46 (GGF) 53 (CGD)

⁴ AGREE II Rigor of Development sub-scale score (see Methods section and Appendix D). Reviewer initials or source are next to RoD score; CDG, Cancer Guidelines Database (Canadian Partnership Against Cancer).

Evidence Summary SMG-2

Focus on management of specific cancer				
American Society of Clinical Oncology (ASCO)	Sohal, 2016 [52]	Metastatic pancreatic cancer	Treatment -Systematic review: PubMed, Cochrane Jan 2000-June 2015 -use pancrelipase replacement if patient has exocrine pancreatic insufficiency; appetite stimulants in severe cases	88 (RC) 82 (CGD)
American Society of Clinical Oncology (ASCO)	Balaban, 2016 [53]	Unresectable pancreatic cancer	Treatment -Systematic review: MEDLINE and Cochrane Jan 2000-June 2015 -use pancrelipase replacement if patient has exocrine pancreatic insufficiency; appetite stimulant medications (megestrol acetate, dronabinol) in severe cases	88 (RC) 82 (CGD)
Supportive care guidelines included in Tables 1 or 2 (Nausea and Vomiting)				
UK Myeloma Forum (UKMF) and the British Society for Haematology (BSH)	Snowden, 2017 [13]	Late effects of myeloma and its treatment	Anorexia is common during HSCT, when significant weight loss and nutritional deficiencies can occur -systematic review, searched Cochrane database and Medline Apr 2006-March 2016	31 (GGF)
National Comprehensive Cancer Network (NCCN)	Dans, 2017 [11]	Palliative care in cancer	Updated search using PubMed for June 2015-May 2017, but not explicit systematic review. Included here as current and widely used	58 (RC) 69 (CGD, 2016 version)
American College of Chest Physicians	Deng, 2013 [34]	Complementary therapies and integrative medicine in lung cancer	Complementary therapies and integrative medicine in lung cancer, though mostly applicable to all cancers -Systematic review: MEDLINE, PubMed, Web of Science 2000-2011 for mind-body modalities; searched further back for exercise and for acupuncture	88 (RC) 77 (CGD)

Abbreviation: HSCT, hematopoietic stem cell transplantation

[Back to Results](#)

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Appendices

Appendix A: Members of the Working Group and their COI declarations

(see the [PEBC Conflict of Interest \(COI\) Policy](#))

Name	Affiliation	COI declaration
Glenn Fletcher, MSc	Health Research Methodologist, Program in Evidence-Based Care, McMaster University	None
Martin R. Chasen, MBChB, MPhil -Pall Med	Palliative Care Physician; Medical Oncologist Medical Director of Palliative Care William Osler Health System, Brampton. Regional Clinical Co-Lead, Central West Palliative Care Network. Professor, University of Toronto, McMaster University, McGill University, University of Ottawa	Published results of a trial on chemotherapy-induced nausea and vomiting
Lynne Penton, RN(EC). MN. CON. (C)	N.P. Adult Oncology Humber River Hospital Clinical Co-Lead Oncology Palliative Care Central LHIN	None

[Back to Methods](#)

Appendix B: Websites Searched (February to March 2018 except as indicated)

