Efficacy and Safety of Inhaled Corticosteroids in Patients With COPD: A Systematic Review and Meta-Analysis of Health Outcomes

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ABSTRACT

PURPOSE We wanted to review systematically the efficacy, effectiveness, and safety of inhaled corticosteroids with respect to health outcomes in patients with chronic obstructive pulmonary disease (COPD).

METHODS We searched MEDLINE, EMBASE, The Cochrane Library, and the International Pharmaceutical Abstracts to identify relevant articles. We limited evidence to double-blinded randomized controlled trials (RCTs) for efficacy, but we also reviewed observational evidence for safety. Outcomes of interest were overall mortality, exacerbations, quality of life, functional capacity, and respiratory tract symptoms. When possible, we pooled data to estimate summary effects for each outcome.

RESULTS Thirteen double-blinded RCTs determined the efficacy of an inhaled corticosteroid compared with placebo; 11 additional studies assessed the safety of inhaled corticosteroid treatment in patients with asthma or COPD. Overall, COPD patients treated with inhaled corticosteroids experienced significantly fewer exacerbations than patients taking placebo (relative risk [RR] = 0.67; 95% CI, 0.59-0.77). No significant difference could be detected for overall mortality (RR = 0.81; 95% CI, 0.60-1.08). Evidence on quality of life, functional capacity, and respiratory tract symptoms is mixed. Adverse events were generally tolerable; pooled discontinuation rates did not differ significantly between inhaled corticosteroid and placebo treatment groups (RR = 0.92; 95% CI, 0.74-1.14). Observational evidence, however, indicates a dose-related risk of cataract and open-angle glaucoma. Severe adverse events, such as osteoporotic fractures, are rare; the clinical importance of the additional risk is questionable.

CONCLUSIONS Overall, the risk-benefit ratio appears to favor inhaled corticosteroid treatment in patients with moderate to severe COPD. Existing evidence does not indicate a treatment benefit for patients with mild COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is among the leading causes of morbidity and mortality worldwide. In 2000 COPD accounted for approximately 20.7 million outpatient visits, 3.4 million emergency department visits, 6.3 million hospitalizations, and 116,513 deaths in the United States. The World Health Organization estimates that by the year 2020, COPD will be the third-leading cause of death and the fifth-leading cause of disability worldwide.

COPD is characterized by a progressive, irreversible limitation of airflow associated with an abnormal inflammatory response to noxious particles or gases. It is caused primarily by smoking.
The beneficial effect of inhaled corticosteroid treatment for COPD remains controversial, in part because only smoking cessation is reliably shown to slow the rate of decline in lung function. Although the Food and Drug Administration (FDA) has not approved inhaled corticosteroids as monotherapy for the treatment of COPD, they are frequently prescribed to reduce or alleviate symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status. The Global Initiative for Chronic Obstructive Lung Disease recommends inhaled corticosteroid treatment for patients with COPD who have a documented spirometric response to inhaled corticosteroids and for patients with moderate to severe COPD (forced expiratory volume in 1 second \([\text{FEV}_1]\) <50% predicted) who have repeated exacerbations that require treatment with antibiotics or oral corticosteroids. Inhaled corticosteroid treatment is, however, associated with rare but potentially serious adverse events, such as osteoporosis, glaucoma, and cataract, that are difficult to identify in efficacy studies.

Six inhaled corticosteroids are available in the United States: beclomethasone dipropionate (beclomethasone), budesonide, flunisolide, fluticasone propionate (fluticasone), mometasone furoate (mometasone) and triamcinolone acetonide (triamcinolone). Table 1 summarizes their generic names, trade names, manufacturers, dosage form with corresponding devices, strengths, and labeled uses.

Most published studies and systematic reviews have focused on systemic corticosteroid reduction, particularly in patients at risk for repeat exacerbations who require antibiotics or oral corticosteroids. In addition, there are emerging data suggesting that inhaled corticosteroids are effective in reducing bronchodilator usage and improving exercise capacity in patients with mild to moderate COPD. The Global Initiative for Chronic Obstructive Lung Disease recommends inhaled corticosteroids for patients with COPD who have a documented spirometric response to inhaled corticosteroids and for patients with moderate to severe COPD (forced expiratory volume in 1 second \([\text{FEV}_1]\) <50% predicted) who have repeated exacerbations that require treatment with antibiotics or oral corticosteroids. Inhaled corticosteroids are also useful in combination with bronchodilators to reduce exacerbations and improve lung function in patients with moderate to severe COPD.

