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REVIEW

Rationale for Earlier Treatment in COPD: A Systematic Review of Published Literature in Mild-to-Moderate COPD

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Abstract

COPD is progressive and typically begins many years before a definite diagnosis is made. As the rate of decline in lung function may be faster in the initial stages of the disease, early intervention could be beneficial to control symptoms and affect disease progression and outcomes. A systematic review of published literature relating to mild-to-moderate COPD (patients with FEV_1 ≥50% predicted) was performed to evaluate the level of impairment and natural history or disease progression over time, and impact of interventions on the outcomes of patients with early-stage disease. Of the 79 published articles included in this analysis, 31 reported randomized controlled trials; the remaining 48 articles reported studies of non-randomized and/or observational design. Nine of the randomized controlled trials were ≥6 months' duration, enabling assessment of outcomes over time. Most of the randomized controlled trials were in patients with moderate COPD (GOLD stage II); few included patients with the mildest stages of the disease (i.e., stage I). The results show that even patients with milder or moderate COPD can have substantial limitations and physical impairment, which worsen over time. Encouragement of smoking cessation, in conjunction with management of symptoms and treating activity limitation and exacerbations by appropriate non-pharmacologic and pharmacologic management at the earliest possible stage, could positively affect the impact and progression of the disease.

Keywords: Bronchodilator Agents, Quality of Life, Respiratory Function Tests, Exacerbations, GOLD Stage I, GOLD Stage II.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation, which is usually progressive (1). It is caused by an abnormal inflammatory response to noxious particles or gases, resulting in a combination of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) (1). Risk factors include smoking, indoor exposure to biomass fuels (2), air pollution, genetic pre-disposition, advancing age, and poor lung health (e.g., previous infection, poor nutrition, and poor lung growth and development) (1).

The impact of COPD on the individual patient depends on the degree of airflow limitation, the severity of symptoms and any systemic effects and co-morbidities (1). The declining lung function results in progressively greater restrictions in daily activity and exercise tolerance, deconditioning, impaired quality of life (QoL), and an increasing number of symptoms and exacerbations. The reduction in daily activity is already present in mild disease (3).

COPD has been classified by several authorities, largely based on spirometry using a simple classification score of airway limitation defined as a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital

capacity (FVC) ratio <0.7. The following Global Initiative for Chronic Obstructive Lung Disease (GOLD) system has been widely used to categorize COPD into 4 stages: stage I (mild), $FEV_1 \geq 80\%$ predicted; stage II (moderate), $FEV_1 \geq 50\%$ and < 80% predicted; stage III (severe), $FEV_1 \geq 30\%$ and <50%; and stage IV (very severe), $FEV_1 <$ 30% or <50% predicted with chronic respiratory failure ($FEV_1 <$ 30% predicted in the 2011 GOLD guideline update) (1,4). An additional category (GOLD stage 0) of symptomatic patients with $FEV_1/FVC > 0.7$, who were considered to be "at risk" of developing COPD, was included in previous GOLD guidelines, but this category was discontinued due to lack of strong evidence for progression to COPD (1).

Patients with COPD often do not seek medical attention until after they have developed chronic respiratory symptoms or have had an exacerbation (increase in, or development of new symptoms requiring a change in treatment and/or hospitalization) (1). However, many patients with COPD are symptomatic long before this, often complaining of chronic cough and sputum production for several years before a diagnosis is made (1). It is unclear what triggers the development of COPD in some individuals while others remain in a chronic non-obstructive bronchitic state.

Awareness of the relevance of these early symptoms is increasing amongst healthcare professionals. Several population-screening studies have also shown that patients with mild COPD can be identified early (5–21). Overall, these studies suggest that early (GOLD stage I) disease (symptomatic but with $FEV_1 > 80\%$ predicted) was found in approximately 2% to 10% of the adult population (5,7,8,19–21). In the international Burden Of Lung Disease (BOLD) study, the prevalence of GOLD stage I was shown to be 1.4% to 15.5% and GOLD stage II, 5.1% to 12.4% (3). The importance of early diagnosis lies in the fact that important manifestations of COPD, such as exercise intolerance (22) and reduced daily activity (3) are already present at this stage of the disease. Also, the presence of mild airflow limitation is associated with increased mortality (23).

As the rate of decline in lung function may be faster in the initial stages of the disease, early intervention could be beneficial (24). Early detection, diagnosis, and management may also help to control symptoms, and potentially affect disease progression—and outcomes (25). For example, although smoking cessation reduces the rate of decline in lung function at all stages of the disease (26–29), the earlier it occurs in the natural evolution of COPD, the better the impact on lung function (29). It is also possible that pharmacotherapy in the initial stages may reduce, or at least delay, decline in lung function, prevent exacerbations, improve symptoms, and QoL, as well as ultimately reduce morbidity and mortality (30,31).

The objective of this study was to review systematically the published literature relating to mild-to-moderate COPD in order to evaluate: the level of impairment and the natural history or disease progression over time; and the impact of interventions on the outcomes of patients with early-stage disease.

Materials and Methods

A systematic review of the literature was conducted to identify data relating to patients with mild-to-moderate COPD. Literature published from January 1, 1980, to July 30, 2010, was searched using 4 databases (Medline, Embase, BIOSIS, and SciSearch) with the following defined search terms: "chronic obstructive pulmonary disease" OR "COPD" AND 1 or more of "earl(-y, -ier, -iest)", "mild(-ly)", "moderate", "Stage 0", "Stage 1", OR "Stage I", "Stage 2", OR "Stage II". The total hits from the search were assessed for relevance by a single researcher based on titles/abstracts, and those publications that were deemed potentially relevant were obtained in full and assessed.

Articles were included if they reported on patients with COPD who had a baseline $FEV_1 \geq 50\%$ predicted, where either the entire cohort or subgroups of patients were stratified according to this inclusion criterion. Also included were studies in which $FEV_1 \geq 50\%$ predicted was not a patient inclusion criterion, but in which the mean baseline FEV_1 was ≥60% predicted (indicating a mild-to-moderate population). Any original clinical data published in English were eligible, including subgroup or secondary analyses and studies of experimental and observational design. There were no restrictions on the intervention (any drug treatment or none), study duration, or outcome measures. *In vitro* and *ex vivo* studies were excluded. Also excluded were unstratified data incorporating patients with $FEV_1 < 50\%$ predicted; where mean baseline FEV_1 was close to 50% predicted.

The most robust studies were considered to be the randomized controlled trials (RCTs) and, of those, studies of ≥6 months' duration were identified as potential for providing information on change in disease course or outcomes over time. Supplementary data from shorter RCTs and non-randomized studies were also included to provide additional relevant information on aspects of the disease.

Results

Literature search results

The search strategy returned a total of 269 hits (Figure 1). Of these, 74 were excluded based on the title and/or abstract, 2 were available only in foreign languages, and 6 could not be sourced.

The remaining 187 papers were deemed potentially relevant based on the title and/or abstract and were obtained in full. Of these, 108 were excluded (see Supplementary Appendix 1) and 79 were included. The reasons for exclusion were: patients were not eligible (n = 76); there were no relevant data (n = 1); the data were duplicated elsewhere (n = 1); the study was *ex vivo* (n = 17); the publication was a review article (n = 13).

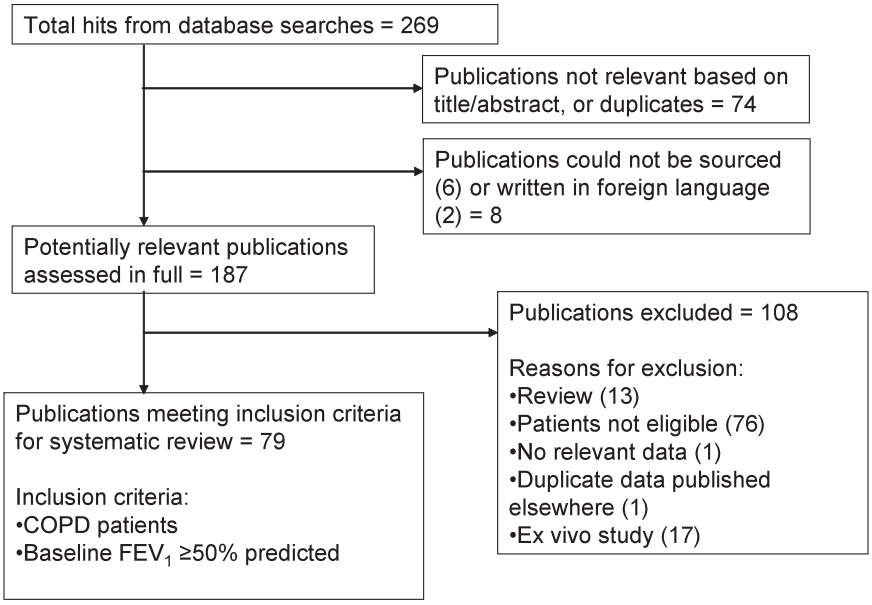

Figure 1. The flow of published articles through the systematic review process.

Of the 79 papers included in this analysis, 31 reported on RCTs and the remaining 48 on studies of non-randomized and/or observational designs. The 31 RCT papers included 11 describing placebo-controlled investigations of pharmaceutical agents (30–40), 6 investigations of pharmaceutical agents that had active controls (41–46), 6 trials of non-pharmaceutical interventions (47–52), and 6 describing combined pharmaceutical and non-pharmaceutical interventions (29,53–57). The remaining 2 papers contained only placebo data (58, 59). Overall, 9 RCTs had the desired duration of ≥6 months (30–33, 34, 38–40, 48, 59).

The 48 non-RCT papers included reports of 2 prospective, controlled, parallel-group studies, while the remainder were of less robust design. Of these, 17 papers were population-based COPD screening studies. For details of these 48 publications, please see Supplementary Appendix 2.

Disease progression in mild-to-moderate COPD

All 31 RCT papers provided baseline data on the status of patients with mild-to-moderate COPD (Table 1). Thirteen of the RCTs provided baseline data only (29, 41–47, 53–57). Eighteen papers reported on RCTs that incorporated a suitable "no treatment" (or placebo) arm, thereby providing outcome data relevant to natural disease progression. These included 2 papers containing only placebo data (58, 59), 11 papers on placebo-controlled investigations of pharmaceutical agents (30–40) and 5 trials of non-pharmacologic interventions, which incorporated a suitable control arm (48–52).

Of the 18 papers reporting disease progression, 9 documented RCTs with ≥6 months' duration (30–32, 34, 38–40, 48, 59).

The majority of the RCTs were in patients with moderate COPD (GOLD stage II); few RCTs included patients with the mildest stages of COPD (i.e., GOLD stage I) (Table 2). The 2-year Detection, Intervention, and Monitoring Program of COPD and Asthma (DIMCA) trial provided data for patients with early signs of COPD (i.e., persistent symptoms and a moderately accelerated rate of lung decline) (32,40). The baseline values and outcomes, in terms of changes in aspects of the disease over the time period studied, in the placebo or control groups of patients are summarized in Table 2.

Lung function—rate of decline in FEV_1

Decline in FEV_1 was reported from 4 RCTs of ≥6 months' duration (30–32, 38). For example, in 24 patients with mild COPD (mean FEV_1 98% predicted) receiving placebo in the 2-year DIMCA trial, estimated post-bronchodilator FEV_1 decline was 14 ml/year (32). In a 3-year study in mild-to-moderate COPD (mean FEV_1 76.9% predicted), the rate of decline in mean post-bronchodilator FEV_1 was 65 ml/year in 643 patients receiving placebo (38).

Among the trials in which patients with moderate COPD (GOLD stage II) were assessed, subgroup analyses of these patients in 2 large trials, Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT®) (n = 2375) and Towards a Revolution in COPD Health (TORCH) (n = 2156) (duration 4 years and 3 years, respectively, mean post-bronchodilator FEV_1 59% predicted) showed rates of decline in FEV_1 of −49 ml/year and −60 ml/year, respectively, in placebo/control patients (30, 31).

Bridevaux et al. reported the results of a large (n = 6671) Swiss population-based study over 11 years, in which the annual rate of decline in symptomatic GOLD stage I patients (n = 224) was significantly greater than in asymptomatic control individuals (n = 3627) (44 ml/

Table 1. Articles meeting the inclusion criteria for the systematic review, which reported baseline data and outcomes with no treatment.

