Long-Term Care Updates

May 2022

Appetite stimulants in the long-term care population

PharMerica

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Introduction

Nutritional status and weight are routinely monitored in the long-term care (LTC) setting. Fifty- to sixty-percent of patients who remain in a LTC facility for at least 2 years experience weight change, with an equal number gaining and losing weight.[1] Unplanned weight change, especially over a short period of time, may lead to negative consequences. Unintended weight loss may be due to protein-energy undernutrition, cachexia, or sarcopenia, which could indicate a worsening health status. Protein-energy undernutrition is caused by inadequate intake or absorption of macronutrients, while cachexia is the accelerated loss of muscle mass due to chronic inflammation. Finally, sarcopenia is the loss of muscle mass and decline in muscle quality due to increasing age. The most frequent causes of weight loss in the LTC setting include chronic infection or inflammatory conditions, advanced dementia, cancer, chronic obstructive pulmonary disease, uncontrolled diabetes, hyperthyroidism, malabsorption syndromes, oral disease, Parkinson's disease, therapeutic diets, and swallowing disorders.[1] A thorough assessment is indicated to identify all treatable conditions and diagnose any illnesses, as detailed in the Guidelines for Altered Nutritional Status published by The Society for Post-Acute and Long-Term Care Medicine. Treatment may include changes in nutritional intake, rehabilitation for functional disabilities, offering a choice in food and fluids and dining alternatives, or controlling/treating the effects of medical conditions associated with unintended weight loss. In certain segments of the elderly population, particularly those where enteral and/or parenteral therapies fail, it may be beneficial to stimulate appetite with medications; however, the evidence for this is conflicting.[2] This article will review the clinical research on the safety and efficacy of appetite stimulants in the elderly and LTC patients.

Clinical Evidence

Mirtazapine

Mirtazapine is a serotonergic norepinephrine uptake inhibitor that is FDA approved for the treatment of depression.[3] Appetite stimulation and weight gain are common side effects of mirtazapine, making it potentially beneficial for patients who are experiencing weight loss and decreased appetite.[4] Mirtazapine is included in the 2019 Beers Criteria as a drug that should be used with caution in older adults due to possible syndrome of antidiuretic hormone secretion or hyponatremia.[4] Clinical evidence for the primary use of mirtazapine as an appetite stimulant in LTC and elderly patients is limited. However, there are studies looking at patients with depression who would also benefit from appetite stimulation and weight gain.

A retrospective study was published as a letter to the editor in the *Journal of the American Geriatric Society* in 2002 that examined weight change associated with mirtazapine in depressed patients in a LTC setting. Patients taking sertraline served as the comparator group. Patients were included if they had a diagnosis of depression or dementia with depression. Patients were 59 to 98 years of age with an average age of 83.6 years. Twenty-five patients were treated with mirtazapine (average dose of 15mg/day), and 25 patients were treated with sertraline (average dose of 61mg/day) for four months. Weight was measured at baseline and after the four months of treatment. The mean weight gain in the mirtazapine group was 2.65 pounds versus 2.68 pounds in the sertraline group, a difference that was not statistically significant. The researchers concluded that mirtazapine may lack a weight gain benefit in this population. They also noted that observed weight gain may have been the result of improved depression.[5]

Mihara et al. published a retrospective cohort study in 2005 examining weight change associated with mirtazapine compared to non-tricyclic antidepressants (non-TCAs) in nursing facility residents. Elderly patients (n=189) ≥65 years of age who had a new episode or diagnosis of depression and stayed in the same facility for at least eight months were selected for inclusion. Weight change was measured at three and six months. In patients taking mirtazapine, change in weight at three months was -0.55 pounds, and -0.30 pounds at six months. The weight change for the mirtazapine group was not significantly different than that seen in the non-TCAs group at three and six months. However, fluoxetine was associated with a 3.8 pound weight gain relative to mirtazapine at three months (p=0.05). The researchers concluded that the study showed the impact on weight in patients taking mirtazapine was not significantly different than that seen in patients taking non-TCA antidepressants, with the exception of fluoxetine, after controlling for factors such as baseline weight, gender, and comorbid diseases.[6]

Megestrol Acetate

Megestrol acetate (MA) is a progestational agent that was originally used as a contraceptive agent. It has a strong impact on appetite and weight gain and is currently FDA approved for the treatment of HIV associated weight loss.[3] Even though there are studies evaluating the use of this agent in the LTC and elderly population, the outcomes are mixed. MA is also associated with unwanted side effects such as fluid retention, nausea, glucose intolerance, venous thromboembolism, and adrenal insufficiency.[3] Additionally, MA may increase all-cause mortality in the LTC and elderly population.[8] The 2019 Beers Criteria include MA as a potentially inappropriate medication for use in elderly adults because its minimal effect on weight gain is outweighed by the potential for thrombotic events and possible increased risk of death.[4]

In 2000, Yeh et. al published a randomized, double-blind trial comparing the effects of MA oral suspension 800mg/day versus placebo on weight in geriatric nursing home patients. The study period was 12 weeks with a 13 week follow up period. Sixty-nine nursing home patients with weight loss ≥5% of usual body weight over the previous 3 months or body weight 20% below their ideal body weight were selected for inclusion. The median age was around 76 years. The primary outcome was measured by weight and appetite change. At week 12 (conclusion of the study), there were no significant differences in weight gain between groups, but patients taking MA reported significantly greater improvement in appetite, enjoyment of life, and well-being. At week 20 (post-treatment period), 45.5% of MA patients had gained at least 1.82kg (4 pounds), compared to 25% of placebo patients (p=0.037). Similar results were found at week 25: 61.9% of MA patients gained at least 1.82 kg, compared to 21.7% of placebo patients (p=0.013). The researchers concluded that given the results, a multi-center trial may be warranted evaluating MA and its mechanism of action with regards to appetite stimulation, weight gain, and survival in the geriatric population.[7] A limitation of this study was a predominantly male study population.