### Table 1. Inhaled Corticosteroid Trade Names, Manufacturers, Formulations, and Labeled Uses

| Generic Name                  | US Trade Name | Manufacturer                  | Dosage Form, Device | Strength | Labeled Uses                     |
|-------------------------------|---------------|--------------------------------|---------------------|----------|----------------------------------|
| Beclomethasone dipropionate   | QVAR          | Ivax / 3M MDI (HFA)            | 40 µg/puff          | Asthma (aged ≥ 6 y)                   |
|                               |               |                                | 80 µg /puff         | Maintenance                        |
|                               |               | Vanceril* Schering-Plough MDI 42 µg /puff | Asthma (aged ≥ 6 y)                   |
|                               |               |                                | 84 µg /puff         | Maintenance                        |
| Budesonide                    | Pulmicort     | AstraZeneca DPI                 | 200 µg /dose        | Asthma (aged ≥ 6 y)                   |
| Turbuhaler                    |               |                                |                     | Maintenance                        |
|                               | Pulmicort Respules | AstraZeneca Inhalation suspension | 500 µg  | Asthma (aged 1-8 y)                   |
|                               |               |                                | 1,000 µg            | Maintenance                        |
|                               |               |                                | 2,000 µg            | Maintenance                        |
| Flunisolide                   | AeroBid       | Forest / 3M MDI†               | 250 µg/puff         | Asthma (aged ≥ 6 y)                   |
|                               |               |                                |                     | Maintenance                        |
|                               | Bronalide‡     | Boehringer Ingelhein (Canada) MDI† | 250 µg/puff         | Asthma (aged ≥ 6 y)                   |
|                               |               |                                |                     | Maintenance                        |
| Fluticasone propionate        | Flovent       | GlaxoSmith-Kline DPI           | 44 µg /puff         | Asthma (aged ≥ 12 y)                   |
|                               |               |                                | 110 µg /puff        | Maintenance                        |
|                               |               | Flovent† Rotadisk              | 100 µg /dose        | Asthma (aged ≥ 4 y)                   |
|                               |               |                                | 220 µg /puff        | Maintenance                        |
|                               | Flovent Diskus‡ | GlaxoSmithKline DPI – breath-activated inhalation device | 50 µg /dose | Asthma (aged ≥ 12 y)                   |
|                               |               |                                | 100 µg /dose        | Maintenance                        |
|                               |               |                                | 100 µg /dose        | Maintenance                        |
|                               |               |                                | 250 µg /dose        | Maintenance                        |
|                               |               |                                | 220 µg /dose        | Maintenance                        |
| Mometasone furoate            | Asmanex       | Schering-Plough DPI            | 250 µg /dose        | Asthma (aged ≥ 12 y)                   |
|                               | Twisthaler    |                                | 220 µg /dose        | Maintenance                        |
| Triamcinolone acetonide       | Aznacort      | Aventis MDI† – with spacer mouthpiece | 100 µg /dose | Asthma (aged ≥ 6 y)                   |
|                               |               |                                |                     | Maintenance                        |

MDI = metered dose inhaler; HFA = hydrofluoroalkane propellant; DPI = dry powder inhaler.

* Currently not available from the manufacturer.
† Contains chlorofluorocarbons.
‡ Not available in the United States.
§ Discontinued by manufacturer; supplies should be depleted by end of first quarter 2005, at which time Flovent HFA will replace Flovent.
have evaluated the effect of inhaled corticosteroid treatment on FEV₁ decline. The rate of FEV₁ descent, however, is an imperfect surrogate outcome for clinically important health outcomes, such as health-related quality of life, functional capacity, and exacerbations. Only one meta-analysis focused primarily on health outcomes; none of these systematic reviews took observational evidence for adverse events into consideration. Limiting adverse events assessment to randomized controlled trials (RCTs) risks missing rare but potentially severe adverse events, such as osteoporotic fractures, glaucoma, or cataract, which RCTs cannot reliably assess because of limitations of sample sizes and study durations.

The objective of this review is to determine the risk-benefit ratio of inhaled corticosteroid treatment for COPD by systematically reviewing the evidence on the efficacy, effectiveness, and safety of inhaled corticosteroid treatment in patients with COPD with respect to health outcomes. Contrary to previous systematic reviews, because our review incorporates observational evidence for adverse events, we provide the first comprehensive assessment of the risk-benefit ratio of inhaled corticosteroid treatment for COPD.

