Megestrol Acetate Stimulates Weight Gain and Ventilation in Underweight COPD Patients*

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**Study objectives:** To assess the effect of megestrol acetate (MA), a progestational appetite stimulant commonly used in patients with AIDS and cancer, on body weight and composition, respiratory muscle strength, arterial blood gas levels, and subjective perceptions in COPD patients.

**Design and setting:** Prospective, double-blind, randomized, placebo-controlled trial conducted on an outpatient basis at 18 sites.

**Patients:** Underweight (< 95% ideal body weight) COPD patients ≥ 40 years old.

**Interventions:** Either MA, 800 mg/d oral suspension, or placebo at a 1:1 ratio for 8 weeks.

**Results:** Of 145 randomized patients (63% men), 128 patients completed the trial. Body weight increased by 3.2 kg in the MA group and 0.7 kg in the placebo group (p < 0.001). Anthropometric and dual-energy radiograph absorptiometry assessments confirmed that weight gain was mainly fat. Spirometry and maximal voluntary ventilation showed no significant changes from baseline in either group, and the difference in the change in maximum inspiratory pressure between groups was not significant. The 6-min walk distances did not differ statistically between groups at week 2 and week 4, but were greater in the placebo group at week 8 (p = 0.012). Consistent with the known ability of MA to stimulate ventilation, PaCO₂ decreased (4.6 mm Hg, p < 0.001) and PaO₂ increased (2.8 mm Hg, p < 0.04) in the MA group. Questionnaires revealed that body image and appetite improved in the MA group but not the placebo group. Adverse event frequency and type were similar in both groups, but cortisol and testosterone (in men) levels decreased substantially in the MA group.

**Conclusions:** We conclude that MA safely increased appetite and body weight, stimulated ventilation, and improved body image in underweight COPD patients, but did not improve respiratory muscle function or exercise tolerance. (CHEST 2002; 121:1070–1078)

**Key words:** COPD; malnutrition; megestrol acetate; weight loss

**Abbreviations:** AE = adverse event; CRP = C-reactive protein; DEXA = dual-energy radiograph absorptiometry; MA = megestrol acetate; MAC = mid-arm circumference; MIP = maximum inspiratory pressure; MVV = maximum voluntary ventilation; 6MWD = 6-min walk distance

COPD is defined as a disease state characterized by the presence of progressive airflow obstruction due to chronic bronchitis or emphysema. The airflow obstruction may be accompanied by airway hyperreactivity, and may be partially reversible.1 Approximately 14 million individuals in the United States have COPD, and it is the fourth-leading cause of death. Individuals with advanced COPD often have progressive weight loss.2–5 Approximately 50% of hospitalized patients with COPD are < 90% of their ideal body weight.2 Moreover, there is also generalized muscle wasting as well as specific wasting of the diaphragm.6 Low body weight and muscle wasting is associated with accelerated mortality and a decline in clinical status independent of lung disease severity.7–9 Appropriate therapy that succeeded in reversing low body weight has been found to improve survival.9

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Megestrol acetate (MA), a progestational agent, has been shown to increase body weight, appetite, performance status, and sense of well-being in patients receiving radiation therapy or chemotherapy, and in AIDS patients.\textsuperscript{10–12} In a randomized trial in AIDS patients, 800 mg/d of MA not only increased weight but also lean body mass.\textsuperscript{12} Progestational agents have also been shown to stimulate ventilation.\textsuperscript{13,14}

There are limited data available on the use of progestational agents or MA in patients with COPD.\textsuperscript{15–18} In this study, we tested the hypotheses that MA ingestion by underweight COPD patients would result in weight gain, stimulation of ventilation, and improvements in respiratory muscle strength.

