Orexigenic and anabolic agents

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Orexigenic agents

A number of drugs have been used to stimulate appetite and produce weight gain in older persons. Historically, the agent first used was cyproheptadine acetate [1], which has proved to be minimally effective and can produce delirium. No controlled trials have been conducted in older persons. Ornithine oxoglutarate, a glutamine precursor, is an orexigenic agent that results in weight gain. It has been used successfully in Europe but is not available in the United States [2]. Two agents are widely used to stimulate appetite, namely, megestrol acetate and dronabinol. The effects of these agents are discussed in detail.

Megestrol acetate

Megestrol acetate (Megace) (Bristol Myers Squibb, Princeton, New Jersey) is a progestational agent that produces an increase in food intake. The mechanisms by which megestrol acetate increases appetite is uncertain but are thought to involve alterations in CNS neurotransmitters involved in the regulation of food intake [3]. In animals, estrogen decreases food intake, and progestational agents antagonize this effect. Megestrol acetate also antagonizes cytokine production [4]. Tumor necrosis factor–alpha (TNF-\textalpha), interleukin-6, and ciliary neurotrophic factor are potent anorectic agents that also cause muscle loss [5–7]. Thus, the effect of megestrol acetate may involve, in part, the inhibition of the effects of cytokines on food intake and muscle.

With use of megestrol acetate, weight gain has been reported in numerous patients with cancer-related anorexia and wasting [8]. Several randomized, placebo-controlled trials have confirmed the effect of megestrol acetate on appetite.
and weight gain [9]. Anorexia in cancer patients has been reversed with doses ranging from 80 mg to 800 mg/day [10]. Westman, Bergman, Albertsson, et al [11] found that although megestrol acetate enhanced appetite and reduced weight loss with minimal toxicity in persons with end-stage cancer, it failed to improve quality of life. The combination of megestrol acetate and the prostaglandin inhibitor, ibuprofen, however, resulted in weight gain and also improved quality of life [12].

A number of studies of the effect of megestrol acetate in patients with AIDS have been carried out. Oster, Enders, Samuels, et al [13] reported increased caloric intake and weight gain in AIDS patients receiving megestrol acetate. Fat mass increased, but there was no increase in body water or lean body mass. Patients receiving megestrol acetate reported an increased sense of well-being. Two other studies have reported a small increase in free fat mass in patients with AIDS receiving megestrol acetate [14,15]. Megestrol acetate improved appetite in a small number of patients with cystic fibrosis [16]. Megestrol acetate also prevents the anorexia and weight loss associated with interferon-alpha (IFN-α) or interleukin-2 antineoplastic therapy [17].

Another progestational agent, medroxyprogesterone acetate, has been associated with increased caloric intake, increased strength, and positive nitrogen balance [10]. A multicenter cooperative trial involving 279 oncology patients showed that 1 g of medroxyprogesterone acetate administered daily as an oral suspension increased body weight and improved performance status [18]. Medroxyprogesterone acetate can produce depression and diabetes in women. Yeh and colleagues [19–21] studied the effects of megestrol acetate (800 mg/day) in 69 nursing home patients with weight losses greater than 5% of usual body weight or with a body weight 20% below ideal body weight. Drug or placebo was administered for 12 weeks. At 12 weeks, persons receiving megestrol acetate had a better appetite, greater enjoyment of life, and stronger sense of well-being but did not have a statistically significant improvement in body weight. In the 12 weeks following megestrol acetate treatment, however, the patients who had received megestrol acetate had a significant increase in weight gain. Cachectic patients had elevated interleukin-6 levels at baseline. The improvement in weight, fat mass, free fat mass, appetite, prealbumin level, albumin level, and quality of life were correlated with the reduction in cytokine levels produced by megestrol acetate. This study suggests that a major effect of megestrol acetate is to reduce cytokine levels, thereby reversing anorexia in older persons with elevated cytokine levels.

