

REVIEWS OF THERAPEUTICS

Megestrol Acetate and Mirtazapine for the Treatment of Unplanned Weight Loss in the Elderly

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A rising concern among clinicians is treatment of unplanned weight loss in the elderly, especially given the predicted growth of this population over the next few decades. Unexpected weight loss in the geriatric patient worsens overall health outcomes. A variety of pharmacotherapeutic options are available for treatment; however, evidence underlying their use is limited, and none has gained approval from the United States Food and Drug Administration for this indication. At present, no guidelines support the choice of one agent over another. Although several drug interventions have been employed for this problem, megestrol acetate and mirtazapine are becoming increasingly used for appetite stimulation. These drugs represent two feasible options for geriatric patients because of their generally favorable adverse-effect profiles and few drug interactions, but they are often misused. In a comprehensive search of the MEDLINE and International Pharmaceutical Abstracts databases, we identified all published reports on the use of megestrol acetate or mirtazapine for the treatment of weight loss and on any adverse events associated with these drugs. Special emphasis was placed on trials performed in an elderly population. Results were conflicting, most likely because of differing study designs and small numbers of patients. Megestrol acetate and mirtazapine appear to be effective for appetite stimulation and weight gain in some settings. However, applicability of the data to elderly individuals is unclear, and adverse events reported in a few of the trials and in case reports were not benign. Therefore, the use of megestrol acetate or mirtazapine for weight loss should be thoroughly evaluated on an individual basis. Pharmacotherapy should be used only after all underlying causes of weight loss are assessed and treated.

Key Words: weight loss, appetite stimulation, megestrol acetate, mirtazapine, elderly, geriatric, cachexia, failure to thrive.

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OUTLINE

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Weight loss is common in the elderly population. It is not unusual for an older person to lose 5% of their body weight over 1–3 years.¹ Body weight starts declining after the age of 60 years for a multitude of reasons, such as decreased food intake, depression, drug therapy, impaired functional status, and certain medical conditions. The National Center for Health Statistics report for 2006 states that the mean decrease in energy and macronutrient intake between the ages of 20 and 74 years is 730 kcal for men and 449 kcal for women.² Approximately 30–50% of nursing home residents have below-average body weight and low serum albumin concentrations.³

What is concerning about these data is the plethora of evidence that relates weight loss in the elderly to poor overall health outcomes. Unintended weight loss can lead to loss of skeletal muscle. As opposed to fat loss, loss of skeletal muscle can cause functional impairments, falls, and an increased risk of protein malnutrition. These effects, in turn, can lead to immune system compromise, anemia, reduced cognition, and, ultimately, increased morbidity and mortality.^{1,3,4}

In one study of 4714 community-dwelling elderly participants, 17% lost 5% or more of their initial weight within 3 years.⁵ Total and risk-adjusted mortality significantly increased over 4 years by 2.09 times (95% confidence interval 1.67–2.62) and by 1.67 times (95% confidence interval 1.29–2.15), respectively, in those with weight loss versus those with stable weight. In the Framingham Heart Study, the relative risk for death was twice as high in subjects older than 65 years who had a body mass index at the lower extremes than in their counterparts who had higher body mass indexes.³ Another report described a significant decrease in 2- and 3-year survival rates in subjects who had an involuntary weight loss of more than 4%.⁶ Researchers from several studies have linked low body weight and low albumin levels (< 3.2 g/dl) to increased hospital mortality rates, lengths of stay, and health care costs.⁷

The risk for weight loss is of particular concern in nursing home residents. The frequency of weight loss in this population varies between 4%

and 65%.⁷ The Centers for Medicare and Medicaid Services require that all nursing home residents be assessed for weight loss.⁸ If a significant loss—defined as 5%/1 month, 7.5%/3 months, or 10%/6 months—occurs, the facility must intervene to address the nutritional problem.

Pharmacotherapy for Treatment of Weight Loss

Data regarding morbidity and mortality, as well as the aforementioned regulations, may be why clinicians are turning to drug therapy options for unplanned weight loss in the elderly. Clinicians caring for a patient experiencing unintended weight loss often feel pressured to reverse the decline and prevent poor health outcomes. Although management of weight loss in the elderly involves evaluation and interventions by multiple health professionals, caregivers are often quick to request pharmacotherapy, and prescribers readily provide it.

A variety of interventions are often used for either appetite stimulation or nutritional support. Typical pharmaceutical agents include nutritional supplements, appetite stimulants, anabolic hormones, and antidepressants.⁹ Unfortunately, drug intervention is often started without thorough consideration of the underlying cause of the patient's weight loss or without an in-depth understanding of the effects or proper use of the agents prescribed. This oversight can lead to additional poor outcomes due to a lack of efficacy, polypharmacy, adverse effects, drug-drug or drug-disease interactions, therapeutic duplications, or increased cost.

Two drugs most commonly prescribed in current practice are megestrol acetate and mirtazapine. Megestrol acetate is a synthetic progestin and antineoplastic agent that the United States Food and Drug Administration (FDA) first approved for the palliative treatment of advanced breast and endometrial cancer.¹⁰ Significant weight gain was an adverse effect of treatment that led to further research in other disease states known to cause anorexia and/or cachexia. Most recently, the use of megestrol acetate has gained FDA approval for the treatment of weight loss related to acquired immunodeficiency syndrome (AIDS).

Mirtazapine is an antidepressant that antagonizes serotonin (5-HT₂ and 5-HT₃) and histamine (H₁) receptors. Mirtazapine causes weight gain in approximately 12% of patients who take this drug for depression.¹¹ This side

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effect is often a limitation of treatment in young adults, but it may prove beneficial in elderly patients with unintentional weight loss.

Although many articles describe the effects of megestrol acetate and mirtazapine on weight in various populations, a thorough review of these agents for treatment of unintended weight loss in elderly patients is lacking. Neither drug is FDA approved for this indication. Thus, we comprehensively searched the MEDLINE and International Pharmaceutical Abstracts databases (1970–January 2008) to identify all literature pertaining to the use of megestrol acetate and mirtazapine for treatment of weight loss in the elderly. All published reports that addressed weight as a primary or secondary outcome were included in our review. Trials were excluded if the study protocol targeted elderly patients with comorbid conditions for which megestrol acetate had already been proven effective for weight gain (e.g., cancer). No studies that examined mirtazapine for weight loss were excluded. Ten trials of megestrol and two of mirtazapine met the criteria. The objective of our review was to increase our understanding of the efficacy and safety of these drugs in the elderly, thereby improving therapeutic decision-making.

