Putting Evidence Into Practice®:
Evidence-Based Interventions to Prevent and Manage Anorexia

Lynn A. Adams, RN, MS, ANP, AOCN®, Nancy Shepard, RN, MS, AOCN®, Rose Ann Caruso, RN, OCN®, Martha J. Norling, RN, OCN®, Heather Belansky, RN, MSN, and Regina S. Cunningham, PhD, RN, AOCN®

Anorexia is defined as an involuntary loss of appetite. Approximately 50% of newly diagnosed patients with cancer experience the symptom, which often is accompanied by weight loss and most typically associated with advanced disease. Anorexia significantly affects the clinical course of cancer; it can lead to the development or exacerbation of disease- or treatment-related symptoms, decreased functional status, and diminished quality of life. As part of the Oncology Nursing Society's Putting Evidence Into Practice® initiative, a team of oncology nurses examined and evaluated published research literature for the purpose of developing an evidence-based practice resource focused on the management of cancer-related anorexia. Even though anorexia is common among newly diagnosed patients and those with advanced disease, interventions to prevent, treat, and manage the symptom are limited. The evidence revealed that only two pharmacologic interventions, corticosteroids and progestins, can be recommended for use in clinical practice, and dietary counseling was identified as likely to be effective. This article summarizes selected empirical literature on interventions used to prevent and manage anorexia in patients with cancer. Familiarity with the literature will assist oncology nurses in proactively identifying and effectively managing patients experiencing this distressing symptom.

Anorexia is a complex clinical problem that can lead to the development or exacerbation of disease- or treatment-related symptoms, affect functional status, and diminish quality of life for patients with cancer (Laviano, Meguid, & Fanelli, 2006). Anorexia is associated with several symptoms that can interfere with food intake and are related to central nervous system regulation of energy intake; these include taste alterations, early satiety, smell alterations, meat aversions, and nausea and vomiting.

Even though anorexia is common among newly diagnosed patients with cancer and those with advanced disease, interventions to prevent, treat, or manage the problem are limited. This article describes the process used to examine and evaluate evidence for the purpose of developing an evidence-based practice resource focused on the management of cancer-related anorexia. Similar to other Oncology Nursing Society Putting Evidence Into Practice® (ONS PEP) initiatives, the work was completed by a team of advanced practice nurses, staff nurses, and a nurse researcher (Tipton et al., 2007). Anorexia was one of several symptoms addressed in ONS PEP resources published in 2008, which can be accessed by the practicing oncology nurse at www.ons.org/outcomes/volume4.

Overview of Anorexia

Anorexia is defined as a loss of desire to eat that is almost invariably accompanied by a decrease in oral intake (Laviano et al., 2006). In acute situations, anorexia may serve as a protective mechanism because the suppression of food intake during disease

Lynn A. Adams, RN, MS, ANP, AOCN®, is a nurse practitioner at Memorial Sloan-Kettering Cancer Center in New York, NY; Nancy Shepard, RN, MS, AOCN®, is an oncology nurse practitioner at California Cancer, Inc., in Fairfax; Rose Ann Caruso, RN, OCN®, is a staff registered nurse at Memorial Sloan-Kettering Cancer Center; Martha J. Norling, RN, OCN®, is a staff nurse at California Cancer Care, Inc.; Heather Belansky, RN, MSN, is a project manager at the Oncology Nursing Society in Pittsburgh, PA; and Regina S. Cunningham, PhD, RN, AOCN®, is a chief nursing officer at the Cancer Institute of New Jersey and an assistant professor in the Family Medicine-Research Division in the Robert Wood Johnson Medical School at the University of Medicine and Dentistry of New Jersey, both in New Brunswick. No financial relationships to disclose. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Oncology Nursing Society. (Submitted August 2008. Accepted for publication September 2, 2008.)

At a Glance

✦ Anorexia is a common and complex clinical problem that occurs in early- and late-stage disease and often is accompanied by other symptoms such as early satiety, taste alterations, and nausea and vomiting.

✦ The available evidence to guide practice on the prevention and management of anorexia is limited, making opportunites for research available in this area.

✦ Nurses need to be familiar with the evidence available on the management of anorexia and use it to guide their decision making in clinical practice.

might be important in reducing the availability of nutrients that are essential for invading organisms and energy expenditure for digestion. In a sustained context, however, anorexia weakens host defenses and ultimately compounds illness (Laviano & Rossi-Fanelli, 2003). Abnormalities in eating behavior are reported in approximately 50% of patients with cancer upon diagnosis and often are among the reasons patients seek medical attention. In later stage disease, the prevalence of anorexia is much higher, with reports ranging from 60%–65% (Priovano et al., 1999).

Anorexia significantly affects the clinical course of cancer. Decreased caloric intake leads to malnutrition and diminished ability to tolerate treatment; more profound disease- and treatment-related toxicities; and derangements in protein, carbohydrate, and fat metabolism. Alterations in metabolism are associated with skeletal muscle wasting, debilitation, changes in functional status, and altered quality of life. Anorexia ultimately increases morbidity and mortality. In a classic study by DeWys et al. (1980), anorexia was identified as an independent prognostic variable in terminally ill patients with cancer.

> **Anorexia and eating are regulated by myriad physiologic, gastrointestinal, metabolic, and nutritional factors as well as neuronal and endocrine mechanisms. Changes in any of these components may lead to anorexia.**

Anorexia and eating are regulated by myriad physiologic, gastrointestinal, metabolic, and nutritional factors as well as neuronal and endocrine mechanisms. Changes in any of these components may lead to anorexia. Anorexia may develop as a result of a decrease in the smell or taste of food, early satiety, dysfunctional hypothalamic activity, increased brain tryptophan, or increased cytokine production (Tisdale, 2003).