Citation	Interventions, follow-up	Outcome measures	Patients and baseline characteristics	Main findings
PBO/control arm analysis only				
Double-blind PBO-controlled parallel-group; analysis of EUROSCOP study data (Watson et al., ref. 59)	PBO arm only, 3 y	FEV_1 and predictors	n = 642 COPD (72% male), current smokers (46% quit during study), median 38.3 (interquartile range 28.5–51.3) pack-years for men, 29.5 (21.0–40.0) pack-years for women, median age: men 54 years (48–58 years); women 52 years (46–58 years). Post-bronchodilator (2) FEV_1 % pred 79.2 (69–88) FEV_1 2.8 L (2.3–3.2 L) for men, FEV_1 % pred 81.5 L (71–89 L) FEV_1 2.1 L (1.7–2.4 L) for women; FEV_1/FVC % pred 63.7 (58–68) (men) 65.5 (60–70) (women); FEV_1/IVC% 63.3 (57.1–66.9) for men 64.5 (59.1–67.9) for women. Median reversibility % pred 2.7 (0–5.1) for men and 2.9 (0–5.7) for women. Wheezing anytime: 54.1% men; 60.5% women. Dyspnea after activity: 34.6% men 39.9% women. Dyspnea at rest: 6.9% men; 6.2% women. Cough in winter: 48.7% men; 58.4% women. Median BMI: 24.7 (22.7–27.1) male; 22.9 (20.5–25.3) female kg/m^2	Rate of FEV_1 decline reported graphically. Symptoms associated with lower baseline FEV_1 in men but not women. Annual decline in FEV_1 not associated with symptoms; less in obese men, more with greater smoking. In women, more severe airway obstruction associated with accelerated decline in FEV_1.
Open-label, crossover (Magnussen et al., ref. 58)	Inhaler A versus inhaler B versus inhaler C; all containing PBO powder, no follow-up	PIF	n = 48 COPD: n = 24 moderate (75% male, 63% current smokers, mean 61.5 ± 25.7 pack-years, age 63 ± 8 y, post-bronchodilator FEV_1 % pred 59.5 ± 6.9, FVC 3.78 ± 1.23 L, FEV_1/FVC 47.8 ± 9.5%, reversibility 19.3 ± 15.1%, BMI 28.0 ± 5.2 kg/m2), n = 24 severe	For moderate patients, highest PIF approximately 50–100 L/min
Pharmacologic intervention only—PBO controlled				
Double-blind, PBO-controlled, parallel-group (DIMCA study) (van Grunsven et al., ref. 32)	Fluticasone propionate 250 µg bid versus PBO, 2 y	Pulmonary function, symptoms, functional status (COOP/WONCA), exacerbations	n = 48 early COPD, 3 months' symptoms, previous FEV_1 decline 109 ± 46 ml/year (fluticasone) 124 ± 66 ml/year (PBO). Mean age 46 ± 10 years and 47 ± 11 years, 50% and 54% male, current smokers 42%, pack-years 11.9 ± 9.5 and 5.8 ± 8.4. Mean baseline post-bronchodilator FEV_1 % pred 98 ± 15 and 99 ± 18 FEV_1 3.16 ± 0.68 L and 3.19 ± 0.79 L; pre-bronchodilator (3) FEV_1 % pred 95 ± 18 and 98 ± 17 FEV_1 3.05 ± 0.7 L and 3.17 ± 0.76 L; pre-bronchodilator FEV_1/FVC 75 ± 10% and 77 ± 6%; FEV_1 reversibility % pred 4.0 ± 5.1 and 3.0 ± 4.0; symptom score 1.7 ± 1.5 and 1.3 ± 1.3. COOP/WONCA scores varied from not impaired (1.2 ± 0.6 for social activities) to slightly impaired (2.4 ± 1.2 for general health)	For PBO, annual decline in FEV_1 –14 ± 17 ml post-bronchodilator and –38 ± 19 ml pre-bronchodilator; 4 exacerbations in 3 patients, no change in COOP/WONCA over study, 57 episodes of increased respiratory symptoms in 17 patients
Double-blind PBO-controlled parallel-group (DIMCA 3a study) (van Grunsven et al., ref. 40)	Fluticasone propionate 250 µg versus PBO, 2 years	Compliance, patient opinion	n = 48 COPD. Mean FEV_1 % pred 96 ± 17, FEV_1 reversibility 3 ± 5% pred, age 47 years (range 29–71 y), 42% smokers, mean pack-years 9 (0–29), 52% male, number of symptoms in past 3 months 1.5 ± 1.4	Only outcomes are compliance
Double-blind PBO-controlled parallel-group, post-hoc analysis of EUROSCOP study (Löfdahl et al., ref. 34)	Budesonide 800 µg/day versus PBO, 3 years	Ischemic events, and baseline predictors	n = 1277 COPD, current smokers, pack-yrs median 36 (range 0–171), 73% male, mean age 52.5 years (range 25–66 y), BMI 24.8 (15–44) kg/m^2, FEV_1 2.5 (1.0–4.7) L, FEV_1 % pred 76.9 (42–103), IVC 4.1 (1.9–7.8) L.	5.3% (31/582) PBO patients had 38 ischemic events. Estimated yearly severe exacerbation rate (oral steroids) 0.07 for PBO.
Double-blind PBO-controlled parallel-group, prespecified subgroup analysis of UPLIFT® trial (Decramer et al., ref. 30)	Tiotropium 18 µg od versus PBO, 4 years	Yearly rates of decline in pre-bronchodilator FEV_1 and in post-bronchodilator FEV_1, other pulmonary function outcomes, SGRQ, time to first exacerbation, numbers of exacerbations	n = 2739 COPD GOLD stage II, 72% male, mean age 65 ± 9 years (tiotropium) 64 ± 9 years (PBO), BMI 27 ± 5 kg/m^2 (both groups), current smokers 31% (tiotropium), and 35% (PBO), pack-years 48 ± 28 (tiotropium) 47 ± 27 (PBO), pre-bronchodilator FEV_1 % pred 49 ± 8 (both groups) 1.36 ± 0.4 L (both groups), post-bronchodilator FEV_1 % pred 59 ± 6 (both groups) 1.63 ± 0.4 L (both groups), SGRQ total score 41 ± 17 units (tiotropium) and 42 ± 17 units (PBO)	For PBO, mean annual rate of decline of post-bronchodilator FEV_1 –49 ± 2 ml; pre-bronchodilator FEV_1 –37 ± 2 ml; pre-bronchodilator FVC –43 ± 4 ml; pre-bronchodilator SVC –43 ± 4 ml; post-bronchodilator FVC –58 ± 4 ml; post-bronchodilator SVC –60 ± 4 ml. Deterioration in SGRQ total score 0.99 ± 0.13 units per year. Exacerbations: 1 or more in 65%, mean number per patient per year 0.70 (95% CI, 0.65–0.75), median time to first 17.5 (95% CI, 15.9–19.7) months. Hospitalized exacerbations: 1 or more in 19%, mean number per patient per year 0.10 (95% CI, 0.08–0.12). Mortality 10%

(Continues)

Table 1. Continued.

Citation	Interventions, follow-up	Outcome measures	Patients and baseline characteristics	Main findings
Double-blind PBO-controlled, parallel-group (Pauwels et al., ref. 38)	Budesonide 400 µg bid versus PBO, 3 years	FEV_1	n = 1227 COPD, mean age 52.4 ± 7.7 years (PBO) and 52.5 ± 7.5 years (budesonide), 72.2% and 73.5% male, current smokers, pack-years 39.2 ± 20.1 and 39.4 ± 20.1, about 10% quit during study. Pre-bronchodilator FEV_1 % pred 76.9 ± 13.2 versus 76.8 ± 12.4, FEV_1 2.54 ± 0.64 L and 2.53 ± 0.64 L, FEV_1/SVC 61.7 ± 7.0, and 62.2 ± 6.8. Reversibility of FEV_1 2.8 ± 3.6 and 2.9 ± 3.8% pred	For PBO, median decline in post-bronchodilator FEV_1 –65 ml per year. Mortality n = 10
Double-blind PBO-controlled, parallel-group, post-hoc analysis of TORCH study (Jenkins et al., ref. 31)	Salmeterol 50 µg versus fluticasone propionate 500 µg versus SFC 50/500 µg versus PBO; 3 years	Pulmonary function, exacerbations, SGRQ	n = 6112 COPD: GOLD stage II (n = 2156, 72% male, 47% current smokers, mean age 64.9 ± 8.7 y, BMI 26.6 ± 5.2 kg/m^2, post-bronchodilator **FEV_1** % pred 58.8 ± 7.4, FEV_1 1616 ± 399 ml, reversibility FEV_1 4.3 ± 4.0% pred, SGRQ total score 45.4 ± 17.7 [for PBO group, 43.9], exacerbations requiring steroids/antibiotics in last year 0.9 ± 1.2, exacerbations requiring hospitalization in last year 0.2 ± 0.5), GOLD stage III (n = 3019), GOLD stage IV (n = 937)	For GOLD stage II PBO patients, 10.6% probability of pneumonia, adjusted mean FEV_1 over 3 years 1522 ml, adjusted rate of decline in FEV_1 –60 ml/y, change in SGRQ total score –1.3, annual rate of moderate/severe exacerbations 0.82. Mortality 11.4%
Double-blind, PBO-controlled, parallel-group (Rennard et al., ref. 39)	Infliximab 3 mg/kg versus infliximab 5 mg/kg versus PBO, 44 weeks	CRQ, pre-bronchodilator FEV_1, 6MWD, SF-36®, TDI, exacerbations	n = 234 COPD: GOLD stage I (n = 7), GOLD stage II (n = 98), GOLD stage III (n = 93), GOLD stage IV (n = 36). Baseline data not stratified for severity	GOLD stage I patients not analyzed. For GOLD stage II PBO patients, at Week 24, mean change from baseline in CRQ total score 12.1, 6MWD 2.4 meters; the SF-36® score, the TDI score, cough symptoms, and sputum production improved. Few 44-week data reported
PBO-controlled, parallel-group (Dal Negro et al., ref. 35)	Erdosteine 300 mg bid versus N-acetylcysteine 600 mg bid versus PBO, 10 days	FEV_1 reversibility to salbutamol	n = 30 COPD GOLD stage I or II, 67% male, mean BMI 24.6 ± 2.1 kg/m^2, mean pre-bronchodilator FEV_1 % pred 63.3 ± 8.4 (erdosteine) 58.8 ± 7 (N-acetylcysteine) 60.1 ± 7.8 (PBO); post-bronchodilator FEV_1 % pred 64.7 ± 8.8, 59.8 ± 9.8, 62.5 ± 7.4; FEV_1/FVC % 61.4 ± 6.2, 54.6 ± 11.1, 61.5 ± 8.5, FEV_1 % pred reversibility 1.38 ± 4.4, 1.02 ± 3.6, 2.38 ± 1.9, age 60.8 ± 12.1 years, 63.6 ± 11.3 years, 60.2 ± 13.4 years, current smokers, pack-years 25.4 ± 3.5, 26.3 ± 3.1, 28.1 ± 2.3. For PBO, FEV_1 0.061 ± 0.05 L	FEV_1 reversibility with PBO: 1.03 ± 2.35% at Day 4 (–1.35 versus baseline) and 1.5 ± 1.62% at Day 10 (–0.88 versus baseline). FEV_1 0.031 ± 0.05 L at Day 4 (–0.03 versus baseline) and 0.035 ± 0.04 L at Day 10 (–0.026 versus baseline)
Double-blind PBO-controlled crossover (O'Donnell et al., ref. 37)	Ipratropium bromide 500 µg versus PBO; 2 days each arm, 7 days between visits (1 month)	Pulmonary function, dyspnea, ventilatory parameters, exercise test	n = 16 COPD GOLD stage I, 63% male, mean age 63 ± 8 years, BMI 27.8 ± 4.6 kg/m^2, BDI focal score 8.3 ± 2, MRC dyspnea scale 1.8 ± 0.7, symptom-limited peak work rate 72% pred, post-bronchodilator FEV_1 % pred 90 (2.5 ± 0.58 L), FVC 108% pred (4.25 ± 1.08 L), FEV_1/FVC 84% (59 ± 7), RV (2.83 ± 0.48, 129% pred), TLC (7.11 ± 1.50, 113%) IC (3.01 ± 0.97, 103%), FRC (4.10 ± 0.91, 122%); smoking history 44 ± 16 pack-years, n = 4 current smokers	After PBO, change in FEV_1 +3%, FVC +1%, FEV_1/FVC +2%, TLC –1%, RV –6%, FRC –2%, IC +1%. At peak of exercise (80–85% W_{max}) exercise time was 8.2 ± 5.3 minutes, dyspnea BORG 7.8 ± 2.9, during constant-load exercise dyspnea BORG was 7.4 ± 2.4
Double-blind PBO-controlled, crossover (Kryger et al., ref. 33)	Ramelteon 8 mg versus PBO, single dose, 1 night each arm	Polysomnography, blood gases, respiratory effort	n = 25 COPD moderate or severe; n = 9 GOLD stage II, n = 16 GOLD stage III. Baseline data not stratified for severity	Only oxygen saturation data are stratified by severity
Double-blind, crossover (Kryger et al., ref. 36)	Ramelteon 16 mg versus PBO, 1 night each arm	FEV_1 and FEV_1/FVC at baseline	n = 26 COPD. Mean FEV_1 % pred of eligible patients (n = 14) 60.6. Mean baseline FEV_1/FVC of eligible patients (n = 14) 59.9%. Baseline characteristics not stratified by severity	Outcomes not stratified by spirographic severity
Non-pharmacologic intervention only, with suitable control arm				
Double-blind PBO-controlled, parallel-group (Soler et al., ref. 48)	OM-85 (bacterial extracts: test) versus PBO, for 30 days then 10-day course for Months 3, 4, 5; total 6 months	Exacerbation rate	n = 273 COPD GOLD stage I or 2, 28–33% smokers, with current exacerbation. Mean age 57.3 years (95% CI, 55.7 to 58.9) (test) and 57.9 years (56.2–59.6) (PBO), 54.9% and 43.5% male, BMI 26.3 (25.4–27.2) and 26.5 (25.7–27.3) kg/m^2. Mean exacerbations in last year 2.96 ± 1.69 and 3.32 ± 1.64. Mean FEV_1 % pred 85 (81.7–88.3) and 82.6 (79.9–86.1). Mean baseline FVC 91 (88.2–93.8)% and 89.7 (86.7–93.3)%.	0.86 exacerbations per PBO patient over 6 months.
Parallel-group (Clark et al., ref. 49)	Weight training versus control (usual activities, no weight training), 12 weeks	Isokinetic and isotonic muscle function, whole body endurance, maximal exercise capacity, and lung function	n = 43 COPD (58% male, mean age 49 ± 11 years, BMI 26 ± 4 kg/m^2, FEV_1 2.29 ± < 0.88 L (training) and 2.38 ± 0.86 L (control), FEV_1 % pred 76 < ± 23 and 79 ± 23, RV 2.22 ± < 0.91 L and 2.41 ± < 0.88 L, RV % pred 113 < ± 48 and 125 ± 41, BORG score peak exercise 3.5 ± 1.9 and 2.4 ± 1.7) versus n = 52 healthy controls	Exercise performance for control patients: $V02_{max}$ ml·min^{-1}·kg^{-1} 19.1 ± < 6.1 (baseline) 16.6 < ± 4.0 (end); HR_{max} beats·min^{-1} 133 < ± 21 versus 129 < ± 21; VE_{max} L·min^{-1} 44.8 < ± 16.7 versus 40.4 < ± 14.3; VT_{max} L 1.69 ± < 0.45 versus 1.55 ± < 0.47; resp rate breaths·min^{-1} 28 ± < 4 versus 28 ± < 4

(Continues)

Table 1. Continued.

