

In the name of God



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Unintentional Weight Loss

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Abstract:

Body weight, as determined by several key components, remains relatively stable over time. Unintentional weight loss, defined as a decrease of more than 5% of usual body weight during a 6 to 12 month period, is an important predictor of morbidity and mortality. However, weight loss is a non-specific finding with multiple possible etiologies, that include organic, psychosocial, and idiopathic etiologies. A rational stepwise approach based on relevant data extracted from the history and physical examination, with special attention to psychological and social issues, is highly effective in establishing a diagnosis and determining effective management. Treatment should be based on the results of the tests and each patient's clinical situation.

Key Words: unintentional weight loss, Evaluation, Management .

Learning Objectives:

By completing this continuing medical education offering course, participants should be able to:

1. Recognize the definition and significance of unintentional weight loss.
2. Describe the causes of unintentional weight loss.
3. Identify the methods to evaluate the patients with unintentional weight loss.
4. Know how to manage and follow the patients with unintentional weight loss.

Significance of weight loss

Body weight is determined by the interplay of calorie intake, activity level, and the metabolic rate. Significant alterations involving any of these factors may result in weight loss. Unexplained weight loss in patients is one of the common enigmas presented to the physician. Despite the frequency of involuntary weight loss, the evaluation of this problem challenges the physician by its broad range of diagnostic possibilities and seemingly endless differential diagnoses. Patients experiencing weight loss are typically alarmed because of underlying fears of malignancy or other serious diseases. Physicians realize that unintentional weight loss is a non-specific manifestation of many conditions. In this day of cost-efficient medicine and increasing constraints of cost containment, an efficient diagnostic strategy is essential.

Clinically important weight loss can be defined as the loss of 10 lb (4.5 kg) or more than 5% of the usual body weight over a period of 6 to 12 months, especially when progressive. Weight loss greater than 10% is considered to represent protein-energy malnutrition, which is associated with impaired physiologic function such as impaired cell mediated and humoral immunity¹.

Weight loss in excess of 20% implies severe protein-energy malnutrition and is associated with pronounced organ dysfunction². As a cumulative effect, low body

weight and weight loss are powerful predictors of morbidity (e.g., wound healing, infectious complications, pressure sores, performance status), response to medical therapy, and mortality^{3, 4}.

Pathophysiology of weight loss

The precise mechanism of weight loss is unknown in many patients. Caloric intake, absorption, utilization, and loss are key components that determine an individual's weight. Alteration in the balance of these components affects a patient's ability to maintain weight. For example, caloric intake may be modified by altered smell or taste, anorexia, nausea, abnormal satiation, etc. Altered gastrointestinal motility, exocrine pancreatic function, mucosal absorptive capacity, luminal bacteria, and medications, among other factors, may modify absorption. Utilization is primarily affected by the metabolic rate, which in turn is affected by the systemic inflammatory response of various medical conditions. In addition to primary gut disease, excessive loss of calories can be secondary to diseases of the skin and kidneys. Mediators of anorexia and weight loss include cytokines such as cachectin (tumor necrosis factor) and interleukins, humoral substances (e.g., bombesin-like substances, hypersensitivity to cholecystokinin), and proposed anorectic agents such as corticotropin-releasing factor⁵.

Etiologies of weight loss

Whereas dieting and eating disorders (i.e., anorexia nervosa and bulimia nervosa) explain most cases of intentional weight loss, unintentional weight loss can be divided into organic, psychosocial, and unknown etiologies (Table 1) ⁶.

Table 1. Clinical studies evaluating etiologies of unintentional weight loss

ETIOLOGIES (% OF PATIENTS)	MARTON ⁷	RABINOVITZ ⁸	THOMPSON ⁹	LEDUC ¹⁰	HUERTA ¹¹
Cancer	19	36	16	1	10
Organic (Other than Cancer)	50	30	40	28	38
GI disorders	14	17	11	--	--
Cardiovascular	9	0	0	--	--
Alcohol	8	0	0	--	--
Pulmonary	6	0	0	--	--
Endocrine	4	4	9	--	--
Infectious	3	4	2	--	--
Inflammatory	2	1	0	--	--
Renal	0	4	0	--	--
Neurologic	0	0	7	--	--
Psychiatric	9	10	20	60	42
Unknown	26	23	24	11	10

Morley has categorized the major causes of weight loss in the geriatric population as either social, psychological, medical, or age related (Table 2)¹².

