

## ORIGINAL ARTICLE

# Outpatient Oral Prednisone after Emergency Treatment of Chronic Obstructive Pulmonary Disease

Shawn D. Aaron, M.D., Katherine L. Vandemheen, B.Sc.N., Paul Hebert, M.D., Robert Dales, M.D., Ian G. Stiell, M.D., Jan Ahuja, M.D., Garth Dickinson, M.D., Robert Brison, M.D., M.P.H., Brian H. Rowe, M.D., Jonathan Dreyer, M.D., Elizabeth Yetisir, M.Sc., Daniel Cass, M.D., and George Wells, Ph.D.

## ABSTRACT

**BACKGROUND**

In this randomized, double-blind, placebo-controlled trial, we studied the effectiveness of prednisone in reducing the risk of relapse after outpatient exacerbations of chronic obstructive pulmonary disease (COPD).

**METHODS**

We enrolled 147 patients who were being discharged from the emergency department after an exacerbation of COPD and randomly assigned them to 10 days of treatment with 40 mg of oral prednisone once daily or identical-appearing placebo. All patients received oral antibiotics for 10 days, plus inhaled bronchodilators. The primary end point was relapse, defined as an unscheduled visit to a physician's office or a return to the emergency department because of worsening dyspnea, within 30 days after randomization.

**RESULTS**

The overall rate of relapse at 30 days was lower in the prednisone group than in the placebo group (27 percent vs. 43 percent,  $P=0.05$ ), and the time to relapse was prolonged in those taking prednisone ( $P=0.04$ ). After 10 days of therapy, patients in the prednisone group had greater improvements in forced expiratory volume in one second than did patients in the placebo group (mean [ $\pm$ SD] increase from base line,  $34\pm 42$  percent vs.  $15\pm 31$  percent;  $P=0.007$ ). Patients in the prednisone group also had significant improvements in dyspnea, as measured by the transitional dyspnea index ( $P=0.04$ ) and by the dyspnea domain of the Chronic Respiratory Disease Index Questionnaire ( $P=0.02$ ), but not in health-related quality of life ( $P=0.14$ ).

**CONCLUSIONS**

Outpatient treatment with oral prednisone offers a small advantage over placebo in treating patients who are discharged from the emergency department with an exacerbation of COPD.

From the Departments of Medicine (S.D.A., P.H., R.D.) and Emergency Medicine (I.G.S., J.A., G.D.), and the Ottawa Health Research Institute (K.L.V., E.Y., G.W.), University of Ottawa, Ottawa, Ont.; the Department of Emergency Medicine, Queen's University, Kingston, Ont. (R.B.); the Division of Emergency Medicine, University of Alberta, Edmonton, Alta. (B.H.R.); the Department of Emergency Medicine, London Health Sciences Centre, London, Ont. (J.D.); and St. Michael's Hospital, Toronto (D.C.) — all in Canada. Address reprint requests to Dr. Aaron at the Division of Respiratory Medicine, Ottawa Hospital, General Campus, Rm. 1812F, 501 Smyth Rd., Ottawa, ON K1H 8L6, Canada, or at [saaron@ottawahospital.on.ca](mailto:saaron@ottawahospital.on.ca).

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**E**XACERBATIONS OF CHRONIC OBSTRUCTIVE pulmonary disease (COPD) are a common cause of visits to the emergency department.<sup>1,2</sup> Although many patients with COPD are ultimately admitted, a substantial percentage are discharged and treated as outpatients. However, currently, relapse after treatment of an acute exacerbation of COPD in the emergency department cannot be reliably predicted.<sup>2-4</sup>

The results of two randomized trials suggest that systemic corticosteroids prevent treatment failure and shorten the hospital stay of patients who are hospitalized for an exacerbation of COPD.<sup>5,6</sup> However, one of these inpatient studies suggested that the benefits of oral corticosteroids did not extend past hospital discharge.<sup>5</sup> Furthermore, despite evidence of efficacy in inpatients, concern remains about using systemic corticosteroids to treat all patients with COPD, especially patients treated outside the hospital who may have clinically milder exacerbations.<sup>7</sup> Outpatient treatment with systemic corticosteroids may be associated with adverse effects, including hyperglycemia, myopathy, secondary infections, mood changes, and adrenal suppression; these complications are more common in elderly patients with COPD, who have other coexisting conditions.<sup>8,9</sup>