- National Guidelines Clearing House <https://www.guideline.gov/>
 - CPG Infobase: Clinical Practice Guidelines <https://www.cma.ca/En/Pages/clinical-practice-guidelines.aspx> (only guidelines from organizations not already looked at)
 - Inventory of Cancer Guidelines (SAGE; last updated January 2013) <http://www.cancerview.ca/sage>. Searched July 2017
 - Cancer Guidelines Database [new version of SAGE database announced Feb 28 2018] (formerly SAGE) searched April 2, 2018 (searched for individual symptoms) <https://www.partnershipagainstcancer.ca/tools/cancer-guidelines-database/>
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- American Cancer Society <https://www.cancer.org/health-care-professionals/american-cancer-society-survivorship-guidelines.html>
 - American College of Chest Physicians <http://www.chestnet.org/Guidelines-and-Resources>
 - American College of Obstetricians and Gynecologists <https://www.acog.org/Resources-And-Publications>
 - American College of Physicians (ACP) <https://www.acponline.org/clinical-information/guidelines>
 - American College of Radiology <https://acsearch.acr.org/list>
 - American Geriatric Society <https://geriatriccareonline.org/ProductTypeStore/clinical-guidelines-recommendations/8/>
 - American Physical Therapy Association <https://www.apta.org/EvidenceResearch/EBPTools/CPGs/>
 - American Society for Therapeutic Radiology and Oncology: www.astro.org; <https://www.astro.org/Clinical-Practice-Statements.aspx>
 - American Society of Clinical Oncology (ASCO) <https://www.asco.org/practice-guidelines/quality-guidelines/guidelines>
 - American Society of Colon and Rectal Surgeons <https://www.fascrs.org/physicians/clinical-practice-guidelines>
 - American Thoracic Society <https://www.thoracic.org/statements/>
 - American Thyroid Association <https://www.thyroid.org/professionals/ata-professional-guidelines/>
 - American Urological Association <http://www.auanet.org/guidelines>
 - An Roinn Slainte Department of Health, Dublin, Ireland ; Royal College of Physicians of Ireland: National Clinical Programme for Palliative Care <http://health.gov.ie/national-patient-safety-office/ncec/national-clinical-guidelines/cpc/>
 - BC Cancer Agency, BC Health <http://www.bccancer.bc.ca/health-professionals/professional-resources/cancer-management-guidelines>
 - Belgian Health Care Knowledge Centre (KCE) <https://kce.fgov.be/en/all-reports?search=guideline>

Evidence Summary SMG-2

- British Association of Dermatologists <http://www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-guidelines>
- British Society for Haematology <http://www.b-s-h.org.uk/guidelines/>
- British Thoracic Society <https://www.brit-thoracic.org.uk/standards-of-care/guidelines/>
- Canadian Association of Psychosocial Oncology <http://oncology.capo.ca/public/#clinical-guidelines>
- Cancer Australia (July 11,2017; updated Feb 20, 2018) <https://canceraustralia.gov.au/publications-and-resources/clinical-practice-guidelines>
- Cancer Care Nova Scotia (Nova Scotia Cancer Care Program) (<http://www.cdha.nshealth.ca/nova-scotia-cancer-care-program-3>)
- Cancer Care Ontario (CCO) <https://www.cancercareontario.ca/en/guidelines-advice>
- Cancer Control Alberta / Alberta Health Services <https://www.albertahealthservices.ca/info/cancerguidelines.aspx>
- Cancer Council Australia <http://www.cancer.org.au/health-professionals/clinical-guidelines/>
- Central European Cooperative Oncology Group (CECOG) <http://www.cecog.org/>
- Clinical Oncology Society of Australia <https://www.cosa.org.au/publications/guidelines/>
- Dutch Association of Comprehensive Cancer Centres (ACCC) (also called IKNL Integraal Kankercentrum Nederland). <http://www.iknl.nl/> or <http://www.oncoline.nl/index.php?language=en>
- European Association for Palliative Care (EAPC) <http://www.eapcnet.eu/Themes/Research/Publications/EAPCResearchNetwork/tabid/275/Default.aspx>
- European Association of Urology <http://uroweb.org/guidelines/> and <https://uroweb.org/wp-content/uploads/EAU-Extended-Guidelines-2016-Edn.pdf>
- European Oncology Nursing Society: <http://www.cancernurse.eu/education/guidelines-recommendations.html>
- European Oral Care in Cancer Group <http://www.eocc.co.uk/guidance/>
- European Palliative Care Research Collaborative (EPCRC) <https://www.ntnu.edu/prc/results/epcrc-guidelines>
- European Respiratory Society <http://www.ers-education.org/guidelines.aspx>
- European Society for Medical Oncology (ESMO) <http://www.esmo.org/Guidelines>
- European Society for Radiotherapy and Oncology (ESTRO) <http://www.estro.org/>
- European Society of Thoracic Surgeons http://www.ests.org/guidelines_and_evidence/default.aspx
- European Society of Urogenital Radiology (ESUR) <http://www.esur.org/esur-guidelines/>
- Fraser Health Hospice Palliative Care Program <http://www.fraserhealth.ca/health-professionals/professional-resources/hospice-palliative-care/>
- Institute for Clinical Systems Improvement (Minnesota and surrounding areas) https://www.icsi.org/guidelines_more/find_guidelines/

