Interventions to Prevent Chronic Obstructive Pulmonary Disease Exacerbations

Dennis E. Niewoehner, MD

Exacerbations of chronic obstructive pulmonary disease (COPD) have a profound effect on the patient's health status and decline in lung function; they also impose a significant burden on healthcare resource utilization. Prevention and treatment of exacerbations is listed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as among the major objectives of COPD management, and it is therefore an important outcome measure when studying any new agent. This article discusses pharmacologic therapy and other measures for preventing exacerbations and hospitalizations due to exacerbations of COPD. *Am J Med.* 2004;117(12A):41S–48S. © 2004 by Elsevier Inc.

From the Pulmonary Section, Veterans Affairs Medical Center, and Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA.

Requests for reprints should be addressed to Dennis E. Niewoehner, MD, Pulmonary Section, Veterans Affairs Medical Center, One Veterans Drive, Minneapolis, Minnesota 55417.

Episodes commonly described as bronchitic exacerbations punctuate the natural history of chronic obstructive pulmonary disease (COPD). Prospective studies indicate that patients with moderate to severe COPD experience an average of 1.5 to 3 exacerbations per year.[1,2] Symptoms typically develop over a 2- to 3-day period and include some combination of fever, worsening dyspnea, cough, increasing volume or purulence of sputum, and chest congestion. Some further impairment of lung function and gas exchange generally accompanies the clinical symptoms. Very mild cases may cause only a few days of discomfort from increased cough and sputum, but a severe exacerbation may include hospitalization, life-threatening respiratory failure, and an extended recovery period. Some patients develop full-blown clinical and x-ray features of infectious pneumonia.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS: A MAJOR PUBLIC HEALTH PROBLEM

Most COPD exacerbations are probably infectious in origin, with a variety of bacterial and viral species having been implicated. Infectious agents commonly found in the sputa of patients with exacerbations include bacteria (*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Enterobacteriaceae,* and *Pseudomonas* species), viruses (rhinoviruses, influenza, parainfluenza, respiratory syncytia, and coronavirus), and atypical organisms (*Mycoplasma pneumoniae*).[3–7] It is difficult to assign a specific etiology in most cases, because many of the potentially pathogenic microorganisms found in sputa during exacerbations may also be isolated from the bronchial tree of these same patients during periods of stable respiratory symptoms.[8] Air pollution and other environmental factors also may have important causative roles.[9]

Individual susceptibility to exacerbations appears to vary widely for reasons that are not fully understood. Some patients rarely experience a COPD exacerbation, whereas others with similar levels of lung function will have many such events.[1] A number of risk factors that predispose patients with COPD to develop severe exacerbations have been identified. For example, of patients being discharged after a COPD hospitalization, nearly one third will be readmitted for COPD within the ensuing 12 months.[10] Other predictors of COPD hospitalization include advanced age, low levels of baseline lung function,

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prior systemic corticosteroid use, severely impaired gas exchange, low body mass index, the presence of comorbidities, underprescription of home oxygen, and poor overall quality of life.[11–14]

The rate of exacerbation is a major factor in the high morbidity associated with COPD. Dyspnea is the single most distressing symptom of this disease, and a severe exacerbation may cause extended periods of ventilatory and exercise impairment.[2] It is not surprising, therefore, that multiple exacerbations have a substantial adverse impact on a patient's quality of life.[15] In addition, there is now evidence that repeated exacerbations may accelerate the natural history of the disease. Smokers with recurrent exacerbations experience temporally related declines in lung function that considerably exceed those seen in smokers with infrequent exacerbations.[16,17]

Antibiotics and systemic corticosteroids are commonly used to treat COPD exacerbations, but their administration is also associated with some unwanted effects.[18,19] Many experts believe that the widespread—and perhaps indiscriminate—prescription of antibiotics for respiratory infections has contributed to the emergence of antibiotic-resistant strains among common bacterial pathogens.[20] Newer and more expensive antibiotics are commonly prescribed for exacerbations, even though they have no proven advantage over older, first-line drugs.[21] Chronic or repeated administration of systemic corticosteroids confers a substantial risk of osteoporosis, cataract development, hyperglycemia, and other serious adverse effects.[22–24]