Pathophysiology of Weight Loss in the Elderly

One of the first hurdles that clinicians must overcome when deciding if drug therapy is appropriate for unintended weight loss is evaluating the most likely etiology and determining whether the drug's mechanism for stimulating appetite or weight gain is likely to address that cause. To do this, it is important to first consider what weight loss means.

Sarcopenia, cachexia, wasting (or anorexia of aging), and failure to thrive are all commonly used to describe weight loss. These terms can be confusing because they are not necessarily interchangeable and are subject to interpretation.

Sarcopenia is defined as involuntary loss of muscle mass to more than 2 standard deviations below the sex-specific, young-normal mean.¹ Cachexia is defined as weight loss in the presence of an immune response, resulting in a loss of nonfat mass (e.g., muscle mass, bone mineral density). This is most notably seen in patients with human immunodeficiency virus infection or AIDS and those with cancer. However, it can also occur among people with pressure sores, infections, or other common causes of inflammation, especially in institutionalized elderly

individuals. Wasting, or anorexia of aging, is a term associated with an age-related decrease in appetite and energy intake, which inevitably results in weight loss.¹²

Failure to thrive tends to be a catch-all term encompassing weight loss, as well as other factors. In fact, the Institute of Medicine defined late-life failure to thrive as a “syndrome manifested by weight loss greater than 5% of baseline, decreased appetite, poor nutrition and inactivity, often accompanied by dehydration, depressive symptoms, impaired immune function and low cholesterol levels.”¹³ In practical use, this term is typically used to describe individuals whose condition, despite intervention, continues to decline.

Physiologic Mechanisms

Cytokines, especially interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α , are thought to play an important role in sarcopenia and cachexia. These markers of inflammation can increase resting energy expenditures in individuals with sarcopenia or cachexia.¹⁴ Circulating concentrations are heightened in patients with inflammatory conditions, and interventions designed to decrease these levels have resulted in weight gain.³

Other common findings in aging individuals, compared with a younger cohort, are increased cortisol and catecholamine concentrations, as well as decreased levels of sex and growth hormones. These changes are similar to those seen in patients under chronic stress, and this observation led to the hypothesis that simple aging is a stressor to the body.¹⁵ The sequela of increased cortisol and catecholamine levels is stimulation of IL-6 and TNF- α that raises circulating levels.³ Sex hormones can inhibit IL-6; therefore, a decrease in sex hormone levels can impair this purported safety net.¹⁶ Megestrol acetate may directly inhibit these cytokines; this proposed mechanism is one of the reasons underlying its use for weight gain.¹⁷

Serotonin is believed to play a role in the pathophysiology of cachexia, as increased levels of serotonin in the central nervous system have led to early satiety.^{18, 19} However, antagonism of serotonin receptors may increase appetite. Mirtazapine is a potent inhibitor of 5-HT₂ and 5-HT₃ receptors; this fact may explain the mechanism by which it stimulates appetite.¹⁸

Several mechanisms are hypothesized to be the causes of appetite loss in the wasting condition.

Cholecystokinin levels and sensitivity to the effects of cholecystokinin increase with age.^{20, 21} Cholecystokinin is the hormone responsible for the rate of gastric emptying, and high levels are implicated in early satiety.^{20, 22} Leptin, a peptide hormone produced mostly in adipose tissue, is hypothesized to play a role in long-term satiety and a decreased hunger drive. However, the relevance of this finding in elderly patients is not clear.¹⁷ No drugs are currently FDA approved to stimulate appetite by directly intervening on any of these targets.

Other Mechanisms

Many other causes can contribute to the distressing condition of weight loss in the aged. Disease states, as well as social and economic factors, can contribute to weight loss. Table 1 lists causes of weight loss in the elderly using a “meals-on-wheels” mnemonic.¹² Of particular interest to pharmacists are the effects of drugs on weight (Table 2).¹² Drugs can induce weight loss in several ways, typically as a result of their adverse effects. Examples of these adverse effects include nausea (e.g., cholinesterase inhibitors), slowing of gastrointestinal motility (e.g., agents with anticholinergic action such as diphenhydramine), and decreased absorption of nutrients (e.g., bile acid sequestrants).

Intervention with drugs, such as megestrol or mirtazapine, is often begun without a thorough review of the etiology of the patient's weight loss. Yet, this type of therapy may be unnecessary and inappropriate if the weight loss can be addressed by using another strategy. A patient's medical history, functional status, and drug regimen should be evaluated for correctable problems before megestrol, mirtazapine, or any drug is considered.

Efficacy of Megestrol Acetate

Megestrol acetate was evaluated in randomized controlled trials for the treatment of anorexia in patients with cancer, AIDS, or chronic obstructive pulmonary disease (COPD).^{23–33} The resulting literature, particularly reports of studies of patients with cancer in the early 1990s, provided the basis for investigating megestrol acetate for the treatment of weight loss in elderly patients. Likewise, the design and end points of these early studies set the stage for trials specific to the elderly population.

Study durations and doses of megestrol acetate varied. Patients with cancer received 160–1280

Table 1. Meals-on-Wheels Mnemonic for Causes of Weight Loss in the Elderly

Mnemonic	Causes of Weight Loss
M	Medications
E	Emotional
A	Alcoholism, anorexia nervosa, abuse
L	Late-life paranoia
S	Swallowing problems (dysphagia)
O	Oral problems
N	No money (poverty)
W	Wandering and other dementia-related problems
H	Hyperthyroidism, pheochromocytoma
E	Enteric problems (malabsorption)
E	Eating problems
L	Low-salt, low-cholesterol diet
S	Shopping and meal preparation problems

From reference 12.

mg/day for 7 days–2 years, patients with AIDS received 100–800 mg/day for 12 weeks, and patients with COPD received 800 mg/day for 8 weeks.^{24–33} Some researchers found no significant differences in weight gain between doses, whereas others noted dose-related effects, with greatest effects observed at 480 and 800 mg/day.^{28–32} Of note, none of the studies of these three disease states specifically targeted elderly patients. Mean ages were 60–66 years in the cancer studies (range 20–89 yrs), 38–40 years in the AIDS studies (range 22–75 yrs), and 67 in the COPD study,^{24–33} although 44% of 145 patients in the study of COPD in 2002 were older than 70 years.³³ Therefore, elderly-specific studies were needed to establish the effectiveness of treatment for weight loss in this population.