Table 2. Etiologies of weight loss in the geriatric population

Social

Isolation

Poverty

Inadequate education

Lack of transportation

Unavailability of preferred foods

Urban decay

Psychological

Depression

Schizophrenia

Bereavement

Bulimia

Manipulation

Sociopathy

Late-life mania

Dementia

Conversion reaction

Anorexia nervosa

Anxiety

Alcoholism

Late-life paranoia

Excessive burden of life (food refusal)

Medical

Increased metabolism-hyperthyroidism, pheochromocytoma ,
parkinson disease

Anorexia-drugs , abdominal ischemia , cancer , hyperparathyroidism

Swallowing problem-dysphagia, cerebrovascular accident

Malabsorption-gluten enteropathy

Increased metabolism and anorexia-COPD, cardiac cachexia

Age-Related

Impaired olfactory sensitivity

Appetite suppression

Impaired taste sensitivity

In the elderly, the most common causes of weight loss are depression, cancer, and benign gastrointestinal disease¹³. Robbins has published a mnemonic consisting of the nine "D's" of weight loss in the elderly population (Table 3)¹⁴. Wise and Craig have added a tenth "D" of "Don't know" to Robbins' list to include the high incidence of unknown etiologies in the evaluation of unexplained weight loss⁶.

Table 3. " D's " of weight loss in the elderly patient

Dentition	Depression
Dysgeusia	Dementia
Dysphagia	Dysfunction
Diarrhea	Drugs
Disease (chronic)	Don't Know

Organic etiologies of unintentional weight loss

The organic etiologies most commonly identified in patients presenting with unintentional weight loss are listed^{1,5}:

Cancer: Malignancies account for approximately one third of all patients presenting with unintentional weight loss. Signs and symptoms suggesting malignancy may be non-specific or subtle but are often identified by history and physical examination. Mechanisms of weight loss due to malignancy vary and often more than one factor is present. Anorexia is common in most types of cancer. Increased metabolism plays a role especially in lymphomas and leukemias. Ectopic production of hormones—such as bombesin, which produces anorexia by sending satiety messages to the central nervous system—is another factor in tumor-related weight loss¹². Patients with malignancies may also produce interleukin and/or cachectin (tumor necrosis factor), which is another anorectic agent¹⁵. Malignancies to consider include gastrointestinal, hepatobiliary, hematologic, lung, breast, genitourinary, ovarian, and prostate.

Gastrointestinal Disorders: Gastrointestinal disorders are the most common non-malignant organic etiologies identified in patients with unintentional weight loss, accounting for about 15% of cases in published series. Mechanisms of weight loss in gastrointestinal disease are often multifactorial, including anorexia, obstruction with vomiting, fear of eating, malabsorption, inflammation, and compression of organs as in massive splenomegaly⁹. Gastroesophageal reflux disease, peptic ulcer disease, inflammatory bowel disease, dysmotility syndromes (e.g., gastroparesis and pseudoobstruction), chronic pancreatitis, celiac disease, constipation, atrophic gastritis, and oral problems (e.g., poor dentition, periodontal disease, and xerostomia) are some of the potential etiologies that can precipitate weight loss. A thorough history and physical examination will usually reveal signs or symptoms suggestive of a primary gastrointestinal etiology.

Endocrine Diseases: Diabetes mellitus, hyperthyroidism, and hypothyroidism are the most common endocrinopathies that cause unintentional weight loss. Less common diagnoses include pheochromocytoma, panhypopituitarism, adrenal insufficiency, hyperemesis gravidarum, and hyperparathyroidism(hypercalcemia).

Infection: Tuberculosis, fungal disease, parasites, subacute bacterial endocarditis, human immunodeficiency virus, and other hidden infections can occasionally cause unintentional weight loss. Asking about risk factors, including travel, occupation, living arrangements, lifestyle, and history of exposure, is essential. There are two major types of weight loss in HIV-infected patients. Rapid weight loss is usually due to a secondary infection, while gradual weight loss is often a reflection of gastrointestinal complications specially diarrhea and reduction in energy intake¹⁶.