Hospitalization and urgent care visits due to severe COPD exacerbations are hugely important in terms both of human and healthcare costs. COPD was the first-listed diagnosis for 662,000 hospital admissions and for 1,400,000 emergency room visits in the United States in 1998.[25,26] Patients hospitalized for COPD spend a disproportionately large amount of time in critical care units. Importantly, COPD was listed as a contributing cause in 2,530,000 additional hospitalizations (7.0% of total hospitalizations). Pneumonia is among the most common comorbid conditions associated with COPD, and community surveys have shown that elderly patients with COPD have up to a 7-fold greater risk of being hospitalized for pneumonia compared with age-matched controls without lung disease.[27,28]

A study of the National Medical Expenditure Survey reported that 68% of direct medical expenditures for patients with COPD were for hospitalization.[29] Prescribed drugs (7.9%) and outpatient clinic visits (9.7%) were far less important in financial terms. A second economic study came to essentially the same conclusions about the economic impact of hospitalization.[30] As stated by Strassels and colleagues,[29] "Interventions that result in persons with COPD spending less time in the hospital with COPD are likely to be cost-effective from a societal perspective."

PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS

COPD exacerbations are morbid and costly events, and treatment of an established exacerbation has only a modest effect in shortening its duration.[18,19] Hence, there is a growing appreciation that greater emphasis should be placed on prevention. Prevention of exacerbations is listed as among the major objectives of COPD management in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[31] The status of various preventive measures is summarized below.

Immunizations

Influenza immunization is arguably the single most effective intervention currently available for the prevention of severe COPD exacerbations. A cohort study of 1,898 elderly patients with chronic lung disease who were enrolled in a large health maintenance organization demonstrated that immunization largely eliminated the excess risk of hospitalization and death due to influenza.[32] Compared with unvaccinated control subjects, patients receiving influenza vaccine had fewer hospitalizations for pneumonia and exacerbations (adjusted odds ratio [OR], 0.48; 95% confidence interval [CI], 0.28–0.82) and fewer cases of mortality (adjusted OR, 0.30; 95% CI, 0.21–0.43) over a period of 3 influenza seasons. Immunized patients also had fewer outpatient visits for all respiratory conditions. Because this was an observational study, and because it included patients with various types of chronic lung disease, the impact of influenza vaccination on COPD specifically remains in some doubt.

Only 2 small randomized trials have compared influenza vaccination with no vaccination, enrolled patients with adequately characterized COPD, and had an adequate follow-up period.[33,34] Both showed that vaccination significantly reduced influenza-related respiratory illnesses. The trial conducted in the United Kingdom showed a reduction of approximately 50% in total COPD exacerbations over a winter season, a finding in accord with the observational study described above.[32,33] The other trial was performed in Thailand and reported that vaccination had no significant effect on total COPD exacerbations. In that locale, influenza appears to be less seasonal and may cause only a smaller proportion of total COPD exacerbations.

Although the evidence is not as strong as for influenza immunization, pneumococcal vaccine also may have some protective effect against serious COPD exacerbations.[35] Specific immunizations against other viral and bacterial pathogens commonly found in the respiratory tract are not currently available, but several are under development. There are intriguing reports that the immune-modulating agent

OM-85 may have a substantial protective effect against COPD exacerbations and hospitalizations, but those findings have yet to be confirmed.[36,37]

Mucolytics and Antioxidants

A group of compounds, including, among others, acetylcysteine, carbocysteine, bromhexine, and ambroxol, are prescribed in many countries with the belief that they improve symptoms of cough and sputum and reduce exacerbation frequency. These agents are commonly described as mucolytics, but many also have antioxidant properties, and it is unclear what their mode of action might be, assuming they have beneficial effects. A meta-analysis of 23 trials that met specific quality criteria indicated that active treatment reduced the mean number of exacerbations per patient by 29%, along with reductions in the average days of illness and average days on antibiotic.[38] However, the authors pointed out that the large amount of unexplained heterogeneity in the results casts doubt on the reliability of the conclusions. None of the trials reported an effect of treatment on hospitalization rates, and there are indications that most patients included in these trials probably had relatively mild airflow obstruction. The Bronchitis Randomized on NAC Cost–Utility Study (BRONCUS), a European randomized clinical trial, is testing the effect of oral acetylcysteine in 523 trial subjects with relatively mild (forced expiratory volume in 1 second [FEV_1], 40% to 70% predicted) COPD.[39] The primary study outcome is the change in the slope of the FEV_1 over a 3-year period of treatment, with exacerbation rate being a secondary outcome measure. Results from this trial should soon be available.