**METHODS**

This study is part of a larger systematic review of the comparative effectiveness and tolerability of inhaled corticosteroids in patients with asthma or COPD conducted for the Oregon Drug Effectiveness Review Project (DERP). We limited outcomes of interest a priori to health outcomes to assure clinical applicability of results.

We searched MEDLINE, EMBASE, The Cochrane Library, and the International Pharmaceutical Abstracts to identify relevant articles. We used either medical subject headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for the selected indication (COPD) and adverse events with 6 specific inhaled corticosteroids (beclomethasone, budesonide, flunisolide, fluticasone, mometasone, and triamcinolone). We limited the electronic searches to ‘human’ and ‘English language’; we searched sources from 1970 to 2005 (April) to capture literature relevant to the scope of our topic.

Two persons independently reviewed abstracts; if both reviewers agreed that the trial did not meet eligibility criteria, it was excluded. We reviewed the full text of all eligible articles. Double-blind RCTs of at least 6 months’ duration and an outpatient study population were eligible for inclusion. Preestablished exclusion criteria concerned study design or duration, patient population, interventions, and outcomes. We excluded open-label studies from the efficacy analysis because empirical evidence indicates that lack of blinding frequently leads to measurement bias and an overestimation of effect sizes. For adverse events we included both experimental and observational studies. For observational studies we included those with large sample sizes (>100 patients) that lasted at least 1 year and reported an included outcome. For adverse events we also included evidence from mixed populations with asthma and/or COPD.

We assessed the internal validity (quality) of trials based on predefined criteria from the US Preventive Services Task Force (ratings: good-fair-poor) and the National Health Service Centre for Reviews and Dissemination. External validity (generalizability) was assessed but did not influence quality ratings. We rated trials with a fatal flaw in one or more categories as poor quality and excluded them from the analysis; we rated trials that met all criteria as good quality. The majority of trials received a quality rating of fair. We accepted the definitions of exacerbation as reported in each study because we did not have access to individual patient data. Although definitions of exacerbation varied across studies, most defined it as an episode requiring oral or parental corticosteroids, antibiotics, emergency department visits, or hospitalizations because of increased respiratory tract symptoms.

When possible, we pooled data to obtain summary effect estimates for a given outcome, using relative risks to measure effect sizes. We used fixed-effects models for all meta-analysis because the observed heterogeneity was low (<20%, assessed using the I² statistic). We assessed publication bias using funnel plots and Kendall’s tests, although the validity of these methods is limited given the small number of component studies. All analyses were conducted using StatsDirect 2.3.8 (StatsDirect Ltd, Sale, Cheshire, UK).

**RESULTS**

Overall we identified 880 citations. Figure 1 illustrates the disposition of citations and articles. Thirteen double-blinded RCTs determined the efficacy of an inhaled corticosteroid compared with placebo in patients with COPD. We excluded 1 study for quality reasons because of a high rate of postrandomization exclusions. We included 11 additional studies conducted in adult patients with COPD or asthma to assess the risk of adverse events of long-term inhaled corticosteroid use. Tables 2 and 3 describe included studies.
Severity of COPD varied from mild to severe across studies; inclusion criteria tended to exclude patients with asthma or good bronchodilator responsiveness. Patients with a history of asthma, allergic disease, or sudden onset of breathlessness were excluded from all studies. Further, FEV1 reversibility after bronchodilator use was frequently assessed before enrollment; cutoff criteria were between 10% and 15%. Nine trials (69%) were funded by pharmaceutical companies and 3 (23%) were supported primarily by governmental agencies or independent funds; 1 study (7%) did not report funding source.