Medications: Medications including antibiotics, nonsteroidal anti-inflammatory drugs, serotonin reuptake inhibitors, Metformin, Levodopa, ACE inhibitors and other drugs are important potential etiologies of unintentional weight loss, particularly in elderly patients¹³. Adverse effects, including anorexia, nausea, diarrhea, and dysgeusia, can alter the intake, absorption, and utilization of nutrients. If not properly asked for, this important cause is usually overlooked.

Cardiovascular Diseases: Cardiovascular diseases can lead to unintentional weight loss via multiple mechanisms, but the primary mechanisms are increased metabolic demand and decreased appetite and calorie intake. Cachexia is a frequent complication of severe congestive heart failure (i.e., cardiac cachexia). Wasting correlated with increased serum concentration of cortisol, TNF-alpha, and norepinephrine, but not with the severity of congestive heart failure (as determined by VO2 max, ejection fraction, and functional class)¹⁷. Routine dietary restrictions for patients with cardiac disease may further accentuate weight loss.

Mesenteric ischemia is relatively uncommon but should be considered. Affected patients present with sitophobia (fear of eating). Inadequate blood flow to the gut postprandially precipitates abdominal discomfort, termed intestinal angina that may improve following revascularization.

Neurological Illness: Nervous system injury or degeneration (e.g., stroke, quadriplegia, multiple sclerosis, and dementia) can contribute to visceral dysfunction (i.e., dysphagia, constipation) and other functional limitations that impair caloric intake. One such example is Parkinson disease, which has been associated with intestinal dysmotility, defecatory dysfunction, and increased caloric demands. In addition, prescribed medications often cause xerostomia, anorexia, and early satiety, which further compromise nutrient intake. Cognitive dysfunction, such as dementia, frequently diminishes interest in nutritional intake, which can lead to unintentional weight loss.

Pulmonary Diseases: As with cardiac diseases, unintentional weight loss may be a secondary manifestation of pulmonary diseases. Severe chronic obstructive pulmonary disease can lead to an increase in metabolic demands secondary to the increased use of accessory muscles of respiration. Dyspnea, aerophagia, and adverse effects of medication often produce anorexia, early satiety, bloating, and dyspepsia, all of which may contribute to reduced nutrient intake. Chronic bronchitis with continuous swallowing of expectoration may lead to gastrointestinal upset and anorexia with subsequent weight loss.

Renal Disease: Uremia often produces anorexia, nausea, and vomiting. Protein loss in the urine, as seen in patients with nephrotic syndrome, often leads to a negative caloric balance. Hemodialysis is accompanied by swings in metabolic balance that have been associated with losses in lean body mass over time.

Connective Tissue Diseases: Acute and chronic inflammatory diseases increase metabolic demand, and associated anorexia may also disrupt nutritional balance. In addition, connective tissue diseases that affect the gut (eg, scleroderma) may produce various motility disturbances, including dysphagia, delayed gastric emptying, pseudo-obstruction, and constipation. Resultant bacterial overgrowth may exacerbate nutrient malabsorption. All these sequelae can compromise the intake, absorption, and utilization of nutrients. Systemic lupus erythematosus and rheumatoid arthritis may present with nausea, anorexia, malaise resulting in poor oral intake, and weight reduction¹⁵.

Age-Related Factors¹:

Physiologic changes: Most men reach their maximum body weight in their early 40s and most women in their early 50s. Beyond these ages, declining lean body mass normally accounts for the majority of weight lost after these peaks. Weight distribution shifts from muscle mass in the extremities to fat stores in the trunk. Fat atrophy may also occur, causing patients to look cachectic despite the absence of significant weight loss. An elderly patient's appearance alone should not trigger an evaluation for weight loss unless this is suggested by findings other than simple fat redistribution.

Decreased Taste and Smell: Some studies have shown a decline in sensitivity to taste with increasing age. Zinc deficiency is at times found in elderly patients and may be associated with ageusia. The acuity of sense of smell may also decline, again decreasing the sense of taste and limiting the pleasure of eating further. Routine oral hygiene has been shown to improve sensitivity to salty and sweet tastes and could improve appetite in some patients.