Citation	Interventions, follow-up	Outcome measures	Patients and baseline characteristics	Main findings
Double-blind crossover (Fujimoto et al., ref. 52)	Compressed air versus O_2 during exercise test	6MWD, lung hemodynamics	n = 75 COPD: mild (n = 16, age 71 ± 2 years, baseline FEV_1 % pred 62.7 ± 2.9, FEV_1 1.39 ± 0.06 L, FEV_1/FVC% 47.0 ± 1.8, air trapping 0.23 ± 0.06 L, VC % pred 100.0 ± 3.0, RV % 211.3 ± 13.4, RV/TLC 54.2 ± 1.2, ex-smokers with > 30 pack-years), moderate (n = 25), severe (n = 34)	In mild patients, 6MWD 475 ± 20 meters (92.9 ± 5.0% pred) on air
Double-blind PBO-controlled, parallel-group (Haider et al., ref. 50)	Hypoxic breathing intervals versus PBO (normoxic breathing), 3 weeks	Blood gases, CV data, respiratory control	n = 18 COPD GOLD stage 0–II with mild symptoms (56% male, mean age 51.7 ± 2.4 y, mean FEV_1 % pred 78.2 ± 3.6 [training] 72.9 ± 1.9 [PBO], FEV_1 2.54 ± 0.2 L and 2.32 ± 0.18 L, FVC 3.53 ± 0.3 L and 3.50 ± 0.26 L, FEV_1/FVC 72.3 ± 1.9% and 66.2 ± 1.5%, n = 8 current smokers, n = 3 former smokers, BMI 26.4 ± 1.9 and 25.4 ± 0.9 kg/m_2) versus n = 14 healthy controls	Mild COPD patients showed CV autonomic abnormalities at baseline (higher heart rate, depressed baroreflex sensitivity)
Open label, crossover (Faager et al., ref. 51)	Pursed lips breathing versus not pursed lips breathing, follow-up time unknown	Lung function and exercise capacity	n = 32 COPD: GOLD stage I (n = 1 female, FEV_1 % pred 89, PEF 390 L/min, endurance shuttle walking test 1, age 76 years), GOLD stage II (n = 6 [1 male], mean baseline FEV_1 % pred 61 ± 9, PEF 305 ± 107 L/min, endurance shuttle walking test 4, age 69 ± 4 years), GOLD stage III (n = 11), GOLD stage IV (n = 14)	Outcomes not stratified by severity
Studies with baseline data only, no PBO outcome data				
Parallel-group (Spencer et al., ref. 47)	Weekly supervised exercise + home exercise versus control (unsupervised home exercise), follow-up 12 months	6MWD, SGRQ, lung function, shuttle walk tests (ISWT, ESWT), HAD Score, hospitalization, exacerbations	n = 48 COPD moderate GOLD stage II, 46% male, n = 11 current smokers (test group mean age 65 ± 8 y, BMI 25 ± 5 kg/m_2, FEV_1/FVC % 51 ± 11, FEV_1 % pred 57 ± 21, 6MWD 523 ± 107 meters; control group age 67 ± 7 y, BMI 27 ± 7 kg/m_2, FEV_1/FVC % 54 ± 11, FEV_1 % pred 60 ± 16, 6MWD 530 ± 86 meters)	No PBO or suitable control arm.
Parallel-group, Lung Health Study (Scanlon et al., ref. 29)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow-up	Smoking cessation rates, lung function	n = 3926 COPD, mean post-bronchodilator FEV_1 % pred (79.4 ± 9.1 [sustained quitters], 78.4 ± 9.2 [intermittent quitters], 78.1 ± 8.9 [continuing smokers]), FEV_1 (2.82 ± 0.64 L, 2.74 ± 0.64 L, 2.75 ± 0.61 L) FEV_1/FVC (63.1 ± 5.6, 62.9 ± 5.5, 63.0 ± 5.4). Wheezing in 74.4%, 76.8%, 76.9%, chronic cough in 39.7%, 40.6%, 44.3%, dyspnea in 39%, 41.3%, 44.1%. Age 49.1 ± 6.8 years, 48.6 ± 6.9 years, 48.3 ± 6.8 years, men 67.1%, 61.9%, 63.9%, pack-years 40.1 ± 18.8, 39.4 ± 18.2, 40.8 ± 19.0, BMI 26.0 ± 3.9, 25.9 ± 3.9, 25.4 ± 3.9 kg/m^2, bronchodilator response % 4.5 ± 4.9, 4.6 ± 4.8, 4.1 ± 5.1	No PBO or suitable control arm
Parallel-group, Lung Health Study (Harber et al., ref. 53)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow-up	Effect of air pollution on lung function, lung function	n = 5724 COPD, mean age 48.4 years (range 34–66 years) (men) and 48.5 years (35–67 years) (women), pack-years 42.8 ± 20.1 (men) and 36.2 ± 16.5 (women). Mean FEV_1% pred for men 75.2 ± 8.8 (pre-bronchodilator) 78.4 ± 9.2 (post-bronchodilator); for women 75.1 ± 8.8 (pre-bronchodilator) 78.2 ± 9 (post-bronchodilator). Mean FVC % pred for men 96.6 ± 10.6 (pre-bronchodilator) 97.6 ± 10.6 (post-bronchodilator); for women 97.3 ± 10.3 (pre-bronchodilator) 98.1 ± 10.4 (post-bronchodilator). Mean FEV_1/FVC for men 62.7 ± 5.7 (pre-bronchodilator) 64.6 ± 6.2 (post-bronchodilator); for women 63.3 ± 5.3 (pre-bronchodilator) 65.5 ± 5.9 (post-bronchodilator)	No PBO or suitable control arm
Parallel-group, Lung Health Study (Kanner et al., ref. 54)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow-up	Quit rate, lower respiratory illness, physician visits, change in FEV_1	n = 5887 COPD, mean age 48.5 ± 6.8 years (intervention) 48.4 ± 6.8 years (usual care), men 62% and 64%, pack-years 40.4 ± 19.2 and 40.5 ± 18.9, FEV_1 % pred 78.3 ± 9.1 and 78.2 ± 9.1, bronchodilator response 4.3 ± 5.1 and 4.2 ± 5.1%, doctor visits for lower respiratory illness 13 ± 33 and 11 ± 32 per year. Chronic bronchitis 35%	No PBO or suitable control arm
Parallel-group, Lung Health Study (Kanner et al., ref. 55)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow-up	Gender effects in airway hyper-responsiveness	n = 5662 COPD, mean age 48.4 ± 7 years (men) 48.5 ± 6.6 years (women), pack-years 42.7 ± 20 and 36.4 ± 16.8, FEV_1 % pred 74.9 ± 9.6 and 75.1 ± 8.8, FEV_1 2.94 ± 0.48 L and 2.08 ± 0.35 L, FEV_1/FVC % 62.7 ± 6.2 and 63.5 ± 5.7. Chronic cough in 42.9% and 40.4%, wheezing history in 78.3% and 74%, no shortness of breath in 63.4% men and 46.7% women	No PBO or suitable control arm

(Continues)

Table 1. Continued.

Citation	Interventions, follow-up	Outcome measures	Patients and baseline characteristics	Main findings
Parallel-group, Lung Health Study (Kanner et al., ref. 56)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow-up	Symptoms	n = 5887 COPD. 49–51% had cough ≥ 3 months per year: mean pre-bronchodilator FEV_1 % pred 74.3 ± 9 versus 76 ± 8.6 for asymptomatic ($p < 0.001$), FEV_1/FVC % 62.6 ± 5.7 versus 63.3 ± 5.3 ($p < 0.001$), age 48.2 ± 6.7 versus 48.7 ± 6.9 y, pack-years 42.2 ± 18.9 versus 38.5 ± 19.1, men 63.2% and 62.4%, BMI 25.6 ± 4 and 25.5 ± 3.9 kg/m^2. Baseline data also provided for phlegm, wheeze, and dyspnea (same patients, stratified by symptom presence/absence)	No PBO or suitable control arm
Parallel-group, Lung Health Study (Tashkin et al., ref. 57)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow-up	Relationship between baseline metacholine reactivity and change in lung function	n = 5733 COPD, mean age 48.4–48.6 years, men 61–64%. FEV_1 % pred 78.2 ± 9.1 (ipratropium), 78.4 ± 9.0 (PBO), 78.3 ± 9.1 (usual care). FEV_1/FVC % 64.9 ± 6.3, 65 ± 6, 65 ± 6. FEV_1 2.73 ± 0.64 L, 2.75 ± 0.62 L, 2.76 ± 0.62 L. Pack-years 40.3 ± 19.6, 40.2 ± 18.8, 40.5 ± 18.9. Bronchodilator response 4.2 ± 5.1, 4.4 ± 5.0, 4.3 ± 5.1%. LMCR for men (0.386 ± 0.365, 0.356 ± 0.355, 0.358 ± 0.360%/mg/ml and women (0.591 ± 0.392, 0.592 ± 0.387, 0.616 ± 0.365)	No PBO or suitable control arm
Open-label, parallel-group (DiLorenzo et al., ref. 41)	Theophylline SR bid versus salmeterol 50 µg bid, 12 months	Peak flow, symptoms, rescue medication, blood theophylline, lung function, assessment of efficacy, SF-36®	n = 178 COPD (ATS), symptomatic, mean age 56 ± 12.9 years, 69% male, n = 12 smokers, n = 81 ex-smokers. Mean baseline FEV_1 2.0 ± 0.6 L (salmeterol) 1.9 ± 0.5 L (theophylline). FVC 2.9 ± 0.9 L and 2.8 ± 0.7 L. PEFR morning 324.0 ± 99.7 L/min and 298.8 ± 88.7 L/min. PEFR evening 340.9 ± 104.7 L/min and 314.0 ± 89.2 L/min	No PBO or suitable control arm
Double-blind parallel-group (Rabe et al., ref. 42)	Tiotropium 18 µg od + formoterol 12 µg bid versus salmeterol 50 µg bid + fluticasone 500 µg bid, 6 weeks	Lung function	n = 399 GOLD stage II (mean FEV_1 1.48 L, FVC 2.86 L) and n = 193 GOLD stage III–IV. Baseline data not stratified	No PBO or suitable control arm
Open-label, crossover (Kanehara et al., ref. 43)	Theophylline 400 mg versus tulobuterol 2 mg, 8 weeks each arm	Pulmonary function, SGRQ	n = 26 COPD: GOLD stage I (n = 15) or GOLD II (n = 11), 77% male. Combined GOLD stage I and II baseline FEV_1 % pred 83.8 ± 16.3, FVC 2.37 ± 0.56 L, FEV_1 1.50 ± 0.39 L, FEV_1/FVC 63.2 ± 4.41%, age 77.3 ± 3.3 y, SGRQ total score 35.7 ± 17.9 (tulobuterol) to 34.0 ± 15.9 (theophylline). n = 8 were never-smokers, n = 4 current smokers (pack-years 23.7 ± 8.69), n = 14 former smokers (pack-years 47.9 ± 35.2)	No PBO or suitable control arm
Open-label, parallel-group (D'Elia et al., ref. 44)	Neltenexine versus carbocysteine, 12 days	Symptoms, lung function	n = 30 COPD (BTS or ERS criteria) with current exacerbation. Mean age 65.43 ± 15.19, 50% male, pack-years 28 ± 13.77, n = 2 were non-smokers, n = 15 current smokers, mean exacerbations 1.23 ± 0.5 per year, FEV_1 1.87 ± 0.54 L (neltenexine) to 1.9 ± 0.51 L (carbocysteine), VC 2.46 ± 0.69 L and 2.46 ± 0.52 L, PEF 3.74 ± 1.3 L and 3.95 ± 1.45 L. Symptoms (scale 0 = absent, 4 = very severe): cough 2.53 ± 0.64/2.47 ± 0.52, dyspnea 2.60 ± 1.06/2.07 ± 0.7. Sputum characteristics (1 = serous, 5 = purulent) 2.53 ± 1.25/1.80 ± 1.61	No PBO or suitable control arm
Open-label, parallel-group (Santra et al., ref. 45)	Doxofylline 400 mg bid versus SR theophylline 400 mg od, 4 weeks	Lung function, salbutamol use	n = 75 moderate COPD, 60% male, aged 40–70 years. For doxofylline group FEV_1 % pred 58.19 ± 5.13, PEFR 49.26 ± 5.32% pred, FEV_1/FVC 59.06 ± 4.95. For theophylline group FEV_1 % pred 57.9 ± 4.88, PEFR 49.76 ± 5.38% pred, FEV_1/FVC 61.7 ± 4.27. No smoking information	No PBO or suitable control arm
Double-blind, crossover (AkkocaYildiz et al., ref. 46)	Formoterol 12 µg bid versus ipratropium bromide 40 µg qid, 2 weeks each arm	Exercise capacity, lung function, functional parameters	n = 10 COPD GOLD stage I or II, 90% male, all heavy smokers, pack-years 47.75 ± 26.50, mean age 51.1 ± 5.45 years. Mean FEV_1 % 68.95 ± 10.64, FVC % 82.65 ± 10.85, FEV_1/FVC % 68.00 ± 6.60, $FEF_{25–75\%}$ 41.40 ± 11.25, TLC % 93.53 ± 12.72, FRC % 95.71 ± 19.45, RV % 121.12 ± 39.19, RV/TLC % 41.59 ± 9.10, IC 2.80 ± 0.62 L, DLCO % 77.89 ± 17.76, exercise time (min) 7.03 ± 0.73, work rate (Watt) 121.50 ± 15.52	No PBO or suitable control arm

6MWD: 6-min walk distance test; ATS: American Thoracic Society; BDI: baseline dyspnea index; bid: twice daily; BMI: body mass index; BTS: British Thoracic Society; CI: confidence interval; COOP/WONCA: Dartmouth COOP Functional Health Assessment Charts/World Organization of General Practice/Family Physicians; COPD: chronic obstructive pulmonary disease; CRQ: Chronic Respiratory Questionnaire; CV: cardiovascular; DIMCA: Detection, Intervention, and Monitoring Program of COPD and Asthma; DLCO: diffusing capacity of the lung for carbon monoxide; ERS: European Respiratory Society; ESWT: endurance shuttle walk test; EUROSCOP: European Respiratory Society Study on Chronic Obstructive Pulmonary Disease; FEF: forced expiratory flow; FEV_1: forced expiratory volume in 1 sec; FRC: functional residual capacity; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HAD: hospital anxiety and depression; HR_{max}: maximum heart rate; IC: inspiratory capacity; ISWT: incremental shuttle walking test; IVC: inferior vena cava; LMCR: light meal combat ration; od: once daily; MRC: Medical Research Council; PBO: placebo; PEF: peak expiratory flow; PEFR: peak expiratory flow rate; PIF: peak inspiratory flow; RV: right ventricle; SF-36®: Short Form (36) Health Survey; SFC: salmeterol/fluticasone propionate combination; SGRQ: St George's Respiratory Questionnaire; SR: sustained release; SVC: slow vital capacity; TDI: transition dyspnea index; TLC: total lung capacity; TORCH: Towards a Revolution in COPD Health; UPLIFT®: Understanding Potential Long-term Impacts on Function with Tiotropium; VC: vital capacity; VE_{max}: maximal ventilatory reserve; $V02_{max}$: maximum oxygen consumption; $V02_{max}$: maximum oxygen consumption; VT_{max}: maximum tidal volume; W_{max}: maximum workload.

Table 2. COPD disease progression: summary of available outcomes data (baseline and over study period) in mild and moderate COPD patients in control groups.

Outcome	Mild COPD (GOLD stage I)	Moderate COPD (GOLD stage II)
Lung function: rate of decline in FEV_1	• –14 ml/year (32)	• –49 to –60 ml/year (30, 31)
Rate of exacerbations	• Severe exacerbations: 0.07/year (34)	• Moderate or severe exacerbations: 0.70 to 0.82/year (29, 30) • Severe exacerbations: 0.10/year (30)
Symptoms (dyspnea)	• Baseline BDI = 8.3; baseline MRC score = 1.8 (chronic exercise-related dyspnea) (37) • 57 symptom episodes in 17/24 (71%) patients over 2 years (32)	• Dyspnea present in ~40% patients at baseline (29, 59)
SGRQ total score (QoL)	• 36 units at baseline (61)	• 39–42 units at baseline (30, 31, 47) • Change over time: 1.3 unit improvement (3 y) (31) to worsening of 0.99 units (4 years) (30)
Exercise capacity	• Baseline exercise capacity 72–75% of pred (37, 61) • Power output > 20% lower than normal individuals (62) • Muscle strength reduced (49)	• Baseline (after PR) 6MWD 523–530 meters (47)
Functional status	• Baseline COOP/WONCA score range: 1.2 for social activities (not impaired) to 2.4 for general health (slightly impaired) (32)	NR
Mortality	NR	• Rates of 1.6 to 11.4% over 3–4 years (30, 31, 38)

COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 sec; SGRQ: St George's Respiratory Questionnaire; QoL: quality of life; COOP/WONCA: Dartmouth COOP Functional Health Assessment Charts/World Organization of General Practice/Family Physicians; PR: pulmonary rehabilitation; 6MWD: 6-minute walk distance test; NR: not reported.

year versus 34 ml/year; $p < 0.01$) (5). The corresponding comparison between asymptomatic GOLD stage I patients (n = 295) and the asymptomatic control individuals was numerically (37 versus 34 ml/year) but not significantly different ($p = 0.08$).

Rate of exacerbations

In total, 5 RCTs of ≥6 months' duration reported the rate of exacerbations over their trial periods (30–32, 34, 48). In a trial reported by Solèr *et al.*, an annual rate of 1.72 exacerbations (0.86 over the 6-month trial period) was experienced by 131 GOLD stage I/II patients (mean FEV_1 82.6% predicted) receiving placebo (48). However, it is important to note that patients had to have a current exacerbation in order to enter the trial.

Among 24 patients with mild COPD (mean FEV_1 98% predicted) receiving placebo in the 2-year DIMCA trial, 4 exacerbations (including mild) were reported among 3 patients (rates not reported) (32). An annual severe exacerbation rate of 0.07 (based on oral steroid use) was reported for the placebo group in the 3-year European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP) trial (mean FEV_1 76.9% predicted) (34).

In the subgroup analysis of patients with moderate COPD (GOLD stage II, mean post-bronchodilator FEV_1 59% predicted) in the UPLIFT® trial, mean annual exacerbation rates of 0.70 (moderate or severe) and 0.10 (severe) were reported in the control group (n = 1355) (30). In the TORCH study, the annual rate of moderate/severe exacerbations was 0.82 in patients with GOLD stage II COPD (mean post-bronchodilator FEV_1 59% predicted) receiving placebo (n = 535) (31).