**Exacerbations**

Two studies did not provide sufficient data on exacerbation rates and could not be included in the meta-analyses.20,21 Overall, pooled results of 4,300 patients from the 10 remaining trials showed a 33% reduction (95% CI, 23%-41%; RR = 0.67; 95% CI, 0.59-0.77) in COPD exacerbation rates over a mean follow-up period of 20.8 months (Figure 2A). Sensitivity analysis showed that this treatment effect derives largely from studies in populations suffering from moderate to severe COPD (respectively, FEV1 ≥50% to <80% predicted and FEV1 <50% predicted according to American Thoracic Association criteria).11 Limiting the analysis to the 7 trials with populations with moderate to severe COPD (ie, excluding populations with mild COPD) produces an estimated benefit of inhaled corticosteroid treatment almost identical to the results of the overall meta-analysis (RR = 0.66; 95% CI, 0.57-0.75) (Figure 2B). The number needed to treat (NNT) in this population is 12 (95% CI, 9-18); ie, 12 patients with moderate to severe COPD need to be treated with an inhaled corticosteroid for 17.7 months to avoid 1 exacerbation. For the population with mild COPD (FEV1 ≥80% predicted), we pooled results of 3 small studies (n = 191); no benefit of inhaled corticosteroid treatment emerged (RR = 0.92; 95% CI, 0.55-1.53).

As noted, the sample size of this analysis is small, and point estimates of both subgroup analyses are within each other’s confidence intervals. Inferences about differences of treatment effects must be made cautiously.

In sensitivity analyses we compared pooled results of studies of newer inhaled corticosteroids (ie, fluticasone) that have a large degree of first-pass metabolism42,43 with those of older inhaled corticosteroids (ie, beclomethasone, budesonide, flunisolide, and triamcinolone). Relative benefits of both groups were almost identical (newer inhaled corticosteroids: RR = 0.69 [0.59-0.80]; older inhaled corticosteroids: RR = 0.65 [95% CI, 0.53-0.79]).

**Mortality**

The pooled relative risks (RR = 0.81; 95% CI, 0.60-1.08) for 4,370 patients resulted in no significant difference in all-cause mortality (Figure 3A). Overall, 2.9% of patients on placebo and 2.5% of patients on inhaled corticosteroids died (P = .27) during the mean follow-up period of 22.3 months. Limiting the analysis to studies of moderate to severe COPD (Figure 3B) yielded almost identical results (RR = 0.84; 95% CI, 0.61-1.15). No differences in mortality were apparent between groups taking newer and older inhaled corticosteroids.

**Functional Capacity and Quality of Life**

In the few studies that assessed functional capacity or quality of life, outcome measures were too heterogeneous to pool results in a meta-analysis; therefore, we analyzed findings qualitatively.

Five studies examined functional capacity and quality of life in patients with moderate to severe COPD.18,19,22,26,27 Two trials...
### Table 2. Summary of Included Randomized Controlled Trials on Efficacy of Inhaled Corticosteroids in COPD

| Author, Year          | Mean Age (years) | No. | Duration | Dosage, Device | Mean Baseline FEV₁ (% of predicted) | Quality Rating |
|-----------------------|------------------|-----|----------|----------------|------------------------------------|----------------|
| Budesonide vs placebo| Bourbeau et al., 1998 | 66  | 79       | 6 mo           | 1,600 µg/d, DPI                    | 36.5           | Fair |
| Calverley et al., 2003 | 64              | 1,277 | 1 y | 800 µg/d, DPI | 77                                 | Fair |
| Pauwels et al., 1999 | 52              | 403  | 1 y       | 800 µg/d, MDI | 36                                 | Fair |
| Vestbo et al., 1999   | 59              | 290  | 3 y       | 1,200 µg/d, DPI | 86                                 | Fair |
| Fluticasone vs placebo| Albers et al., 2004 | 50  | 85       | 2 y           | 500 µg/d, MDI                      | 90             | Good |
| Calverley et al., 2003 | 64              | 751  | 3 y | 1,000 µg/d, MDI | 50                                 | Fair |
| Paggiaro et al., 1998 | 63              | 281  | 6 mo     | 1,000 µg/d, MDI | 57                                 | Good |
| van Grunsven et al., 2003 | 47          | 48   | 2 y       | 500 µg/d, DPI | 96                                 | Fair |
| Triamcinolone vs placebo| Lung Health Study, 2004 | 56  | 1,116 | 3 y, 4 mo | 1,200 µg/d, MDI | 64 | Fair |

COPD = chronic obstructive pulmonary disease; DPI = dry powder inhaler; MDI = metered dose inhaler.

