

EPEEC for Veterans

Education in Palliative and End-of-life Care for Veterans

Trainer's Guide

Module 6b

Constitutional Symptoms

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Contact EPEC by E-mail at info@epec.net, or

EPEC®

750 N. Lake Shore Drive, Suite 601

Chicago, IL 60611

USA

Phone: +1 (312) 503-EPEC (3732)

Fax: +1 (312) 503-4355

Module 6b trainer's notes

Principal message

Facility with the management and treatment of common physical symptoms encountered in end-of-life care is important if quality of life and relief of suffering are to be achieved.

Module overview

Module 6b presents an approach to the assessment and management of a number of constitutional symptoms. It includes:

- Anorexia/cachexia
- Fatigue
- Insomnia
- Skin problems

Each section covers the pathophysiology, assessment, and management of these symptoms.

Preparing for a presentation

1. Assess the needs of your audience

Choose from the material provided in the syllabus according to the needs of your expected participants. It is better for participants to come away with a few new pieces of information, well learned, than to come away with a deluge of information, but remembering nothing.

2. Presentation timing

Allow sufficient time to collect participants' demographic data and complete the pre-test.

The suggested timing for each part of this module is:

Introduction	2-3 minutes
Presentation	35 minutes
Summary	2-3 minutes
<u>Post-test & Evaluation</u>	<u>5 minutes</u>
Total	44-46 minutes

3. Number of slides: 41

4. Preparing your presentation

The text in the syllabus was not designed to be used as a prepared speech. Instead, the slides have been designed to trigger your presentation. Although the slides closely follow the text of the syllabus, they do not contain all of the content. Their use presumes that you have mastered the content. You may want to make notes on the slide summary pages to help you prepare your talk in more detail and provide you with notes to follow during your presentation.

You will not want to use all of the slides for a single 45-minute session. You will only be able to cover 1 or possibly 2 of the symptoms well. By giving a handout, you can refer participants to it for the information you choose not to cover. Alternatively, you might choose to present this material in several sessions in order to cover all of the symptoms comprehensively.

Practice your presentation using the slides you have chosen, and speaking to yourself in the kind of language you expect to use, until it is smooth and interesting and takes the right amount of time.

5. Preparing a handout for participants

The syllabus text and slides in the **Trainer's Guide** were designed to be reproduced and provided to participants as a handout, either in its entirety, or module by module. If the entire curriculum is not being offered, please include the following in each handout:

- **EPEC for Veterans Front Cover Page**
- **EPEC for Veterans Acknowledgment Pages** (to acknowledge the source of the material)
- Syllabus and slides for **Module 6b**

6. Equipment needs

- computer with DVD capability or separate DVD player
- flipchart and markers for recording discussion points

Making the presentation

1. Introduce yourself

If you have not already done so, introduce yourself. Include your name, title, and the organization(s) you work for. Briefly describe your clinical experience related to the information you will be presenting.

2. Introduce the topic

Show the title slide for the module. To establish the context for the session, make a few broad statements about the importance of managing symptoms as a clinical skill. Identify which symptoms you will be covering. Tell participants the format and time you will take to present the session. Identify any teaching styles other than lecture that you intend to use.

3. Review the session objectives

Show the slide with the session objectives listed. Read each objective and indicate those that you are planning to emphasize.

4. Show the trigger tape or present the clinical case

After reviewing the objectives for the session, show the trigger tape or present one of the clinical cases below. It has been designed to engage the audience and provide an appropriate clinical context for the session. It was not designed to demonstrate an ideal interaction, but to ‘trigger’ discussion.

Clinical case (Part 1: Anorexia/Cachexia)

J.F. is a 56-year-old electrician and Desert Storm Veteran presents to his local VAMC with low-grade, constant epigastric pain, increasing fatigue, an eight pound weight loss over the past two months, and change in appetite associated with a sense of ‘constantly being full.’ A diagnosis of cancer of the pancreas with liver metastases is established. J.F. agrees to enter an experimental chemotherapy trial. In addition, he and his family ask for a nutritional consult.

Clinical case (Part 2: Fatigue)

L.M. is an 85-year-old female Veteran who served as a Navy WAVE during WWII with a long history of chronic obstructive pulmonary disease and newly diagnosed lung cancer. She comes in today with the following complaint: “Doctor, I can’t understand it. I’m tired all the time. I don’t have the energy to do any of my usual activities. It’s so frustrating to me. Can’t something be done about this?”

Four months ago she developed hemoptysis and sought evaluation. Chest x-ray demonstrated a large right lower lobe lung mass. Computed tomography (CT) scan of the chest revealed a 6 cm right lower lobe lung mass with bulky mediastinal adenopathy. Fine needle aspiration of the lung mass confirmed a diagnosis of non-small cell lung cancer. The patient declined further evaluation or treatment because she, overall, felt well. She returns today for follow-up. Her only complaint is fatigue.

Clinical case (Part 3: Insomnia)

A.P. is a 53-year-old female Veteran who is admitted to a home hospice program with metastatic breast cancer, mild dyspnea, and bone pain. She is able to walk with assistance and enjoys visiting with family and friends and playing with her two small grandchildren. Her hospice nurse reports that she is not sleeping well at night and the family has requested a sleeping medication.

Her sleep problems began in the past two weeks. She has difficulty falling asleep and wakes up at least twice during a typical night, but does not have early morning awakening. She often takes brief naps in the daytime. She is reluctant to take sustained-release oral morphine as prescribed (60 mg twice daily) for fear of addiction and sedation, and uses caffeinated beverages to prevent sedation from the 10 mg immediate release breakthrough doses she does take. Daytime pain control is acceptable (usually a 2 out of 10), but pain flares late at night are common.

Clinical case (Part 4: Skin problems)

P.L. is a 74-year-old Veteran residing in the community living center (CLC). He has moderate to severe dementia and is bed-bound. The Veteran had developed a pressure ulcer before being admitted to the CLC. This caused pain with turning and personal care expressed by grimaces and some calling out.

Examination shows a reddened area with skin breakdown, partial epithelialization and some white tissue in the wound bed covered by a disposable diaper. The dressing is saturated with a serous discharge. When the dressing is removed, the smell is foul.

5. Present the material

Recommended style: Interactive lecture

An interactive lecture will permit you to engage your audience, yet cover 2 to 3 symptoms within 45 to 60 minutes. Identify the symptoms you plan to cover and select the slides to go with those symptoms. Use your own case vignettes to illustrate clinical applications for the information presented.

Alternative style: Case-based

If you have mastered the material and the method, a case-based approach to teaching this module can be very effective.

Turn off the projector and turn up the lights. Use a flipchart or overhead projector.

There is a case vignette at the beginning of each symptom in this module. Ask a participant to read the vignette. In a Socratic way, ask participants to help 'solve' the cases. Ask them questions about assessment and management. Ask them to explain the known pathophysiology that underlies the management of each symptom. Write points on the

overhead or flipchart. Draw diagrams yourself. Don't be concerned about your artistry, the points will come across.

Use the discussion to interweave the key take-home points from the syllabus.

6. Key take-home points

Anorexia/cachexia

1. Chronic inflammation plays a pathophysiologic role in cachexia.
2. Thorough evaluation of secondary causes of anorexia/cachexia is critical.
3. Calories alone cannot reverse cachexia.
4. Progestational agents and steroids stimulate appetite.

Fatigue/weakness

5. Fatigue is the symptom with the greatest impact on every day life.
6. Anemia is the most common cause of reversible fatigue. Increases in quality of life appear greatest when the hemoglobin is in the range of 11-13 g/dl.
7. Treatment of depression, pain hypothyroidism, hypogonadism and other modifiable conditions may improve subjective fatigue in select patients.
8. Moderate exercise often helps with subjective fatigue. This is sometimes counter-intuitive to Veterans.
9. A trial of therapy with psychostimulants and/or corticosteroids is warranted when fatigue is a distressing symptom, there are no other modifiable causes for fatigue and the Veteran has no contraindication to the medication.

Insomnia

10. Assessment of insomnia often reveals one or more modifiable issues related to sleep hygiene. Counsel Veterans and their families on nonpharmacological ways to improve sleep.
11. Caregivers may misinterpret delirium as insomnia.
12. Trazodone may be particularly useful in the frail and elderly and for more chronic insomnia.
13. Benzodiazepines frequently manage insomnia effectively short-term but tolerance often develops and may contribute to the development of delirium.
14. Quetiapine may be useful in treating PTSD-related nightmares and insomnia.

Skin problems

15. Prevention of pressure ulcers requires skin protection to vulnerable areas and pressure reduction and relief.
16. Multiple dressings are used, depending on whether the skin wound is dry or wet. Some of these dressings provide chemical debridement.
17. Pain control for pressure ulcers, especially during debridement, is critical.
18. Malignant and infected wound may have significant odor – introducing competing odors into the room may help. Topical metronidazole gel may help as well.

7. Summarize the discussion

Briefly review each part of the presentation. Recap 2 or 3 of the most important points that were discussed.

8. Post-test/evaluation

Ask the participants to evaluate the session.

Module 6b: Constitutional Symptoms

Slide 1



Overall Introduction

This module discusses common constitutional symptoms experienced by Veterans in palliative care. These include:

- Anorexia/cachexia
- Fatigue
- Insomnia
- Skin Problems

For each of these symptoms/syndromes, a brief discussion of pathophysiology is presented followed by a discussion on assessment and management.

Objectives

Slide 2



After studying this module, clinicians will be able to:

- discuss pathophysiology of four constitutional symptoms in palliative care;
- discuss assessment strategies; and
- understand management strategies.

Part 1: Anorexia/cachexia

Clinical case

J.F. a 56-year-old electrician and Desert Storm Veteran presents to his local VAMC with low-grade, constant epigastric pain, increasing fatigue, an eight pound weight loss over the past two months, and change in appetite associated with a sense of ‘constantly being full.’ A diagnosis of cancer of the pancreas with liver metastases is established. J.F. agrees to enter an experimental chemotherapy trial. In addition, he and his family ask for a nutritional consult.

Introduction

Slide 3

Anorexia/cachexia

Cachexia – wasting syndrome

- ↓ Lean tissue
- ↓ Performance status
- Altered resting energy expenditure
- ↓ Appetite

Slide 4

Impact

- ≥ 5% weight loss and poor prognosis
- Trend toward lower chemotherapy response rates
- Anorexia and poor prognosis
- ↓ QOL, function
- Affects caregivers

Anorexia is a lack or loss of appetite. **Cachexia** is a wasting syndrome characterized by loss of muscle and fat and may be directly related to cancer or other chronic progressive disease processes.¹

Cachexia, with rare exception, is accompanied by anorexia. The syndrome of anorexia/cachexia occurs in the majority of patients with advanced, end-stage chronic diseases such as dementia, lung disease, heart disease, and malignancies. The signs and symptoms of the anorexia/cachexia syndrome include loss of lean tissue, a decline in performance status, and loss of appetite.^{2,3,4,5} Anorexia/cachexia also correlates with functional decline and morbidity.⁶

Anorexia/cachexia represents a common and almost universal result of chronic disease progression at end-of-life. At the end-of-life, these symptoms may be regarded as normal and expected with intervention strategies aimed at managing associated symptoms, e.g., dry mouth, fatigue, rather than reversing the anorexia/cachexia.

Societal, cultural, and family perceptions about anorexia/cachexia drive much of the concern with how these symptoms are treated. As functional capacity is lost, Veterans become increasingly dependent on family, friends, and institutions. Sharing a meal is often a cornerstone of family life; thus, friends and family also suffer as they observe the wasting of a loved one. It is not uncommon to hear a family say “if only his appetite was better and he ate more, then he would get better” or “I don’t want her to starve,” or “if she would only eat, she would get stronger.”

