CLINICAL
INVESTIGATION

Combination therapy for COPD: emerging evidence from recent clinical trials

Chronic obstructive pulmonary disease (COPD) is a heterogeneous syndrome encompassing the clinical presentations of chronic bronchitis and emphysema. Moderate-to-severe COPD is estimated to affect 80 million people worldwide. The diagnosis of COPD is made using spirometry, demonstrating the presence of obstruction that does not completely reverse with the administration of an inhaled bronchodilator. Treatment of COPD is titrated to severity, and in stage II–IV disease, combinations of different classes of bronchodilators, and bronchodilator and anti-inflammatory combinations, are recommended. Treatment of COPD is multimodal, including pharmacologic therapy, long-term oxygen therapy, smoking cessation, cardiopulmonary rehabilitation (including breathing retraining) and disease education. This article focuses on pharmacologic therapies, and more specifically the evidence for combination pharmacologic therapy that has emerged over the past few years. Prominent human clinical trials are reviewed and results are summarized with a focus on the steps required to change clinical practice. Finally, a perspective on future changes in the field of COPD pharmacotherapy is provided in light of recent changes.

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous syndrome encompassing the clinical presentations of chronic bronchitis and emphysema. It is defined by the WHO as "a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible." Moderate to severe COPD is estimated to affect 80 million people worldwide [101]. It is strongly associated with exposure to tobacco smoke and burning of biomass fuel. The diagnosis of COPD is made using spirometry, demonstrating the presence of obstruction (i.e., forced expiratory volume in 1 s [FEV1]:forced vital capacity [FVC] ratio less than 0.7) that does not completely reverse with the administration of an inhaled bronchodilator [1]. Increasingly, the diagnosis of obstruction is being made using a lower limit of normal, which encompasses 95% of normal subjects, instead of using the fixed ratio of 0.7, which tends to overdiagnose obstruction in older subjects and underdiagnose obstruction in younger subjects [2].

Once a diagnosis of COPD is established, it is important to stage the disease via global initiative for chronic obstructive lung disease (GOLD) guidelines based on severity of obstruction (Figure 1) [102]. Treatment is titrated to severity, and in stage II–IV disease, combinations of different classes of bronchodilators, and bronchodilator and anti-inflammatory combinations, are recommended. Combination therapy is frequently used in COPD by combining different agents in a fixed drug combination (e.g., long-acting β-agonists [LABA]/inhaled corticosteroids [ICS]), by combining different devices (e.g., formoterol and tiotropium dry powder
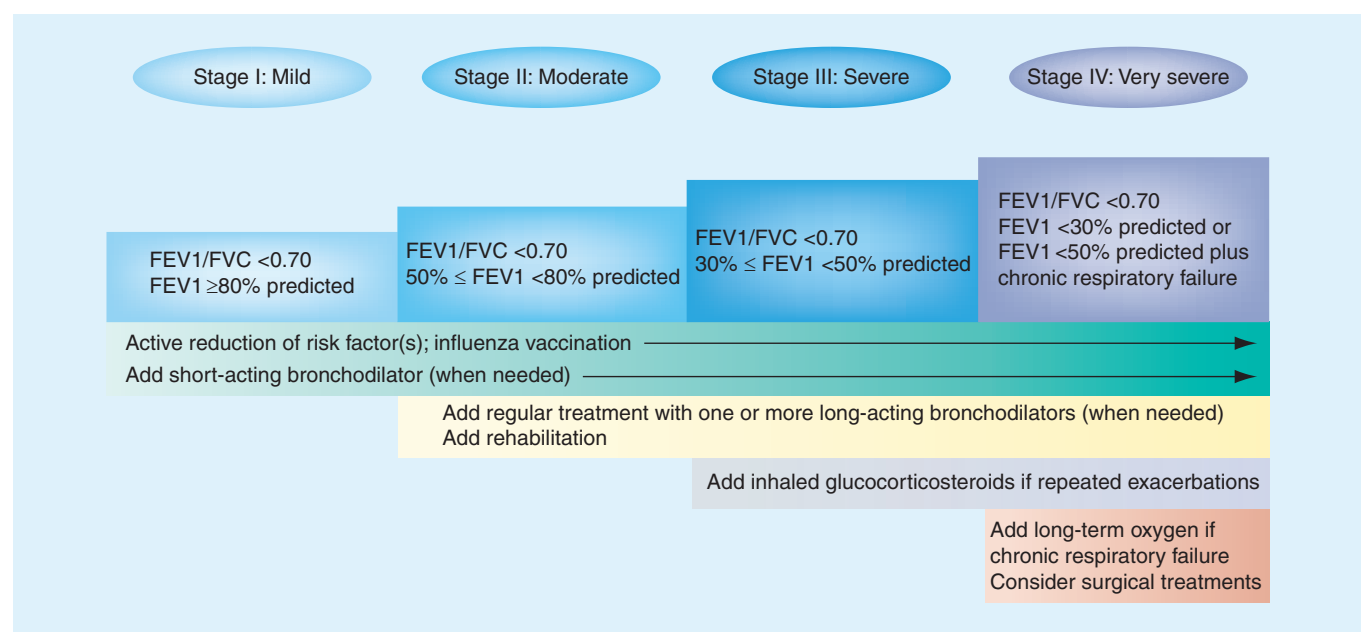
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Figure 1. Therapy at each stage of chronic obstructive pulmonary disease.
Postbronchodilator FEV1 is recommended for the diagnosis and assessment of severity of chronic obstructive pulmonary disease.
FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity.
Data taken with permission from [102].