The controlled trials that have assessed the use of oral corticosteroids for exacerbations of COPD in the outpatient setting have been small.<sup>10</sup> A recent Cochrane Review concluded that "further research is required to determine the place of systemic corticosteroid treatment in acute COPD."<sup>7</sup> We conducted a randomized, double-blind, placebo-controlled clinical trial that assessed relapse rates, lung function, the severity of dyspnea, and the health-related quality of life in patients with exacerbations of COPD treated with prednisone and patients who received placebo after being discharged from the emergency department.

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## METHODS

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### PATIENTS

We enrolled patients who presented to the emergency departments of 10 participating hospitals because of an exacerbation of COPD, defined as the presence of at least two of the following three clinical criteria: a recent increase in breathlessness, sputum volume, or sputum purulence.<sup>11</sup> All enrolled patients either had previously been given a diagnosis

of COPD by a physician or had at least a one-year history of chronic dyspnea or cough with sputum production. Additional inclusion criteria necessary for enrollment were an age greater than 35 years, a history of 15 pack-years or more of cigarette smoking, and evidence of irreversible airflow obstruction in the emergency department, defined as a ratio of forced expiratory volume in 1 second (FEV<sub>1</sub>) to forced vital capacity of 0.70 or less, an FEV<sub>1</sub> that was no more than 70 percent of the predicted value, and an improvement in the FEV<sub>1</sub> of less than 20 percent after the administration of a bronchodilator.<sup>12</sup> We excluded patients who were admitted to the hospital, had been given a diagnosis of asthma or atopy, had used oral or intravenous corticosteroids within the preceding 30 days, had received oral or intravenous corticosteroids in the emergency department, had findings on chest radiography consistent with the presence of pneumonia or congestive heart failure, had had adverse reactions to oral corticosteroids, or had severe uncontrolled diabetes mellitus or renal, hepatic or cardiac failure. The research-ethics boards of the participating hospitals approved the study, and all patients gave written informed consent.

### STUDY INTERVENTION

Before they were discharged from the emergency department, we randomly assigned patients to one of two groups. Patients in the active-treatment group received a 40-mg prednisone capsule once daily for 10 days, and patients in the placebo group received identical-appearing placebo capsules. All study medications were prepared by one central pharmacy, and the prednisone and placebo capsules were identical in taste and appearance and were packaged identically.

Randomization was through central allocation of a randomization schedule prepared through a computer-generated random listing of the two treatment assignments blocked in groups of four and stratified according to the emergency department. Randomization occurred at the time of discharge from the emergency department. Neither research staff nor patients were aware of the treatment assignment before or after randomization. Both study groups received oral broad-spectrum antibiotics for 10 days (160 mg of trimethoprim with 800 mg of sulfamethoxazole twice daily or, if they were allergic to sulfa drugs, 100 mg of doxycycline twice daily). Both groups received two puffs of inhaled albuterol

(100 µg per dose) four times daily, and three puffs of inhaled ipratropium bromide (20 µg per dose) four times daily for 30 days. Patients were provided with spacer devices and were taught correct inhalation technique before discharge. Inhaled corticosteroids and all other medications used by the patients at the time of enrollment were continued throughout the study in both groups.

#### OUTCOME MEASURES

The primary outcome was defined as an unscheduled visit to a physician's office or a return to the emergency department because of worsening dyspnea within 30 days after randomization.<sup>13</sup> We assessed patients 3, 10, and 30 days after randomization to determine whether a relapse had occurred. For every suspected relapse we contacted both the patient and the physician to ensure that the visit had been prompted by dyspnea and had been urgent and unscheduled, and we obtained a copy of the written medical record of the encounter. An adjudication committee whose members were unaware of the patients' treatment assignments confirmed that all relapses met the study definition of relapse.

