Management of Stable COPD: Focus on Pharmacotherapy
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ABSTRACT

• Objective: To review contemporary concepts and agents used in pharmacotherapy for chronic obstructive pulmonary disease (COPD).
• Methods: Qualitative assessment of recent trials with emphasis on impact of pharmacotherapy on clinical outcome measures.
• Results: Pharmacotherapy for COPD has become multifaceted to reflect the pathogenesis of the condition. Long-acting anti-muscarinic agents, long-acting β2-agonists, inhaled corticosteroids in combination with long-acting β2-agonists, phosphodiesterase inhibitors, and mucolytics have been associated with improved outcomes. Combination therapies incorporating different classes of medications hold promise for altering disease progression.
• Conclusion: Pharmacotherapy holds promise in significantly altering disease progression in COPD in addition to providing symptom relief.

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow obstruction associated with airway inflammation and mucus production [1]. It represents a major worldwide health problem resulting in a large socioeconomic burden. The World Health Organization reported that COPD was the fifth leading cause of death in the world in 2002, and projected to become the third by the year 2030 due to continued tobacco use and an aging population [2]. COPD may already be the third leading cause of death in the United States [2,3]. It is estimated that COPD will become the seventh leading cause of disability-adjusted life years (DALYs) in the year 2030 [2,4], ranked 11th in 2002.

Factors that could account for the mortality and morbidity of COPD include the prevalence of smoking, progression of airflow obstruction, and persistent airway inflammation. Specifically, despite previous declines in smoking prevalence in US adults from a peak of over 40% in the 1950s, rates appear to have remained stable at about 21% between 2005 and 2009 [5]. Additionally, data from the Framingham cohort document continued and pronounced progression of airflow obstruction, indistinguishable from continuous smokers in patients who quit smoking after the age of 40 [6]. The significance of inflammation in the pathogenesis of COPD has been increasingly recognized over the past decade. Airway inflammation in small airways correlates with the degree of severity of airflow obstruction [7]. While the inflammation in COPD is thought to be an amplified response to noxious stimuli (eg, tobacco abuse), the inflammatory process persists, albeit reduced and altered in pattern, after cessation of exposure [8,9]. Protease–antiprotease imbalance is closely related to lung inflammation and results in lung parenchymal destruction [10]. Oxidative stress promotes inflammatory response via direct cellular injury [11] and inhibition of histone deacetylation [12,13]. Exacerbation of COPD is defined as an acute inflammatory event superimposed on chronic inflammation associated with COPD. The excess inflammatory burden is frequently brought on by infections [14] and results in increased mortality [15] and faster decline in lung function [16].

These findings indicate that there may be room for targeted therapeutic intervention in certain groups of patients with COPD. Enhanced understanding of disease pathogenesis and natural history has instigated a paradigm shift in the management of COPD. Traditionally, pharmacotherapy of COPD targeted symptomatic relief, improvement in quality of life, and prevention of exacerbations, which remain worthy goals. The new frontier, however, is prevention of disease progression and reduction in mortality (GOLD update). Information from recent mega-trials of pharmacotherapy garnered enthusiasm that these may be achievable goals. Table 1 provides a list of agents currently available for

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COPD PHARMACOTHERAPY

Table 1. Pharmacotherapeutic Agents Available in the US for the Treatment of COPD*

<table>
<thead>
<tr>
<th>LAMA</th>
<th>Tiotropium 18 mcg once a day</th>
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<tr>
<td></td>
<td>Aclidinium (FDA application pending)</td>
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<tr>
<td>LABA</td>
<td>Salmeterol 50 mcg twice daily</td>
</tr>
<tr>
<td></td>
<td>Formoterol 9 mcg twice a day (powder inhalation), 20 mcg twice a day (inhalation solution)</td>
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<tr>
<td></td>
<td>Arformoterol 15 mcg twice a day (inhaled solution)</td>
</tr>
<tr>
<td></td>
<td>Indacaterol 75 mcg once a day</td>
</tr>
<tr>
<td>ICS</td>
<td>Inhaled corticosteroids are only approved as part of combination therapy with LABA in the treatment of COPD.</td>
</tr>
<tr>
<td>LABA/ICS</td>
<td>Fluticasone 250 mcg/salmeterol 50 mcg – one inhalation twice a day</td>
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<tr>
<td></td>
<td>Fluticasone 500 mcg/salmeterol 50 mcg – one inhalation twice a day†</td>
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<tr>
<td></td>
<td>Budesonide 160 mcg/formoterol 4.5 mcg – one inhalation twice a day</td>
</tr>
<tr>
<td></td>
<td>Mometasone/formoterol – one inhalation twice a day ‡</td>
</tr>
<tr>
<td>PDE inhibitors</td>
<td>Theophylline – blood concentration titrated to 5–15 mcg/ml or 300 mg tablet/capsule orally once a day †</td>
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<tr>
<td></td>
<td>Roflumilast 500 mcg tablet orally once a day †</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Erythromycin 250 mg tablet orally twice a day ‡</td>
</tr>
<tr>
<td></td>
<td>Azithromycin 250 mg tablet orally twice a day ‡</td>
</tr>
<tr>
<td>Mucolytics</td>
<td>N-acetylcysteine 600 mg once or twice a day ‡</td>
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</table>

ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting anticholinergic.
* FDA-approved formulations and dosage unless indicated otherwise.
† Dose used in TORCH trial.
‡ No specific FDA indication for COPD.

the pharmacotherapy of COPD in the United States. The internationally acknowledged Global Initiative for Chronic Obstructive Lung Disease (GOLD) program suggests stepwise introduction of pharmacotherapeutic agents for the treatment of COPD following a combined assessment of symptoms, airflow obstruction, and risk of acute exacerbation of COPD (Table 2).

The aim of our review is to provide a synopsis of contemporary pharmacotherapy for management of the stable COPD patient. In doing so, we have chosen to review pharmacotherapeutic agents in the respective classes based on mechanism of action.