**Materials and Methods**

**Patients**

Underweight COPD patients (<95% of ideal body weight) ≥ 40 years of age in a stable phase of their disease were recruited at 18 study centers. Patients included had a clinical history of COPD and postbronchodilator FEV\textsubscript{1} between 25% predicted and 65% predicted. In order to include patients whose weight loss was due only to their COPD, patients were excluded if they had another concurrent illness, or other significant and/or uncontrolled medical conditions that might contribute to weight loss. Patients were also excluded if they had received long-term oral corticosteroids (prednisone, >10 mg/d), as this could lead to weight gain. Participants were receiving stable bronchodilator regimens prescribed by their physicians. The institutional review board or ethics committee of each participating center approved the study, and all patients provided written informed consent. There were 145 patients randomized, with 128 patients completing the trial.

**Study Protocol**

The study design was randomized, double blind, and placebo controlled. Patients were randomized equally into MA or placebo groups. Patients self-administered 20 mL of placebo (inert oral suspension) or MA, 800 mg/d for 8 weeks. Each patient visited the study center for assessment at baseline (screening visit), and body weight was measured at screening and at week 8. Nonfasting serum glucose was measured, adverse events (AEs) were recorded, and a physical examination was performed at each visit.

**Assessments**

**Height and Body Weight:** Height was measured at the screening visit, and body weight was measured at all visits using a balance-beam scale. Only light indoor clothing was allowed. Ideal body weight was determined from the Metropolitan Life Insurance Company reference chart.\textsuperscript{19}

**Spirometry and Maximum Voluntary Ventilation:** Spirometry was performed at all visits using methodology recommended by the American Thoracic Society.\textsuperscript{20} The reference values used were from Crapo et al.\textsuperscript{21} Maximum voluntary ventilation (MVV) maneuvers were performed at all visits and were 12 to 15 s in duration. At least two MVV maneuvers were performed, with the highest value reported.

**Maximum Inspiratory Pressure (MIP):** was measured at all visits according to standardized methods.\textsuperscript{22} Briefly, the patient had a nose clip in place attached to a mouthpiece that was connected to a valve and pressure transducer system. The patient was instructed to exhale slowly and completely into the mouthpiece. The valve was then closed, and the patient was instructed to inhale with as much force as possible for at least 1 s. The highest value of three repetitions was recorded.

Body composition was assessed using anthropometry at each visit. The same individual at each center measured mid-arm circumference (MAC) using a flexible tape, and triceps skin-fold thickness was measured using a caliper at each visit. The average of three measurements for each parameter was recorded. Additionally, in a subset of patients (25 in each group), body composition was assessed by dual-energy radiograph absorptiometry (DEXA)\textsuperscript{23} at the screening visit and at week 8 in the 6 of 18 sites at which DEXA was available.

**Arterial Blood Gas Analysis:** Arterial blood samples were obtained by radial artery puncture at each visit while the patient breathed room air. Samples were analyzed for blood gas and pH composition in duplicate.

**6-min Walk:** A 6-min self-paced walk in a measured corridor was performed at each visit using a standardized approach.\textsuperscript{24–25} Three repetitions were performed at the first visit (with 15 min of rest between repetitions, and the greatest distance walked recorded), and one walk was performed at subsequent visits.

**Questionnaire:** Three questionnaires were completed at baseline and week 8: (1) the chronic respiratory disease questionnaire of Guyatt et al\textsuperscript{26}; (2) the baseline and transitional dyspnea index of Mahler et al\textsuperscript{27}; and (3) nine questions concerning appetite and body image previously used in published studies\textsuperscript{28,29} of MA in patients with AIDS and cachexia.

**Acute-Phase Proteins:** Serum albumin, prealbumin, transferrin, and C-reactive protein (CRP) were determined at screening, week 4, and week 8 using standard laboratory procedures at 3 of 18 sites.

**Safety:** Serum cortisol and testosterone (in men) levels were measured at screening and at week 8. Nonfasting serum glucose was measured, adverse events (AEs) were recorded, and a physical examination was performed at each visit.

