Appetite Stimulants in Long Term Care: A Literature Review
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Citation

Abstract
Weight loss and malnutrition present a significant challenge to providers in the long term care arena who frequently must evaluate and treat residents for these issues. Reasons for the incidence of unintentional weight loss includes multiple comorbid conditions, polypharmacy, depression and the cachexia of aging. The purpose of this review was to identify current research related to the use of appetite stimulants in long term care. Methods: a review of the literature was conducted from 1956 to present with a focus on long term care, appetite stimulants and weight loss. Results: Traditional approaches to address this issue have included comprehensive nutritional assessment, oral supplements and the use of appetite stimulants. These have included medications such as mirtazapine, oxandrolone, dronabinol, and megesterol acetate. Of these medications, megesterol acetate has been the most widely studied but with mixed results. Providers are encouraged to provide a comprehensive approach to the management of unintentional weight loss in nursing home residents and to consider an appetite stimulant as a last resort, if at all.

BACKGROUND
Unintentional weight loss (UIWL) is a common problem in the long term care (LTC) population. UIWL is often defined as a loss of 5% of the actual body weight in one month or 10% in a six month period [1]. Weight loss is associated with a number of complications including anemia, immune deficiency, postoperative complications, a decline in activities of daily living, pressure ulcers, falls, fractures, and increased mortality [2]. Weight loss and malnutrition in the elderly represent a major concern among health care providers as those aged 80 and older are currently the fastest growing segment of the nation’s population. The incidence of involuntary weight loss among nursing home residents is high and ranges from 30-50% in a population of more than 1.7 million residents [3].

In the long term care setting, unintentional weight loss is thought to be multifactorial. Most older adults have at least one chronic disease such as cardiovascular disease, diabetes, hypertension, or renal insufficiency. As a result, they often have a restricted diet which can lead to decrease oral intake. Depression, a highly prevalent condition in this group, also leads to a decrease in food intake [4]. Polypharmacy is another important cause of unintentional weight loss. Medications such as angiotensin converting enzyme (ACE) inhibitors, quinolones, and metronidazole, for example, can cause dysguesia leading to decreased appetite. Cholinesterase inhibitors and selective serotonin reuptake inhibitors can cause nausea, vomiting and diarrhea. Antidepressants and psychotropics can lead to sedation and decreased attentiveness during mealtimes. Consequently, such medications can lead to decreased food intake [5]. Other causes of weight loss in the elderly include difficulty with chewing due to dental problems, swallowing disorders, cognitive impairment, loss of taste and sensation, and difficulty with self feeding [6, 7].

Regulation of food intake changes with increasing age, leading to what has been described as the “physiologic anorexia of aging” The amount of circulating cholecystokinin, a satiety hormone, increases in the circulation [8]. Leptin, a peptide hormone produced in adipose tissue may also play a role in long term satiety and hunger drive, although the relevance of peptide hormones in older adults remains unclear [9, 10].

The role of elevated cytokines, including tumor necrosis factor (TNF) and interleukin 6 (IL-6) have also been implicated in this syndrome. In the geriatric populations, anorexia and cachexia leading to diminished host defenses are often unexplained. One possible etiology is an association with elevated cytokine levels such as tumor
necrosis factor (TNF), Interleukin-6 (IL-6), and soluble Interleukin-2 receptor (sIL-2) which have been noted in cancer, HIV, and more recently in geriatric wasting syndrome. Production of these cytokines therefore may be involved in unintentional weight loss in older adults and specifically in long term care residents. [11].

Evaluation and treatment of unintentional weight loss in the older adult in long term care settings involves a comprehensive approach. Evaluation includes screening, assessment and treatment. Specific treatments may include the use of nutritional supplementation, and pharmacological approaches. Identification and management of the underlying cause(s) of weight loss is the goal of care. In some cases, however, oral supplements and appetite stimulants have been used in an effort to reverse the process. The goal of this paper is to review the specific role of appetite stimulants in the long term care setting for unintentional weight loss.