LONG-ACTING ANTI-MUSCARINIC ANTAGONISTS (LAMAS)

In patients with COPD, the vagal cholinergic tone is considered to be the major component of reversible airflow obstruction and mucus secretion [17]. Cholinergic action is mediated by muscarinic receptors, designated M1, M2 and M3, in the lung. Stimulation of M1 (ganglionic receptor) and M3 (smooth muscle and mucus gland receptor) result in bronchoconstriction and mucus secretion. The presynaptic M2 receptor, on the other hand, is part of the feedback mechanism and its stimulation results in inhibition of the cholinergic response. Ipratropium bromide was the first inhaled anticholinergic agent for the treatment of COPD. In 2002, tiotropium bromide was approved by the FDA and offered certain advantages over ipratropium, including more rapid dissociation from M2 receptors and a substantially higher affinity for M1 and M3 receptors, thereby potentiating the bronchodilator action and its duration [18]. Tiotropium has a half-life of 5 to 6 days with no drug accumulation at steady state. No tachyphylaxis has been reported in studies lasting up to a year [18]. When compared to its short-acting counterpart ipratropium, tiotropium improved dyspnea, health-related quality of life, and lung function and reduced exacerbations [19]. In preliminary studies, tiotropium reduced hyperinflation [20] and improved exercise capacity [21,22] and dyspnea scores [23] compared with placebo. In a study of 443 patients with COPD, tiotropium led to a significant improvement in health-related quality of life as measured by the St. George’s Respiratory Questionnaire (SGRQ) when compared with ipratropium [19]. A recent meta-analysis of 11 studies
A study of 13,124 patients (n = 13,124) that compared tiotropium with placebo showed significant reduction in the likelihood of COPD exacerbation (odds ratio [OR] 0.83, 95% confidence interval [CI] 0.72 to 0.94, P = 0.004) [24].

The largest study exploring effects of tiotropium has been the UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) trial [25]. UPLIFT was a double-blind randomized trial that compared tiotropium with placebo in 5993 patients with a mean FEV1 of 48% of predicted over a 4-year period of follow-up. The patients were allowed use of other respiratory medications as needed except for short-acting anticholinergic agents. Although there were significant improvements in mean pre- and postbronchodilator FEV1 (87 to 103 mL and 47 to 65 mL respectively, P < 0.001) in the tiotropium arm compared with placebo, the rate of decline in mean FEV1, the study endpoint, was not different between tiotropium and placebo before (30 ± 1 vs. 30 ± 1 mL/year, P = 0.95) and after bronchodilation (40 ± 1 vs. 42 ± 1 mL/yr, P = 0.21). Since most of the patients in UPLIFT were on maintenance medications and overall effect on the lung function decline was negative, it has been proposed that there may be a ceiling effect to bronchodilator therapy in the modulation of disease progression, and further improvements would require interventions that impact lung regeneration and repair [25]. In a targeted prespecified analysis of patients aged ≤50 years, there was a significant reduction in the rate of decline of postbronchodilator FEV1 (58 mL/year vs. 38 mL/yr, P = 0.01) [26]. Similarly, patients with GOLD stage II disease who received tiotropium had slower rate of decline in FEV1 (43 ± 2 vs. 49 ± 2 mL/yr, P = 0.024) compared with placebo [27]. These findings suggest that earlier introduction of tiotropium may impact disease progression. In a similar vein, UPLIFT patients who were not on other maintenance treatments at randomization (n = 810) had slower rate of decline in FEV1 (42 ± 4 vs. 53 ± 4 mL/yr, P = 0.026) [28].

Importantly, a number of clinically relevant outcomes were improved in patients treated with tiotropium. Health-related quality of life as measured by SGRQ improved in favor of tiotropium with higher proportion

<table>
<thead>
<tr>
<th>PATIENT CATEGORY BASED ON COMBINED COPD ASSESSMENT</th>
<th>FIRST CHOICE</th>
<th>SECOND CHOICE</th>
<th>ALTERNATIVE CHOICES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk Less symptoms</td>
<td>SAMA or SABA as needed</td>
<td>LAMA or LABA or SABA and SAMA</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Low risk More symptoms</td>
<td>LAMA or LABA</td>
<td>LAMA and LABA</td>
<td>SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>High risk Less symptoms</td>
<td>LABA/ICS or LAMA</td>
<td>LAMA and LABA</td>
<td>PDE4 inhibitors. SABA and/or SAMA Theophylline</td>
</tr>
<tr>
<td>High risk More symptoms</td>
<td>LABA/ICS or LAMA</td>
<td>ICS and LAMA or LABA/ICS and LAMA or LABA/ICS and PDE4 inhibitors or LAMA and LABA or LAMA and PDE4 inhibitors</td>
<td>Carbocysteine SABA and/or SAMA Theophylline</td>
</tr>
</tbody>
</table>

ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting anticholinergic; SABA = short-acting β2-agonist; SAMA = short-acting anticholinergic. (Adapted from the GOLD document, available at www.goldcopd.com.)

* Symptom assessment is based on modified MRC (mMRC) breathlessness scale or the COPD assessment tool (CAT, available at cates-tonline.org). Less symptoms corresponds to an mMRC of 0–1 or CAT < 10, more symptoms correspond to mMRC ≥ 2 or CAT ≥ 10. Risk level is based on the more severe of airflow limitation or exacerbation history. Low risk corresponds to GOLD 1 or 2 (FEV1 ≥ 50%) or ≤1 exacerbation per year. High risk corresponds to GOLD stages 3 or 4 (FEV1 < 50%) or ≥2 exacerbations per year.
of patients (45% vs. 36%, \(P < 0.001\)) showing clinically significant improvement of 4 units or more. Tiotropium reduced the number of exacerbations per patient year (0.73 ± 0.02 vs. 0.85 ± 0.02, risk ratio [RR] 0.86, CI 0.81 to 0.91; \(P < 0.001\)) and the risk of respiratory failure (RR 0.67, 95% CI 0.51 to 0.89). There were no significant differences in risk of myocardial infarction, stroke, and pneumonia. In another post hoc analysis of UPLIFT trial database, Hanania et al showed that improvements in spirometry and health outcomes were not determined by acute bronchodilator responsiveness at baseline [29]. The beneficial effects of tiotropium were independent of smoking status [30].

Aclidinium bromide is a novel long-acting inhaled anti-muscarinic agent which awaits approval from the FDA. Aclidinium has a slightly faster onset of action and considerably shorter half-life (29 hr vs. 64 hr) compared with tiotropium [31,32]. It provides sustained bronchodilation over 24 hours and may have a favorable side effect profile as it undergoes rapid hydrolysis in human plasma [33]. A phase 1 trial in patients with COPD has shown significant improvements in specific airway conductance, resistance, bronchial responsiveness [34], and the FEV1 area under curve [35] compared with placebo 24 hours following the administration of aclidinium bromide. In 181 patients with moderate to severe COPD, aclidinium 200 mcg once daily improved exercise endurance time (constant work rate cycling), FEV1, inspiratory capacity, and Borg dyspnea scores compared with placebo [36]. In a more recent randomized, double-blind, double-dummy crossover phase IIa study, twice daily aclidinium 400 mcg was compared with tiotropium 18 mcg daily and placebo in 30 patients with COPD [37]. Aclidinium was associated with superior FEV1 area under the curve values compared with placebo and tiotropium. Improvement in COPD symptoms was similar to tiotropium. In 2 double-blind studies conducted over 52 weeks, aclidinium administered at 200 mcg daily significantly improved pulmonary function and SGRQ scores [38]. Aclidinium is currently in phase III trials, which should delineate its role in COPD pharmacotherapy.

