Controversies Surrounding the Use of Megestrol Acetate for the Treatment of Geriatric Weight Loss

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OBJECTIVES
By the end of this presentation, participants will be able to:
1. Describe the FDA approved indications for megestrol acetate.
2. Identify common usages for megestrol acetate in elderly patients.
3. Describe potential adverse effects of megestrol acetate.
4. Evaluate the evidence for the use of megestrol acetate in geriatric populations.
BACKGROUND
Geriatric Weight Loss

1. Description
   a. Sarcopenia: age-related decrease in muscle mass
   b. Anorexia: decrease in appetite and oral intake
   c. Dehydration: due to decrease in fluid intake
   d. Cachexia: loss of muscle and fat related to cytokine excess
   e. Malabsorption: physiological abnormalities
   f. Hypermetabolism: endocrine and disease-related processes

2. Factors in the Elderly

<table>
<thead>
<tr>
<th>Meals on Wheels</th>
<th>11 &quot;Ds&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>M: Medications</td>
<td>Disease</td>
</tr>
<tr>
<td>E: Emotional/depression</td>
<td>Dementia</td>
</tr>
<tr>
<td>A: Alcoholism</td>
<td>Delirium</td>
</tr>
<tr>
<td>L: Late life paranoia</td>
<td>Drinking of Alcohol</td>
</tr>
<tr>
<td>S: Swallowing problems</td>
<td>Drug use</td>
</tr>
<tr>
<td>O: Oral factors</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>N: Nosocomial Infections</td>
<td>Deafness/sensory deficit</td>
</tr>
<tr>
<td>W: Wandering/dementia</td>
<td>Depression</td>
</tr>
<tr>
<td>H: Hyperthyroidism, hypercalcemia, hypoadrenalism</td>
<td>Desertion</td>
</tr>
<tr>
<td>E: Enteral problems</td>
<td>Destitution</td>
</tr>
<tr>
<td>E: Eating problems</td>
<td>Despair</td>
</tr>
<tr>
<td>L: Low salt, low cholesterol, therapeutic diet</td>
<td></td>
</tr>
<tr>
<td>S: Stones/cholecystitis</td>
<td></td>
</tr>
</tbody>
</table>

   a. Decreased appetite
   b. Declining cognitive function
   c. Physical impairment
   d. Social isolation
   e. Access to food and meals

3. Implications for Survival
   a. Higher Mortality
      i. Predictive
         1. Continued weight loss: 30% chance of death within 6 months
         2. Weight stabilizes: 20% chance of death
         3. Weight gain: 10% chance of death
   b. Increased risk of infection
   c. Poor wound healing
   d. Component of "frailty"

4. Quality Measures
   a. OBRA 1987: Nursing Home Reform Act
      1. Response to problems with nursing home care
      2. Set standards for acceptable nursing home practices
   b. 42 CFR 483.25: "Nursing homes must maintain acceptable parameters of nutritional status"
      1. Body weight
      2. Protein status
      3. Therapeutic diet
c. Federal definitions
   i. Weight loss: 5% loss in 1 month or 10% loss in 6 months
   ii. Poor oral intake: consume less than 75% of most meals

5. Common Strategies\textsuperscript{1-4,9}
   a. Meal assistance
   b. Changes in food texture/thickness
   c. Enteral feeding
   d. Meal supplements
   e. Pharmacologic interventions
      i. Discontinuation of medications that may contribute to weight loss
      ii. Addition of medications promoting weight gain
         1. Dronabinol
         2. Anabolic Agents
         3. Testosterone/Selective Androgen Receptor Modulators
         4. Growth Hormone/Insulin-like Growth Factor
         5. Cyproheptadine
         6. Mirtazapine
         7. Amino Acids
         8. Megestrol Acetate

Megestrol Acetate
1. Formulations\textsuperscript{6-8}
   a. Tablets: 20mg, 40mg
   b. Suspension: 40mg/mL
   c. Megace \textregistered ES: 125mg/mL
      i. Microcrystalized formulation
      ii. Brand-name only

2. Approved Indications\textsuperscript{6-8}
   a. AIDS Cachexia:
      i. 400-800mg daily for suspension
      ii. 650mg daily for Megace ES\textregistered
   b. Palliative treatment of breast and endometrial cancer
      i. Breast Cancer: 40mg 4 times daily
      ii. Endometrial Cancer: 40-320mg daily in divided doses; Max 800mg daily

