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IN PALLIATIVE CARE

Interprofessional Webinar Series

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Management of Anorexia/Cachexia

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Disclosure Slide

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Russell K. Portenoy, MD, Planner, has indicated a relationship with the following: Pfizer Inc. No other Planning Committee Member has any disclosures.

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Objectives

- Discuss the prevalence and significance of anorexia/cachexia in patients receiving palliative care.
- Recognize the clinical features and assessment criteria for anorexia/cachexia.
- Identify the treatment options for anorexia/cachexia and recognize its impact on quality of life.

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Cachexia: Definition

- Multifactorial syndrome that is defined by an ongoing ***loss of skeletal muscle mass*** (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and that leads to progressive functional impairment. Usually diagnosed when pts have weight loss more than 5% of preillness weight in previous 2 to 6 months.

- Pathophysiology: negative protein and energy balance that is driven by a variable combination of **reduced food intake (anorexia)** and **abnormal metabolism**.

Fearon, K. *et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol. 12, 489–495 (2011).*

Conditions Associated with Cachexia

- Occurs in ~ 70% of patients during the terminal course of disease
- Cancer
  - Cancer of the upper GI and lung have the highest prevalence of weight loss
- Acquired Immunodeficiency Syndrome
- Chronic obstructive pulmonary disease
- Congestive heart failure
- Other chronic illness:
  - Dementia, rheumatoid arthritis, tuberculosis, malaria, chronic kidney disease

Payne-James et al., 2001. Artificial Nutritional Support in Clinical Practice, 2nd edition.

Von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: Facts and numbers. J Cachexia Sarcopenia Muscle 2010;pp.1-5.

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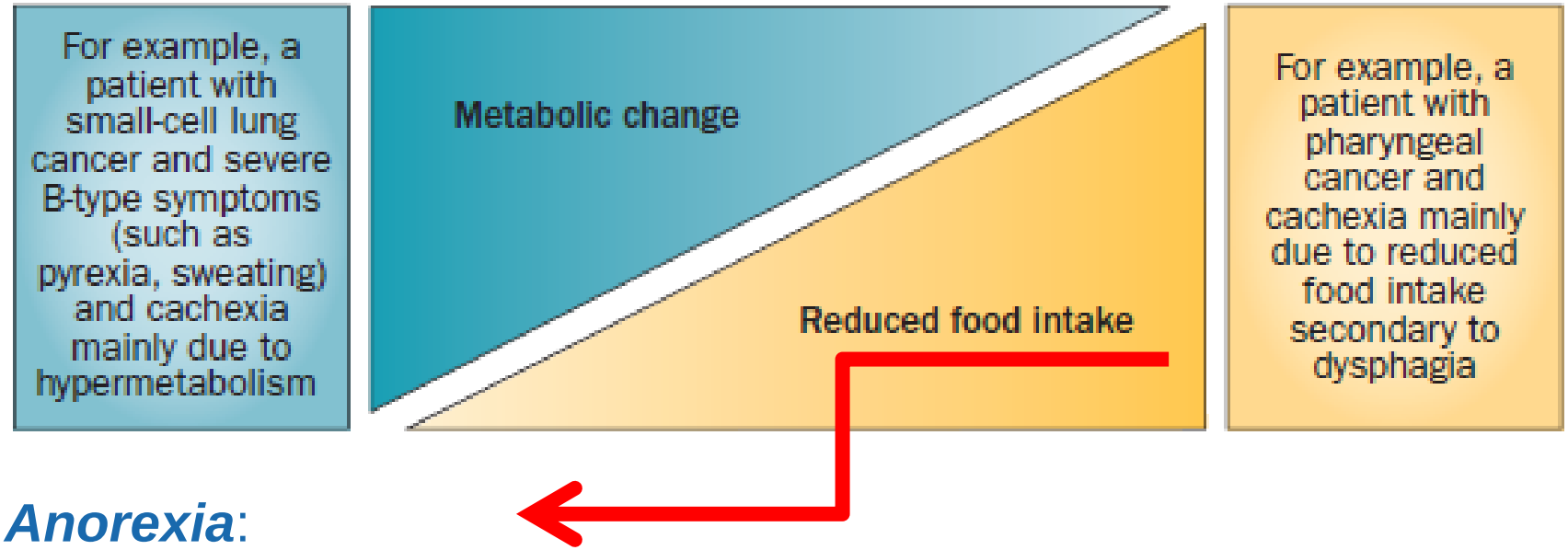
Cause of Cachexia



Anorexia:

- Loss of appetite or reduced caloric intake.
- It is a common complication of advance cancer and other terminal illnesses.