Concern has been raised based on several trials that reported an increase in cardiovascular risks, subsuming stroke, cardiovascular events, and death, with the use of anticholinergic agents. In a pooled analysis of 29 trials of tiotropium (25 with the dry powder device and 4 with the soft mist device) encompassing 13,544 individuals, there was an increase in stroke (RR 1.37, 95% CI 0.73 to 2.56) [39]. Similarly in a meta-analysis of 17 randomized trials that included tiotropium by dry powder and ipratropium, the use of inhaled anticholinergics was associated with an increased risk of myocardial infarction, cardiovascular deaths or strokes (RR 1.58, 95% CI 1.21 to 2.06) [40]. In a cohort study of 82,717 veterans, there was also an increased risk of cardiovascular event with the use of tiotropium [41].

Particular limitations of those studies include non-adjustment for the multiple safety endpoints with broad inclusion of a number of terms in the analysis of “stroke” as an adverse event [39], a selection bias towards studies reporting cardiovascular events, inclusion of active- and placebo-controlled trials, and higher discontinuation rates in the placebo groups (healthy survivor effect) [42].

Several other reports, including most notably the UPLIFT study, which appropriately addressed those concerns, did not show an increase in cardiovascular risk. Specifically, the UPLIFT trial used mortality adjudication worksheet for classification of stroke-related events and had a large sample size with pre-specified safety endpoints. In that study, treatment with tiotropium by dry powder was found to be associated with reduced mortality, including cardiac mortality (hazard ratio 0.86, 95% CI 0.75 to 0.99) [43]. Similar favorable results were reported in a pooled study of 30 clinical trials (including the UPLIFT study) [44].

An unresolved question is whether different drug delivery systems would be similarly safe. For instance, in a combined analysis of trials of the soft mist formulation of tiotropium (Respimat, which is not available in the United States), there was an increased RR for death compared with placebo (RR 1.7, 95% CI 1.1 to 2.8) that was no longer significant after adjustment for a potential healthy survivor effect (RR 1.4, 95% CI 0.9 to 2.0) [43]. Similarly, in a meta-analysis of 6522 patients with COPD, the use of the soft mist formulation of tiotropium was associated with a 52% increase in all-cause mortality compared with placebo [45].

Our approach follows the FDA conclusion, based on the rigorous data of the UPLIFT trial, that there is no evidence for an increased risk of adverse cardiovascular events with the use of the dry powder (handihaler) form of tiotropium [42].

**LONG-ACTING β2-AGONISTS (LABAS)**

Stimulation of airway β2 receptors result in smooth muscle relaxation and consequent bronchodilatation via the cAMP-dependent pathway [46]. Short-acting
β2-agonists such as albuterol and terbutaline have long been used as rescue medications for obstructive lung diseases. Their short half-life, however, limits efficacy as maintenance medications. LABAs provide sustained bronchodilation and offer greater convenience for patients with COPD. Salmeterol, formoterol, arformoterol, and indacaterol are approved for use in the United States at the time of this writing.

LABAs provide significant improvements in FEV1 when compared with placebo [47–49]. Dyspnea as measured by patient reported diary cards is reduced with salmeterol [50] and formoterol [51]. Salmeterol and formoterol improve indices of dynamic hyperinflation and exercise tolerance during cycling [52,53]. However, in contrast to long-acting antimuscarinic agents, there have been reports of tachyphylaxis with the use of LABAs [54,55].

LABAs have been associated with significant improvements in health-related quality of life indices and exacerbation frequency [56,57]. Of the twice-daily LABAs (salmeterol, (ar)formoterol), formoterol's onset of action is faster than salmeterol with no evidence of significant differences in other outcome measures [58,59].

Indacaterol is the first once-daily LABA (“ultra LABA”) approved for use in the European Union in 2009 and approved by the FDA in July 2011. Possibly owing to its high affinity for the lipid raft domain of the cell membrane where β2 receptors are coupled to second messengers [60], the drug has 24-hour duration of action. In patients with COPD, inhaled indacaterol 300 mcg improved airflow obstruction and hyperinflation (as measured by an increase in inspiratory capacity) significantly greater than twice-daily formoterol [61]. When compared with salmeterol, indacaterol provides greater improvements in FEV1, health-related quality of life measures, and dyspnea while reducing rescue medication use [62]. The drug has also shown equivalent bronchodilator efficacy at 150 and 300 mcg daily dosing compared to tiotropium [63]. The benefits of a longer-acting bronchodilator such as indacaterol are likely mediated via smoothing out of airway bronchomotor tone over 24 hours without the dips seen in shorter-acting agents and improvement of the FEV1 trough before the subsequent dose is due, aptly named “pharmacological stenting” [64]. Once-daily dosing should also foster improved adherence [65].

A significant concern regarding long-acting β-agonists in asthma has been raised by the Salmeterol Multicenter Asthma Research Trial (SMART) [66], which was terminated due to the finding that there were 13 deaths out of 13,176 subjects randomized to the long-acting β-agonist group compared with 3 deaths out of 13,179 subjects randomized to the placebo group, thereby imparting a relative risk of death of 4.3 in the treatment group compared with the placebo group. Similarly, data provided for the FDA advisory committee indicates that asthma-related serious adverse events were more frequent in patients on formoterol compared with placebo, suggesting a possible class effect [67]. Note that those concerns have not been confirmed in patients with COPD. For instance, in the TORCH study, a potential survival advantage was noted in patients with COPD receiving a combination of inhaled corticosteroids and LABA [68], with further analysis suggesting that the mortality benefit in the TORCH study is entirely due to the LABA component (17% reduction in mortality) rather than the inhaled corticosteroid component (0% reduction in mortality) [69].

**INHALED CORTICOSTEROIDS**

Inhaled corticosteroids (ICS) reduce eosinophilic airway inflammation, the major reason for airflow obstruction and symptoms, and thus have become the mainstay of treatment in asthma [70]. Patients with COPD also display significant airway inflammation [71] that correlates with disease severity [7] and bronchodilator responsiveness [72], allowing parallels to be drawn between the disorders. Inflammation in patients with COPD is predominantly a neutrophil and CD8+ T lymphocyte–rich process in contrast with asthma, which is predominantly an eosinophilic and CD4+ T lymphocytic inflammation [70]. Nevertheless, mast cells have also been reported to play a role in bronchiolar inflammation in the COPD airway [73].