Bodenner et al. published a retrospective cohort study in 2007 evaluating the association between MA and mortality among nursing home residents with clinically significant weight loss. Residents who received MA therapy within 30 days of their weight loss documentation were matched (1:2) with non-MA-treated residents. A total of 709 patients (mean age 84.1 years) who received MA therapy were matched with 1418 non-MA-treated patients (mean age 84.2 years). Results showed that the median survival of the MA-treated patients (23.9 months; 95% CI 20.2-27.5) was significantly less than untreated residents (31.2 months; 95% CI 27.8-35.9) [$p<0.001$]. Baseline weight for the MA-treated patients was 121.0 pounds, compared to 122.0 pounds in non-MA patients. In the MA-treated patients, median weight at three and six months was 119.0 pounds and 120.0 pounds, respectively. For the non-MA-treated group, median weight at three and six months was 122.0 pounds and 124.0 pounds, respectively. The researchers concluded that MA treatment in elderly LTC residents with significant weight loss was associated with a significant increase in all-cause mortality without a significant increase in weight. Randomized, prospective trials are needed to fully evaluate the morbidity and mortality associated with the use of MA in elderly LTC populations.[8]

Dronabinol

Dronabinol is a synthetic form of tetrahydrocannabinol, which is similar to the active ingredient in cannabis.[3] Dronabinol is FDA-approved to treat chemotherapy-induced nausea/vomiting refractory to conventional antiemetic agents and for the treatment of anorexia associated with weight loss in patients with HIV. It has also been used off-label as an appetite stimulant in the treatment of anorexia in patients with cancer.[4] Dronabinol has not been well studied in older adults.

Wilson et al. published a retrospective observational study in 2007 examining the effects of a 12 week course of dronabinol among residents in five LTC facilities with anorexia and weight loss. Twenty-eight patients were included in the study and the mean age was 79.5 years (range 46-98). Fifteen patients (53.5%) gained weight while taking dronabinol, of which 10 gained more than 5 pounds. Five patients gained less than 5 pounds. Overall, the mean weight gain while taking dronabinol was 3 +/- 8.01 pounds ($p=0.2$). Eleven subjects lost weight, and these patients were younger than those that gained weight (70.9 years vs. 90.8 years). The therapy was overall well tolerated with a trend towards weight gain in LTC residents treated with dronabinol; however, the weight gain was not statistically significant.[9] The authors also concluded that dronabinol may have an increased risk of death, but no tests were performed to explore their hypothesis.[3] Further prospective studies are needed to evaluate the effects of dronabinol in the LTC population.

Cyproheptadine

Cyproheptadine is an antihistamine that is used off-label for the treatment of anorexia.[4] This medication has anticholinergic effects in older patients, which limits its use in the LTC population. Because of these anticholinergic effects, cyproheptadine is included in the Beers Criteria as a potentially inappropriate medication to use in older adults.[4] Research related to this this medication is mainly found in the pediatric population, as well as in the treatment of weight loss in cancer and anorexia nervosa.[3] One recently published study demonstrated efficacy and good tolerability of cyproheptadine in poor appetite, but the study population was aged 19-64.[10]

Ghrelin mimetics

Ghrelin is an endogenous growth hormone secretagogue (GHS) that has been shown to stimulate appetite and increase fat-free mass. Capromorelin is an oral GHS that stimulates GHS-1 alpha receptors. There have been studies assessing the use of growth hormones in older adults to increase body composition and physical performance.[11] While capromorelin has shown promise, it remains investigational in the United States.

Conclusion

Several medications have been studied for their role as potential appetite stimulants in the elderly population. Most have shown minimal effect on weight gain and have been limited by adverse events. Mirtazapine has been compared to other antidepressants in patients with depression who would also benefit from weight gain. The studies showed no improvement in weight gain with mirtazapine compared to other antidepressants. Additionally, dronabinol did not show a statistically significant difference in weight compared to baseline in the LTC population. MA has shown benefit in weight gain, but has also been associated with an increase in all-cause mortality in elderly patients. Cyproheptadine has been used for weight gain in the pediatric population, but should be avoided in the elderly population due to anticholinergic side effects. The oral GHS agent capromorelin may improve body composition and physical function in adults; however, it remains investigational in the United States. Overall, evidence for the use of appetite stimulants in the elderly population is limited and the studies tend to be dated. Newer, more robust studies are necessary to determine the best therapeutic options for weight gain in these patients.

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