inhalers [DPI]) or by combining different routes of administration or methods of delivery (e.g., oral the-ophylline with salmeterol DPI or nebulized formoterol with tiotropium via DPI). The added efficacy from combining different classes may be offset by changes in adverse-event profiles. The minimal clinically impor-tant difference (MCID) for the second agent is unclear, but regulatory authorities have approved combina-tions of short-acting β-agonists (SABA) with short-acting anticholinergics and fixed-drug combinations of LABA/ICS. Similarly, no regulatory standard for triple therapy is established. As will be discussed below, the numerous studies of combination therapy have yet to define an optimal evidence- and outcomes-based combination treatment strategy.

Despite treatment, the presence of COPD is asso-ciated with significant increases in morbidity and mortality. Patients primarily experience a sensation of dyspnea that impacts on quality of life. Other com-mon symptoms include cough, wheezing, sputum pro-duction, chest discomfort, fatigue, anxiety and sleep disturbances. In patients with severe COPD, decreases in lean body mass, bone mineral density and exercise capacity, and increases in systemic inflammation [3], lung cancer [4], cardiovascular disease, diabetes and hypertension [5], have been demonstrated. People who have COPD experience periodic worsening of their symptoms, usually including both increased dyspnea and sputum production, which is termed a COPD

'exacerbation.' It is well established that during a COPD exacerbation, lung function declines significantly and often does not fully return to baseline [6]. Mortality is increased significantly in COPD. According to the most recent CDC report, COPD was the underlying cause of approximately one in 20 deaths in the USA during 2000–2005 [7] and COPD is currently estimated to become the third-leading cause of death worldwide by 2030 [101].

Measuring treatment effect in COPD

Treatment of COPD results in significant improvement in a number of measurable end points (Table 1). For many of these end points, there is a MCID that quanti-fies the smallest amount of change that patients perceive as improvement and for which a change in manage-ment would be justified [8]. Most classically measured end points represent changes in respiratory function; these include FEV1, inspiratory capacity (IC), exercise capacity (as most often measured by the 6-min walk distance or incremental shuttle walk test), dyspnea and quality of life. Fewer end points are believed to repre-sent modifications in the natural history of the disease; these include rate of decline in FEV1 [9,10], frequency of exacerbations (after which a significant portion of patients do not recover baseline lung function [11]) and the body-mass index, airflow obstruction, dyspnea and exercise capacity index [12], which correlates well with mortality [13].

Initially, studies were aimed towards improvement in respiratory performance without seeking long-term disease modification [14–16]. More recent studies have sought to establish improvements in disease-modifying end points [17,18]. Interestingly, although severity staging of COPD depends heavily on the measurement of predicted FEV1%, the individual patient variation in this measure makes it difficult to use as a gauge of response to treatment [19,20]. As a measure of long-term disease modification, the rate of decline in FEV1 and the frequency of COPD exacerbations are both used to represent the natural history of the disease. To date, no studies have proven a prespecified improvement in rate of decline in FEV1, although the Towards a Revolution in COPD Health (TORCH) study [17] demonstrated an improvement in exacerbation frequency in the group of subjects assigned to a combination of ICS and LABA, to a nearly significant (p = 0.052) reduction in mortality risk of 17.5%. A *post hoc* analysis of the TORCH trial data revealed a reduction in the rate of decline in FEV1 in subjects treated with combination therapy or single-agent therapy compared with placebo; however, this was not an original end point of the trial [21]. The magnitude of this reduction in FEV1 decline was 13–16 ml/year. The Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study demonstrated a numerically lower mortality and rate of decline in FEV1 in subjects assigned to the long-acting muscarinic antagonist (LAMA) tiotropium; however, this was not found to be statistically significant [18]. The frequency of exacerbations in the UPLIFT study was significantly lower among subjects assigned to tiotropium. Thus, treatment with inhaled fluticasone and salmeterol, as well as treatment with inhaled tiotropium, are currently the only treatments to demonstrate long-term disease modification through their ability to reduce the frequency of COPD exacerbations.

Treatment options for COPD

Treatment of COPD is multimodal, including pharmacologic therapy, long-term oxygen therapy, smoking cessation, cardiopulmonary rehabilitation (including breathing retraining) and disease education. This review focuses on pharmacologic therapies, of which, most are delivered via inhalation. Table 2 lists the currently available pharmacologic categories and representative agents from each category. Society guidelines recommend initiation of pharmacotherapy with a single agent, but as the disease severity worsens, combination therapy is universally recommended [1]. Figure 1 summarizes the currently recommended therapy for each stage of COPD based on the GOLD recommendations [102].