Evidence Summary SMG-2

- Japanese Society for Palliative Medicine <https://www.jspm.ne.jp/guidelines/index.html>
- Japanese Urological Association <https://www.urol.or.jp/en/>
- Korean Liver Cancer Association; Korean Liver Cancer Study Group http://livercancer.or.kr/eng/html/sub06_01.asp
- Multinational Association of Supportive Care in Cancer (MASCC) <http://www.mascc.org/guidelines>
- National Comprehensive Cancer Network (NCCN) (Guidelines for supportive care only) https://www.nccn.org/professionals/physician_gls/default.aspx#supportive
- National Health and Medical Research Council (Australia) <https://www.nhmrc.gov.au/guidelines-publications>
- National Institute for Health and Care Excellence (NICE) <https://www.nice.org.uk>
- National Cancer Institute (NCI) PDQ's <https://www.cancer.gov/publications/pdq/information-summaries/supportive-care> (supportive care only)
- New Zealand Ministry of Health <http://www.health.govt.nz/publication>
- Oncology Nursing Society <https://www.ons.org/>
- Program in Evidence-Based Care / Cancer Care Ontario (PEBC/CCO) <https://www.cancercareontario.ca/en/guidelines-advice>
- Registered Nurses' Association of Ontario (RNAO): <http://rnao.ca/bpg>
- Saskatchewan Cancer Agency <http://www.saskcancer.ca/Default.aspx?DN=b1586bc3-431f-4998-a55c-ec2c34c090ba>
- Scottish Intercollegiate Guidelines Network (SIGN) <http://www.sign.ac.uk>
- Scottish Palliative Care Guidelines <http://www.palliativecareguidelines.scot.nhs.uk/>
- SIOG - International Society of Geriatric Oncology <http://www.siog.org/content/siog-guidelines-0>
- Society for Immunotherapy of Cancer <http://www.sitcancer.org/research/cancer-immunotherapy-guidelines>
- Society for Integrative oncology (SIO) <https://integrativeonc.org/integrative-oncology-guidelines>
- The Association of the Scientific Medical Societies in Germany (AWMF), the German Cancer Society and the German Cancer Aid jointly launched the [German Guideline Program in Oncology \(GGPO\)](http://www.krebsgesellschaft.de/gcs/german-cancer-society/guidelines.html) in 2008. <https://www.krebsgesellschaft.de/gcs/german-cancer-society/guidelines.html>; <http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html>
- UK and Ireland Neuroendocrine Tumour Society <http://www.ukinets.org/net-clinics-clinical-practice/>
- UK Oral Mucositis in Cancer Group (UKOMIC) <http://www.ukomic.co.uk/>

[Back to Methods](#)

Appendix C: Literature Search Strategy

Database(s): AMED (Allied and Complementary Medicine) 1985 to March 2018, Embase 1996 to 2018 April 03, Ovid Emcare 1995 to 2018 week 13, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to March 28 2018

Search Strategy:

#	Searches	Results
1	exp Neoplasms/ or exp tumor/ or exp cancer/ or (cancer: or neoplasm: or tumor?: or carcinom: or malignan: or oncolog:).mp.	8718088
2	limit 1 to yr="2009-current"	4557745
3	exp guideline/ or exp practice guideline/ or exp consensus development conference/ or guideline.pt. or practice parameter\$.tw. or practice guideline\$.mp. or (guideline: or recommend: or consensus or standards).ti,kw.	967896
4	(abstract* or conference abstract* or note or letter or comment or commentary or editorial).pt.	7134536
5	(2 and 3) not 4	71020
6	exp nausea/ or exp vomiting/ or exp "nausea and vomiting"/ or exp antiemetics/ or exp emetics/ or exp antiemetic agent/ or exp antiemetic activity/ or (nause* or vomit* or vomisement or emetic* or emesis* or emesia* or antiemetic* or antiemesis*).mp.	713204
7	exp cachexia/ or exp Anorexia/ or exp weight loss/ or exp "loss of appetite"/ or (cachexia or cachectic or anorexia or anorexic or (loss adj2 appetite) or (weight adj2 loss) or wasting syndrome or energy malnutrition or protein malnutrition).mp.	445626
8	5 and 6	3313
9	5 and 7	1521
10	remove duplicates from 8	2263
11	remove duplicates from 9	1026
12	10 not 11	1824
13	11 not 10	587
14	10 and 11	439

[Back to Methods](#)