Secondary outcomes included a change from day 1 to day 10 in FEV<sub>1</sub> measured after the administration of a bronchodilator, the severity of dyspnea, and disease-specific quality of life. These outcomes were assessed on the day of randomization (day 1) and on study day 10, and changes were expressed as the difference in values (day 10 values minus day 1 values) for each patient. Patients who relapsed before day 10 were assessed within 24 hours after relapse, and this observation was carried forward to day 10.

FEV<sub>1</sub> was measured after the administration of a bronchodilator, according to established criteria of the American Thoracic Society.<sup>14</sup> Dyspnea was evaluated with use of the base-line dyspnea index, and the transitional dyspnea index was used to rate changes in dyspnea from base line. Ratings from the transitional dyspnea index were added to yield a total score (range, -9 to 9, with higher positive scores indicating greater improvement in dyspnea). A change of one unit is considered clinically significant.<sup>15</sup>

Disease-specific quality of life was evaluated with use of the Chronic Respiratory Disease Index Questionnaire. Scores on the questionnaire range from 1 to 7, with higher scores indicating better self-reported, disease-specific quality of life. A change

of 0.5 or greater in the score represents the minimal clinically important difference.<sup>16</sup> Both the transitional dyspnea index and the Chronic Respiratory Disease Index Questionnaire have been validated for the assessment of dyspnea and the quality of life in patients with an exacerbation of COPD.<sup>17</sup>

We evaluated the known adverse effects of prednisone using directed questions administered on day 10, and we noted other major adverse clinical consequences, including hospitalizations, clinical complications, and deaths within the 30-day follow-up period. Patients' compliance was assessed on the basis of capsule counts.

#### STATISTICAL ANALYSIS

The final analysis was conducted on an intention-to-treat basis. The primary comparison of the 30-day relapse rates was performed with use of an unadjusted Pearson chi-square test. For the primary analysis, relapse data for seven patients (four of whom were assigned to prednisone) whose outcomes were unknown because of premature withdrawal or hospitalization for reasons other than COPD were regarded as censored observations and were excluded. The Kaplan-Meier estimates of the time to relapse included all patients who underwent randomization, and the results were tested for significance with use of the log-rank test. Values for FEV<sub>1</sub>, the transitional dyspnea index, and the Chronic Respiratory Disease Index Questionnaire were compared between groups with t-tests. The frequencies of hospitalization and relapse were compared between groups with use of the chi-square test. We report absolute P values as two-tailed, without corrections for multiple comparisons.