### Table 3. Summary of Included Studies on Adverse Events of Inhaled Corticosteroids in COPD

| Author, Year          | N  | Design         | Population               | Results                                                                 | Quality Rating |
|-----------------------|----|----------------|--------------------------|------------------------------------------------------------------------|----------------|
| Bone density and osteoporotic fractures | | | | | |
| Jones et al., 2004    | NA | Systematic review | Asthma and COPD          | No difference in BMD and osteoporotic fractures between ICS and placebo | Fair |
| Hubbard et al., 2002  | 16,341 | Case-control | Asthma and COPD          | Nonspecific ICS use associated with a small increase in the risk of hip fracture | Good |
| Israel et al., 2001   | 109 | Prospective cohort | Women (aged 18-45 y)    | Triamcinolone associated with dose-related decline in BMD (total hip and trochanter) of 0.00044 g/cm² per puff/year | Fair |
| Johnell et al., 2002  | 1,277 | RCT             | COPD                     | No difference in bone density between BUD and placebo over 3 y; no difference in bone density or vertebral fractures in subgroup of 912 smokers | Fair |
| Lee & Weiss, 2004     | 8,525 | Nested case-control | COPD                   | Nonspecific ICS use associated with increased risk of fractures at high doses | Good |
| Posterior subcapsular cataracts | | | | | |
| Cumming et al., 1997  | 3,654 | Cross-sectional | Adults; asthma and COPD; aged 49-97 y | Increased risk of nuclear and PSC among ICS users | N/A |
| Garbe et al., 1998    | 25,545 | Case-control   | RAMQ; asthma and COPD; aged >70 y | Increased risk of cataract extraction for ICS users only at high dose and duration | Good |
| Jick et al., 2001     | 201,816 (3,581) | Cohort + case-control | GPRD; asthma and COPD; aged 3-90 y | Dose-, duration-, and age-related increased risk of cataracts among ICS users; no increase in risk for age <40 | Good |
| Smedeth et al., 2003  | 30,958 | Case-control    | GPRD; asthma and COPD; aged >40 y | Dose- and duration-related increased risk of cataracts among ICS users | Good |
| Ocular hypertension and open-angle glaucoma | | | | | |
| Garbe et al., 1997    | 48,118 | Case-control | RAMQ aged ≥66 y          | Dose-related increased risk of elevated IOP and open-angle glaucoma for ICS users with glaucoma family history | N/A |
| Mitchell et al., 1999 | 3,654 | Cross-sectional | Adults; asthma and COPD; aged 49-97 y | Dose-related increased risk of elevated IOP and open-angle glaucoma for ICS users with glaucoma family history | Good |

COPD = chronic obstructive pulmonary disease; NA = not applicable; BDP = beclomethasone dipropionate; BMD = bone mineral density; ICS = inhaled corticosteroid; RCT = randomized controlled trial; BUD = budesonide; PSC = posterior subcapsular cataracts; RAMQ = regi de l’assurance maladie du Quebec database; GPRD = general practice research database; IOP = intraocular pressure.
administered a 6-minute walking test after 6 months of inhaled corticosteroid treatment. In one, 6-minute walking distance was significantly greater for patients on fluticasone 1,000 mg/d than for patients on placebo (+27 m vs +9 m, \( P = .032 \)).27 A smaller Canadian study did not detect any significant difference in walking distances for patients when comparing budesonide 1,600 mg/d with placebo (-15 m vs +13 m, \( P = NR \)).18 This trial also reported no significant differences in scores on the Chronic Respiratory Disease Questionnaire.

Three studies of patients with severe COPD reported greater improvements in St. George's Respiratory Questionnaire for patients on budesonide 800 mg/d or fluticasone 1,000 µg/d than for patients on placebo19,22,26; however, the clinical importance of the reported differences (range: -0.8 to -3.0) is uncertain.

Two Dutch studies originating from the DIMCA (Detection, Intervention, and Monitoring of COPD and Asthma) program, which recruited patients with mild COPD through population screening, did not find any differences in functional capacity for patients on fluticasone 500 mg/d and those on placebo after 2 years of treatment.24,28

**Respiratory Symptoms**

Most studies assessed respiratory system symptom scores, but the reported data were mixed and insufficient for meta-analysis.

Four studies reported no significant differences in respiratory system symptoms when comparing inhaled corticosteroid with placebo.18,23,26,28 Three studies detected no overall differences in respiratory systems symptoms but did detect significant improvements in subscales, such as daily cough scores, sputum volume,27 night time awakenings,19 and dyspnea.29 In comparisons with placebo, 1 trial reported significantly lower symptom scores in patients during 2 years' treatment with budesonide 1,600 mg/d21 and another during 3 years' treatment with fluticasone 1,000 mg/d.25

**Adverse Events**

Efficacy trials commonly reported rhinitis, oral candidiasis, sore
Inhaled Corticosteroids and COPD

Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Short study durations and small sample sizes limited the validity of adverse events assessment in many trials. Many studies excluded eligible participants that did not tolerate treatment during the run-in period, limiting the generalizability of adverse events assessment.