Wallengren O, Lundholm K, Bosaeus I. Diagnostic criteria of cancer cachexia: relation to quality of life, exercise capacity and survival in unselected palliative care patients. Support Care Cancer 2013; 21:1569.

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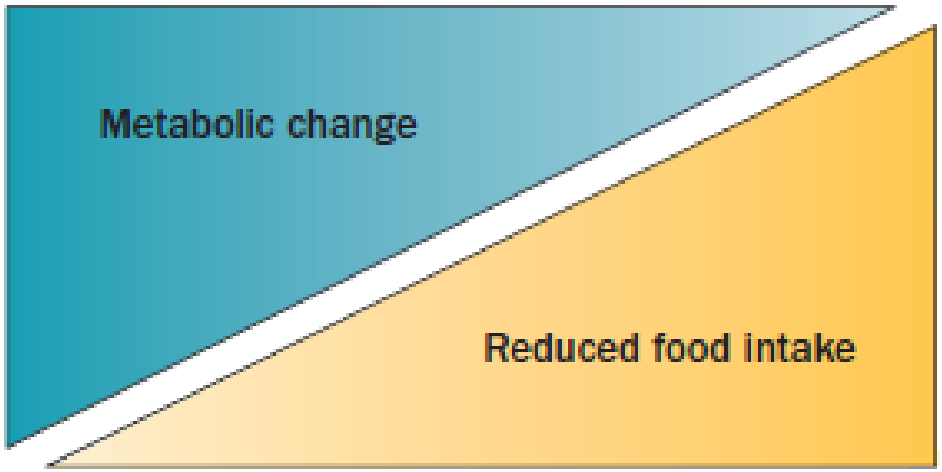
Phases of Cachexia

- Precachexia
- Cachexia

} ***Partially reversible***

- Refractory cachexia ← ***Irreversible***

For example, a patient with small-cell lung cancer and severe B-type symptoms (such as pyrexia, sweating) and cachexia mainly due to hypermetabolism



For example, a patient with pharyngeal cancer and cachexia mainly due to reduced food intake secondary to dysphagia

Claire L. Donohoe, Aoife M. Ryan, and John V. Reynolds, "Cancer Cachexia: Mechanisms and Clinical Implications," Gastroenterology Research and Practice, vol. 2011, Article ID 601434, 13 pages, 2011. doi:10.1155/2011/601434.