The physiologic basis of action for β-agonists is believed to relate to their ability to bind G-protein coupled β-2 adrenergic receptors and activate intracellular adenylyl cyclase. This increases levels of protein kinase A in a cAMP-dependent manner [22]. This leads to increases in intracellular Ca^{++} and relaxation of airway smooth muscle. There are differences in intrinsic activity and pharmacodynamics among agents in this group, which are beyond the scope of this discussion [23], but the primary distinction lies in the duration of action. SABAs act over 4–6 h, LABAs act over approximately 12 h and ultra-LABAs act over approximately 24 h.

Methylxanthines nonselectively inhibit phosphodiesterase (PDE) to act as a weak bronchodilator and respiratory stimulant. The classic agent in this class is theophylline, which has been limited in clinical use due to a narrow therapeutic index when traditional dosing

Table 1. Measurable end points in chronic obstructive pulmonary disease with their minimal clinically important difference.

Measures of respiratory function	MCID	Measures of disease modification	MCID
FEV1 [65,66]	112 ml or 4% predicted	Exacerbation frequency	Any significant difference
Inspiratory capacity [62,67]	100 ml	Rate of yearly decline in FEV1 [6]	50 ml/year (smokers) 25 ml/year (nonsmokers)
Exercise capacity (6MWD [68], ISWT [69])	6MWD: 54 m ISWT: 47.5 m	BODE index [12,13]	Two points
Dyspnea (BDI, TDI) [51]	1 unit change	Mortality	Any significant difference
Quality-of-Life (SGRQ [50], CRQ [52])	SGRQ: 4 units CRQ: 0.5 units		
6MWD: 6-min walk distance; BDI: Baseline dyspnea index; BODE: Body-mass index, airflow obstruction, dyspnea and exercise capacity index; CRQ: Chronic respiratory questionnaire; FEV1: Forced expiratory volume in 1 s; ISWT: Incremental shuttle walk test; MCID: Minimal clinically important difference; SGRQ: St George Respiratory Questionnaire; TDI: Transitional dyspnea index.			

Table 2. Currently available pharmacologic agents for chronic obstructive pulmonary disease.	
Pharmacologic category	Representative agents
Short-acting β-agonists	Albuterol/salbutamol
Short-acting muscarinic antagonists	Ipratropium bromide
Long-acting β-agonists	Albuterol/salbutamol, formoterol and arformoterol
Ultra-long-acting β-agonists	Indacaterol and tulobuterol
Long-acting muscarinic antagonists	Tiotropium
Methylxanthines	Theophylline
Selective phosphodiesterase inhibitors	Roflumilast and cilomilast
Inhaled corticosteroids	Fluticasone propionate, fluticasone furoate, budesonide, ciclesonide, beclomethasone, mometasone and triamcinolone

is utilized. Selective PDE-3 and -4 inhibitors have been developed to ameliorate the side-effect profile, but significant gastrointestinal side effects remain clinically apparent. One PDE4 inhibitor, roflumilast, was recently approved by the US FDA to reduce exacerbations in patients with severe COPD [103]. Of note, recent studies [24–26] have demonstrated the ability of low-dose theophylline to restore activity of histone deacetylase, suggesting its ability to restore and/or enhance corticosteroid sensitivity. Several past studies have shown beneficial effects from the addition of theophylline to other therapies for COPD [27–30], but it cannot be recommended as a first-line agent.

Muscarinic antagonists act via antagonism at muscarinic receptors M1, M2 and M3. M1 and M3 receptors mediate parasympathetic activity in the airways, causing smooth muscle contraction, mucus secretion and possibly increased ciliary activity [22,31]. Antagonism at these receptors leads to a decrease in parasympathetic tone in the airways, decreased secretions and decreased smooth muscle contraction. The M2 receptors, located on the post-ganglionic parasympathetic nerves, inhibit acetylcholine release from the nerve terminals. Ipratropium bromide is a short-acting antimuscarinic, which antagonizes all three receptor subtypes (M1, M2 and M3) with a duration of action approximately 6 h. Tiotropium bromide is a long-acting antimuscarinic antagonist, which rapidly dissociates from M2 receptors but provides prolonged antagonism at M1 and M3 receptors, up to 32 h.

The mechanism of action for ICS is less clear. In the large TORCH study, inhaled fluticasone propionate resulted in significant reductions in exacerbations (both moderate and severe), although mortality was the same. A meta-analysis of 13,000 subjects with stable COPD [32] found similar reductions in exacerbations, with no effect on mortality with the use of ICS. Some *in vitro* studies suggest interactions between the steroid receptor and the β-2 adrenergic receptors as an explanation for this benefit. The magnitude of benefit attributable to ICS has been disputed based on critique of the trials' design [33]. Systemic absorption of ICS does occur, especially at high doses, with side effects including oral candidiasis, hoarseness, cataract formation, skeletal fractures, and pneumonia having been reported [34]. It is unclear whether the increased incidence of pneumonia leads to increased mortality, but most recent studies have suggested no significant increase in mortality in patients taking ICS who are treated for pneumonia [35,36]. Studies of ICS have not monitored activity of histone deacetylase and investigations to date have been *in vitro,* with no data on clinical effects. Currently, ICS are recommended by society guidelines only in combination with bronchodilator therapy in those patients with predicted FEV1 < 50% and frequent exacerbations [1,102].