Anorexia/cachexia and the frequently associated problem of fatigue are among the most common symptoms encountered in Veterans with advanced chronic disease and cancer. Anorexia is also a powerful predictor of early death in patients with cancer.⁷ Patients with a loss of appetite have a far worse prognosis compared to those who maintain their appetite. This observation persists even after adjusting for several other prognostic parameters. Thus, both weight loss and anorexia predict a poor prognosis for Veterans with advanced chronic disease and/or cancer.

Pathophysiology

Slide 5

Pathophysiology

- Chronic inflammation
- Metabolic changes
- Lipolytic / proteolytic substances
- Hormonal changes
- Role of neurotransmitters
- Cytokine impact on hypothalamus

Cachexia is not due to reduced nutritional intake and enteral/parenteral feeding does not reverse the syndrome.^{8,9}

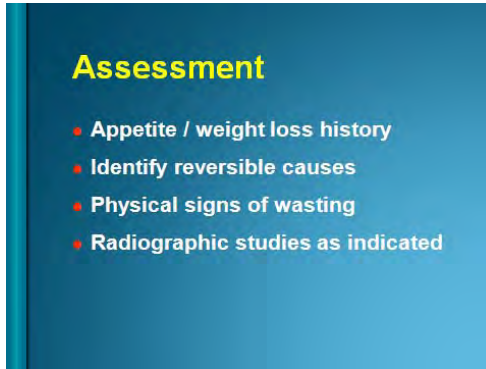
The anorexia/cachexia syndrome is a multifactorial entity. Chronic inflammation has been identified as a core mechanism.¹⁰ Lipolysis, muscle protein catabolism, increases in acute phase proteins (including C-reactive protein) and a rise in pro inflammatory cytokines (notably IL-1, IL-6, TNF Alpha, and leukemia inhibitory factor) are associated with the syndrome and are similar to the metabolic response to an acute injury.

Anorexia and cachexia in the setting of cancer has been most intensively researched. In the setting of malignancy both lipolytic and proteolytic substances have been discovered in rodents and humans.^{11,12} Some tumors also directly produce inflammatory cytokines.¹³ Raised basal metabolism, changes in autonomic control mechanisms (favoring increased

sympathetic activity), and alterations in hormone production, e.g., reduced testosterone levels, are often observed.^{14,15} Inflammatory cytokines, specifically tumor necrosis factor alpha (TNF- α), interleukin-1 beta, interleukin-6, as well as others, may also play a role.^{16,17,18,19,20,21,22,23}

Assessment

Slide 6



Assessment

- Appetite / weight loss history
- Identify reversible causes
- Physical signs of wasting
- Radiographic studies as indicated

At the first Veteran contact record weight, appetite, and factors affecting food intake. Note variations in taste and smell, swallowing, and evidence of early satiety. As Veterans are subject to many secondary problems contributing to anorexia/cachexia, clinicians should consider a wide range of contributing factors (see **Table 1**). Although the fundamental cause may be disease progression, considering the contributing factors may help to direct interventions.

It is important to assess Veteran and family concern about anorexia/cachexia and determine if interventions are required. While some Veterans and their caregivers are not concerned with these symptoms and do not want further assessment or treatments, others will want a detailed discussion and potential work up for a variety of causes. It is important to address Veteran and caregiver emotional concerns with these symptoms, e.g., ‘hunger’, ‘starvation.’ The factors causing anorexia/cachexia vary from Veteran to Veteran.

Slide 7



Potentially reversible causes of weight loss

- Psychological factors
- Mucositis
- Nausea / vomiting
- Constipation
- Early satiety
- Malabsorption
- Pain
- Endocrine
- Comorbid conditions
- Social / economic

Table 1. An approach to identify potentially correctable causes of cachexia

This assessment is made easier by the routine use of simple patient-completed questionnaires. Examples of such scales include the Edmonton Symptom Assessment Scale,²⁴ the EORTC quality of life questionnaire (QLQ C-30) and its associated disease-specific modules,²⁵ and the Edmonton Functional Assessment Tool.²⁶

Potentially correctable problems	Possible approaches
Psychological factors: Anxiety	Anxiolytics
Depression	Antidepressants and counselling
Family distress	Social assistance
Spiritual distress	Counselling
Eating problems: Appetite	Referral to a nutrition clinic or a dietician
Disturbed taste or smell	Zinc supplementation, multivitamins
Oral: Dentures, mouth sores	Topical anesthetic
Thrush	Antifungal medication
Dry mouth	Artificial saliva preparations
Stomach: Early satiety	Gastric stimulants
Nausea and vomiting	Related to cause
Bowel: Obstruction	Related to cause
Constipation	Laxatives
Malabsorption: Pancreas	Pancreatic enzymes
Fatigue: Inability to sleep	Anxiolytics, Exercise protocol, Sleep protocol
Pain	Appropriate analgesics
Metabolic: Diabetes	As indicated
Adrenal insufficiency	Steroid replacement
Hypogonadism	Testosterone
Thyroid insufficiency	Thyroid replacement

Management

Slide 8



Management

- Treat comorbid conditions
- Educate, support
- Favorite foods / nutritional supplements / counseling
- Treat reversible causes (e.g., early satiety, mucositis)

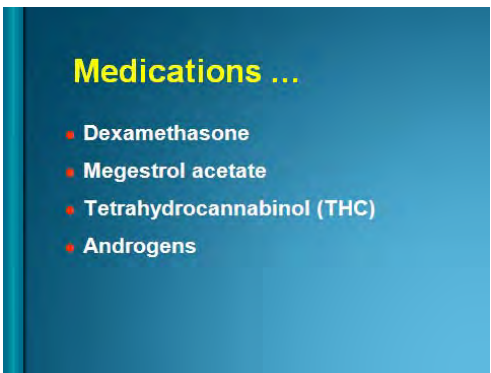
Enteral or parenteral feeding of Veterans in primary catabolic states, e.g., cancer, cardiac-cachexia, either enterally or parenterally, does not appear to reverse or slow anorexia/weight loss syndrome or improve appetite. In 1989, the American College of Physicians addressed the role of total parenteral nutrition in patients with advanced cancer receiving chemotherapy and radiation with the following statement:⁹

“The routine use of parenteral nutritional for patients undergoing chemotherapy should be strongly discouraged.”

Similarly, dietary counseling alone does not improve outcomes.²⁷ Therefore, attempts at increasing caloric intake do not reverse the cancer anorexia/weight loss syndrome.

Medications

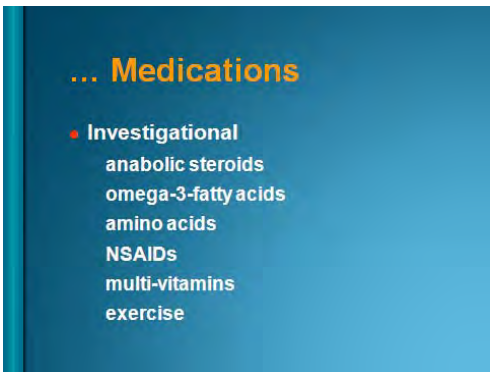
Slide 9



Medications ...

- Dexamethasone
- Megestrol acetate
- Tetrahydrocannabinol (THC)
- Androgens

Slide 10



... Medications

- Investigational
 - anabolic steroids
 - omega-3-fatty acids
 - amino acids
 - NSAIDs
 - multi-vitamins
 - exercise

Treat reversible causes (see **Table 1**) such as anxiety-depression, oral thrush, constipation, poorly controlled pain and early satiety each of which, if present, can influence appetite, motivation, and mobility.

Corticosteroids

The relative efficacy of various corticosteroids is thought to be equivalent. Dexamethasone is often selected because of its absence of mineralocorticoid effects. It has been demonstrated to improve appetite on a short-term basis in those with advanced disease.^{28,29}

A common dosing regimen is the following:

- Dexamethasone 2-8 mg PO q AM

While corticosteroids increase appetite, they are catabolic and reduce muscle mass and function. Appetite stimulation is usually transient, and ceases to be helpful after 3-4 weeks. Moreover, fluorinated corticosteroids, e.g., dexamethasone, are particularly prone to cause muscle breakdown.

Although progestational agents increase appetite in 35-60% of patients, less than 10% actually gain weight and the weight gain is primarily fat and fluid retention. Megestrol acetate is the best studied progestational agent.³⁰ The evidence to support improved appetite and weight gain is weak and limited time trials should be used to assess effect of the medication in any given patient – if a patient is not responding at maximal tolerated doses at ~2-4 weeks it should be stopped.

Consider the following:

- Megestrol acetate 400 mg/day; if appetite has not improved within approximately two weeks, escalate to 600–800 mg/day.

The length of response to megestrol acetate is longer than with corticosteroids. A study in the elderly suggests that megestrol also has catabolic effects on muscle.³¹ Adrenal suppression may also occur as with any agent with glucocorticoid effects.

The mode of action of corticosteroids and progestational agents is not fully established. They both reduce the production of inflammatory cytokines. Whether direct positive efforts on the hypothalamic feeding centers occur is not certain.

Both megestrol acetate and dexamethasone are relatively well tolerated overall. There is a slight risk of thromboembolic episodes with megestrol acetate. This risk is higher in Veterans receiving concomitant chemotherapy. A history of thrombophlebitis is a relative contraindication for prescribing megestrol acetate or another progestational agent.

In contrast, dexamethasone puts Veterans at risk for myopathy, cushingoid body habitus, and gastric bleeding.²⁷ These side-effect profiles play some role in determining which agent might be better for a specific Veteran.

In general, Veterans with a life expectancy of a few months or more may do better with megestrol acetate. Those with a life expectancy of only a few weeks, or those with a history of thrombophlebitis, may be able to get by with dexamethasone, as they are less likely to suffer side effects from corticosteroids in the short term.

Androgens

Fluoxymesterone can increase appetite, although not to the level achieved with megestrol.³² More recent reports show that oxandrolone, an androgenic steroid said to be more anabolic with less androgenic properties will boost appetite, lean body mass and function.^{33,34,35} In hypogonadal Veterans, consider testosterone replacement. In Veterans with prostate cancer this medication is contraindicated and in those with prostate hypertrophy should be used with caution.

Nutritional supplements

Amino acids

Protein intake should be assured and amino acid mixtures, readily available in the form of whey protein, should be offered to weight losing Veterans. A combination of glutamine, arginine, and β hydroxyl methyl butyrate (the latter a metabolite of leucine) has been studied in small controlled trials in both AIDS and cancer populations.^{36,37} Evidence of weight gain and increase in lean body mass was noted.

Multivitamins

The geriatric literature supports the routine use of multivitamin support for institutionalized patients and malnourished cancer patients are at risk for developing unrecognized deficiencies.^{38,39} There have not been clinical trials of multivitamins in patients in palliative care.

Dietary advice

Through simple, easily understood counseling, Veterans and families can improve the quality and quantity of eating, and take satisfaction in their role as partners in combating wasting. Suggestions to assist Veterans or family members involved in food preparation follow are included in the **Appendix** of this section. This general advice can be offered by busy clinicians. Ideally, a dietitian who can tailor a Veteran-specific program and follow up on suggestions should be involved in the care of our Veterans.

Summary

Slide 11



The cancer anorexia/weight loss syndrome remains challenging. Although some aspects of its pathophysiology have recently been clarified, there remains no treatment that improves all aspects of this syndrome. Today, progestational agents and corticosteroids offer the best opportunities for improving appetite. As our understanding of this entity advances, it is hoped that other, more effective interventions will emerge.

Key take-home points

1. Chronic inflammation plays a pathophysiologic role in cachexia.
2. Thorough evaluation of secondary causes of anorexia/cachexia is critical.
3. Calories alone cannot reverse cachexia.
4. Progestational agents and steroids stimulate appetite.

Appendix: Dietary advice

This is an example of a handout that can be used for Veterans and their families.

Taste and taste changes

Taste changes decrease appetite and the enjoyment of food. A bitter, metallic or sour taste in the mouth is quite common, as are aversions to certain foods. Many foods normally enjoyed are no longer appreciated and the desire to eat diminishes. Sometimes food seems to have no taste which further leads to poor food intake.