3. Mechanism of Action\textsuperscript{9-14}
   a. Inhibition of inflammatory cytokines
      i. TNF-\textgreek{a}, IL-1, IL-6, IL-8, IL-10
   b. Potential androgen receptor modulator

4. Potential Side Effects\textsuperscript{6-14}
   a. Adrenal insufficiency
   b. Venous thromboembolism
   c. Altered mental status
## Studies

| Objective | To evaluate the effect that megestrol acetate suspension has on oral food and fluid intake in nursing home patients receiving optimal feeding assistance vs. those receiving standard care  
| Design | Prospective, blind-rater crossover study conducted at 4 nursing home sites  
| Enrollment | 178 patients identified from a larger study evaluating nutritional care quality  
| | 17 patients completed the MA pilot study and were included in data analysis  
| | Inclusion:  
| | - Long-stay (non-Medicare)  
| | - Consistent intake of less than 75% of provided meals during 2-day (six meal) lead-in period  
| | | - Usual nursing home care  
| | | - Optimal mealtime feeding assistance  
| | Exclusion | Feeding Tubes  
| | | Hospice  
| | | Active GI or dental disease  
| | | Active cancer  
| | | Recent (past 6 months) thromboembolic disease  
| | | Uncontrolled hypertension  
| | | Previous adverse reaction to Megace®  
| | | Current use of megestrol acetate, cyproheptadine or mirtazapine  
| Methods | Treatment  
| | Megestrol acetate suspension 400mg daily for 63 days  
| | Optimal feeding assistance weeks 2, 4, 6  
| | Usual care weeks 1, 3, 5  
| Endpoints | Primary Endpoints:  
| | - Change in oral intake compared to baseline vs. weeks 1, 2, 3, 4, 5, 6 and Day 63  
| | | - Assessed as % of meal consumed  
| | | - Patient reports in changes of appetite and/or energy  
| | Secondary Endpoints:  
| | - Weight change at baseline vs. day 63  
| | - Side effects  
| Statistics | Group comparison of oral intake  
| | - Repeated measures analysis of variance with Bonferroni adjustments for multiple comparisons  
| | - 95% confidence intervals, p<0.05  
| Weight status | Paired t-tests  

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Results

**Patient Characteristics**
- Female: 88%
- White: 88%
- Average age: 91.9±5.8 years
- MMSE (0-30): 16.2±5.0

**Change in Oral Intake**

*Table 1: Usual Care: 2.8±4.0 minutes of staff assistance per meal*

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Average Total Percent Consumed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>43% ± 12%</td>
</tr>
<tr>
<td>Week 1</td>
<td>33% SD not given</td>
</tr>
<tr>
<td>Week 3</td>
<td>41% SD not given</td>
</tr>
<tr>
<td>Week 6</td>
<td>48% SD not given</td>
</tr>
<tr>
<td>Day 63</td>
<td>43% ± 20%</td>
</tr>
</tbody>
</table>

*Table 2: Optimal Feeding Assistance: 31.0±7.54 minutes of staff assistance per meal*

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Average Total Percent Consumed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>50%± 15%</td>
</tr>
<tr>
<td>Week 2</td>
<td>59% SD not given</td>
</tr>
<tr>
<td>Week 4</td>
<td>66% ± 26% (p&lt;0.05)</td>
</tr>
<tr>
<td>Week 6</td>
<td>63% ± 14% (p&lt;0.05)</td>
</tr>
</tbody>
</table>

*Table 3: Change in Weight Status- Baseline compared to Day 63*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Average Weight Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=17)</td>
<td>-2.13±9.32 pounds</td>
</tr>
<tr>
<td>Weight Gainers (n=8)</td>
<td>+5.9±4.9 pounds</td>
</tr>
<tr>
<td>Weight Losers (n=9)</td>
<td>-9.3±5.4 pounds</td>
</tr>
</tbody>
</table>

**Adverse Effects**
- Decreased Strength (n=8)
- Increased Fatigue (n=7)
- Nervousness; Cough (n=5)
- Increased Weakness; Leg Swelling; Rash (n=4 for each)

**Authors’ Conclusions**
Megestrol acetate in the absence of optimal feeding assistance, was not effective at increasing oral food and fluid intake in nursing home residents; megestrol acetate is effective in improving oral intake only when used in combination with optimal mealtime feeding assistance.