The preponderance of data for megestrol acetate for the treatment of anorexia came from patients with cancer. However, some cancer studies were limited by a median patient survival shorter than the study duration. Likewise, completion rates are a consideration when one evaluates studies targeting patients of advanced age because of possible comorbidities and expected life spans.

End points evaluated in patients with cancer, AIDS, or COPD varied, but positive improvements were demonstrated in body weight for all three diseases.^{24–33} Reported mean weight gains were 1.06–5.4 kg in patients with cancer, 0.863–4.16 kg in patients with AIDS, and 3.2 kg in patients with COPD.^{24, 25, 29, 31–33} Effects were observed as early as 7 days in some studies but not until at least 4 weeks in others, although further increases were seen for up to 12 weeks.^{24, 25, 29, 33} Increases in appetite were also noted in patients with cancer. Daily caloric or food intake

Table 2. Drugs That May Contribute to Weight Loss

Drug Category	Examples
Agents with anorectic potential	
Psychiatric	Antidepressants (tricyclic, selective serotonin reuptake inhibitors [especially fluoxetine], serotonin-norepinephrine reuptake inhibitors), cholinesterase inhibitors, stimulants (methylphenidate, modafinil), drugs for Parkinson's disease (levodopa-carbidopa, dopamine agonists), lithium, phenothiazines, butyrophenones
Cardiovascular	Digoxin, amiodarone, procainamide, quinidine, spironolactone
Gastrointestinal	Cimetidine, interferon, diphenoxylate-atropine
Antiinfective	Metronidazole, griseofulvin, most antibiotics
Nutritional	Calcium carbonate, ferrous sulfate, potassium
Antirheumatic	Nonsteroidal antiinflammatory drugs, colchicine, penicillamine, aspirin
Pulmonary	Theophylline
Antineoplastic	Cyclophosphamide, most other antineoplastic drugs
Other	Bisphosphonates, agents with anticholinergic adverse effects
Malabsorptive agents	Laxatives, bile acid sequestrants, proton pump inhibitors, methotrexate, colchicine, neomycin
Metabolic agents	Theophylline, thyroid replacement therapy (excessive doses), pseudoephedrine, stimulants

From reference 12.

improved in patients with cancer and in those with AIDS, and body mass index and fat mass increased in patients with AIDS.^{24–26, 28, 31, 32} Of interest, among patients with cancer, megestrol acetate did not positively affect end points such as quality of life, mood, performance status, and overall survival.^{24, 25, 27, 29, 30} Still, the drug's positive effects on weight and its associated end points of appetite and caloric intake contributed to the hypothesis that megestrol acetate could have beneficial effects on unintentional weight loss in elderly patients.

Efficacy in the Treatment of Weight Loss in the Elderly

Data from randomized controlled trials supporting the use of megestrol acetate for the treatment of weight loss in the elderly are limited, and most studies had heterogeneous methods. For example, in six of 10 reported studies of megestrol use in the elderly, weight change was a primary outcome; in the others, it was a secondary outcome.^{34–43} Furthermore, time points for weight assessment varied. Other end points also varied and included appetite and/or nutritional intake, body composition, laboratory values indicative of nutrition, inflammation or possible adverse effects, quality of life, functional status, and survival.

Most evaluations were performed in patients residing in long-term care facilities. Dosages of megestrol acetate were 20–2400 mg/day, most commonly 400–800 mg/day. Durations of therapy were 6–12 weeks. Influences of concomitant

factors, such as dementia, depression, and the subjects' ability to eat independently, were intermittently accounted for in these trials. Details regarding these studies are summarized in Table 3.^{34–43}

Initial Trial

The first published evaluation of megestrol acetate in elderly patients was a prospective study of 400 mg/day in four patients residing in a nursing home.³⁴ One subject completed the study and gained 6.4 kg at 6 weeks. In the other three patients, megestrol acetate was discontinued because of adverse effects (discussed later). One of these patients gained a modest 1.8 kg. Both patients who gained weight had increased levels of cytokines, including IL-6, at baseline. The other two patients had no change in weight. The presence of concomitant dementia or depression among evaluated subjects was not specified. No descriptive statistics were noted.

Retrospective Trials

Four retrospective analyses addressed the use of megestrol acetate. The first involved six patients receiving long-term care.³⁵ For 30 days, they had received the usual protocol measures of the facility—which included high-calorie, high-protein diets and supplementation as indicated—without cessation of weight loss. Then, megestrol acetate 480 mg/day was added. The investigators did not mention any specific focused evaluation of eating or aid to promote eating, although two subjects had dementia. Depression was evaluated