People with a change in appetite are particularly sensitive to the way in which food is prepared and offered. Previously tasty food may taste bland or overly bitter. Suggestions which may help:

1. Experiment with various spices and flavoring. It is common for a person's preferences to change during illness. Try using basil, oregano, rosemary, tarragon or mint with meat, fish, chicken. Garlic and onions may or may not help.
2. Try flavoring foods with lemon, orange or various other fruit juices.
3. Use sugar in your cooking as this can help to eliminate metallic or salty tastes.
4. Add sauces, gravies or broth to food that tends to be dry. Try fruit based sauces using peaches, pears, oranges, plums or pineapple.
5. Marinate meat, chicken or fish in lemon juice, soy sauce, vinaigrettes or pickle juice or a combination of marinades.
6. If you develop a dislike for meat, try alternative high protein foods such as eggs, cottage cheese and fruit plate, cheese, legumes, vegetable soup, chili, and casseroles.
7. If milk products taste different, try adding chocolate or strawberry syrup to milk, custard, pudding or ice cream or add a little fruit and make a milkshake.
8. If the taste of water bothers you, try adding a slice of orange or lemon or mix with fruit juice or fruit punch.
9. If the taste of food is too overwhelming try serving foods cold. The hotter the food the stronger the taste.
10. If the smell of drinks bothers you, use a straw. Try cold beverages rather than hot.
11. Try water, including sparkling water, Ginger Ale, Sprite, 7-UP, or tea to take away a strange taste.
12. Try sucking on a lemon drop or lifesavers. Try to freshen and clean your mouth before and after eating.
13. Cleanse your mouth with soda water, tea or ginger ale. Rinse with a mixture of baking soda and water.

Temperature

14. Foods that are normally enjoyed when they are warm should be presented when they are warm. However, if appetite for warm food is lost, in part because of food odors, try a cold plate such as cold cheeses, chicken, salmon or egg salad, various sandwiches, yogurt and fruit, pudding, or a homemade milkshake.

Presentation

15. Try and eat food in an atmosphere free of other food smells.
16. Serve smaller portions of food. Appetite can be lost when presented with an overwhelming amount of food on a plate; one can always have a second helping.

Atmosphere

17. Mealtime is a social occasion. This should not change; it is important to continue to eat with family and friends. Veterans should not feel badly if they eat smaller amounts than others. For their part, family and friends should avoid forcing loved ones to eat; this will not help and may indeed cause problems with abdominal distress and nausea.
18. Eat in a calm, relaxed atmosphere.
19. To relax, turn on favorite music.
20. If you are in the custom of consuming alcohol, before or during your meal, try a little wine, or beer to help stimulate your appetite.

Meal preparation

21. The Veteran who is making meals should prepare some meals in advance of treatment and freeze them. Alternatively one of the many varieties of prepared meals that are available in the grocery stores can be tried.
22. Before treatments begin, stock your cupboard or freezer with foods that are particularly enjoyed.
23. Try protein rich foods such as peanut butter, various nuts, cheese, eggs, canned tuna, as well as dried and canned fruit and puddings.
24. If meal preparation is a problem, organizations such as 'Meals on Wheels' will make meals to be delivered to the home. They are active in many communities.
25. Eat a sandwich and a bowl of soup with a glass of milk or juice. This is a quick and nutritious meal.
26. Remember that a small container of yogurt with a piece of bread or small muffin contains almost the same amount of calories as a shake.

How many meals?

Often, because of delayed stomach emptying, the Veteran may be hungry but rapidly lose appetite after a few bites. If this common problem is present:

27. Eat small frequent meals 5 – 6 times through the day. Don't force eating, particularly if the Veteran is nauseated.
28. For a small meal, a nutrient-dense snack will help meet nutritional requirements, examples are a small container of yogurt with a small muffin, or an ounce (30 grams) of cheese on one piece of bread.
29. Drink beverages or soup after your meals as liquids tend to fill a person up.
30. Make breakfast the largest meal. Appetite tends to decrease as the day progresses. Try to consume more protein rich foods in the morning. For example, if an egg is usually eaten try adding another egg or consider adding a piece of cheese or make a cheese omelet.
31. Take time eating, and pause occasionally during the meal to avoid feeling full too quickly.

Snacks for appetite loss

32. Snacks using milk products are great choices for protein and energy. Choose a variety of these foods each day such as cheese and crackers, toast or bagel with cheese or cream cheese, cheese and various fruits, yogurt, frozen yogurt, milkshakes, chocolate milk, ice cream, sour cream, or yogurt vegetable dips.
33. Grains and carbohydrates are good for energy; these include bread, toast with peanut butter or cheese, sandwiches, rolls, muffins, bagels, various crackers, pizza, cookies or cakes made with nuts and fruits, cereals, granola.
34. Protein foods (meat and alternatives) such as nuts, hummus, milk products, egg dishes, egg salad, smoked salmon or other fish, tuna salad, chicken salad.
35. Fruit choices provide a source of quick energy, they includes fruit juices, fruit smoothies, dried fruits such as apricot, apples, pineapple, mango, raisins and mix with various nuts and seeds to create your own trail mix, canned or fresh fruit.

Adapted from The Dietary Guide

Swinton N and MacDonald N McGill University 2004

Part 2: Fatigue

Clinical case

L.M. is an 85-year-old female Veteran who served as a Navy WAVE during WWII with a long history of chronic obstructive pulmonary disease and newly diagnosed lung cancer. She comes in today with the following complaint: “Doctor, I can’t understand it. I’m tired all the time. I don’t have the energy to do any of my usual activities. It’s so frustrating to me. Can’t something be done about this?”

Four months ago she developed hemoptysis and sought evaluation. Chest x-ray demonstrated a large right lower lobe lung mass. Computed tomography (CT) scan of the chest revealed a 6 cm right lower lobe lung mass with bulky mediastinal adenopathy. Fine needle aspiration of the lung mass confirmed a diagnosis of non-small cell lung cancer. The patient declined further evaluation or treatment because she, overall, felt well. She returns today for follow-up. Her only complaint is fatigue.

Introduction

Slide 12



Fatigue is a *persistent sense of tiredness, which may be secondary to an illness or its treatment and interferes with usual functioning*. It is unrelieved by rest and may affect both physical and mental capacity.⁴⁰ Fatigue is present in multiple diseases including HIV/AIDS, end stage cardiac disease and end stage pulmonary disease.⁴¹ From a patient perspective, progressive fatigue is feared, not only as a symptom, but also because it may be a sign of progressive disease.

Fatigue is one of the most common symptoms in end-stage illness. Its prevalence is high, with estimates ranging from 80% to 96%.^{42,43,44,45} It is also the symptom with the greatest impact on everyday life.⁴⁶

Pathophysiology

Slide 13

Pathophysiology

- Multifactorial
- Abnormal energy metabolism
- Increased cytokine production
- Contributing factors
 - depression
 - sleep disorders
 - neuromuscular dysfunction

Fatigue is a result of both physiologic and psychosocial factors. Proposed mechanisms include abnormalities in energy metabolism related to increased need, decreased substrate, or the production of abnormal substances that impair metabolism or normal function of muscle. An alternate proposed mechanism is the increased production of cytokines; particularly interleukin-6.^{47,48} Depression, sleep disorders, and neuromuscular dysfunction are all potential contributors to the development of fatigue.

Assessment

Slide 14

Assessment ...

- Subjective report
- Screen with 0-10 rating scale
 - 4-6 = moderate fatigue
 - 7-10 = severe fatigue
- Fatigue history

Mock V, Atkinson, et al. NCCN, 2003.

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... Assessment

History / physical exam

- Disease status
- Current medications
- Associated symptoms
- Malnutrition / deconditioning
- Comorbidities

Fatigue is a subjective experience and, like the assessment of pain, is best evaluated by patient report. Although many of the scales for fatigue were developed in a cancer population, a recent review advocated using the Edmonton Symptom Assessment Scale

for fatigue which has been validated in non-cancer populations.^{24,45} Consider the following protocol:

1. Ask the Veteran to rate the severity of fatigue on a 0-10 scale, with 0 being ‘no fatigue’ and 10 ‘the worst fatigue imaginable.’ If fatigue is moderate (4-6, on a 0-10 scale) or worse, initiate a thorough history and physical examination.
2. An in-depth assessment of fatigue includes its onset, pattern, duration, and change over time, associated or alleviating factors, and interference with function.
3. Evaluate the Veteran for the presence of treatable, contributing factors, e.g., pain, depression, insomnia, anemia, malnutrition, and deconditioning; and comorbidities, e.g., infection, cardiac, pulmonary, renal, hepatic, neurologic, or endocrine dysfunction.⁴⁹ (see **Table 1**)

Table 1. Potential predisposing etiologies of fatigue

Psychosocial factors	Anxiety disorders Depressive disorders Substance use
Medical illnesses	Anemia Infection Pulmonary disorders Hepatic failure Heart failure Renal failure Malnutrition Neuromuscular disease Dehydration or electrolyte imbalance Endocrine dysfunction Malignancies
Alterations in activity level	Deconditioning
Sleep disorders	
Pain	
Medications	Use of centrally acting medications Opioids Antiemetics Hypnotics Anxiolytics Antihistamines

Management

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Management ...

Treatable etiologies

- Anemia
- Depression
- Pain
- Hypothyroidism
- Hypogonadism

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... Management

Non-pharmacologic therapies...

- Educate – patterns of fatigue
- Clarify role of underlying illness, treatment
- Optimize fluid, electrolyte intake, nutrition

Winningham ML. Cancer, 2001.

General management approaches to fatigue include:

- treatment of reversible causes and contributing factors;
- review of medications and discontinuation of centrally active agents;
- correction of sleep disorders or metabolic abnormalities;
- treatment of depression, if present; and
- treatment of pain, if present, as it is frequently associated with fatigue.

Some specific etiologies of fatigue are discussed below.

Anemia

Anemia is a common cause of fatigue and occurs in about half of all cancer patients undergoing treatment. It has also been shown to be a specific cause of fatigue in patients in palliative care settings.⁵⁰ Multiple, randomized, controlled trials have demonstrated clinically significant improvement in overall quality of life in association with an increase in hemoglobin.^{51,52,53,54} Increases in quality of life are greatest when the hemoglobin is in the range of 11-13 g/dl.⁵⁴

In patients with cancer, erythropoietin alfa administered to prevent significant anemia can sustain quality of life, energy level, ability to perform daily activities and prevent transfusions.⁵⁵ Darbepoetin is a newer erythroid stimulator. Dosing options include:

- Erythropoietin alpha 40,000 IU SC once q week.
- Darbepoetin alfa 200 mcg SC, once q 2 weeks.^{56,57} Weekly dosing results in more rapid improvements in quality of life than q 2 week therapy.⁵⁸

In patients with chronic medical illnesses, anemia and fatigue, an attempt to transfuse may be a reasonable option to try to improve fatigue. In Veterans with congestive heart failure, transfusions should be monitored carefully for the possibility of volume overload.

Depression

Depression often contributes to fatigue. Its treatment with either immediate acting psychostimulants (see EPEC for Veterans Module 5: Psychological Symptoms) or a Selective Serotonin Reuptake Inhibitor (SSRI) is recommended. Even when Veterans do not meet all of the criteria for clinical depression, some practitioners advocate antidepressant therapy for the symptom of fatigue.

Pain

Pain and its treatment with opioids can contribute to fatigue. Pain should be treated (see EPEC for Veterans Module 4: Pain Management). When opioids are thought to be contributing to sedation and fatigue, a clinician can either try to taper the dose or rotate to a different opioid. If this is not effective, treatment with immediate-acting psychostimulants (see next section) is recommended.

Hypothyroidism

Hypothyroidism is a known contributor to fatigue and other systemic symptoms. It is unlikely to be the Veterans primary diagnosis but may be a comorbidity. In Veterans with hypothyroidism, thyroid function tests should be monitored and thyroid hormone replacement prescribed if necessary.

