

CLINICAL COMMENTARY

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Is 'GOLD' standard for the management of COPD in clinical practice?

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable but usually progressive obstructive lung disease most often associated with tobacco smoking in 'developed' countries and accentuated by exposure to biomass fuel smoke in 'developing' countries [1]. COPD affects more than 200 million people worldwide. It is the third leading cause of mortality in the USA [2], and is predicted to become the third most common cause of death worldwide by 2030 [3]. COPD is the 'umbrella' term for emphysema and chronic bronchitis. Emphysema is the abnormal permanent enlargement and destruction of the airspaces distal to the terminal bronchioles, and is a pathologic description that is often recognized by imaging. Chronic bronchitis is a syndrome defined as a chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of chronic cough have been excluded.

COPD is characterized by alveolar destruction, loss of alveolar attachments, loss of elastic recoil and increased airway resistance. This leads to limitations in expiratory flow and inadequate lung emptying upon expiration, resulting in lung hyperinflation [4]. Static hyperinflation occurs at rest and dynamic hyperinflation occurs with increased ventilation, such as during exercise [5]. Hyperinflation is usually experienced as dyspnea, and dynamic hyperinflation as dyspnea upon exertion. Patients with COPD often experience a chronic productive cough as well as significant and progressive deteriorations in lung function, peripheral muscle function, exercise capacity, activity level and quality of life (QoL) [1].

COPD is associated with several important comorbidities. These include osteoporosis, anxiety, muscle wasting and weight loss, depression, coronary artery disease (CAD), con-

gestive heart failure, cancer (especially that of the lung) and pulmonary vascular disease [6]. Some of the morbidities are associated with smoking and coexist with COPD, whereas others (e.g. muscle wasting, weight loss and depression) may be associated with the pathophysiology and impact of COPD itself [7, 8]. A significant proportion of COPD patients die from non-respiratory causes [1].

The progressive airflow limitation in COPD is due, in large part, to fibrosis and inflammation-induced narrowing in the small airways [8]. Destruction of the lung parenchyma, edema, secretions, smooth-muscle contraction and decrements in lung elastic recoil also play a part in limiting expiratory airflow. However, airflow limitation is not the only pathophysiologic mechanism at play. Abnormalities in gas exchange, primarily due to emphysema [9], are also characteristic of COPD, and can cause hypoxemia and hypercapnia. Respiratory pathogens (e.g. bacteria, atypical bacteria, viruses and fungi) are common in the lungs of patients with COPD even in the absence of respiratory symptoms, in contrast with the sterile lung environment seen in healthy lungs [8].

COPD is accompanied by inflammation in the lower airways and lung parenchyma. This inflammation is associated with abnormally high counts of neutrophils, activated macrophages, activated T lymphocytes and, sometimes, eosinophils [1, 9]. COPD begins with a localized inflammatory response to environmental stimuli, but it is now understood to be a systemic inflammatory disease that extends beyond the lungs. The precise mechanisms of the inflammatory processes in COPD are incompletely understood. The systemic inflammation seen in COPD may result from a 'spillover' of inflammatory mediators from the airways or from independent pathways, which may include physical inactivity in

conjunction with the metabolic syndrome, genetic abnormalities, systemic oxidative stress caused by cigarette smoking, and other factors. Systemic inflammation may be at the root of many of the extrapulmonary sequelae and associated comorbidities of COPD, such as osteoporosis and CAD [7, 8]. The multiple morbidities commonly seen in people with COPD means that the lungs should not be treated in isolation without consideration of the needs of the whole person [6, 7].