**Compliance:** Patients were asked to record on a diary card the date and time of study-drug administration. Study coordinators examined all study-drug bottles for remaining study drug to determine compliance.

**Statistical Analysis**

The intent-to-treat population, consisting of all randomized patients who received at least one dose of study medication and had at least one postbaseline assessment, was used for efficacy and safety analysis. For patients who withdrew, or when measurements were not obtained at a visit, missing data were imputed using last-observation-carried-forward methodology. Discrete outcomes were summarized by frequency and percentages, and treatment groups were compared using Fisher’s Exact Tests. Continuous outcomes were summarized by mean, SD, median, minimum, and maximum; and treatment groups were compared using analysis of covariance, with change from baseline as the outcome.\textsuperscript{29,30} The criteria for significance was \( p < 0.05 \).

The primary efficacy variable was the change in MIP from baseline to postbaseline visits. The secondary efficacy variables included body weight and composition, spirometry, 6-min walk distance (6MWD), arterial blood gas values, and questionnaire results. The sample size was calculated based on the primary
the additional mass consisted mainly of fat tissue. The mean triceps skin-fold thickness values increased significantly from baseline to week 8 in the MA group, when compared to the placebo group (1.35 ± 2.78 mm vs 0.13 ± 2.24 mm, respectively; p = 0.002). The mean MAC values did not change significantly from baseline to week 8 in either group. The arm circumference index (an indirect calculation [MAC − 3.14 × triceps skin-fold thickness], thought to reflect the amount of lean tissue in the arm) in the MA group did not change significantly from baseline to week 8 when compared to the placebo group (0.07 ± 3.44 vs 0.34 ± 1.77, respectively; p = 0.645).

DEXA was performed in 28 of 72 patients (39%) in the MA group, and 28 of 73 patients (38%) in the placebo group. Total body fat mass increased 42% from baseline to week 8 in the MA group (8.90 ± 4.61 to 11.45 ± 4.76 kg), while the placebo group increased 0.1% (9.34 ± 4.84 to 9.35 ± 4.51 kg). The difference in fat mass increase between groups was highly significant (p < 0.001). The changes in triceps skin-fold thickness and DEXA fat mass were significantly correlated in the subgroup of patients in whom DEXA was performed (p < 0.01). In contrast, lean body mass was essentially unchanged in the MA and placebo groups after 8 weeks of treatment (−2.3% and −0.1%, respectively).

Spirometry and MVV measurements showed no significant changes from baseline in either group. MIP increased mildly (ie, became more negative) in both groups, and the changes did not differ significantly between groups (Table 2).

PaO₂ values decreased significantly in the MA group, but not in the placebo group. Similarly, PaO₂ values increased significantly in the MA group but not in the placebo group.

Because the mean baseline values for PaCO₂ and PaO₂ in both groups were in the normal range (ie, PaCO₂ = 35 to 45 mm Hg, and PaO₂ = 70 to 90 mm Hg), subsets of patients with elevated baseline PaCO₂ (≥ 45 mm Hg) and decreased baseline PaO₂ (≤ 70 mm Hg) were examined (Tables 3, 4). Due to the much smaller sample size in these subsets, the linear mixed model was not adjusted for study center. PaCO₂ decreased from baseline in the MA-treated subset of hypercapnic patients at all measurement periods and was statistically significantly different at week 4 and week 8. PaO₂ increased from baseline in the MA-treated subset of hypoxic patients at all measurement periods and was statistically significantly different at week 2 and week 4.