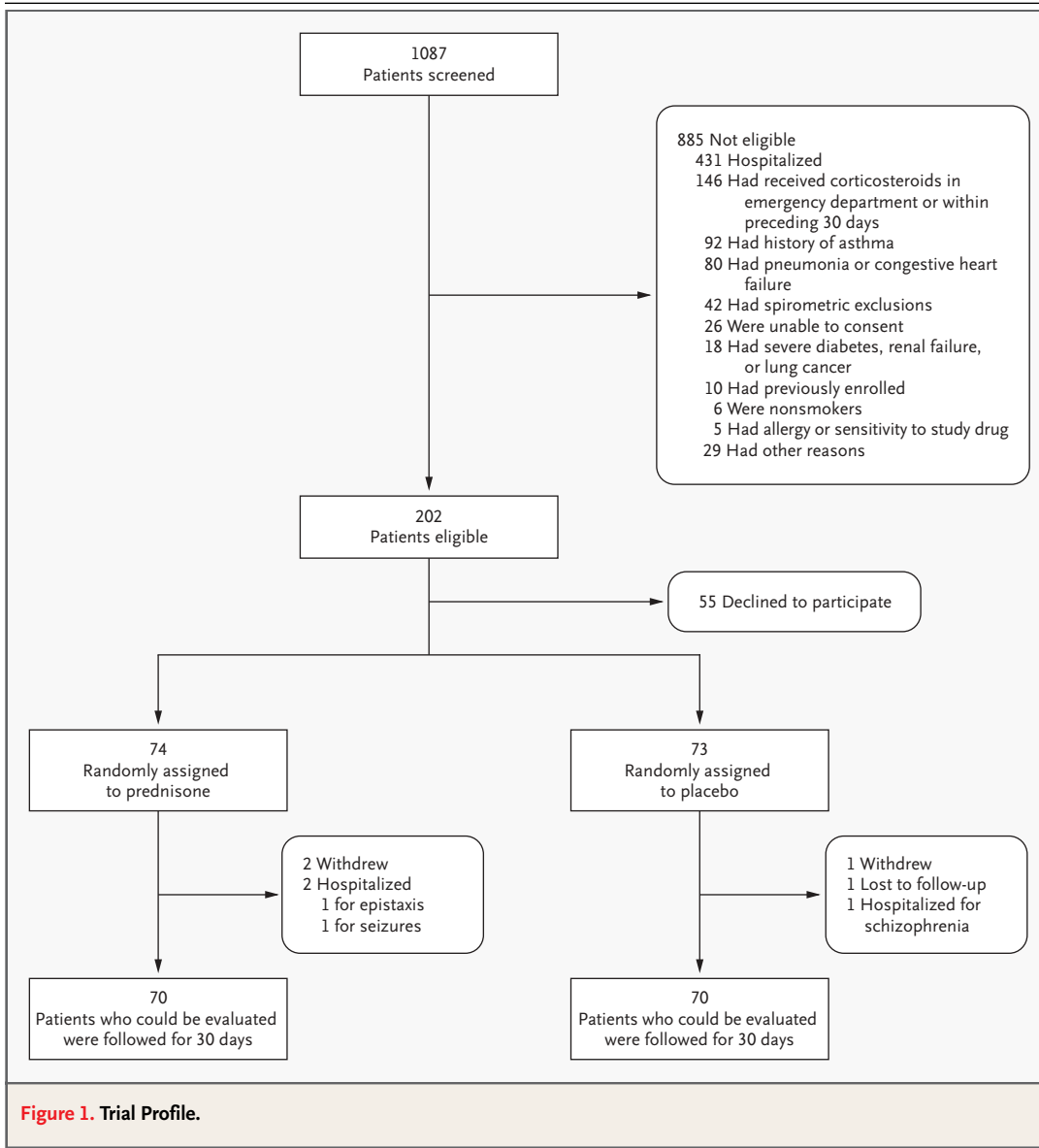
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## RESULTS

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#### STUDY POPULATION

A total of 1087 potential patients were screened for the study, of whom 202 (19 percent) were eligible (Fig. 1). Of these 202 patients, 147 (73 percent) consented to enter the study. Among the screened patients who were not eligible, 49 percent were ultimately hospitalized and 16 percent had received systemic corticosteroids in the emergency department or within the previous 30 days. A total of 74 patients were assigned to receive prednisone for 10 days, and 73 patients were assigned to receive placebo. The two groups were similar with respect to base-line characteristics (Table 1). A similar pro-



portion of patients in the prednisone and placebo groups (51 percent and 55 percent, respectively) were taking inhaled corticosteroids at the time of randomization.

Three patients withdrew from the study, two in the prednisone group and one in the placebo group. One patient in the placebo group was lost to follow-up. Three patients (two in the prednisone group and one in the placebo group) were hospitalized for medical conditions other than COPD. Because these three patients were hospitalized for an illness other than COPD, the primary outcome variable could not

be assessed in these patients. Thus, the primary outcome — relapse — could not be assessed at day 30 in 7 of the 147 randomized patients.

**PRIMARY OUTCOME**

As compared with placebo, oral prednisone significantly reduced the rate of relapse at 30 days for all randomized patients included in the primary analysis (27 percent vs. 43 percent,  $P=0.05$ ). The relative risk of 30-day relapse after oral prednisone therapy was 0.63 (95 percent confidence interval, 0.40 to 1.01). As compared with placebo, prednisone sig-