METHODOLOGY
A comprehensive literature review of Pub Med, Medline (1956-present), and Scopus was performed. Search terms included unintentional weight loss, long term care, nursing home, appetite stimulants, orexigenics, megesterol acetate, dronabinol, mirtazepine, cyproheptadine, and oxandrolone. A total of 128 articles were retrieved. Any studies or reviews dealing with the use of appetite stimulants specifically in HIV, cancer, or AIDS populations were excluded. Literature reviews, randomized control trials, non randomized trials, case control studies and clinical practice guidelines were included. A total of 21 articles were retained for review.

RESULTS
Numerous pharmacologic agents have been used as appetite stimulants to treat unintentional weight loss in the long term care setting. These agents include mirtazepine, cyproheptadine, oxandrolone, dronabinol, and megesterol acetate. Interestingly, a paucity of evidence is available on most of these agents used in this setting. Many agents have been used based on anecdotal evidence or in off label applications. What appears in the literature to date on these agents is limited. The following represents what is known to date on the use of appetite stimulants in the long term care population

MIRTAZEPINE (REMERON)
Mirtazepine is a serotonergic norepineprine uptake inhibitor that has been used in the treatment of depression. As such, mirtazepine has demonstrated efficacy in treating depression among older adults in the long term care setting [12]. In one study using mirtazepine to treat late life depression, there was an increase in weight of 1.1 pounds in 4 weeks and 1.32 pounds in 12 weeks, however, the outcome was not found to be statistically significant [13]. In other studies comparing mirtazepine with other antidepressants for the treatment of depression, no significant changes in weight were reported [14, 15]. Morley[16] suggested that mirtazepine is the drug of choice in treating older adults with both depression and weight loss. Although commonly used for the purposes of promoting weight gain, no studies exist to date that have specifically explored the use of mirtazepine as an appetite stimulant in the long term care setting.

CYPROHEPTADINE (PERIACTIN)
Cyproheptadine is an antihistamine that has been used as an appetite stimulant in nursing home residents. This medication has a number of anticholinergic effects that may cause symptoms such as blurred vision, dry mouth, urinary retention constipation, tachycardia and delirium in older patients. These effects generally limit its utility in long term care. Although cyproheptadine has anectodally been used in this setting, no studies have been undertaken to date using cyproheptadine as an Orexigenic in this population. Much of the data regarding its benefit as such comes from studies involving the pediatric population. Cyproheptadine has also been studied in the treatment of weight loss in both cancer and anorexia nervosa [17].

OXANDROLONE (OXANDRIN)
Oxandrolone is a synthetic anabolic steroid that helps to restore lean muscle mass and increase visceral protein stores. Oxandrolone is the only anabolic steroid approved by the Federal Drug Administration (FDA) for the treatment of cachexia. Oxandrolone has also been found to demonstrate a significant improvement in wound healing over a 12 week period in eight out of eight patients with weight loss and non healing chronic wounds [18]. In another study by Yeh et al. [19], oxandrolone was found improve appetite and increase weight gain in patients with COPD associated weight loss. No studies to date were found that specifically address the use of this agent in the nursing home population. Oxandrolone is contraindicated for use in patients with prostate or breast cancer and may lead to hirsutism and fluid retention. Oxandrolone should also be used with caution in patients with hepatic disease [4].
DRONABINOL (MARINOL)

Dronabinol is a synthetic form of tetrahydrocannabinol, an active ingredient of cannabis or marijuana. Dronabinol has been found to have both antiemetic and appetite stimulant properties. Dronabinol may improve mood and decrease pain as well, making this agent an efficacious option in managing end of life symptoms. The mechanism of action is not well understood. Anorexia and progressive weight loss are often observed in patients with advanced stages of cancer and HIV infection. Dronabinol in several studies was found to convey some benefit to these populations [20, 21]. Dronabinol has only been studied to limited extent in older adults. In a placebo controlled crossover design, dronabinol was studied over a 6 week period in 15 patients with Alzheimer’s disease who displayed food refusal [22]. A minimal but statistically significant improvement in weight gain (1.5 pounds) was noted as compared to placebo. No difference in caloric intake was noted between the control and treatment group. During dronabinol treatment disturbed behavior decreased and was attributed to the weight gain exhibited, possibly due to a decrease in overall activity levels. The study was unclear in terms of whether weight gain resulted from decreased energy expenditure or from the treatment itself. In a retrospective observational pilot study [23], 28 subjects with anorexia and significant weight loss were treated with dronabinol over a 12 week period. Fifteen subjects, or 53.5%, gained weight on dronabinol with a mean gain of 3 +/- 8.01 pounds, however, such weight gain was not found to be statistically significant. Eleven subjects lost weight on dronabinol and were younger in age than those who gained weight (70.9 years versus 90.8 years) and the outcome was statistically significant. The authors in this study surmised that failure to respond to dronabinol may indicate increased risk of death; however, no statistical tests to explore this particular hypothesis were conducted.