Table 3. Comparison of Study Characteristics of Megestrol Acetate³⁴⁻⁴³

Patient Population	Daily Dose of Megestrol	Study Duration ^a	Completion Rate	Primary Outcome
4 M, mean age 87.5 yrs (range 72-103 yrs) ³⁴	400 mg	6 wks	25%	Weight
1 M, 5 F; mean age 87.3 yrs (range 80-94 yrs) ³⁵	480 mg	45 days	Not reported	Weight
2 M, 12 F; mean age 84.1 yrs ³⁶	40-800 mg	Median 4.5 wks	Not reported	Weight
12 M, 32 F; mean age 79.1 yrs (range 31-93 yrs) ³⁷	200-2400 mg	5.4 mo (2-14 mo)	40.9% at 6 mo, 11.4% at 12 mo	Weight
56 M, 1 F; mean age 78.5 yrs (range 65-91 yrs) ³⁸	120-800 mg	3.2 mo (1-11 mo)	Not reported	Weight
619 M, 1508 F; mean \pm SD age 84.1 \pm 9.7 yrs ³⁹	20-2400 mg	90 days (7-934 days)	Megestrol: 60.6% (430/709) Control: 67.6% (959/1418)	Median survival
2 M, 15 F; mean \pm SD age 91.9 \pm 5.8 yrs ⁴⁰	400 mg	63 days	100%	Percent change in oral intake
16 M, 31 F; mean age 83.5 yrs ⁴¹	200, 400, or 800 mg	63 days	95.7%	Appetite; albumin, prealbumin, and cortisol levels; thromboembolic events; diarrhea
66 M, 3 F; mean age 75.5 yrs (range 50-95 yrs) ⁴²	800 mg	12 wks	73.9%	Weight, appetite
24 M, 5 F; mean age 79.4 yrs (range 65-93 yrs) ⁴³	800 mg	12 wks	82.8%	Muscle strength

^aData are mean or mean (range) unless otherwise indicated.

and treated in all subjects; one was receiving ongoing treatment for depression that persisted despite use of multiple antidepressants. No significant weight change from baseline was noted 1 month after treatment. However, a significant increase in weight occurred at 2 months ($p < 0.05$), with five of six subjects responding. Mean weight gain across all subjects was 5.98% (response range -3.0-12.7%) or 2.65 kg (response range -1.4-6.1 kg). Of note, the subject with treatment-resistant depression was the one who lost weight despite treatment with megestrol acetate. Whether this subject's continuing weight loss was due to a lack of response to megestrol alone or to ongoing depression or other factors is impossible to determine.

The second retrospective analysis was conducted in 14 elderly patients residing in a long-term care facility.³⁶ Researchers evaluated the effects of megestrol acetate on weight for an indication of weight loss, anorexia, cachexia, or

appetite stimulation. About 71% received a dosage of 400-800 mg/day. Concomitant dementia, Alzheimer's disease, and depression were noted in four, five, and three subjects, respectively. Overall effects on weight from baseline to completion of therapy were mixed. Six subjects (43%) gained a mean of 6.8 lbs over 4-14 weeks of therapy, six (43%) lost a mean of 4.4 lbs over 1-7 weeks of therapy, and two (14%) had no changes in weight after 2 weeks of therapy. Doses of megestrol acetate ranged in each group. It was unclear if dosing differences among patients might have accounted for differences in the effects among patients, as no statistical analyses were performed. Baseline weights of two subjects who continued to lose weight were low at 70% of their ideal body weights; however, baseline data of all the subjects were not presented for comparison.

The third retrospective evaluation focused on the effects of megestrol acetate on weight gain

among residents of a skilled nursing facility.³⁷ Of 44 patients, 82% received 400 or 800 mg/day. No information was available regarding their concomitant disease status or interventions that might have affected their weight. Changes in weight were assessed monthly for up to 6 months after the start and after the discontinuation of therapy. Because of transfers from the facility or a lack of follow-up weights, 18 subjects (40.9%) were evaluated at 6 months after the start, and five (11.4%) were evaluated at 6 months after discontinuation. Mean changes in weight were consistently negative from 1–6 months after the beginning of therapy (range -1.1 to -2.2 kg). Of note, in months 1 and 2 after the start of megestrol therapy, when at least 43 subjects underwent follow-up evaluation, mean weight losses were 1.4–1.5 kg. Changes across all (five to 16) evaluated subjects 1–6 months after discontinuation varied from a mean loss of 0.07 kg to a mean gain of 3.07 kg. Whether this late improvement in weight was in any way related to megestrol acetate cannot be determined. The imprecise entry criteria, low follow-up rate, and inability to account for possible confounding disease states and treatments make it difficult to apply the results of this study to the treatment of elderly patients with weight loss.

In the fourth retrospective analysis, investigators administered megestrol acetate 120–800 mg/day to 57 subjects at a Veterans Affairs medical center.³⁸ Approximately 74% received the drug on an outpatient basis. No baseline data regarding concomitant depression or dementia, treatment, or other nutritional intervention (e.g., dietary supplementation) were reported. Similar to the previous study,³⁷ the number of subjects with evaluable weights after the start of treatment declined from 34 (60%) at 3 months and 37 (65%) at 6 months to 22 (39%) at 9 months and 8 (14%) at 12 months. At 3 months (mean duration of therapy was 3.2 mo), 18 subjects (53%) gained a mean of 4.6 kg (range 0.5–14 kg), whereas 16 subjects (47%) lost a mean of 7.2 kg (range 1.4–19 kg). By 6 months, the number of subjects who gained weight from baseline fell to 14 (38%); their mean gain from baseline was 6.2 kg (range 1.6–27.9 kg). The number of subjects who lost weight at 6 months increased to 22 (59%); their mean weight loss from baseline was 5.9 kg (range 0.7–17 kg). One subject's weight had not changed at 6 months. Over time, fewer subjects experienced weight gain. No adverse effects attributed to megestrol acetate were noted.

Case-Control Cohort Study

Investigators conducted a case-control cohort study to determine whether exposure to megestrol acetate increased mortality rates in 709 case patients and 1418 matched control subjects living in a nursing home.³⁹ They observed no significant differences in baseline matching variables between the groups other than mean number of drugs, which was 10/patient versus 9.4/control subject ($p < 0.001$). Doses of megestrol acetate ranged from 20–2400 mg/day; 47% received a mean dose of less than 400 mg/day. Median survival, the primary end point, was shorter at 23.9 months (95% confidence interval 20.2–27.5 mo) in patients versus at 31.2 months (95% confidence interval 27.8–35.9) in control subjects ($p < 0.001$). No significant difference in survival was noted among patients receiving less than 200 mg/day of megestrol acetate, those given 200–400 mg/day, or those given more than 400 mg/day.

Weight change, a secondary end point, did not significantly differ between patients and control subjects at 3 or 6 months after baseline, even when only patients who received more than 400 mg/day were compared with control subjects. The researchers attempted to control for confounding factors, and their results suggested that use of megestrol acetate to promote weight gain in this population may not provide benefit and could result in harm.