Combination therapy for COPD

The use of combination therapy is supported by multiple clinical trials and by guidelines from the European Respiratory Society and American Thoracic Society [37], as well as the GOLD [102]. These guidelines reflect the most well-established combinations of pharmacotherapy, but other dual combinations can be conceived (Table 3). Most studies of combination inhalers have been powered to detect changes in FEV1 between 75 and 100 ml [38,39].

Initial trials on combination therapy focused on combining LABA with ICS, based on the dual-effect hypothesis of bronchoconstriction and inflammation common to COPD and asthma. Indeed, significant benefit from this combination was noted in the TORCH trial [17], as well as a subsequent systematic review from the Cochrane Collaboration. A meta-analysis of the combination LABA plus ICS vs placebo noted reduction in exacerbation rates of approximately 25% and a significant reduction in all-cause mortality (3-year number-needed-to-treat: 36) [40]. The effects seen were dominated by the large TORCH trial, but studies of both salmeterol/fluticasone and formoterol/budesonide were included for analysis. This meta-analysis also noted an increased risk of pneumonia, with a 3 year number-needed-to-harm of 13. The combination of LABA with ICS has now become well established in clinical practice; the reader is referred to the Cochrane review [40] for a detailed analysis of the trials' results.

More recent trials have examined different combinations of therapy, addressing many potential dual combinations, noted in Table 3.

LAMA plus LABA

Table 4 includes pertinent features of recent trials evaluating the combination of LAMA plus LABA, which are discussed below.

Ichinose and colleagues evaluated the combination of the unique transdermal LABA tulobuterol and the inhaled LAMA tiotropium compared with tiotropium alone, in subjects with GOLD stage II and III COPD [41]. Subjects were not allowed to continue any other long-acting bronchodilator. The investigators found statistically significant improvements in respiratory-related quality of life, as measured by the St George Respiratory Questionnaire (SGRQ). However, a baseline imbalance in the SGRQ scores limits the impact of this finding.

Tashkin and coworkers evaluated the combination of nebulized arformoterol and tiotropium, compared with therapy alone, in subjects with GOLD stage II and III COPD [42]. No other LABA or anticholinergic could be used, nor could leukotriene modifiers or methylxanthines. Oral or ICS were permitted, provided the dose had been stable over 14 days prior to the study period. Approximately 20% of subjects in each group were using corticosteroids. The primary study outcome, mean FEV1 AUC, improved above baseline for each individual drug group, with a greater increase observed in the combined therapy group. Among secondary end points, the IC also increased significantly with combination therapy than with individual therapy, as did the improvement in mean transitional dyspnea index.

In 2005, van Noord and colleagues examined the combination of formoterol and tiotropium once daily compared with either daily tiotropium or twice daily formoterol, in subjects with mostly GOLD stage III COPD [43]. Subjects were allowed to continue inhaled or oral steroid use up to a daily dose equivalent of 10 mg, and prednisone and theophylline use was not allowed. A total of 90% of subjects were using corticosteroids (63 inhaled, two oral). As the primary outcome, the pre-dose morning FEV1 was significantly higher in subjects treated with combination therapy than when they received formoterol alone, but was similar to when they received tiotropium alone. As a secondary outcome, evaluation of 24-h FEV1 profiles was performed. This revealed that combination therapy produced superior FEV1 between hours 8–12 and again at hour 24 (trough). Use of rescue salbutamol was also lower during the daytime among patients taking the combination tiotropium plus formoterol.

Van Noord et al. later evaluated the combination of salmeterol (once or twice daily) and tiotropium compared with either agent alone (tiotropium daily or salmeterol twice daily) in subjects with GOLD stage II or III COPD [44]. Prior to randomization, subjects could not have used tiotropium and theophylline preparations for 4 weeks, but inhaled or oral steroid use was permitted up to a daily dose equivalent of prednisone 10 mg. Again, 90% of subjects were using corticosteroids (81 inhaled, five oral). The primary end point of average FEV1 over 24 h was significantly higher when subjects were receiving the combination of tiotropium and salmeterol once daily than with either tiotropium or salmeterol alone. The addition of an additional evening salmeterol dose resulted in similar daytime bronchodilation but superior night-time bronchodilation. In this study, transitional dyspnea index was also noted to improve more with once-daily combination therapy than with tiotropium or salmeterol alone. The addition of the second daily dose of salmeterol in combination with tiotropium did not increase the transitional dyspnea index (TDI) significantly more than with salmeterol once daily.