The role of ICS in improving COPD-related clinical outcomes was assessed in 4 large randomized controlled trials (RCTs) of 3 years’ duration that compared ICS with placebo [74–77] and one 3-year-long RCT with 4 arms, 2 of which were an ICS and placebo [68]. In these studies, bronchodilator responsiveness was an exclusion criterion. In a group of 1277 patients with mild COPD, mean FEV1 77% of predicted, inhaled budesonide 800 mcg/day seemed to improve FEV1 decline during the first 6 months followed by comparable rates thereafter [76]. Similarly, inhaled budesonide dosed at 1200 mcg daily for 6 months followed by 800 mcg daily had no impact on FEV1 decline or number of COPD exacerbations in 290 patients with mild COPD (mean FEV1 86% of predicted) [77]. In the third trial, 751 patients
with moderately severe COPD (mean FEV1 50% of predicted) from 18 UK hospitals were randomized to receive fluticasone propionate 1000 mcg daily versus placebo [74]. The decline in FEV1 in the intervention group was not different than placebo, however, exacerbation rate was reduced by 25%. In the Lung Health Study, 1116 patients with COPD of varying severities received triamcinolone 1200 mcg daily or placebo [75]. Again, there was no difference in rate of FEV1 decline between intervention and placebo groups (44.2 ± 2.9 vs. 47.0 ± 3.0 mL/yr, P = 0.50). However, patients who received triamcinolone had less respiratory symptomatology, less methacholine reactivity, and decreased physician visits due to respiratory illness. Finally, a mega-trial of 6112 patients (TORCH trial) with COPD who had FEV1 < 60% included a group that received fluticasone 1000 mcg daily (n = 1534) as well as placebo, salmeterol, and salmeterol-fluticasone combination [68]. In the TORCH trial, the primary endpoint was a reduction in mortality, which did not materialize for any of the intervention groups. Fluticasone did reduce moderate or severe exacerbation rate (rate ratio 0.82, 95% CI 0.76 to 0.89; P < 0.001) and improve SGRQ scores (−2.0, 95% CI −2.9 to −1.0, P < 0.001) compared with placebo. In a post hoc analysis of the TORCH trial, fluticasone was shown to reduce FEV1 decline compared to placebo (42 mL/yr vs. 55 mL/yr) between 6 months and 3 years after randomization [78]. Importantly, similar magnitude of reduction in the rate of FEV1 decline were also shown for salmeterol and salmeterol-fluticasone combination.

In a recent Cochrane review of studies that involved ICS with placebo control, 47 trials (including the aforementioned 5) with 13,139 patients were evaluated in a meta-analysis [79]. The study concluded that ICS had no statistically significant effect on mortality and rate of FEV1 decline. However, there was a favorable effect on exacerbations (weighted mean difference −0.26 exacerbations per patient per year; 95% CI 0.37 to −0.14) and the rate of decline in quality of life as measured by SGRQ scores (weighted mean difference −1.22 units/year, 95% CI −1.83 to −0.60).

More recently, in a meta-analysis of 7 randomized trials (5997 patients) that compared the use of ICS versus LABA in the treatment of stable COPD, no difference was found in the number of patients experiencing exacerbations (OR 1.22, 95% CI 0.89 to 1.67) or the rate of exacerbations per patient year (rate ratio 0.96, 95% CI 0.89 to 1.02) [80]. There was a trend toward increased mortality (OR 1.17, 95% CI 0.97 to 1.42) for patients on ICS compared with those on LABA. The incidence of pneumonia was significantly higher for patients who received ICS (OR 1.38, 95% CI 1.10 to 1.73). There was a small difference in SGRQ scores favoring ICS, however the magnitude was not clinically significant (mean difference −0.74, 95% CI −1.4 to −0.06).

The prescription of ICS for management of chronic stable COPD remains a controversial issue on various accounts. A particular concern with the presumed potential benefits of ICS relates to the difficulty in reconciling the minor impact (if any) of ICS on the rate of decline of lung function with its reported benefits on the rate of COPD exacerbations.

Critical review of those results by Suissa et al uncovers several methodological concerns that may have skewed the results towards a favorable effect of ICS. These include:

1. An unweighted method of exacerbation assessment based on an average of individual COPD exacerbation rates, with each COPD patient contributing equally to the group mean of exacerbations [81].

2. Failure to use an intent-to-treat principle such that patients were followed only until discontinuation of the study drug instead of the planned follow-up. Because of a generally higher withdrawal rate in patients assigned to placebo, this flaw would have the effect of magnifying the beneficial effect of ICS on mortality and rate of exacerbations. Specifically, in an analysis of several randomized studies, the greater the imbalance in withdrawal rates between the placebo and ICS groups, the greater was the increase in exacerbation rate in the placebo group compared to the ICS group [69]. In the OPTIMAL trial, which followed patients for exacerbations for the planned year of follow-up, there was no benefit of ICS on the rate of exacerbations [82]. In the TORCH study, which similarly applied an intent to treat analysis and followed patients for 3 years, there was no difference between the 3-year all-cause mortality in the ICS compared with placebo groups (16% vs. 15.2%) [68].

3. 26% to 77% of patients in the various randomized trials involving ICS were already on ICS before randomization and were required to discontinue them if assigned to the placebo group [69]. For these previous users, the trials effectively evaluated the effect of discontinuation of steroids rather than the introduction of steroids. In the OPTI-
MAL trial, a differential analysis showed that the presumed benefit of ICS in delaying the first exacerbation was present only in the group that was previously on ICS and not in the steroid-naive patients [69], suggesting that discontinuation of ICS use in the placebo groups may have been associated with side effects [83]. Moreover, in an analysis of 6 RCTs, there was an inverse relation between the proportion of prior ICS users and ratio of exacerbations [69].

4. Factorial analysis of the TORCH data to assess the individual effect of each of the components of the ICS/LABA combination indicates that the mortality benefit in the TORCH study is entirely due to the LABA component (17% reduction in mortality) rather than the ICS component (0% reduction in mortality) [69].

In the context of the prominent inflammatory component of COPD, these criticisms of the role of ICS are striking. Corticosteroid resistance has been found to occur in patients with COPD [84]. Specifically, corticosteroids can decrease the chronic inflammatory process by recruiting histone deacetylase (HDAC) and inhibition of histone acetylation, which otherwise would have increased the transcription of genes encoding inflammatory proteins. A reduction in HDAC expression in COPD, perhaps mediated by oxidative stress, has been proposed as a mechanism of steroid resistance [13]. Theophylline can restore HDAC activity and in combination therapy with ICS has been found to increase total HDAC in peripheral monocytes compared to ICS alone in patients with COPD, and to reduce markers of airway inflammation [85].

Reports have consistently shown an increased risk of pneumonia associated with ICS use in patients with COPD. These include population-based cohort studies [86], meta-analyses of RCTs [87], and the TORCH study [68]. The magnitude of this effect is such that the annualized number of individuals to treat in order to cause 1 case of serious pneumonia was estimated at 47 [87]. In the TORCH study, the 3-year rate of pneumonia in patients receiving 1000 mcg daily of fluticasone was 19% (1.6-fold increase over the placebo group) [68].