Respiratory symptoms

Overall, 5 studies have assessed aggravated respiratory symptoms, such as dyspnea, wheezing, and chronic cough in patients with mild-to-moderate COPD (29, 32, 37, 54, 59). O'Donnell et al. described a small study of 16 patients with GOLD stage I COPD (mean post-bronchodilator FEV_1 90% predicted), in which chronic activity-related dyspnea scores, measured on the Medical Research Council scale and the baseline dyspnea index, were 1.8 and 8.3, respectively (37), indicating long-term activity-related dyspnea.

Among the 24 patients with mild COPD (mean FEV_1 98% predicted) receiving placebo in the 2-year DIMCA trial, the mean symptom score at baseline was 1.3 (0 = no complaints to 3 = occurs every day) and there were 57 episodes of increased respiratory symptoms among 17 patients (32).

In the 5-year Lung Health Study in 3926 smokers with moderate COPD (mean FEV_1 78.1% to 79.4% predicted), respiratory symptoms were common at baseline, with wheezing in 74.4% to 76.9%, chronic cough in 39.7% to 44.3%, and dyspnea in 39% to 44.1% of patients (29).

The 3-year EUROSCOP trial in 642 patients (median post-bronchodilator FEV_1 79.2% predicted [men] and 81.5% predicted [women]) reported symptoms at baseline in most patients, especially wheezing (54.1% men; 60.5% women), dyspnea after activity (34.6% men; 39.9% women), and cough in winter (48.7% men; 58.4% women) (58).

Quality of life

Overall, 4 RCTs assessed QoL using the St George's Respiratory Questionnaire (SGRQ) at baseline or during

Table 3. Articles meeting the inclusion criteria for the systematic review and which reported outcomes with intervention (the effect of treatment on mild-to-moderate COPD).

Citation	Interventions, follow up	Outcome measures	Patients and baseline characteristics	Main findings
Pharmacologic intervention only—PBO-controlled				
Double-blind, PBO-controlled, parallel-group (DIMCA study) (van Grunsven 2003) (32)	Fluticasone propionate 250 µg bid versus PBO, 2 years	Pulmonary function, symptoms, functional status (COOP/WONCA), exacerbations	n = 48 early COPD, 3 months' symptoms, previous FEV_1 decline 109 ± 46 ml/year (fluticasone) 124 ± 66 ml/year (PBO). Mean age 46 ± 10 years and 47 ± 11 years, 50% and 54% male, current smokers 50% and 33%, pack-years 11.9 ± 9.5 and 5.8 ± 8.4. Mean baseline post-BD FEV_1 % pred 98 ± 15 and 99 ± 18 FEV_1 3.16 ± 0.68 L and 3.19 ± 0.79 L; pre-BD FEV_1 % pred 95 ± 18 and 98 ± 17; FEV_1 3.05 ± 0.7 L and 3.17 ± 0.76 L; pre-BD FEV_1/FVC 75 ± 10% and 77 ± 6%; FEV_1 reversibility % pred 4.0 ± 5.1 and 3.0 ± 4.0; symptom score 1.7 ± 1.5 and 1.3 ± 1.3. COOP/WONCA scores varied from not impaired (1.2 ± 0.6 for social activities) to slightly impaired (2.4 ± 1.2 for general health)	Over 2-year study, annual rate of post-BD FEV_1 decline –93 ± 30 ml (fluticasone, n = 24) versus –14 ± 17 (PBO, n = 24; p = 0.001); for pre-BD FEV_1 decline, –85 ± 32 mL (fluticasone) versus –38 ± 19 ml (PBO, p = 0.078). At 2 years, difference between groups was 47 ± 63 ml for post-bronchodilator FEV_1 (favoring PBO, p = 0.458) and 60 ± 70 ml for pre-bronchodilator (favoring fluticasone, p = 0.394). No difference between groups in PC_{20} at any time point. Exacerbations: 6 in 5 fluticasone patients versus 4 in 3 PBO patients. No difference between groups for COOP/WONCA scores. 57 episodes of increased respiratory symptoms in 17 patients (PBO) versus 127 episodes in 18 patients (fluticasone)
Double-blind PBO-controlled parallel-group (DIMCA 3a study) (van Grunsven 2000) (40)	Fluticasone propionate 250 µg versus PBO, 2 years	Compliance, patient opinion	n = 48 COPD. Mean FEV_1 % pred 96 ± 17, FEV_1 reversibility 3 ± 5% pred, age 47 years (range 29–71 years), 42% smokers, mean pack-years 9 (0–29), 52% male, number of symptoms in past 3 months 1.5 ± 1.4	Only outcomes are compliance
Double-blind PBO-controlled, parallel-group, post-hoc analysis of EUROSCOP study (Lofdahl 2007) (34)	Budesonide 800 µg/day versus PBO, 3 years	Ischemic events, and baseline predictors	n = 1277 COPD, current smokers, pack-years median 36 (range 0–171), 73% male, mean age 52.5 years (range 25–66 y), BMI 24.8 (15–44) kg/m_2 FEV_1 2.5 (1.0–4.7) L, FEV_1 % pred76.9 (42–103), IVC 4.1 (1.9–7.8) L	Estimated annual severe exacerbation rate (oral steroids) reduced by 37% for budesonide (n = 593) versus PBO (n = 582) (0.05 versus 0.07; p = 0.002); yearly exacerbation rate ratio of 0.63 (95% CI, 0.47–0.85). Ischemic events significantly lower for budesonide (3%) versus PBO (5.3%; p = 0.048)
Double-blind, PBO-controlled, parallel-group, pre-specified subgroup analysis of UPLIFT® trial (Decramer et al., ref. 30)	Tiotropium 18 µg od versus PBO, 4 years	Yearly rates of decline in pre-bronchodilator FEV_1 and in post-bronchodilator FEV_1, other pulmonary function outcomes, SGRQ, time to first exacerbation, numbers of exacerbations	n = 2739 COPD GOLD stage II, 72% male, mean age 65 ± 9 years (tiotropium) 64 ± 9 years (PBO), BMI 27 ± 5 kg/m_2 (both groups), current smokers 31% (tiotropium), and 35% (PBO), pack-years 48 ± 28 (tiotropium) 47 ± 27 (PBO), pre-BD FEV_1 % pred 49 ± 8 (both groups) 1.36 ± 0.4 L (both groups), post-BD FEV_1 % pred 59 ± 6 (both groups) 1.63 ± 0.4 L (both groups), SGRQ total score 41 ± 17 units (tiotropium) and 42 ± 17 units (PBO)	Lower rate of decline of post-bronchodilator FEV_1 for tiotropium (n = 1384) versus PBO (n = 1355) (43 ± 2 ml/year versus 49 ± 2 ml/year; p = 0.024); no difference for FVC and SVC and no difference for pre-bronchodilator values. Mean values of pre-bronchodilator and post-bronchodilator FEV_1 were higher in the tiotropium group than in the control group at all time points during the trial ($p < 0.0001$ for all time points—between-group differences 101–119 ml and 52–82 ml, respectively). Mean pre-bronchodilator FVC was 164–194 ml higher and mean pre-bronchodilator SVC was 44–175 ml higher in the tiotropium group ($p < 0.001$ at all time points). Differences for post-bronchodilator FVC and SVC were 42–68 ml ($p < 0.01$ at all time points) and 15–35 ml ($p > 0.05$ at all time points), respectively. SGRQ total score deteriorated in both groups (tiotropium 0.89 units/year [SE 0.13]; control 0.99 units/year [SE 0.13]; p = 0.58), but better at all time points for tiotropium versus PBO ($p \leq 0.006$ for all time points). Differences in SGRQ scores between groups ranged from 2.7–4.0 units (total score) and 2.3–3.9 units (impact), 2.7–4.1 units (symptom) and 3.1–4.4 units (activity). One or more exacerbations in 60% tiotropium and 65% PBO patients; mean number per patient per year significantly less for tiotropium (HR 0.80; 95% CI, 0.72–0.88; $p < 0.0001$). One or more hospitalized exacerbations in 15% tiotropium and 19% PBO patients. Time to first exacerbation (HR 0.82; 95% CI; 0.75–0.90; $p < 0.0001$) and time to hospitalized exacerbation (0.74; 95% CI, 0.62–0.88; p = 0.001) longer for tiotropium versus PBO. Risks of mortality during trial from lower respiratory tract conditions and all causes lower for tiotropium versus PBO; but no significant effect on mortality

(Continues)

Table 3. Continued.

Citation	Interventions, follow up	Outcome measures	Patients and baseline characteristics	Main findings
Double-blind PBO-controlled, parallel-group (Pauwels et al., ref. 38)	Budesonide 400 µg bid versus PBO, 3 years	FEV_1	n = 1227 COPD, mean age 52.4 ± 7.7 (PBO) and 52.5 ± 7.5 years (budesonide), 72.2% and 73.5% male, current smokers, pack-years 39.2 ± 20.1 and 39.4 ± 20.1, about 10% quit during study. Pre-bronchodilator FEV_1 % pred 76.9 ± 13.2 versus 76.8 ± 12.4, FEV_1 2.54 ± 0.64 L and 2.53 ± 0.64 L, FEV_1/SVC 61.7 ± 7.0 and 62.2 ± 6.8. Reversibility of FEV_1 2.8 ± 3.6 and 2.9 ± 3.8% pred	Median decline in post-bronchodilator FEV_1 over 3-year period 140 ml (budesonide, n = 634) versus 180 ml (PBO, n = 643; p = 0.05), or 4.3% and 5.3% pred value, respectively. FEV_1 improved with treatment over first 6 months, then declined at similar rate to PBO from 9 months to end of treatment. Similar mortality both groups
Double-blind PBO-controlled, parallel-group, *post-hoc* analysis of TORCH study (Jenkins et al., ref. 31)	Salmeterol 50 µg versus fluticasone propionate 500 µg versus SFC 50/500 µg versus PBO; 3 years	Pulmonary function, exacerbations, SGRQ	n = 6112 COPD: GOLD stage II (n = 2156, 72% male, 47% current smokers, mean age 64.9 ± 8.7 years, BMI 26.6 ± 5.2 kg/m2, post-BD FEV_1 % pred 58.8 ± 7.4, FEV_1 1,616 ± 399 ml, reversibility FEV_1 4.3 ± 4.0% pred, SGRQ total score 45.4 ± 17.7, exacerbations requiring steroids/ antibiotics in last year 0.9 ± 1.2, exacerbations requiring hospitalization in last year 0.2 ± 0.5), GOLD stage III (n = 3019), GOLD stage IV (n = 937)	For GOLD stage II patients, SFC (n = 562) versus PBO (n = 535) resulted in improvements in FEV_1 (101 ml; 95% CI, 71–132), reduction in rate of decline in FEV_1 by 16 ml/year (95% CI, 0–32), 31% (19–40) reduction in annual rate of moderate/ severe exacerbations (mean 0.57/year for SFC versus 0.82/year for PBO) and reduced mortality (by 33% [HR 0.67; 95% CI, 0.45–0.98; absolute risk reduction 3.6%]. Difference in adjusted mean change in SGRQ for SFC versus PBO was –2.3 (–4.0 to –0.7)
Double-blind, PBO-controlled, parallel-group (Rennard et al., ref. 39)	Infliximab 3 mg/kg versus infliximab 5 mg/kg versus PBO, 44 weeks	CRQ, pre-BD FEV_1, 6MWD, SF-36®, TDI, exacerbations	n = 234 COPD: GOLD stage I (n = 7), GOLD stage II (n = 98), GOLD stage III (n = 93), GOLD stage IV (n = 36). Baseline data not stratified for severity	GOLD stage I patients not analyzed. For GOLD stage II patients, no effect of infliximab (versus PBO) on any outcome. At Week 24, for GOLD stage II, mean change from baseline in CRQ total score 12.1 for PBO versus 10.8 for infliximab (p = 0.74), 6MWD 2.4 meters for PBO versus 17.6 for infliximab (p = 0.39); the SF-36® score, the TDI score, cough symptoms, and sputum production improved, with no significant differences between groups. Few 44-week data reported; no difference between groups in CRQ.
PBO-controlled, parallel-group (Dal Negro et al., ref. 35)	Erdosteine 300 mg bid versus N-acetylcysteine 600 mg bid versus PBO, 10 days	FEV_1 reversibility to salbutamol	n = 30 COPD GOLD stage I or II, 67% male, mean BMI 24.6 ± 2.1 kg/m2, mean pre-bronchodilator FEV_1 % pred 63.3 ± 8.4 (erdosteine) 58.8 ± 7 (N-acetylcysteine) 60.1 ± 7.8 (PBO); post-BD FEV_1 % pred 64.7 ± 8.8, 59.8 ± 9.8, 62.5 ± 7.4; FEV_1/FVC % 61.4 ± 6.2, 54.6 ± 11.1, 61.5 ± 8.5, FEV_1 % pred reversibility 1.38 ± 4.4, 1.02 ± 3.6, 2.38 ± 1.9, age 60.8 ± 12.1 years, 63.6 ± 11.3 years, 60.2 ± 13.4 years, current smokers, pack-years 25.4 ± 3.5, 26.3 ± 3.1, 28.1 ± 2.3. For PBO, FEV_1 0.061 ± 0.05 L	FEV_1 response to salbutamol significantly enhanced after erdosteine (6.45 ± 4.3% at Day 4 [p = 0.0038 versus PBO] and 6.42 ± 4.2% Day 10 [p = 0.0047]; absolute changes of +0.1461 [95% CI, –0.002–0.294], and +0.1411 [95% CI, 0.065–0.217], respectively); no change with PBO or N-acetylcysteine. Slight increase in FVC with erdosteine (–0.002 L at baseline to 0.147 L at Day 10) only
Double-blind PBO-controlled crossover (O'Donnell et al., ref. 37)	Ipratropium bromide 500 µg versus PBO; 2 days each arm, 7 days between visits (total 1 month)	Pulmonary function, dyspnea, ventilatory parameters, exercise test	n = 16 COPD GOLD stage I, 63% male, mean age 63 ± 8 y, BMI 27.8 ± 4.6 kg/ m_2, BDI focal score 8.3 ± 2, MRC dyspnea scale 1.8 ± 0.7, symptom-limited peak work rate 72% pred, post-BD FEV_1 % pred 90 (2.5 ± 0.58 L), FVC 108% pred (4.25 ± 1.08 L), FEV_1/ FVC 84% (59 ± 7), RV (2.83 ± 0.48, 129% pred), TLC (7.11 ± 1.50, 113%) IC (3.01 ± 0.97, 103%), FRC (4.10 ± 0.91, 122%); smoking history 44 ± 16 pack-years, n = 4 current smokers	Ipratropium increased FEV_1 by 5 ± 9% pred, decreased RV 12 ± 20% pred and specific airway resistance 81 ± 93% pred (all p < 0.05). During exercise, dynamic IC and VT significantly increased (p < 0.05), dyspnea decreased (p = 0.07) and dyspnea/ventilation ratios decreased (p < 0.05). At peak of exercise (80–85% W_{max}) exercise time was 8.2 ± 4.8 min, dyspnea BORG 7.7 ± 2.5; at constant-load exercise dyspnea BORG was 6.6 ± 2.4 (p < 0.07 versus PBO)
Double-blind, crossover (Kryger et al., ref. 36)	Ramelteon 16 mg versus PBO, 1 night each arm	FEV_1 and FEV_1/FVC at baseline	n = 26 COPD. Mean FEV_1 % pred of eligible patients (n = 14) 60.6. Mean baseline FEV_1/FVC of eligible patients (n = 14) 59.9%. Baseline characteristics not stratified by severity	Outcomes not stratified by spirographic severity
Double-blind PBO-controlled crossover (Kryger et al., ref. 33)	Ramelteon 8 mg versus PBO, single dose, 1 night each arm	Polysomnography, blood gases, respiratory effort	n = 25 COPD moderate or severe; n = 9 GOLD stage II, n = 16 GOLD stage III. Baseline data not stratified for severity	Only oxygen saturation data are stratified by severity

(Continues)

Table 3. Continued.