Recently, the combination of formoterol and tiotropium was compared with tiotropium alone in a meta-analysis by Wang et al. [45]. The authors concluded that treatment with the combination of tiotropium and formoterol resulted in significantly greater improvements in average FEV1, average FVC and trough FEV1. The mean improvement in transitional dyspnea index was also greater with the combination. There was a non-significant trend towards fewer adverse events (including COPD exacerbations) with combination therapy, but this did not reach statistical significance.

Table 3. Potential dual combinations of scheduled pharmacotherapy for chronic obstructive pulmonary disease†.						
	LABA	LAMA	ICS	Ultra-LABA	PDE3/4i	Methylxanthines
LABA		✓	✓		✓	✓
LAMA	✓		✓	✓	✓	✓
ICS	✓	✓		✓	✓	✓
Ultra-LABA		✓	✓		✓	✓
PDE3/4i	✓	✓	✓	✓		
Methylxanthines	✓	✓	✓	✓		

†Short-acting agents are excluded due to their recommended use only on an as-needed basis.
ICS: Inhaled corticosteroids; LABA: Long-acting β-agonists; LAMA: Long-acting muscarinic antagonists; PDEi: Phosphodiesterase inhibitor.

Table 4. Long-acting muscarinic antagonists and long-acting β-agonists trial characteristics.					
Study (year)	Patients (n)	Intervention duration (weeks)	Comparison	Statistically significant outcomes	Ref.
Ichinose *et al.* (2010)	103	8	Tiotropium plus tulobuterol vs tiotropium	SGRQ: -6.48 vs -1.90 units	[41]
Tashkin *et al.* (2009)	234	2	Tiotropium plus arformoterol vs arformoterol vs tiotropium	Mean FEV1 AUC: 0.22 vs 0.10 vs 0.08 liter IC: 0.15 vs 0.07 vs 0.02 liter TDI: 3.1 vs 2.3 vs 1.8 liter	[42]
Van Noord *et al.* (2005)	71	6	Tiotropium plus formoterol q.d. vs formoterol b.i.d. vs tiotropium	Pre-dose FEV1: 1.134 vs 1.091 vs 1.127 liter Use of rescue salbutamol: 1.81 vs 2.37 vs 2.41 puffs/day	[43]
Van Noord *et al.* (2010)	95	6	Tiotropium plus salmeterol q.d. vs tiotropium plus salmeterol b.i.d. vs salmeterol b.i.d. vs tiotropium	Average FEV1 increase over 24 h: 0.142 vs 0.185 vs 0.045 vs 0.070 liter TDI: 2.56 vs 2.71 vs 0.97 vs 1.18 liter	[44]
Wang *et al.* (2010)	1868 (pooled)	2–24	Tiotropium plus formoterol vs tiotropium	Average FEV1 increase over 24 h: 105 ml with combination Average FVC increase over 24 h: 135 ml with combination Trough FEV1 increase: 53.4 ml with combination Mean improvement in TDI: 1.50 units with combination	[45]
Rabe *et al.* (2008)	605	6	Tiotropium plus formoterol vs salmeterol plus fluticasone	FEV1 AUC$_{0-12}$: 1.64 vs 1.56 liter Peak FEV1: 1.78 vs 1.67 liter FVC AUC$_{0-12}$: 3.14 vs 2.97 liter Peak FVC: 3.38 vs 3.16 liter Pre-dose FVC: 2.95 vs 2.87 liter	[46]

b.i.d.: Twice daily; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; IC: Inspiratory capacity; q.d.: Daily; SGRQ: St George Respiratory Questionnaire; TDI: Transitional dyspnea index.

Rabe compared the combination of tiotropium daily plus formoterol twice daily to the combination of salmeterol plus fluticasone twice daily in subjects with GOLD stage II–III COPD [46]. During the study, ICS other than study medication were not permitted and oral steroids were only allowed in order to control acute exacerbations. The primary study end points were FEV1 AUC for hours 0–12 (FEV1 AUC$_{0-12}$) and peak FEV1. There was a statistically significant higher FEV1 AUC$_{0-12}$ and peak FEV1 with tiotropium plus formoterol than with salmeterol plus fluticasone. Statistically significant increases with the tiotropium plus formoterol combination compared with the salmeterol plus fluticasone combination were also seen in the secondary end points of FVC AUC$_{0-12}$, peak FVC and pre-dose FVC.

In summary, the trials above that have evaluated the combination of LABA plus LAMA have found consistently greater improvements in markers of lung function (FEV1 and FVC) with combination therapy compared with monotherapy. In addition, the transitional dyspnea index has consistently shown improvement with combination therapy, a change that has been both statistically (p < 0.05) and clinically (MCID + 1 unit) meaningful. In the large study by Rabe and colleagues, greater improvement in spirometry was seen with the combination of LAMA plus LABA versus the combination of LABA plus ICS, supporting guideline recommendations that for patients where a single bronchodilator does not suffice, the addition of two separate classes of bronchodilators is superior to bronchodilator monotherapy plus ICS [46]. The combination of LAMA plus LABA therapy has not caused an observed increase in adverse effects compared to either monotherapy or LABA plus ICS therapy, but the small size of these studies leave open the possibility of type II error, and larger, longer duration trials would be necessary to increase confidence in the safety of LAMA plus LABA therapy.