Controversy exists regarding whether a drug effect exists in that regard. Specifically, in a meta-analysis encompassing 5212 patient-years of exposure to budesonide, there was no increased risk of pneumonia at 1 year in patients with COPD [88]. Additionally, there was no increased risk of pneumonia in a retrospective analysis of budesonide in patients with asthma [89]. In contrast, the reports from Ernst and Singh showing an increase in pneumonia risk included diverse ICS, raising the question of whether differences between ICS, such as the more rapid airway clearance of budesonide, could account for this difference [86,87].

It should be noted that a significant limitation of all these studies is the low overall rate of observed pneumonia (around 3%) [68,88] and the absence of a formal definition of pneumonia [90].

Another controversy concerns whether therapy with ICS is associated with an increased mortality rate after development of pneumonia. Whereas the study of Ernst showed that ICS were associated with an increase in mortality within 30 days after development of pneumonia in elderly COPD patients [86], a more recent retrospective review by Chen et al showed a decreased risk of mortality and of mechanical ventilation in individuals with COPD who had prior use of ICS compared to those who did not [91].

In the context of these uncertainties, our recommendations are to include ICS according to established guidelines for their use (Table 2). The concern for the development of pneumonia should probably be tempered by the observation that the risk is low (3%) and probably overestimated due to the inclusion of self reported cases. Finally, there are some indications that there may be no clear increase in pneumonia deaths with prior use of ICS [91].

**COMBINATION THERAPY**

**LABA/ICS**

Akin to the management of asthma, a step-up paradigm is recommended for COPD pharmacotherapy. In the current guidelines, following the prescription of long-acting bronchodilators (eg, LAMA and LABA), uncontrolled symptoms or increased exacerbations necessitate the use of inhaled therapy that combines a LABA and ICS.

LABA/ICS combination may have synergistic clinical effects via molecular interactions. Corticosteroids augment B2 receptor expression protecting against tolerance to LABAs while the B2 receptor agonists accelerate nuclear translocation of glucocorticoid receptor complex and enhance transcription of corticosteroid inducible genes [92].

The TORCH trial is the largest RCT that compared combination therapy (salmeterol 50 mcg/fluticasone 500 mcg twice daily), ICS (fluticasone 500 mcg twice daily), and inhaled LABA (salmeterol 50 mcg twice daily) against placebo [68]. The trial enlisted 6112 patients with COPD who had FEV1 < 60%, no bronchodilator response, and at
least a 10 pack-year smoking history. All-cause mortality, the primary endpoint of the trial, was reduced by 17.5% in the combination therapy group compared with placebo (hazard ratio 0.825, 95% CI 0.681 to 1.002, \( P = 0.052 \)) and 22.6% compared with fluticasone (hazard ratio 0.774, 95% CI 0.641 to 0.934, \( P = 0.007 \)). Combination therapy also reduced annual rate of exacerbations compared to placebo (1.13 to 0.85, \( P < 0.001 \)), salmeterol (0.97 to 0.85, \( P = 0.002 \)) and fluticasone (0.93 to 0.85, \( P = 0.02 \)). Statistically significant improvements in spirometric values and SGRQ-determined health status were also observed in the combination therapy group against all comparators. There were, however, increased number of pneumonias reported in combination therapy (19.6%) and fluticasone (18.3%) groups compared with placebo (12.3%).

A recent meta-analysis of 7 high-quality RCTs (\( n = 5708 \)) with low heterogeneity also supports the finding that combination therapy provides superior outcomes when compared with its ICS component alone [93]. Combination therapy reduced mortality (OR 0.77, 95% CI 0.63 to 0.94). The number needed to treat to prevent 1 death varied greatly between the studies, from 16 in the TORCH study to 547 in the TRISTAN study [94]. A significant reduction in exacerbation rate (rate ratio 0.91, 95% CI 0.85 to 0.97, \( P < 0.001 \)), and improvement in spirometric indices and quality of life indices were also evident. Incidence of pneumonia was not different between combination therapy and corticosteroid monotherapy. There appeared to be no difference between salmeterol/fluticasone combination versus formoterol/budesonide combination.

While the data strongly point toward using LABA/ICS therapy over ICS alone in the management of patients with advanced stages of COPD, the relative benefit compared with LABA alone is less clear. In the TORCH trial, there was no difference in mortality between LABA/ICS and LABA alone (hazard ratio 0.932, 95% CI 0.765 to 1.134, \( P = 0.48 \)) [94]. Moreover, as discussed above, some analyses credit the decrease in mortality in COPD with the LABA/ICS combination to the LABA component alone [69]. However, there were significant reductions in moderate to severe exacerbations, improvement in postbronchodilator FEV1 and health status favoring combination therapy. A systematic review of efficacy of combination therapy versus LABA concluded that the addition of ICS may not confer clinically significant benefits [95]. In this meta-analysis of 18 RCTs that included 12,446 patients, LABA/ICS was shown to have no significant effects on all-cause mortality and severe exacerbations compared with LABA alone [95]. Some benefit was noted in moderate exacerbations and improvement in SGRQ scores, however this analysis was limited by significant heterogeneity in the dataset.

Given these considerations, we support the GOLD guidelines updated in 2010, which recommend combination therapy with LABA/ICS for symptomatic patients in GOLD stage III (FEV1 < 50%) and higher who have had 3 or more exacerbations over the last 3 years (Table 2). Recently, a post hoc analysis of the TORCH trial focused on GOLD stage II patients who had FEV1 values between 50% and 60% of predicted and comprised a third of the trial population [96]. Combination therapy was associated with reduced mortality and exacerbations as well as improved spirometric indices and quality of life. Clearly, more studies will be needed to delineate the role of LABA/ICS in the management of earlier stages of COPD.

**LAMA/LABA**

Combination of 2 classes of bronchodilators (LAMA and LABA) may potentially improve clinical outcomes in COPD based on the following theoretical considerations. First, due to different mechanism of action at the receptor level, combination treatment may result in additive bronchodilation. Furthermore, LABA provide a comparatively faster onset of action and a greater peak bronchodilator efficacy whereas LAMA affects sustained bronchodilator action [97]. In addition to pharmacodynamic complementarity, LABA may improve mucus clearance, which may not be a feature of LAMA [98]. To this end, van Noord et al reported improvement in airflow obstruction and resting hyperinflation in a group patients with severe COPD when formoterol was added to tiotropium compared with tiotropium alone [99]. In an RCT from Germany, 847 patients with COPD were randomized to receive formoterol 10 mcg bid plus tiotropium 18 mcg qd, formoterol 10 mcg bid, tiotropium 18 mcg qd, and placebo over 6 months [100]. Combination therapy improved FEV1 measured 2 hours post dose by 70 mL compared with formoterol alone (\( P = 0.044 \)) and by 60 mL compared with tiotropium alone (\( P = 0.066 \)) after 6 months of treatment. A recent multicenter double-blind RCT with tiotropium as the active control confirmed salutary effect on lung function and extended these to clinical outcome measures [101]. In this study, Tashkin et al randomized 255 patients with
moderate to very severe COPD to receive either formoterol 12 mcg bid plus tiotropium 18 mcg or tiotropium 18 mcg daily for 3 months. At the end of 3 months, statistically significant improvements in area under the curve for FEV1 over the first 4 hours post dose was observed favoring combination treatment (340 mL vs. 170 mL, \( P < 0.001 \)). Similarly, trough FEV1 measurements were higher in the group that received combination therapy (180 mL vs. 100 mL, \( P < 0.01 \)). Furthermore, symptom scores, health-related quality of life as measured by SGRQ, and rescue medication use improved in the combination therapy group compared with tiotropium alone [101]. In a post hoc analysis of this trial, the benefits in lung function were shown to be independent of gender, ICS use, smoking status, and severity of COPD [102]. Similar benefits in lung function and clinical endpoints have been reported when LABAs were administered by mobilization instead of handheld devices in combination with tiotropium versus either agent alone [103–105].