Hypogonadism

In patients with advanced cancers, hypogonadism has been shown to contribute to fatigue and other symptoms.⁵⁹ There are limited data suggesting that testosterone replacement in men with testosterone levels of <200 ng/dL may help combat fatigue.⁶⁰

Non-pharmacologic therapies

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Non-pharmacologic therapies

- Promote physical activity
- Include other disciplines
- Energy conservation strategies

Winingham ML. Cancer, 2001.

A variety of non-pharmacologic therapies have been evaluated and utilized for the treatment of fatigue. Two specific ones include exercise and energy conservation.

Excessive rest may contribute to cancer-related fatigue rather than lessening it.

Structured exercise programs have been shown to improve fatigue as well as the patient's emotional and overall sense of wellbeing.⁶¹ The beneficial effects of exercise have been observed in patients undergoing cancer treatment as well as in survivors who have already completed their therapy.^{62,63,64,65,66,67,68} Whether the prescribed exercise is walking or bicycling or some combination, the outcomes are equivalent.^{64,67,69} A simple, practical prescription for exercise might include walking 20 minutes a day, 10 minutes out and 10 minutes back.⁷⁰ Additional benefits of exercise include potential improvements in appetite, weight, strength, self-image, and bowel habits.

If fatigue is severe, **energy conservation strategies** are often recommended. Such strategies include setting priorities to perform the tasks that are most important to the patient first, scheduling activities at times of peak energy, postponing nonessential activities, structuring a daily routine, and attending to one activity at a time. Consultation with an occupational therapist may be valuable for identifying the best strategies for an individual patient.⁶⁹

Pharmacologic therapies

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Pharmacologic management

- Methylphenidate
- Modafinil
- Dexamethasone, prednisone

Bruera E. Cancer Treatment Rep, 1985; Bruera E, et al. JCO, 2004; Rammohan KW, et al. J Neurol Neurosurg Psychiatry, 2002.

Pharmacologic therapies for fatigue include psychostimulants and steroids.

Methylphenidate can improve cancer and AIDS-related fatigue. It is also used for opioid-induced sedation and as a short-term treatment for depression. A standard dosing regimen is:

- Methylphenidate 5-30 mg PO daily.

Response rates up to 100% have been noted.^{67,71} Start with 2.5 to 5 mg every morning and noon. The recommendation for this fixed dose schedule is largely anecdotal, arising from concerns that treatment late in the day will cause insomnia. A recent preliminary report of patient-controlled methylphenidate for the management of cancer-related fatigue raises questions about this assumption.⁶⁷ Significant improvement in fatigue, functional and physical wellbeing was reported by patients using methylphenidate while taking opioids. All of the patients took afternoon and evening doses and 93% took three or more doses daily. Adverse effects include anorexia, insomnia, anxiety, confusion, tremor, and tachycardia. The beneficial effects of methylphenidate may decrease over time, and dose escalation may be needed to maintain benefit.

Modafinil is a CNS stimulant approved for the treatment of narcolepsy in doses of 200 mg/day. This agent has been shown to improve fatigue in patients with multiple sclerosis.⁷² A standard dosing regimen is the following:

- Modafinil, start with 100 mg in the morning and at noon. Titrate to effect, up to the maximum does of 400 mg/day.

Corticosteroids may improve fatigue for patients with advanced disease and fatigue.^{73,74} Dosing options include:

- Dexamethasone 4 mg PO q AM.
- Prednisone 20 mg PO q AM.⁷⁵

Summary

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Summary

Use comprehensive assessment and pathophysiology-based therapy to treat the cause and improve end-of-life care

Despite the high prevalence and altered quality of life associated with fatigue, there is little knowledge about pathogenesis or management. Treatment requires careful assessment of potentially reversible factors and utilization of both pharmacologic and non-pharmacologic interventions. Provide all patients with information about treatment-

related fatigue and recommendations about the effect of exercise on fatigue. Anemia is an important, reversible cause of fatigue, treat it preventively. Fatigue is often not readily reversible. A trial of a pharmacologic stimulant, such as methylphenidate, is an option for treatment.

Key take-home points

1. Fatigue is the symptom with the greatest impact on every day life.
2. Anemia is the most common cause of reversible fatigue. Increases in quality of life appear greatest when the hemoglobin is in the range of 11-13 g/dl.
3. Treatment of depression, pain hypothyroidism, hypogonadism and other modifiable conditions may improve subjective fatigue in select patients.
4. Moderate exercise often helps with subjective fatigue. This is sometimes counterintuitive to Veterans.
5. A trial of therapy with psycho-stimulants and/or corticosteroids is warranted when fatigue is a distressing symptom, there are no other modifiable causes for fatigue and the Veteran has no contraindication to the medication.

Part 3: Insomnia

Clinical case

A.P. is a 53-year-old female Veteran who is admitted to a home hospice program with metastatic breast cancer, mild dyspnea, and bone pain. She is able to walk with assistance and enjoys visiting with family and friends and playing with her two small grandchildren. Her hospice nurse reports that she is not sleeping well at night and the family has requested a sleeping medication.

Her sleep problems began in the past two weeks. She has difficulty falling asleep and wakes up at least twice during a typical night, but does not have early morning awakening. She often takes brief naps in the daytime. She is reluctant to take sustained-release oral morphine as prescribed (60 mg twice daily) for fear of addiction and sedation, and uses caffeinated beverages to prevent sedation from the 10 mg immediate release breakthrough doses she does take. Daytime pain control is acceptable (usually a 2 out of 10), but pain flares late at night are common.

Introduction

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Insomnia ...

- **Definition: inadequate or poor quality sleep**
 - difficulty falling asleep
 - difficulty maintaining sleep
 - early morning awakening
 - non-refreshing sleep

Slide 22

... Insomnia

- **Impact: tiredness or fatigue, anergia, poor concentration, or irritability**
- **Up to 63% of cancer patients**
- **Restful sleep can often be restored**

Insomnia is the experience of inadequate or poor quality sleep characterized by one or more of the following: difficulty falling asleep, difficulty maintaining sleep, early

morning awakening, non-refreshing sleep or daytime consequences of inadequate sleep, such as tiredness or fatigue, anergia, poor concentration, or irritability.⁷⁶

Insomnia has a negative impact on quality of life. Poor sleep has effects on fatigue, energy, and mental and physical stamina. Insomnia interferes with a patient's ability to get relief from the management of other symptoms. Additionally, inadequate sleep has been associated with increases in pain and perceived discomfort, diminished coping capacity, and reductions in measures of global quality of life.^{77,78,79,80}

The goal of insomnia management in the Veteran with advanced disease is to restore the quality and restfulness of sleep.

Insomnia is a common complaint. Up to 30-40% of adults in the general primary care population report difficulty sleeping at some time over a 12-month period, and 10-15% report chronic problems with insomnia.⁷⁶ The prevalence of insomnia increases with age and is associated with physical illness such as cancer. Studies show prevalence rates as high as 63%.^{81,82} Along with the frequency of insomnia, there is also high use of sedatives among patients in palliative care. In one study of patients on a palliative care unit, 77% were taking sedative-hypnotic medications at the time of admission.⁸³

Pathophysiology

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Pathophysiology

- Multiple possible cause
- Prior sleep disorder
- Uncontrolled symptoms
 - pain, pruritis
 - depression, anxiety
- Medications

Insomnia can be caused by a variety of factors, ranging from disruptions of the neurophysiology of sleep to the consequences of physical or mental disorders to simple interruption of normal sleep habits.

During a typical night of restful sleep, an adult cycles through physiologic stages of sleep multiple times.⁸⁴ These stages progressively deepen until rapid eye movement (REM) sleep is achieved. Many primary sleep disorders, e.g., sleep apnea, restless leg syndrome, and periodic limb movement disorder cause disruptions to the normal sleep architecture and can be detected by observation and polysomnography in a sleep lab.

Physical symptoms common in advanced illnesses, e.g., pain, dyspnea, cough, nausea, or pruritus, whether due to the illness itself or treatment, may interfere with sleep.

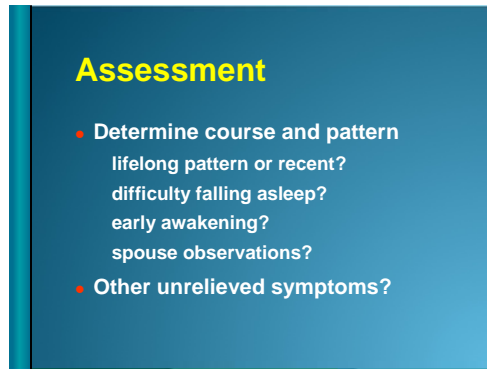
Prescription medications, e.g., psychostimulants, corticosteroids or other substances with stimulating effects, can interfere with sleep. Caffeine, even in modest amounts, can

interfere with sleep. Certain drugs of abuse such as methamphetamine and cocaine can cause insomnia, as can withdrawal from alcohol, benzodiazepines, and opioids.

Nonphysical factors can also lead to disturbed sleep. Depression is commonly associated with or complicated by insomnia. One of the most common signs of a major depressive episode is sleep disturbance characterized by early morning awakening.⁸⁵ Worry, tension, or anxiety can cause insomnia by interfering with the ability to relax and fall asleep. Anxiety disorders, such as PTSD and generalized anxiety disorders are not uncommon among Veterans and can lead to chronic insomnia. Patients who are hospitalized may suffer from sleep disturbance as a consequence of being in an unfamiliar environment at night, with unfamiliar surroundings, or intrusive ambient noises.

Assessment

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Assessment

- Determine course and pattern
 - lifelong pattern or recent?
 - difficulty falling asleep?
 - early awakening?
 - spouse observations?
- Other unrelieved symptoms?

While diagnostic instruments for insomnia⁸⁶ exist, especially for specific types or causes of insomnia, the best approach to diagnosing insomnia is a careful history.

Focus on determining the course and pattern of the sleep problem. If the insomnia is of fairly recent onset, focus on concurrent nighttime symptoms, such as pain, dyspnea, recent medication changes, or substance use (especially caffeine and alcohol), stress related to recent life events, or any necessity of sleeping away from home. More chronic sleep problems may indicate an underlying problem such as a primary sleep disorder, anxiety disorder, or depression.

Definitive assessment of primary sleep disorders is best performed in a sleep laboratory using polysomnography and overnight monitoring.⁷⁶ Specific sleep disorders have some specific findings: For example, patients with *restless leg syndrome* often complain of ‘crawling feelings’ in the lower extremities as they try to fall asleep.⁸⁷ Bed partners of those with *periodic limb movement disorder* often report jerky movements or kicks while their partners sleep. In patients with sleep apnea, typical symptoms include loud snoring punctuated by apneic spells.⁸⁸

The high degree of variability among individuals in the ‘normal’ amount of sleep needed to feel rested makes judging insomnia based on hours spent sleeping difficult. As adults age, total sleep time and percentage of time spent in REM sleep naturally decrease.⁸⁹ As

long as sleep is of sufficient quality and duration to be satisfying and restful, the number of hours spent asleep or frequency of sleep periods required is less important.

As illnesses progress and death approaches, wakefulness is commonly punctuated by periods of sleep, and vice versa. Day-night reversal is can occur. Any disruption of the sleep-wake cycle in a patient with advanced illness should prompt an assessment for the presence of delirium (see EPEC for Veterans, Module 5: Psychological Symptoms).

Management

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Management ...

- **Sleep hygiene**
 - regular sleep schedule, avoid staying in bed
 - avoid caffeine / nicotine, assess alcohol intake
 - cognitive / physical stimulation
 - avoid overstimulation
 - control pain during the night

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... Management

- **Behavioral management**
 - relaxation, imagery
 - sleep restriction
 - stimulus control
 - cognitive therapy

The overall goals of management are restoration of adequate restful and satisfying sleep and optimization of perceived quality of life. Once complicating disorders, e.g., anxiety, depression, symptoms (pain, cough, etc.) and other factors (caffeine overuse, situational factors, etc.) have been ruled out or treated appropriately, three general approaches to managing insomnia remain:

- Improving sleep hygiene.
- Behavioral interventions to improve sleep quality.
- Pharmacologic treatments to promote sleep.