Methods

Although anorexia frequently is associated with cachexia (often referred to as the anorexia-cachexia syndrome), it warrants consideration as a unique symptom. For the purpose of developing the ONS PEP resource, anorexia was defined as an involuntary loss of appetite and investigated as an independent symptom. A systematic database search for the years 2002–2007 was conducted to identify research papers investigating interventions designed to prevent, treat, or manage anorexia. Databases included were CINAHL®, MEDLINE®, EMBASE, UpToDate®, DynaMed, PubMed (MEDLINE was searched as part of both EMBASE and PubMed), and the Cochrane Collection. Search terms were *anorexia*, *cachexia*, *loss of appetite*, *early satiety*, and *weight loss*. Database searches were performed by the advanced practice nurse leader, the researcher, and the ONS information resources supervisor, who is a medical librarian. Results of the search within the time points revealed a limited number of citations. As a result, the team decided to expand the search to include landmark studies that had been published prior to 2002 and several studies that were identified through a review of the reference lists of manuscripts included as part of the process.

The abstract of each study was reviewed by the team via conference call, and those meeting inclusion criteria were integrated into the review. Studies were included if the findings were published in English; the sample consisted of adult patients who were experiencing anorexia or weight loss; the publication was a complete report of a study; and dependent variables included anorexia, weight gain, oral intake, or some measure of appetite assessed using instruments designed to quantify the variables.

Critical Review of the Evidence

The researcher on the team reviewed the first two studies and initiated the Table of Evidence (see www.ons.org/outcomes/volume4/anorexia/pdf/AnorexiaEvidenceTable.pdf). The example then was presented to all team members during a conference call to provide information on how to critique studies and build the Table of Evidence. Each member of the team was responsible to review specific studies, which were grouped by intervention, and transfer key information to the Table of Evidence. The Table of Evidence included the study author and year; a brief description of the intervention; the study sample, setting, and methods; the design and conceptual approach; the specific measures, including instruments used and time frames for measurement; the results and conclusions; limitations; minor and major flaws; contraindications; any special training required; and cost data. The final section of the table included information on the levels of evidence previously established for use with ONS PEP evaluations and the reviewer comments. Once completed, the Table of Evidence was sent out for external review by two nurse experts. Minor adjustments were made based on reviewer feedback.

Highlights of the Evidence Review

Key interventions identified in the review of evidence included dietary interventions and counseling, oral supplements, and the use of pharmacologic agents. A brief review highlighting salient interventions from the categories follows. Interventions listed by ONS PEP weight-of-evidence classification (see www.ons.org/outcomes/volume1/nausea/nausea_woe.shtml) are shown in Figure 1.

Recommended for Practice
- Costicosteroids
  – Dexamethasone
  – Methylprenisolone
  – Prednisolone
- Progestins
  – Medroxyprogesterone and megestrol acetate

Likely to Be Effective
- Dietary counseling

Effectiveness Not Established
- Cyproheptadine
- Eicosapentaenoic acid (EPA)
  – EPA in fish oil capsules
  – EPA in supplement form
- Erythropoietin
- Ghrelin
- Metoclopramide
- Oral branched-chain amino acids
- Pentoxifylline
- Thalidomide

Effectiveness Unlikely
- Cannabinoids
- Hydrazine sulfate

Figure 1. Interventions for Anorexia by Oncology Nursing Society Putting Evidence Into Practice® Weight-of-Evidence Classification

Note. Based on information from Adams et al., 2008.

Dietary Interventions Counseling

A study by Ravasco, Monteiro-Grillo, Vidal, and Camilo (2005) confirmed that individualized dietary counseling has been shown to improve nutritional intake and body weight, resulting in reduced incidence of anorexia and improved quality of life. In a prospective, randomized, clinical trial designed to investigate the impact of dietary counseling or nutritional supplements on morbidity and quality of life, 111 patients with colorectal cancer were assigned to receive dietary counseling (group 1), to receive two cans of a high-protein liquid in addition to their regular diets (group 2), or to maintain their diets ad lib (group 3). All patients were receiving radiation therapy combined with 5-fluorouracil and folinic acid (Ravasco et al.).

Dietary counseling included the prescription of a therapeutic diet with regular foods that was modified to provide for individual choice. Counseling was based on principles of good nutrition and took into consideration patients' abilities to digest and absorb nutrients, symptom issues, and psychosocial factors as well as food preferences. Researchers found that protein intake was increased in groups 1 and 2 and decreased in group 3. Moreover, only patients in the group receiving dietary counseling were able to sustain their nutritional intake three months after completing radiation therapy (Ravasco et al., 2005).

A systematic review by Brown (2002) included seven randomized clinical trials examining the effects of nutritional counseling and commercial oral liquid supplements on oral intake. Samples were mixed with regard to diagnosis, treatment, and other demographic and clinical characteristics. The review in-dicated that all trials reported improved caloric intake resulting from nutritional counseling or liquid oral supplements.

Supplements

Eicosapentaenoic acid: Eicosapentaenoic acid (EPA) is an essential omega-3 fatty acid, distinguished from other long-chain polyunsaturated fatty acids by a double bond that sits three carbons from the N-terminal of the molecule. Bluefish, swordfish, salmon, and mackerel are rich in EPA (Jatoi et al., 2004). EPA has been found to lower levels of proinflammatory cytokines, which have been associated with the cancer and anorexia syndrome (Bruera et al., 2003). A systematic review by Yavuzsen, Davis, Walsh, Legrand, and Lagman (2005) reported on three studies that were designed to evaluate the efficacy of EPA on appetite and weight gain in patients with cancer.