Historically, the fact that the airflow limitation seen in COPD is progressive and often associated with worsening debilitation has led to unjustified pessimism on the part of many physicians treating COPD [10]. In fact, appropriate treatment is associated with significant improvements in mortality, and in patient-centered outcomes such as health-related QoL, dyspnea, exercise capacity, exacerbations and hospitalizations [11]. Very limited data are available on COPD genotypes other than the important subgroup of people with COPD associated with alpha-1-antitrypsin deficiency [12]. Recent updates on COPD guidelines recommend that all individuals with COPD should be screened for this genetic subtype [1]. Recent interest has focused upon COPD phenotypes that may affect treatment decisions. These include the ‘frequent exacerbators’ defined by Hurst and colleagues [13] and ‘hyperinflators’ being studied by Celli et al [11]. How these phenotypes can be identified early in COPD is not clear, nor have studies confirmed the best therapeutic approach for either phenotype.

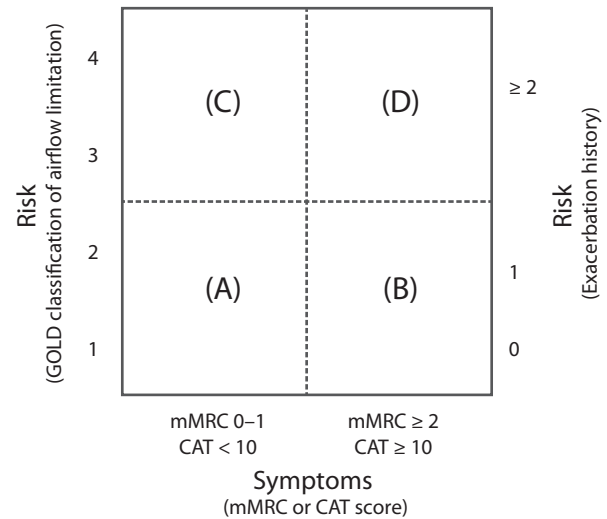
Over the past decade, the issue of ‘mixed’ obstructive lung disease (usually asthma and COPD) has been increasingly recognized [14, 15]. However, therapy of mixed disease is beyond the scope of this review.

Guidelines for COPD

Several guidelines have been developed and published related to COPD management. These include combined North American and European guidelines [16], as well as the most widely distributed international COPD guidelines: Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1]. These guidelines are based primarily on the new 2011 version of GOLD but do not alter the basic recommendations for diagnosing COPD.

Firstly COPD must be suspected or included in the differential diagnosis. Symptoms and signs such as chronic/recurrent cough, sputum production, progressive dyspnea or functional decline due to ‘breathing’ problems or recurrent respiratory infections in individuals with exposure to noxious gases such as tobacco smoke should be considered as possibly due to COPD [1]. The diagnosis of COPD is based on post-bronchodilator spirometry testing with a forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio of less than 0.70 and an FEV_1 less than 80% of predicted for the height, sex and race of the individual. Most people with symptomatic COPD, those who are candidates for therapy other than smoking cessation, usually have a FEV_1 less than 70% of predicted [1].

Figure 1. Combined assessment of chronic obstructive pulmonary disease according to GOLD guidelines [1].



Abbreviations

CAT, COPD Assessment Test; mMRC, modified Medical Research Council Dyspnea scale
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After confirming the diagnosis of COPD, the new guidelines can help in initiating or modifying therapy. Before the 2011 update, therapy recommendations were based primarily on lung-function values. Current treatment recommendations are based on a combination of lung function, symptoms and number of exacerbations in the previous year [1]. The new grading for COPD begins with mild (I) through to very severe (IV) stages using post-bronchodilator FEV_1 and adds the impact of symptoms using the modified Medical Research Council (MRC) dyspnea scale or the COPD Assessment Test (CAT) [17] with a final additional stratification based on the number of COPD exacerbations in the previous 12 months. The final categories are A–D and fit nicely into a square (Figure 1). Not everyone will ‘fit’ into these four categories, but this system does recognize the fact that FEV_1 alone does not predict symptoms or the prevalence of exacerbations, and is therefore not an adequate predictor of the therapeutic needs of people with COPD [1]. As with all newly developed models for the conceptualization of obstructive lung disease, this model will undoubtedly be modified over time but appears to be much more patient-oriented than the older system of mild-to-very-severe classification according to FEV_1 alone.