Functional Disabilities: A number of different factors may make it increasingly difficult for elderly patients to shop or prepare food. These factors include arthritis, stroke, visual impairment, cardiac disease, and dementia.

Psychiatric and Behavioral Causes:

Depression: Depression is an especially frequent disorder in later life. Blazer and Williams reported that 14.7% of free-living elderly subjects had depressive symptoms and 3.6% had a major depressive disorder. An even higher incidence of depression has been found in the institutionalized elderly. Depression may be present as a vague complaint without a patient's awareness that anything is wrong emotionally or psychologically. It may lead to apathy, anorexia, and weight loss. Depressed patients have decreased ability to care for themselves, and they may lose interest in eating. Depression may be difficult to diagnose because it may present atypically with pseudodementia, somatization, or pain syndromes. Standardized screening tests are useful for confirming the diagnosis.

Anxiety: Anxiety is a less common cause of weight loss. Increased agitation may result in increased metabolic demands. Patients may be preoccupied and forget to eat.

Bereavement: Loss of a loved one may cause grieving over an extended period of time accompanied with a loss of interest in eating entirely.

Alcoholism: Alcoholism may occur for the first time at any point in life and may or may not be associated with depression. It frequently may result in poor nutrition and subsequent weight loss. The diagnosis of alcoholism can be difficult, and vague complaints such as anorexia or weight loss may be the only signs of an underlying problem.

Sociopathy:Elderly people may lose a sense of control. Food refusal may be used as a way to gain back some degree of control and increase interaction with others, including the staff in an institution. Some patients also develop abnormal attitudes about eating. They may fear being overweight and may believe that decreasing their food intake will allow them to stay healthy.

Social Causes^{1, 13}:

Isolation:People tend to eat more in social situations, and social isolation for any reason may result in decreased food intake. Hearing impairment, for instance, may make some people reluctant to enter into social situations.

Economic Hardship:Economic hardships may result in difficult financial choices, and healthy food may not always be affordable.

Evaluation of Unintentional Weight loss

Documentation

An elaborate workup of weight loss is hardly indicated without adequate documentation of the weight loss. Perception of weight loss may be influenced by the rate of weight change, gender, original body size, and underlying disorders present. Up to 50% of patients with weight loss as a complaint do not have corroboration by medical records or family⁷. The most accurate documentation would be previous medical records, but if records are unavailable a patient's report of previous weight or change in clothing size confirmed by others is sufficient documentation.

Evaluation

The cause of involuntary weight loss is rarely occult. Careful history and physical examination, in association with directed diagnostic testing, will identify the cause of weight loss in 75% of patients¹³. The etiology of weight loss will not be found in the remaining patients, despite extensive testing. Patients with negative evaluations tend to have lower mortality rates than those found to have organic disease.

- In the history taking the following details should be asked^{1, 13,15};

1-Fever, pain

2-Shortness of breath or cough

3-Palpitation

4-Changes in pattern of urination

5-Gastrointestinal disturbance (anorexia, dysphasia, change in bowel habits)

6-Evidence of neurological disease

7-Risk factor for HIV infection

8-Cigarette smoking

9-Alcohol use

10-Current and past medication

11-Psychiatric problems

12-Previous abdominal surgeries

13- Financial issues (affect food intake)

- In the physical examination the following information should be sought^{1, 13,15},

1-Vital signs

2-Appearance and skin; for pallor, jaundice, scars of previous surgeries, skin turgor

3-Oral cavity; for thrush and dental disease

4-Thyroid; for thyromegaly

5-Lymphatic system; for lymphadenopathy

6-Heart and lung; for signs of cardiac or pulmonary diseases

7-Abdomen; for organomegaly

8-Breast; for lumps

9-Rectal/pelvic exam

10-Neurological evaluation, including Mini-Mental State Examination

Diagnostic testing^{13, 18} should first be directed at clues or areas of concern found on history physical examination, an undirected ("Shotgun") approach to laboratory tests is rarely fruitful. If no clues are discovered during history and physical exam, initial following tests are indicated:

1-Complete blood count with differential

2-ESR

3-Electrolytes, Calcium, Glucose

4-Renal and liver function tests

5-Urinalysis

6-TSH

7-Chest X-ray

8-Stool hemoccult (OB)