Most of the side effects seen with megestrol acetate are mild. These side effects include fluid retention, flushing, erectile dysfunction, and vaginal bleeding. In some older patients who are bed-bound, megestrol acetate has been associated with an increase in deep vein thrombosis [22]. Megestrol acetate can also cause adrenal insufficiency in some cases [10].

Persons receiving megestrol acetate often add fat mass out of proportion to muscle mass [23]. In men, this disproportionate addition of fat seems to result from the megestrol acetate–induced decrease in testosterone levels, resulting in a
decline in anabolism in the patient [24]. Thus, it is now recommended that men receiving megestrol acetate also be given testosterone.

In general, megestrol acetate seems to be useful for stimulating appetite in older persons with anorexia caused by cytokine excess. These patients include persons with cancer, AIDS, recurrent infections, pressure ulcers, and severe arthritis. Using this approach in older nursing home residents, the authors have successfully produced weight gain and increased albumin and hematocrit levels [25].

Dronabinol

“in all that I have seen voraciously hungry.”
–W.B. O’Shaugnassey, 1838

Cannabis was used as an appetite stimulant in ancient Aryuvedic and Arabic medicine. In the early 1970s, cannabis was objectively demonstrated to increase food intake [26,27]. A study of the subjective effects of cannabis demonstrated that it increases the desire for food and also improves taste, makes substances smell richer, decreases pain, and improves mood [28]. This combination of attributes strongly suggests its utility in end-of-life care.

The active ingredient of cannabis is Δ9-tetrahydrocannabinol. There are two endogenous receptors for cannabis, namely, the CB1 or CNS receptor and the CB2 or peripheral receptor [29]. The endogenous ligand for the cannabis receptor is arachidonyl-ethanolamide, which has the trivial name anandamide, from the Sanskrit word meaning “inner bliss.”

Dronabinol (Marinol) (Solvay Pharmaceuticals, Inc., Manette, Georgia) is a synthetic Δ9-tetrahydrocannabinol. It has been demonstrated to be an effective appetite stimulant in patients with AIDS [30]. It also improves appetite in patients with cancer. The doses used range from 2.5 to 20 mg/day. The orexigenic effects may not be apparent for 2 to 4 weeks. The major reported side effects of dronabinol are delirium, abdominal pain, occasional nausea, and, at very high doses, ataxia. Dronabinol has also been used as an antiemetic in patients with AIDS or cancer [31]. It is particularly effective in combination with chlorpromazine in patients with severe vomiting. It may be useful in the treatment of anticipatory nausea and vomiting in patients undergoing chemotherapy.

A single study has examined the effect of dronabinol in older, demented patients. Eleven patients aged 65 to 82 years were studied utilizing a double-blind crossover study design [32]. The mean weight gain was 9.3 lbs in the dronabinol group and 6.3 lbs in the placebo group. Agitation was decreased in the dronabinol group, as measured by the Cohen-Mansfield Agitation Index.

Besides its appetite and antiemetic effects, dronabinol decreases pain and improves mood. These attributes make it an ideal drug for end-of-life patients. It has a potential calming effect in dementia patients. To limit the occurrence of delirium in older patients, dronabinol should be given in the evening and at a low starting dose. Appetite stimulation usually occurs with low doses of 5 to 7.5 mg. There is a major need for more studies of this orexigenic agent.
Anabolic agents

Testosterone is the prototypic anabolic agent. Because testosterone levels, and particularly the free or bioavailable testosterone levels, decline with age [33,34], it is not surprising that older men lose muscle mass. This loss of muscle mass has been shown to be related directly to the decline in free testosterone levels [35]. Bio-effective testosterone levels are even lower in persons with systemic illness [36].