The 2 combination treatments, LABA/ICS and LAMA/LABA, were recently compared head to head in a multicenter, randomized, double-blind study that included 605 patients with moderately severe COPD [106]. After 6 weeks of treatment, patients who received tiotropium 18 mcg daily and formoterol 12 mcg bid had superior improvements in area under the curve for FEV1 in 12 hours post dose compared with patients who received combination therapy with salmeterol 50 mcg bid and fluticasone 500 mcg bid (mean difference 78 mL, \( P < 0.001 \)).

**Triple Therapy (LABA/ICS/LAMA)**

Addition of a LABA/ICS to existing LAMA treatment has been termed triple therapy, a term which may potentially be confusing as it disregards other classes of drugs in COPD pharmacotherapy and places no importance on the sequence of addition of the components. Several lines of reasoning may be offered for justification of “triple therapy.” As discussed, there is complementarity in the pharmacodynamic profiles of LABA and LAMA. Furthermore, addition of LAMA to LABA/ICS combination may improve the paradoxical increase in airway resistance which is speculated to be due to \( \beta_2 \) receptor down regulation [107]. A 2-week double-blind, double-dummy 3-way crossover study showed further improvements in specific conductance and inspiratory capacity in patients who received salmeterol/fluticasone (SF) plus tiotropium (Tio) compared with patients who received SF or Tio alone [108]. The INSPIRE trial compared the utility of SF versus Tio in prevention of acute exacerbation of COPD in 1323 patients with severe COPD [109]. Although no difference was observed between the intervention groups, the SF cohort had acute exacerbations that required antibiotics more frequently (0.97 vs. 0.82/yr, \( P = 0.028 \)) compared with the Tio cohort. In contrast, the patients in the tiotropium cohort had more exacerbations requiring oral corticosteroids (0.85 vs. 0.69/yr, \( P = 0.039 \)), implying potential differences in the biological nature of exacerbations, which may benefit from combining treatment with Tio and SF.

Despite sound theoretical background, there are currently only a few high-quality studies that have examined utility of “triple therapy” in patients with COPD. The Canadian Optimal therapy of COPD trial (OPTIMAL trial) randomized 449 patients with moderate to severe COPD to receive Tio and placebo, Tio and salmeterol (S) or Tio and SF for 1 year [82]. Although there was a 2.8% absolute reduction in patients who experienced at least 1 exacerbation in the triple therapy group compared with Tio+placebo, this was not statistically significant. However, triple therapy improved lung function, number of hospitalizations for COPD exacerbation, and health-related quality of life as measured by SGRQ compared with Tio+placebo. The reduction in number of hospitalizations may indicate a reduction in the severity of COPD exacerbations when triple therapy is employed. The study has been criticized for a very high dropout rate (47% in Tio+placebo, 43% in Tio+S and 26% in triple therapy). Nevertheless, various techniques of analysis (intention to treat, and sensitivity analyses) did not alter the primary results.

A larger but shorter duration (3 months) study by Welte et al randomly assigned 660 patients with severe COPD to treatment with tiotropium plus budesonide/formoterol or tiotropium plus placebo [110]. Triple therapy improved post dose FEV1, which was the primary outcome, by 11% (131 mL at 60 minutes post-dose) compared with tiotropium (\( P < 0.001 \)). Severe exacerbations were reduced by 62% in the triple therapy group compared with tiotropium plus placebo (rate ratio 0.38, 95% CI 0.25 to 0.57, \( P < 0.001 \)). There were also significant improvements in rescue medication use, COPD symptom scores, morning lung function assessments favoring triple therapy group. More patients in the triple therapy group had clinically significant improvements in SGRQ compared with active comparator (49.5% vs. 40%, \( P = 0.016 \)).
Triple therapy was the subject of a recent Cochrane review [111]. This careful meta-analysis that included 3 trials (the 2 trials discussed above and a pilot study by Cazzola et al that recruited 1021 patients [112]) concluded that there was insufficient evidence and significant heterogeneity in studies to date to make firm recommendations in regard to the use of triple therapy in severe COPD. Nevertheless, pooled data showed improvements in average health-related quality of life scores and lung function.

More recently, a retrospective cohort study from the United Kingdom examined 1857 patients who were prescribed triple therapy and 996 patients who were prescribed ICS/LABA from a large health registry [113]. Mean follow-up was 4.65 years. Use of triple therapy was associated with reduced all-cause mortality (hazard ratio 0.65, 95% CI 0.57 to 0.75, P < 0.001), hospital admissions (hazard ratio 0.85, 95% CI 0.73 to 0.99, P < 0.04) and oral corticosteroid bursts (hazard ratio 0.71, 95% CI 0.63 to 0.8, P < 0.001).

Addition of tiotropium to LABA/ICS may have salutary effects on lung function and health-related quality of life. However, incremental benefit on exacerbation rate compared with tiotropium has not been definitively shown. Furthermore, studies that compare triple therapy to LAMA/LABA combination, which is the guideline-recommended step-up therapy after tiotropium, are lacking.

**PHOSPHODIESTERASE INHIBITORS**

Phosphodiesterases (PDEs) are enzymes that inactivate cyclic AMP and GMP, second messengers that regulate inflammatory cell function and smooth muscle contraction. Among the 11 isoforms of the enzyme, PDE-3 and PDE-4 are the most relevant to respiratory disease. PDE-3 is prominently localized in smooth muscle cells and mediates smooth muscle contraction. PDE-4, on the other hand, is ubiquitous in immune and inflammatory cells and promotes inflammatory responses. In vitro PDE-4 inhibition suppresses T-lymphocyte cytokine production and proliferation, decreases neutrophil chemotaxis, oxidative burst and cytokine production, reduces TNF-α production from dendritic cells and macrophages, and decreases mast cell degranulation and eosinophil leukotriene production [114]. In clinical studies, PDE-4 inhibition reduced sputum neutrophil and eosinophils in patients with COPD after treatment for 4 weeks [115].