9-HIV test for persons at risk

In the absence of localizing symptoms or signs or findings on the laboratory work listed above, routine screening test for cancer is indicated, as recommended by American Cancer Society¹⁵:

1-Flexible sigmoidoscopy (if fecal occult blood negative and age \geq 50)

2-Cervical Pap smear in women

3-Mammography in women aged \geq 40 years

4-Prostate-specific antigen in men aged \geq 50 years

Additional laboratory (Iron studies, B12, Folate, Endomyosial antibody, PTH, ACTH...) and radiological (Abdominal and chest CT, Barium studies) tests should be based on the diagnoses suspected by history, physical exam, and previous laboratory data. For example, if gastrointestinal signs or symptoms are present, upper and/or lower endoscopy and abdominal imaging have relatively high yields.

A rational stepwise approach to the patient presenting with unintentional weight loss is outlined in Figure 1⁵.

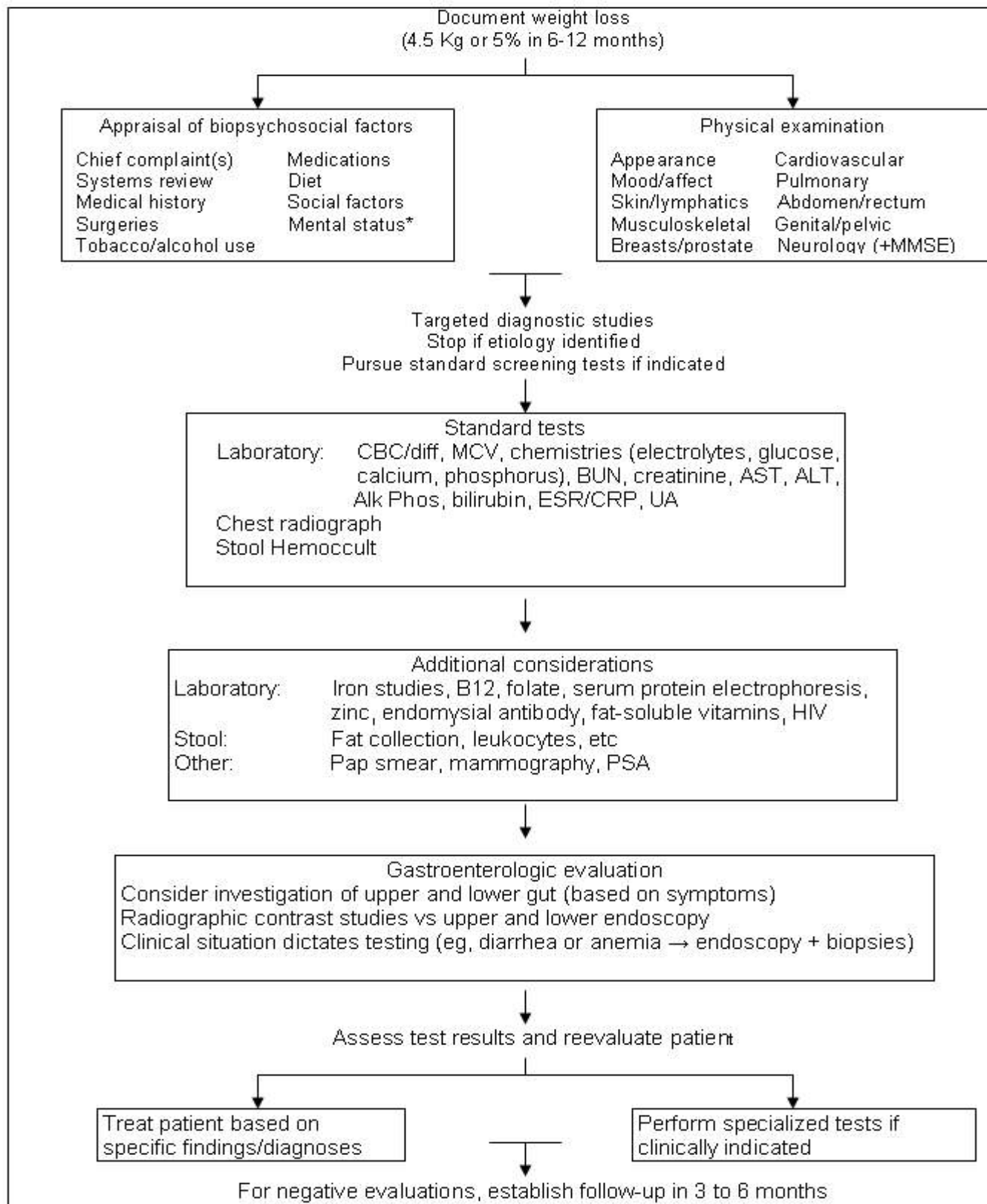


Figure 1. Stepwise approach to patients with unintentional weight loss. Alk Phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood cell count; CRP = C-reactive protein; diff = white blood cell count differential; ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; MCV = mean corpuscular volume; MMSE = Mini-Mental State Examination; Pap = Papanicolaou; PSA = prostate-specific antigen; UA = urinalysis. *Depression inventories may be useful.⁵

Patients with a negative evaluation are unlikely to have a serious organic explanation for weight loss. If a satisfactory evaluation is negative (in about 25% of patients), one should establish a management plan that includes a predetermined follow-up in 3 to 6 months because some causes of weight loss can be subtle and may be revealed with time and continued vigilance. Additionally, many patients' nutritional status should be monitored even if a specific etiology of weight loss cannot be determined.

Management Principles⁵:

Early intervention based on the findings of the diagnostic evaluation provides the greatest opportunity for success. The severity of weight loss should be determined by a nutritional assessment, including a biochemical analysis combined with a thorough dietary history, evaluation of the patient's psychosocial situation, and consideration of anthropometric or other qualitative evaluations. A simple and common anthropometric evaluation is the body mass index (BMI). The BMI is defined as body weight (kilograms)/height (meters²). A BMI lower than 17 is consistent with undernutrition. The specific etiologies of weight loss should be treated accordingly, with medications, structural or functional modifications (e.g., gut revascularization, dentistry), nutritional supplementation, psychosocial modulation, or multimodal therapy.