Appendix D: AGREE II Rigour of Development Scores

1. Guidelines on Nausea and Vomiting

Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score ⁵
<u>Nausea and vomiting</u>									
Roila, 2016 [9]	6	7	7	7	3	5	3	4	42
	Advanced Cancer: PubMed, Medline to 2009-Feb 2016 + reviews for earlier publications; Chemotherapy/ radiotherapy induced: to 2015 (exact date varied among subtopics). Search terms reported; number of hits and included given	Yes	Yes	Yes	Adverse effects not mentioned for most trials or in recommendations	Evidence is described and recommendations graded according to level of evidence	Reviewed by multi-disciplinary panel of experts (n=37) (guideline panel) involved in other topics of series; included 2 patient advocates. No details about external review.	Is update of previous (2010 and 2002) guidelines, suggesting updates will occur, but no explicit statement	71 (GGF)
Brahmer, 2018 [10]	4	4	2	4	2	1	4	6	27
	PubMed (MEDLINE in process only), Embase, Cochrane 2000-2017; search terms and strategy not reported	Reported target population and interventions but not inclusion/exclusion criteria	Notes only that informal consensus was used due to limitations in available evidence; no summary of evidence	States informal consensus was used and lists participants	States “all recommendations in this guideline are based on expert consensus, benefits outweigh harms, moderate strength of recommendation” but no other mention of harms	Notes only that informal consensus was used due to limitations in available evidence	One external reviewer and open public comment	Reviewed annually according to methodology supplement, but information not in guideline	40 (GGF)
Dans, 2017 [11]	5	3	2	6	6	6	1	7	36
	PubMed Oct 2014-June 2015, provided search terms	Inclusion: humans, English, study design	Benefits and harms described. Nothing else about quality. Categories of	Info for development is on NCCN website. Based on high level	Balanced discussion on benefits and adverse events	Could have been formatted in table or next to each other for	No info	update methodology on NCCN website	58 (RC)

⁵ The first number for each guideline is the total score (i.e., the sum of scores for questions 7 to 14), while the second number is the Domain Score, which is a type of percentage taking into consideration the minimum and maximum values possible (see Methods section). Initials of rater or source are in parentheses; CDG, Cancer Guidelines Database (Canadian Partnership Against Cancer).

Evidence Summary SMG-2

Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score ⁵
			evidence given	evidence. Consensus when there is no high level evidence. Degree of consensus is shown by category number. Steps in consensus not explained		greater ease			
NICE, 2015 [12] (NICE NG31)	7 MEDLINE, Embase, Cochrane to Jan 2015, full search strategies reported (appendix G)	7 English. Appendix C has inclusion/exclusion criteria	7 Critically appraised using the checklist in the NICE guidelines manual. GRADE tables	3 Recommendations were drafted on the basis of the committee's interpretation of the available evidence. Done informally. Consensus recommendations agreed through discussion	7 Balanced discussion	7 Evidence tables in appendix H. clearly linked	6 Consultation by stakeholder. 6-week public consultation and feedback. Comments were responded and posted on NICE website	5 When progressed significantly. Methods in guidelines manual	49 85 (RC)
Snowden, 2017 [13]	5 Cochrane, Medline Apr 2006-March 2016; search terms reported but not strategy or results	1 No	3 Recommendations are assigned a grade.	3 Development of key recommendations based on RCT evidence. Based on literature review and a consensus of expert opinion if no RCTs	2 No mention of risks other than consideration is part of GRADE process.	3 Recommendations follow literature review for each question	5 Review by 50+ members of British Society for Hematology plus involvement of patient perspective	1 Not reported	23 31 (GGF)
SIGN, 2013 [14] (SIGN 135)	7 MEDLINE, Embase, CINAHL, PsycINFO, Cochrane, 2003-2012. Search strategies given (separate document on website)	1 No info	7 Graded levels of evidence, and grading for recommendations	3 From manual: usually the GDG forms recommendations through informal consensus	6 Balanced discussion	7 Clearly linked	6 Public consultation. Also reviewed by expert referees. Addresses every comment made by an external reviewer and must justify any disagreement. Names of reviewers given	5 Will be considered for review in 3 years	42 71 (RC)
NICE, 2012 [15]	7 Cochrane reviews and RCTs, DARE,	6 Inclusion/exclusion criteria under	4 Guidelines manual: section 9. concept	2 Guidelines manual: formal consensus	7 Balanced discussion	7 Clear link	4 Guidelines manual says	5 In the guidelines	42 71