MEGESTEROL ACETATE (MEGACE)

Megesterol acetate (MA) is a progestational agent with a strong impact on appetite. MA was originally used as a contraceptive agent; however, its side effect of weight gain led to its use as an orixogenic agent. MA is currently FDA approved for the treatment of HIV associated weight loss and is also used to suppress estrogen levels in women with breast and endometrial cancer [24]. MA is associated with side effects such as fluid retention, nausea, glucose intolerance, venous thrombosis and adrenal insufficiency with chronic usage [4]. MA has also been associated with the development of osteoporosis in some patients [25]. In the long term care population, MA has been widely used as an appetite stimulant. In terms of studies that specifically address the use of this agent in this population, a total of 9 studies were found with mixed outcomes. In a pilot study by Castle et al. [26], four patients and a history of weight loss greater than or equal to their ideal body weight with a mean age of 87.5 years were treated with a dose of 400 mg daily for a period of six weeks. Only one of the four completed the study due to reports of confusion, early mental status changes or not “feeling right”. Of the four subjects, one gained 6.4 kg and one gained 1.8 kg. This study was too small to draw any significant conclusions and lasted only 6 weeks. In this study, confusion among the residents appeared to be a major side effect. Such side effects are clearly a concern in this frail population. Potentially these side effects might be ameliorated in a future study with a smaller dose; however, an adjustment in dosing may also affect the efficacy of treatment and needs to be further explored.

In a retrospective chart review by Karcic et al. [27], the authors identified 13 residents in two long term care facilities who were treated with MA for malnutrition. The usual dose was 800 mg daily but varied from 200 to 800 mg. The residents had a variety of conditions which included depression, dementia, and terminal neoplasms. Parameters such as food intake, body mass index (BMI), albumin, prealbumin, hemoglobin, white blood cell count and absolute lymphocyte count were assessed over six month period. With MA treatment, all of the nutritional parameters improved (P<0.05). In this study, MA was discontinued in one patient due to an episode of heart failure. The authors concluded that MA is a safe and efficient means of improving malnutrition in nursing home residents. What has not been established in this study is what other confounding factors play into these results and if the improvement in nutritional parameters is related to other interventions or supplements that were not noted by the authors. Another issue which has not been addressed is the long term effects of MA treatment and whether a correlation exists between increased nutritional parameters and long term survival.

In an effort to explore the interrelationship between baseline nutritional status, changes in nutritional status over time and the incidence of adverse outcomes, Sullivan et al. [28] underwent a prospective observational study of nutritionally at risk nursing home residents. This study is referred to as the GAIN Registry (Geriatric Anorexia Nutrition). In this case, the investigators looked at many of the same parameters as Karcic et al. [27]; however, their sample size

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was considerably larger with 1000 participants from 96 facilities. Of these, a final sample of 894 was evaluated over a 6 month period. The inclusion criteria for nutritional risk were clearly defined. Outcome measures included appetite improvement, weight gain, and mortality. Specifically, the authors hypothesized that patients who experienced weight loss during this period would have a higher rate of mortality compared to those who did not. Sullivan et al. [28] reported that younger age was the strongest correlate of appetite improvement. The odds of gaining weight were negatively correlated with body mass index (BMI), age and feeding dependency. A weight loss during this period was associated with a two fold increase in the likelihood of dying (adjusted RR; 1.95, 95% CI 1.43-2.66). Interestingly, residents who received appetite stimulants (12% of the sample) were 70% more likely to gain weight. Unfortunately, the authors did not address each stimulant separately. Consequently drawing more definitive conclusions about the efficacy of using orixigenics in general is difficult. Determining which specific agents are most likely to produce more optimal outcomes also presents a challenge.