Pharmacotherapy of COPD

Pharmacological treatment can provide symptom relief, improve health status, improve exercise capacity and reduce the frequency and severity of COPD exacerbations [1]. Table 1 lists the drug combinations for COPD care that are available for inhalation via nebulizers, pressurized metered-dose inhalers (pMDIs) and dry-powder inhalers (DPIs). Combinations being tested in Phase I to Phase III clinical trials are denoted in italics.

Table 1. Pharamcotherapy for chronic obstructive pulmonary disease.

Goal	Classes of medications
Dyspnea relief [1, 18]	<ul style="list-style-type: none"> ● Short-acting β_2-adrenergic bronchodilators ● Short-acting anticholinergic bronchodilators ● Long-acting β_2-adrenergic bronchodilators (LABAs) ● Long-acting anticholinergic (or antimuscarinic) bronchodilators (LAMAs) ● <i>Combination LABA/LAMA</i>
Improvement in quality of life [19–21]	<ul style="list-style-type: none"> ● LABAs ● LAMAs ● LABA/inhaled corticosteroid (ICS) combinations ● Combination LABA/ICS plus LAMAs ● <i>Combination LAMA/ICS</i>
Improvement in exercise capacity [1, 18]	<ul style="list-style-type: none"> ● Short-acting β_2-adrenergic bronchodilators ● Short-acting anticholinergic bronchodilators ● LAMAs ● LABAs ● Combination LABA/ICS ● <i>Combination LABA/LAMA</i> ● <i>Combination LAMA/ICS</i>
Reduction in the number of exacerbations [1, 18]	<ul style="list-style-type: none"> ● LAMAs ● LABAs ● Combination LABAs/ICS ● <i>Combination LABA/LAMA</i> ● <i>Combination LAMA/ICS</i>
Possible reduction in age-related loss of lung function [19, 20, 22, 23]	<ul style="list-style-type: none"> ● LAMAs ● LABAs/ICS combinations ● Combination LABA/ICS plus LAMAs ● <i>Combination LABA/LAMA</i> ● <i>Combination LAMA/ICS</i>
Possible increase in lifespan [19, 20, 23]	<ul style="list-style-type: none"> ● LAMAs ● LABAs alone ● Combination LABA/ICS ● <i>Combination LABA/LAMA</i> ● <i>Combination LAMA/ICS</i>

Combinations being tested in Phase I to Phase III clinical trials are denoted in italics.

Abbreviations

LABAs, long-acting β_2 -adrenergic bronchodilators; LAMAs, long-acting anticholinergic (or muscarinic) bronchodilators; ICS, inhaled corticosteroid
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Guidelines for the treatment of patients with FEV₁ less than 70% of predicted plus modest dyspnea (mMRC 0 or 1) (Table 2) recommend the use of one of the available long-acting bronchodilators [1]. Long-acting bronchodilators are central to COPD management and are used regularly for maintenance treatment. Inhaled long-acting bronchodilators are considered to be effective and convenient [1], and include the long-acting β_2 -agonists (LABAs) and long-acting anticholinergic (or antimuscarinic) bronchodilators (LAMAs).

LABAs act primarily to relax airway smooth muscle by stimulating β_2 -adrenergic receptors and providing functional antagonism to bronchoconstriction [24]. The resulting bronchodilation leads to increased functional lung capacity (via lung deflation), lessening the dyspnea and the limitations placed upon the ability to undertake everyday activities [19, 21, 25–27]. LABAs have been shown to provide significant improvements in airway obstruction and outcomes (decreased symptoms and use of rescue medication, and im-

Table 2. Modified Medical Research Council dyspnea scale.