**Table 1. Base-Line Characteristics of the Patients.\***

Characteristic	Placebo Group (N=73)	Prednisone Group (N=74)
Age — yr	69.9±10.4	68.9±11.2
Male sex — no. (%)	42 (58)	42 (57)
White race — no. (%)†	70 (96)	72 (97)
Smoking status		
Current smoker — no. (%)	33 (45)	32 (43)
Pack-yr history	48.6±23.8	52.4±33.4
COPD diagnosed — no. (%)		
Before presentation	56 (77)	55 (74)
On day of presentation	8 (11)	9 (12)
Unknown	9 (12)	10 (14)
Presenting symptoms — no. (%)		
Increasing dyspnea	73 (100)	72 (97)
Increasing cough	61 (84)	58 (78)
Increasing sputum production	47 (64)	48 (65)
Change in sputum purulence	31 (42)	28 (38)
Fever	18 (25)	19 (26)
FEV <sub>1</sub>		
On day of exacerbation		
Liters	1.00±0.46	1.00±0.45
% of predicted	38.3±13.4	38.2±15.8
FEV <sub>1</sub> :FVC on day of exacerbation — %	50.5±11.9	50.1±12.3
Coexisting illnesses — no. (%)		
Coronary artery disease	27 (37)	18 (24)
Congestive heart failure	5 (7)	8 (11)
Renal dysfunction	4 (5)	0
Liver dysfunction	4 (5)	1 (1)
Diabetes	8 (11)	6 (8)
Medications for COPD — no. (%)		
Inhaled corticosteroids	40 (55)	38 (51)
Long-acting beta-agonists	7 (10)	13 (18)
Ipratropium bromide	41 (56)	48 (65)
Antibiotics	13 (18)	10 (14)
Theophylline	5 (7)	9 (12)
Any bronchodilator	53 (73)	60 (81)
Home oxygen	8 (11)	11 (15)

\* Plus-minus values are means ±SD. COPD denotes chronic obstructive pulmonary disease, FEV<sub>1</sub> forced expiratory volume in one second, and FVC forced vital capacity.

† Race was self-reported by the patients.

nificantly prolonged the time to relapse ( $P=0.04$ ) (Fig. 2). The hazard ratio was 0.56 (95 percent confidence interval, 0.32 to 0.99) (Table 2). Relapse occurred in 25 percent of the patients in the placebo group by 7 days and in 25 percent of the patients in the prednisone group by 23 days (Table 2).

#### SECONDARY OUTCOMES

Ten days of prednisone treatment significantly improved dyspnea after an exacerbation of COPD, as

compared with 10 days of placebo (Table 3). The total base-line dyspnea index score was similar in the two groups on the day of exacerbation. After 10 days of therapy, however, the mean ( $\pm$ SD) transitional dyspnea index score was significantly higher in the prednisone group than in the placebo group ( $3.95\pm4.62$  vs.  $2.07\pm5.53$ ,  $P=0.04$ ), indicating greater improvement in dyspnea in the prednisone group. Similarly, the mean improvement in the dyspnea domain of the Chronic Respiratory Disease Index Questionnaire was significantly higher in the prednisone group than in the placebo group ( $1.69\pm1.55$  vs.  $0.97\pm1.83$ ,  $P=0.02$ ) (Table 3).

The prednisone group also had greater improvements in lung function after 10 days of therapy. The FEV<sub>1</sub> of patients in the prednisone group increased by a mean of  $34\pm42$  percent from base line (absolute increase, 0.30 liter), as compared with a mean increase of  $15\pm31$  percent from base line (absolute increase, 0.16 liter) in the placebo group ( $P=0.007$ ). Despite improvements in dyspnea, the total Chronic Respiratory Disease Index Questionnaire score did not improve to a greater extent in the prednisone group than in the placebo group. The mean improvement per question was  $1.42\pm1.43$  units in the prednisone group, as compared with  $1.04\pm1.47$  in the placebo group ( $P=0.14$ ).

During the 30 days of follow-up, two patients died in the prednisone group and one in the placebo group. One death in each group was attributed to relapse of COPD, and one patient in the prednisone group was hospitalized with a seizure (not attributed to corticosteroids) and subsequently died of a myocardial infarction. There were no significant differences in hospitalization rates. Twenty-three percent of patients in the placebo group required hospitalizations for any cause within 30 days, as compared with 14 percent of patients in the prednisone group ( $P=0.18$ ). Twenty-one percent of patients in the placebo group required hospitalization within 30 days for COPD, as compared with 11 percent of patients in the prednisone group ( $P=0.11$ ).