'Triple therapy'
In the above-mentioned trials of LAMA plus LABA combination therapy, the proportion of subjects using corticosteroids at baseline varied widely, from 20 [42]

to 90% [44]. Two small randomized trials have evaluated the combination of tiotropium and fluticasone/salmeterol for severe COPD [47,48] and current guidelines recommend combination therapy with inhaled LAMA, LABA and ICS, for patients with GOLD stage III or IV COPD who suffer from frequent exacerbations [1,102]. Two large trials of triple therapy deserve further mention, with pertinent details included in Table 5.

In 2007, the Canadian Thoracic Society and Canadian Respiratory Clinical Research Consortium published the results of The Canadian Optimal Therapy of COPD Trial [49]. Subjects with GOLD stage II or III COPD were treated with tiotropium, plus either placebo, salmeterol alone or salmeterol plus fluticasone. The primary outcome was the proportion of patients in each group experiencing a COPD exacerbation. As secondary outcomes, investigators examined the mean number of exacerbations per patient per year, the total number of exacerbations resulting in urgent care or emergency department visits, number of hospitalizations for COPD, number of hospitalizations in total, changes in health-related quality of life (as determined by SGRQ [50]), changes in dyspnea (as measured by the transitional dyspnea index [51] and the dyspnea domain of the Chronic Respiratory Questionnaire [52]) and lung function as measured by FEV1. There was no difference among groups in the primary outcome; between 60 and 65% of patients in all three groups experienced an exacerbation. Among secondary outcomes, there was a lower rate of hospitalizations, both all-cause and those specifically for COPD, in the triple-therapy group compared with the tiotropium plus placebo group. This benefit was not seen in the group treated with tiotropium plus salmeterol compared with tiotropium plus placebo. Quality of life per SGRQ was improved more with each additional therapy. Dyspnea did not differ significantly among groups, but lung function measured by FEV1 increased significantly more in the triple-therapy group than in the tiotropium plus salmeterol group. However, this improvement was still less than the

MCID for FEV1. There was not a significant difference from placebo in the group assigned to tiotropium plus salmeterol. No difference in adverse events, including death and hospitalizations, was observed.

Welte performed a trial of budesonide/formoterol in addition to tiotropium ('triple therapy') versus tiotropium alone in subjects, with predominantly GOLD stage III COPD [53]. The primary end point was the change in pre-dose FEV1 over weeks 0–12. As secondary end points, measurement of pre-dose FVC and IC, and post-dose FEV1, FVC and IC, were performed. Quality of life was assessed using SGRQ at each of the six clinic visits. Over the treatment period, triple therapy significantly increased pre- and post-dose FEV1. This change was more than the MCID in post-dose FEV1, but not in pre-dose FEV1 [8]. Overall, the improvement in SGRQ was statistically significant, but also below the MCID of 4 units [51,54]. An improvement in SGRQ by more than 4 units was seen in 49.5 and 40% of subjects in the triple-therapy and tiotropium-alone groups, respectively (p = 0.016), but 27.6 and 29.7% of subjects had a deterioration in SGRQ of more than 4 units (p = nonsignificant). There was a significantly lower incidence of severe exacerbations in the triple-therapy group compared with the tiotropium-alone group.

The trial by Welte et al. of triple therapy compared with LAMA alone thus demonstrated improvements in lung function and dyspnea approximately equivalent to those seen in the aforementioned trials of LAMA plus LABA therapy [53]. The reduction in severe exacerbations seen in this trial was not seen in trials of LAMA plus LABA, suggesting that the reduction in exacerbations is attributable to the addition of ICS. However, the 52-week Canadian Optimal Trial found no difference in the number of patients experiencing exacerbations, although there was a numerically longer median time to first exacerbation in the triple-therapy group and the trial was underpowered to detect a true difference [49]. Based on these data, one could postulate that the true benefit of ICS in triple therapy is less than

Table 5. 'Triple therapy' trial characteristics.					
Study (year)	Patients (n)	Intervention duration (weeks)	Comparison	Statistically significant outcomes	Ref.
Aaron *et al.* (2007)	449	52	Tiotropium vs tiotropium plus salmeterol vs tiotropium plus salmeterol/fluticasone	SGRQ: -4.5 vs -6.3 vs -8.6 units Pre-dose FEV1 increase at week 52: 0 (reference) vs +0.027 vs +0.086 liter	[49]
Welte *et al.* (2009)	660	12	Tiotropium vs tiotropium plus formoterol/budesonide	Pre-dose FEV1: 1.08 vs 1.15 liter Post-dose FEV1: 1.13 vs 1.25 liter SGRQ: -1.5 vs -3.8 units Severe exacerbations: 18.5 vs 7.6%	[53]
FEV1: Forced expiratory volume in 1 s; SGRQ: St George Respiratory Questionnaire.					

that seen in the short-duration trial by Welte *et al.*, or alternatively, that the small significant improvement in lung function measures seen in the longer Canadian Optimal Trial is a result of properties unique to salmeterol, fluticasone or the combination. A large trial comparing salmeterol plus fluticasone to formoterol plus budesonide would be informative but is unlikely to occur without funding from outside industries.