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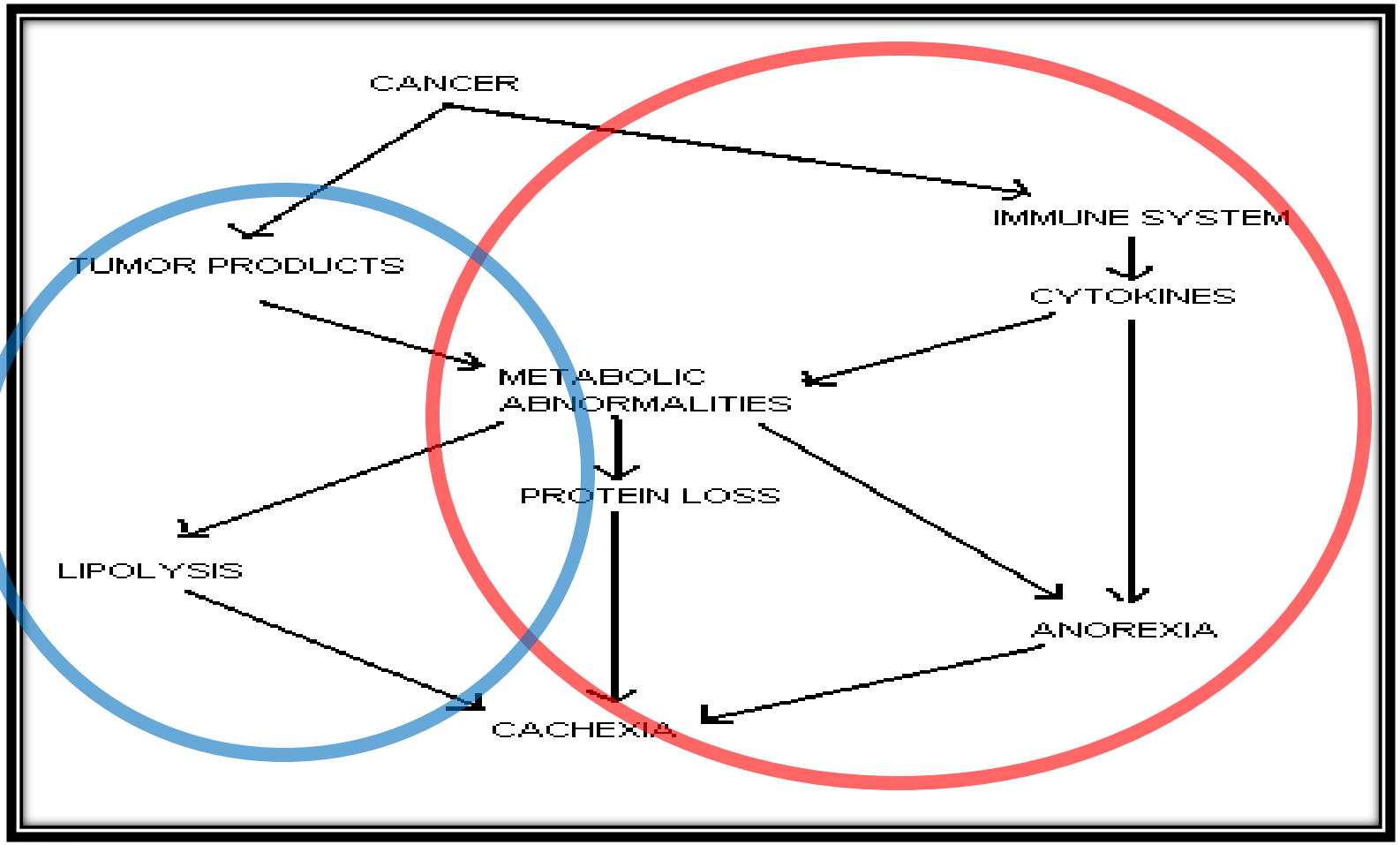
Mechanism of Cachexia



Tisdale MJ. Cachexia in cancer patients. Nat Rev Cancer 2002; 2:862.
Davis MP, Dreicer R, Walsh D, et al. J Clin Oncol 2004; 22:1510.

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Effect on Patient Quality of Life

- Physical activity is impaired by the loss of muscle tissue
- Concentration and alertness are diminished by fatigue
- Mood is dominated by lethargy and increasing indifference
- Isolated owing to reduced physical, mental, and emotional activity
- Caregiver stress

Stewart, G. D., Skipworth, R. J. & Fearon, K. C. Clin. Med. 6, 140–143 (2006).
Reid, J., McKenna, H., Fitzsimons, D. & McCance, T. Oncol. Nurs. Forum 36, 439–445 (2009).

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Characteristics of Cachexia

- Anorexia
    - Lack of appetite signals, early satiety
- Asthenia
    - Weakness, fatigue, lethargy
- Unintended weight loss
    - >10% premorbid body weight
- Anemia
- Edema

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Assessment

- The ***objective measures***: serial measurement of body weight and assessment of dietary intake
- The ***subjective measures***: malnutritional assessment tools
- The ***laboratory measures:*** e.g., albumin, transferrin are rarely needed

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Diagnostic Criteria for Cachexia

Unintentional weight loss	≥ 5%

BMI	< 20 in those aged < 65 years old < 22 in those aged ≥ 65 years old
Albumin	< 35 g/L (3.5 g/dL)
Low fat-free mass	Lowest 10%
Evidence of cytokine excess	E.g., elevated C-reactive protein
Symptoms	Anorexia, fatigue, decreased muscle strength

Morley JE, et. Al. Am J Clin Nutr 2006;83:735-43.

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Cachexia

- An international consensus group recommended that five domains be encompassed in cachexia assessment:
  1. stores depletion
  2. muscle mass and strength
  3. anorexia/reduced food intake
  4. catabolic drivers
  5. functional/psychosocial effects

- Malnutrition assessment tools are generally in use to assess cachexia.

Fearon K, et al. Lancet Oncol 2011; 12:489.