Sleep hygiene

The simplest and best understood of these approaches is promoting the practice of good sleep hygiene.⁹⁰ Though these pointers are fairly intuitive and may be limited in how much benefit they yield for Veterans with complicated insomnia problems, they are often

neglected and can improve sleep without cost or adverse effects. Veterans should be encouraged to adhere to as much of the following advice about good sleep habits as is practical given their situation and their treatments:

- try to go to sleep and wake up at the same time each day;
- minimize use of caffeine and nicotine (especially late in the day, though use at any time can interfere with sleep);
- avoid alcohol use at night;
- avoid heavy meals late at night (although a light snack at bedtime may help induce sleep);
- avoid excessive fluids before bedtime;
- consider moderate regular exercise, but not just prior to retiring;
- minimize noise, light, and temperature extremes in the bedroom; and
- consider a bedtime ritual, e.g., ‘winding down’ with a warm bath or reading, before attempting to fall asleep .

Behavioral interventions

Behavioral measures, including relaxation techniques, sleep restriction, stimulus control, and cognitive therapy interventions are underutilized and likely to be more effective for chronic insomnia problems than hypnotic medications.⁹¹ Each of these is briefly reviewed below.

Relaxation techniques range from simple maneuvers that can be easily taught and practiced, e.g., simple abdominal breathing, progressive muscle relaxation, to techniques such as hypnosis or biofeedback which are administered by trained professionals. Relaxation tapes, meditation, or contemplative prayer can also be sufficiently relaxing to promote sleep. All relaxation techniques require a commitment to practicing the technique so that the patient can gain enough facility with the technique to use it to their benefit when needed. Relaxation techniques are most helpful in promoting sleep onset.

Sleep restriction is a technique aimed at reducing fragmentation of sleep by improving sleep efficiency, i.e., the percentage of total time spent in bed that one spends asleep.⁹¹ This technique is initiated by limiting the time one spends in bed to the estimated number of hours one spends asleep, e.g., if one estimates sleeping only four hours total of ten hours spent in bed at night, bedtime is adjusted to spend only four hours in bed. The wake time is kept constant and bedtime is adjusted to limit time spent in bed. Although a brief daytime nap may be needed in the first few days of the trial, effort should be made to limit sleep to nighttime as much as possible. The goal is to induce enough sleep deprivation to improve sleep efficiency for the restricted time in bed as close to 100% as possible. Once this is achieved, bedtimes can be moved back (in 30-minute increments

every few days) until a fully restful night of sleep is achieved, as long as high sleep efficiency is maintained.

The theory behind **stimulus control** emerges from a conditioned learning view of insomnia. The goal of this intervention is for the patient to ‘unlearn’ associations between being in bed and doing anything other than sleeping.⁹¹ Veterans are instructed to go to bed only when they feel sleepy, and not to stay in bed making futile attempts to sleep if sleep does not come. After twenty minutes without sleep, patients should get out of bed and not return until feeling sleepy again. Other activities such as reading, eating, or sexual activity, must be undertaken in other parts of the home during a stimulus control intervention. Sleeping is prohibited anywhere other than the bed, and patients must maintain a regular wake up time. For motivated patients, stimulus control can be very helpful in promoting sleep onset and improving sleep hygiene.

Interventions incorporating **cognitive therapy** approaches have also shown potential to relieve insomnia. In a series that included cancer survivors, sleep was improved after a brief series of cognitive intervention sessions aimed at reducing dysfunctional, self-critical, or counterproductive thoughts that can lead to dysphoria, worry, and distress.^{92,93}

Pharmacological management

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Pharmacological management

- Antihistamines
- Benzodiazepines
- Sedating antidepressants
- Careful titration
- Attention to adverse effects
- GABA-receptor agonists

Pharmacologic interventions have an important role in the management of insomnia in patients.⁹⁴ Most prescription hypnotics are indicated for brief periods of use (usually less than 14 days) because the development of tolerance can lead to loss of effectiveness, dependence on medication for sleep onset, and changes in sleep architecture that paradoxically worsen the quality and restfulness of sleep.⁹⁵ Although newer agents may hold promise for prolonged efficacy and tolerability, a medication alone is not the answer for most patients with sleep problems over the long term.⁹⁶

Benzodiazepines are the most commonly used prescription hypnotics, because of their reliable short-term efficacy and favorable safety profile relative to other medication classes, e.g., barbiturates. Use benzodiazepines, e.g., lorazepam (0.5-2 mg PO nightly as needed), temazepam (15-30 mg PO nightly as needed) at the lowest effective dose for short periods of time. Titrate the dose to achieve good sleep without residual sedation the

following day. Longer-acting benzodiazepines, e.g., diazepam, clonazepam are more likely to have carryover sedation.

Antidepressant medications are indicated when sleep disturbance is judged to be a consequence of clinical depression. Sedating antidepressants, while commonly used to promote sleep even in the absence of a clinical depression, are not formally indicated for management of insomnia and are not well studied as off-label treatments for this indication. Tricyclic antidepressants (amitriptyline, desipramine, nortriptyline) are sometimes used as hypnotics. These medications, especially amitriptyline, may have a number of adverse anticholinergic side effects, such as constipation, dry mouth, orthostasis and confusion. Tricyclic antidepressants may be helpful when insomnia is comorbid with neuropathic pain. However, because of their side effects they should generally be avoided in the elderly and very frail. Mirtazapine (7.5-15 mg PO nightly) also has the advantage of promoting appetite as well as sleep onset, and has a milder adverse effect profile than tricyclics.⁹⁷ Trazodone is commonly used for sleep, though orthostasis and priapism are potential adverse effects.^{98,99} Start with 25-50 mg PO nightly and titrate up by 25-50 mg every seven days to effect (400 mg maximum). In Veterans with PTSD or depression, quetiapine (beginning at a dose of 12.5 mg) has been shown to be effective for insomnia.¹⁰⁰

Antihistamines, as contained in common over-the-counter sleep aids are also often used by patients suffering from insomnia. Unless a Veteran has had previous good results with these and no adverse effects, these should generally be avoided. Diphenhydramine is associated with falls and delirium in the elderly^{101,102} and should generally be avoided unless a patient has been on a stable dose without adverse consequences.

Other newer GABA-receptor agonists, e.g., eszopiclone, zaleplon, and zolpidem (5-10 mg PO nightly as needed), may have some modest advantages relative to benzodiazepines (such as less alteration of normal sleep architecture and less risk of amnesia and dependence). Whether such differences translate into clinically relevant advantages for these more expensive medications is unclear.¹⁰³

Summary

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Summary

Use comprehensive assessment and pathophysiology-based therapy to treat the cause and improve end-of-life care

Insomnia is a common problem that complicates and compounds the suffering of patients with advanced illness. Although it is a subjective symptom and requires a clinical diagnosis, the practical rule of thumb - that insomnia results when the quality or restfulness of sleep is disturbed to the extent that it causes consequences - can be helpful in detecting problems of clinical significance. Effective management requires recognition of remediable problems that cause or complicate insomnia. Once other treatable conditions are recognized and adequately managed, management of remaining insomnia should attend to good sleep hygiene. While hypnotic medications have a role, particularly in the short-term management of insomnia, behavioral interventions are underutilized and can be effective in promoting sleep over the long term.

Key take-home points

1. Assessment of insomnia often reveals one or more modifiable issue related sleep hygiene. Counsel Veterans and their families on nonpharmacological ways to improve sleep.
2. Caregivers may misinterpret delirium as insomnia.
3. Trazodone may be particularly useful in the frail and elderly and for more chronic insomnia.
4. Benzodiazepines frequently manage insomnia effectively short term but tolerance often develops and may contribute to the development of delirium.
5. Quetiapine may be useful in treating PTSD-related nightmares and insomnia.

Part 4: Skin problems

Clinical case

P.L. is a 74-year-old Veteran residing in the community living center (CLC). He has moderate to severe dementia and is bedbound. The Veteran had developed a pressure ulcer before being admitted to the CLC. This caused pain with turning and personal care expressed by grimaces and some calling out.

Examination shows a reddened area with skin breakdown, partial epithelialization and some white tissue in the wound bed covered by a disposable diaper. The dressing is saturated with a serous discharge. When the dressing is removed, the smell is foul.

Introduction

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Skin problems ...

- Acute vs. chronic; likely to heal or not
- Chemotherapy agent extravasation
- Radiation damage
- Decubitus ulcers
- Malignant wounds

Slide 30

... Skin problems

Associated with:

- Pain
- Depression
- Anxiety
- Poorer interpersonal interactions

Basic principles that underlie the management of skin problems include:

- Classification of the skin problem as acute or chronic.
- Determination of whether the skin problem is likely to heal or not.¹⁰⁴

These principles can be applied to a variety of specific situations including pressure (pressure) ulcers, lymphedema/peripheral edema, and malignant wounds.

Other symptoms and conditions are frequently associated with skin problems. The incidence of depression is high.¹⁰⁵ Pain and psychological effects can also accompany skin disorders.

Importantly, the skin is the most visible organ. Changes in appearance may have profound consequences for the person who has them. One of the most common examples is hair loss during some chemotherapies. From a purely medical model, hair loss is a trivial, reversible consequence of some types of chemotherapy. However, for a Veteran receiving chemotherapy, its impact on body image may be profound.

The psychosocial impact of skin disorders is significant. Disfigurement can be distressing and disfiguring skin conditions can lead to psychological, social, and spiritual distress.¹⁰⁶ In addition, it can affect the care provided. Veterans who look or smell bad may receive less care and perceive more distance because their caregivers do not want to be with them or to touch them.

Pathophysiology

The skin is an organ system with highly developed physiology. It is essential in the regulation of homeostasis and immunity. For example, a skin wound permits infectious organisms to bypass some of the essential immunological barrier functions of intact skin.

The skin is also highly innervated. This innervation helps the body sense the environment and avoid injury. However, if the skin is involved in a pathological process, there may be a source of considerable suffering. In fact, many of the pathological processes that involve the skin lead to sensitization of the cutaneous nerves. Though opioid receptors are not present in normal skin, within minutes to hours of inflammation, opioid receptors are present in peripheral sensory nerves.¹⁰⁷

Skin injury and symptoms can be divided into two broad categories: **Acute** and **chronic**.

Acute injuries to skin, such as operations or radiation, are associated with an acute pathophysiological response. Products of inflammation, chemotactic factors, hyperemia, and swelling are all initiated. This leads to increased pain and an increased pain response to ordinarily non-painful stimuli.

In contrast, **chronic injury** and symptoms may not be associated with the same pathophysiological responses. In fact, chemotaxis and increased blood supply may be absent from chronic wounds and symptoms. Pain may or may not be associated with chronic wounds.

Wounds tend to fall into distinct categories, each with its own pathophysiology. Two categories include pressure ulcers and malignant wounds.

Pressure ulcers

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Pressure ulcers

- Pathophysiology
ischemia
- Fat is protective

Pressure ulcers are frequently encountered in those debilitated who are by their illness or by treatment. Intrinsic risk factors for their development are limited mobility, medical conditions that reduce tissue oxygenation, age-related changes in skin, and poor nutrition.^{108,109}

Closure of microarterioles secondary to pressure leads to cutaneous ischemia with pressure points at particular risk for the development of pressure ulcers.¹¹⁰ Examples are heels, sacrum, and elbows. Skin can withstand 30-60 minutes of poor perfusion. Fat normally provides a cushion and more evenly distributes pressure. Therefore, thin and cachectic Veterans lack a fundamental protective mechanism. Other risk factors include shear, friction, and moisture.