Evidence Summary SMG-2

Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score ⁵
(NICE CG140)	HTA, CINAHL, Embase, MEDLINE, PsycINFO, web of science 1950-2011. search strategy given	review protocols	of strength is reflected in the wording of the recommendation	techniques may be used, no particular approach recommended			they have stakeholders comment on guideline, and they respond to them. Quality assurance and peer review	manual: The formal process for updating begins 3 years after publication. In exceptional circumstances , and only if significant changes to the process of clinical guideline development are anticipated, this interval will be reduced to 2 years	(RC)
Caraceni, 2012 [16]	5 Lit search up to 2009-2010 MEDLINE, Embase, CINAHL, Cochrane. Appendix has more details. No search terms used or full search strategy	7 Included if carried out in adult patients with chronic cancer pain, data on efficacy or side effects, English, RCT or non-randomized	6 Followed GRADE, balance between desirable and undesirable effects. Quality assessment based on study design and quality of studies.	3 Expert consensus process, formalised, step wise, referenced a modified 2 round Delphi,	7 Balanced discussion on benefits and adverse events	7 Clearly linked, recommendations placed next to summaries	1 No info	4 Potential clinical effects of new pharmacology need further research and continuous updating of the guidelines is required	40 67 (RC)
Simoff, 2013 [17]	5 MEDLINE, CINAHL, PsycINFO, Cochrane, Embase, Web of Science, Google Scholar, until 2012	3 Original research. No limiters of language or article type	6 Assessed for quality. Documentation and appraisal review tool. Used GRADEpro	5 Recommendations were developed with supporting evidence and the consensus of the writing committees. Controversial recommendations were identified for further consultation by the entire panel, anonymous voting used GRADE grid, at least 80% in favour	7 Balanced discussion	6 Clearly linked	5 Provided external review. Authors were required to respond to all mandatory issues. Included nearly 30 individual reviewers	6 Embarking on a new living guidelines model for revising existing recommendations, continual assessment of the currency of these recommendations, will begin 1 year after	43 73 (RC)

Evidence Summary SMG-2

Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score ⁵
				to be approved				publication	
Chemotherapy- or radiotherapy-induced nausea and vomiting									
Hesketh, 2017 [29]	6 PubMed and Cochrane Nov 2009-June 2016; search strategy reported	5 RCTs (> 25 patients per arm) or meta-analyses of RCTs	5 Evaluation of each study reported in data supplement but not commented on elsewhere	6 Process is described	3 These are indicated in the data tables but rarely in the recommendations or accompanying literature analysis	6 Relevant evidence is indicated after each recommendation as a literature analysis	5 Submitted to 2 external reviewers with content expertise	7 Review annually	43 73 (GGF)
Ettinger, 2018 [30]	2 PubMed for key literature; only 2 search terms used	4 English, phase 2-4 trials, guidelines, systematic reviews, meta-analyses	3 Indicates recommendations are Category 2A (lower-level evidence but uniform consensus) unless otherwise indicated	6 Described in methodology document on NCCN website	7 Adverse effects summarized in Discussion (literature review) section and recommendations; Panel weighs the overall balance of therapeutic benefit, efficacy, safety and toxicity	2 Most do not have links	1 Not mentioned	7 Updated at least once a year	32 50 (GGF)
Toward Optimized Practice, 2018 [31]	4 Medline 1946-April 2017, Cochrane until May 2017. Searched only for other systematic reviews; search terms reported	4 Reviews of RCTs in adults only	4 Focused on largest and highest-quality RCTs instead of all data. Assessed reviews with modified (shorter) AMSTAR. Overall evidence limitations summarized	4 Some information reported.	2 Used only adverse effects data reported in other-meta-analyses, not all trials/reviews found. No mention whether adverse effects are serious, no balance of benefit vs harm	1 No direct link to evidence	3 Distribution to outside clinicians and patients for peer review and feedback; no mention of who these were or comments received	1 No mention of update	24 33 (GGF)
Lee, 2017 [32]	6 PubMed, CINAHL, Cochrane Collaboration, NCCN Jan 2009 to Jan 2017; search strategy reported	5 Inclusion and exclusion criteria stated	4 Considered in evaluating each drug/agent	3 Consensus of team working on topic	3 Part of consideration in categorization of recommendations	4 Supporting studies, reviews, guidelines given for each potential intervention	1 No information	6 Classifications updated twice a year. Has been ongoing since 2006	32 50 (GGF)
Greenlee, 2017 [33]	7 Embase, MEDLINE, PsycINFO, CINAHL Jan 2014-Dec 31 2015. 1990-2013 in earlier version.	7 Inclusion and exclusion criteria stated	6 Scored each article (Jadad scale and Delphi scoring). Grades of evidence determined for each	3 Clinical guideline development process as outlined by the Institute of Medicine	6 Taken into consideration in assigning grade, and summarized later in guideline	6 Citations given for each recommendation	3 Externally reviewed; comments integrated into final version	3 Not stated, though previous document indicated	41 69 (GGF)