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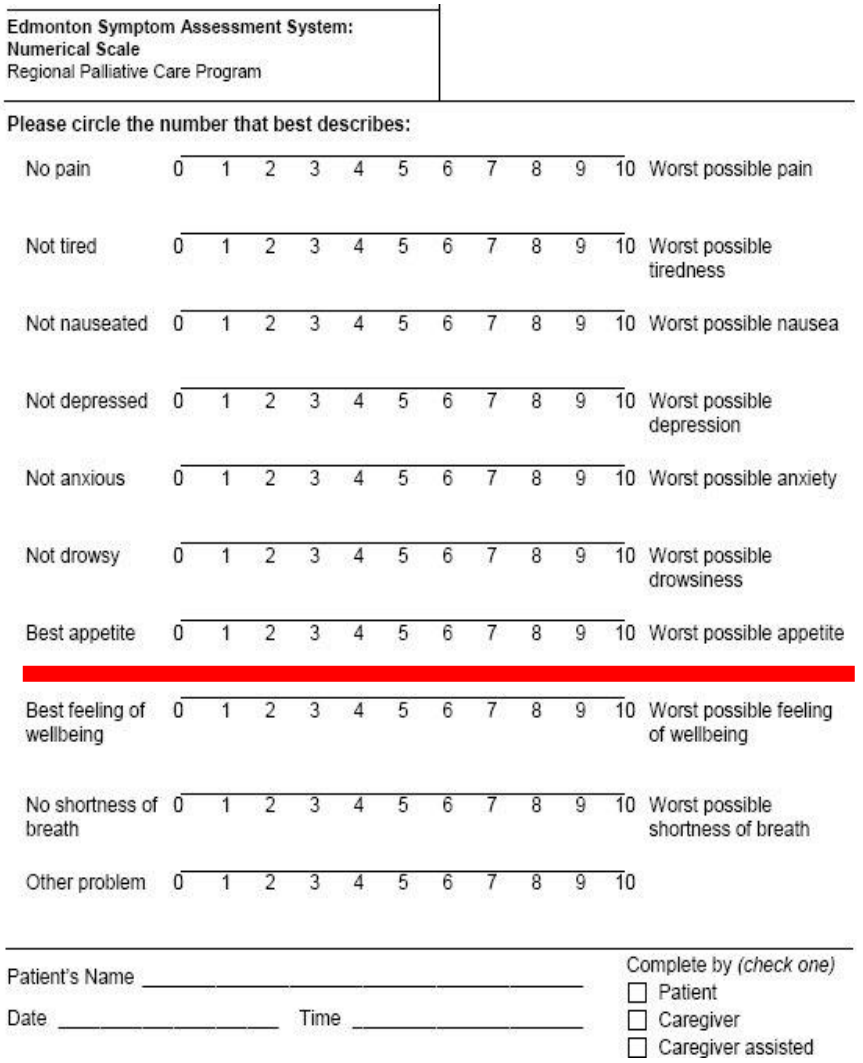
Malnutrition Assessment Tools

- Several screening tests have been developed to assess for malnutrition, including:
  - Patient-Generated Subjective Global Assessment (PG-SGA)
  - Mini-nutritional assessment (MNA)
  - Malnutrition Universal Screening Tool (MUST)
  - Simplified Nutritional Appetite Questionnaire (SNAQ)
- No single screening tool has been universally agreed upon as the best way.

Appetite

- Although the reliability of subjective assessments of appetite is debated, they are probably the simplest and most practical measures available.
- The patient's subjective loss of appetite can be assessed with a numeric rating scale, such as the Edmonton Symptom Assessment System (ESAS).



Edmonton Symptom Assessment System:
Numerical Scale
Regional Palliative Care Program

Please circle the number that best describes:

No pain	0 1 2 3 4 5 6 7 8 9 10	Worst possible pain
Not tired	0 1 2 3 4 5 6 7 8 9 10	Worst possible tiredness
Not nauseated	0 1 2 3 4 5 6 7 8 9 10	Worst possible nausea
Not depressed	0 1 2 3 4 5 6 7 8 9 10	Worst possible depression
Not anxious	0 1 2 3 4 5 6 7 8 9 10	Worst possible anxiety
Not drowsy	0 1 2 3 4 5 6 7 8 9 10	Worst possible drowsiness
Best appetite	0 1 2 3 4 5 6 7 8 9 10	Worst possible appetite
Best feeling of wellbeing	0 1 2 3 4 5 6 7 8 9 10	Worst possible feeling of wellbeing
No shortness of breath	0 1 2 3 4 5 6 7 8 9 10	Worst possible shortness of breath
Other problem	0 1 2 3 4 5 6 7 8 9 10	

Patient's Name _____

Date _____ Time _____

Complete by *(check one)*
☐ Patient
☐ Caregiver
☐ Caregiver assisted

Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. Cancer 2000; 88:2164-2171.
Richardson LA, Jones GW. A review of the reliability and validity of the Edmonton Symptom Assessment System. Curr Oncol 2009;16:55.