**Critique**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addressed the value of non-pharmacologic intervention</td>
<td>Small Study</td>
</tr>
<tr>
<td>Utilized national standards for oral intake</td>
<td>Not randomized</td>
</tr>
<tr>
<td>Assessed oral intake rather than weight gain</td>
<td>No control group</td>
</tr>
<tr>
<td>Removed possible independent confounder: optimal feeding assistance</td>
<td>Per-protocol</td>
</tr>
<tr>
<td>Rater-blinded intake assessment</td>
<td>Subjective measurement of oral food intake</td>
</tr>
<tr>
<td>Attempted to minimize dosing for geriatric patients</td>
<td>Nursing home residents only</td>
</tr>
<tr>
<td></td>
<td>Inconsistent timing of intake assessment</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Objective</td>
<td>To provide preliminary evidence regarding optimal dosing and efficacy of megestrol acetate for elderly patients with impaired appetite post-hospitalization</td>
</tr>
<tr>
<td>Design</td>
<td>Randomized, placebo-controlled clinical trial</td>
</tr>
</tbody>
</table>
| Enrollment | • 7,203 patients screened for inclusion  
• Potential subjects identified for pre-screening by workers in the skilled nursing facility or home health agency  
• 47 patients randomized into 4 treatment groups |
| Inclusion | • Age 60 years and older  
• Hospitalization for acute illness of injury within prior 3 weeks  
• Self-reported poor or fair appetite at the time of recruitment  
• Discharged to a skilled nursing facility for postacute rehab OR to receive skilled home health visits at home |
| Exclusion | • Active cancer  
• Dementia (MMSE score <20)  
• Current treatment with mirtazapine or megestrol acetate  
• Active GI, medical or dental disease that precludes eating  
• Feeding tubes  
• TPN  
• History of thromboembolic disease  
• Uncontrolled hypertension  
• Current systemic glucocorticoid therapy  
• Cirrhosis or other serious hepatic disease  
• Chronic renal failure or other serious renal disease  
• Non-English speaking  
• No available telephone  
• Planned placement to location >30 miles away from UCLA |
| Methods | • Intent-to-treat analysis  
• 9 week treatment duration  
• Study outcomes measured at baseline and each follow-up visit (20, 42 and 63 days) |
| Treatment groups | • Placebo (n=12)  
• 200mg megestrol acetate daily (n=12)  
• 400mg megestrol acetate daily (n=12)  
• 800mg megestrol acetate daily (n=11) |
## Methods

### Primary Outcomes
- Change in appetite
  - Three-question assessment
- Serum albumin
- Prealbumin
- Change in serum cortisol
- Occurrence of thromboembolic events
- Diarrhea

### Secondary Outcomes
- Changes in functional status
  - Self-reported
    - Activity of Daily Living Scale
    - Instrumental Activity of Daily Living Scale
  - Performance based
    - Physical Performance Test
    - Physical Performance Score
- Health-related quality of life
  - Medical Outcomes Study Short-form
- Weight
- Body composition

## Statistics
- Continuous outcomes: Generalized linear model
- Covariate structure AR(1) was used
- Ordinal outcomes: Generalized estimating equation method
- Event counts: Poisson distribution
- Dichotomous outcomes: Binomial distributions
- Ordinal outcomes: Multinomial distributions

## Results

### Baseline Characteristics
- Average age: 83.6 years
- Female (66.4%)
- White (82.8%)
- Mean BMI 22.3 kg/m²
- Average serum albumin 3.2 g/dL
- Average prealbumin 19.3 mg/dL

### Primary Outcomes
- Appetite
  - 20-day point, 800mg treatment group: Appetite better than at baseline (P=0.04)
  - 42-day point, 400mg treatment group: Appetite at start of last meal better than at baseline (P=0.02)
  - No differences between treatment groups for any of the appetite measures
Results
Continued

Figure 1: Changes in Appetite

- **Albumin**
  - No significant changes from baseline for any of the treatment groups

- **Prealbumin**
  - 20-day point, 400mg and 800mg treatment groups: Significant increases in prealbumin compared to placebo (P=0.009, P=0.004 respectively)
  - 62-day point, 400mg treatment group: Significant increase in prealbumin compared to placebo (P=0.02)

- **Adverse effects**
  - No patients developed clinical symptoms of adrenal insufficiency
  - 3 patients developed diarrhea (n=2 in 400mg group, n=1 in 800mg group)
  - 1 patient developed DVT (n=1 in 200mg group)
  - 1 patient developed DVT with multiple PEs (n=1 in 400mg group)
## Results Continued

- **Cortisol**
  - 20-day point, 400mg and 800mg treatment groups: Significantly lower cortisol levels compared to placebo (P=0.003, P=0.02 respectively)
  - Overall, 400mg and 800mg treatment groups: Significantly more likely to have cortisol levels below the lower limit of normal (<8ng/mL) (P=0.005, P=0.02 respectively)