There were statistically nonsignificant changes from baseline in both groups for the 6MWD at week 2 and week 4. At week 8, there was a decrease of

**Table 1—Baseline Characteristics of COPD Patients in the MA and Placebo Groups**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MA Group (n = 72)</th>
<th>Placebo Group (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>46 (64)</td>
<td>45 (62)</td>
</tr>
<tr>
<td>Women</td>
<td>26 (36)</td>
<td>28 (38)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>68.4 (9.0)</td>
<td>66.3 (11.5)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169.3 (9.9)</td>
<td>167.7 (9.6)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>53.1 (9.0)</td>
<td>51.7 (8.6)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>18.6 (1.7)</td>
<td>18.3 (1.9)</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.51 (1.03)</td>
<td>2.31 (0.77)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.05 (0.46)</td>
<td>1.04 (0.40)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD) unless otherwise indicated.*

**Results**

**Patients**

Of 145 randomized patients, 128 patients completed the trial. The baseline characteristics (Table 1) were similar for the two groups, and there were no statistically significant differences for gender, age, height, weight, body mass index, FVC, and FEV₁.

For all randomized patients, FEV₁ averaged 1.05 L and FEV₁/FVC ratio averaged 44%. There were approximately twice as many men as women in the study (63% vs 37%, respectively). The average age was 67 years, with 44% of the patients > 70 years old. The majority of patients were white (84%).

The compliance rates for receiving the study drug were similar for the two groups. Approximately 90% of the patients in both groups received between 80% and 120% of the prescribed study medication.

**Physiologic Parameters**

There were no significant differences in baseline variables between the two groups. The physiologic parameters at baseline and after 8 weeks of treatment are displayed in Table 2.

Body weight increased significantly in the MA group compared to the placebo group. Changes were seen as early as 2 weeks, when the MA group had an increase of 1.2 ± 1.4 (mean ± SD), while the placebo group increased 0.6 ± 1.1 kg (p = 0.009; Fig 1).

Both anthropometry and DEXA confirmed that...
81 feet in the MA group, and an increase of 18 feet in the placebo group (p = 0.012).

Analyses of acute phase proteins (albumin, prealbumin, transferrin, and CRP) were performed in 17 of 72 patients (24%) in the MA group, and 15 of 73 patients (21%) in the placebo group. Values in the two groups were not statistically significantly different and within the normal range at baseline. Serum prealbumin in the MA group increased from a mean baseline value of 26.1 mg/dL to 28.7 mg/dL at week 4, vs the mean value in the placebo group increasing from a baseline value of 26.1 mg/dL to 26.6 mg/dL (p < 0.01). At week 8, the mean serum prealbumin value in the MA group was 28.7 ± 9.5 mg/dL vs 27.5 ± 8.7 mg/dL in the placebo group (p = 0.095). The changes from baseline for albumin, transferrin, and CRP in the MA and placebo groups were not statistically significant.

Questionnaires

The mean scores of the Mahler questionnaire (assessing dyspnea on a 1 to 7 scale, a higher value indicating less dyspnea, for five daily activities) were assessed at baseline and week 8. In the MA group, the mean score decreased slightly (but not significantly) from baseline (0.028 ± 0.570), while the placebo group mean score increased (0.644 ± 0.957 [ie, patients became less dyspneic]. This change between groups was statistically significant (p < 0.001).

The mean scores of the chronic respiratory disease questionnaire (emotional function scores of 1 to 7 for a standard set of 10 questions) were mostly unchanged in both groups. At week 8, the mean score of the MA group had increased slightly from baseline (0.28 ± 1.28), while the mean score of the placebo group also increased slightly from baseline (0.47 ± 1.12). This change between groups was not statistically significant (p = 0.44).

A nine-item questionnaire was used to evaluate the patient’s assessment of the effect of therapy on their overall sense of well-being (Table 5). Questions addressed the effect of therapy on weight change (questions 1 and 2), appearance (questions 3 and 4), appetite (questions 5 and 6), and overall perception of the effect of the study treatment (questions 7, 8, 9, 10).
and 9). A linear analog scale (−5 to +5) was used for scoring. At week 8, the mean responses to five of the nine questions (questions 1, 3, 4, 5, and 6) were statistically higher (favorable) in the MA group, while mean responses to the other four questions were higher in the MA group but not statistically different between groups.