Citation	Interventions, follow up	Outcome measures	Patients and baseline characteristics	Main findings
Pharmacologic intervention only—non-PBO controlled				
Open-label, parallel-group (DiLorenzo et al., ref. 41)	Theophylline SR bid versus salmeterol 50 µg bid, 12 months	Peak flow, symptoms, rescue medication, blood theophylline, lung function, assessment of efficacy, SF-36®	n = 178 COPD (ATS), symptomatic, mean age 56 ± 12.9 y, 69% male, n = 12 smokers, n = 81 ex-smokers. Mean baseline FEV_1 2.0 ± 0.6 L (salmeterol) 1.9 ± 0.5 L (theophylline). FVC 2.9 ± 0.9 L and 2.8 ± 0.7 L. PEFR morning 324.0 ± 99.7 L/min and 298.8 ± 88.7 L/min. PEFR evening 340.9 ± 104.7 L/min and 314.0 ± 89.2 L/min	At 3 months, salmeterol (n = 91) improved PEFR morning significantly more than theophylline (n = 87) (difference between groups 16.56 L/min, p = 0.02), and increased number of symptom-free nights (from baseline 23.4–67.2% for salmeterol, 18.4–49.3% for theophylline; p < 0.01) and days (14.6–59.7% for salmeterol, 13.7–46.1% for theophylline; p < 0.01) and amount of rescue medication (p < 0.001). FEV_1 and FVC improved in both groups (significant difference in max FEV_1 at 1, 2, and 3 months); improvements in FEV_1 with salmeterol persisted over 12 months, while those with theophylline were not maintained at 9 and 12 months. Significantly higher mean FVC for salmeterol versus theophylline at 2 months (p = 0.03), and higher mean increases over baseline for salmeterol: 0.24 L (1 month), 0.26 L (2 months) and 0.29 L (3 months), compared with theophylline (0.13 L, 0.12 L, 0.16 L). Salmeterol improved 3 SF-36® domains more than theophylline (physical functioning at 3 months [adjusted mean changes 10.34 versus 3.79, p = 0.02], change in health perception at 9 months [24.25 versus 14.41, p = 0.03] and social functioning at 12 months [15.13 versus 6.84, p = 0.04])
Double-blind, parallel-group (Rabe et al., ref. 42)	Tiotropium 18 mg qd + formoterol 12 µg bid versus salmeterol 50 µg bid + fluticasone 500 µg bid, 6 wks	Lung function	n = 399 GOLD stage II (mean FEV_1 1.48 L, FVC 2.86 L) and n = 193 GOLD stage III/IV. Baseline data not stratified	For GOLD stage II patients, significant benefit for tiotropium/formoterol versus SFC at 6 weeks (FEV_1 AUC0–12 [1.84 ± 0.02 versus 1.77 ± 0.02 L], peak FEV_1 [1.98 ± 0.02 versus 1.89 ± 0.03 L], FVC AUC0–12 [3.33 ± 0.03 versus 3.18 ± 0.04 L], peak FVC [3.55 ± 0.04 versus 3.38 ± 0.04]; all p < 0.05. No difference between treatments for pre-dose FEV_1 or FVC). Other data not stratified by severity
Open-label, crossover (Kanehara et al., ref. 43)	Theophylline 400 mg versus tulobuterol 2 mg, 8 weeks each arm	Pulmonary function, SGRQ	n = 26 COPD: GOLD stage I (n = 15) or GOLD stage II (n = 11), 77% male. Combined GOLD stage I/II baseline FEV_1 % pred 83.8 ± 16.3, FVC 2.37 ± 0.56 L, FEV_1 1.50 ± 0.39 L, FEV_1/FVC 63.2 ± 4.41%, age 77.3 ± 3.3 y, SGRQ total score 35.7 ± 17.9 (tulobuterol) to 34.0 ± 15.9 (theophylline). n = 8 were never-smokers, n = 4 current smokers (pack-years 23.7 ± 8.69), n = 14 former smokers (pack-years 47.9 ± 35.2)	For GOLD stage I/II patients (not stratified), no significant change from baseline in SGRQ total for either treatment (activity domain worsened p < 0.05 versus baseline in both treatment groups, other domains no change). Theophylline increased pulmonary function significantly versus baseline: FEV_1 % pred 80.49 ± 14.3 to 86.0 ± 11.6 (p < 0.05); FVC 2.30 ± 0.5 to 2.4 ± 0.47 L (p < 0.05); FEV_1 1.46 ± 0.34 to 1.56 ± 0.32 L (p < 0.05); PEF 3.93 ± 1.57 to 4.56 ± 1.64 L/sec (p < 0.05); MEF50 1.22 ± 0.44 to 1.36 ± 0.44 L/s (p < 0.05); MEF25 0.39 ± 0.14 to 0.43 ± 0.14 L/s (p < 0.05). Tulobuterol no effect
Open-label, parallel-group (D'Elia and Sechi, ref. 44)	Neltenexine versus carbocysteine, 12 days	Symptoms, lung function	n = 30 COPD (BTS or ERS) with current exacerbation. Mean age 65.43 ± 15.19, 50% male, pack-yrs 28 ± 13.77, n = 2 were nonsmokers, n = 15 current smokers, mean exacerbations 1.23 ± 0.5 per year, FEV_1 1.87 ± 0.54 L (neltenexine) to 1.9 ± 0.51 L (carbocysteine), VC 2.46 ± 0.69 L and 2.46 ± 0.52 L, PEF 3.74 ± 1.3 L and 3.95 ± 1.45 L. Symptoms (scale 0 = absent, 4 = very severe): cough 2.53 ± 0.64 and 2.47 ± 0.52, dyspnea 2.60 ± 1.06 and 2.07 ± 0.7. Sputum characteristics (1 = serous, 5 = purulent) 2.53 ± 1.25 and 1.80 ± 1.61	Neltenexine improved cough (0.40 ± 0.63 neltenexine, 1.13 ± 0.52 carbocysteine) and sputum characteristics (1.40 ± 0.51 and 2.13 ± 0.64) significantly better (p < 0.05 for both) at Day 12 than did carbocysteine; and significantly faster improvement in expectoration, cough and sputum characteristics. Neither drug had any effect on change from baseline in FEV_1, PEF, or VC
Open-label, parallel-group (Santra, ref. 45)	Doxofylline 400 mg bid versus theophylline 400 mg od, 4 weeks	Lung function, salbutamol use	n = 75 moderate COPD, 60% male, aged 40–70 years. For doxofylline group FEV_1 % pred 58.19 ± 5.13, PEFR 49.26 ± 5.32% pred, FEV_1/FVC 59.06 ± 4.95. For theophylline group FEV_1 % pred 57.9 ± 4.88, PEFR 49.76 ± 5.38% pred, FEV_1/FVC 61.7 ± 4.27. No smoking information	Compared with baseline, both drugs resulted in significant increase in FEV_1, FEV 125–75, and PEFR, but not FEV_1/FVC. At Day 28 for doxofylline FEV_1 % pred 63.36 ± 4.77, PEFR 57.20 ± 6.22% pred, FEV_1/FVC 61.46 ± 4.94; for theophylline FEV_1 % pred 61.8 ± 4.84, PEFR 56.33 ± 5.20% pred, FEV_1/FVC 64.03 ± 4.20 (no difference between groups). Both drugs significantly reduced salbutamol use.

(Continues)

Table 3. Continued.

Citation	Interventions, follow up	Outcome measures	Patients and baseline characteristics	Main findings
Double-blind, crossover (AkkocaYildiz et al., ref. 46)	Formoterol 12 µg bid versus ipratropium bromide 40 µg qid, 2 weeks each arm	Exercise capacity, lung function, functional parameters	n = 10 COPD GOLD stage I or II, 90% male, all heavy smokers, pack-years 47.75 ± 26.50, mean age 51.1 ± 5.45 years. Mean FEV_1 % 68.95 ± 10.64, FVC % 82.65 ± 10.85, FEV_1/FVC % 68.00 ± 6.60, FEF25–75% 41.40 ± 11.25, TLC % 93.53 ± 12.72, FRC % 95.71 ± 19.45, RV % 121.12 ± 39.19, RV/TLC % 41.59 ± 9.10, IC 2.80 ± 0.62 L, DLCO % 77.89 ± 17.76%, exercise time (min) 7.03 ± 0.73, work rate (Watt) 121.50 ± 15.52	Formoterol significantly improved FEV_1 % (76.60 ± 9.05, $p < 0.05$) and FEV_1/FVC % (71.50 ± 6.24 $p < 0.05$) at 90 min post-dose, and FEV_1/FVC % (71.20 ± 6.19 $p < 0.05$) at Day 14. Ipratropium significantly improved FEV_1 % (75.00 ± 8.98 $p < 0.05$) and FEF25–75 (48.20 ± 16.92 $p < 0.05$) at 90 min post-dose and peak oxygen uptake and minute ventilation at 90 min. Both treatments increased exercise time (8.10 ± 1.17 [formoterol] 8.00 ± 0.94 [ipratropium] both $p < 0.05$ versus baseline at Day 14). No difference between treatments on exercise capacity and functional parameters. Improvement in exercise capacity also correlated with increase in FEV_1
Nonpharmacologic intervention only				
Parallel-group (Spencer et al., ref. 47)	Weekly supervised exercise + home exercise versus control (unsupervised home exercise), follow-up 12 months	6MWD, SGRQ, lung function, shuttle walk tests (ISWT, ESWT), HAD Score, hospitalization, exacerbations	n = 48 COPD moderate GOLD stage II, 46% male, n = 11 current smokers (test group mean age 65 ± 8 y, BMI 25 ± 5 kg/m2, FEV_1/FVC % 51 ± 11, FEV_1 % pred 57 ± 21, 6MWD 523 ± 107 meters; control group age 67 ± 7 y, BMI 27 ± 7 kg/m2, FEV_1/FVC % 54 ± 11, FEV_1 % pred 60 ± 16, 6MWD 530 ± 86 meters)	At 12 months, mean difference (n = 24/group) showed no significant change from baseline in 6MWD (test –11 meters, 95% CI, –21 to 10 meters; control –6 meters, 95% CI, –34 to 11 meters) or total SGRQ score (test 3, 95% CI, –0.8 to 7; control –3; 95% CI, –7 to 3). At 12 months, no significant change from baseline, nor difference between groups, for lung function, ISWT, ESWT, HAD Score, hospital admissions, or length of hospital stay in either group. No difference in number of exacerbations between groups: exacerbation rate 2.3 ± 3 (test) 1.4 ± 1.8 (control) in 12 months. Prior to the study, 8-wk pulmonary rehabilitation significantly improved 6MWD and SGRQ
Double-blind, PBO-controlled, parallel-group (Soler et al., ref. 48)	OM-85 (bacterial extracts: test) versus PBO, for 30 days then 10-day course for Months 3, 4, 5; total 6 months	Exacerbation rate	n = 273 COPD GOLD stage I or II, 28–33% smokers, with current exacerbation. Mean age 57.3 (95% CI, 55.7–58.9) years (test) and 57.9 years (56.2–59.6) (PBO), 54.9% and 43.5% male, BMI 26.3 (25.4–27.2), and 26.5 (25.7–27.3) kg/m2. Mean exacerbations in last year 2.96 ± 1.69 and 3.32 ± 1.64. Mean FEV_1 % pred 85 (81.7–88.3) and 82.6 (79.9–86.1). Mean baseline FVC % 91 (88.2–93.8) and 89.7 (86.7–93.3)	29% fewer exacerbations over 6 months for test (n = 142) (0.61 per patient) versus PBO (n = 131) (0.86, p = 0.03)
Parallel-group (Clark et al., ref. 49)	Weight training versus control (usual activities, no weight training), 12 weeks	Isokinetic and isotonic muscle function, whole body endurance, maximal exercise capacity and lung function	n = 43 COPD (58% male, mean age 49 ± 11 years, BMI 26 ± 4 kg/m2, FEV_1 2.29 ± < 0.88 L (training) and 2.38 ± < 0.86 L (control), FEV_1 % pred 76 < ± 23 and 79 < ± 23, RV 2.22 ± < 0.91 L and 2.41 ± < 0.88 L, RV % pred 113 < ± 48 and 125 < ± 41, BORG score peak exercise 3.5 < ± 1.9 and 2.4 < ± 1.7) versus n = 52 healthy controls	At baseline, COPD patients had reduced isokinetic muscle function (with the exception of sustained upper limb strength) versus healthy controls. Muscle function and whole body endurance during treadmill walking improved after 12 weeks' training. Mean improvement on treadmill (joules) was 344 (95% CI, 109–579) for control and 4205 (95% CI, 1404–5650) for training ($p < 0.001$). No effect on lung function
Double-blind PBO-controlled, parallel-group (Haider et al., ref. 50)	Hypoxic breathing intervals versus PBO (normoxic breathing), 3 weeks	Blood gases, CV data, respiratory control	n = 18 COPD GOLD stages 0–II with mild symptoms (56% male, mean age 51.7 ± 2.4 years, mean FEV_1 % pred 78.2 ± 3.6 [training] 72.9 ± 1.9 [PBO], FEV_1 2.54 ± 0.2 L and 2.32 ± 0.18 L, FVC 3.53 ± 0.3 L and 3.50 ± 0.26 L, FEV_1/FVC 72.3 ± 1.9% and 66.2 ± 1.5%, n = 8 current smokers, n = 3 former smokers, BMI 26.4 ± 1.9 and 25.4 ± 0.9 kg/m2) versus n = 14 healthy controls	The CV autonomic abnormalities seen at baseline (higher heart rate, depressed baroreflex sensitivity) normalized with hypoxic training
Open-label, crossover (Faager et al., ref. 51)	Pursed lips breathing versus not pursed lips breathing, same-day follow-up?	Lung function and exercise capacity	n = 32 COPD: GOLD stage I (n = 1 female, FEV_1 % pred 89, PEF 390 L/min, ESWT 1, age 76 years), GOLD stage II (n = 6 [1 male], mean baseline FEV_1 % pred 61 ± 9, PEF 305 ± 107 L/min, ESWT 4, age 69 ± 4 years), GOLD stage III (n = 11), GOLD stage IV (n = 14)	Outcomes not stratified by severity

(Continues)

Table 3. Continued.