Notably, no regulatory standard is established regarding the efficacy of combination treatment with triple therapy. It is not unexpected that incremental benefit on measures of lung function (FEV1, IC and TDI) is small as agents are added, and the use of composite end points combining measures of lung function with number of exacerbations might enable a significant effect to be seen. In addition, the regulatory approval of triple therapy may be aided by the development of new fixed-dose combination inhalers and novel dual-ligand molecules combining β-agonist and muscarinic-antagonist effects (termed muscarinic antagonist β-agonist) [55].

PDE4 inhibitors plusLABA or LAMA

Roflumilast is a selective inhibitor of PDE4 inhibitors that was studied in combination with salmeterol or tiotropium by Fabbri *et al.* in two separate trials, with results published concomitantly [56]. After a 4-week run-in period where subjects took daily placebo pills, 935 subjects were randomized to either roflumilast or placebo plus salmeterol, and 744 subjects were randomized to either roflumilast or placebo plus tiotropium for a duration of 24 weeks. These subjects all had GOLD stage II or III COPD and were not permitted to use inhaled steroids or any other bronchodilator during the study period, except for the supplied SABA as needed. For the primary end point, change in mean pre-bronchodilator FEV1 was 49 ml in the salmeterol plus roflumilast group versus salmeterol plus placebo, and 80 ml in the tiotropium plus roflumilast group versus tiotropium plus placebo. A similar magnitude of increase was noted in mean post-bronchodilator FEV1 (60 and 81 ml), mean pre-bronchodilator FVC (47 and 95 ml) and mean post-bronchodilator FVC (58 and 101 ml). Improvements in other secondary measures, including TDI, shortness of breath questionnaire and baseline use of rescue medications were variable, some reaching statistical significance but none greater than the MCID. The presence of adverse reactions related to study medication was higher in the groups receiving roflumilast; most of these were gastrointestinal in nature, consistent with previous studies. The likelihood of study withdrawal was statistically higher for roflumilast plus salmeterol than placebo plus salmeterol, but not for roflumilast plus tiotropium compared with placebo plus tiotropium. A nonstatistically significant decrease in mean

bodyweight was also noted in the groups treated with roflumilast (-2.0 kg for roflumilast plus salmeterol; -1.8 kg for roflumilast plus tiotropium).

Despite the relatively short duration of these trials, there were statistically significant decreases in exacerbation rates and increases in time to first exacerbation demonstrated in both. When added to salmeterol, roflumilast decreased the proportion of patients with any exacerbation by 6% and increased the time to first moderate or severe exacerbation by 12 days. When added to tiotropium, roflumilast decreased the proportion of patients with any exacerbation by 8% and increased the time to any exacerbation by 13 days. On the FDA advisory panel review in April 2010, these data, in addition to two earlier studies [57], were a major part of the discussion. The FDA advisory panel presentation noted that effects on FEV1 and SGRQ were modest (less than the MCID) and the clinical significance was uncertain. The reduction in exacerbations was considered a clinically relevant effect, but it was noted that the use of concomitant standard therapies for COPD was heavily restricted during these trials and the risk:benefit ratio may be better characterized with additional study [104]. After reviewing the recommendations of the advisory panel, the FDA granted approval to roflumilast on 1 March 2011 to "decrease the frequency of flare-ups (exacerbations) or worsening of symptoms from severe chronic obstructive pulmonary disease (COPD)" [103]. The magnitude of benefit from roflumilast compared with that from ICS has not yet been rigorously studied. At this time the best candidates for treatment with roflumilast appear to be those patients already taking a bronchodilator who experience ongoing risk for exacerbations, and who cannot tolerate ICS.

Methylxanthine plus ICS

There is a well-established decrease in histone deacetylase activity in asthma and COPD [26,58]. Theophylline has been shown to perform poorly as a bronchodilator due to its narrow therapeutic window, but at low-doses can activate cellular histone deacetylase and potentially restore responsiveness to corticosteroids [59]. Ford *et al.* recruited 30 patients with COPD (primarily stage II) and randomized them to receive either inhaled fluticasone propionate or placebo for 4 weeks [60]. Subjects then underwent a 2-week washout period and were crossed over to treatment with the alternate inhaler. During the first 4-week period all subjects took placebo capsules twice daily and during the second 4-week period all subjects took active theophylline capsules. Apart from study medication, subjects who were already taking a LABA or LAMA were permitted to continue the medication. Use of oral corticosteroids was an exclusion criterion and inhaled steroids were discontinued during