Malignant wounds

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Malignant wounds

- Disrupted physiology
- Products of inflammation
- Neovascularization
bleeding
- Necrosis
anaerobic and fungal infections

Malignant wounds are an example of a chronic wound. Malignancies may involve the skin either as a primary site or as metastases.¹¹¹ Malignant cutaneous wounds are most commonly associated with cancer of the breast and lung.¹⁰⁷ A malignant wound is frequently painful because of the local tissue reaction and the products of inflammation. However, due to neovascularization and subsequent necrosis as the tumor outgrows its blood supply, there may be significant bleeding. In addition, necrosis may lead to infection, particularly with anaerobic and fungal species. The most common organisms associated with these lesions are proteus, klebsiella, and pseudomonas. These infections can be painful and can also cause foul odors.

Assessment

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Assessment

- Acute versus chronic
- By wound type

Pressure ulcers

Slide 34

Pressure ulcers

- Assessment
risk factors
- Prevention
skin protection-shear / tear / moisture
pressure reduction and pressure relief

A widely used staging system for pressure ulcers is helpful in determining management.^{108,110} Pressure ulcers progress in a stepwise fashion. If they are caught early and appropriate prevention and treatment are initiated, the ulcer will not progress. Stages include:

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Pressure ulcers: Staging

- Non-blanchable erythema
- Partial-thickness skin loss
- Full-thickness skin loss
- Extensive necrosis exposing muscle or bone

Stage I: The heralding lesion of skin ulceration is non-blanchable erythema.

Stage II: Partial-thickness skin loss involving epidermis, dermis, or both. The ulcer is superficial and looks like an abrasion, shallow crater, or blister.

Stage III: Full-thickness skin loss involving subcutaneous tissue. The ulcer may extend down to, but not through, the underlying fascia. The ulcer looks like a deep crater, with or without undermining of adjacent tissue.

Stage IV: The ulcer is deep enough to include necrosis and damage to underlying muscle, bone, and/or other supporting structures such as the tendon or joint capsule. Undermining of adjacent skin and sinus tracts may also be present.

The treatment approach rests on an assessment of whether the overall goal is to heal the wound or not. For many Veterans with a short prognosis, it is unrealistic to expect the wound to heal. However, for some Veterans, healing is possible.

If the goal is to heal, then debridement and the application of dressings that promote healing are appropriate.

If the wound will not heal, then the primary goals are pain control and comfort. In addition, steps should be taken to prevent worsening of the wound.

Management

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Management

- Acute versus chronic
- By wound type

General approach

The first management principle that underlies the approach to skin symptoms is prevention.^{108,109,111} Some skin symptoms can be prevented. For example, careful attention to planning and technique will prevent chemotherapy extravasation and radiation injuries. Attention to pressure points and adequate skin protection will prevent pressure ulcers. Time spent in prevention will avoid the time, expense, and suffering associated with these preventable skin injuries.

Management will be influenced by whether or not the wound or symptom is likely to resolve and heal. For wounds that will heal, management will focus on relieving associated symptoms and promoting healing. For situations that will not resolve, management will focus only on relieving associated symptoms.

Dressings

There are five general types of dressings. They are distinguished by the wear time and whether they donate or remove fluid in order to maintain an ideal moist interactive wound healing environment. A dry wound needs to have moisture given to it through a hypotonic gel (donates water). If there is a lot of wet exudate, a hypertonic gel or foam should be used to remove water from the wound.

Foams: Most absorptive. Used under a covering dressing.

Alginates (seaweed): Works to desiccate an overly wet wound. Prevents maceration of surrounding skin from excess fluid. Hemostatic may reduce risk of infection.

Hydrogels: Used for wounds with larger volumes of exudates.

Hydrocolloids: Self-adhesive. Promote autolysis, angiogenesis, and granulation. Remain in place for 5-7 days. Often used to 'seal' a wound that is otherwise clean in order to promote healing. It can also be used to seal an underlying dressing in order to maintain a moist environment in which the wound can heal. However, it is important not to use an occlusive dressing if there is a substantial risk of infection.

Cotton gauze: Used to cover the primary dressing. Rarely the appropriate dressing for a significant skin wound.

Debridement

For necrotic tissue, debridement is required. The goal is to debride to clean margins. Before debriding assess the viability and perfusion of surrounding tissues. Delaying debridement and considering a maneuver such as hyperbaric oxygen therapy to enhance vascularization may be appropriate.¹¹²

Consideration of nonsurgical debridement may be an option: debridement gels are available with or without enzymes, and encourage autolytic or enzymatic debridement. These are appropriate for wounds when surgery is either not indicated or incomplete. Occlusive dressings with hydrocolloid dressings promote autolysis by maintaining a moist environment for autolytic enzymes to work.

Cleansers may be used to clear away slough, exudate, and debris. Although normal saline was once the preferred cleanser, a recent Cochrane review suggests that saline is no better than plain tap water, and a few of the studies reviewed suggested tap water was superior.¹¹³

Pressure used to clean the wound should never exceed 15 pounds per square inch as it damages new epithelial cells. A 60 cc syringe filled with normal saline connected to a 19-20 gauge angiocath can be used.

Cleansers that are cytotoxic to granulation tissue should not be used to clean an open wound. This includes cleansers designed to clean normal skin, e.g., hydrogen peroxide, povidone.

Mechanical debridement can be utilized using saline wet to dry dressings, although it is not recommended. This is accomplished by placing gauze wetted with saline on the wound. After the gauze has dried, it is peeled off. Not surprisingly, this is usually painful. In addition, it does not promote healing because it also peels off the new epithelial cells as part of healthy granulation tissue. In other words, saline wet-to-dry dressings should be used rarely, if at all.

Pain control

Pain control is a critical component of debridement and should be managed aggressively. Appropriate wound analgesia is likely to include a topical anesthetic and/or infiltration of surrounding tissues with a local anesthetic. For example, lidocaine gel or spray can be applied topically, as well as infused locally. If lidocaine is infused, epinephrine can be used to decrease bleeding and limit diffusion away from the wound. Liquid morphine can be mixed (in a 1:1 concentration, 1 mg morphine/1 ml gel) with gel (or other aqueous based cream or gel) for local pain control.^{114,115} Benzocaine is contraindicated because it is an ester and a topical sensitizer for hypersensitivity reactions.

EMLA (lidocaine/prilocaine) cream may be used, although it is an off-label indication in the United States. It takes an hour to start working and an application provides local anesthesia for 4 hours. It can be placed under a dressing. There is no evidence that it retards the healing process.

Specific skin conditions in palliative care

Infection

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Infection

- Debridement
 - surgical
 - enzymes and gels
 - mechanical
 - pain control
- Cleansing

Purulent exudates or erythema and infection of surrounding tissues should be treated. If there is superficial infection, topical treatment with metronidazole or silver sulfadiazine may be sufficient. However, if there is evidence of deeper tissue infection, systemic antibiotics should be used. If the wound is non-healing, topical agents such as povidone that are cytotoxic to bacteria can be used. Povidone will help keep the wound clean although some Veterans find it irritating and painful. Because of its cytotoxic effect on granulation tissue, povidone should not be used for wounds that are expected to heal.

In addition to managing infection, there are other approaches to the management of odors. Odor absorbers can be used in the room. Cat litter or activated charcoal can be placed on a tray underneath the bed. In addition, a secondary covering dressing that contains charcoal or a disposable diaper can be used to cover a particularly odorous wound. Additional approaches include putting a candle in the room in an attempt to combust the chemicals causing the odor. One can also introduce a competing odor. The simplest are bowls of vinegar, vanilla, or coffee. Fragrances and perfumes are often poorly tolerated by Veterans and should be avoided. Finally, uncontrolled studies using topical metronidazole in the wound bed have shown effectiveness in reducing odor, drainage and pain.¹¹⁶

Pressure ulcers

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Pressure ulcers

- **Goals: healing vs non-healing**
- **Healing**
 - debridement
 - dressings that promote healing
- **Non-healing**
 - pain control, comfort
 - prevent worsening

Prevention of ulcers is essential.^{108,110} Skin should be protected from friction, moisture, and shear. High-risk areas should have either thin film or hydrocolloid dressings applied. Skin also needs to be protected from pressure. Veterans need either to be turned regularly or a pressure-reducing surface should be used.

There are three groups of support surfaces that have demonstrated efficacy:

Air or water mattress overlays are ideal for most Veterans to prevent decubiti.

Examples of Veterans who would benefit from their use include any Veteran who is bedbound, has limited mobility, or is cachectic.

Low-air-loss beds are usually used for Veterans who are at high-risk, or who have developed ulcers where the goal is to prevent worsening and/or promote healing.

Air-fluidized beds are reserved for Veterans who need maximum pressure reduction and pressure relief. However, Veterans frequently describe them as overly confining (even ‘coffin-like’) and they are very expensive.

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Pressure ulcers dressing

- Moist, interactive environment
- Control infection
- 6 types of dressing
 - foams
 - hydrogels
 - thin films
 - alginates
 - hydrocolloids
 - cotton gauze

Simple foam pads are often ineffective. If they are used, they may need to be layered. If a hand is placed under the pads, there should be at least one inch of uncompressed foam between the hand and the Veteran for them to be effective.

Avoid use of round cushions commonly called “donuts.” They occlude blood flow and do not prevent ulcers.

In addition to support surfaces in bed, Veterans need to be assessed professionally for the use of special pressure reducing cushions for wheelchairs.

Malignant wounds

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Malignant wounds: management

- Healing vs non-healing
- Infections
- Odors
- Pain
- Exudate
- Bleeding

The management principles and dressing choices are the same as for pressure ulcers. However, malignant wounds bring up a few additional areas that deserve comment.

Exudates from malignant wounds can be substantial and sometimes associated with bleeding, thus absorbent foam and alginates should be used to minimize the frequency of dressing changes, maximize absorption, and help with hemostasis. The overall goal is to prevent the exudate from macerating other normal tissues and soiling clothing.

In some cases with the bleeding malignant wound, a mesh synthetic polymer with a nonstick, nonabsorbent dressing can be used. This should be cleaned off once a week with an absorbent dressing placed over it. As mentioned earlier, alginates are hemostatic and can be useful. Topical thromboplastin can also be used; a low dose, i.e., 100 units/ml is as good as higher doses and is less expensive. Antifibrinolytics, such as topical aminocaproic acid (amicar), are sometimes used, although their role is not clear since

fibrinolysis is not a major mechanism in wound bleeding. Silver nitrate or cautery can be used for frank bleeding.

Summary

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Basic principles that underlie the management of skin problems include: first, classification of the skin problem as acute or chronic; and second, determination of whether the skin problem is likely to heal or not. These basic principles can be applied to a variety of specific situations: pressure ulcers, lymphedema/peripheral edema, radiation damage, malignant wounds, and chemotherapy extravasation. As in other symptoms, medical providers can use comprehensive assessment and pathophysiology-based therapy to treat the cause and improve skin problems that will provide enhanced care to our Veterans in need.

Key take-home points

1. Prevention of pressure ulcers requires skin protection to vulnerable areas and pressure reduction and relief.
2. Multiple dressings are used, depending on whether the skin wound is dry or wet. Some of these dressings provide chemical debridement.
3. Pain control for pressure ulcers, especially during debridement, is critical.
4. Malignant and infected wound may have significant odor – introducing competing odors into the room may help. Topical metronidazole gel may help as well.