Citation	Interventions, follow up	Outcome measures	Patients and baseline characteristics	Main findings
Double-blind crossover (Fujimoto et al., ref. 52)	Compressed air versus O2 during exercise test	6MWD, lung hemodynamics	n = 75 COPD: mild (n = 16, age 71 ± 2 years, baseline FEV_1 % pred 62.7 ± 2.9, FEV_1 1.39 ± 0.06 L, FEV_1/FVC% 47.0 ± 1.8, air trapping 0.23 ± 0.06 L, VC % pred 100.0 ± 3.0, RV % 211.3 ± 13.4, RV/TLC 54.2 ± 1.2, ex-smokers with > 30 pack-years), moderate (n = 25), severe (n = 34)	In mild patients, 6MWD 475 ± 20 meters (92.9 ± 5.0 % pred) on air and 487 ± 20 meters (95.4 ± 5.4 % pred) on O2 (a 2.6 ± 0.8% increase, $p < 0.05$ versus air). No effect of supplemental oxygen on 6MWD in mild patients with mild desaturation
Mixed interventions (pharmacologic plus non-pharmacologic)				
Parallel-group, Lung Health Study (Scanlon et al., ref. 29)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow up	Smoking cessation rates, lung function	n = 3926 COPD, mean post-BD FEV_1 % pred (79.4 ± 9.1 [sustained quitters], 78.4 ± 9.2 [intermittent quitters], 78.1 ± 8.9 [continuing smokers]), FEV_1 (2.82 ± 0.64 L, 2.74 ± 0.64 L, 2.75 ± 0.61 L) FEV_1/FVC (63.1 ± 5.6, 62.9 ± 5.5, 63.0 ± 5.4). Wheezing in 74.4%, 76.8%, 76.9%, chronic cough in 39.7%, 40.6%, 44.3%, dyspnea in 39%, 41.3%, 44.1%. Aged 49.1 ± 6.8 years, 48.6 ± 6.9 years, 48.3 ± 6.8 years, men 67.1%, 61.9%, 63.9%, pack-years 40.1 ± 18.8, 39.4 ± 18.2, 40.8 ± 19.0, BMI 26.0 ± 3.9, 25.9 ± 3.9, 25.4 ± 3.9 kg/m2, bronchodilator response % 4.5 ± 4.9, 4.6 ± 4.8, 4.1 ± 5.1	Rate of FEV_1 decline for sustained quitters with usual care –30 ± 54 ml/year and with smoking cessation intervention –32 ± 46 ml/year; –62 ± 55 ml/year for continuing smokers, –43 ± 57 ml/year for intermittent smokers and –52 ± 56 for all smokers combined. Smoking cessation improved FEV_1 and reduced the rate of decline. Predictors of change in lung function included responsiveness to β-agonist, baseline FEV_1, methacholine reactivity, age, sex, race, and baseline smoking rate; but not respiratory symptoms
Parallel-group, Lung Health Study (Harber et al., ref. 53)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow up	Effect of air pollution on lung function, lung function	n = 5724 COPD, mean age 48.4 years (range 34–66 years) (men) and 48.5 years (35–67 years) (women), pack-years 42.8 ± 20.1 (men) and 36.2 ± 16.5 (women). Mean FEV_1 % pred for men 75.2 ± 8.8 (pre-bronchodilator) 78.4 ± 9.2 (post-bronchodilator); for women 75.1 ± 8.8 (pre-bronchodilator) 78.2 ± 9 (post-bronchodilator). Mean FVC % pred for men 96.6 ± 10.6 (pre-bronchodilator) 97.6 ± 10.6 (post-bronchodilator); for women 97.3 ± 10.3 (pre-bronchodilator) 98.1 ± 10.4 (post-bronchodilator). Mean FEV_1/FVC for men 62.7 ± 5.7 (pre-bronchodilator) 64.6 ± 6.2 (post-bronchodilator); for women 63.3 ± 5.3 (pre-bronchodilator) 65.5 ± 5.9 (post-bronchodilator)	Reduction in FEV_1 was related to fume exposure in men (not significant), and continued smoking and airway hyper-responsiveness (men and women). At 5 years (not stratified by intervention): mean FEV_1 % pred for men 71.1 ± 12.3 (pre-bronchodilator) 75.0 ± 12.0 (post-bronchodilator); for women 70.6 ± 12.7 (pre-bronchodilator) 74.8 ± 12.3 (post-bronchodilator). Mean FVC % pred for men 93.3 ± 12.0 (pre-bronchodilator) 95.9 ± 11.7 (post-bronchodilator); for women 93.3 ± 12.6 (pre-bronchodilator) 96.3 ± 11.8 (post-bronchodilator). Mean FEV_1/FVC for men 60.7 ± 7.8 (pre-bronchodilator) 62.4 ± 8.0 (post-bronchodilator); for women 61.0 ± 7.4 (pre-bronchodilator) 62.8 ± 7.9 (post-bronchodilator)
Parallel-group, Lung Health Study (Kanner et al., ref. 54)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow up	Quit rate, lower respiratory illness, physician visits, change in FEV_1	n = 5887 COPD, mean age 48.5 ± 6.8 years (intervention) 48.4 ± 6.8 years (usual care), men 62% and 64%, pack-years 40.4 ± 19.2 and 40.5 ± 18.9, FEV_1 % pred 78.3 ± 9.1 and 78.2 ± 9.1, BD response 4.3 ± 5.1 and 4.2 ± 5.1%, doctor visits for lower respiratory illness 13 ± 33 and 11 ± 32 per year. Chronic bronchitis 35%	At 5 y, 21.8% sustained quitters with intervention versus 5.2% usual care. Quitting smoking associated with fewer lower respiratory illnesses. Decline of FEV_1 was associated with lower respiratory illness in smokers; mean 0.24 doctor visits per year
Parallel-group, Lung Health Study (Kanner et al., ref. 55)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow up	Gender effects in airway hyper-responsiveness	n = 5662 COPD, mean age 48.4 ± 7 years (men) 48.5 ± 6.6 years (women), pack-years 42.7 ± 20 and 36.4 ± 16.8, FEV_1 % pred 74.9 ± 9.6 and 75.1 ± 8.8, FEV_1 2.94 ± 0.48 L and 2.08 ± 0.35 L, FEV_1/FVC % 62.7 ± 6.2 and 63.5 ± 5.7. Chronic cough in 42.9% and 40.4%, wheezing history in 78.3% and 74%, no shortness of breath in 63.4% men and 46.7% women	High prevalence of airway hyper-responsiveness, associated with decrease in airway caliber. 87% women and 62.5% men had positive response to methacholine. Seen especially in women due to smaller caliber

(Continues)

Table 3. Continued.

Citation	Interventions, follow up	Outcome measures	Patients and baseline characteristics	Main findings
Parallel-group, Lung Health Study (Kanner et al., ref. 56)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow up	Symptoms	n = 5887 COPD. 49–51% had cough ≥ 3 months per year: mean pre-bronchodilator FEV_1 % pred 74.3 ± 9 versus 76 ± 8.6 for asymptomatic ($p < 0.001$), FEV_1/FVC % 62.6 ± 5.7 versus 63.3 ± 5.3 ($p < 0.001$), age 48.2 ± 6.7 versus 48.7 ± 6.9 years, pack-years 42.2 ± 18.9 versus 38.5 ± 19.1, men 63.2% and 62.4%, BMI 25.6 ± 4 and 25.5 ± 3.9 kg/m2. Baseline data also provided for phlegm, wheeze, and dyspnea (same patients, stratified by symptom presence/absence)	Prevalence of symptoms (cough, phlegm, wheezing, shortness of breath) higher with usual care than with interventions ($p < 0.0001$). Smoking associated with symptoms. Symptoms associated with greater decline in FEV_1 during study ($p < 0.001$). Ipratropium had no effect on symptoms
Parallel-group, Lung Health Study (Tashkin et al., ref. 57)	Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow up	Relationship between baseline metacholine reactivity and change in lung function	n = 5733 COPD, mean age 48.4–48.6 years, men 61–64%. FEV_1 % pred 78.2 ± 9.1 (ipratropium), 78.4 ± 9.0 (PBO), 78.3 ± 9.1 (usual care). FEV_1/FVC % 64.9 ± 6.3, 65 ± 6, 65 ± 6. FEV_1 2.73 ± 0.64 L, 2.75 ± 0.62 L, 2.76 ± 0.62 L. Pack-years 40.3 ± 19.6, 40.2 ± 18.8, 40.5 ± 18.9. Bronchodilator response 4.2 ± 5.1, 4.4 ± 5.0, 4.3 ± 5.1%. LMCR for men (0.386 ± 0.365, 0.356 ± 0.355, 0.358 ± 0.360%/mg/ml and women (0.591 ± 0.392, 0.592 ± 0.387, 0.616 ± 0.365)	Methacholine reactivity is a predictor of decline in FEV_1 in smokers

6MWD: 6-min walk distance test; ATS: American Thoracic Society; AUC: area under the curve; BD: bronchodilator; BDI: baseline dyspnea index; bid: twice daily; BMI: body mass index; BTS: British Thoracic Society; CI: confidence interval; COOP/WONCA: Darthmouth COOP Functional Health Assessment Charts/World Organization of General Practice/Family Physicians; COPD: chronic obstructive pulmonary disease; CRQ: Chronic Respiratory Questionnaire; CV: cardiovascular; DIMCA: Detection, Intervention, and Monitoring Program of COPD and Asthma; DLCO: diffusing capacity of the lung for carbon monoxide; ERS: European Respiratory Society; ESWT: endurance shuttle walk test; EUROSCOP: European Respiratory Society Study on Chronic Obstructive Pulmonary Disease; FEF: forced expiratory flow; FEV_1: forced expiratory volume in 1 sec; FRC: functional residual capacity; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HAD: hospital anxiety and depression; HR: hazard ratio; IC: inspiratory capacity; ISWT: incremental shuttle walking test; IV: intravenous; IVC: inferior vena cava; LMCR: light meal combat ration; MEF: mid-expiratory flow; MRC: Medical Research Council; od: once daily; PBO: placebo; PEF: peak expiratory flow; PEFR: peak expiratory flow rate; qid: 4 times daily; RV: right ventricle; SE: standard error; SF-36®: Short Form (36) Health Survey; SFC: salmeterol/fluticasone propionate combination; SGRQ: St George's Respiratory Questionnaire; SR: sustained release; SVC: slow vital capacity; TDI: transition dyspnea index; TLC: total lung capacity; TORCH: Towards a Revolution in COPD Health; UPLIFT®: Understanding Potential Long-term Impacts on Function with Tiotropium; VC: vital capacity; VT: tidal volume.

the study. The SGRQ includes 50 items (76 weighted responses) across 3 domains: symptoms, activity, and impact (range: 0–100) (60). A 4-point decrease in score is considered to be a clinically meaningful improvement in a patient's health-related QoL. A small study by Kanehara et al. reported mean baseline SGRQ total scores of 34.0–35.7 in 26 patients with GOLD stage I or II COPD (mean FEV_1 83.8% predicted) (43).

Spencer et al. summarized a 48-patient trial in GOLD stage II patients with a mean baseline SGRQ total score of 39 units in the control group (n = 24). (47). Patients with moderate COPD (GOLD stage II) in the control group of UPLIFT® (n = 1355) (30) had a mean SGRQ total score at baseline of 42 units, and this worsened by 0.99 units per year, corresponding to a further deterioration in health status. In GOLD stage II patients involved in the TORCH trial, the mean baseline SGRQ total score for the placebo group (n = 535) was 43.9, and this decreased (improved) by –1.3 points per year (31).

In a sub-analysis of the non-randomized SAlute Respiration nell'Anziano (Respiratory Health in the Elderly) (SaRA) study (n = 381) that used the former GOLD classification system (61) , worse baseline SGRQ scores (impacts and total) correlated with worse disease severity: total mean scores were 30, 36, and 38 units in GOLD stage 0, I, and IIa patients, respectively (n = 266) (62).

Exercise capacity

Exercise capacity in patients with mild-to-moderate COPD has been evaluated in several studies, and using different endpoints. O'Donnell et al. examined exertion symptoms in 16 GOLD stage I patients (mean post-bronchodilator FEV_1 90% predicted). At baseline, symptom-limited peak work rate and oxygen consumption were reduced; 72% and 79% predicted, respectively (37).

Clark et al. compared muscle strength and endurance in 43 patients with mild COPD (mean FEV_1 76–79% predicted) with healthy but sedentary subjects (49). Patients with mild COPD showed a significant reduction in isokinetic muscle strength compared with healthy controls (no p-value reported). Baseline BORG scores for breathlessness at peak exercise were 2.4–3.5 among the patients with mild COPD.

AkkocaYildiz *et al.* reported that in a small study of 10 patients with GOLD stage I or II COPD (mean FEV_1 68.95% predicted), baseline mean exercise time (symptom-limited incremental cycle exercise test) was

Table 4. Top-line summary of the effects of different interventions on selected efficacy outcomes in studies of patients with mild-to-moderate COPD.

Interventions, follow-up	Citation	Outcome measures*			
		Lung function	Rate of exacerbations	Quality of life/symptoms/ rescue medication use	Exercise capacity
Pharmacologic intervention only—PBO-controlled					
Budesonide 800 µg/day versus PBO, 3 years	Double-blind PBO-controlled, parallel-group, *post-hoc* analysis of EUROSCOP study (Löfdahl et al., ref. 34)	NR	Significant reduction in annual severe exacerbation rate with budesonide versus PBO	NR	NR
Budesonide 400 µg bid versus PBO, 3 years	Double-blind PBO-controlled, parallel-group (Pauwels et al., ref. 38)	Mean decline in post-bronchodilator FEV_1 significantly reduced with budesonide versus PBO over 3-year period FEV_1 improved with budesonide over first 6 months then declined at similar rate to PBO (9 months to end of treatment)	NR	NR	NR
Fluticasone propionate 250 µg bid versus PBO, 2 years	Double-blind, PBO-controlled, parallel-group (DIMCA study) (van Grunsven et al., ref. 32)	Significantly higher decline in post-bronchodilator FEV_1 with fluticasone versus PBO; no between-groups difference in pre-bronchodilator FEV_1 decline	Similar between groups	Higher number of episodes of increased respiratory symptoms in fluticasone group versus PBO	NR
Salmeterol 50 µg versus fluticasone propionate 500 µg versus SFC 50/500 µg versus PBO; 3 years	Double-blind PBO-controlled, parallel-group, *post-hoc* analysis of TORCH study (Jenkins et al., ref. 31)	In GOLD stage II patients, SFC improved FEV_1 and reduced rate of decline in FEV_1 versus placebo	In GOLD stage II patients, SFC reduced annual rate of moderate/severe exacerbations versus PBO	In GOLD stage II patients, SFC improved SGRQ score versus placebo	NR
Tiotropium 18 µg od versus PBO, 4 years	Double-blind, PBO-controlled, parallel-group, pre-specified sub-group analysis of UPLIFT® trial (Decramer et al., ref. 30)	Significantly higher pre-and post-bronchodilator FEV_1, pre-bronchodilator FVC and pre-bronchodilator SVC versus PBO at all time points. Significantly lower rate of decline in post-bronchodilator FEV_1 with tiotropium versus PBO	Mean number per patient year significantly lower for tiotropium versus PBO. Time to first exacerbation and first hospitalized exacerbation significantly longer for tiotropium versus. PBO	SGRQ total score deteriorated in both groups but to lesser extent in the tiotropium group	NR
Ipratropium bromide 500 µg versus PBO; 2 days each arm, 7 days between visits (total 1 month)	Double-blind PBO-controlled crossover (O'Donnell et al., ref. 37)	Ipratropium increased FEV_1, decreased RV, and specific airway resistance versus PBO	NR	NR	During exercise, ipratropium significantly increased dynamic IC and VT, and decreased dyspnea and dyspnea/ ventilation ratios
Erdosteine 300 mg bid versus N-acetylcysteine 600 mg bid versus PBO, 10 days	PBO-controlled, parallel-group (Dal Negro et al., ref. 35)	FEV_1 response to salbutamol significantly enhanced after erdosteine. Slight increase in FVC with erdosteine versus PBO	NR	NR	NR
Infliximab 3 mg/kg versus infliximab 5 mg/kg versus PBO, 44 weeks	Double-blind, PBO-controlled, parallel-group (Rennard et al., ref. 39)	In GOLD stage II patients, no effect of infliximab versus PBO	In GOLD II patients, no effect of infliximab versus PBO	In GOLD stage II patients, no effect of infliximab versus PBO	NR

(Continues)

Table 4. Continued.