The first of the studies (Bruera et al., 2003) included EPA in fish oil capsules, which were investigated in a small, randomized, controlled trial (N = 60). The capsule contained 1.8 g of EPA and 1.2 g of docosahexaenoic acid, which was compared to placebo (olive oil capsules). At study onset, the dose of EPA actually was three times higher, but gastrointestinal complaints and a high rate of attrition (31%) led researchers to dose reduce. No significant differences in appetite or weight outcomes were reported between the two groups.

The second investigation (Jatoi et al., 2004) was a double-blind, three-armed, randomized, controlled trial (N = 421) designed to evaluate EPA in supplement form. Patients received 2.18 g per day of EPA, megesterol acetate, or a combination of the two. Megesterol acetate was selected as a control based on its previously proven efficacy. The primary endpoint was a weight gain greater than or equal to 10%, which was achieved in 6% of patients in the EPA arm, 18% of those receiving megesterol acetate, and 11% receiving both (p = 0.01).

Appetite was measured using the North Central Cancer Treatment Group (NCCTG) questionnaire and the Functional Assessment of Anorexia and Cachexia Therapy (FAACT) (Lai, Cella, Peterman, Barocas, & Goldman, 2005). The NCCTG questionnaire demonstrated equitable results across all three groups. The FAACT, however, demonstrated significantly more favorable appetite scores among patients who received megesterol acetate or the combination. Because the study did not have a true placebo arm, whether EPA had a favorable effect on appetite or weight gain is uncertain. A third randomized, double-blind trial (Fearon et al., 2006) included in the systematic review used an energy-dense omega-3 fatty acid-enriched supplement with an EPA dose of 2.2 g per day versus a control group during a period of eight weeks. A significant correlation existed between EPA and weight gain in patients who were at least 80% compliant based on capsule count; however, the intent-to-treat analysis, which included all subjects who were randomized and consumed at least one dose of study drug, was negative.

Oral branched-chain amino acids: Tryptophan, an amino acid precursor of serotonin, is believed to play a role in the pathogenesis of cancer anorexia. Uptake of tryptophan into the brain is regulated by a specific transport system, which is competitively shared with branched-chain amino acids. Therefore, the administration of oral branched-chain amino acids should result in the reduced concentrations of tryptophan in the brain, limiting its anorexic effects (Cangiano et al., 1996).

One small (N = 25), randomized trial (Cangiano et al., 1996) evaluated the effects of oral branched-chain amino acids versus placebo on anorexia and food intake in patients with cancer over a seven-day period. Patients were newly diagnosed with resectable cancers and had anorexia but were not losing weight. Daily caloric intake (measured by weighing food before and after each meal) was significantly increased and the incidence of anorexia was significantly decreased in the treatment but not in the placebo arm. Evaluation of the significance of the results was difficult because of a lack of description of the validity and reliability of the tool used to assess anorexia. Furthermore, the short duration and small sample size of the study limit its external generalizability. Additional studies need to be conducted in larger populations during a longer period with patient weight as an outcome variable before recommendations for oral branched-chain amino acids can confidently be made.

Pharmacologic Interventions

Corticosteroids: The recommendation for the use of corticosteroids in patients with anorexia is based on a systematic review that included six randomized, placebo-controlled trials evaluating the agents on appetite in patients with cancer. Most patients included in the trials (N = 647), however, had advanced cancer, and the trials used different types of corticosteroids: oral dexamethasone, oral methylprednisolone and prednisolone, and IV methylprednisolone and dexamethasone. In three studies comparing oral methylprednisolone or IV methylprednisolone to placebo (N = 402), with doses ranging from 32–125 mgs per day for periods of one to eight weeks, statistically significant (p < 0.05) improvement was seen in appetite. An improvement also was reported in quality of life, well-being, performance status, pain, and vomiting (Yavuzsen et al., 2005).

One randomized, controlled trial (Inoue et al., 2003) compared oral dexamethasone at two dose levels, 0.75 mg and 1.5 mg, to placebo in patients (N = 116) with advanced cancer. Improvement was seen in appetite in the dexamethasone arms at two weeks and reached statistical significance at four weeks compared to placebo (p < 0.05). No differences in appetite were noted between the doses of dexamethasone. A second trial of 68 patients randomized to placebo or 8 mg of dexamethasone for a period of four days did not demonstrate improvement in anorexia (Moertel, Schutt, Reitemeier, & Hahn, 1974).

In a crossover study (Willox et al., 1984) involving 61 patients, prednisolone at a dose of 10 mg per day was compared to placebo. At six weeks, a statistically significant improvement was observed in self-reported appetite in both arms, although the level of significance was higher in the prednisolone versus placebo arm (p < 0.001) than the placebo versus prednisolone arm (p < 0.01).

Another clinical trial (Loprinzi et al., 1999) randomized 475 patients with cancer to receive dexamethasone 0.75 mg four times per day, megesterol acetate 800 mg orally every day, or fluoxymesterone 10 mg orally twice per day. Patients receiving dexamethasone or megesterol acetate reported improvement in appetite and food intake compared to the fluoxymesterone group, but the difference was not statistically significant. More toxicity was reported in patients receiving dexamethasone as well as a higher rate of study drug discontinuation.