Evidence Summary SMG-2

Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score ⁵
	Search terms in previous version		therapy.					planned every 3 years	
Deng, 2013 [34]	7	7	7	5	7	7	4	6	50
	Ovid, MEDLINE, PubMed, web of science (2000-2011), keywords given, search strategies described, full descriptions available on request	Searches limited to meta-analyses, SR, and RCTs. Narrative reviews and single arm studies were excluded. Studies exclusively involving adult patients with cancer that provided subjects with mind body interventions. Intervention included. English	(ref 1) SRs and meta-analyses assessed using DART. GRADE assessed risk of bias, precision, consistency, directness. Supplementary material	The overall process for the development of these guidelines... described in the methodology article (ref 1) anonymous voting to achieve consensus. he voting procedure used the GRADE grid, at least 67% consensus	Balanced discussion on benefits and adverse events	Evidence placed next to recommendations	(ref 1)	(Ref 1) guidelines must be updated and kept current. Use a new living guidelines model	88 (RC)

Abbreviations: ASCO, American Society of Clinical Oncology; DSG, Disease Site Group; EFNS, European Federation of the Neurological Societies; GDG, Guideline Development Group; GIN, Guidelines International Network; LOE, level of evidence; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; NNH, number needed to harm; NNT, number needed to treat; RCT, randomized controlled trial; RT, radiation therapy; SIGN, Scottish Intercollegiate Guidelines Network; SR, systematic review

Evidence Summary SMG-2

2. Guidelines on Loss of Appetite, Anorexia, or Cachexia

Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score ⁶
Focus on anorexia and cachexia									
Arends, 2017 [47]	7	7	6	7	7	7	7	7	55
	PubMed, Cochrane Library for systematic reviews and meta-analyses 2006-June 2013; if none found then looked for comparative studies. Search strategy reported	PICO (population, intervention, comparison, outcome) reported; evidence from observational and randomized trials and systematic reviews	Data tables in Appendix A; evidence evaluated with GRADE	Subset of guideline group members, then full guideline group; disagreement resolved at two consensus meetings; external review	Benefit and risks considered and reported	Recommendations include commentary linking to evidence	External review on ESPEN website (145 responses); all responses considered by the guideline group and written responses prepared for each recommendation	Will be updated at 3-year intervals, including literature review, Delphi process, external review; yearly literature check	98 (GGF)
Thorpe, 2017 [49]	6	5	4	3	3	4	1	6	32
	PubMed, CINAHL, Cochrane Collaboration, NCCN 2009-Dec 2016; search strategy reported	Inclusion and exclusion criteria stated	Considered in evaluating each drug/agent	Consensus of team working on topic	Part of consideration in categorization of recommendations	Supporting studies, reviews, guidelines given for each potential intervention	No information	Classifications updated twice a year. Has been ongoing since 2008	50 (GGF)
Senesse, 2014 [50]	6	4	5	7	6	6	5	1	40
	Medline/PubMed Started 2000 for most topics, and searched until about 2011 (2010-2012 depending on topic); search terms reported	Reported language (English or French), study design	GRADE for levels of evidence; discussed in text	Working group then consensus with peer review group (30-50 professionals + users / patients)	Risks and benefits discussed prior to each recommendation	Link to evidence where available, otherwise consensus only	Peer review and public consultation; approved by HAS Board	Not reported	67 (Glenn)
Radbruch, 2010 [51]	3	2	7	6	5	5	1	1	30
	Scoping review up to about 2008, no details reported	Patients with advanced cancer; no other details reported	Indicates RCT evidence on cachexia in advanced cancer is scarce; discusses for each	GRADE for strength of recommendations; Delphi Method consensus	Adverse effects are mentioned for several interventions	Evidence precedes recommendation for each intervention	Not mentioned	No information; update not found	46 (GGF) 53 (CGD)

⁶ The first number for each guideline is the total score (i.e., the sum of scores for questions 7 to 14), while the second number is the Domain Score, which is a type of percentage taking into consideration the minimum and maximum values possible (see Methods section). Initials of rater or source are in parentheses; CDG, Cancer Guidelines Database (Canadian Partnership Against Cancer).