Inhaled Corticosteroids

The proven effectiveness of inhaled corticosteroids in treating asthma suggested a potential role in the long-term management of patients with COPD. Inflammation is thought to play a pivotal role in the pathogenesis of COPD, and a potent anti-inflammatory agent might therefore have a disease-modifying effect. Results from a number of large, multicenter, randomized controlled trials have been published in recent years.[40–44] Four of these trials assessed the long-term effect of inhaled corticosteroids on the rate of lung function loss in patients with mild-to-moderate COPD.[41–43] The primary outcome variables in these trials were uniformly negative, indicating that there was no disease-modifying effect. Most trials did show a small one-time improvement in the FEV_1 from inhaled corticosteroid therapy that persisted for the duration of treatment. One trial was specifically designed to determine whether inhaled corticosteroids would decrease the proportion of patients who experienced ≥ 1 COPD exacerbation over a 6-month period.[40] There was a trend toward fewer exacerbations in the active treatment group, but it did not reach statistical significance.

Although the primary outcomes of the trials cited above were negative, analyses of secondary outcomes indicate that inhaled corticosteroids might be effective in decreasing COPD exacerbation rates. Alsaeedi and colleagues[45] performed an interval review of published randomized controlled trials that evaluated the long-term effects ($\geq$6 months) of inhaled corticosteroids for stable COPD. The meta-analysis of data from the 6 trials that provided information about total exacerbations showed that inhaled corticosteroids reduced exacerbation rates in COPD by nearly one third relative to placebo (relative risk [RR], 0.70; 95% CI, 0.58–0.84).

These results are consistent with the recently reported Trial of Inhaled Steroids and Long-Acting Beta2 Agonists (TRISTAN trial), which compared placebo with salmeterol 50 μg b.i.d., fluticasone 500 μg b.i.d., and the combination of salmeterol and fluticasone over a 1-year period in patients with moderately severe COPD.[46] Exacerbation data were collected as a secondary outcome measure. Compared with placebo, all active treatments reduced the mean exacerbation rate by 25% to 30%. Interestingly, differences among the 3 active treatment arms were small and not statistically different. That is, fluticasone conferred little or no added benefit in reducing exacerbation risk if the patient was also taking salmeterol.[46]

Observational studies generally support trial results. Sin and Tu[10] analyzed a large provincial database in Canada and identified patients who were and were not prescribed inhaled corticosteroids at the time of hospital discharge for a COPD exacerbation. Patients who received inhaled corticosteroids experienced a 24% relative reduction in hospital readmission rate (RR, 0.76; 95% CI, 0.80–0.71) and a 29% reduction in all-cause mortality rate (RR, 0.71; 95% CI, 0.65–0.78) over the ensuing year. Soriano and co-workers[47] performed a similar analysis of the United Kingdom General Practice Research Database. They showed a 20% relative reduction in death rates over a 3-year period among patients with COPD who were treated with inhaled corticosteroids.

The relatively high doses of inhaled corticosteroids administered in most of the published COPD trials have had clear-cut systemic effects, as assessed by the presence of skin bruising and depressed serum cortisol levels.[45] Based on observational studies, long-term inhaled corticosteroid therapy may reduce bone mineral density, increase the risk of vertebral and hip fractures, and increase the risk for cataracts and glaucoma in a dose-dependent manner.[23,48–52] Consequently, there are persistent concerns about the safety of inhaled corticosteroids, particularly when they are administered in high doses to large numbers of susceptible elderly patients.

Long-Acting Inhaled Bronchodilators

The long-acting inhaled β_2-adrenergic agonists salmeterol and formoterol have been introduced recently into

clinical practice for the treatment of COPD. Clinical trials consistently show that twice-daily administration of these agents provides more extended bronchodilator effects than do short-acting anticholinergic or short-acting β_2-adrenergic agonist agents.[31,53–60]

Information concerning selected clinical outcomes, including exacerbations, has been collected as part of secondary outcomes analysis in some of these trials. Of those studies providing information, most suggest that the long-acting β_2-adrenergic agonists do reduce exacerbation rates, but the magnitude of the effect appears modest and many of the differences are not statistically significant.