Prospective Trials

Four additional trials were performed to prospectively evaluate megestrol acetate in the elderly population. In the first, megestrol acetate 400 mg/day, along with either optimized or usual-care feeding assistance, was given to 36 elderly nursing home residents.⁴⁰ Optimized feeding assistance encompassed continuous one-to-one assistance, proper positioning, prompting, social stimulation, extended meal durations, as well as consultation regarding patients' preferences for dining location, types of assistance provided, and meal substitutions (about 30 min/meal of nursing time). A diagnosis of depression was noted in 35% of subjects, and a diagnosis of dementia was noted in 41%. About 94% of these patients were receiving dietary supplements, and 59% had specialized dietary orders.

Of the original 36 patients who consented, only 17 were evaluated; the others were excluded because of hospitalization, other medical reasons,

or death. Of the evaluated subjects, only those who received both megestrol acetate and optimized feeding assistance had an increase in the total percentage of meals consumed compared with baseline (16% increase at 4 wks and 13% increase at 6 wks, $p < 0.005$). Baseline consumption did not change in those receiving drug therapy with usual mealtime assistance. This study did not demonstrate a positive effect on weight, which was a secondary end point, as an overall mean \pm SD weight loss of 2.13 ± 9.32 lbs was observed across all study subjects. No descriptive statistics were mentioned.

As with previous evaluations, results for weight were mixed, with nine subjects losing a mean \pm SD of 9.3 ± 5.4 lbs and eight gaining 5.9 ± 4.9 lbs. The evaluated patient population was older than any other population studied to date, but weight loss was not the primary end point. Of interest, the study highlighted the potential confounding factor of self-care (feeding) on outcomes, irrespective of pharmacotherapy, in patients with weight loss and clinically significant cognitive impairment. Most studies of megestrol acetate in the elderly have not specifically addressed this potential confounder.

The next prospective study was only one of two randomized placebo-controlled trials performed to evaluate the effects of megestrol acetate 200, 400, or 800 mg/day in 47 elderly subjects.⁴¹ Investigators studied patients who were hospitalized within 3 weeks before the trial who received follow-up at either a rehabilitation facility or a home health setting. Rates of depression or dementia were not specified, but only subjects with a Mini-Mental State Examination score above 20 were included. This criterion could have significantly limited the risk for the contribution of poor self-care feeding to affect these subjects' weight loss or gain.

Positive effects were noted in self-reported appetite, a primary outcome, from baseline with megestrol 800 mg/day at 20 days ($p = 0.04$) and megestrol 400 mg/day at 42 days ($p = 0.02$). Likewise, prealbumin levels, another primary outcome, significantly increased from baseline in the 400-mg ($p = 0.009$) and 800-mg ($p = 0.004$) groups at 20 days but only in the 400-mg group at 63 days ($p = 0.02$). No significant effects were reported in albumin concentrations or in any of the secondary outcomes, which included weight, functional status, health-related quality of life, and body composition.

This study population differed from those of other studies in that the patients had to be

cognitively intact to participate. Application of these data to a longstanding nursing home population would likely be unfeasible in terms of efficacy or adverse effects. However, the lack of significant effects on weight gain is notable.

Another research group conducted the only randomized, double-blind, placebo-controlled study of the effects of megestrol acetate 800 mg/day on weight and appetite; they enrolled 69 nursing home residents.⁴² Concurrent depression affected 39.4% of patients in the placebo group and 47.2% of patients in the megestrol group, but patients were excluded from the study if the depression was thought to contribute to weight loss. Dementia was a concurrent condition in 45.5% and 36.1% of patients in the placebo and megestrol groups, respectively (no significant difference at baseline). Active treatment lasted 12 weeks, and follow-up was 13 weeks.

Weight did not significantly increase among megestrol-treated patients versus those receiving placebo until week 20 (mean \pm SD 2.45 ± 1.1 vs -0.41 ± 0.82 kg, $p = 0.037$), a notable 8 weeks after megestrol acetate was discontinued. This weight gain was maintained at 25 weeks (2.95 ± 1.41 kg for megestrol vs -0.45 ± 0.86 kg for placebo, p value not reported). Likewise, clinically significant weight gain, defined as 1.82 kg (4 lbs) or more, was not seen in the megestrol group versus the placebo group until after megestrol acetate was discontinued at week 25 ($p = 0.011$).

Significant improvements in patients receiving megestrol versus placebo at 12 weeks were noted in self-reported appetite, as well as the secondary end points of enjoyment and sense of well-being ($p = 0.004$, $p = 0.0245$, and $p = 0.045$, respectively). No significant effects on the secondary end points of total body fat, depression scores, nutritional intake, prealbumin levels, or adverse effects were observed.

These data seemed to suggest that changes in weight may begin but that full effects may not be seen for at least 5 or 6 months after the start of treatment with megestrol acetate. This time frame has not been evaluated in many studies.

The final evaluation that we assessed was a randomized, double-blind, intervention-control study of 29 elderly outpatients and inpatients in a Veterans Affairs hospital system who had a recent illness-induced decline in functioning.⁴³ Subjects received low-resistance muscle toning or high-intensity muscle strength training either alone or in combination with megestrol acetate 800 mg/day.

Overall muscle strength, the primary end

point, decreased in subjects receiving megestrol acetate plus exercise versus those who received either exercise program alone ($p=0.04$). Increased weight, a secondary end point, was noted in patients receiving megestrol plus exercise versus those who received placebo in addition to exercise (mean \pm SD 3.2 ± 0.6 vs -0.1 ± 0.6 kg, $p=0.001$). Body fat and percentage calculated nutritional intake rose in subjects treated with megestrol ($p=0.05$ and $p=0.03$, respectively). Mid-thigh cross-sectional muscle area or lean body mass did not significantly change. (Decreases in morning testosterone and cortisol levels are discussed later in relation to adverse effects.)

These findings add to the evidence suggesting that weight gain with megestrol acetate is related to increases in body fat. However, they also raise the issue of whether this type of weight gain, potentially at the risk of loss of muscle strength, truly improves long-term morbidity and mortality in elderly individuals.

