Contemporary Management of Chronic Obstructive Pulmonary Disease
Scientific Review

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CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) affects more than 5% of the adult population,1 and it is the only major cause of death in the United States in which morbidity and mortality are increasing.2 Although COPD is currently the 4th-leading cause of mortality and the 12th-leading cause of disability, by the year 2020 it is estimated that COPD will be the 3rd-leading cause of death and the 5th-leading cause of disability worldwide.3,4 In 1993, the total economic costs of COPD were estimated to be $24 billion in the United States alone; more than 60% of these costs were direct expenditures related to hospital-based care.3 While these figures are alarming, they most certainly underestimate the true health burdens of COPD because airflow obstruction is an important contributor to other common causes of morbidity and mortality, including ischemic heart disease, stroke, pneumonia, and lung cancer.3,4

Chronic obstructive pulmonary disease is characterized by irreversible airflow obstruction, secondary to airway inflammation and emphysema.

Context The care of patients with chronic obstructive pulmonary disease (COPD) has changed radically over the past 2 decades, and novel therapies can not only improve the health status of patients with COPD but also modify its natural course.

Objective To systematically review the impact of long-acting bronchodilators, inhaled corticosteroids, nocturnal noninvasive mechanical ventilation, pulmonary rehabilitation, domiciliary oxygen therapy, and disease management programs on clinical outcomes in patients with COPD.

Data Sources MEDLINE and Cochrane databases were searched to identify all randomized controlled trials and systematic reviews from 1980 to May 2002 evaluating interventions in patients with COPD. We also hand searched bibliographies of relevant articles and contacted experts in the field.

Study Selection and Data Extraction We included randomized controlled trials that had follow-up of at least 3 months and contained data on at least 1 of these clinical outcomes: health-related quality of life, exacerbations associated with COPD, or death. For pulmonary rehabilitation, we included studies that had a follow-up of at least 6 weeks. Using standard meta-analytic techniques, the effects of interventions were compared with placebo or with usual care. In secondary analyses, the effects of interventions were compared against each other, where possible.

Data Synthesis Long-acting β2-agonists and anticholinergics (tiotropium) reduced exacerbation rates by approximately 20% to 25% (relative risk [RR] for long-acting β2-agonists, 0.79; 95% CI, 0.69-0.90; RR for tiotropium, 0.74; 95% CI, 0.62-0.89) in patients with moderate to severe COPD. Inhaled corticosteroids also reduced exacerbation rates by a similar amount (RR, 0.76; 95% CI, 0.72-0.80). The beneficial effects were most pronounced in trials enrolling patients with FEV1 between 1 L and 2 L. Combining a long-acting β2-agonist with an inhaled corticosteroid resulted in an approximate 30% (RR, 0.70; 95% CI, 0.62-0.78) reduction in exacerbations. Pulmonary rehabilitation improved the health status of patients with moderate to severe disease, but no material effect was observed on long-term survival or hospitalization rates. Domiciliary oxygen therapy improved survival by approximately 40% in patients with PaO2 lower than 60 mm Hg, but not in those without hypoxia at rest. The data on disease management programs were heterogeneous, but overall no effect was observed on survival or risk of hospitalization. Noninvasive mechanical ventilation was not associated with improved outcomes.

Conclusions A significant body of evidence supports the use of long-acting bronchodilators and inhaled corticosteroids in reducing exacerbations in patients with moderate to severe COPD. Domiciliary oxygen therapy is the only intervention that has been demonstrated to prolong survival, but only in patients with resting hypoxia.
tous changes in the lung parenchyma. Airway hyperresponsiveness also is a common feature of COPD, affecting 60% to 80% of patients with COPD. In more than 80% of cases, cigarette smoking is causally linked to the development of COPD. Other risk factors include exposure to noxious gases, ambient pollution, and chronic respiratory infections. A diagnosis of COPD should, therefore, be considered in current or former smokers (or in never smokers with other risk factors) who present with cough, sputum production, or dyspnea, with spirometric evidence of irreversible airflow obstruction. The latter sign is defined as a postbronchodilator forced expiratory volume in 1 second (FEV$_1$) value of less than 80% of predicted, in association with an FEV$_1$/forced vital capacity ratio (FEV$_1$/FVC) of less than 70%. Smoking cessation is the single most important therapy for improving health outcomes in patients with COPD. Unfortunately, even in the best programs, less than one third of smokers become “sustained” quitters. Furthermore, once individuals develop demonstrable airflow obstruction, their symptoms (cough and/or dyspnea) may persist even after smoking cessation.

Over the past 20 years, several novel therapies, such as inhaled corticosteroids, long-acting $\beta_2$-agonists, and anticholinergics, have been introduced for patients with COPD, with the aim of favorably altering lung function and improving patient symptoms. However, most of the studies that have evaluated these therapies have been short and powered to evaluate the impact on physiological end points, such as FEV$_1$ values. Relatively few studies have evaluated the long-term effects of these interventions on clinical end points, such as health-related quality of life, COPD exacerbations, hospitalizations, or mortality. Because the rate of descent in FEV$_1$ is an imperfect surrogate for these clinical end points, we conducted a systematic review of the literature to evaluate the effects of commonly used anti-COPD therapies on patient-centered outcomes, such as health-related quality of life, exacerbations associated with COPD, hospitalizations, and/or mortality.

**METHODS**

We decided a priori to examine the published evidence for the following anti-COPD therapies: long-acting $\beta_2$-agonists, long-acting inhaled anticholinergics (tiotropium), combination therapy with short-acting $\beta_2$-agonists and short-acting anticholinergics, inhaled corticosteroids, combination therapy with inhaled corticosteroids and long-acting $\beta_2$-agonists, pulmonary rehabilitation, long-term administration of nocturnal noninvasive mechanical ventilation (NIMV), domiciliary oxygen therapy, and disease management programs (which include any combination of patient education, enhanced follow-up, and/or self-management sessions).