Nutritional Therapy⁵:

Nutritional therapy, including dietary education and/or use of dietary supplements supervised by a dietician, is beneficial for most patients. One should consider reducing dietary restrictions instituted for an underlying disease if they are

further aggravating nutritional balance. The goal of nutrient intake in patients with low body weight and pronounced weight loss should be 30 to 35 kcal/kg per day with 20% or greater protein content. For malnourished elderly patients and those with mild to moderate illness, a goal of 40 kcal/kg per day should be used. High caloric snacks and nutritionally complete supplements are useful; however, one should be mindful of the timing of supplement delivery (snacks between rather than with meals) and the type of supplement prescribed (composition, patient tolerance, etc). Nutritional supplementation should be enteral, with the oral route preferred. For patients who are unable to ingest adequate calories, tube feeding, either with a temporary nasojejun tube or more permanent access with a percutaneous gastric or jejunal tube, should be considered. The addition of a daily multivitamin will help restore deficient micronutrients. Parenteral nutrition should be reserved for highly selected patients.

Pharmacological Therapy:

Various agents⁴ that have been used to stimulate appetite and promote weight gain are listed in Table 4.

Table 4. Agents Used to Stimulate Appetite and Promote Weight Gain

Category	Examples
<i>Orexigenic agents</i>	
Corticosteroids	Dexamethasone, methylprednisolone
Progestational agents	Megestrol acetate, medroxyprogesterone acetate
Dronabinol	Marinol
Serotonin antagonist	Cryoheptadine
<i>Anabolic agents</i>	
Growth hormones	Growth hormone, insulin-like growth factor
Androgen therapy	Testosterone, dihydrotestosterone, testosterone analogues
<i>Anticatabolic agents</i>	
Dietary anticytokine	w-3 Fatty acids
Methylxanthine derivative	Pentoxifylline

Inhibitor of
gluconeogenesis

Hydrazine sulfate

Proposed anticytokine
activity

Thalidomide, melatonin

Although some studies involving selected patients (e.g., those with AIDS and cancer) suggest efficacy manifested as improved appetite and weight, studies demonstrating improvement in long-term survival are not available. Some of these drugs have serious potential adverse effects and should be used with caution. Any therapeutic trials with these agents necessitate close supervision.

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