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Secondary Nutrition Impact Symptoms (S-NIS)

- S-NIS: Other symptoms that may impact appetite and caloric intake, including symptoms:
  - May be related to the underlying illness
  - May contribute to reduced caloric intake
  - Might be the consequence of cachexia, e.g., pain, xerostomia, n/v, constipation, and depression

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Other Reasons for Cachexia

- Potentially reversible metabolic abnormalities including:
  - hypothyroidism
  - adrenal insufficiency (bilateral adrenal metastasis)
  - hypogonadism (in male patients)
- Gastroparesis: multifactorial
  - chemotherapy-induced autonomic dysfunction
  - medications, such as opioids or anticholinergics
  - radiation enteritis
  - tumor infiltration
  - result of a paraneoplastic syndrome

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Importance of Better Recognition and Treatment

- More ‘silent’ symptoms than pain or dyspnea; often go unrecognized, unaddressed
- Probably a common pathway for many diseases
- Targeted therapies may do much to improve QOL

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Treatment and Supportive Care

- Pharmacotherapy
- Preparing favorite foods; the pleasure of tasting food should be emphasized over total caloric intake
- The social benefits of eating at the dining table with other family members should be encouraged
- Small, frequent meals that are dense in calories
- Ensuring optimal mouth care
- Providing a relaxed eating environment
- Avoiding strong odors or heavy spices

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Treatment Approach

- Optimizing management of major contributors to anorexia

- Patients and families should be counseled that increasing caloric intake ***does not*** reverse the underlying process and that anorexia/cachexia is not an uncommon symptom. It is different from starvation and is a natural process that occurs at the end of life.

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Treatment: Assessment of Other Causes

- M: Medications (digoxin, theophylline)
- E: Emotional (depression)
- A: Anorexia
- L: Late-life paranoia
- S: Swallowing disorders
- O: Oral problems
- N: Nosocomial infections (tuberculosis, H.pylori)
- W: Wandering and other dementia-related behavior
- H: Hyperthyroidism/ hypercalcemia/hypoadrenalism
- E: Enteric problems (malabsorption)
- E: Eating problems
- L: Low-salt, low-cholesterol diets
- S: Stones (gallstones)

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Pharmacological Approaches

- Megestrol acetate
- Glucocorticoids
- Mirtazapine
- Dronabinol
- Anabolic steroids
- Cyproheptadine
- Others:
  - Thalidomide
  - Amino Acids/ L-Carnitine
  - Celecoxib
  - Fish Oil (EPA)

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Megestrol Acetate

- Synthetic derivative of progesterone
- Acts as progestational, anti-inflammatory and intrinsic androgen agent
- Approved by the FDA for the treatment of anorexia, cachexia, or unexplained significant weight loss in patients with AIDS
- Should be used no more than 8-12 weeks at a time
- ***No effect*** on overall quality of life or lean body mass

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Megestrol Acetate (Cont'd)

- Many randomized placebo-controlled trials
  - Improved appetite and weight gain in patients with cancer and AIDS
  - Increased appetite and body weight in patients with COPD
- Dose-related effect appetite, food intake, weight, and subjective sensation of well-being
- Dosing range: 160-1600 mg/day
  - Dose-related side effect profile
  - Thromboembolic events, peripheral edema, hyperglycemia, hypertension, breakthrough bleeding, increased liver enzymes

Mantovani G, et al. Drugs 2001; 61 (6): 499-514.

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Corticosteroids

- A 2005 systematic review of six double-blind randomized controlled studies of glucocorticoids (dexamethasone, prednisolone, and methylprednisolone) in cancer patients concluded that, compared to placebo, they **improved appetite and quality of life**, but the beneficial effects diminished over time.
- Produce temporary appetite stimulation
  - No studies have shown a beneficial effect on body weight
- Optimal dose not clearly defined

Mantovani G, et al. Drugs 2001; 61 (6): 499-514.
Yavuzsen T, et al. J Clin Oncol 2005; 23:8500.