For each of these therapies, we conducted a literature search using MEDLINE. We limited our search to English-language articles published from January 1, 1980, to May 1, 2002, reporting studies of adults (>19 years of age) in randomized clinical trials. To identify only studies in COPD, we used the following terms: obstructive or chronic obstructive or bronchitis or pulmonary emphysema or airway obstruction or emphysema or mediastinal emphysema or subcutaneous emphysema or COPD or lung diseases, obstructive or pulmonary diseases, obstructive. Detailed search terms for each of the therapies and search results are available on the author’s Web site (Table 1e at http://www.mrl.ubc.ca/sin). To supplement this search, we examined the Cochrane Database of Systematic Reviews of Effectiveness as well as bibliographies of published articles and contacted experts in the field. Although we wanted to include only those studies with follow-up times of at least 6 months, we found insufficient numbers of such studies for most of the interventions, so a follow-up time of 3 months was used as the threshold for inclusion (with the exception of pulmonary rehabilitation programs, for which 6 weeks was used as the threshold). Given the controversy over the value of scoring systems for the quality of randomized controlled trials, we did not use a scoring system to adjudicate the quality of the trials included in this review, but we did restrict our analysis to trials that were randomized, placebo-controlled, had blinded ascertainment of end points, had complete or near complete follow-up data, and had baseline characteristics that were well balanced between treatment and control groups. We discarded studies reporting only physiological variables, such as changes in FEV$_1$, because the correlation between spirometric changes and long-term clinical outcomes in COPD has been shown to be weak. Crossover trials were included in this review. We restricted analysis of health-related quality of life to 2 well-standardized and validated instruments in COPD: St George’s Respiratory Questionnaire (SGRQ) and Chronic Respiratory Questionnaire (CRQ). These instruments quantify the extent of physical and psychological impairments related to COPD and allow investigators to determine the (beneficial) effects of specific interventions on the functional status of patients with COPD.

Where possible, for each end point we combined the results from individual studies to produce summary effect estimates (risk ratios). Heterogeneity of results across individual studies was checked using the Cochran $Q$ test. If significant heterogeneity was observed ($P<.05$), we used the Dersimonian and Laird random-effects model to combine the results; otherwise, a fixed-effects model was used. As part of a sensitivity analysis for the latter situation, we used a random-effects model to determine the robustness of the data. In all cases, the results obtained from the random-effects model and fixed-effects model were similar. Continuous variables were merged using weighted mean difference technique. The use of the standardized
mean difference technique produced similar results. All analyses were conducted using Review Manager version 4.1 (Revman; The Cochrane Collaboration, Oxford, England). For completeness, we also present a general overview of other anti-COPD therapies, such as smoking cessation, oral theophyllines, surgical procedures, and vaccine therapies.

RESULTS

Smoking Cessation and Pneumococcal Vaccination

Smoking cessation is the only therapy proven to slow the accelerated decline in lung function related to COPD. While the rate of FEV1 decline is approximately 60 mL per year in smokers, it is only approximately 30 mL per year among ex-smokers. Moreover, smoking cessation reduces all-cause mortality rates by approximately 27% (95% confidence interval [CI], 1%-47%), driven largely by very significant reductions in cardiovascular mortality (relative risk [RR] compared with continued smokers, 0.54; 95% CI, 0.32-0.92). However, smoking cessation is difficult to achieve and even more difficult to sustain over the long term. A single physician recommendation for smoking abstinence is associated with an approximate 5% long-term abstinence rate. If abstinence is followed by cessation counseling, education, and nicotine replacement therapy (or treatment with antidepressants such as bupropion and nortriptyline), the long-term abstinence rates can be as high as 25% in patients with early COPD. Thus, physicians should make every attempt to convince their patients to stop smoking. A detailed evaluation of various smoking cessation methods and programs is beyond the scope of this article, but they are available elsewhere. Although smoking cessation improves the natural history of COPD, once COPD becomes clinically apparent many sustained quitters remain symptomatic and their airways are persistently inflamed. Thus, in symptomatic patients with COPD, additional therapies are indicated.

Although little evidence is available for the usefulness of influenza and pneumococcal vaccinations for patients with COPD per se, they have been demonstrated in the general elderly population to reduce all-cause, pneumonia, and cardiac hospitalizations and deaths by 30% to 40% with only minor excess risks to recipients. Since most patients with COPD are elderly and also are at increased risk of hospitalizations and mortality from various cardiovascular conditions and pneumonia, influenza and pneumococcal vaccination also should be instituted for most patients with COPD.

Pharmacological Therapies

Bronchodilators. Airflow obstruction is present in all patients with COPD. Accordingly, bronchodilators are used almost universally to provide symptomatic relief for patients with COPD. Traditionally, inhaled short-acting β2-agonists and short-acting anticholinergics most commonly were used either on an as-needed basis for rescue care or on a regular basis to prevent or to reduce symptoms. Although these medications produce only a modest improvement in lung function in patients with COPD, studies have demonstrated that they reduce symptoms and improve exercise tolerance. However, no evidence shows that these medications have any effect on the rate of decline in lung function or survival.

Because β2-agonists and anticholinergics produce bronchodilation through different pathways, combination products were introduced in the hopes of achieving greater bronchodilation (and, in turn, better symptom control) than with monotherapy. In 3 trials (1399 patients with advanced COPD, mean FEV1 approximately 1 L in all 3 studies) with follow-up of 3 months or longer, combination therapy with a short-acting β2-agonist and an anticholinergic resulted in 32% (95% CI, 9%-49%) fewer COPD exacerbations compared with monotherapy with a short-acting β2-agonist. However, combination therapy was not superior to monotherapy with ipratropium (Table 1). Mortality rates over the 3-month follow-up were low and similar among patients treated with combination therapy, short-acting β2-agonist, or ipratropium monotherapy. We did not identify any published studies wherein combination therapy was compared directly with a placebo.