Corticosteroids were recommended as appetite stimulants for patients with cancer in clinical guidelines developed by the French National Federation of Cancer Centres (Desport et al., 2003). The authors indicated that the randomized trials provided good (level B1) evidence, but they did not recommend corticosteroids as a standard of care given the insufficient data defining optimal dose and scheduling of the agents (Desport et al.).

None of the studies evaluating the effect of corticosteroids demonstrated weight gain. Moreover, the most effective type, dose, and route of corticosteroids in the setting of cancer-associated anorexia have not been established in clinical trials. Corticosteroids confer a significant but short-lived benefit on anorexia. Long-term use of corticosteroids is associated with significant toxicities that include immunosuppression, hyperglycemia, muscle weakness and wasting, fat redistribution, decrease in bone density, fluid retention, easy bruising, and skin fragility. Therefore, use of corticosteroids in the setting of cancer-associated anorexia is recommended for patients in whom short-term benefit is desired or those with limited life expectancy (Desport et al., 2003).

Progestins: Progestins are synthetic analogs of progesterone that have been used in the treatment of hormone-dependent tumors. The effects of progestins on increasing body weight and appetite were first noted during the evaluation of antitumor activity in those cancers (Maltoni et al., 2001). The safety and efficacy of the progestinal agents (medroxyprogesterone and megestrol acetate) in the setting of cancer-associated anorexia have been well studied and are summarized in systematic reviews by Gagnon and Bruera (1998) and Yavuzsen et al. (2005). Megestrol acetate was the subject of an additional systematic review by Berenstein and Ortiz (2005). Overall, strong evidence supports the use of progestinal agents in patients with cancer for increasing appetite and body weight (Yavuzsen et al.).

Megestrol acetate has been the most extensively studied of the progestinal agents for its orexigenic, or appetite-stimulating, effect (Gagnon & Bruera, 1998) and is widely used to improve appetite and increase weight in cancer-associated anorexia. In the systemic review by Yavuzsen et al. (2005), 29 randomized, clinical trials reviewed the safety and efficacy of progestins, 23 examined megestrol acetate, and 6 investigated medroxyprogesterone acetate. Results favored progestins over placebo or rather than drugs, and side effects were tolerable. The six controlled trials of oral medroxyprogesterone also demonstrated improved appetite when compared to placebo, but side effects were more significant.

Berenstein and Ortiz (2005) investigated the safety and efficacy of megestrol acetate in improving anorexia in patients with cancer, AIDS, and other underlying pathologies. The review included 30 randomized, clinical trials designed to assess the effect of megestrol acetate compared to placebo or other drug treatment in patients diagnosed with cancer-related anorexia. The authors concluded that megestrol acetate was more effective in improving appetite and increasing weight in patients with cancer than placebo.

The mechanism of action by which megestrol acetate increases appetite is not well understood. One hypothesized mechanism is that the agent acts on cytokines, which inhibit the action of tumor necrosis factor (TNF) on fatty tissue and its products (Berenstein & Ortiz, 2005); or it may be related to glucocorticoid activity, making the drugs similar to corticosteroids (Gagnon & Bruera, 1998). Megestrol acetate has demonstrated a dose-response benefit (dosages ranging from 160–1,600 mg per

day) on appetite, caloric intake, body weight, and the sensation of well-being when compared with placebo (Gagnon & Bruera). Although evidence of a dose response existed, information was insufficient to define the optimal dosages of the agent. The highest dose did not confer any additional benefit with regard to appetite but did increase weight (Yavuzsen et al., 2005).

Adverse events associated with the use of megestrol and medroxyprogesterone include thrombotic events, breakthrough vaginal bleeding, peripheral edema, hyperglycemia, hypertension, Cushing syndrome, alopecia, and adrenal suppression and adrenal insufficiency if abruptly stopped (Gagnon & Bruera, 1998). Patients rarely needed to discontinue the drug because of adverse events in clinical trials. Adverse events are thought to be dose-related, so starting low and titrating upward to clinical response is justifiable.

Thalidomide: Although the underlying pathogenesis of anorexia in patients with cancer has not been explicated definitively, one of the suggested mechanisms is the role of circulating proinflammatory cytokines produced by the host in response to the tumor. One of the cytokines believed to act as an effector in the development of the cancer and anorexia syndrome is TNF (Gordon et al., 2005).

Thalidomide is an immunomodulating agent that has been shown to decrease TNF activity and has been associated with weight gain in patients with tuberculosis or HIV infection. In clinical trials, thalidomide was effective in ameliorating the wasting and weight loss associated with HIV infection and active pulmonary tuberculosis (Gordon et al., 2005). Thalidomide currently is indicated for treatment of multiple myeloma (Celegene Corporation, 2007).

In an open-label clinical trial of 72 patients with advanced cancer (Bruera et al., 1999), thalidomide, 100 mg administered at night for 10 days, improved nausea, appetite, caloric intake, and well-being. In a subsequent randomized, placebo-controlled trial (Gordon et al., 2005) in patients with advanced pancreatic cancer, thalidomide 200 mg daily was shown to be effective in attenuating loss of weight and lean muscle mass. Appetite was not measured in the investigation. Side effects of thalidomide include dizziness, drowsiness, somnolence, constipation, and increased incidence of thromboembolic events. No prospective, randomized, controlled studies of oral thalidomide in the treatment of anorexia in cancer have been completed.