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Cannabinoids

- Increased appetite is a well-known side effect of the cannabinoids
- Synthetic agents include dronabinol
- Dronabinol is FDA approved for anorexia/weight loss associated with AIDS
- One comparative trial published in patients with cancer-induced anorexia/cachexia comparing dronabinol to megestrol
  - Megestrol was significantly better in terms of both stimulating appetite and weight, and the combination of both agents was not better than megestrol alone.

Jatoi A, et al. J Clin Oncology 2002; 20(2): 567-73.

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Anabolic Steroids

- The Endocrine Society has published clinical practice guidelines for replacing testosterone in chronic illnesses with hypogonadism, such as advanced HIV/AIDS, type 2 DM, ESRD, and COPD, and not in cancer.

- In such men, physiologic testosterone supplementation has been shown to increase lean body mass, and in some studies, improve muscle strength.

Bhasin S, et al. J Clin Endocrinol Metab. 2010 Jun;95(6):2536-59.
Dev R, et al. Curr Oncol Rep. 2014 Apr;16(4):378.

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Cyproheptadine

- Histamine antagonist
- Shown to produce slight improvement in appetite in patients with cancer cachexia
  - No effect on body weight
- Produce significant sedation limiting use

Moertel CG, Kvols LK, Rubin J. A study of cyproheptadine in the treatment of metastatic carcinoid tumor and the malignant carcinoid syndrome. Cancer 1991; 67:33.

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Mirtazapine

- Antidepressant approved by the FDA for the treatment of major depressive disorder. It is known to cause appetite stimulation and weight gain at standard treatment doses.
- In controlled trials, 17% of patients taking mirtazapine reported an increase in appetite, compared with 2% of patients receiving placebo. Almost 8% of patients receiving mirtazapine had weight gain ≥ 7% of body weight, whereas patients receiving placebo had 0% weight gain.
- Most studies involved geriatric patients with established diagnosis of depression or dementia with depression.

Riechelmann RP, Burman D, Tannock IF, Rodin G, Zimmermann C. Phase II trial of mirtazapine for cancer-related cachexia and anorexia. Am J Hosp Palliat Care. 2010;27:106-110.
Suzuki H, Asakawa A, Amitani H, Nakamura N, Inui A. Cancer cachexia -- pathophysiology and management. J Gastroenterol. 2013;48:574-594.

Others

Thalidomide

- Potent inhibitor of TNF-alpha production
- Associated with weight gain in patients with TB or HIV infection
- Possible role in cancer patients
- Cochrane Review: insufficient evidence to support or refute in cancer-associated cachexia

Gordon J, Trebble T, Ellis R, et al. Thalidomide in the treatment of cancer cachexia: A randomized placebo controlled trial. Gut 2005.
Kaplan G, Thomas S, Fierer DS, et al. Thalidomide for the treatment of AIDS-associated wasting. AIDS Res Hum Retroviruses 2000; 16:1345.
Reyes-Terán G, Sierra-Madero JG, Martínez del Cerro V, et al. Effects of thalidomide on HIV-associated wasting syndrome: A randomized, double-blind, placebo-controlled clinical trial. AIDS 1996; 10:1501.

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Others (Cont'd)

Amino Acids/L-carnitine

- Required for the transport of fatty acids to the mitochondria where they are utilized to generate metabolic energy
- An RCT showed a trial of L-carnitine (4 g daily) in 72 patients with advanced pancreatic cancer reported an increase in body mass index (BMI), quality of life, and a trend toward improved survival

Kraft M, Kraft K, Gartner S, et al. L-Carnitine-supplementation in advanced pancreatic cancer (CARPAN)--a randomized multicentre trial. Nutr J 2012; 11:52.

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Others (Cont'd)

Celecoxib

- Placebo-controlled pilot study of cachectic cancer patients; celecoxib (200 mg BID) was associated with weight gain, increased body mass index (BMI), improved quality of life

- Larger prospective randomized study reported those on both megestrol and ibuprofen had gain in weight and improvements in QOL scores

Lai V, et al. Results of a pilot study of the effects of celecoxib on cancer cachexia in patients with cancer of the head, neck, and gastrointestinal tract. Head Neck 2008; 30:67.
McMillan DC, et al. A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. British Journal Cancer, 1999.