Interventions, follow-up	Citation	Outcome measures*			
		Lung function	Rate of exacerbations	Quality of life/symptoms/ rescue medication use	Exercise capacity
Pharmacologic intervention only—non-PBO controlled					
Tiotropium 18 mg qd + formoterol 12 µg bid versus salmeterol 50 µg bid + fluticasone 500 µg bid, 6 weeks	Double-blind, parallel-group (Rabe et al., ref. 42)	In GOLD stage II patients, tiotropium/formoterol significantly improved FEV_1 AUC0-12, peak FEV_1, FVC AUC0-12 , and peak FVC versus SFC	NR	NR	NR
Formoterol 12 µg bid versus ipratropium bromide 40 µg qid, 2 weeks each arm	Double-blind, crossover (AkkocaYildiz et al., ref. 46)	Formoterol significantly improved FEV_1 (90 min post-dose) and FEV_1/FVC at Day 14 Ipratropium improved FEV_1 % pred and FEF_{25-75} at 90 min post-dose	NR	NR	No difference between groups on exercise capacity or functional parameters
Theophylline SR bid versus salmeterol 50 µg bid, 12 months	Open-label, parallel-group (DiLorenzo et al., ref. 41)	Salmeterol improved morning PEFR versus theophylline FEV_1 and FVC improved in both groups and FEV_1 improvement persisted over 12 months with salmeterol Significantly higher FVC with salmeterol at 2 months with higher mean increases over baseline at 1, 2, and 3 months versus theophylline	NR	Salmeterol increased number of symptom-free nights and amount of rescue medication versus theophylline. Salmeterol improved SF-36® domains of physical functioning, change in health perception and social functioning versus theophylline	NR
Theophylline 400 mg versus tulobuterol 2 mg, 8 weeks each arm	Open-label, crossover (Kanehara et al., ref. 43)	In GOLD stage I/II patients, theophylline increased FEV_1 % pred, FVC, FEV_1, PEF, MEF50 and MEF25 versus baseline. Tulobuterol had no effect on lung function	NR	No significant change from baseline in SGRQ total score in either treatment group (activity domain worsened)	NR
Doxofylline 400 mg bid versus theophylline 400 mg od, 4 weeks	Open-label, parallel-group (Santra et al., ref. 45)	Both drugs significantly increased FEV_1, FEV 125–75 and PEFR, but not FEV1/FVC	NR	Both drugs significantly reduced salbutamol use	NR
Neltenexine versus carbocysteine, 12 days	Open-label, parallel-group (D'Elia and Sechi, ref. 44)	No change from baseline in FEV_1, PEF or VC with either drug	NR	Neltenexine improved cough and sputum characteristics versus carbocysteine and improved expectoration, cough, and sputum characteristics faster than carbocysteine	NR
Non-pharmacologic intervention only					
Weekly supervised exercise + home exercise versus control (unsupervised home exercise), follow-up 12 months	Parallel-group (Spencer et al., ref. 47)	No significant change from baseline or difference between groups	No difference in number of exacerbations between groups	No change from baseline in SGRQ score	No change from baseline in 6MWD test
Weight training versus control (usual activities, no weight training), 12 weeks	Parallel-group (Clark et al., ref. 49)	No effect of intervention on lung function	NR	NR	Weight training improved muscle function and whole body endurance during treadmill walking versus control
Compressed air versus O_2 during exercise test	Double-blind crossover (Fujimoto et al., ref. 52)	NR	NR	NR	In patients with mild COPD, increased 6MWD on oxygen versus air

(Continues)

Table 4. Continued.

Interventions, follow-up	Citation	Outcome measures*			
		Lung function	Rate of exacerbations	Quality of life/symptoms/ rescue medication use	Exercise capacity
OM-85 (bacterial extracts: test) versus PBO, for 30 days then 10-day course for Months 3, 4, 5; total 6 months	Double-blind, PBO-controlled, parallel-group (Soler et al., ref. 48)	NR	Fewer exacerbations for test versus PBO	NR	NR
Mixed interventions (pharmacologic plus non-pharmacologic)					
Smoking cessation intervention + ipratropium versus smoking cessation intervention + PBO versus advice to quit, 5-year follow-up	Parallel-group, Lung Health Study (Scanlon et al., ref. 29)** (Harber et al., ref. 53)† (Kanner et al., ref. 56)‡	Smoking cessation improved FEV_1 and reduced rate of decline.** Increase in pre- and post-bronchodilator FEV_1 % pred, FEV % pred and FEV_1/FVC in both men and women at 5 years (not stratified by intervention)†	NR	Prevalence of symptoms (cough, phlegm, wheezing, and shortness of breath) significantly lower with interventions than with usual care; ipratropium had no effect on symptoms‡	NR

*Studies selected for the review but not reporting data on these outcomes are excluded from the table. **N = 3818. †N = 5724. ‡N = 5887.
6MWD: 6-min walk distance test; AUC0-12: area under the curve from 0 to 12 hours; bid: twice daily; COPD: chronic obstructive pulmonary disease; DIMCA: Detection, Intervention, and Monitoring Program of COPD and Asthma; EUROSCOP: European Respiratory Society Study on Chronic Obstructive Pulmonary Disease; FEF: forced expiratory flow; FEV_1: forced expiratory volume in 1 sec; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IC: inspiratory capacity; MEF: mid-expiratory flow; od: once daily; NR: not reported; PBO: placebo; PEF: peak expiratory flow; PEFR: peak expiratory flow rate; qid: 4 times daily; RV, residual volume; SF-36®: Short Form (36) Health Survey; SFC: salmeterol/fluticasone propionate combination; SGRQ: St George's Respiratory Questionnaire; SR: sustained release; SVC: slow vital capacity; TORCH: Towards a Revolution in COPD Health; UPLIFT®: Understanding Potential Long-term Impacts on Function with Tiotropium; VC: vital capacity; VT: tidal volume.

7.03 minutes, and work rate was 121.5 Watts (46). In 48 patients with GOLD stage II COPD (FEV_1 57% to 60% predicted), Spencer et al. found that the mean distance covered during the 6-minute walk distance (6MWD) test at baseline was 523–530 meters (47).

These RCT data are supported by non-randomized studies. For example, a trend towards a decreased number of steps taken per day and decreased time spent in moderately intense physical activity for GOLD stage I patients (n = 9) was reported compared with healthy controls (n = 30) (3). For GOLD stage II patients (n = 28), all physical activity-related outcomes were significantly reduced compared with controls ($p < 0.05$).

A study by Ofir et al. examined exercise capacity in GOLD stage I patients (mean FEV_1 91% predicted) compared with healthy controls (n = 21 in each group) (63). Among the COPD patients, significant reductions in peak oxygen consumption and power output (>20%) were observed and dyspnea ratings were higher for a given work rate and ventilation ($p < 0.05$) compared with healthy controls. Changes in end-expiratory lung volume during exercise were also greater in COPD patients compared with controls (0.54 L versus 0.06 L; $p < 0.05$) and their breathing was more shallow and rapid.

In a further non-randomized study, Antonelli-Incalzi et al. assessed physical performance by the 6MWD test (0–100); the test values were 78, 75, and 72% predicted in GOLD stage 0, I, and IIa patients, respectively (62).

Functional status

Functional status (6 domains of general health) was only reported in 1 RCT, the 2-year DIMCA trial in patients with mild COPD using the Dartmouth COOP Functional Health Assessment Charts/World Organization of General Practice/Family Physicians (COOP/WONCA) scores (range: 1 = very good to 5 = very bad). Among the 24 patients (mean baseline FEV_1 98% predicted) receiving placebo, baseline mean scores ranged from not impaired (1.2 for social activities) to slightly impaired (2.4 for general health), and most patients perceived no change in their functional status during the trial period (32).

Mortality

No information was available regarding mortality rates in patients with GOLD stage I disease among the included articles. However, an overall mortality rate of 10% was reported in GOLD stage II patients receiving placebo over 4 years during the UPLIFT® trial (n = 1355) (30). Similarly, an overall mortality rate of 11.4% was recorded in patients at GOLD stage II who were given placebo over 3 years in the TORCH trial (n = 535) (31). Pauwels et al. reported a 1.6% mortality rate over 3 years in the placebo-group patients with mild-to-moderate COPD (mean baseline FEV_1 76.8–76.9% predicted, n = 643) (38).

Risk factors

Several studies have assessed risk factors for disease progression. Data from the EUROSCOP study indicated that gender, body mass index, and smoking may be associated with worsening of COPD (59). For example, in men, symptoms were associated with lower baseline FEV_1 and obesity was associated with a reduced decline

in FEV_1. In women, more severe airway obstruction was associated with an accelerated decline in FEV_1. An increased number of cigarettes smoked was also associated with an accelerated decline in FEV_1. In the non-randomized SaRA study (266 patients with GOLD stage 0–IIa COPD), female gender, comorbidity, and older age was associated with worse QoL (62).

Effects of interventions in mild-to-moderate COPD

A total of 29 RCTs provided data on the effect of intervention on mild-to-moderate COPD (Table 3). These included 11 placebo-controlled investigations of pharmaceutical agents (30–40), 6 trials of pharmacologic interventions without a placebo control (41–46), 6 trials of non-pharmacologic interventions (47–52), and 6 papers from the Lung Health Study with mixed interventions (29,53–57). Of these, 16 had a duration ≥6 months (29–32,34,38–41,47,48,53–57). Table 4 provides a top-line summary of the most commonly-reported efficacy outcomes associated with different interventions from the selected studies of patients with mild-to-moderate COPD.

Lung function—absolute improvements

In a group of 16 GOLD stage I patients (mean post-bronchodilator FEV_1 90% predicted), O'Donnell *et al.* demonstrated that ipratropium bromide provided moderate improvements in lung function outcomes (FEV_1, residual volume) and in selected variables during constant work-rate cycle exercise (inspiratory capacity, tidal volumes, and dyspnea) compared with placebo ($p < 0.05$) (37).

In the 3-year TORCH trial, 2156 patients who were GOLD stage II or above (including 28 GOLD stage I; mean post-bronchodilator FEV_1 59% predicted) received salmeterol monotherapy (n = 522), fluticasone monotherapy (n = 537), salmeterol and fluticasone (n = 562), or placebo (n = 535) (31). Sub-group analysis of GOLD stage II patients revealed that, compared with placebo, salmeterol and fluticasone improved FEV_1 (by 101 ml) at 3 years (p-value not reported).

The sub-group analysis of GOLD stage II patients (mean post-bronchodilator FEV_1 59% predicted) in the 4-year UPLIFT® trial showed that mean pre- and post-bronchodilator FEV_1 values were significantly higher in the tiotropium group compared to the control group at all time points (with differences between groups ranging from 101–119 ml and 52–82 ml, respectively; $p < 0.0001$) (30).

In a 1-year study of patients with GOLD stage II COPD (FEV_1 50–80% predicted), Di Lorenzo *et al.* compared salmeterol (n = 91) with theophylline (n = 87) (40). FEV_1 improved in both groups; the improvements with salmeterol persisted over 12 months, while those with theophylline were not maintained at 9 months or at 12 months.

In a 1-year study reported by Spencer et al., supervised exercise (n = 24) and unsupervised exercise (n = 24) in GOLD stage II patients (FEV_1 57–60% predicted) failed to show an improvement from baseline in lung function, with no difference between groups (47).

Lung function—rate of decline in FEV_1

During the 2-year DIMCA trial in mild COPD (mean FEV_1 95% to 99% predicted), the annual rate of post-bronchodilator FEV_1 decline was significantly greater for patients receiving fluticasone compared with placebo: −93 versus −14 ml/year ($p = 0.001$), although the sample size was small (n = 24 in each group) (32).

Pauwels et al. conducted a 3-year comparison of budesonide (n = 634) with placebo (n = 643) in patients with moderate COPD (mean pre-bronchodilator FEV_1 77% predicted), and found that FEV_1 initially improved with budesonide, then declined at a similar rate to placebo (38). Overall, the median decline in post-bronchodilator FEV_1 over the 3-year period was 140 ml for budesonide versus 180 ml for placebo ($p = 0.05$), equating to an annual rate of decline of 47 ml and 60 ml, respectively.

In the 3-year TORCH trial, salmeterol + fluticasone reduced the rate of FEV_1 decline by 16 ml/year (95% confidence interval [CI], 0–32) compared with placebo in the subgroup of GOLD stage II patients (p-value not reported).

The sub-group analysis of GOLD stage II patients (mean post-bronchodilator FEV_1 59% predicted) in the 4-year UPLIFT® trial reported a lower rate of decline of post-bronchodilator FEV_1 for tiotropium (n = 1218) compared with placebo (n = 1157) (43 versus 49 ± 2 ml/year; $p = 0.024$) (30).

A 5-year follow-up of patients with mild-to-moderate COPD (mean post-bronchodilator FEV_1 78% to 79% predicted) who received smoking cessation as an intervention in the Lung Health Study revealed a rate of FEV_1 decline approximately 50% of that observed in patients who continued to smoke: 31 versus 62 ml/year (29).

Rate of exacerbations

During the 2-year DIMCA trial in 48 patients with mild COPD (mean post-bronchodilator FEV_1 98% to 99% predicted), a low rate of exacerbations was reported in both groups; 6 episodes in 5 fluticasone patients, compared with 4 episodes in 3 placebo patients (32).

A 37% reduction in estimated annual severe exacerbation rate (based on oral steroid use) was reported for budesonide (n = 593) compared with placebo (n = 582): 0.05 versus 0.07 per year; rate ratio 0.63; $p = 0.002$) in the 3-year EUROSCOP trial in patients with mild-to-moderate COPD (mean baseline FEV_1 76.9% predicted) (34).

In the GOLD stage II subgroup of the TORCH study, rates of moderate or severe exacerbations were 31% lower for salmeterol plus fluticasone (n = 562) versus placebo (n = 535) groups: mean 0.57 versus 0.82 exacerbations/year (p-value not reported) (31). In the subgroup analysis of 2739 GOLD stage II patients in the UPLIFT®

trial, a 20% reduction in the mean number of moderate or severe exacerbations (0.56 versus 0.70 per patient year; $p < 0.0001$) was reported for tiotropium compared with placebo (30).

Solèr et al. demonstrated that exacerbations were reduced by 29% in GOLD stage I or II patients (mean FEV_1 83% to 85% predicted) receiving a bacterial extract (n = 142) compared with placebo (n = 131): 0.61 versus 0.86 exacerbations over 6 months ($p = 0.03$), equivalent to annual exacerbation rates of 1.22 versus 1.72, respectively (48).

Spencer et al. showed that in a 1-year study in GOLD stage II patients (FEV_1 57% to 60% predicted), exacerbation rates following pulmonary rehabilitation were similar for the supervised and unsupervised exercise groups (mean 2.3 and 1.4 exacerbations per year, respectively), as were hospital admissions and length of hospital stay (47).

Respiratory symptoms

During the 2-year DIMCA trial in patients with mild COPD (mean post-bronchodilator FEV_1 98% to 99% predicted), there were 127 episodes of increased respiratory symptoms in 18 patients treated with fluticasone compared with 57 episodes in 17 placebo patients (32). Among the 16 GOLD stage I patients enrolled in the study by O'Donnell et al., ipratropium bromide moderately improved dyspnea during exercise compared with placebo (37).