Yeh et al. [11] conducted a prospective, double blind, placebo controlled trial. These investigators evaluated 69 nursing home residents with a weight loss of > 5% over the past 3 months or body weight 20% less than their ideal weight. Patients were randomly assigned to receive either placebo or MA 800mg daily for 12 weeks with a subsequent follow up period of 13 weeks. The authors published a series of reports on their findings. In their initial study [29] data were collected on appetite, weight, nutritional status, quality of life (QOL), and cytokine levels at baseline and at week 12. Appetite, sense of well being, and QOL were significantly improved in the MA arm. A negative correlation between prealbumin levels and cytokine levels was noted. Improvement in appetite, correlated positively with improvement in nutritional parameters, and weight. Although promising, the study is limited by the fact that the majority of the patients in the sample was male and may not be predictive of the effect on females. Further study of the safety of long term usage is warranted.

In a follow up report by Yeh et al. [11], the authors used results from the same study to evaluate the effects of MA versus placebo on weight. In this instance, the primary outcome was measured by weight and appetite change. At 12 weeks, (the end of the study), no significant difference in weight gain was observed between treatment groups, however at 25 weeks, 61.8% of the MA treated group gained weight (1.82 kg) compared with 21.7% of the placebo patients. Statistically this weight gain was significant at p=0.13, suggesting that a minimum of 3 months of treatment or longer is required to realize a significant difference.

In a subsequent analysis on this same sample, Yeh et al. [30] explored the correlation between cytokine levels and body weight. The hypothesis was based on findings in lab animals in which a reduction of proinflammation cytokines was noted in animals exhibiting weight gain. In this study, a decrease in cytokine levels in both the placebo group and the MA treated group was observed; however, no significant difference was identified between the groups. In the MA treated group, a negative correlation was noted between cytokine levels and weight, fat mass, and fat free mass (FFM) which was significant at P<0.05.

Yeh et al [31] in a later report evaluated cytokine levels and nutritional markers such as prealbumin, white cell counts, and C reactive protein at baseline and after 12 weeks of therapy on survival rates. No significant difference in survival between the placebo and MA treated groups was observed. In terms of confounding factors, it was not clear as to whether elevated cytokines were independent variables leading to decreased survival or a result of an underlying chronic health condition. This area clearly is in need of further study. The cumulative reports by Yeh and colleagues raise some interesting clinical questions and underscore the need for future studies with larger sample sizes and control of possible confounding factors such as underlying conditions [11,29,30,31].

Interest in treating weight loss in the nursing home population prompted Simmons et al. [32] to conduct a nonrandomized clinical trial to assess the effect of megesterol acetate on oral food and fluid intake. In this pilot study, 36 participants were recruited from a larger study and treated with a daily dose of 400 mg of megesterol acetate daily for 63 days. The MA was administered under two conditions: usual nursing home care and when optimal feeding assistance was provided during meals. Of the 36 participants, only 17 completed the study. MA had a significant effect on oral food and fluid intake but only under optimal feeding conditions. No change was made in food or fluid intake under the usual nursing home conditions. Limitations of this study include a very small sample size, a high rate of attrition, and lack of a control group receiving optimal feeding assistance alone. The results of this study suggest that optimal feeding conditions may play a greater role on food and fluid intake than the use of MA. Consequently, the
question of whether optimizing feeding is more effective than the use of orexigenics in LTC is raised and clearly warrants further investigation.

In an effort to examine the effects of megesterol acetate on weight and overall mortality, Bodenner et al. [33] conducted a case control cohort study of 17,332 nursing home residents admitted to a nursing home system over a three year period with a history of a 5% weight loss over 3 months or 10% over 6 months. Seven hundred nine MA treated patients were matched with 1418 non MA treated patients. The median survival of MA treated patients (23.9 months, 95% CI 20.2-27.5) was significantly less than non MA treated patients (31.2 months, 95% CI 27.8-35.9) (P< 0.001). Median weight differences after 6 months were unchanged. MA treatment of elderly nursing home residents according to the findings of this study was associated with an increase in all cause mortality without a significant increase in weight. This study is compelling and again underscores the need for randomized prospective studies with adequate sample sizes are needed to more fully understand the efficacy (or lack thereof), morbidity, and mortality associated with this treatment.