Summary of Clinical Studies

Overall, data from well-designed, randomized, placebo-controlled clinical trials to support the use of megestrol acetate in elderly patients with weight loss are sparse. Four of 10 reported trials were retrospective reviews. Of the six prospective evaluations, weight was evaluated as a primary end point in only three, and only two were placebo controlled. Control for confounding factors such as depression, dementia, and the ability to perform self-care activities (e.g., feeding) was inconsistent. This is of particular concern since 70% of the studies involved nursing home patients who may be most likely to have functional impairments.

The most commonly studied dosages were 400 and 800 mg/day, although effects of megestrol acetate on stimulating weight gain in elderly patients conflicted from evaluation to evaluation. This variation may have been due to a number of factors, including inherent differences among patient groups (e.g., baseline weight, weight loss history, concurrent disease, functional status, underlying pathology). Several evaluations revealed almost equal numbers of subjects gaining and losing weight, but factors associated with these differences were not fully elucidated.

Data from one of the largest, most robustly designed studies of megestrol acetate in the elderly suggested a benefit for weight loss.⁴² However, the overarching situation of conflicting

data implies that the ideal geriatric population for whom a trial of megestrol acetate may provide consistent benefit has not been clearly identified. Meanwhile, data have suggested that, even in subjects who may gain weight, the gain might not be seen for as long as 5 or 6 months, a factor to consider in future evaluations.⁴²

Efficacy of Mirtazapine

Mirtazapine is an antidepressant drug that is structurally related to the tetracyclic antidepressant mianserin. Its main effect occurs at serotonin receptors, but its activity differs from that of serotonin reuptake inhibitors, as mirtazapine exerts antagonist activity on 5-HT₂ and 5-HT₃ receptors and possesses low affinity for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1C} receptors. Mirtazapine also has antagonistic activity at histamine and α_2 -receptors. Data suggest that mirtazapine's antihistaminic effects are more predominant at low doses than at high doses.⁴⁴

Great interest has been expressed in the ability of mirtazapine to cause weight gain. In most studies, such weight gain is described as an unwanted adverse effect of antidepressant therapy.^{45, 46} However, this has been interpreted as a desirable effect among elderly patients with unintended weight loss. Many antidepressants have been associated with a weight gain of 3–4 kg over 6–12 months of treatment.^{47, 48} However, mirtazapine appears to induce substantial weight gain early in therapy.^{47–49} For instance, in a 4-week comparison of mirtazapine and venlafaxine, mirtazapine was associated with a mean 2.4-kg weight gain after the first week of therapy, whereas venlafaxine was associated with a slight mean decrease of 0.4 kg after 4 weeks.⁴⁹

The mechanism of action by which mirtazapine causes weight gain is not fully understood. Weight gain early in therapy may be associated with increased plasma levels of TNF- α , soluble TNF receptors, and leptin.⁴⁹ However, whether these changes or the antagonistic effects at serotonin receptors are the mechanism of weight gain is unclear. Also unclear is if mirtazapine-induced weight gain is related to glucose dysregulation. At least one case report described severe hyperglycemia in association with a 16-kg weight gain after 5 months of mirtazapine treatment; however, a conflicting report from a study of 11 patients described improved oral glucose tolerance with no changes in insulin sensitivity despite a mean \pm SD weight gain of 2.17 ± 1.97 kg after 2–6 weeks.^{50, 51} A more

recent evaluation of the effects of mirtazapine on body composition demonstrated increases in body weight, body mass index, fat mass, and leptin with no effects on insulin sensitivity or lipid parameters.⁵²

The use of mirtazapine for treating failure to thrive and unintended weight loss in the geriatric patient has gained considerable interest. Most of the studies have involved geriatric patients with an established diagnosis of depression or of dementia with depression.⁵³⁻⁵⁵

Although previous literature from relatively young populations demonstrated that mirtazapine may have a greater effect on weight than other antidepressants, this possibility has not been demonstrated consistently in the elderly. For instance, mirtazapine given at a mean dose of 15 mg/day was compared with sertraline at a mean dose of 60 mg/day in 50 elderly patients with depression or dementia with depression.⁵⁴ After 4 months, mean weight gain was 2.65 lbs among mirtazapine-treated patients and 2.68 lbs among sertraline-treated patients. The proportion of patients who achieved at least a 7% increase or a 5-lb weight gain did not significantly differ between groups.

In another study, mirtazapine was compared with other nontricyclic antidepressants in 189 nursing facility residents older than 65 years who had a new diagnosis of depression.⁵⁵ Weight changes among mirtazapine-treated patients at 3 and 6 months did not significantly differ from changes in patients taking other non-tricyclic antidepressants, with the exception of fluoxetine. Given these findings, clinicians may question whether the weight-gain benefit is purely from mirtazapine or is associated with the alleviation of depression. For this reason, it is important to remember that, even among relatively young populations, the effect of mirtazapine on weight has been demonstrated in patients receiving the drug to treat a primary psychiatric diagnosis, including major depression, depression with anxiety, or anorexia nervosa with depression.^{53, 56-58}

In practice, mirtazapine has become a popular intervention for geriatric patients with unintended weight loss. For many patients with underlying depression, this approach may be appropriate because mirtazapine is generally an effective and well-tolerated antidepressant that is an acceptable first-line choice for treating depression among elderly individuals. However, it is unclear if mirtazapine offers a significant advantage over other antidepressants when weight loss is a predominant symptom. For this

reason, the selection of mirtazapine over other agents might not be justified if tolerability, antidepressant response, or cost might otherwise lead a prescriber to choose an alternate agent. Also, no literature exists that suggests that mirtazapine is effective for weight gain in the absence of depression.

Adverse Effects

Adverse effects of drugs occur frequently in the elderly population because of pharmacokinetic and pharmacodynamic changes due to aging, a number of comorbid diseases, and use of multiple drugs. In addition to reviewing adverse effects reported in clinical trials, we searched postmarketing case reports in the MEDLINE and International Pharmaceutical Abstracts databases to provide additional evidence of the need for careful selection of treatment.