The TRISTAN trial provides the most reliable information about the effects of long-acting β_2-adrenergic agonists on COPD exacerbations, because of its large size and extended 1-year follow-up.[46] As compared with placebo, salmeterol reduced the mean number of exacerbations per patient by 20% and the mean number of exacerbations requiring oral corticosteroids per patient by 29%. These differences were highly significant. However, in those patients who were receiving fluticasone, the addition of salmeterol did not significantly reduce total exacerbations or exacerbations requiring oral corticosteroids. TRISTAN reported no significant differences among any of the 4 treatment groups in terms of COPD-related hospitalizations. No numbers are provided, so it is impossible to judge whether the study was adequately powered to show such an effect.

Clinical trials indicate that the long-acting anticholinergic tiotropium 18 μg, given once daily, provides extended bronchodilation when compared with either placebo or the short-acting anticholinergic bronchodilator ipratropium.[61,62] Improved spirometric function was in turn associated with less dyspnea and better health status scores over a 1-year period. Information also was collected concerning total exacerbations and COPD-related hospitalizations. Tiotropium significantly increased the time to first exacerbation and decreased the mean number of exacerbations and mean number of exacerbation days when compared with either ipratropium (**Figure 1**) or placebo. The relative reduction in mean exacerbations was 20% in one trial and 24% in the other. Perhaps even more importantly, tiotropium also significantly increased the time to first COPD-related hospitalization when compared with ipratropium (**Figure 2**) or placebo. The mean number of COPD-related hospitalizations was decreased by 47% in one trial and 39% in the other.

Tiotropium was directly compared with salmeterol and with placebo over a 6-month period in 2 trials.[63,64] In the combined studies, tiotropium caused significantly larger improvements in spirometric function as compared with either salmeterol or placebo. In the larger of the 2 trials (approximately 400 patients per arm), tiotropium delayed the time to first exacerbation, reduced the mean number of exacerbations, and reduced the mean number of exacerbation days compared with patients who received placebo (**Figure 3**).[64] Only the differences between the tiotropium and placebo arms were statistically significant ($P < 0.05$); the differences between tiotropium and salmeterol were not significant. There also were trends or significant differences favoring tiotropium in terms of COPD-related hospitalizations, total hospitalizations, unscheduled physician visits, oral corticosteroid bursts, and days of increased disability.

Methylxanthines

Theophylline and related compounds, once favored as treatment for COPD, have now been relegated to a marginal role.[31] The reasons for the ascendancy of theophylline are as mysterious as the reasons for its decline, because neither circumstance was based on large, adequately designed trials to evaluate important clinical outcomes. Because of certain previously unappreciated anti-inflammatory properties, there is some resurgent interest in theophylline.[65] Several large trials suggest that theophylline might have some benefit in preventing or ameliorating severe COPD exacerbations, but confirmatory trials are needed.[59,66,67]

Antibiotics

The authors of a systemic review of 9 randomized placebo-controlled trials concluded that regular administration of oral antibiotics reduced bronchitic exacerbation rates by a small but statistically significant degree ($P < 0.05$).[68] The authors voiced doubts about the clinical significance of this finding because of their concerns about costs, the emergence of bacterial resistance, and other adverse effects. Moreover, all of those studies were performed before 1970, and the results may no longer be relevant because patterns of bacterial antibiotic susceptibility have changed appreciably in the interval. More recent retrospective studies have suggested that the choice of antibiotic might delay the time to the next COPD exacerbation, but these observations have not yet been subjected to appropriately designed clinical trials.[69,70]

Rehabilitation and Education

Pulmonary rehabilitation in patients with severe COPD produces some benefit in terms of symptoms, exercise capability, and quality of life, at least in the short term. However, hopes that rehabilitation programs might reduce the health resource utilization that is attributable to exacerbations have been rather disappointing for the most part.[71,72] A recently published trial demonstrated that an intense education and self-management program reduced total exacerbations by 17% and disease-related hospitalizations by 27% in patents with severe COPD.[73] It will be important to determine whether the results of this relatively small trial are reproducible and generalizable.