CONCLUSIONS AND IMPLICATIONS FOR PRACTICE

The evidence available to date regarding the use of orexigenics in long term care is substantially lacking with no evidence to support the use of cyproheptadine, oxandolone, or mirtazepine as an appetite stimulant for treating unintentional weight loss in long term care residents. Limited evidence that suggests that dronabinol may be of benefit in this population and some evidence that suggests that megesterol acetate may be of benefit; however, its use is not without risks and has not been studied for long term periods of time (>6 months). (See Table 1)

Of the nine studies identified that specifically addressed the issue of megesterol acetate in long term care, most were limited by small sample sizes and short treatment duration [11, 26, 27, 28,29, 32]. Confounding factors were difficult to identify, and in the case of the work of Yeh et al. [11, 29, 30,31], the sample of 69 mostly male residents was not representative of a typical nursing home distribution (mostly female). Treatment duration was of particular concern in that many of the studies did not address adverse outcomes that might be more apparent with longer periods of therapy. The literature cites many potential complications associated with MA such as thrombus formation, fluid retention, increase fat deposition, osteoporosis, impaired glucose regulation and death [33]. To date, no longitudinal studies have been conducted to look at these issues. Ironically, many literature reviews advocate the use of MA as a possible adjunctive treatment for unintentional weight loss in long term care residents [16, 34,35] Other authors do not advocate the use of MA and recommend additional studies in this area [5, 17, 21, 24]. The findings of Bodenner et al.[33], in the most recently published study to date, strongly suggest that MA not only lacks efficacy in the long term care population but may increase mortality. Evans [24] noted that with the use of MA, fat gain is the principle component in the increase in body weight, thus MA is not effective in restoring lean muscle mass associated with nutritional syndromes and unintentional weight loss in the older adults. Perhaps one of the most significant concerns is the risk of thromboembolism (deep vein thrombus or pulmonary embolus) with the use of MA. Residents of long term care who are less mobile in general and more prone to mild dehydration, may be at greater risk for the these complications. For the clinician in the long term care setting, a careful evaluation of risk benefit ratio must be considered and based on the evidence to date; MA is not an ideal pharmacotherapeutic agent for treating unintentional weight loss in this population. Based on the strength of the evidence available, none of the appetite stimulants mentioned in this review are recommended for treating unintentional weight loss in this population. The clinician dealing with this type of issue ideally should consider a comprehensive review of all contributing factors associated with unintentional weight loss and rule out any reversible causes. Periodic monitoring of weights, protein stores, labs and functional status should be included as part of a comprehensive plan of care. Consultation with a dietician and modification of diet and the addition of nutritional supplements should also be considered as first line treatment. The use of appetite stimulants should be carefully considered as a last resort, if at all [8].

ACKNOWLEDGEMENT

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### Table 1 Appetite Stimulants in Long Term Care

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Property of the study</th>
<th>Sample population</th>
<th>Results/presentation</th>
<th>Recommendations</th>
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<td>Miller et al. (2012)</td>
<td>Proportional test</td>
<td>Long-term care patients</td>
<td>Significant difference in weight gain between groups</td>
<td>Increase appetite and maintain nutritional status</td>
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<tr>
<td>Gilbert, J., Faller, J., &amp; Allender (2010)</td>
<td>Comparative study</td>
<td>Long-term care residents</td>
<td>No significant difference in weight gain between groups</td>
<td>Increase appetite and maintain nutritional status</td>
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<tr>
<td>St John et al. (2008)</td>
<td>Observational study</td>
<td>Long-term care residents</td>
<td>Significant difference in weight gain between groups</td>
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<td>Wang &amp; Wang (2016)</td>
<td>Case study</td>
<td>Long-term care patients</td>
<td>Significant difference in weight gain between groups</td>
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<td>Michnovicz et al. (2016)</td>
<td>Retrospective study</td>
<td>Long-term care residents</td>
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<td>Tanaka et al. (2015)</td>
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<td>Zhao et al. (2014)</td>
<td>Prospective study</td>
<td>Long-term care residents</td>
<td>Significant difference in weight gain between groups</td>
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</tbody>
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*Note: All studies were conducted in long-term care facilities and aimed to evaluate the effectiveness of appetite stimulants in improving weight gain among residents.*
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References

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