Testosterone replacement in older men has been demonstrated to increase muscle mass [37,38] and in some cases to increase muscle strength [39–41]. In addition, testosterone replacement decreases fat mass, increases bone mineral density, and enhances cognition [38,42,43]. Bakshi, Elliott, Gentili, et al [44] showed that testosterone replacement in older men undergoing rehabilitation improves muscle strength and increases the functional index measure (FIM). There is some evidence that low-dose testosterone replacement might improve functionality in older women [45].

A small amount of data supports the use of anabolic steroids in older persons with cachexia. Use of both oxandrolone and anadrol has enhanced weight gain in patients with AIDS [46,47]. Results in cancer patients have been less promising [48,49]. Anecdotally, oxandrolone has been reported to increase appetite and improve wound healing [50], but controlled trials are lacking. Nandrolone decanoate has been shown to increase anabolism in patients with renal failure receiving dialysis [51]. Nandrolone increases appetite and sense of well-being in cancer patients [52]. Because nandrolone is given as an injection into muscle rather than orally, it avoids the first-pass liver toxicity associated with oral anabolic steroids. Danazol produces weight gain and fluid retention in patients with breast cancer [53]. Anabolic steroids potentiate the effects of warfarin.

Growth hormone and insulin growth factor-1 decline with aging [54]. Insulin growth factor-1 levels decrease even more in malnourished older persons [55–57]. A number of years ago Kaiser, Silver, Morley, et al [58] reported a preliminary study suggesting that growth hormone might be useful in reversing catabolism in older persons with malnutrition. Subsequently, a number of studies have suggested that growth hormone may have some value in treating severely ill, malnourished patients [59]. Osterzeil, Dietz, Ranke, et al [60], however, in a large, controlled trial in critically ill, malnourished patients found an increased death rate in those receiving growth hormone.

Chu, Lam, Tam, et al [61] administered recombinant growth hormone to 19 malnourished older patients. They found an increase in lean body mass and in albumin and hemoglobin levels. In addition, 5-minute walking distances increased. Treatment lasted 8 weeks, and no adverse effects were seen.

Glucocorticoids have been widely used in hospice patients. Glucocorticoids decrease production of TNF-α and inhibit prostaglandin metabolism. In animals prostaglandins are potent inhibitors of appetite [62], as is TNF-α. Both dexamethasone and prednisolone improve appetite and mood but have minimal effects on weight gain or function in persons with the cancer cachexia syndrome [63]. Side effects include delirium, depression, insomnia, suppression of the
hypothalamic-pituitary-adrenal axis, and gastrointestinal bleeding. There seems to be little reason to use glucocorticoids purely for their appetite-stimulating effect.

Overall, testosterone seems to be the safest of the anabolic agents. Testosterone has been shown to increase muscle mass and to improve muscle strength and should be the anabolic agent of choice in men. In women, low-dose testosterone or an anabolic steroid with a lower androgenic:anabolic ratio would seem to be the drug of choice. Oral anabolic steroids can produce liver toxicity and renal failure. Their use should be limited to 3 months.

**Experimental drugs**

**Thalidomide**

Thalidomide (alpha-N-phthalimido-glutarimide) is an old drug that suppresses TNF-\( \alpha \) production from human monocytes in vitro and in vivo reduces circulating levels of TNF-\( \alpha \) in patients with leprosy and tuberculosis [64]. In 30 male patients with tuberculosis, thalidomide caused significant weight gain with minimal side effects [64]. Production of interferon-\( \gamma \) was increased.

Thalidomide (100 mg four times/day) was compared with placebo in 28 adults with AIDS receiving antiretroviral therapy [65]. Eight of 14 patients receiving thalidomide gained weight, as did 1 of 14 in the placebo group. Side effects of thalidomide included sleepiness and an erythematous macular skin rash. At the end of the study, the Karnofsky index was greater in the thalidomide group than in the placebo group. In a second study, 103 male patients with AIDS were randomly assigned to receive placebo or thalidomide at dosages of 100 or 200 mg/day [66]. Both doses of thalidomide resulted in significant weight gain. Half of the weight gain was in lean body mass. Side effects included rashes and fevers.