Long-acting β2-agonists were introduced several years ago to achieve longer and more predictable improve-

Table 1. Summary of Clinical Trials for Combination of Ipratropium and Short-Acting β2-Agonists for COPD

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients at Risk</th>
<th>Intervention</th>
<th>Duration (wk)</th>
<th>Age, Mean (SD), y</th>
<th>FEV1, Mean (SD), L</th>
<th>vs β2-Agonists vs Ipratropium</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMBivent Inhalation Aerosol Group, 1994</td>
<td>534</td>
<td>Ipratropium + albuterol</td>
<td>12</td>
<td>63 (NR)</td>
<td>1.0 (NR)</td>
<td>0.37 (0.16-0.86)</td>
</tr>
<tr>
<td>COMBivent Inhalation Study Group, 1997</td>
<td>652</td>
<td>Ipratropium + albuterol</td>
<td>12</td>
<td>65 (NR)</td>
<td>0.9 (NR)</td>
<td>0.68 (0.42-1.09)</td>
</tr>
<tr>
<td>Tashkin et al, 1986</td>
<td>213</td>
<td>Ipratropium + metaproterenol</td>
<td>12</td>
<td>61 (8)</td>
<td>1.1 (0.4)</td>
<td>0.86 (0.57-1.29)</td>
</tr>
<tr>
<td>Pooled summary</td>
<td>1399</td>
<td></td>
<td></td>
<td></td>
<td>0.68 (0.51-0.91)</td>
<td>1.18 (0.34-4.08)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; NR, not reported/could not be ascertained; RR, relative risk.

*Exacerbation was defined as a clinical episode requiring administration of oral corticosteroids.

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ments in lung function than what was possible with short-acting β₂-agonists.42 Nine placebo-controlled clinical trials (4198 patients with moderate to severe COPD and followed up for ≥3 months) demonstrated a 21% reduction (95% CI, 10%-31%) in COPD exacerbation rates (Figure 1).43-51 They also improved health-related quality of life of patients with COPD (SGRQ, 2.8-unit improvement; 95% CI, 1.6-4.1 vs placebo; CRQ, 4.3-unit improvement; 95% CI, 1.6-7.0). The RR for all-cause mortality compared with placebo was 0.76 (95% CI, 0.39-1.48). The effect on FEV₁ was variable. In the 2 trials that evaluated FEV₁ changes over at least 1 year, long-acting β₂-agonists nonsignificantly increased trough FEV₁, on average, by 82 mL (95% CI, –26 to 190 mL per year) compared with placebo.52,53

Five clinical trials of tiotropium (3574 patients with moderate to severe COPD) uniformly have demonstrated a beneficial effect in reducing exacerbation rates compared with either placebo (RR, 0.74; 95% CI, 0.62-0.89) or with ipratropium bromide (RR, 0.78; 95% CI, 0.63-0.95) (Figure 2).55-59 Tio-

### Table 1: Meta-analysis of Clinical Trial Data Evaluating the Effects of Long-Acting β₂-Agonists on Chronic Obstructive Pulmonary Disease Exacerbations

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Drug</th>
<th>Study Duration, wk</th>
<th>Age, Mean (SD), y</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;, Mean (SD), L</th>
<th>Mean Units of Change for SGRQ (95% CI)</th>
<th>Relative Risk of Exacerbation (95% CI)</th>
<th>Favors Long-Acting β₂-Agonist</th>
<th>Favors Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wadbo et al,42 2002</td>
<td>183</td>
<td>Formoterol</td>
<td>12</td>
<td>64 (NR)</td>
<td>&lt;1.0 (NR)</td>
<td>–1.5 (–4.6 to 1.6)</td>
<td>NR</td>
<td>0.49 (0.13 to 1.88)</td>
<td></td>
</tr>
<tr>
<td>Van Noord et al,44 2000</td>
<td>144</td>
<td>Salmeterol</td>
<td>12</td>
<td>64 (7)</td>
<td>1.2 (0.4)</td>
<td>NR</td>
<td>0.65 (0.34 to 1.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapman et al,45 2002</td>
<td>408</td>
<td>Salmeterol</td>
<td>12</td>
<td>63 (8)</td>
<td>1.3 (0.5)</td>
<td>–5.4 (–9.0 to 1.8)*</td>
<td>NR</td>
<td>0.79 (0.58 to 1.07)</td>
<td></td>
</tr>
<tr>
<td>Jones and Bosh,46 1997</td>
<td>326</td>
<td>Salmeterol</td>
<td>24</td>
<td>NR</td>
<td>1.2 (NR)</td>
<td>–1.5 (–4.3 to 1.3)</td>
<td>NR</td>
<td>0.79 (0.58 to 1.07)</td>
<td></td>
</tr>
<tr>
<td>Rossi et al,47 2002</td>
<td>854</td>
<td>Formoterol</td>
<td>52</td>
<td>63 (NR)</td>
<td>1.4 (NR)</td>
<td>–3.0 (–5.3 to –0.8)†</td>
<td>NR</td>
<td>0.81 (0.64 to 1.03)</td>
<td></td>
</tr>
<tr>
<td>Dahl et al,48 2002</td>
<td>790</td>
<td>Formoterol</td>
<td>52</td>
<td>64 (8.6)</td>
<td>1.3 (0.4)</td>
<td>–3.3 (–5.8 to –0.8)†</td>
<td>NR</td>
<td>0.87 (0.60 to 1.26)</td>
<td></td>
</tr>
<tr>
<td>Aalbers et al,49 2002</td>
<td>687</td>
<td>Formoterol</td>
<td>52</td>
<td>63 (NR)</td>
<td>1.5 (NR)</td>
<td>NR</td>
<td>0.78 (0.44 to 1.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rennard et al,50 2001</td>
<td>405</td>
<td>Salmeterol</td>
<td>52</td>
<td>64 (8.1)</td>
<td>1.5 (0.6)</td>
<td>3.5 (–0.4 to 7.4)</td>
<td>NR</td>
<td>0.95 (0.65 to 1.37)</td>
<td></td>
</tr>
<tr>
<td>Mahler et al,51 1999</td>
<td>411</td>
<td>Salmeterol</td>
<td>52</td>
<td>63 (8.6)</td>
<td>1.5 (NR)</td>
<td>NR</td>
<td>5.0 (1.3 to 8.7)</td>
<td>NR</td>
<td>0.63 (0.42 to 0.95)</td>
</tr>
<tr>
<td>Pooled Summary</td>
<td>4198</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.79 (0.69 to 0.90)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SGRQ indicates St George’s Respiratory Questionnaire; CRQ, Chronic Respiratory Questionnaire; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; and NR, not reported. A positive score on the CRQ and a negative score on the SGRQ denote improvement in health status with β₂-agonists compared with placebo.