References

- ¹ MacDonald N, Eason AM, Mazurak VC, Dunn GP, Baracos VE. Understanding and managing cancer cachexia. *J Am Coll Surg*. 2003; 197(1): 143-161.
- ² Cohn SH, Gartenhaus W, Sawitsky A, et al. Compartmental body composition of cancer patients by measurement of total body nitrogen, potassium, and water. *Metabolism*. 1981; 30(3): 222-229.
- ³ Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med*. 1980; 69(4): 491-497.
- ⁴ Staal-van den Brekel AJ, Shols AM, ten Velde GPM, Buurman WA, Wouters EF. Analysis of the energy balance in lung cancer patients. *Cancer Res*. 1994; 54(24): 6430-6433.
- ⁵ Stallings VA, Vaisman N, Chan HS, Weitzman SS, Hahn E, Pencharz PB. Energy metabolism in children with newly diagnosed acute lymphoblastic leukemia. *Pediatr Res*. 1989; 26(2): 154-157.
- ⁶ Ribaldo JM, Cella D, Hahn EA, et al. Re-validation and shortening of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. *Qual Life Res* 2000; 9(10): 1137-1146.
- ⁷ Loprinzi CL, Laurie JA, Wieand HS, et al. Prospective evaluation of prognostic variables from patient-completed questionnaires. North Central Cancer Treatment Group. *J Clin Oncol*. 1994; 12(3): 601-607.
- ⁸ McGeer AJ, Detsky AS, O'Rourke K. Parenteral nutrition in cancer patients undergoing chemotherapy: a meta-analysis. *Nutrition* 1990; 6(3): 233-240.
- ⁹ Anonymous. Parenteral nutrition in patients receiving cancer chemotherapy. *Ann Intern Med*. 1989; 110(9): 734-736.
- ¹⁰ Balkwill F and Mantovani A. Inflammation and cancer: back to Virchow? *Lancet*. 2001; 357(9255): 539-545.
- ¹¹ Khan S and Tisdale MJ. Catabolism of adipose tissue by a tumor-produced lipid-mobilising factor. *Int J Cancer*. 1999; 80(3): 444-447.
- ¹² Cariuk P, Lorite MJ, Todorov PT, Field WN, Wigmore SJ, Tisdale MJ. Induction of cachexia in mice by a product isolated from the urine of cachectic cancer patients. *Br J Cancer*. 1997; 76(5): 606-613.
- ¹³ Hyltander A, Drott C, Körner U, Sandström R, Lundholm K. Elevated energy expenditure in cancer patients with solid tumours. *Eur J Cancer*. 1991; 27(1): 9-15.

- ¹⁴ Simons JP, Schols AM, Buurman WA and Wouters EF. Weight loss and low body cell mass in males with lung cancer: relationship with systemic inflammation, acute-phase response, resting energy expenditure, and catabolic and anabolic hormones. *Clin Sci (Lond)*. 1999; 97(2): 215-223.
- ¹⁵ Laviano A, Meguid MM, Rossi-Fanelli F. Cancer anorexia: clinical implications, pathogenesis, and therapeutic strategies. *Lancet Oncol*. 2003; 4(11): 686-694.
- ¹⁶ Torelli GF, Meguid MM, Moldawer LL, et al. Use of recombinant human soluble TNF receptor in anorectic tumor-bearing rats. *Am J Physiol*. 1999; 277(3 Pt 2): R850-855.
- ¹⁷ Baracos VE, DeVivo C, Hoyle DH, Goldberg AL. Activation of the ATP-ubiquitin-proteasome pathway in skeletal muscle of cachectic rats bearing hepatoma. *Am J Physiol*. 1995; 268(5 Pt 1): E996-1006.
- ¹⁸ Llovera M, Garcia-Martinez C, Lopez-Soriano J, et al. Role of TNF receptor 1 in protein turnover during cancer cachexia using gene knockout mice. *Mol Cell Endocrinol*. 1998; 142(1-2): 183-189.
- ¹⁹ Llovera M, Garcia-Martinez C, Lopez-Soriano J, et al. Protein turnover in skeletal muscle of tumor-bearing transgenic mice overexpressing the soluble TNF receptor-1. *Cancer Lett*. 1998; 130(1-2): 19-27.
- ²⁰ Todorov P, Cariuk P, McDevitt T, Coles B, Fearon K, Tisdale M. Characterization of a cancer cachectic factor. *Nature*. 1996; 379(6567): 739-742.
- ²¹ Todorov PT, McDevitt TM, Meyer DJ, Ueyama H, Ohkubo I, Tisdale MJ. Purification and characterization of a tumor lipid-mobilizing factor. *Cancer Res*. 1998; 58(11): 2353-2358.
- ²² Hirai K, Hussey HJ, Barber MD, Price SA, Tisdale MJ. Biological evaluation of a lipid-mobilizing factor isolated from the urine of cancer patients. *Cancer Res*. 1998; 58(11): 2359-2365.
- ²³ Woods D, Onambele G, Woledge R et al. Angiotensin-I converting enzyme genotype-dependent benefit from hormone replacement therapy in isometric muscle strength and bone mineral density. *J Clin Endocrinol Metab*. 2001; 86(5): 2200-2204.
- ²⁴ Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. *Cancer*. 2000; 88(9): 2164-2171.
- ²⁵ EORTC quality of life questionnaire (QLQ C-30). Available at http://groups.eortc.be/qol/downloads/modules/specimen_20qlq_c30.pdf. Accessed January 31, 2011.

- ²⁶ Kaasa T, Loomis J, Gillis K, Bruera E, Hanson J. The Edmonton Functional Assessment Tool: preliminary development and evaluation for use in palliative care. *J Pain Symp Manage*. 1997; 13(1): 10-19.
- ²⁷ Ovesen L, Allingstrup L, Hannibal J, Mortenson EL, Hansen OP. Effect of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomized study. *J Clin Oncol*. 1993; 11(10): 2043-2049.
- ²⁸ Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG. Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer*. 1974; 33(6): 1607-1609.
- ²⁹ Loprinzi CL, Kugler JW, Sloan JA, et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol*. 1999; 17(10): 3299-3306.
- ³⁰ Loprinzi CL, Michalak JC, Schaid DJ, et al. Phase III evaluation of four doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. *J Clin Oncol*. 1993; 11(4): 762-767.
- ³¹ Lambert CP, Sullivan DH, Freeling SA, Lindquist DM, Evans WJ. Effects of testosterone replacement and/or resistance exercise on the composition of megestrol acetate stimulated weight gain in elderly men: a randomized controlled trial. *J Clin Endocrinol Metab*. 2002; 87(5): 2100-2106.
- ³² Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, Krook JE, Wilwerding MB, Rowland KM Jr, Camoriano JK, Novotny PJ, Christensen BJ. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol*. 1999 Oct; 17(10): 3299-306.
- ³³ Von Roenn JH, Tchekmedyian S, Hoffman RM, Chang C-Y. Safety of oxandrolone in cancer-related weight loss. *Proc Am Soc Clin Oncol*. 22: 2003 (abstr 3013).
- ³⁴ Morley JE. Orexigenic and anabolic agents. *Clin Geriatr Med*. 2002; 18(4): 853-866.
- ³⁵ Orr R, Fiatarone Singh M: The anabolic androgenic steroid oxandrolone in the treatment of wasting and catabolic disorders: review of efficacy and safety. *Drugs*. 2004; 64: 725-750.
- ³⁶ Fearon KC, Von Meyenfeldt MF, Moses AG, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. *Gut*. 2003; 52(10): 1479-1486.
- ³⁷ Clark RH, Feleke G, Din M, et al. Nutritional treatment for acquired immunodeficiency virus-associated wasting using beta-hydroxy beta-methylbutyrate, glutamine, and arginine: a randomized, double-blind, placebo-controlled study. *JPEN J Parenter Enteral Nutr*. 2000; 24(3): 133-139.

- ³⁸ Girodon F, Galan P, Monget AL, et al. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. MIN. VIT. AOX. geriatric network. *Arch Intern Med*. 1999; 159(7): 748-754.
- ³⁹ Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention in adults: a scientific review. *JAMA*. 2002; 287(23): 3116-3126.
- ⁴⁰ Cella D, Peterman A, Passik S, Jacobsen P, Breitbart W. Progress toward guidelines for the management of fatigue. *Oncology (Williston Park)*. 1998; 12(11A): 369-377.
- ⁴¹ Radbruch L, Strasser F, Ferraz J, Gonçalves J Løge, get first initial, Stein S, Nauck, F Stone, P, Fatigue in palliative care patients – an EAPC approach, *Palliative Medicine* 2008; 22: 13–32.
- ⁴² Irvine D, Vincent L, Graydon JE, Bubela N, Thompson L. The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. A comparison with the fatigue experienced by healthy individuals. *Cancer Nurs*. 1994; 17(5): 367-378.
- ⁴³ Greenberg DB, Sawicka J, Eisenthal S, Ross D. Fatigue syndrome due to localized radiation. *J Pain Symptom Manage*. 1992; 7(1): 38-45.
- ⁴⁴ Vogelzang NJ, Breitbart W, Cella D, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tri-part assessment survey. The Fatigue Coalition. *Semin Hematol*. 1997; 34(3 Suppl 2): 4-12.
- ⁴⁵ Yennurajalingam S, Bruera E. Palliative management of fatigue at the close of life: "it feels like my body is just worn out." *JAMA*. 2007; 297(3): 295-304.
- ⁴⁶ Stone P, Richardson A, Ream E, Smith AG, Kerr DJ, Kearney N. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer Fatigue Forum. *Ann Oncol*. 2000; 11(8): 971-975.
- ⁴⁷ Weber J, Yang JC, Topalian SL, et al. Phase I trial of subcutaneous interleukin-6 in patients with advanced malignancies. *J Clin Oncol*. 1993; 11(3): 499-506.
- ⁴⁸ Gordon MS, Nemunaitis J, Hoffman R, et al. A phase I trial of recombinant human interleukin-6 in patients with myelodysplastic syndromes and thrombocytopenia. *Blood*. 1995; 85(11): 3066-3076.
- ⁴⁹ Berger AM, Abernathy AP, Atkinson A, et al. [Chair plus 26-Member Panel] Cancer-Related Fatigue Guidelines. NCCN Practice Guidelines in Oncology – v.1.2009. Jenkintown, PA: National Comprehensive Cancer Network, 2009.
- ⁵⁰ Munch, TN, Zhang T, Willey, J, Palmer, JL, Bruera, E. The Association between Anemia and Fatigue in Patients with Advanced Cancer Receiving Palliative Care, *Journal of Palliative Medicine* 2005, 8(6): 1144-1149.

- ⁵¹ Glaspy JA, Jadeja JS, Justice G, Fleishman A, Rossi G, Colowick AB. A randomized, active-control, pilot trial of front-loaded dosing regimens of darbepoetin-alfa for the treatment of patients with anemia during chemotherapy for malignant disease. *Cancer*. 2003; 97(5):1312-1320.
- ⁵² Quirt I, Robeson C, Lau CY et al. Epoetin alfa therapy increases hemoglobin levels and improves quality of life in patients with cancer-related anemia who are not receiving chemotherapy and patients with anemia who are receiving chemotherapy. *J Clin Oncol*. 2001; 19(21): 4126-4134.
- ⁵³ Rizzo JD, Lichtin AE, Woolf SH, et al. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. *J Clin Oncol*. 2002; 20(19): 4083-4107.
- ⁵⁴ Crawford J, Cella D, Cleeland CS, et al. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. *Cancer*. 2002; 95(4): 888-895.
- ⁵⁵ Chang J, Couture F, Young S, McWatters KL, Lau CY. Weekly epoetin alfa maintains hemoglobin, improves quality of life, and reduces transfusion in breast cancer patients receiving chemotherapy. *J Clin Oncol*. 2005; 23(12): 2597-2605.
- ⁵⁶ Vadhan-Raj S, Schreiber F, Thomas LC, et al. Every 2-week darbepoetin alfa improves fatigue and energy rating scores in cancer patients (pts) undergoing chemotherapy. *Proc Am Soc Clin Oncol*. 22: 2003 (abstr 2942).
- ⁵⁷ Mirtsching BC, Beck JT, Charu V, et al. Darbepoetin alfa administered every two weeks (Q2W) reduces chemotherapy-induced anemia (CIA) to the same extent as recombinant human erythropoietin (rHuEPO) but with less-frequent dosing. *Proc Am Soc Clin Oncol*. 22: 2003 (abstr 2944).
- ⁵⁸ Schwartzberg L, Hesketh P, Rossi G, Tomita D, Colowick A, Glaspy J. Optimizing management of chemotherapy-induced anemia: a combined analysis of data using a darbepoetin alfa frontloading/maintenance approach. *Proc Am Soc Clin Oncol* 22:2003 (abstr 2945).
- ⁵⁹ Strasser F, Palmer JL, Schover LR, et al. The impact of hypogonadism and autonomic dysfunction on fatigue, emotional function, and sexual desire in male patients with advanced cancer: a pilot study. *Cancer* 2006; 107(12): 2949-2957.
- ⁶⁰ Snyder PJ. Hypogonadism in elderly men—what to do until the evidence comes. *N Engl J Med*. 2004; 350: 440-442
- ⁶¹ Pinto BM, Maruyama NC. Exercise in the rehabilitation of the breast cancer survivors. *PsychoOncology*. 1999; 8(3): 191-206.