Megestrol Acetate

The most common adverse effects of megestrol acetate are diarrhea, flatulence, rash, hypertension, nausea, insomnia, and headache. Adverse effects, except for headache (which occurred with 100 mg/day), appear to be most prevalent with the 800-mg/day dose.⁵⁹ Adverse effects were reported in four of the 10 trials evaluated. Researchers from only one of the trials examined differences in adverse effects among different dose ranges.⁴¹ They reported a reduction in cortisol levels to less than 8 ng/ml at doses greater than 400 mg/day, compared with placebo and 200 mg/day. They also reported one incident each of deep vein thrombosis (DVT) and diarrhea in the 800-mg/day group and two each in the 400-mg/day group.

In another study, adverse events were weakness (47%), fatigue (41%), nervousness (29%), and rash (24%).⁴⁰ Others reported adverse effects not previously associated with megestrol acetate: two cases of COPD exacerbation, two cases of aspiration pneumonia, and one case each of dysphagia, gastritis, worsening Parkinson's disease, hip fracture, worsening Paget's disease, and death. This profile was observed at a dosage of 800 mg/day for 12 weeks.⁴²

In the smallest trial, of four participants given 400 mg/day, two had to discontinue the drug because of mental status changes.³⁴ The subjects had a mean age of 87.5 years (range 72-103 yrs). However, too few patients were enrolled to permit evaluation of a true causal relationship.

In postmarketing case reports, megestrol use

was linked to an increased risk for DVT, adrenal suppression, hyperglycemia, and osteoporosis. A retrospective review revealed that six (32%) of 19 nursing home residents developed DVT during treatment with megestrol.⁶⁰ The risk increased among residents treated longer than 50 days (DVT rate of 43%, mean duration of treatment 117 days). Other risk factors were similar among all patients. A retrospective review of 246 nursing home residents revealed a DVT rate of 4.9% (mean duration of treatment 183 days).⁶¹ However, other risk factors were not controlled. Two other case reports of DVT were most likely related to megestrol use.⁹ Therefore, prescribers should carefully weigh the risks versus benefits, especially in an elderly population that is prone to have other risk factors of DVT, such as arrhythmias and immobility.

A summary of case reports linking megestrol to glucocorticoid activity was published in 1997.⁶² Cases of Cushing syndrome, new-onset and exacerbation of diabetes mellitus, and adrenal insufficiency related to the use of megestrol were described. The duration of therapy in these cases varied from 1 month for acute onset of hyperglycemia to several years for Cushing syndrome and adrenal insufficiency. *In vitro* studies have revealed that megestrol has 46% binding affinity at the glucocorticoid receptor, compared with 100% for dexamethasone and 25% for the naturally occurring ligand cortisol.⁶³ Several small prospective trials demonstrated low fasting cortisol levels and suboptimal responses to tests of corticotrophin-releasing hormone in patients being treated with megestrol. The authors of these studies concluded that this compound may act directly on the hypothalamus, leading to central suppression of the hypothalamic-pituitary axis.⁶⁴⁻⁶⁶ A case report suggested that a peripheral glucocorticoid effect may occur.⁶⁷ The evidence came from two women with osteoporosis and spinal compression fractures who received 2 years and 8 months, respectively, of treatment with megestrol for cancer. Their cases also presented evidence and symptoms of adrenal insufficiency, from which they fully recovered after megestrol was discontinued.

Some have suggested that clinicians must keep in mind the glucocorticoid activity of megestrol and the symptoms of hypoadrenalism (fatigue, anorexia, nausea, vomiting, diarrhea), which are common symptoms of other disease states.^{42, 62, 64} Others advise that patients taking megestrol may need a stress dose of steroids during hospitalization for infection or before surgical intervention.¹⁰

Mirtazapine

Mirtazapine is generally well tolerated and has a favorable safety profile. Sedation, dry mouth, constipation, fatigue, and weight gain are the most commonly reported adverse effects.⁶⁸ Because of its sedative properties, mirtazapine is usually administered at bedtime. Caution should be exercised in patients at risk for falls because mirtazapine antagonizes α_1 -adrenergic receptors, possibly causing orthostatic hypotension and/or dizziness. A few case reports have described hepatotoxicity, bone marrow suppression, restless legs syndrome, arthralgia, and coagulopathy; however, a lack of clinical trial data renders these findings inconclusive.⁶⁹ The risk for serotonin syndrome may increase when mirtazapine is used in combination with other serotonergic agents. This possibility should be taken into account when mirtazapine is prescribed for appetite stimulation along with other serotonergic agents.

Dosing and Duration of Treatment

Although data to support the choice of megestrol acetate or mirtazapine to treat unplanned weight loss in the elderly are limited, these agents continue to be used in clinical practice. Therefore, dosing considerations, duration of treatment, and appropriate monitoring are addressed to guide pharmacotherapeutic recommendations.

Megestrol Acetate

Doses of megestrol acetate 20–2400 mg/day have been studied, but those most commonly evaluated and most likely to be associated with efficacy are between 400 and 800 mg/day. Of the 10 studies discussed, only one addressed differences in adverse effects among dose ranges.⁴¹ Multiple daily dosing is required for all but the extended-release suspension.

To our knowledge, the efficacy of different dosages of megestrol for the treatment of unplanned weight loss in the elderly has not been evaluated. As shown in Table 3, the data do not appear to support a dose-related effect on weight gain observed; however, none of the studies were designed to evaluate this end point. Because the use of megestrol for this purpose is off label, little published guidance is available to prescribers for this kind of dosing from drug information resources. The assumption that the low dosage is the geriatric dosage may lead prescribers to assume that 20–40 mg taken 1–3 times/day is appropriate for weight gain or appetite outcomes.

No evidence supports this assumption, and potentially subtherapeutic dosing subjects the patient to increased cost and a risk of adverse effects without a high likelihood of benefit. The availability of a 20-mg tablet formulation may also be a factor that influences a prescriber's dose selection, as multiple tablets must be consumed to attain 400–800-mg/day doses. For these reasons, pharmacists may often be in a position to provide drug information about the optimal dose range and the use of the suspension formulation as a means to provide that dose.