Ghrelin: Ghrelin is a 28-amino acid peptide that is produced by the P/D1 cells lining the fundus of the stomach, which increase appetite through action on hypothalamic feeding centers. Two randomized, clinical trials of ghrelin were identified in the literature. The first (Neary et al., 2004) investigated ghrelin at a dose of 5 picomoles (one trillionth of a mole) per kg per minute, infused in seven patients; this dose was based on previous studies in healthy subjects. Researchers noted improvements in meal appreciation scores among patients who received ghrelin versus those receiving saline infusions. No side effects were observed. Long-term data regarding the ability of ghrelin to improve appetite could not be identified.

In a subsequent randomized, placebo-controlled, double-blind, double-crossover study (Strasser et al., 2008) evaluating the safety, tolerability, and pharmacokinetic profiles of IV ghrelin for cancer-related anorexia, 21 adults with advanced cancer experiencing a lack of appetite and weight loss received low-dose (2 mcg/kg, n =

4) IV ghrelin versus placebo (n = 5) or upper-dose (8 mcg/kg, n = 4) IV ghrelin versus placebo (n = 7) given over 60 minutes times two doses. Outcome measures included appetite, hunger, early satiety, weight, nutritional intake, and nausea measured during and after the infusion using visual analog scales. Nutritional intake and nutrition-related symptoms did not differ between the ghrelin or placebo groups. No differences in toxicity were reported; ghrelin was well tolerated by all patients. Researchers concluded that ghrelin administered via IV was safe and effective at the doses tested. Evidence on the effectiveness of ghrelin currently is insufficient to make any recommendations for use in clinical practice. Currently, no evidence suggests that it is harmful.

Cyproheptadine: Cyproheptadine is an antihistamine marketed for the treatment of various allergic conditions that has established antiseretonergic properties and demonstrated S1 and S2 blocking activity. In early clinical trials, cyproheptadine was noted to result in unexpected weight gain and has been marketed in Europe for the indication (Kardinal et al., 1990). Two randomized, clinical trials evaluating the safety and efficacy of cyproheptadine versus placebo on appetite and weight have been completed. The smaller and earlier (Pawlowski, 1975) of the two studies (N = 51) compared cyproheptadine 12 mg orally per day for eight weeks to placebo and found that appetite (assessed using a 0–4 rating scale) (p < 0.05) and weight gain (p < 0.05) were improved in the cyproheptadine group. The second study (Kardinal et al.), conducted in patients with advanced malignant disease (N = 293) compared cyproheptadine at a dose of 24 mg per day for 12 weeks to placebo. Results demonstrated improved appetite (determined by a six-item questionnaire) in patients receiving cyproheptadine versus those receiving placebo (p = 0.02) but found no significant difference in weight gain. Reports of considerable sedative effects limit the use of the intervention. Although the earlier study demonstrated promising results, the findings were not replicated in the larger study. Moreover, the sedative properties of cyproheptadine and its effect on quality of life must be considered if additional studies are to be undertaken.

Erythropoietin: Erythropoietin (EPO) is a naturally occurring glycoprotein that stimulates production of red blood cells and hemoglobin in bone marrow. In combination with cyclooxygenase-2 inhibitors, EPO is believed to decrease metabolic stress, slow the progression of weight loss, and decrease energy expenditure in patients with malignant disease (Daneyrd et al., 1998; Lundholm, Daneryd, Bosaeus, Koerner, & Lindholm, 2004). The safety and efficacy of EPO in this context was investigated in two studies, involving a total of 417 patients receiving doses ranging from 12,000–40,000 units weekly for a duration of eight weeks to two and a half years (Yavuzsen et al., 2005). The first study (Daneyrd et al.) involved patients with advanced cancer who were randomized to receive 50 mg of indomethacin (a nonspecific cyclo-oxygenase inhibitor) given orally twice a day plus EPO at a range of 12,000–13,000 units subcutaneously weekly (n = 50) or indomethacin 50 mg given orally twice a day (n = 58). No difference was observed in food intake or body weight between the groups at the end of the study period.

The experimental condition (n = 139) of the second investigation (Lundholm et al., 2004) involved the use of indomethacin 50 mg twice daily plus EPO 15,000–40,000 units per week along with a specialized nutrition program (oral nutritional support

and home total parenteral nutrition provided on a patient-by-patient basis). Control patients (n = 170) received identical indomethacin and EPO doses without the specialized nutritional support. The intent-to-treat analysis, which included all patients randomized, demonstrated few differences in food intake and estimated energy balance in patients who were nutritionally supported. Given the results of the investigations, the use of EPO in the treatment of anorexia currently is not supported.

Metoclopramide: A systematic review (Yavuzsen et al., 2005) included two studies of 55 patients receiving the prokinetic drug, metoclopramide, for anorexia. Doses of 80 mg per day of controlled-release or immediate-release metoclopramide were administered during a period of one to two weeks. Although improvement in nausea was reported in both studies, no improvement in caloric intake or appetite was observed. Currently, metoclopramide is a useful agent in the treatment of early satiety, delayed gastric emptying, and delayed nausea and vomiting associated with chemotherapy, but evidence is insufficient to support its use in the treatment of cancer-related anorexia.

Cannabinoids, melatonin, and hydrazine sulfate: The effectiveness of cannabinoids, melatonin, and hydrazine sulfate in the prevention, management, or treatment of cancer-related anorexia is unlikely based on negative or conflicting evidence from a small number of studies (Yavuzen et al., 2005).