- ⁶² Winningham ML, MacVicar MG, Bondoc M, Anderson JI, Minton JP. Effect of aerobic exercise on body weight and composition in patients with breast cancer on adjuvant chemotherapy. *Oncol Nurs Forum*. 1989; 16(5): 685-689.
- ⁶³ MacVicar MG, Winningham ML. Promoting the functional capacity of cancer patients. *Cancer Bull*. 1986; 38: 235-239.
- ⁶⁴ Mock V, Burke MB, Sheehan PK, et al. A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. *Oncol Nurs Forum*. 1994; 21(5): 899-908.
- ⁶⁵ Dimeo FC, Stieglitz RD, Novelli-Fischer U, Fetscher S, Keul J. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. *Cancer*. 1999; 85(10): 2273-2277.
- ⁶⁶ Schwartz AL. Daily fatigue patterns and effect of exercise in women with breast cancer. *Cancer Pract*. 2000; 8(1): 16-24.
- ⁶⁷ Dimeo FC, Tilmann MH, Bertz H, Kanz L, Mertelsmann R, Keul J. Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. *Cancer*. 1997; 79(9): 1717-1722.
- ⁶⁸ Galvao DA, Newton RU. Review of exercise intervention studies in cancer patients. *J Clin Oncol*. 2005; 23(4): 899-909.
- ⁶⁹ Winningham ML. Strategies for managing cancer-related fatigue syndrome: a rehabilitation approach. *Cancer*. 2001; 92(4 suppl): 988-997.
- ⁷⁰ Fatigue. Optimizing Cancer Care – The Importance of Symptom Management. Volume I. Alexandria, VA: *American Society of Clinical Oncology*. 2003.
- ⁷¹ Sugawara Y, Akechi T, Shima Y, et al. Efficacy of methylphenidate for fatigue in advanced care patients, a preliminary study. *Palliat Med*. 2002; 16(3): 261-263.
- ⁷² Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollak CP, Nagaraja HN. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *J Neurol Neurosurg Psychiatry*. 2002; 72(2): 179-183.
- ⁷³ Bruera E, Roca E, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treat Rep*. 1985; 69(7-8): 751-754.
- ⁷⁴ Tannock I, Gospodarowicz M, Meakin W, Panzarella T, Stewart L, Rider W. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol*. 1989; 7(5): 590-597.

- ⁷⁵ Miaskowski C and Portenoy RK. Assessment and management of cancer-related fatigue. In: Berger AM, Shuster JL, Von Roenn JH eds. *Principles and Practice of Supportive Oncology*. 3rd ed. Philadelphia, PA: Lippincott-Raven. 2007: 95-104
- ⁷⁶ National Center on Sleep Disorders Research and Office of Prevention, Education, and Control: Insomnia; Assessment and management in primary care. Bethesda, Maryland: National Institutes of Health/National Heart, Lung, and Blood Institute. NIH Publication No. 98-4088, 1998.
- ⁷⁷ Owen DC, Parker KP, McGuire DB. Comparison of subjective sleep quality in patients with cancer and healthy subjects. *Oncol Nurs Forum*. 1999; 26(10): 1649-1651.
- ⁷⁸ Fortner BV, Stepanski EJ, Wang SC, Kasprowicz S, Durrence HH. Sleep and quality of life in breast cancer patients. *J Pain Symptom Manage*. 2002; 24(5): 471-480.
- ⁷⁹ Redeker NS, Lev EL, Ruggiero J. Insomnia, fatigue, anxiety, depression, and quality of life of cancer patients undergoing chemotherapy. *Sch Inq Nurs Pract*. 2000; 14(4): 275-290.
- ⁸⁰ Katz DA, McHorney CA. The relationship between insomnia and health-related quality of life in patients with chronic illness. *J Fam Pract*. 2002; 51(3): 229-235.
- ⁸¹ Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics, and distress. *Eur J Cancer*. 1994; 30A(9): 1326-1336.
- ⁸² Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol*. 2001;19(3):895-908.
- ⁸³ Bruera E, Fainsinger RL, Schoeller T, Ripamonti C. Rapid discontinuation of hypnotics in terminal cancer patients: a prospective study. *Ann Oncol*. 1996; 7(8): 855-856.
- ⁸⁴ Weilberg JB, Winkelman JW. Sleep disorders. In: Wise MG, Rundell JR, eds. *The American Psychiatric Press Textbook of Consultation-Liaison Psychiatry*. 2nd ed. Washington, DC: American Psychiatric Press; 2002: 495-518.
- ⁸⁵ *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, text revision (DSM-IV-TR). Arlington, VA: American Psychiatric Association, 2000.
- ⁸⁶ Douglass AB, Bornstein R, Nino-Murcia G, et al. The Sleep Disorders Questionnaire. I: creation and multivariate structure of SDQ. *Sleep*. 1994; 17(2): 160-167.
- ⁸⁷ Kushida CA. Clinical presentation, diagnosis, and quality of life issues in restless legs syndrome. *Am J Med*. 2007; 120(1 Suppl 1): S4-S12.

- ⁸⁸ Saboisky JP, Chamberlin NL, Malhotra A. Potential therapeutic targets in obstructive sleep apnoea. *Expert Opin Ther Targets*. 2009; 13(7), 795-809.
- ⁸⁹ Morin CM and Gramling SE. Sleep patterns and aging: comparison of older adults with and without insomnia complaints. *Psychol Aging*. 1989; 4(3): 290-294.
- ⁹⁰ Berger AM, Shuster JL, Von Roenn JH. Principles and practice of palliative care and supportive oncology. Lippincott Williams & Wilkins, 2006; 103.
- ⁹¹ Insomnia assessment and management in primary care. National Heart, Lung, and Blood Institute Working Group on Insomnia. *Am Fam Physician*. 1999; 59(11): 3029-3038.
- ⁹² Davidson JR, Waisberg JL, Brundage MD, MacLean AW. Nonpharmacologic group treatment of insomnia: a preliminary study with cancer survivors. *Psychooncology*. 2001; 10(5):389-397.
- ⁹³ Quesnel C, Savard J, Simard S, Ivers H, Morin CM. Efficacy of cognitive-behavioral therapy for insomnia in women treated for nonmetastatic breast cancer. *J Consult Clin Psychol*. 2003; 71(1): 189-200.
- ⁹⁴ Kupfer DJ, Reynolds CF. Management of insomnia. *N Engl J Med*. 1997; 336(5): 341-346.
- ⁹⁵ Greenberg DB. Strategic use of benzodiazepines in cancer patients. *Oncology (Williston Park)*. 1991; 5(4): 83-88.
- ⁹⁶ Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep*. 2003; 26(7): 793-799.
- ⁹⁷ Davis MP, Dickerson ED, Pappagallo M, Benedetti C, Grauer PA, Lycan J. Mirtazapine: heir apparent to amitriptyline? *Am J Hosp Palliat Care*. 2001; 18(1): 42-46.
- ⁹⁸ Parrino L, Spaggiari MC, Boselli M, Di Giovanni G, Terzano MG. Clinical and polysomnographic effects of trazodone CR in chronic insomnia associated with dysthymia. *Psychopharmacology (Berl)*. 1994; 116(4): 389-395.
- ⁹⁹ Mashiko H, Niwa S, Kumashiro H, et al. Effect of trazodone in a single dose before bedtime for sleep disorders accompanied by a depressive state: dose-finding study with no concomitant use of hypnotic agent. *Psychiatry Clin Neurosci*. 1999; 53(2): 193-194.
- ¹⁰⁰ Wine JN, Sanda C, Caballero J. Effects of quetiapine on sleep in nonpsychiatric and psychiatric conditions. *Ann Pharmacother*. 2009; 43(4): 707-713.

- ¹⁰¹ Bates DW, Pruess K, Souney P, Platt R. Serious falls in hospitalized patients: Correlates and resource utilization, *The American Journal of Medicine* 1995; 99: 137-143.
- ¹⁰² Moylan KC, Binder EF. Falls in older adults: risk assessment, management and prevention, *The American Journal of Medicine* 2007; 120: 493-497.
- ¹⁰³ Voshaar RC, van Balkom AJ, Zitman FG. Zolpidem is not superior to temazepam with respect to rebound insomnia: a controlled study. *Eur Neuropsychopharmacol.* 2004 ; 14(4): 301-306.
- ¹⁰⁴ Hale LR, Ryan TJ. Palliative care and clinical approach to disorders of the skin. In: Portenoy RK, Bruera E, eds. *Topics in Palliative Care Volume III*. New York, NY: Oxford University Press; 1998: 233-252.
- ¹⁰⁵ Fried RG, Gupta MA, Gupta AK. Depression and Skin Disease. *Dermatol Clin* 2005; 23(4): 657-664.
- ¹⁰⁶ Basra, MK; Shahrukh, M, Burden of skin diseases. *Expert Review of Pharmacoeconomics and Outcomes Research* 2009; 9: 271-283.
- ¹⁰⁷ Hassan AH, Ableitner A, Stein C, Herz A. Inflammation of the rat paw enhances axonal transport of opioid receptors in the sciatic nerve and increases their density in the inflamed tissue. *Neuroscience.* 1993; 55(1): 185-195.
- ¹⁰⁸ Ferris FD. Management of pressure ulcers and fungating wounds. In: Berger AM, Shuster JL, Von Roenn JH eds. *Principles and Practice of Supportive Oncology*. 3rd ed. Philadelphia, PA: Lippincott-Raven. 2007: 239-252.
- ¹⁰⁹ Brem H, Lyder C. Protocol for the successful treatment of pressure ulcers. *Am J Surg.* 2004; 188(1A Suppl): 9-17.
- ¹¹⁰ Walker P. The pathophysiology and management of pressure ulcers. In: Portenoy RK, Bruera E, eds. *Topics in Palliative Care Volume III*. New York, NY: Oxford University Press; 1998: 253-270.
- ¹¹¹ Froiland KG. Wound care of the advanced cancer patient. *Hematol Oncol Clin North Am.* 2002; 16(3): 629-639.
- ¹¹² Monstrey SJ, Mullick P, Narayanan K, Ramasastry SS. Hyperbaric oxygen therapy and free radical production: an experimental study in doxorubicin (Adriamycin) extravasation injuries. *Ann Plast Surg.* 1997; 38(2): 163-168.
- ¹¹³ Fernandez R, Griffiths R. Water for wound cleansing. *Cochrane Database Syst Rev.* 2008; 23(1): CD003861.
- ¹¹⁴ Twillman RK, Long TD, Cathers TA, Mueller DW. Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage.* 1999; 17(4): 288-292.

- ¹¹⁵ Zeppetella G, Paul J, Ribeiro MD. Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain Symptom Manage*. 2003; 25(6): 555-558.
- ¹¹⁶ Paul JC, Pieper BA. Topical metronidazole for the treatment of wound odor: a review of the literature. *Ostomy Wound Manage*. 2008; 54(3): 18-27.