Durations of megestrol therapy ranged from 6–12 weeks (Table 3). Results of one study suggest that megestrol acetate may have positive posttreatment effects on weight gain up to 13 weeks after discontinuation (roughly 6 mo total observation).⁴² However, statistical significance was not determined. Because of conflicting results and differing study designs, no conclusive evidence supports a duration-related effect on weight gain; however, a duration of 3–6 months in clinical practice is consistent with the durations of therapy in this limited evidence base. Duration of therapy does not appear to be linked to the onset of adverse events, as these occurred anytime from days to years into treatment.^{9, 59, 61, 62, 64, 67}

Mirtazapine

A particular dosage range for mirtazapine was not specified in existing trials. In one study, the mean dosage was 15 mg/day.⁵⁴ The recommended initial dose in the elderly is 7.5 mg/day with a slow titration (every 2–4 wks) to effect.¹¹ Because of the clinically significant sedative properties of this drug, titration should occur with caution, especially in patients with a high risk for falls. None of the studies evaluated in this report were designed to compare the dosage or duration of treatment relative to weight gain or adverse effects.

Monitoring of Therapy

The effect of treatment on weight and nutrient intake should be monitored frequently with both megestrol and mirtazapine. Monitoring is perhaps most easily accomplished by following the model in the long-term care setting, where specific protocols have been established. Weight is typically monitored every month; however, individuals with weight loss are often weighed weekly. Appetite is assessed by monitoring the percentage of food consumed on the plate at each

meal. If these parameters do not favorably change over 3–6 months, the effectiveness and continued need for the pharmacotherapeutic intervention should be reassessed. This recommended monitoring period is only partially based on the duration of therapy in some of the clinical trials of megestrol. It is also a reasonable follow-up period based on the cycles of care planning and follow-up required in long-term care.

During megestrol therapy, it is advisable to monitor for common adverse events, such as gastrointestinal upset, central nervous system changes, and signs and symptoms of thromboembolism. Possible effects on the adrenal system should be kept in mind. With mirtazapine, the most frequent adverse effect to monitor is depression or sedation of the central nervous system. A rare but serious adverse effect of mirtazapine is agranulocytosis. Periodic monitoring of complete blood counts may be advisable during treatment.¹¹

Other Considerations

Unintended weight loss in an elderly patient is a grave problem, and the desire of many clinicians to address this problem aggressively is appreciated. However, the paucity of supportive evidence and of well-designed prospective trials should lead clinicians to exercise caution when prescribing megestrol or mirtazapine to manage unplanned weight loss in the elderly. Although some weight gain is associated with the use of these drugs, they also have a propensity to cause adverse effects that are especially concerning in the elderly population with multiple comorbidities. For this reason, the selection of either megestrol or mirtazapine must make sense given the suspected etiology or pathophysiology of the weight loss so as not to expose patients to unnecessary drug or cause iatrogenic complications. For instance, a patient with a medical history suggesting that weight loss may be the result of cytokine-mediated wasting might be a better candidate for megestrol than for mirtazapine, but megestrol might be avoided in a patient with a history of DVT. A patient with weight loss and depression may respond best to mirtazapine, but if another antidepressant was previously prescribed, a thorough assessment of the patient's mood status and response to the initial antidepressant is needed before therapy is changed. Not recommended is the addition of mirtazapine to promote weight gain while the patient continues

to take another antidepressant for depression. By contrast, neither megestrol nor mirtazapine is recommended as an initial intervention for a patient whose weight loss is associated with poor intake due to swallowing difficulties.

When weighing risk-benefit balance, one must also consider what is ultimately achieved for the patient with each pound gained. Although weight loss in the elderly increases morbidity and mortality, the correlation of weight gain with an opposite effect (e.g., increased muscle mass or decreased mortality rate) has not been confirmed. On the contrary, researchers found that megestrol acetate negatively affected physical function, compared with placebo, when it was combined with exercise.⁴³ Also, the rate of mortality substantially increased in patients treated with megestrol acetate versus control subjects.³⁹

Hospice providers may commonly prescribe appetite stimulants to reduce the frequency of painful pressure ulcers in bed-bound patients by helping them maintain appetite and good nutrient intake. However, in our literature review we found no study data that suggested a link between this therapy and wound prevention or healing. It would make clinical sense that weight gain should correlate with improved nutritional status and, therefore, improved functional status or wound healing. However, this relationship has yet to be proven.

To our knowledge, the cost-effectiveness of drug therapy for weight loss in the elderly has not been evaluated. The out-of-pocket cost of one dose of megestrol acetate can range from about \$0.50/tablet to about \$17.50/dose of extended-release suspension.⁷⁰ With multiple daily dosing required (except for the extended-release suspension), the cost can be considerable. Mirtazapine is much cheaper by comparison, ranging from \$1.50–1.60/day depending on the dosage prescribed.⁷⁰ If mirtazapine is being used to treat depression or insomnia as well as weight loss, this cost might well be a bargain. However, the prescriber should remember that the cost of either drug may prohibit adherence in some patients. Costs and benefits must be weighed on an individual basis, and the benefit of any expenditure for drug intervention should be reassessed if the desired weight gain or increase in appetite is not observed in 3–6 months.

It bears mentioning that seven of the 10 trials^{34–43} of megestrol acetate and both trials^{54, 55} of mirtazapine were conducted in a nursing home population. Therefore, their results may not be generalizable to a population of community-

dwelling elderly people with different functional statuses and comorbidities.

Conclusion

Further clinical trials to examine the safety and efficacy of megestrol acetate and mirtazapine for treating unintentional weight loss in the elderly are recommended. Of particular importance are their effects on hard outcomes, such as falls due to the sedative properties of mirtazapine and the possible negative effect of megestrol acetate on physical strength. The current evidence base lacks a thorough investigation of improvement in clinical outcomes. This unknown should be further explored, especially in light of some of the adverse effects of drug therapy. A comprehensive, interdisciplinary evaluation to rule out and treat underlying causes of weight loss should always be performed before pharmacotherapeutic intervention is pursued.

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