<table>
<thead>
<tr>
<th>Day</th>
<th>Placebo</th>
<th>200mg daily</th>
<th>400mg daily</th>
<th>800mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0%</td>
<td>33%</td>
<td>70%</td>
<td>78%</td>
</tr>
<tr>
<td>63</td>
<td>11%</td>
<td>33%</td>
<td>56%</td>
<td>37%</td>
</tr>
</tbody>
</table>

### Table 4: Patients with cortisol below lower limit of normal (<8ng/mL)

![Figure 2: Changes in Lab Values](image)

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Palacios, K.
### Results Continued

#### Secondary Outcomes
- There were no statistically significant findings regarding the secondary endpoints
- This data was not presented in the trial

#### Authors’ Conclusions
Megestrol acetate 400mg and 800mg doses increase prealbumin in recently hospitalized older persons; cortisol suppression was common and may be persistent at higher doses; additional benefit for other nutritional or clinical outcomes was not observed.

### Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes defined to assess both potential risks and benefits</td>
<td>Selection of rehabilitation facilities or home health agencies not defined</td>
</tr>
<tr>
<td>Objective measurements for nutritional status were used</td>
<td>Rehab facilities and home health agencies responsible for pre-screen and referral of patients to the study</td>
</tr>
<tr>
<td>Randomized, placebo-controlled</td>
<td>Small study size</td>
</tr>
<tr>
<td></td>
<td>Non-numerical data presented poorly</td>
</tr>
</tbody>
</table>

### Title

### Objective
To examine the effects of megestrol acetate on weight and overall mortality in elderly nursing home residents

### Design
Retrospective case-control cohort matched study

### Enrollment
- 17,328 nursing home residents identified for screening from the National Medicare and Medicaid MDS (minimum data set) database
- 709 residents receiving ≥ 7 days of megestrol acetate treatment within 30 days of defined index event were matched (1:2) with 1418 residents not treated with megestrol acetate who were alive within 30 days of defined index event

**Inclusion (All patients)**
- Admitted to a Beverly Healthcare nursing home between 01/01/2000-12/31/2003
- 5% loss of total body weight in 3 months OR 10% loss of total body weight in 6 months
- Defined Index date: first MDS report of weight loss defined by above criteria

**Exclusion (All Patients)**
- No recorded index weight
- Index date same as last follow-up date
- Comatose

**Exclusion (Patients Receiving Megestrol Acetate)**
- Received < 7 days megestrol acetate therapy
- Followed up < 30 days after index date
- Megestrol acetate initiated > 30 days from index date
Methods

Primary endpoint
Overall survival: time from 30 days post-index date to last follow-up or death

Matching
- Individual
  - Age, sex, race, index date, index weight
- Propensity Score
  - ADLs, cognitive function, unstable condition, acute episode of current problem, end-stage disease, number of medications during previous 7 days, cancer diagnosis, HIV diagnosis

Statistics

Baseline information
- Mean ± SD for continuous variables
- Percentages, counts for categorical variables
- Student 2-sample t-tests and Pearson χ² used to compare cohorts

Study Outcomes
- Wilcoxon rank sum tests: weight comparisons
- Wilcoxon signed rank tests: weight change comparisons
- Kaplan-Meier method: estimate survival distributions
- Log-rank tests: compare distributions
- Cox proportional hazards model: adjust for potential confounders

Results

Baseline Characteristics
- Female: 71%
- White: 80%
- Average Age: 84 ±9 years
- ADL Score: 2.9±1.0
- Cognitive Function Score: 3.0±1.6
- Number of Medications 10.0±4.2 on megestrol vs. 9.4±4.0 control (p<0.001)

Table 5: Mortality Findings

<table>
<thead>
<tr>
<th>Last Follow-up</th>
<th>Megestrol Acetate Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive and in nursing home</td>
<td>281 (39.6%)</td>
<td>651 (45.9%)</td>
</tr>
<tr>
<td>Alive and discharged</td>
<td>149 (21.0%)</td>
<td>308 (21.7%)</td>
</tr>
<tr>
<td>Died in nursing home</td>
<td>279 (39.4%)</td>
<td>459 (32.4%)</td>
</tr>
</tbody>
</table>

Median Survival

<table>
<thead>
<tr>
<th></th>
<th>Megestrol Acetate Group (95% CI 20.2-27.5)</th>
<th>Control Group (95% CI 27.8-35.9)</th>
</tr>
</thead>
</table>
Results Continued