Evidence Summary SMG-2

Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score ⁶
			recommendation						
Management in pancreatic cancer									
Sohal, 2016 [52]	7 PubMed, Cochrane Jan 2000-June 2015. search strategy in data supplement 3	6 Inclusion: population, study design, comparison, English	6 Type and strength of recommendation, evidence and potential bias provided	5 On basis of the consideration of the evidence, authors contribute to the development of the guideline. Crafted using BRIDGE wiz. Evidence lacking-informal consensus	7 Balanced discussion	7 Clearly linked	5 Circulated for external review and submitted to JCO for editorial review. 2 external reviewers. Rated as high quality. Comment were reviewed and integrated	7 Work to keep abreast of any newly published data that signal an update to this guideline, methodology supplement provides info about the signals update approach	50 88 (RC)
Balaban, 2016 [53]	7 MEDLINE and Cochrane Jan 2000-June 2015. search strategy in data supplement 3	6 Inclusion: population, study design, comparison, English	6 Type and strength of recommendation, evidence and potential bias provided	5 On basis of the consideration of the evidence, authors contribute to the development of the guideline. Crafted using BRIDGE wiz. Evidence lacking-informal consensus	7 Balanced discussion	7 Clearly linked	5 Circulated for external review and submitted to JCO for editorial review. 2 external reviewers. Rated as high quality. Comment were reviewed and integrated	7 Work to keep abreast of any newly published data that signal an update to this guideline, methodology supplement provides info about the signals update approach	50 88 (RC)
Supportive Care									
Snowden, 2017 [13]	5 Cochrane, Medline Apr 2006-March 2016; search terms reported but not strategy or results	1 No	3 Recommendations are assigned a grade.	3 Development of key recommendations based on RCT evidence. Based on literature review and a consensus of expert opinion if no RCTs	2 No mention of risks other than consideration is part of GRADE process.	3 Recommendations follow literature review for each question	5 Review by 50+ members of British Society for Hematology plus involvement of patient perspective	1 Not reported	23 31 (GGF)
Dans, 2017 [11]	5 PubMed Oct 2014-June 2015, provided search	3 Inclusion: humans, English, study design	2 Benefits and harms described. Nothing else about quality.	6 Info for development is on NCCN website.	6 Balanced discussion on benefits and	6 Could have been formatted in table or next to each	1 No info	7 update methodology on NCCN	36 58 (RC)

Evidence Summary SMG-2

Agree II item Reference	7. Systematic methods for evidence search	8. Clearly described evidence selection criteria	9. The strengths and limitations of the body of evidence are clearly described	10. The methods for formulating the recommendations are clearly described	11. Considered health risks and benefits in recommendations	12. Explicit link between recommendations and evidence	13. Externally reviewed by experts	14. Updating procedure provided	Total; Domain score ⁶
	terms		Categories of evidence given	Based on high level evidence. Consensus when there is no high level evidence. Degree of consensus is shown by category number. Steps in consensus not explained	adverse events	other for greater ease		website	
Deng, 2013 [34]	7 Ovid, MEDLINE, PubMed, web of science (2000-2011), keywords given, search strategies described, full descriptions available on request	7 Searches limited to meta-analyses, SR, and RCTs. Narrative reviews and single arm studies were excluded. Studies exclusively involving adult patients with cancer that provided subjects with mind body interventions. Intervention included. English	7 (ref 1) SRs and meta-analyses assessed using DART. GRADE assessed risk of bias, precision, consistency, directness. Supplementary material	5 The overall process for the development of these guidelines... described in the methodology article (ref 1) anonymous voting to achieve consensus. he voting procedure used the GRADE grid, at least 67% consensus	7 Balanced discussion on benefits and adverse events	7 Evidence placed next to recommendations	4 (ref 1)	6 (Ref 1) guidelines must be updated and kept current. Use a new living guidelines model	50 88 (RC)

[Back to Methods](#)

[Back to Results](#)