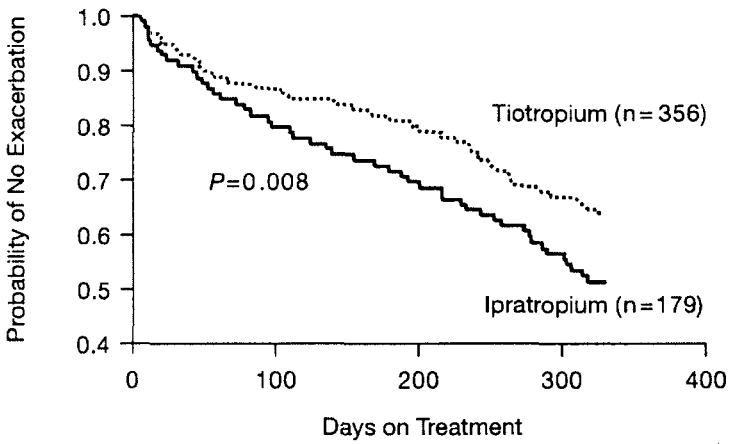

Figure 1. Kaplan-Meier estimates of the probability of no chronic obstructive pulmonary disease exacerbation for the tiotropium and ipratropium treatment groups. (Reproduced with permission from *Eur Respir J.*[62])

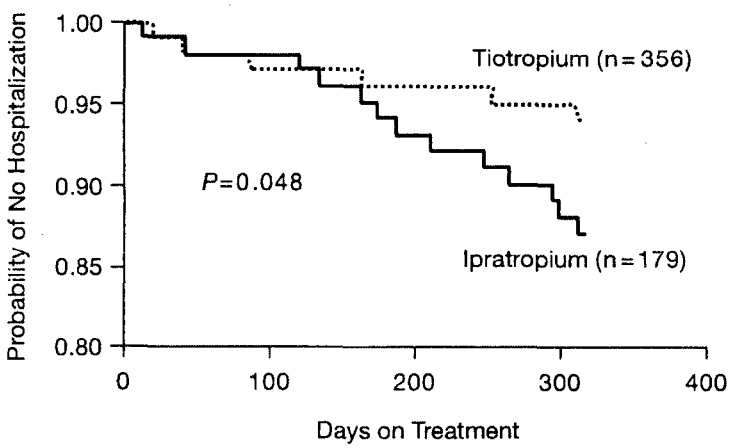

Figure 2. Kaplan-Meier estimates of the probability of no chronic obstructive pulmonary disease–related hospitalization for the tiotropium and ipratropium treatment groups. (Reproduced with permission from *Eur Respir J.*[62])

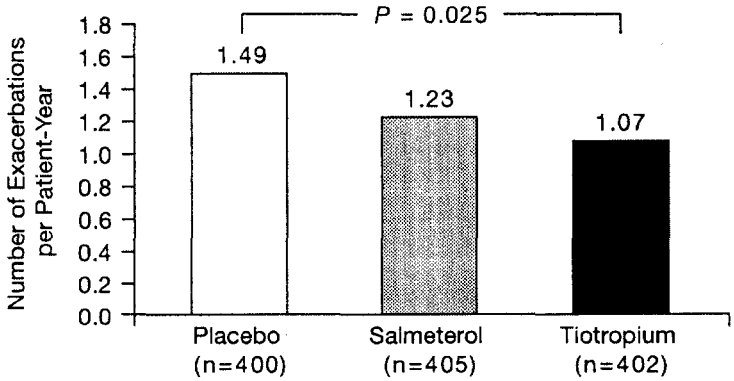

Figure 3. Mean number of chronic obstructive pulmonary disease exacerbations for the tiotropium, salmeterol, and placebo treatment groups. (Reproduced with permission from *Thorax.*[64])

FUTURE CLINICAL RESEARCH

There is growing awareness that COPD exacerbations represent a major public health problem to which too few research resources have been devoted.[74] In the short term, the prevention of severe exacerbations may offer the best hope for making substantive improvements in the overall management of COPD. Observational studies indicate a strong benefit from regular immunizations, particularly for influenza. Vaccines against other suspected viral and bacterial pathogens are in development and hold some promise for further reducing exacerbation rates. Numerous randomized controlled trials suggest that inhaled corticosteroids and long-acting bronchodilators decrease exacerbation rates. However, with a single exception, no trial has been designed expressly for the purpose of assessing differences in exacerbation rates, and that exception produced a negative result.[40] Hence, large, appropriately designed, confirmatory trials are still needed. Given the enormity of their associated human and economic impacts, it is particularly important that trials be designed to adequately assess hospitalization rates. In this regard, tiotropium is particularly interesting, because the trial results to date indicate that it might reduce hospitalization rates by $\geq$40%.

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