Thalidomide was originally marketed for its sedative properties but was found to be teratogenic when taken by women of childbearing age or by their spouses. Preliminary studies suggest that thalidomide may be useful in the treatment of some cachectic older persons who are overproducing cytokines.

**Eicosapentanoic acid**

Eicosapentanoic acid is one of the components of fish oil. Dietary n-3 fatty acids decrease the production of TNF-\( \alpha \) and interleukin-1 in vitro [67]. In rodents, n-3 fatty acids also reduce cytokine-induced anorexia [67] and lipid mobilizing factor, a cachectic substance produced directly by tumors [68].

A single study has examined the effect of dietary n-3 fatty acid supplementation (18 g/day) in AIDS patients [67]. Patients who did not develop new AIDS-related complications had a small increase in weight. Overall, however, there was no significant increase in weight in this population. Cytokine production was
mildly suppressed. Overall, this study does not support the use of fish oil as an anticytokine for stimulating appetite and reversing cachexia.

**Tumor necrosis factor–alpha antibodies**

The central role of TNF-α in producing inflammation associated with anorexia has led to the use of infliximab to treat a number of inflammatory conditions. Infliximab halted the progression of joint damage and improved quality of life in patients with chronically persistent rheumatoid arthritis [69]. Similar improvements have been seen in patients with Crohn’s disease [70], sarcoidosis [71], and Behcet’s disease [72]. Animal studies suggest inhibition of TNF-α in rodents with inflammation increases food intake and decreases weight loss [73]. Infliximab would seem to be worth trying in older persons with severe weight loss and cytokine disease.

**Cholecystokinin antagonists**

Animal studies have demonstrated that older animals are more sensitive than younger animals to the anorectic effects of cholecystokinin (CCK) [74]. In humans, basal and lipid-stimulated CCK levels are higher in older persons [75,76], and this effect is more marked in older persons with malnutrition [77]. When CCK is administered to older humans, it is a more potent anorectic agent than it is in younger persons [78], perhaps, in part, because plasma clearance is slower in older persons than in younger persons.

A number of CCK antagonists have been developed [79]. Animal studies have shown that CCK antagonists can increase food intake [80]. It would seem worthwhile to examine the effects of CCK antagonists in persons with the anorexia of aging.

**Nitric oxide donors**

Early satiation occurs in older persons because of a loss of adaptive relaxation of the fundus and more rapid antral filling [81,82]. In older rodents there is a decrease in fundal nitric oxide, which is the mediator of adaptive relaxation [83]. Inhibition of nitric oxide results in a decrease in food intake in animals [84,85], although this effect could not be demonstrated with low-dose nitric oxide inhibition in humans [86]. Infusion of glyceryl trinitrite in humans results in an increase in the size of the fundus of the stomach [87]. Older persons with early satiation sometimes improve their food intake after taking glyceryl trinitrite sublingually [88]. Nitric oxide donors are a potentially important therapeutic option for older persons suffering from early satiation.

**Antidepressants**

Depression is the most common treatable cause of anorexia and weight loss in older persons [89,90]. Although any agent that improves mood is likely to in-
crease weight gain, some antidepressants seem to be more orexigenic than others. Monoamine oxidase inhibitors are classic enhancers of weight but have fallen into disfavor because of their side-effect profile [91].

Mirtazapine is a multireceptor alpha-2 noradrenergic presynaptic antagonist/serotonergic agonist antidepressant [92]. By antagonizing the presynaptic receptor, mirtazapine increases noradrenergic transmission. It has agonist properties on the 5-HT1 receptor but is a 5-HT2-receptor antagonist [93]. This combination of effects on the noradrenergic and serotonergic receptors suggests that mirtazapine would have specific appetite-enhancing effects [94]. Clinical studies have confirmed that use of mirtazapine results in increased appetite and more weight gain than does the use of selective serotonin reuptake inhibitors [95–97]. Mirtazapine would seem to be the antidepressant of choice for older depressed persons with weight loss.