Safety

The maximum duration of exposure to 800 mg of MA was 8 weeks (56 days), by study design. There were 60 patients (83.3%) in the MA group and 51 patients (69.9%) in the placebo group who had at least one AE. The most frequent AEs involved respiratory symptoms (with shortness of breath, bronchitis, and upper respiratory tract infection being the most frequent), but incidence was similar between treatment groups. There were 23 patients (31.9%) in the MA group and 24 patients (32.9%) in the placebo group reporting AEs involving the GI system. For AEs involving the body system as a whole (general disorders), 20 patients (27.8%) in the MA group reported AEs vs 20 patients (27.4%) in the placebo group. There were four patients (6%) reporting the AE of ankle edema in the MA group and one patient (1%) in the placebo group. There were seven patients (9.7%) reporting an AE of edema (other than ankle) in the MA group (mild [n = 6], moderate [n = 1]) vs three patients (4.1%) in the placebo group (all mild). While there were differences between groups, the overall incidences were low and the severity in the majority of cases was mild.

Of the 17 patients not completing the trial, 9 patients had AEs: 5 patients in the MA group (eight AEs with one severe AE) and 4 patients in the PL group (eight AEs with one severe AE). One patient had a protocol violation (placebo group), and seven patients (six patients in the placebo group and one patient in the MA group) did not complete the study because of other reasons (five patients were unavailable for follow-up, and two patients withdrew consent). There were no deaths in this study, and there were six serious AEs in the MA group (shortness of breath [n = 1], COPD [n = 3], and pneumonia [n = 2]) and seven serious AEs in the placebo group (COPD [n = 3], pneumothorax [n = 1], respiratory

### Table 4—PaO\textsubscript{2} Values in Hypoxic Patients\textsuperscript{*}

<table>
<thead>
<tr>
<th>Group</th>
<th>PaO\textsubscript{2} Values, mm Hg</th>
<th>p Value\textsuperscript{†}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MA</strong> (n = 35)</td>
<td>60.8 (6.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong> (n = 29)</td>
<td>58.5 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>68.5 (10.7)</td>
<td>60.8 (9.9)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>7.7</td>
<td>2.3</td>
</tr>
<tr>
<td>Week 4</td>
<td>70.7 (14.1)</td>
<td>60.8 (9.9)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>9.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Week 8</td>
<td>66.5 (11.3)</td>
<td>61.2 (11.5)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>5.7</td>
<td>2.7</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Data are presented as mean (SD) unless otherwise indicated. Data are from patients with baseline PaO\textsubscript{2} ≤ 70 mm Hg.

\textsuperscript{†}p value for treatment effect using change from baseline.

### Table 5—Questions and Scores at Week 8 From Third Questionnaire\textsuperscript{*}

<table>
<thead>
<tr>
<th>Questions</th>
<th>MA (n = 66)</th>
<th>PL (n = 62)</th>
<th>p Value\textsuperscript{†}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Since you began treatment with the test drug, do you feel that any change in weight has had a significant (+ or −) impact on your health?</td>
<td>2.0 (2.1)</td>
<td>1.0 (2.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>2 Are you more (−) or less (+) concerned about your weight now than when you started treatment? A “more concerned” response would be a negative answer.</td>
<td>2.1 (2.1)</td>
<td>1.1 (2.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>3 To what extent has your appearance changed for the better (+) or worse (−) since treatment was started?</td>
<td>1.9 (2.0)</td>
<td>1.0 (1.6)</td>
<td>0.010</td>
</tr>
<tr>
<td>4 Based on comments from friends, loved ones, and coworkers, how do you feel your appearance has changed for the better (+) or worse (−) since the start of treatment?</td>
<td>2.1 (2.1)</td>
<td>1.1 (1.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>5 To what extent has your appetite changed for the better (+) or worse (−) since the start of the treatment?</td>
<td>3.3 (1.7)</td>
<td>1.9 (1.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6 Do you enjoy eating more (+) or less (−) than before?</td>
<td>3.1 (1.8)</td>
<td>1.7 (2.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>7 Since beginning this treatment do you feel better (+) or worse (−) overall?</td>
<td>2.1 (2.1)</td>
<td>1.9 (1.9)</td>
<td>0.498</td>
</tr>
<tr>
<td>8 Do you think this treatment has been of benefit (+ or −) to you?</td>
<td>2.7 (2.1)</td>
<td>2.1 (1.9)</td>
<td>0.080</td>
</tr>
<tr>
<td>9 Since beginning treatment, has your quality of life become better (+) or worse (−)?</td>
<td>1.7 (2.2)</td>
<td>1.6 (1.7)</td>
<td>0.799</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Scores are presented as mean (SD). A −5 to +5 analogue scale was used for scoring.