an initial 2-week washout period. Subsequently, seven subjects were recruited into an open-label repeat of arm two for the purpose of determining histone deFacetylase activity using peripheral blood mononuclear cells. Subjects tolerated theophylline well, with dose reduction required in four subjects due to mild nausea and gastrointestinal upset. The primary study end point was a reduction in absolute sputum neutrophils, and secondary end points were sputum total and cell-specific counts, chemokine ligand 5, IL-8 and neutrophil elastase levels in sputum, lung function and quality of life data measured by self-administered chronic respiratory questionnaire. Significant differences in lung function could only be demonstrated for FEV1% predicted in the ICS plus theophylline arm (from 52 to 58.6% predicted; p = 0.024) and forced expiratory flow 25–75% (470–555 ml/s; p = 0.029). No significant change in sputum neutrophils was noted, but sputum eosinophils were reduced in the ICS plus theophylline arm compared with ICS alone (0.05×10^6/ml vs 0.13×10^6/ml; p = 0.023). An analysis of sputum chemokines showed only a small reduction in IL-8 in the combination group compared with ICS alone. Quality of life score did not differ significantly between arms. Total histone deacetylase activity increased from 95 to 875 units in the seven patients who repeated arm two of the study. In summary, this preliminary data was not designed to detect clinically significant differences in lung function or disease natural history, but does suggests some attenuation of inflammation in COPD, as well as an increase in histone deacetylase activity. Additional subjects and additional time would be required to observe for any clinically significant effect of low-dose theophylline on COPD.

Future perspective

The recent clinical trials discussed highlight a process of systematically evaluating the myriad of possible combinations of current pharmacologic agents for the treatment of COPD. To date, combination therapy with LABA plus LAMA, LABA plus ICS and 'triple therapy' with LAMA plus LABA plus ICS, have the largest data sets and support from clinical guidelines. The combination of LAMA plus ICS has been described in a single human trial [61] and an additional study is warranted. Similarly, the role of PDE4 inhibitors (primarily roflumilast) will be better clarified via investigations of its effects on exacerbation rates when added to standard guideline-based treatment; the recent FDA approval should allow for such studies to take place more easily.

One of the commonly faced difficulties in designing trials of COPD therapy is choosing appropriate end points. Unlike for the management of the other major obstructive lung diseases, such as asthma, COPD has no consistent system to grade control, which is reflective of daily impairment. Recent trials have adopted measurement of the transitional dyspnea index as a primary measure of dyspnea [49] and this value performs similarly to measures of IC [62]. While rate of decline of FEV1 and body-mass index, airflow obstruction, dyspnea, and exercise capacity index [12] will remain important as a measure of the natural history of COPD [10,63], future trials will likely use additional measures to ascertain day-to-day impairment of subjects with COPD. More consistent use of these additional measures (e.g., TDI [51] and IC) will improve homogeneity of trials, the ability to detect early changes in quality of life, and lead to better quality meta-analyses of large data sets.

Another difficulty that is being recognized with increasing consensus is the heterogeneity among patients who suffer from COPD. Indeed, the WHO definition includes patients classically diagnosed with either emphysema or chronic bronchitis, highlighting two major phenotypic expressions of this syndrome. It is likely that underlying predispositions in patients that lead to differing phenotypes will also lead to a differential response to pharmacotherapy. Future work to identify phenotypic clusters of patients with COPD will be greatly aided by the creation of large COPD registries, such as the subpopulations and intermediate outcome measures in COPD study (SPIROMICS, [105]). With a clearer picture of the COPD population, clinical trials can be undertaken in discrete subpopulations of this disease. It is conceivable that, similarly to emerging research in patients with asthma, we will discover genetic markers of certain COPD phenotypes that predict differential response to pharmacotherapy and those patients at greatest risk for disease progression. In the interim period, large trials should routinely consider responder analysis to assist in the identification of distinct phenotypes [64].

Executive summary

- Chronic obstructive pulmonary disease (COPD) is a disease characterized by airflow obstruction that is not fully reversible and is a cause of significant morbidity and mortality worldwide.
- Pharmacologic treatment of COPD is primarily accomplished with inhaled bronchodilators and inhaled corticosteroids.
- Previous clinical trials have shown the superiority of combining bronchodilators with different mechanisms of action compared with use of a single agent, and society guidelines recommend this approach to treatment.
- Recent clinical trials have explored novel combinations of agents and continue to demonstrate increased efficacy with various combinations.
- Future clinical trials using newly developed agents will lead to further clarity of the optimal combination for patients with COPD.
- The standards for measuring effects of combination therapy are evolving and additional studies are necessary to define an acceptable minimal clinically important difference for the incremental addition of agents.
- The use of consistent disease-modifying and quality of life end points among clinical trials will allow for more direct comparisons and higher quality meta-analysis of large data sets. Forced expiratory volume in 1 s will be de-emphasized as a measure of daily impairment in COPD.
- Population and genomic research will lead to better selection of agents on an individual patient basis and assist in predicting those patients most at risk for progression of COPD.

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