Gastroprokinetic agents

In older persons, slowed gastric emptying has been shown to be associated with decreased hunger [98]. Most agents that enhance gastric emptying are antidopinergic agents. These include metoclopramide, cisapride, and domperidone. Cisapride was removed from the market in the United States because of its effects on the heart. Domperidone is not available in the United States. Metoclopramide crosses the blood-brain barrier and thus can worsen Parkinson’s disease and produce delirium. Cisapride is more effective than the other two agents in accelerating gastric emptying [99].

Cisapride increases the rate of gastric emptying and hunger but does not increase weight gain in patients with anorexia nervosa [100]. Cisapride also decreases early satiation in patients with nonulcer dyspepsia [101]. Cisapride is less effective than megestrol acetate in improving appetite and decreasing weight loss in patients with head and neck cancer [102]. Metodopramide decreases anorexia, bloating, and nausea in patients with advanced cancer [103]. Domperidone decreases weight loss in advanced cancer [103]. Domperidone decreases nausea, anorexia, dysphagia, and abdominal bloating in Parkinson’s patients without interfering in their treatment [104]. Cisapride reverses the delayed gastric emptying and decreases anorexia in patients receiving IFN-α [105].

Overall, gastroprokinetic agents have minimal effects on food intake in older persons unless they have severe delays in gastric emptying or gastroesophageal reflux disease.

Summary

Anorexia and weight loss represent a major cause of morbidity and mortality [106–112]. At present in the United States two effective anorectic agents are commonly used, namely, megestrol acetate and dronabinol. These two agents are
compared in Table 1. In persons with a large excess cytokine production, megestrol acetate should be tried at a dose of 800 mg per day for no longer than 3 months. Megestrol acetate should be administered with testosterone in men. It should be avoided in persons who are bed-bound because of the risk of deep vein thrombosis. Dronabinol should be used for most anorectic patients. Dronabinol should initially be given in a low dose (2.5 mg) in the evening. The dose should be increased to 5 mg per day if no improvement in appetite is seen after 2 to 4 weeks. Dronabinol can be continued indefinitely. It seems to have a particularly good profile for persons with anorexia who are at the end of life. In persons with depression and anorexia, mirtazapine seems to be the antidepressant

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**Table 1**  
Comparison between megestrol acetate and dronabinol

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<th>Megestrol acetate</th>
<th>Dronabinol</th>
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<tbody>
<tr>
<td>Increased appetite</td>
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<td>Yes</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Decreased nausea</td>
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<td>Yes</td>
</tr>
<tr>
<td>Muscle mass gain</td>
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</tr>
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<td>No</td>
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<td>Decreased adrenal function</td>
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<tr>
<td>Hypercoaguable state</td>
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<td>No</td>
</tr>
<tr>
<td>Delirium</td>
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<td>Yes (rare)</td>
</tr>
<tr>
<td>Improved mood</td>
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<td>Yes</td>
</tr>
<tr>
<td>Decreased pain</td>
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**Fig. 1.** The use of orexigenic and anabolic drugs in managing decreased appetite and weight loss in older persons.
of choice. In addition, the use of taste enhancers can be considered in persons who complain that the food does not taste good [113].

The appropriate use of anabolic agents in older persons with weight loss is controversial. Certainly all older men who are losing weight should have bioavailable testosterone measured [114] and, if the testosterone level is low, should receive testosterone replacement therapy [115]. Women who are losing weight may benefit from the use of low-dose testosterone (eg, Estratest). Anabolic agents, such as oxandrolone, should be reserved for those who have profound cachexia.

An approach to the management of anorexia and weight loss in older persons is given in Fig. 1. Thomas et al [116] have provided a more complex algorithm for the management of weight loss in nursing home residents.

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