\textsuperscript{†}p value for treatment effect using change from baseline.
distress \( [n = 1] \), metabolic disorder \( [n = 1] \), and alcohol-related problem \( [n = 1] \).

The nonfasting glucose values fell slightly in both groups (by an average of 4.8\% and 1.5\% in the MA and placebo groups, respectively, at week 8), but differences between groups were not statistically significant. Serum cortisol values in the two groups were similar at baseline. At week 8, the mean value of the MA group was 13.4 \( \pm \) 5.9 \( \mu g/dL \), an increase of 0.7 \( \mu g/dL \) from baseline. The difference in change from baseline between the two groups was significant \( (p < 0.001) \). Serum cortisol levels shifted from normal to low in 45\% of the MA group vs 3\% of the placebo group.

Total serum testosterone levels were measured at baseline and week 8 in 45 of 46 men (98\%) in the MA group and 42 of 45 men (93\%) in the placebo group. The mean values in the two groups were not statistically different at baseline. At week 8, the mean value of the MA group was 73.1 \( \pm \) 89.4 \( ng/dL \), a dramatic decrease of 402.6 \( ng/dL \) from baseline. The mean value of the placebo group was 533.7 \( \pm \) 231.1 \( ng/dL \), an increase of 5.6 \( ng/dL \) from baseline. The difference in change from baseline between the two groups was highly significant \( (p < 0.001) \). Serum testosterone levels shifted from normal to low in 76\% of the men in the MA group vs 2\% of the men in the placebo group.

There were only minor changes in BP and pulse rate in both groups. There were no incidents in the MA group and one incident in the placebo group of shifts in systolic BP from normal to low. There were no incidents in the MA group and five incidents in the placebo group of shifts in diastolic BP from normal to low.

**DISCUSSION**

In this randomized, double-blind, placebo-controlled study of MA ingestion at a dose of 800 mg/d, patients with COPD manifested a significant weight gain and changes in arterial blood gas values consistent with ventilatory stimulation. The additional weight gained was mainly in the form of fat mass. MIP improved \( (ie, \) became more negative) in both groups, and there was no significant treatment effect. There were no significant differences between groups in the 6MWD at week 2 and week 4, but a significant \( (although \) possibly not clinically meaningful) difference at week 8 \( (with \) the placebo group having a greater increase).

The exact mechanism by which MA stimulates appetite is unknown. Weight loss has been found to be a negative prognostic factor in COPD, though the mechanisms of wasting in COPD are unclear. Both hypermetabolism and reduced dietary intake have been hypothesized as contributing factors. Reversing weight loss has assumed new urgency with the demonstration of Schols et al\(^9\) that inducing a weight gain of \( > 2 \text{ kg} \) in underweight COPD patients significantly improved survival. The ability of MA to induce a weight gain averaging approximately 3 kg in an 8-week period is impressive, in comparison with other available methods.