### Table 2: Meta-analysis of Clinical Trial Data Evaluating the Effects of Tiotropium on Chronic Obstructive Pulmonary Disease Exacerbations

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Study Duration, wk</th>
<th>Age, Mean (SD), y</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;, Mean (SD), L</th>
<th>Mean Units of Change for SGRQ (95% CI)</th>
<th>Relative Risk of Exacerbation (95% CI)</th>
<th>Favors Tiotropium</th>
<th>Favors Placebo or Ipratropium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casaburi et al,52 2002</td>
<td>921</td>
<td>52</td>
<td>65 (9)</td>
<td>1.0 (0.4)</td>
<td>–3.7 (–7.2 to –0.2)</td>
<td>NR</td>
<td>NR</td>
<td>0.78 (0.59 to 1.02)</td>
</tr>
<tr>
<td>Donohue et al,53 2002</td>
<td>623</td>
<td>24</td>
<td>65 (9)</td>
<td>1.1 (0.4)</td>
<td>–2.7 (–5.3 to –0.1)</td>
<td>NR</td>
<td>0.96 (0.75 to 1.22)</td>
<td>0.69 (0.47 to 1.03)</td>
</tr>
<tr>
<td>Brunasco et al,54 2003</td>
<td>1207</td>
<td>24</td>
<td>64 (8)</td>
<td>1.1 (0.4)</td>
<td>–2.7 (–4.6 to –0.8)</td>
<td>–1.4 (–3.3 to 0.5)</td>
<td>0.92 (0.75 to 1.11)</td>
<td>NR</td>
</tr>
<tr>
<td>Van Noord et al,55 2000</td>
<td>288</td>
<td>13</td>
<td>64 (8)</td>
<td>1.2 (0.4)</td>
<td>–2.9 (–4.3 to –1.5)</td>
<td>NR</td>
<td>(0.80 to 1.08)</td>
<td>0.78 (0.63 to 0.95)</td>
</tr>
<tr>
<td>Vincen et al,56 2002</td>
<td>535</td>
<td>52</td>
<td>64 (8)</td>
<td>0.3 (0.4)</td>
<td>NR</td>
<td>3.3 (6.5 to –0.2)</td>
<td>NR</td>
<td>0.76 (0.61 to 0.94)</td>
</tr>
<tr>
<td>Pooled Summary</td>
<td>3574</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.79 (0.69 to 0.90)</td>
<td></td>
</tr>
</tbody>
</table>

FEV₁ indicates forced expiratory volume in 1 second; SGRQ, St George’s Respiratory Questionnaire; CI, confidence interval; and NR, not reported. A negative score on the SGRQ denotes improvement in health status vs placebo.
tropium also improved health-related quality of life relative to placebo (SGRQ, 2.9 unit improvement; 95% CI, 1.5-4.3). However, no convincing data to date have shown that they are superior (or inferior) to long-acting $\beta_2$-agonists in reducing exacerbation rates or improving health status in patients with moderate to severe COPD (RR for exacerbations vs long-acting $\beta_2$-agonists, 0.93; 95% CI, 0.80-1.08). Moreover, the current trials are too short and underpowered to evaluate the effects of these drugs on all-cause mortality.

Long-acting anticholinergics have a powerful effect on FEV$_1$. In the 2 trials that had 1-year follow-up, the trough FEV$_1$ increased by 121 mL (95% CI, 102-141 mL per year) compared with placebo or ipratropium monotherapy. In the 2 trials that compared long-acting anticholinergics with long-acting $\beta_2$-agonists over 6 months, long-acting anticholinergics had a more favorable effect on trough FEV$_1$ (37 mL; 95% CI, 12-61 mL). In 6 placebo-controlled trials (1741 patients) with at least a 6-month follow-up period, inhaled corticosteroids led to a 24% reduction in COPD exacerbations (95% CI, 20%-28%) (Table 2). Importantly, this beneficial effect was modified by disease severity, as measured by FEV$_1$/FVC. Whereas the study that had the highest mean FEV$_1$ value failed to demonstrate a beneficial effect of inhaled corticosteroids, trials that had a mean FEV$_1$ of less than 2.0 L (or <70% of predicted) almost uniformly demonstrated a positive effect of inhaled corticosteroids on exacerbations, regardless of the duration of the study or the specific formulation used. The pooled RR for COPD exacerbation among trials enrolling patients with a mean FEV$_1$ of 2.0 L or less was 0.75 (95% CI, 0.71-0.80) compared with an RR of 0.96 (95% CI, 0.77-1.20) in a trial with an FEV$_1$ greater than 2.0 L. The