Figure 3: Mortality Findings

Mortality Findings Summary
- 23.4% decrease in median survival in megestrol acetate group vs. control group
- Difference statistically significant (p<0.001)
- Adjusted for medical, demographic and quality of life variables
  - Megestrol acetate exposure effect was still significant
  - HR 1.37 (95% CI 1.17-1.75)
- Median survival times were not statistically significant between differing megestrol acetate dosages (<200mg/day, 200-400mg/day, >400mg/day compared)

Weight Findings

Table 6: Weight

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Number</th>
<th>Median</th>
<th>IQR</th>
<th>Number</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>709</td>
<td>121.0 lbs</td>
<td>103-137</td>
<td>1418</td>
<td>122.0 lbs</td>
<td>104-138</td>
</tr>
<tr>
<td>3 months</td>
<td>493</td>
<td>119.0 lbs</td>
<td>102-137</td>
<td>1069</td>
<td>122.0 lbs</td>
<td>106-139</td>
</tr>
<tr>
<td>6 months</td>
<td>339</td>
<td>120.0 lbs</td>
<td>104-139</td>
<td>793</td>
<td>124.0 lbs</td>
<td>106-141</td>
</tr>
</tbody>
</table>

Table 7: Change in Weight

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Megestrol Acetate Cohort</th>
<th>Control Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>Number</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>493</td>
<td>0 lbs</td>
</tr>
<tr>
<td>6 months</td>
<td>339</td>
<td>1.0 lbs</td>
</tr>
</tbody>
</table>

Authors’ Conclusions

Treatment of elderly nursing home residents with megestrol acetate was associated with a significant increase in mortality without a significant increase in weight

Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large study population</td>
<td>Retrospective selection bias</td>
</tr>
<tr>
<td>Adjustment for possible confounders</td>
<td>Didn’t account for regional differences or local prescribing culture</td>
</tr>
<tr>
<td>Utilized a nationally standardized database</td>
<td>Causes of death not investigated</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Objective</td>
<td>To determine the effects of progressive resistance muscle strength training (PRMST) and megestrol acetate (as independent and combined interventions) on strength, muscle mass and function in elderly recuperative care patients</td>
</tr>
<tr>
<td>Design</td>
<td>Randomized, double blind/single blind, placebo controlled trial</td>
</tr>
</tbody>
</table>
| Enrollment | • 34 patients referred for the study from inpatient, outpatient and transitional care Geriatric Evaluation and Management Services at a University-affiliated VA hospital  
  • 29 patients enrolled between 1999 and 2001 |
| Inclusion | • 65 years of age and older  
  • Recent illness-induced functional decline  
  • Capable of giving informed consent |
| Exclusion | • Near-terminal medical disorder  
  • Unresolved malignancy  
  • Unrealistic goal of independent ambulation  
    - Disabling arthritis  
    - Irreversible neurological disease  
  • Unstable cardiovascular disease |
| Methods | Intent-to-treat, baseline measurements carried forward for non-completers |
| Treatment | • 12 week intervention period  
  • Daily dose of megestrol acetate titrated to 800mg daily over 9 days  
  • 4 treatment arms  
    • Low-resistance muscle toning + placebo (n=7)  
    • Low-resistance muscle toning + megestrol acetate (n=7)  
    • High-intensity PRMST + Placebo (n=7)  
    • High-intensity PRMST + megestrol acetate (n=8) |
| Primary Outcome | • Change in muscle strength |
| Secondary Outcomes | • Change in physical performance  
  • Change in mid-thigh cross-sectional area |
| Statistics | • Two-factor ANOVA for muscle strength data  
  • One-group paired t-test for statistical significance (P=0.05)  
  • ANCOVA adjustment for between-group baseline differences  
  • Tukey's multiple comparison procedure for significant differing baseline variables |
Results

Baseline Characteristics
- Average Age: 79.4±7.4 years
- White (90%)
- Male (83%)
- 83% had lost ≥ 10 pounds over previous 12 months
- 86% scored below median reference range for health older adults on ambulatory speed tests