Other reported approaches to the therapeutic management of weight loss and cachexia in COPD patients include nutritional supplementation and administration of anabolic agents. Trials of nutritional supplementation have been disappointing, unless the patient is confined and closely monitored to enforce dietary supplementation. Most studies have shown minimal or no weight increases.\(^{33}\)

There is limited information concerning the effects of anabolic hormone supplementation. Schols et al\(^{34}\) administered a low dose of nandrolone \( (an \text{ anabolic steroid}) \) or placebo to 217 men and women with COPD who were also randomized to receive nutritional supplementation. An exercise program was also included in this trial. The combined intervention yielded an average 2.6-kg increase in body weight at the end of 8 weeks and a 1.9-kg gain in lean tissue mass.\(^{34}\) Burdet et al\(^{35}\) administered growth hormone or placebo for 3 weeks to 16 underweight COPD patients. While lean body mass increased significantly in the growth hormone group by 2.3 kg \( (\text{vs placebo increase of 1.1 kg}) \), there was not a significant increase in body weight.\(^{35}\) Ferreira et al\(^{36}\) reported a weight gain in 17 underweight male COPD patients of 1.8 kg after 6 months of treatment with anabolic steroids \( (250 \text{ mg of testosterone IM at baseline and 12 mg/d oral stanozolol}) \).

In our study, the gain in weight by the patients receiving MA consisted mainly of fat mass gain. Similar results have been reported in cancer and AIDS patients receiving MA.\(^{11,28,37}\) Von Roenn\(^{12}\) reported a significant increase in lean tissue mass \( (\text{averaging 1.1 kg}) \) in AIDS patients receiving 800 mg/d of MA for 12 weeks, but used a different methodology \( (bioelectrical impedance analysis) \) than we used here to evaluate changes in body composition. Failure to gain lean body mass in our study was not unexpected, since the trial did not include a structured exercise program aimed at increasing muscle mass. However, patients expressed satisfaction with improvements in their body image, enjoyment of food, and increased appetite, but we did not study the effects of long-term administration of MA on weight gain or survival.

Development of edema was not a significant factor in weight gain. If it were, DEXA would have revealed an increase in lean mass. However, there were more reports of any type of edema in the MA
group than in the placebo group (11 reports vs 4 reports, respectively). We did not explicitly measure total body water, but in other trials using 800 mg/d of MA, no significant difference from placebo in body water was reported.

Reliable ventilatory stimulants for COPD patients with carbon dioxide retention have been sought. Progestational agents have been shown to stimulate ventilation and/or increase the respiratory neuromuscular response to carbon dioxide. Ventilatory stimulation likely occurs through stimulation of the brainstem respiratory center. In this study, there were significant reductions in PaCO₂ and increases in PaO₂ in the MA group.

In this study, the study population had, on average, normal resting PaCO₂ values (40.8 ± 5.6 mm Hg and 40.1 ± 6.4 mm Hg in the MA and placebo groups, respectively). We performed a post hoc analysis on a subset of patients (n = 27; 15 patients in the MA group and 12 patients in the placebo group) whose baseline PaCO₂ values were elevated (ie, ≥ 45 mm Hg). We found that the PaCO₂ values decreased in the MA subset group by about the same amount as we observed in the entire MA group at each visit (ie, 4.6 mm Hg). There was no significant change in the PaCO₂ values of the placebo group in this subset of patients. Similarly, the mean baseline PaO₂ values were in the normal range at 71.4 ± 13.2 mm Hg and 74.2 ± 13.3 mm Hg in the MA and placebo groups, respectively. A post hoc analysis of a subset of patients (n = 64; 35 patients in the MA group and 29 patients in the placebo group) with baseline PaO₂ values ≤ 70 mm Hg was examined. We found that the PaO₂ values increased from baseline in the MA subset group at each visit by a greater amount than occurred in the placebo group. Thus, it appears that patients with carbon dioxide retention and/or hypoxemia may benefit from the ventilatory stimulation induced by MA.