### Table 2. Summary of Clinical Trials for Inhaled Corticosteroids for COPD*

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients at Risk</th>
<th>Drug</th>
<th>Duration</th>
<th>Age, Mean (SD), y</th>
<th>FEV$_1$, Mean (SD), L</th>
<th>RR (95% CI)</th>
<th>Mean Difference of SGRQ Scores (95% CI)§</th>
<th>Mortality</th>
<th>Fracture</th>
<th>Femoral Neck BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourbeau et al, 1998</td>
<td>79</td>
<td>Budesonide</td>
<td>6 mo</td>
<td>66 (7)</td>
<td>0.93 (0.53)</td>
<td>0.97 (0.54 to 1.11)</td>
<td>0.53 (0.24 to 1.17)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Weir et al, 1999</td>
<td>98</td>
<td>Beclomethasone</td>
<td>2 y</td>
<td>66 (7)</td>
<td>1.23 (0.49)</td>
<td>0.62 (0.41 to 0.95)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Borge et al, 2000</td>
<td>751</td>
<td>Fluticasone</td>
<td>3 y</td>
<td>64 (7)</td>
<td>1.42 (0.47)</td>
<td>0.75 (0.71 to 0.80)</td>
<td>0.77 (0.54 to 1.11)</td>
<td>0.53 (0.24 to 1.17)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Paggiaro et al, 1998</td>
<td>279</td>
<td>Fluticasone</td>
<td>6 mo</td>
<td>63 (9)</td>
<td>1.56 (0.60)</td>
<td>0.67 (0.49 to 0.90)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Van der Valk, et al, 2002</td>
<td>244</td>
<td>Fluticasone</td>
<td>6 mo</td>
<td>64 (7)</td>
<td>1.75 (0.53)</td>
<td>0.83 (0.59 to 1.15)</td>
<td>0.98 (0.06 to 15.55)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>LHS-2, 2000</td>
<td>1116</td>
<td>Triamcinolone</td>
<td>4.5 y</td>
<td>56 (7)</td>
<td>2.22 (0.65)</td>
<td>NR</td>
<td>0.79 (0.40 to 1.53)</td>
<td>-1.78 (−2.72 to −0.84)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Vestbo et al, 1999</td>
<td>290</td>
<td>Budesonide</td>
<td>3 y</td>
<td>59 (9)</td>
<td>2.33 (0.82)</td>
<td>0.96 (0.77 to 1.20)</td>
<td>0.80 (0.22 to 2.92)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pauwels et al, 1999</td>
<td>1277</td>
<td>Budesonide</td>
<td>3 y</td>
<td>52 (8)</td>
<td>2.54 (0.64)</td>
<td>NR</td>
<td>0.81 (0.22 to 2.04)</td>
<td>1.71 (0.41 to 7.11)</td>
<td>−0.87 (−2.59 to 0.85)</td>
<td>NR</td>
</tr>
<tr>
<td>Pooled summary</td>
<td>4134</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.76 (0.72 to 0.80)</td>
<td>−1.4 (−2.1 to −0.6)</td>
<td>0.78 (0.58 to 1.05)</td>
<td>0.70 (0.26 to 1.38)</td>
<td>−1.57 (−2.40 to −0.74)</td>
</tr>
</tbody>
</table>

* Included trials that had a follow-up of 6 months or longer and contained only 2 groups in the experimental design.

** Heterogeneity, $P = .23$ for exacerbation.

§ Mean difference in scores between inhaled steroid and placebo arms.

Table taken from the ISOLDE trial.

### Figure 3. Relationship Between FEV$_1$ Values and Effect on Inhaled Corticosteroids for Chronic Obstructive Pulmonary Disease Exacerbations

The relative risks have been log transformed. The inverse weighted regression line is the solid line and the dashed lines represent 95% confidence intervals. The diameter of the circle of each trial is proportional to its weight ($R^2=78%$; $P=.02$).

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effect of inhaled corticosteroids on mortality is uncertain. However, a trend was observed toward reduced mortality in patients randomized to inhaled corticosteroid therapy (Table 2). In a sensitivity analysis, we added the inhaled corticosteroid and placebo data from 2 trials that contained 3 treatment groups (inhaled corticosteroids, inhaled corticosteroids/long-acting $\beta_2$-agonists, and long-acting $\beta_2$-agonists) to the original steroid analysis.52,54 The results were materially unchanged (RR for exacerbation, 0.76; 95% CI, 0.73-0.80; RR for mortality, 0.75; 95% CI, 0.57-1.00). Inhaled corticosteroids also accelerated the rate of decline in health status (SGRQ, 1.4-unit improvement relative to placebo; 95% CI, 0.6-2.1; Table 2).