To take the limitations of RCTs into consideration and to assess rare but potentially serious adverse events, we also reviewed observational studies (Table 3). Specifically, we were interested in osteoporosis, posterior subcapsular cataracts, ocular hypertension, and open-angle glaucoma.

Bone Density and Osteoporotic Fractures

Overall, the evidence of an association between inhaled corticosteroid products and osteoporosis is mixed. A meta-analysis of randomized trials found no evidence of increased risk of loss of bone mineral density (BMD) or fractures, which is consistent with findings from an RCT not included in that meta-analysis.

The strongest observational evidence comes from 2 case-control studies that measured fractures, both reported a slight increase in the risk of fracture for inhaled corticosteroid-treated patients. In 1 study, only current high-dose users (≥700 µg/d) had an increased risk of nonvertebral fractures (OR = 1.68, 95% CI, 1.10-2.57). In the other, the
risk of hip fracture was significantly higher in patients using an inhaled corticosteroid (OR = 1.19; 95% CI, 1.10-1.28). Additionally, evidence of an inhaled corticosteroid-associated reduction in BMD comes from a prospective cohort study in 109 premenopausal women: an estimated bone loss of 0.00044 g/cm² per puff per year of treatment. We view BMD as an intermediate outcome measure of osteoporosis; although a causal relationship exists between loss of BMD and risk of fractures from osteoporosis, the clinical importance of modest changes in BMD is often questionable.

Cataracts
The association between systemic corticosteroids and cataracts, especially at high doses administered for extended periods, is well documented in both children and adults. Systemic corticosteroid-induced cataracts typically are located on the posterior side of the lens and are referred to as posterior subcapsular cataracts.

Four observational studies evaluated the risk of adult patients developing cataracts, comparing nonspecific inhaled corticosteroid use with no inhaled corticosteroid use. A British case-control study of 15,479 patients with cataracts detected a modest but significant increase in risk for the overall use of inhaled corticosteroids (adjusted OR = 1.10; 95% CI, 1.00-1.20). A subgroup analysis of COPD patients, however, showed no significant increase in risk (adjusted OR = 1.03; 95% CI, 0.94-1.13). These results suggest a cumulative risk of inhaled corticosteroid use for the development of cataracts, because patients with asthma are generally exposed to inhaled corticosteroids for longer periods of their lives than are patients with COPD.

These findings are consistent with other observational evidence in patients with asthma or COPD. A retrospective cohort study with a nested case-control study, a case-control study, and a cross-sectional study reported increased dose- and duration-dependent risks of inhaled corticosteroids use for posterior cataracts. These studies do not report on COPD patients alone.

Ocular Hypertension and Open-Angle Glaucoma
In 1 case-control study of 48,118 Canadians aged 66 years and older and 1 cross-sectional population-based eye study of 3,654 Australians aged 49 to 97 years, the risk of increased intraocular pressure or open-angle glaucoma was compared in patients using inhaled corticosteroids and patients not using inhaled corticosteroids. Both studies adjusted for age, sex, oral steroid use, history of diabetes, and history of hypertension but did not stratify by COPD patients. Both reported a dose-related increase in the risk of open-angle glaucoma for inhaled corticosteroid-treated patients compared with patients who had not used an inhaled corticosteroid. The case-control study observed this relationship only among current users of high doses of inhaled corticosteroids prescribed regularly for 3 or more months (adjusted OR = 1.44; 95% CI, 1.01-2.06); patients on low to medium doses did not have an increased risk (adjusted OR = 0.95; 95% CI, 0.77-1.19). In the cross-sectional study the association between ever using inhaled corticosteroids and elevated intraocular pressure or glaucoma occurred only in patients with a family history of glaucoma (OR = 2.8; 95% CI, 1.2-6.8).

DISCUSSION
Our meta-analysis suggests that COPD patients treated with inhaled corticosteroids experience significantly fewer exacerbations than patients on placebo. The relative risk reduction is 33%; the NNT to prevent 1 exacerbation during 20.8 months is 12. This treatment effect is apparently stronger in patients with moderate to severe COPD. Pooled estimates for patients with mild COPD did not suggest a reduction of exacerbations. Sample sizes are too small, however, for clear inferences about the efficacy of inhaled corticosteroid treatment in patients with mild COPD.