Cannabinoids refer to a group of substances that are structurally related to delta-9-tetrahydrocabinol (THC) that bind to cannabinoid receptors (Lambert & Fowler, 2005). Appetite stimulation and weight gain are recognized effects of THC. Two randomized, clinical trials investigated the use of cannabinoids for cancer-related anorexia. The first study (Jatoi et al., 2002) was designed to determine whether dronabinol administered alone or in combination with the progestinal agent, megestrol acetate, was more, less, or equally effective in palliating cancer-associated anorexia. Results indicated that a greater number of patients receiving megestrol acetate had improvement in appetite compared to the dronabinol group (75% versus 49%; p = 0.0001). Researchers concluded that the use of megestrol acetate alone was more effective in improving appetite compared with dronabinol alone in patients with advanced cancer. The combination did not confer any additional benefit.

The second trial (Strasser et al., 2006) was designed as a randomized, double-blind, placebo-controlled investigation to compare the effects of cannibis extract (a combination of 2.5 mg of dronabinol and 1 mg of cannabidiol), THC (dronabinol 2.5 mg), and placebo on appetite and quality of life in patients with advanced cancer. A total of 243 subjects were randomized, and 164 completed treatment (cannibis extract, n = 66 of 95 patients; THC, 65 of 100 patients; and placebo, 33 of 48 patients). Although subroup analyses demonstrated improvement in appetite scores among patients treated with cannabis extract or THC, the intent-to-treat analysis, which involved all patients randomized, showed no significant differences between the arms in terms of appetite, quality of life, or cannabinoid-related toxicity. Based on the findings, an independent data review board recommended termination of the study. Researchers concluded that no differences between cannibis extract, THC, or placebo existed at the dosages investigated. Side effects of cannabinoid use include dizziness, nausea, and fatigue.

Melatonin is a hormone that is produced by the pineal gland. Melatonin was included in systematic reviews by Gagnon and Bruera (1998) and Yavuzsen et al. (2005). Two clinical trials (Lissoni et al., 1996; Lissoni, Chilelli, Villa, Cerizza, & Tancini, 2003) involving a total of 186 subjects using oral melatonin have been completed. The investigations used doses of 20 mg per day of melatonin for duration of 1–16 weeks. Although weight loss was observed less frequently in the melatonin groups, no differences in appetite or nutritional intake could be appreciated. Side effects of the agent include sleepiness.

Hydrazine sulfate is a chemical compound that is sold as a dietary supplement in the United States. Evaluations of the efficacy and safety of hydrazine sulfate in improving appetite in patients with cancer were included in systematic reviews by Gagnon and Bruera (1998) and Yavuzsen et al. (2005). Five studies that included a total of 796 subjects have been conducted. Dosage ranged from 60–180 mg per day for a duration of four weeks (two studies did not report duration). An early study of patients with cancer experiencing weight loss demonstrated improvement in appetite with an increase or maintenance in weight; however, in multicenter, randomized, placebo-controlled trials in patients with lung and colorectal cancer, the findings were not corroborated. The lack of significant difference among the groups in the trials provides strong evidence that hydrazine sulfate is ineffective in improving appetite.

Pentoxifylline: Pentoxifylline is a methylxanthine derivative used for the treatment of intermittent claudication, which inhibits TNF-α production. A double-blind, placebo-controlled trial randomized 70 patients with a history of cancer-related anorexia or weight loss (Goldberg et al., 1995) to receive pentoxifylline 400 mg three times per day versus placebo. The study failed to provide any evidence that pentoxifylline is effective in inducing weight gain or improving appetite.

Implications

Based on the findings of this review, only a limited number of empirically-based interventions can be recommended for the management of anorexia. Although many pharmacologic interventions have been investigated in the context of anorexia, with the exception of corticosteroids and progestins, current evidence does not support their use in clinical practice. The complexity of anorexia, including its close association with other symptoms and the current limitations in understanding the pathophysiologic mechanisms underlying the development of the symptom, makes the management of it particularly challenging. Clearly, additional research is needed on anorexia as a unique symptom and on symptoms that are closely related and often occur with anorexia, such as early satiety and taste changes. Future studies need to use a more clear and uniform definition of anorexia, unambiguous eligibility criteria, and measurement tools that have established validity and reliability in assessing anorexia and anorexia-related outcomes in the cancer population.

> The complexity of anorexia makes the management of this common and distressing symptom particularly challenging.

A more refined understanding of the basic mechanisms underlying anorexia is needed to facilitate the development of rational therapeutic interventions. A recent example of such an approach is reflected in the work of Jatoi et al. (2007), who designed a proof-of-concept study to test the principle that TNF-α inhibition (accomplished via the administration of etanercept) could provide a means of palliating symptoms associated with cancer-related anorexia. Etanercept is a dimeric fusion protein consisting of the extracellular binding portion of the human 75-kilodalton TNF receptor linked to the Fc portion of the human immunoglobulin G1. Etanercept binds to TNF-α in vivo, blocking its interaction with cell surface receptors. TNF-α is hypothesized to play a role in the development of cancer-related anorexia-cachexia.

Subjects in the investigation were randomized to receive 25 mg of etanercept (n = 33) or placebo (n = 30) twice per week for 24 weeks. Outcome measures included weight gain and anorexia (assessed using the NCCTG and FAACT scales). No differences were demonstrated in any of the outcome categories. Researchers concluded that etanercept as prescribed in the study did not result in any improvement in appetite or weight and that additional study was warranted.

In addition, more research is needed on nonpharmacologic interventions. Determining better ways to provide nutritional counseling and caloric support and understanding the role of food preferences and aversions and the implications of various cultural beliefs on anorexia also are important areas of inquiry. In the clinical setting, oncology nurses need to take a proactive approach to the management of anorexia, be aware of current and emerging evidence on the management of the symptom, and understand how to translate the information into their practice settings. Oncology nurses also should consider opportunities to participate in the design and development of studies investigating anorexia.