The reporting of adverse effects related to corticosteroid use varied across the studies. Six studies reported the incidence of oral thrush, and its risk was increased among users of inhaled corticosteroids (RR, 2.98; 95% CI, 2.09-4.26)53,54,64,65,69; 3 studies reported incidence of dysphonia (RR, 2.02; 95% CI, 1.43-2.83)53,64,65,67,69; 4 studies reported incidence of bruising (RR, 1.62; 95% CI, 1.18-2.22)53,54,65,67, and 2 studies reported the risk of cataract (RR, 1.05; 95% CI, 0.84-1.31).64,67 Bone mineral density data from the femoral neck and lumbar spine were reported by the Lung Health Study and EUROSCOP.67,70

Inhaled corticosteroids have a modest effect on FEV$_1$. In the first 6 months of therapy, they increased baseline trough FEV$_1$, on average, by 45 mL (95% CI, 22-69 mL) in the 6 largest trials.64-69 However, after the initial 6 months, the rate of FEV$_1$ decline was unaffected by inhaled corticosteroid therapy (5 mL/y; 95% CI, −1 to 11 mL/y relative to placebo) in the 4 trials reporting this outcome over that time frame.64,67-69

Three clinical trials (2951 patients) demonstrated that combination therapy with inhaled corticosteroids plus long-acting $\beta_2$-agonists is associated with lower exacerbation rates compared with monotherapy with long-acting $\beta_2$-agonists (RR, 0.80; 95% CI, 0.71-0.90) or with placebo (RR, 0.70; 95% CI, 0.62-0.78).52,54 A trend was observed toward decreased COPD exacerbations compared with inhaled corticosteroid monotherapy, but it did not achieve statistical significance (Table 3).52-54 The beneficial effects of inhaled corticosteroids and long-acting $\beta_2$-agonists appeared, therefore, to be additive, not synergistic. The effect of this combination on mortality is uncertain (RR vs placebo, 0.52; 95% CI, 0.20-1.34). Combination therapy, however, was effective in improving trough FEV$_1$ compared with placebo (101 mL/y; 95% CI, 76-126 mL/y), long-acting $\beta_2$-agonists (34 mL/y; 95% CI, 11-57 mL/y), and inhaled corticosteroids (50 mL/y; 95% CI, 26-74 mL/y).

### Nonpharmacological Therapies

Respiratory muscle fatigue and dynamic hyperinflation commonly are observed in patients with severe COPD.71,73 Even at rest patients with COPD work harder than patients without COPD because they have to overcome dynamic lung hyperinflation and airflow obstruction, which limit their tidal volume.71,73 Long-term NIMV therapy potentially should unload the inspiratory muscles of respiration and help restore depleted energy stores and partially reverse respiratory muscle fatigue.73 Moreover, nocturnal NIMV may improve central ventilatory drive and responsiveness to chemical and mechanical stimulation by lowering nocturnal PaCO$_2$ levels and improving daytime sleepiness, which help the body

### Table 3. Summary of Clinical Trials for Long-Acting $\beta_2$-Agonists and Inhaled Corticosteroids in COPD*

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Drugs</th>
<th>Duration, mo</th>
<th>Age, Mean (SD), y</th>
<th>FEV$_1$, Mean (SD), L</th>
<th>RR (95% CI) of Exacerbation†</th>
<th>RR (95% CI) of Mortality</th>
<th>Mean Difference in SGRQ Scores (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szefinski et al, 52 2003</td>
<td>812</td>
<td>Budesonide + formoterol</td>
<td>12</td>
<td>64 (NR)</td>
<td>0.99 (NR)</td>
<td>0.77 (0.66 to 0.87)</td>
<td>0.77 (0.67 to 0.89)</td>
<td>0.89 (0.77 to 1.03)</td>
</tr>
<tr>
<td>Calverley et al, 53 2003</td>
<td>1465</td>
<td>Fluticasone + salmeterol</td>
<td>12</td>
<td>63 (8.6)</td>
<td>1.42 (0.53)</td>
<td>0.61 (0.50 to 0.73)</td>
<td>0.85 (0.70 to 1.04)</td>
<td>0.92 (0.75 to 1.13)</td>
</tr>
<tr>
<td>Mahler et al, 54 2002</td>
<td>674</td>
<td>Fluticasone + salmeterol</td>
<td>6</td>
<td>63 (NR)</td>
<td>1.27 (NR)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Pooled summary 2951 | 0.70 (0.62 to 0.78) | 0.80 (0.71 to 0.90) | 0.90 (0.80 to 1.02) | 0.52 (0.20 to 1.34) | −2.4 (−3.4 to −1.4) |

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 second; NR, not reported/could not be ascertained; RR, relative risk; SGRQ, St George’s Respiratory Questionnaire.

*Included trials that had a follow-up of 6 months or longer and contained 4 groups in the experimental design.

†Heterogeneity for exacerbation end point, $P = .08$.

‡Mean difference in scores between active medication and placebo arms.

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Disease management is an approach to coordinate resources across the health care system with the aim of fostering continuity of care and increasing patients’ knowledge and control over their chronic disease. Because the care of patients with COPD frequently requires multiple caregivers, including physicians (both generalists and specialists), nurses, physiotherapists, pharmacists, and nutritionists, a process to promote integration and seamless care may improve clinical outcomes in COPD. However, the efficacy of pulmonary rehabilitation varies from center to center, with most programs containing 4 major components: exercise training, education, behavioral modification, and nutritional support.

### Table: Meta-analysis of Clinical Trial Data Evaluating the Effects of Pulmonary Rehabilitation on Health-Related Quality of Life