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Others (Cont'd)

Fish Oil (EPA)

- Alpha 3-omega fatty acid, stimulates adenylate cyclase activity and lipolysis
- Evidence is inconclusive on cancer-associated cachexia
- A 2007 Cochrane database meta-analysis concluded that there were insufficient data to establish that EPA was better than placebo

Dewy A, et al. Eicosapentaenoic acid for the treatment of cancer cachexia. Cochrane Database Systematic Review, 2007.
Murphy RA, et al. Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. Cancer 2011; 117:1775.

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Investigational: Combination Therapies

- Incorporate multimodal therapy, targeting multiple underlying pathophysiological processes

- Large randomized study of 332 cachectic cancer; patients were given either: megestrol acetate, fish oil, L-carnitine, thalidomide OR a combination of all of the above. Most effective treatment in attaining primary endpoints was the combination arm.

Mantovani G. Randomized phase III clinical trial of 5 different arms of treatment on 332 patients with cancer cachexia. European Rev Med Pharmacol Sci. 2010 Apr; 14 (4): 292-301.
Maddedu et al. Randomized phase III trial of a combined treatment with carnitine + celecoxib +/- megestrtol acetate for patients with cancer-related anorexia/cachexia syndrome. Clinical Nutrition 2012.

Future Drugs: Growth Hormone and Ghrelin

- Promising results have been seen with ghrelin, a growth hormone (GH)-releasing peptide that induces positive energy.
  - Some studies in cachectic patients with COPD suggest that repeated intravenous administration of ghrelin lessens muscle wasting and improves body composition, functional capacity, and sympathetic augmentation.

- A preliminary report of two large double-blind placebo-controlled trials of anamorelin in patients with lung cancer-related cachexia (the ROMANA 1 and ROMANA 2 studies) noted significantly increased lean body weight and clinically meaningful improvements in appetite with anamorelin compared to placebo.

Temel J, Currow D, Fearon K, et al. Anamorelin for treatment of cancer anorexia-cachexia in NSCLC: Results from the phase III studies ROMANA 1 and 2 (abstract 14830-PR). Data presented at the 2014 Congress of the European Society for Medical Oncology, Madrid, Spain, September 27, 2014.

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Artificial Nutritional Support

- **No evidence that artificial nutrition**, including hyperalimentation, prolongs life or improves functional status, and it is ***not indicated***, with some **exceptions**.

- For highly selected patients (e.g., high-grade bowel obstruction or malabsorption from advanced cancer)

    - Good functional status, good prognosis

- Other disease: controversial

Hoda D, et al. Cancer 2005; 103:863.
Brard L, et al.Gynecol Oncol 2006; 103:176.

CASE 1

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A 53-year-old woman with advanced hepatocellular carcinoma, currently receiving oral chemotherapy, is seen in your outpatient palliative care clinic. Her pain is controlled, but both the patient and her husband are concerned that she has had little appetite and has lost 10 pounds since her last visit. She is still ambulatory and enjoying most of her former activities, but she misses the enjoyment of eating. On physical examination, you find that she is a thin woman with normal vital signs. She has no signs of candida infection or other lesions in her oropharynx. She has normal dentition, minimal ascites, and no lower-extremity edema.

Of the following medications, which has the best evidence supporting effectiveness in treating her anorexia and helping her gain weight?

A. Dronabinol
B. Dexamethasone
C. Mirtazipine
D. Megestrol acetate

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CASE 2

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GF is a 68-year-old woman with metastatic colorectal cancer who is receiving palliative care only. She reports a decreased appetite and a weight loss corresponding to 8% of her body weight over the past 2 months. In providing education to this patient about her conditions and/or possible treatment options, which of the following statements would be most appropriate?

A. Cancer-related cachexia is associated with increased mortality, so she should try to increase her food intake.

B. It is likely that the muscle mass in her body is declining, so she should consider hospitalization to receive parenteral nutrition.

C. Most patients with advanced cancer who have decreased appetite and weight loss should receive a corticosteroid, such as dexamethasone.

D. Megestrol acetate may increase her appetite but has not been associated with an improvement in survival.

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Megesterol acetate is associated with which of the following side effects?

A. Somnolence

B. Constipation

C. Drowsiness

D. Thromboembolic events

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Conclusion

- Cachexia is a core clinical feature of many advanced illnesses.
- Cachexia too often goes undiagnosed or untreated, with adverse consequences for patients.
- Feeding is not the answer, especially with advanced illness.
- Pharmacological options are available, but require risk vs. benefit assessment.

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Management of Anorexia/Cachexia

Q/A