Conclusions

Oncology nurses are integral to the delivery of quality cancer care; they must be aware of evidence-based interventions to manage symptoms and use the information to guide decision making in clinical practice. The ONS PEP resources are readily available (www.ons.org/outcomes) and easy to use in the clinical setting. The pocket-sized format and user-friendly design of the ONS PEP resources truly facilitates the "translation" of research evidence from the empirical literature to the bedside. Familiarity with the evidence on the management of anorexia will help nurses to identify and manage patients experiencing this distressing symptom more proactively. Attention to anorexia is an important part of the care provided by all members of the healthcare team.

Author Contact: Regina S. Cunningham, PhD, RN, AOCN®, can be reached at rcunning@umdnj.edu, with copy to editor at CJONEditor@ons.org.

References

Adams, L., Cunningham, R., Shepard, N., Caruso, R.A., Norling, M.J., & Belansky, H. (2008). *Oncology Nursing Society Putting Evidence Into Practice®: Anorexia*. Retrieved January 16, 2008, from http://www.ons.org/outcomes/volume4/anorexia/pdf/ShortCard_Anorexia.pdf

Berenstein, E.G., & Ortiz, Z. (2005). Megestrol acetate for the treatment of anorexia-cachexia syndrome. *Cochrane Database of Systematic Reviews, 2*(2), CD004310.

Brown, J.K. (2002). A systematic review of the evidence on symptom management of cancer-related anorexia and cachexia. *Oncology Nursing Forum, 29*(3), 517–530.

Bruera, E., Neumann, C.M., Pituskin, E., Calder, K., Ball, G., & Hanson, J. (1999). Thalidomide in patients with cachexia due to terminal cancer: Preliminary report. *Annals of Oncology, 10*(7), 857–859.

Bruera, E., Strasser, F., Palmer, J.L., Willey, J., Calder, K., Amyotte, G., et al. (2003). Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: A double-blind, placebo-controlled study. *Journal of Clinical Oncology, 21*(1), 129–134.

Cangiano, C., Laviano, A., Meguid, M.M., Mulieri, M., Conversano, L., Preziosa, I., et al.. (1996). Effects of administration of oral branched-chain amino acids on anorexia and caloric intake in cancer patients. *Journal of the National Cancer Institute, 88*(8), 550–552.

Celegene Corporation. (2007). Thalomid®. Retrieved July 31, 2008, from http://www.thalomid.com/thalomid_pi.aspx

Daneryd, P., Svanberg, E., Korner, U., Lindholm, E., Sandstrom, R., Brevinge, H., et al. (1998). Protection of metabolic and exercise capacity in unselected weight-losing cancer patients following treatment with recombinant erythropoietin: A randomized prospective study. *Cancer Research, 58*(23), 5374–5379.

Desport, J.C., Gory-Delabaere, G., Blanc-Vincent, M.P., Bachmann, P., Beal, J., Benamouzig, R., et al. (2003). Standards, options and recommendations for the use of appetite stimulants in oncology (2000). *British Journal of Cancer, 89*(Suppl. 1), S98–S100.

DeWys, W.D., Begg, C., Lavin, P.T., Band, P.R., Bennett, J.M., Bertino, J.R., et al. (1980). Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *American Journal of Medicine, 69*(4), 491–497.

Fearon, K.C., Barber, M.D., Moses, A.G., Ahmedzai, S.H., Taylor, G.S., Tisdale, M.J., & Murray, G.D. (2006). Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. *Journal of Clinical Oncology, 24*(21), 3401–3407.

Gagnon, B., & Bruera, E. (1998). A review of the drug treatment of cachexia associated with cancer. *Drugs, 55*(5), 675–688.

Goldberg, R.M., Loprinzi, C.L., Mailliard, J.A., O'Fallon, J.R., Krook, J.E., Ghosh, C., et al. (1995). Pentoxifylline for treatment of cancer anorexia and cachexia? A randomized, double-blind, placebo-controlled trial. *Journal of Clinical Oncology, 13*(11), 2856–2859.

Gordon, J.N., Trebble, T.M., Ellis, R.D., Duncan, H.D., Johns, T., & Goggin, P.M. (2005). Thalidomide in the treatment of cancer cachexia: A randomized placebo controlled trial. *Gut, 54*(4), 540–545.

Inoue, A., Yamada, Y., Matsumura, Y., Shimada, Y., Muro, K., Gotoh, M., et al. (2003). Randomized study of dexamethasone treatment for delayed emesis, anorexia and fatigue induced by irinotecan. *Supportive Care in Cancer, 11*(8), 528–532.

Jatoi, A., Dakhil, S.R., Nguyen, P.L., Sloan, J.A., Kugler, J.W., Rowland, K.M., Jr., et al. (2007). A placebo-controlled double blind trial of etanercept for cancer anorexia/weight loss syndrome. *Cancer, 110*(6), 1396–1403.

Jatoi, A., Rowland, K., Loprinzi, C.L., Sloan, J.A., Dakhil, S.R., MacDonald, N., et al. (2004). An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer associated wasting: A North Central Cancer Treatment Group and National Cancer Institute of Canada Collaborative Effort. *Journal of Clinical Oncology, 22*(12), 2469–2476.

Jatoi, A., Windschitl, H.E., Loprinzi, C.L., Sloan. J.A., Dakhil, S.R.,

Mailliard, J.A., et al. (2002). Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: A North Central Cancer Treatment Group study. *Journal of Clinical Oncology, 20*(2), 567–573.