MA is structurally similar to glucocorticoids. Thus, the potential exists for adrenal insufficiency during and after withdrawal after prolonged therapy. A few cases of adrenal suppression have been reported in adults and children treated with MA. In our study, we did not look specifically for signs and symptoms of adrenal insufficiency, such as abnormal electrolytes, adrenocorticotropic hormone, fatigue, or orthostatic BP. We did collect resting BP data and found no incidents of systolic or diastolic BP shifts from normal or high to low. However, because we observed substantial falls in serum cortisol levels, it seems prudent to monitor patients receiving MA for adrenal insufficiency.

Despite the serum testosterone level decrease in the men in the MA group, there were only two incidents (4%) of impotence reported. In other MA studies, impotence was also shown to have a low incidence. Further, there was no apparent decrease in muscle mass, as has been reported in hypogonadal men. Free testosterone levels were not measured. However, since sex hormone binding globulin (the major plasma binding protein of testosterone) has been reported to be reduced by MA administration, the plasma free testosterone levels may have been reduced proportionately less than total testosterone levels.

There are reports of isolated cases of hyperglycemia in patients receiving MA. Consistent with these reports, there was only one case of hyperglycemia in the MA group in our study.

There was a modest decrease in 6MWD in the final, but not the intermediate, study visits in the MA group (average decrease of 81 feet [8.2%] in the MA group compared to an increase of 18 feet [1.8%] in the placebo group). Possible mechanisms by which MA might decrease exercise tolerance in these patients include the following: (1) ventilatory stimulation might decrease breathing reserve at a given level of exercise, (2) weight gain might increase metabolic demand at a given level of exercise, and (3) decreases in testosterone level might induce muscle weakness. We attempted to determine whether any of these factors might be responsible for the decreased 6MWD at the 8-week visit. However, we found that the decrease from baseline in 6MWD was not significantly correlated with decrease in PaCO₂, weight gain, or decrease in serum testosterone level. It also should be noted that a statistically significant difference in 6MWD might not be clinically significant. Redelmeir et al suggested that for individual patients with COPD, an improvement of at least 70 m in the 6MWD after an intervention is necessary to be 95% confident that the improvement was clinically significant. Therefore, the decrease of 81 feet in the MA group and the increase of 18 feet in the placebo group (difference of 99 feet between groups, or approximately 30 m) observed at (only) the final visit, although statistically different, may not be clinically meaningful.

We conclude that MA administration safely increased appetite and body weight, stimulated ventilation, and improved body image in underweight COPD patients, but did not improve respiratory muscle function or exercise tolerance. Future studies might investigate the effects of MA in combination with an exercise program, anabolic hormone supplementation, or specific dietary modification.

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APPENDIX

The results of this study are reported on behalf of the study group of the Improving Nutrition, Hypoventilation and Living Enhancement study. The investigators participating in the study were Richard Gasaburi, PhD, MD, FCCP, Harbor-UCLA Research and Education Institute, Torrance, CA; Richard Cornwell, MD, University of Wisconsin, Madison, WI; Charles Fogarty, MD, Spartanburg Pharmaceutical Research, Spartanburg, SC; Jonathon Howite, MD, Winthrop University Hospital, Mineola, NY; John Keppel, MD, The Oregon Clinic, Portland, OR; Dana Kissner, Wayne State University School of Medicine, Detroit, MI; James Law, MD, Pulmonary Consultants of Orange County, Orange, CA; Thomas Martin, MD, Salem Veterans Affairs Medical Center, Salem, VA; Navdeep Rai, MD, Kelsey Seymour Clinic, Houston, TX; Eric Schroeder, MD, Consultants in Pulmonary Medicine, Olathe, KS; William Sexauer, MD, Medical Pulmonary Associates, Tacoma, WA; Simon Tchekmedyan, MD, Pacific Shores Medical Group, Long Beach, CA; Idelle Weisman, MD, Beaumont Army Medical Center, El Paso, TX; and Shing-Shing Yeh, PhD, MD, Northport VA Medical Center, Northport, NY.

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