Theophylline is a nonspecific oral PDE inhibitor that has been used as a bronchodilator in the treatment of airway diseases for over 70 years [116]. Nevertheless, enthusiasm for its use has waned given the high serum concentrations that are required for clinical efficacy, which lead to significant side effects (ie, a narrow therapeutic window). Recently, theophylline has been used at lower doses to promote anti-inflammatory action independent of its PDE inhibition. Histoneacetylase 2 (HDAC2) is a nuclear enzyme that inhibits expression of inflammatory genes and is reduced in the lungs of patients with COPD, most likely secondary to increased oxidative stress [13]. As alluded to earlier, HDAC2 appears essential for anti-inflammatory action of corticosteroids [13,117]. At lower plasma concentrations than would be required for bronchodilation, theophylline activates HDAC2 and reverses corticosteroid resistance in patients with COPD [116]. Ford et al randomized 30 patients with COPD to treatment with theophylline and either inhaled fluticasone propionate (500 mcg twice per day) or inhaled placebo for 4 weeks [85]. Theophylline and fluticasone combination reduced total sputum eosinophils, percentage of sputum neutrophils and sputum chemokine (C-X-C motif ligand 8/IL-8). Combination treatment was also associated with improvements in FEV1 predicted and midexpiratory flow rates [85].

Roflumilast, the only compound approved for clinical use in its class, is an oral PDE-4 inhibitor with prominent anti-inflammatory properties and no acute bronchodilator effects [118]. Several phase III placebo controlled efficacy trials demonstrate beneficial effects of the compound. Calverley and colleagues reported the results of 2 placebo-controlled double-blind randomized trials (AURA and HERMES), which recruited participants with clinical diagnosis of COPD from an outpatient setting if they had chronic cough, sputum production, at least 1 recorded COPD exacerbation and FEV1 ≤ 50% [119]. Patients were randomized to receive roflumilast 500 mcg once a day (n = 1537) versus placebo (n = 1554) for 1 year. Importantly, ICS and long-acting anticholinergic drugs were not allowed. The first primary endpoint, prebronchodilator FEV1, increased by 48 mL compared with placebo in the intervention group (P < 0.001). The second primary endpoint, rate of moderate to severe exacerbations, was also improved in patients who received roflumilast (1.14 vs. 1.37/year, 17% reduction, 95% CI 8 to 25, P < 0.001). Adverse events were significantly more common with roflumilast and were related to the known side effect of gastrointestinal irritation.
effects of the drug, namely diarrhea, weight loss, decreased appetite, and nausea. Dropouts from the study, however, occurred at a similar rate (roflumilast 35% and placebo 31%). In another publication combining 2 placebo-controlled double-blind multicenter trials (EOS, n = 933, and HELIOS, n = 743), Fabbi et al studied the combinations of roflumilast with salmeterol and roflumilast with tiotropium compared with placebo controls in patients with COPD who had postbronchodilator FEV1 of 40% to 70% of predicted [120]. The patients in the HELIOS trial also had to have chronic cough and sputum production as well as frequent use of rescue medications, defined as at least 28 puffs per week. Mean prebronchodilator FEV1 improved by 49 mL ($P < 0.001$) in the salmeterol plus roflumilast trial (EOS) and by 80 mL ($P < 0.001$) in the tiotropium plus roflumilast trial (HELIOS) compared with placebo arm. The proportion of patients with an exacerbation (of any severity) was reduced with roflumilast in both trials (RR 0.82, $P = 0.0419$ in EOS and RR 0.75, $P = 0.0169$ in HELIOS). Study discontinuation was significantly higher for the roflumilast group in the EOS trial compared with placebo. There was no reported increase in mortality rates or cardiovascular events in these 2 trials.

Studies involving PDE-4 inhibitors in the management of COPD were reviewed by the Cochrane Collaboration recently [121]. The analysis included cilomilast, another PDE-4 inhibitor whose development was terminated due to lack of efficacy in phase 3 trials. Pooled analysis of 23 RCTs including over 15,000 patients showed that use of a PDE-4 inhibitor was associated with significant improvement in FEV1 regardless of concomitant treatment and also with a reduced likelihood of COPD exacerbation.

Roflumilast was approved by the FDA for the treatment of exacerbations and symptoms of chronic bronchitis in patients with severe COPD in March 2011. Nevertheless, questions remain in regard to the utility of the drug in the current paradigm of COPD management. Roflumilast addresses the inflammatory component of COPD disease process. By reducing inflammation and recurrent exacerbations, it has potential to impact disease progression. To this end, its intuitive place in the treatment algorithm may be as a combination treatment with long-acting bronchodilators with or without ICS. While data from clinical trials indicate additional benefit over tiotropium or salmeterol monotherapy, there are no trials yet addressing the incremental benefit over LAMA/LABA combination or a new “triple therapy” substituting for ICS in the combination. A recent meta-analysis utilizing the mixed treatment comparison approach provides interesting insight into this issue [122]. Mixed treatment comparison approach allows estimation of the relative effects of pairs of treatments based on direct and indirect evidence provided by RCTs. Based on 26 RCTs including 36,312 patients, it was estimated that roflumilast would reduce exacerbations if added to triple therapy by 16% (rate ratio 0.84, 95% CI 0.74 to 0.95). Similar benefit was suggested when roflumilast was added to LABA/LAMA. When absolute treatment effects were considered, addition of roflumilast to triple therapy appears to lead to the greatest reduction in exacerbations (rate ratio 0.53, 95% CI 0.43 to 0.64).

The place of roflumilast in the treatment algorithm of COPD should be further clarified with clinical trials that enroll patients susceptible to exacerbation and include treatment arms with combination inhaled therapy (eg, triple therapy).