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Intervention</th>
<th>Control</th>
<th>Duration of Rehabilitation Program, wk</th>
<th>Mean FEV₁ (SD, L or % Predicted)</th>
<th>Mean Units of Change (95% CI)</th>
<th>Improvement in Health</th>
<th>Decline in Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnerty et al.¹⁴ 2001</td>
<td>65</td>
<td>ET/Education</td>
<td>Usual Care</td>
<td>6</td>
<td>1.03 (0.4)</td>
<td>CRQ for Dyspnea: NR, -8.1 (-14.7 to -1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Griffths et al.⁸⁶ 2000</td>
<td>200</td>
<td>ET</td>
<td>Usual Care</td>
<td>6</td>
<td>0.90 (0.4)</td>
<td>SGRQ: NR, -4.3 (-6.5 to -2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ringbaek et al.⁸⁷ 2000</td>
<td>45</td>
<td>ET/Education</td>
<td>Placebo</td>
<td>8</td>
<td>47% (15%)</td>
<td>CRQ: NR, -0.1 (-9.8 to 10.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engstrom et al.⁸⁸ 1999</td>
<td>55</td>
<td>ET</td>
<td>Usual Care</td>
<td>6</td>
<td>32% (11%)</td>
<td>SGRQ: NR, -4.1 (-7.8 to 4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedzicha et al.⁹¹ (Moderate) 1998</td>
<td>66</td>
<td>ET/Education</td>
<td>Education</td>
<td>8</td>
<td>0.98 (0.4)</td>
<td>CRQ: NR, -2.9 (-17.0 to 11.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedzicha et al.⁹¹ (Severe) 1998</td>
<td>60</td>
<td>ET/Education</td>
<td>Education</td>
<td>8</td>
<td>0.82 (0.3)</td>
<td>SGRQ: NR, -3.9 (-5.8 to -2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled Summary</td>
<td>491</td>
<td></td>
<td></td>
<td></td>
<td>4.1 (2.2 to 6.0)</td>
<td>CRQ: NR, -4.4 (-8.4 to -0.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FEV₁ indicates forced expiratory volume in 1 second; SGRQ, St George’s Respiratory Questionnaire; CRQ, Chronic Respiratory Questionnaire; CI, confidence interval; ET, exercise training; and NR, not reported. A positive score on the CRQ and a negative score on the SGRQ denote improvement in health status with pulmonary rehabilitation compared with no pulmonary rehabilitation.
of disease management programs in COPD remains uncertain (Table 4).110-117 On average, these programs appear to improve health status of patients but may not meaningfully impact hospitalization rates. However, because of marked heterogeneity in the content of the programs and their effects, these data need to be interpreted cautiously and further study is required.

Controversial Therapies

The effects of oral theophyllines on exacerbation and mortality in COPD are uncertain and few well-conducted randomized trials are available powered on these end points.118 However, theophyllines appear to have some beneficial effects on FEV₁ as well as on the arterial contents of oxygen and carbon dioxide of patients with moderate to severe COPD.118 Oral theophyllines, however, increase the risk of nausea by approximately 7 fold. Three well-conducted clinical trials (1321 patients) demonstrated that lung volume reduction surgery (LVRS) improves health-related quality of life and exercise tolerance of patients with an FEV₁ less than 30% of predicted.119-121 However, even among carefully selected patients, LVRS did not modify all-cause mortality rates over 5 years.119 The short-term mortality was higher among patients who received LVRS than among those who were treated medically.119,121 In those patients with FEV₁ less than 20% predicted, LVRS increased the risk of mortality by approximately 4 fold (beyond medical therapy).122 Accordingly, for most patients with COPD, LVRS cannot be recommended at this time. Lung transplantation should be reserved for patients with very advanced COPD (and without major comorbid conditions) and whose projected survival is less than 2 to 3 years.123 Although lung transplantation may improve functional status and exercise tolerance of patients with COPD, no well-conducted studies have been performed to demonstrate survival benefits.124

**COMMENT**

Chronic obstructive pulmonary disease is common and associated with immense health and economic burdens.9 Airflow obstruction is a cardinal feature of COPD, and therapies that produce bronchodilation have been demonstrated to improve patients’ health status and reduce exacerbations. Long-acting β₂-agonists and tiotropium both reduce exacerbation rates by approximately 25% in patients with moderate to severe COPD. Long-acting β₂-agonists induce bronchodilation by relaxing smooth muscle cells through activation of the adenylate cyclase pathways, which in turn increases intracellular concentrations of cyclic adenosine monophosphate.42 In addition, in vitro experiments have suggested that these compounds may have certain anti-inflammatory properties.125 Anticholinergic bronchodilators, on the other hand, induce bronchodilation by attenuating vagal tone in the airways.126 While both ipratropium and tiotropium are nonselective antagonists with similar binding affinity for the muscarinic receptors, tiotropium dissociates more than 100 times more slowly from the receptor complex than ipratropium, making the former more potent and longer acting.

### Table 4. Summary of Clinical Trials for Disease Management/Follow-up Studies in COPD*

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Intervention</th>
<th>Duration, mo</th>
<th>Age, Mean (SD), y</th>
<th>FEV₁, Mean (SD), L or % Predicted</th>
<th>RR (95% CI) Hospitality†</th>
<th>Mean Difference in SGRQ Scores (95% CI)‡</th>
<th>RR (95% CI) Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourbeau et al,2003</td>
<td>191</td>
<td>Self-management/telephone follow-up</td>
<td>12</td>
<td>70 (7)</td>
<td>0.99 (0.32)</td>
<td>0.64 (0.45 to 0.91)</td>
<td>0.55 (0.19 to 1.58)</td>
<td>−2.0 (−5.9 to 1.8)</td>
</tr>
<tr>
<td>Hermiz et al,2002</td>
<td>177</td>
<td>Education/enhanced follow-up</td>
<td>3</td>
<td>67 (NR)</td>
<td>NR</td>
<td>1.27 (0.66 to 2.43)</td>
<td>1.00 (0.43 to 2.33)</td>
<td>−1.3 (−5.6 to 3.0)</td>
</tr>
<tr>
<td>Weinberger et al,2002</td>
<td>453</td>
<td>Education/peak flows</td>
<td>12</td>
<td>62 (11)</td>
<td>48% (20)</td>
<td>0.98 (0.65 to 1.47)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Watson et al,1997</td>
<td>69</td>
<td>Self-management</td>
<td>6</td>
<td>68 (9)</td>
<td>37% (15)</td>
<td>NR</td>
<td>NR</td>
<td>−4.0 (−8.1 to 0.1)</td>
</tr>
<tr>
<td>Gallefoss and Bakke,2000</td>
<td>62</td>
<td>Education</td>
<td>12</td>
<td>58 (10)</td>
<td>58% (10)</td>
<td>0.78 (0.19 to 3.15)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Littlejohns et al,1991</td>
<td>166</td>
<td>Education/enhanced follow-up</td>
<td>12</td>
<td>63 (8)</td>
<td>47% (23)</td>
<td>0.93 (0.46 to 1.87)</td>
<td>0.36 (0.10 to 1.28)</td>
<td>NR</td>
</tr>
<tr>
<td>Cockcroft et al,1987</td>
<td>79</td>
<td>Enhanced follow-up</td>
<td>8</td>
<td>70 (NR)</td>
<td>0.82 (0.37)</td>
<td>NR</td>
<td>0.56 (0.20 to 1.61)</td>
<td>NR</td>
</tr>
<tr>
<td>Weinberger et al,1996</td>
<td>583</td>
<td>Enhanced follow-up</td>
<td>6</td>
<td>63 (11)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pooled summary</td>
<td>1780</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.86 (0.68 to 1.08)</td>
<td>0.63 (0.38 to 1.04)</td>
<td>−2.5 (−4.8 to −0.1)</td>
</tr>
</tbody>
</table>

*Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; NR, not reported/could not be ascertained; RR, relative risk; SGRQ, St George’s Respiratory Questionnaire.
†Heterogeneity for hospitalization end point, P = .34.
‡Mean difference in scores between usual care and disease management and usual care only groups.
§For analysis, nonsignificance was assumed to be P = .20.
MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

than the latter. In most situations, tiotropium may be used once daily, while ipratropium generally is given 4 to 6 times per day. The current evidence suggests that these 2 classes of long-acting bronchodilators (long-acting β₂-agonists and anticholinergics) have similar efficacy, although only 2 trials (1830 patients) have directly compared them. Whether a combination of these 2 classes of long-acting bronchodilators would have an additive benefit on clinical outcomes (over monotherapy) is unknown. Until such data are published, this practice cannot be routinely recommended.

Inhaled corticosteroids also reduce exacerbation rates by approximately 25%. The mechanisms by which inhaled corticosteroids exert their beneficial effects on COPD outcomes are unclear. However, they attenuate airway hyperresponsiveness, which may be an important predictor of COPD mortality, and reduce some but not all components of airway inflammation and oxidative stress. Some caution should be exercised in using inhaled corticosteroids because they are associated with increased risk of certain adverse effects including thrush, oral candidiasis, and bruising. Inhaled corticosteroids also have some deleterious effect on bone mineral density, but the effect was very modest and was not associated with an excess risk of clinically evident fractures during these admittedly short-term trials. While the trials may have been too short to detect any changes, it is possible that inhaled corticosteroids may not decrease fracture rates as, by reducing the frequency of COPD exacerbations by one quarter, they will spare patients from exposure to higher doses of systemic corticosteroids.

Theoretically, adding long-acting β₂-agonists to inhaled corticosteroid use may amplify the anti-inflammatory effects of corticosteroids since long-acting β₂-agonists may enhance nuclear localization of glucocorticoid receptors in inflammatory cells, making it easier for corticosteroids to effectively block cytokine expression in these cells. Long-acting β₂-agonists also may increase the effectiveness of corticosteroids in suppressing expression of adhesion molecules such as intracellular adhesion molecule 1. Consistent with these observations, clinical studies suggest that by combining long-acting β₂-agonists and inhaled corticosteroids, exacerbation rates are lowered beyond that achieved by individual component therapy. However, the beneficial effects are additive (not synergistic) (RR, 0.70 vs placebo).

Supplemental oxygen therapy improves dyspnea scores, reduces pulmonary arterial pressure, and prolongs survival in those patients with COPD with a PaO₂ lower than 60 mm Hg. Pulmonary rehabilitation is effective in improving exercise tolerance and health status of patients with an FEV₁ less than 1.5 L. The relative improvements in patients’ health status are maintained during the 18 months of follow-up in some studies, but its effects beyond that time frame are uncertain. No compelling evidence is available showing that pulmonary rehabilitation reduces frequency of hospitalizations or death in patients with COPD.

Although conceptually appealing, disease management programs have not yet been shown to improve clinical outcomes in patients with COPD (Table 4). However, this finding may reflect differences in the core components of disease management strategies across various studies. In general, studies that taught self-management skills and provided comprehensive educational services to patients had better outcomes than those that provided closer follow-up (Table 4). Well-designed comparative studies are needed to validate these initial observations.

In summary, consistent with the guidelines from the Global Initiative for Chronic Obstructive Lung Disease committee, smoking cessation is the cornerstone of chronic COPD management. Inhaled bronchodilator therapy on an as-needed basis should be considered for patients who experience occasional exacerbations. Regular bronchodilator therapy may be instituted for those with persistent symptoms. Combination therapy (with both a β₂-agonist and an anticholinergic) or the use of long-acting agents would appear to be the best approaches in this setting. In symptomatic individuals with moderate to severe disease, addition of inhaled corticosteroids with or without long-acting β₂-agonists and pulmonary rehabilitation should be considered. In patients with hypoxia at rest, supplemental oxygen therapy should be instituted. Although little evidence is available specifically examining the effects of influenza and pneumococcal vaccinations in the COPD population, they have been demonstrated to reduce hospitalizations and deaths in the general elderly population with only minor excess risks to recipients, and, thus, they are recommended for most patients with symptomatic COPD.

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tients with chronic respiratory disability. Br Med J (Clin
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We simply need that wild country available to us, even if we never do more than drive to its edge and look in.
For it can be a means of reassuring ourselves of our sanity as creatures, a part of the geography of hope.
—Wallace Stegner (1909-1993)