Kardinal, C.G., Loprinzi, C.L., Schaid, D.J., Hass, A.C., Dose, A.M., Athmann, L.M., et al. (1990). A controlled trial of cyproheptadine in cancer patients with anorexia and/or cachexia. *Cancer, 65*(12), 2657–2662.

Lai, J., Cella, D., Peterman, A., Barocas, J., & Goldman, S. (2005). Anorexia/cachexia-related quality of life for children with cancer. *Cancer, 104*(7), 1531–1539.

Lambert, D.M. & Fowler, C.J. (2005). The endocannabinoid system: Drug targets, lead compounds, and potential therapeutic applications. *Journal of Medicinal Chemistry, 48*(16), 5059–5087.

Laviano, A., Meguid, M.M., & Fanelli, F.R. (2006). Anorexia. In G. Montovani, S.D. Anker., A. Inui, J.E. Morley, F. Rossi Fanelli, D. Scevols, et al. (Eds.), *Cachexia and wasting: A modern approach* (pp. 139–148). Springer: Milan.

Laviano, A., & Rossi-Fanelli, F. (2003). Pathogenesis of cancer anorexia: Still doubts after all these years? *Nutrition, 19*(1), 67–68.

Lissoni, P., Chilelli, M., Villa, S., Cerizza, L., & Tancini, G. (2003). Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: A randomized trial. *Journal of Pineal Research, 35*(1), 12–15.

Lissoni, P., Paolorossi, F., Tancini, G., Barni, S., Ardizzoia, A., Brivio, F., et al. (1996). Is there a role for melatonin in the treatment of neoplastic cachexia? European Journal of Cancer, 32(8), 1340-1343.

Loprinzi, C.L., Kugler, J.W., Sloan, J.A., Mailliard, J.A., Krook, J.E., Wilwerding, M.B., et al. (1999). Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *Journal of Clinical Oncology, 17*(10), 3299–3306.

Lundholm, K., Daneryd, P., Bosaeus, I., Koerner, U., & Lindholm, E. (2004). Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignancy disease: Effects on survival, metabolism, and function. *Cancer, 100*(9), 1967–1977.

Maltoni, M., Nanni, O., Scarpi, E., Rossi, D., Serra, P., & Amadori, D. (2001). High-dose progestins for the treatment of cancer anorexia-cachexia syndrome: A systematic review of randomised clinical trials. *Annals of Oncology, 12*(3), 289–300.

Moertel, C.G., Schutt, A.J., Reitemeier, R.J., & Hahn, R.G. (1974). Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer, 33*(6), 1607–1609.

Neary, N.M., Small, C.J., Wren, A.M., Lee, J.L., Druce, M.R., Palmieri, C., et al. (2004). Ghrelin increases energy intake in cancer patients with impaired appetite: Acute, randomized, placebo-controlled trial. *Journal of Clinical Endocrinology and Metabolism, 89*(6), 2832–2836.

Pawlowski, G.J. (1975). Cyproheptadine: Weight-gain and appetite stimulation in essential anorexic adults. *Current Therapeutic Research, Clinical and Experimental, 18*(5), 673–678.

Priovano, M., Maltoni, M., Nanni, O., Marinari, M., Indelli, M., Zaninetta, G., et al. (1999). A new palliative score: A first step for the staging of terminally ill cancer patients. Italian Multicenter and Study Group on Palliative Care. *Journal of Pain and Symptom Management, 17*(4), 231–239.

Ravasco, P., Monteiro-Grillo, I., Vidal, P.M., & Camilo, P.E. (2005). Dietary counseling improves patient outcomes: A prospective, randomized, controlled trial, in colorectal cancer patients undergoing radiotherapy. *Journal of Clinical Oncology, 23*(7), 1431–1438.

Strasser, F., Luftner, D., Possinger, K., Ernst, G., Ruhstaller, T., Meissner, W., et al. (2006). Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: A multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *Journal of Clinical Oncology, 24*(21) 3394–4000.

Strasser, F., Lutz, T.A., Maeder, M.T., Thuerlimann, B., Bueche, D., Tschop, M., et al. (2008). Safety, tolerability, and pharmacokinetics of intravenous ghrelin for cancer related anorexia/cachexia: a randomized, placebo-controlled, double-blind, double-crossover study. *British Journal of Cancer, 98*(2), 300–308.

Tipton, J.M., McDaniel, R.W., Barbour, L., Johnston, M.P., Kayne, M., LeRoy, P., et al. (2007). Putting Evidence Into Practice®: Evidence-based interventions to prevent, manage, and treat chemotherapy-induced nausea and vomiting. *Clinical Journal of Oncology Nursing, 11*(1), 69-78

Tisdale, M.J. (2003). Pathogenesis of cancer cachexia. *Supportive Oncology, 1*(3), 159–168.

Willox, J.C., Corr, J., Shaw, J., Richardson, M., Calman, K.C., & Drennan, M. (1984). Prednisolone as an appetite stimulant in patients with cancer. *BMJ, 288*(6410), 27.

Yavuzsen, T., Davis, M.P., Walsh, D., Legrand, S., & Lagman, R. (2005). Systematic review of the treatment of cancer-associated anorexia and weight loss. *Journal of Clinical Oncology, 23*(33), 8500–8511.

Receive free continuing nursing education credit for reading this article and taking a brief quiz online. To access the test for this and other articles, visit http://evaluationcenter.ons.org. After entering your Oncology Nursing Society profile username and password, select CNE Listing from the left-hand tabs. Scroll down to *Clinical Journal of Oncology Nursing* and choose the test(s) you would like to take.