**MACROLIDES**

Macrolides have been successfully used in the long-term treatment of chronic suppurative respiratory diseases such as cystic fibrosis [123] and diffuse panbronchiolitis [124]. The benefit is evident at lower doses than those used to treat infections and therefore attributed to an anti-inflammatory effect rather than antimicrobial. It was hypothesized that macrolides would reduce inflammation inherent in COPD and reduce acute exacerbations of COPD, which are heightened states of inflammation. There are 2 RCTs of 1-year duration that support the use of macrolides in the treatment of COPD patients, particularly those with susceptibility to exacerbation. Seemungal and colleagues randomized 109 patients with COPD to receive erythromycin 250 mg orally twice a day versus placebo in a carefully conducted prospective trial [125]. Patient population included those with FEV1 between 30% to 70%, past or present smoking history, and lack of a bronchodilator response. Compared with placebo, erythromycin reduced exacerbation frequency (rate ratio 0.648, $P = 0.003$) and shifted the severity of exacerbations to milder episodes with reductions in hospitalizations (7.4% vs. 11.2%). The authors reported no significant adverse events or microbial resistance to erythromycin in this study (only a single case). The benefit was independent of ICS use. In the second study by the COPD Clinical Research Network, Albert and colleagues assigned 1142...
patients with COPD to receive azithromycin 250 mg daily versus placebo [126]. In contrast to the Seemungal study, patients with history of exacerbation (corticosteroid use, ER visit or hospitalization) during the year prior to enrollment or those on domiciliary oxygen were included in the study. Patients with mild COPD, asthma, prolonged QT interval, or hearing impairment were excluded. Hazard ratio for having an acute exacerbation of COPD was reduced favoring the azithromycin group (0.73, 95% CI 0.63 to 0.84, \(P < 0.001\)). More patients in the azithromycin group achieved clinically significant (≥ 4 reduction in SGRQ score) improvements in quality of life (43% vs. 36%, \(P = 0.03\)). Patients who took azithromycin were more likely to develop audiographically determined hearing decrements (25% vs. 20%) and more likely to develop macrolide-resistant strains in nasopharyngeal secretions (81% vs. 41%). Patients over 65 years of age, those on domiciliary oxygen and those with GOLD stages II and III (as opposed to stage IV) were shown to benefit more in reduction of exacerbations in subgroup analysis. Importantly, those patients who were on triple therapy (close to half of the patients) did not experience statistically significant reductions in acute exacerbations.

Although the aforementioned studies provide strong support for use of macrolides in the management of stable COPD, similar questions remain regarding its place among the existing agents that were effective in reducing COPD exacerbations. Whether it should be added to the regimen of patients who are already on triple therapy will need to be addressed in a separate study. The possibility of distinct patient populations (eg, those patients with 2 or more exacerbations/year) where the benefit would be greatest and similar success with lower doses of the drugs to prevent adverse effects and change of resident flora are also issues of interest. Clearly, attention will need to be paid to increasing macrolide resistance and its consequences in the community if this strategy is to be adopted.

**Mucolytics**

Mucolytics reduce viscosity of sputum, improving its clearance. Reduced secretions may potentially improve symptoms, lung function, and overall patient satisfaction. Various mucolytics have been used in the treatment of chronic bronchitis and COPD. A number of these agents belong to the cysteine family of drugs, which also have antioxidant properties [127]. For instance, N-acetylcysteine (NAC) and carbocysteine reduce pulmonary oxidant stress, which is thought to be an instigator of acute exacerbations of COPD [128,129]. NAC may reduce air trapping, improving endurance during exercise in patients with moderate to severe COPD [130]. Mucolytics may also have anti-inflammatory effects during viral infections, which are common instigators of acute exacerbation of COPD [131,132]. There have been numerous clinical trials of mucolytics involving patients with COPD. Decramer and colleagues randomized 523 patients with GOLD stage II–III COPD to NAC 600 mg/day versus placebo (BRONCUS study) with a 3-year follow-up [133]. The patients used concomitant ICS (70%), long-acting β2-agonists (60%) and theophylline (35%). There was no change in the rate of decline in FEV1 or vital capacity, exacerbation rate or quality of life as assessed by SGRQ and EuroQol-5D. In those patients who were not on ICS, however, there was a reduction in exacerbation rate favoring NAC (RR 0.790, 95% CI 0.631 to 0.989, \(P = 0.040\)). In a multicenter study from China, Zheng and colleagues randomized assigned 709 patients with history of COPD exacerbations in the previous 2 years to receive 1500 mg carbocysteine or placebo with a 1-year follow-up (PEACE study) [134]. In contrast to the BRONCUS study, there was a significant reduction in COPD exacerbations (RR 0.75, 95% CI 0.62 to 0.92, \(P = 0.004\)) and improvement in quality of life as measured by SGRQ (−4.06 vs. −0.05, \(P = 0.13\)). Exacerbation was defined based on symptoms and not health care utilization. Notably, ICS were used in a minority of patients in this study (16.7%). In the recent Cochrane review of mucolytic agents, 28 trials involving 7042 participants were included in a meta-analysis [135]. Compared with placebo, mucolytics were associated with a 21% reduction in annual exacerbation rate when used for at least 2 months, particularly in the winter months. There was significant statistical heterogeneity in the data. The meta-analysis was also confounded by use of various agents may have properties in addition to mucolysis and inclusion of patients with nonobstructive chronic bronchitis. There were no significant untoward effects from the use of mucolytics.

Taken together, the role of mucolytics in the treatment of stable COPD remains controversial. Future studies of mucolytics should involve patients who are already on a regimen with proven clinical efficacy in COPD. COPD patients with predominant features of chronic bronchitis who remain symptomatic and experience frequent exacerbations despite treatment with LAMA and/or LABA/ICS would be a particularly interesting group to study.
CONCLUSION

The past decade has ushered in a new era in COPD pharmacotherapy, wherein a shift in focus from symptom treatment to affecting clinical outcomes has occurred. Mega-trials have established LAMA and LABA/ICS as efficacious drug categories in multiple outcome measures. The salutary effects on outcome measures based on literature discussed in this article are displayed by drug category in Table 3. In this table, we labeled outcome categories with a “yes” in the presence of evidence from an RCT. We judged outcome benefits that were shown in post hoc analyses as “probable.” Finally, the term “possible” was used when the evidence came from retrospective analyses or in the presence of strong trends that straddled statistical significance, eg, mortality benefit from LABA/ICS in the TORCH trial. With better understanding of COPD pathogenesis, it is clear that a single agent will not address the many facets of this devastating disease. Adequately powered trials that incorporate combination therapies will provide guidance and finesse the approach to pharmacotherapy the patient with stable COPD.

*When used in the absence of ICS.

**Table 3. Drug Classes and Effects on Outcome Measures**

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Risk</th>
<th>Lung Function Improvement</th>
<th>Reduced Lung Function Decline</th>
<th>Improved Quality of Life</th>
<th>Reduction in Exacerbations</th>
<th>Reduction in Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMA</td>
<td>Pharmacologic side effects</td>
<td>Yes</td>
<td>Yes; in earlier disease</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>LABA</td>
<td>Cardiovascular</td>
<td>Yes</td>
<td>Probable</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ICS</td>
<td>Pneumonia</td>
<td>Yes</td>
<td>Probable</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>LABA/ICS</td>
<td>Pneumonia</td>
<td>Yes</td>
<td>Probable</td>
<td>Yes</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>Pharmacologic side effects</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>PDE inhibitors</td>
<td>Pharmacologic side effects</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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</tr>
<tr>
<td>Macrolides</td>
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<td>No</td>
<td>Yes</td>
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<td>No</td>
</tr>
<tr>
<td>Mucolytics</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>Yes*</td>
<td>Yes*</td>
<td>No</td>
</tr>
</tbody>
</table>

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