We could not detect a significant benefit of inhaled corticosteroid treatment with respect to overall mortality, which in part may be attributable to short study durations (maximum 3 years) relative to the long natural course of disease and to the lack of power to detect such an outcome. We chose overall mortality as an outcome measure rather than COPD mortality, as it does not depend on a subjective judgment by outcome assessors and is therefore less prone to bias. The body of evidence concerning quality of life and functional capacity is mixed and yields no basis for clear conclusions. Empirical evidence suggests, however, that patient quality of life is related to the frequency of COPD exacerbation. Thus, fewer exacerbations resulting from inhaled corticosteroid treatment can provide indirect evidence for improved quality of life. In addition, inhaled corticosteroid treatment will spare some patients from dealing with systemic corticosteroids.

Efficacy data indicate that adverse events are usually mild and do not lead to significantly higher discontinuation rates for inhaled corticosteroid-treated than for placebo-treated patients. Osteoporotic fractures are rare; the clinical importance of the additional risk is questionable. Evidence from large observational studies consistently indicates a modest risk of cataracts and open-angle glaucoma; it is attributable largely to high dosage and long duration of inhaled corticosteroid use.

Our findings are partly consistent with earlier meta-analyses that assessed exacerbation rates.
Grunsvn et al\textsuperscript{9} reported no significant differences in exacerbation rates between the group on inhaled corticosteroids and the group on placebo. Results of a meta-analysis by Sin et al\textsuperscript{12} are consistent with our findings. Point estimates from our analyses, however, are more precise because of the greater number of component studies. Furthermore, neither of the 2 previous reviews included observational evidence for adverse events to assess the risk-benefit ratio of inhaled corticosteroid treatment. Results of long-term observational studies with respect to exacerbations and mortality are mixed.\textsuperscript{48-53} The COPE study, a double-blind discontinuation study of fluticasone (1,000 μg/d), reported that patients who discontinued inhaled corticosteroid therapy had a significantly higher recurrence risk of exacerbations than patients who remained on fluticasone treatment.\textsuperscript{49}

We note several limitations in this literature and our work. Durations of efficacy studies are usually too short and sample sizes too small to assess reliably the effects on rare long-term outcomes (eg, mortality) and on rare but severe adverse events. Observational studies posed methodological concerns that precluded meta-analysis.

Because we did not have access to individual patient data, we assumed that definitions of exacerbations did not differ substantially across trials. Although this assumption could lead to some imprecision with respect to efficacy, it might also increase external validity because it synthesizes various definitions of exacerbation used in clinical practice. Moreover, we reviewed inhaled corticosteroids as a class, not taking differences in potency, delivery device, systemic exposure, and dosage into consideration. No treatment regimen appeared to be underdosed, however, because we could not conduct quantitative analyses on adverse events, we were unable to assess whether inhaled corticosteroids with low systemic absorption lead to fewer adverse events than inhaled corticosteroids with high systemic absorption. Our pooled efficacy results might underestimate treatment effects for patients with severe COPD who usually receive high-dose treatments. Differential loss to follow-up might also dilute treatment effects. Placebo groups consistently had a higher dropout rate than inhaled corticosteroid groups. The frequency of exacerbations and mortality might therefore be underestimated for placebo treatment.

None of the included studies can be viewed as an effectiveness trial with a high degree of generalizability. The patient populations often were highly selected and included exclusively current or former smokers. Patients with FEV\textsubscript{1} reversibility of more than 10% to 15% were typically excluded. These factors further limit the generalizability of results for non-smoking patients with asthma who have chronic airways obstruction. Even so, good evidence exists from multiple trials that inhaled corticosteroid treatment is efficacious in patients with asthmatic features.\textsuperscript{13}

Finally, we could not include unpublished studies; their absence may lead to an overestimation of treatment effects.

Additional large studies are needed that have the necessary power to address such health outcomes as mortality and quality of life. Results of the ongoing TORCH (Towards a Revolution in COPD Health) survival study may provide answers to some remaining questions.\textsuperscript{34} This 3-year, multicenter trial is randomizing approximately 6,200 patients with moderate to severe COPD to placebo, fluticasone, fluticasone/salmeterol, or salmeterol; it will end in 2006.

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