Serious adverse events requiring hospitalization for reasons other than COPD occurred in two patients in the prednisone group and one patient in the placebo group (Fig. 1). Patients in the prednisone group were more likely than those in the placebo group to report an increase in appetite (46 percent vs. 22 percent,  $P=0.003$ ) and weight gain (13 percent vs. 1 percent,  $P=0.01$ ). Insomnia was more prevalent in the prednisone group than in the placebo group (48 percent vs. 21 percent,  $P=0.001$ ),

and there was a nonsignificant trend toward a higher incidence of depression (19 percent vs. 10 percent,  $P=0.14$ ) and anxiety (27 percent vs. 19 percent,  $P=0.28$ ) in the prednisone group. Two patients with diabetes in each group reported hyperglycemia, but serum glucose levels were not measured as part of the study protocol; therefore, the incidence of unreported hyperglycemia is not known.

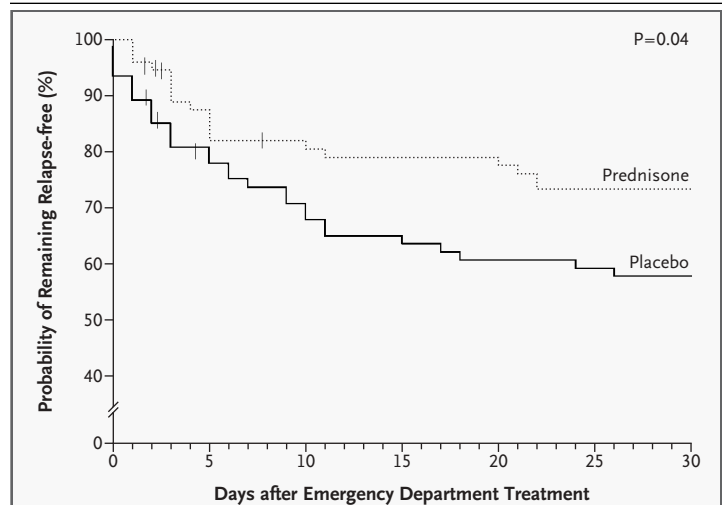
**COMPLIANCE AND SUBGROUP ANALYSIS**

As specified by the protocol, we performed subgroup analyses for the following variables: FEV<sub>1</sub>, smoking status, and use of inhaled corticosteroids. Patients who were taking inhaled corticosteroids were more likely to have a response to prednisone therapy than were those who were not receiving inhaled corticosteroids (relative risk of 30-day relapse in the subgroup taking inhaled corticosteroids, 0.44; 95 percent confidence interval, 0.22 to 0.86). The patients' smoking status and the FEV<sub>1</sub> on the day of presentation did not influence the response to prednisone.

Five patients in the placebo group and one in the prednisone group had an FEV<sub>1</sub> that was more than 80 percent of the predicted value when they returned for pulmonary-function testing 30 days after entry into the study. On the basis of counts of returned study capsules, the compliance rate was 92 percent in the placebo group and 96 percent in the prednisone group.

**DISCUSSION**

Our findings indicate that prednisone reduces the risk of relapse for at least 30 days after presentation to the emergency department for an exacerbation of COPD. The absolute reduction in the risk of relapse of 16 percent suggests that for every six outpatients treated with a 10-day course of prednisone, one relapse in 30 days is prevented. The social and economic consequences of preventing a relapse may be substantial. A recent pharmaco-economic study calculated that the average total direct cost of a COPD relapse was \$477.50.<sup>18</sup> Given that a course of prednisone costs pennies per day, one would expect not only clinical benefits but also substantial potential economic benefits if the use of prednisone was widely adopted for the treatment of exacerbations of this common disease. Nevertheless, the short-term improvements in relapse rates, dyspnea, and lung function demonstrated in this study must be balanced against the long-term cumulative risk and



**Figure 2. Kaplan-Meier Estimates of the Probability of Remaining Relapse-free at 30 Days in the Prednisone and Placebo Groups.**

Tick marks represent censored data.  $P=0.04$  by the log-rank test.