The Lung Health Study assessed the effect of smoking cessation plus ipratropium (n = 1961), smoking cessation plus placebo (n = 1962), and advice to quit smoking (usual care) (n = 1964) on respiratory symptoms (mean pre-bronchodilator FEV_1 74% to 76% predicted) (56). At the 5-year follow-up, the prevalence of symptoms (cough, phlegm, wheezing, shortness of breath) was significantly lower in both smoking cessation groups ($p < 0.0001$) than with usual care, although ipratropium conferred no additional effect.

QoL

In the GOLD stage II subgroup of the 3-year TORCH study, salmeterol plus fluticasone (n = 562) improved SGRQ total score compared with placebo (n = 535), with a difference between groups of -2.3 units (p-value not reported) (31).

In the subgroup analysis of GOLD stage II patients in the UPLIFT® trial, QoL with tiotropium (n = 1179) was superior to placebo (n = 1119) at all time points ($p \leq 0.006$) (30). Differences in SGRQ scores between groups ranged from 2.7–4.0 (total score), 2.3–3.9 (impact), 2.7–4.1 (symptoms), and 3.1–4.4 (activity) units for tiotropium and placebo, respectively. However, the slope of decline in SGRQ total score did not improve significantly.

In a 1-year study of patients with GOLD stage II COPD, Di Lorenzo *et al.* found that salmeterol (n = 91) improved Short Form-36 Health Survey (physical functioning) domains to a greater extent than theophylline (n = 87) (change in health perception at 9 months, $p = 0.03$; social functioning at 12 months, $p = 0.04$) (41).

In GOLD stage II patients, Rennard *et al.* showed that infliximab showed no effect at 3 mg/kg (n = 31) or 5 mg/kg (n = 28) compared with placebo (n = 39) on the chronic respiratory questionnaire at 44 weeks (39).

The 1-year study of supervised exercise (n = 24) versus unsupervised exercise (n = 24) in GOLD stage II patients (FEV_1 57% to 60% predicted) by Spencer *et al.* showed no difference in the change from baseline of SQRQ total score (3 versus -3 and there was also no difference in hospital anxiety and depression) scores (47).

Exercise capacity

Exercise capacity was reported in 1 interventional study (37, 47). Spencer et al. showed, in 48 GOLD stage II patients following pulmonary rehabilitation, that there was no difference between patient groups receiving supervised versus unsupervised exercise in the change from baseline of 6MWD (-11 [95% CI, -21, 10] meters versus -6 [95% CI, -34, 11] meters) (47); there was also no difference in incremental and endurance shuttle walk test, although patients in both groups successfully maintained the 6MWD (47). Symptom-limited exercise endurance time during constant work rate exercise (an index of exercise capacity) in 16 GOLD stage I patients (O'Donnell et al.) was comparable after ipratropium or placebo (8.2 minutes in both groups), and the reasons for stopping exercise also did not differ between groups (37).

Functional status

Functional status was reported in only 1 RCT, the 2-year DIMCA trial (32) in patients with mild COPD (mean post-bronchodilator FEV_1 98% to 99% predicted). Overall, there was no significant difference between fluticasone and placebo in COOP/WONCA scores.

Mortality

The reviewed data showed no significant effect on mortality for budesonide (38) or tiotropium (30); although salmeterol plus fluticasone reduced the risk of mortality by 33% in GOLD stage II patients, no p-value was reported (31).

Compliance

Only a small number of studies reported compliance rates. In patients with early COPD in a 2-year trial, mean compliance was 72% with fluticasone (40).

Discussion

This systematic review revealed a wealth of data in patients with moderate COPD (e.g., GOLD stage II). However, only 2 RCTs of exclusive populations with mild COPD (e.g., GOLD stage I) were identified; 1 conducted

over 2 years (32) and 1 of a short duration (37). In most of the other trials, the patients were GOLD stage II or more severe, or were an unstratified combination of GOLD stage I and II patients. Some of the non-randomized studies also used exclusive or stratified populations of GOLD stage I patients, but they were generally very small and usually observational (63–69).

The results from this review show that even patients with milder or moderate COPD ($FEV_1 \geq 50\%$ predicted) can have substantial limitations and physical impairment relative to normal individuals, and these impairments worsen over time. The progressive deterioration in lung function over the course of a patient's lifetime is likely to be greatest in those diagnosed with mild-to-moderate COPD at a younger age than in elderly patients (e.g., > 65 years) with more severe COPD. Although the effect of patient age was not addressed by the current systematic review, evidence suggests that intervening early with effective respiratory therapy may not only improve patient outcomes, but also modify the course of disease (70).

Among the RCTs identified in our analysis, FEV_1 decline in patients with mild COPD was reported at a rate of 14 ml/year (32), however this result should be interpreted with caution due to the small number of patients (n = 24), and the relatively large standard error (17 ml/year). In much larger groups of patients with moderate (GOLD stage II) disease in the UPLIFT® and TORCH RCTs, rate of decline in FEV_1 was in the range of 49–60 ml/year (30,31). In a large population-based study, rates of decline in FEV_1 of 44 ml/year were reported for symptomatic GOLD stage I patients compared with 34 ml/year in individuals with normal lung function (6). As a comparison, decline in FEV_1 was 17.6–19.6 ml/year in healthy never-smokers in the Framingham Cohort Study (71).

Even patients with mild disease experience exacerbations (32, 34). For GOLD stage II patients, the annual rate of exacerbations leading to hospitalization (severe exacerbations) appears to be in the region of 0.7% to 0.9%, taken from 2 studies (30, 31).

Patients with mild (32, 37) and more moderate COPD (29, 58, 59) also frequently experienced aggravated respiratory symptoms, and these were also shown to worsen over time (32). It is possible that patient selection in the EUROSCOP study may have been biased towards those with symptoms (all were current smokers at the start of the study) (59).

Additionally, QoL was shown to be reduced in patients with mild or moderate COPD (43). The GOLD stage II subgroup analyses from the 2 large trials, UPLIFT® and TORCH, demonstrated conflicting trends for SGRQ scores over time (30, 31), although the absolute changes were small and not clinically significant. A recently published paper by Jones *et al.* reported impaired SGRQ total scores at baseline in patients with GOLD stage I and stage II disease (38.5 and 40.4 units, respectively), which are comparable to those reported in the studies analyzed in this review (72).

One study suggested that patients with mild COPD do not experience much functional impairment (32), but several studies showed that exercise capacity was reduced in patients with mild or moderate COPD (37,46,47,49). However, the findings by O'Donnell et al. (37) that symptom-limited peak work rate and oxygen consumption was reduced in 16 GOLD stage I patients is not a universal finding (73), and this discrepancy between studies illustrates the need to study a larger number of individuals randomly selected from the general population to obtain an unbiased study population.

Among the papers identified, there were no data available for mortality rates in GOLD stage I patients. However, in 1 study that did not meet our search criteria GOLD stage I and II patients had a significantly higher risk of mortality compared to control subjects with normal lung function (hazard ratios of 1.4 [95% CI, 1.1–1.6] and 2.4 [95% CI, 2.0–2.9]) (74), highlighting that, even in patients with the earliest stages of COPD, mortality is increased compared to patients without COPD. Among the RCTs reporting on GOLD stage II patients, there were mortality rates of 10% to 11% over 3–4 years in the placebo groups (30,31), and a further study reported 0.8% mortality in mild-to-moderate COPD patients (mean pre-bronchodilator FEV_1 76.8% to 76.9% predicted) (38).

It is important to note that, when considering disease progression in placebo groups, the data may be confounded by the use of different concomitant medications permitted during some of the trials. For example, in the UPLIFT® study, all concomitant respiratory drugs, apart from inhaled anticholinergic drugs, were allowed during the trial (30). In the TORCH study, patients could receive concomitant short-acting bronchodilators, short-term oral corticosteroids, theophyllines, and oxygen <12 hours per day, but no other medications (such as long-acting anticholinergics) (31).

In terms of pharmaceutical interventions, the longer-term (≥6 months) RCTs suggest that certain medications such as long-acting bronchodilators, alone or in combination, can slow the rate of decline in lung function and improve exacerbations and QoL or health status outcomes of GOLD stage II patients, whilst other medications showed little benefit. In the UPLIFT® study, tiotropium reduced the decline in lung function, exacerbation rates and QoL in GOLD stage II patients compared with placebo (30). Similar findings were reported for the TORCH trial where the rate of decline in FEV_1 appeared to be reduced by salmeterol plus fluticasone and, to a lesser extent, salmeterol monotherapy (31); salmeterol plus fluticasone also improved exacerbations and health status compared with placebo (31). In a further study, salmeterol was shown to be better than theophylline for improving lung function and QoL, and theophylline appeared not to be effective at preventing lung function decline (41).

In terms of ICS monotherapy, budesonide has been shown to reduce the exacerbation rate (34) and decline

in lung function (38) compared with placebo in GOLD stage I/II patients. However, in the EUROSCOP study, the pattern of lung function improvement with budesonide showed the "inverted hockey stick" phenomenon (75), whereby an early increase in FEV_1 (over the first 6 months of the trial) was followed by a decline approximately parallel to that of the placebo arm (from 9 months until the end of treatment) (38). This "inverted hockey stick" effect suggests that, although corticosteroid therapy treats inflammation in COPD, the course of disease progression remains unaltered (75). Another 3-year, parallel-group, randomized, double-blind, placebo-controlled trial of budesonide including patients with mild COPD (mean FEV_1 86% predicted) demonstrated no difference in outcomes versus placebo for rate of decline in FEV_1, respiratory symptoms or exacerbations (76). However, this study was excluded from the current systematic analysis because the outcomes reported for the patient population were not stratified by disease severity, and a sizeable proportion had severe or very severe COPD (FEV_1 < 50% predicted).

The evidence for fluticasone monotherapy in early COPD was more variable. For example, fluticasone monotherapy had a detrimental effect on lung function, exacerbations and symptoms in early COPD compared with placebo, but this may be confounded by the small size of the study (32). The larger TORCH study found small benefits for fluticasone monotherapy versus placebo in GOLD stage II patients, although a higher rate of pneumonia was also reported with fluticasone (31). A shorter-term RCT in 592 patients found a significant improvement in lung function with a combination of tiotropium and formoterol compared with salmeterol with fluticasone at 6 weeks ($p = 0.0006$) (42).

The Lung Health Study showed that predictors of change in lung function include responsiveness to a β_2-agonist, baseline FEV_1, methacholine reactivity, age, sex, race, and baseline smoking rate—but not baseline respiratory symptoms (29). In women, more severe airway obstruction was associated with an accelerated decline in FEV_1 (59).

In terms of mortality, current data show no significant effect for budesonide (38) or tiotropium (30) on mortality rates in GOLD II stage patients. In a further study, a combination of salmeterol plus fluticasone reduced the risk of mortality by 33% in GOLD stage II patients (31). A reduction in mortality was seen in the UPLIFT® overall population with tiotropium compared with control, although it was not observed in the GOLD stage II patients (30). This may be because fewer patients died in the GOLD stage II group. Therefore, other endpoints may be more useful in this milder population. Overall, mortality is generally reduced (at least numerically) by long-acting bronchodilators, which have a good safety profile.

Several studies have shown that smoking cessation is beneficial in COPD. For example the Lung Health Study showed that smoking cessation decreased the rate of decline in FEV_1 by 50% compared with continued smoking (29). Smoking cessation is still the most effective way to modify the natural course of the disease and as such, is a fundamental aspect of COPD treatment (1).

Little benefit was observed for both supervised exercise and unsupervised exercise in 1 study (47), although a shorter-term study found that exercise capacity increased with training (48). In a further short-term study, improvement in exercise capacity correlated with an increase in FEV_1 (46). However, there are many benefits to maintaining physical activity in all stages of the disease, including early COPD (77). Indeed, there is also evidence that higher levels of physical activity even in normal individuals lead to slower decline in lung function and reduced mortality (78).

This review highlights the challenges faced in the management of patients with milder COPD (e.g., GOLD stage I), for whom few evidence-based guidelines exist and in whom few RCTs have been performed. One limitation is that patients with COPD may discontinue their treatment program early, although this can vary depending on the treatment (74).

Despite its systematic nature, the present literature review has some limitations. Due to wide scope of the subject matter, search criteria were limited in a relatively stringent manner to identify a manageable number of publications to assess and review; therefore some relevant articles may have been unintentionally omitted. Additionally, no statistical methods were employed to analyze the results from the included studies, therefore the results can be considered descriptive only. Nonetheless, the review covers comprehensively the available literature relating to mild-to-moderate COPD up until July 30, 2010, and the benefits of interventions in patients with this earlier-stage disease.

Interesting results from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study have become available since the literature search was conducted for the current systematic review. This large observational study included patients with COPD (n = 2164), smokers with normal lung function (n = 337), and never smokers (n = 245), and was conducted at 46 centers in 12 countries (79). The aim was to define COPD phenotypes and identify parameters that help to predict disease progression. The results showed that comorbidities were more prevalent in COPD patients than in controls, but occurred to the same extent, irrespective of GOLD stage.

For the 954 patients with moderate (GOLD stage II) COPD, mean FEV_1 was 63.6% predicted in women and 62.8% in men. The mean distances covered on the 6MWD test were 391 and 415 meters, and the mean SGRQ total score was 43.8 and 41.6, respectively. The COPD exacerbation rate in the year prior to the study was 0.8 in women and 0.5 in men. As expected, despite considerable heterogeneity within each GOLD category, symptoms and exercise capacity generally deteriorated with advancing disease stage and the number

of exacerbations increased. Supporting the conclusions of our literature review, even patients with moderate (GOLD stage II) COPD reported symptoms, exercise limitation and frequent exacerbations; a more detailed analysis of exacerbations in ECLIPSE over 3 years (80) found that 22% of patients with GOLD stage II COPD (n = 945) experienced two or more exacerbations in the first year of follow-up. The occurrence of exacerbations was related to a susceptibility phenotype, independent of disease severity, and associated with factors including exacerbation history and impaired health status (80).

Conclusions

Patients with mild-to-moderate COPD experience considerable morbidity and mortality. Early intervention could reduce this and may potentially affect disease progression. Further RCTs are needed in GOLD stage I and II patients, with complete stratification to assess disease progression and outcomes fully, compared with more severe COPD. It would also be important to determine the prognosis of different patient subgroups, for example, gender, age, and smoking status.

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Declaration of interest

FM has received fees for speaking at conferences sponsored by Boehringer Ingelheim, Pfizer, and GlaxoSmithKline, and has served on advisory boards for GlaxoSmithKline and Boehringer Ingelheim. He has received research grants for participating in multicenter trials sponsored by GlaxoSmithKline, Boehringer Ingelheim, Altana Pharma, Merck, Astra Zeneca, Nycomed, and Novartis, and has received unrestricted research grants from Boehringer Ingelheim and GlaxoSmithKline. He holds a CIHR/GSK research chair on COPD. ND is employed by PAREXEL, and her work was funded jointly by Boehringer Ingelheim and Pfizer. CC has received honoraria or consultancy fees from Abbott, Actelion, AstraZeneca, Bayer, Bioavail, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, InterMune, Janssen-Ortho, Merck, Novartis, Nycomed, Ortho-McNeill, Pfizer, and Sanofi-Aventis. He has also received grants from Actelion, AstraZeneca, Biogen, Gilead, InterMune, and Janssen-Ortho, and speaker bureau fees from VitalAire. All authors were involved in the drafting and editing of the manuscript, and approved the final article.

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