Table 8: Primary Outcome: Changes in strength from baseline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Low + Placebo</th>
<th>Low + MA</th>
<th>PRMST+ Placebo</th>
<th>PRMST + MA</th>
<th>P for exercise</th>
<th>P for drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Press (%)</td>
<td>1.61±5.46</td>
<td>2.66±5.46</td>
<td>17.12±5.46</td>
<td>9.53±5.11</td>
<td>0.048</td>
<td>0.55</td>
</tr>
<tr>
<td>Chest Press (kg)</td>
<td>0.08±1.11</td>
<td>-0.16±1.11</td>
<td>3.77±1.11</td>
<td>2.17±1.03</td>
<td>0.01</td>
<td>0.41</td>
</tr>
<tr>
<td>Leg Press (%)</td>
<td>8.30±5.93</td>
<td>-1.53±5.98</td>
<td>23.56±6.05</td>
<td>-2.90±5.70</td>
<td>0.25</td>
<td>0.006</td>
</tr>
<tr>
<td>Leg Press (kg)</td>
<td>4.57±5.88</td>
<td>0.18±5.89</td>
<td>1.49±3.38</td>
<td>-3.00±3.17</td>
<td>0.30</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Figure 4: Lower Extremity Muscle Strength

Table 9: Secondary Outcomes: Changes from baseline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Low + Placebo</th>
<th>Low + MA</th>
<th>PRMST+ Placebo</th>
<th>PRMST + MA</th>
<th>P for exercise</th>
<th>P for drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-thigh cross-sectional area (%)</td>
<td>3.45±3.38</td>
<td>2.07±3.38</td>
<td>1.49±3.38</td>
<td>-3.00±3.17</td>
<td>0.30</td>
<td>0.39</td>
</tr>
<tr>
<td>Aggregate functional score</td>
<td>0.21±0.61</td>
<td>-0.93±0.58</td>
<td>0.76±0.59</td>
<td>-0.66±0.54</td>
<td>0.49</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 10: Other Outcomes: Changes from baseline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Low + Placebo</th>
<th>Low + MA</th>
<th>PRMST+ Placebo</th>
<th>PRMST + MA</th>
<th>P for exercise</th>
<th>P for drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM cortisol</td>
<td>99.3±70.90</td>
<td>-173.2±70.90</td>
<td>-1.66±70.90</td>
<td>-154.7±66.49</td>
<td>0.56</td>
<td>0.005</td>
</tr>
<tr>
<td>AM testosterone</td>
<td>-33.8±69.99</td>
<td>-281±69.99</td>
<td>12.8±69.99</td>
<td>-346.2±65.4</td>
<td>0.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight</td>
<td>0.68±0.89</td>
<td>5.61±0.89</td>
<td>-0.85±0.89</td>
<td>0.72±0.83</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Body Fat</td>
<td>0.75±1.69</td>
<td>9.50±1.69</td>
<td>0.34±1.69</td>
<td>1.98±1.59</td>
<td>0.03</td>
<td>0.005</td>
</tr>
<tr>
<td>Non-fat mass</td>
<td>-0.07±1.23</td>
<td>-3.89±1.23</td>
<td>-0.59±1.23</td>
<td>-1.25±1.50</td>
<td>0.39</td>
<td>0.08</td>
</tr>
<tr>
<td>Nutrient Intake</td>
<td>0.9±8.1</td>
<td>15.6±6.7</td>
<td>0.3±6.7</td>
<td>21.0±7.7</td>
<td>0.76</td>
<td>0.03</td>
</tr>
</tbody>
</table>
High-intensity PRMST is an exercise regimen that is safe and well-tolerated in frail elderly patients; megestrol acetate, when added to PRMST, is associated with less muscle strength and functional performance gains and appears to blunt the beneficial effects associated with this exercise regimen.

### Critique

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intent-to-treat analysis</td>
<td>• Small sample size</td>
</tr>
<tr>
<td>• Non-pharmacological interventions</td>
<td>• Skewed study population gender</td>
</tr>
<tr>
<td>• Meaningful clinical measurements of functional status</td>
<td></td>
</tr>
<tr>
<td>• Objective measures of functional change</td>
<td></td>
</tr>
</tbody>
</table>

### CONCLUSIONS

1. The evidence regarding the use of megestrol acetate to promote weight gain and improve other markers of nutritional status in geriatric patients is inconsistent.
2. Megestrol acetate should not be considered a sole intervention to promote geriatric weight gain.
3. MA is associated with several adverse events including adrenal insufficiency and venous thromboembolism, so use in high-risk patients should generally be avoided.
4. MA may be considered last-line for patients non-responsive to other non-pharmacologic interventions to improve nutritional status.
5. MA in these patients should be discontinued before 12 weeks of therapy or sooner if an adverse event occurs or if medication is not beneficial or initial benefit begins to decline.
REFERENCES