**Table 2. Rates of Relapse and Hospitalization.**

Outcome	Placebo Group (N=73)	Prednisone Group (N=74)	P Value
Relapse at 30 days — no./total no. (%)	30/70 (43)	19/70 (27)	0.05
Absolute reduction in risk (%)*	16 (0 to 32)		
Time to relapse in 25% of patients — days	7	23	
Hazard ratio in all patients*	0.56 (0.32 to 0.99)		0.04
Hospitalization for COPD — no./total no. (%)	15/71 (21)	8/72 (11)	0.11
Absolute reduction in risk (%)*	10 (–2 to 22)		

\* Values in parentheses are 95 percent confidence intervals.

costs of side effects associated with prednisone treatment.

Clinical trials summarized in a Cochrane systematic review have established that prednisone benefits patients with asthma who are discharged from the emergency department.<sup>13,19</sup> We therefore tried to exclude patients with a history of asthma in order to avoid any bias toward showing a positive effect of prednisone. Only 6 of 147 patients (4 percent) had mild or no airflow obstruction 30 days after randomization. These six patients may have had asthma, since their airflow obstruction improved dramatically after the exacerbation of COPD. This

**Table 3. Change in Forced Expiratory Volume in One Second (FEV<sub>1</sub>), Dyspnea, and Disease-Specific Quality of Life.\***

Outcome	Placebo Group (N=73)	Prednisone Group (N=74)	P Value
Change in FEV <sub>1</sub> from day 1 to day 10 (%)	15±31	34±42	0.007
Transitional dyspnea index score on day 10	2.07±5.53	3.95±4.62	0.04
Chronic Respiratory Disease Index Questionnaire			
Mean change per question in dyspnea score from day 1 to day 10	0.97±1.83	1.69±1.55	0.02
Mean change per question in total score from day 1 to day 10	1.04±1.47	1.42±1.43	0.14

\* Plus-minus values are means ±SD. Scores for the transitional dyspnea index can range from -9 to 9, with higher positive scores indicating greater improvement in dyspnea. A change of one unit is considered clinically significant. Scores for the Chronic Respiratory Disease Index Questionnaire can range from 1 to 7, with higher scores indicating better self-reported, disease-specific quality of life. A change of 0.5 or greater represents the minimal clinically important difference.

finding underscores the difficulty in distinguishing an exacerbation of asthma from an exacerbation of COPD in the acute care setting<sup>20</sup> and argues for treating exacerbations of both asthma and COPD with prednisone after a patient is discharged from the emergency department.

Previous studies have shown that short-term changes in the quality of life after an exacerbation of COPD correlate strongly with the incidence of relapse.<sup>17,21</sup> Although prednisone reduced the incidence of relapse and improved both lung function and dyspnea in this study population, its use did not result in a significant overall benefit in disease-specific quality of life. This may relate to some of the less desirable effects of the drug. More patients taking prednisone reported insomnia and weight gain, and there was a trend toward a higher incidence of anxiety and depression in the prednisone group than in the placebo group. These findings suggest that although prednisone had beneficial effects on the patient's underlying lung disease, its psychotropic effects may have partially offset any beneficial effects on the patient's overall sense of well-being.

An important consideration in the evaluation of whether to treat patients with prednisone is that patients with advanced COPD are often elderly and have other conditions as well. Typically, they have more than one exacerbation per year and they are likely to be exposed to repeated short courses of systemic corticosteroids.<sup>22</sup> Although the intermittent use of corticosteroids is not as dangerous as continuous use, even brief courses of these drugs can reduce bone mineral density in patients with COPD.<sup>23</sup>

We conclude that oral corticosteroids decrease the risk of 30-day relapse and improve lung function and dyspnea in patients who are discharged from the emergency department after an acute exacerbation of COPD. Our analysis of the time to relapse suggests that the beneficial effects of prednisone in preventing relapse become apparent after 5 days of therapy and extend throughout a 30-day follow-up period. The beneficial short-term effects of oral corticosteroids on the rate of relapse, dyspnea, and lung function should be balanced against the potential risk of short-term and long-term side effects in individual patients.

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