Grade	Description of breathlessness
0	I get breathless only with strenuous exercise.
1	I get short of breath if hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath if walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

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proved health status) [21, 28–30]. Currently available inhaled LABAs include salmeterol and formoterol (which have a 12-hour duration of effect and are administered twice daily) and indacaterol (which provides 24-hour bronchodilation with once-daily dosing). Older agents (salmeterol and formoterol) are indicated for asthma and COPD [24, 31, 32], but indacaterol (currently approved for use in more than 80 countries, including the USA) is indicated only for COPD [33].

Regular use of LABAs also results in a significant reduction in the number of exacerbations with individual LABAs compared with placebo and for LABAs overall (odds ratio [OR] 0.81 [95% confidence interval (CI) 0.75, 0.88]). Donohue et al. [34] examined a database of pooled clinical-trial data (all data from studies of ≥ 12 weeks' duration) with indacaterol, salmeterol and formoterol. They found that the incidence of worsening COPD with all LABAs was significantly lower than that seen with placebo. Similarly, the prevalence of COPD exacerbations (as an efficacy outcome) was significantly reduced with all LABAs compared with placebo [34]. LABAs provide an important means of improving the symptoms and health status of patients with COPD [19, 21, 25–27]. They may also be beneficial for reducing the number of COPD exacerbations [34], and LABA treatment is not associated with an increase in the incidence of the worsening of COPD as an adverse event. Review of safety and tolerability suggests that LABA monotherapy in patients with COPD is likely to be associated with a favorable therapeutic index [35].

A new LABA, indacaterol (Arcapta Neohaler – dry powder) was approved by the US Food and Drug Administration (FDA) in July 2011. The approved dose in the USA is 75 μg once daily as a bronchodilator for patients with COPD [36, 37]. The European Medicines Agency (EMA) approved indacaterol (150 μg and 300 μg) in 2009 [38]. The FDA approved lower doses due to concerns related to possible adverse effects at higher doses and an apparent therapeutic plateau affect at ≈ 75 μg (i.e. the FDA believed that little additional therapeutic benefit was seen at higher doses). In the FDA review of indacaterol, its use in patients with COPD did not show worrisome findings, particularly at the lower doses of 75 μg and 150 μg [36]. With respect to death, intubation, and hospitalization related to asthma, COPD, or pneumonia, a meta-analysis of 23 trials and 11,755 patients with COPD found no safety signals for the 75- μg and 150- μg doses of indacaterol. Statistically significant improvement in the Saint George's Respiratory Questionnaire (SGRQ) used to assess COPD-specific QoL was seen with the 75- μg dose and did not improve significantly with higher doses. Therefore, the FDA chose to approve only the 75- μg dose in the USA. Most studies comparing once-daily and twice-daily LABAs have reported drug efficacy to be equivalent [39], but other studies have reported that indacaterol may have greater improvement in QoL as measured by the SGRQ or decreased rescue inhaler use over a 12-week period [17, 40]. For most COPD patients, a 12-week period is very short compared with years of medication use. Therefore, longer-term data may be helpful in determining the relative place of all of LABAs in COPD care.

Adverse cardiac side-effects (specifically arrhythmias) have been reported with long-term bronchodilator use [41, 42]. In the most recently published study using a cohort of slightly over 6000 patients, the rates of arrhythmias were elevated with LABAs and new use of short acting iatropium but not with short acting β agonists or methylxanthines. The data used were prior to approval of long-acting anticholinergics in Canada from which the cohort of patients was identified. The rates of arrhythmias were estimated to be 1.37 events per 100 persons per year. ORs were 4.5 (95% CI 1.4–14.4) for LABAs within the group of all individuals with arrhythmias. These data were from a relatively small group of individuals, and confirmation from larger studies is needed. Indacaterol was not included in the studies because it was also not available at the time. However, data from studies comparing all currently available LABAs showed few differences related to cardiac safety [43, 44].

LAMAs

Tiotropium is the first LAMA approved for once-daily therapy for COPD. Tiotropium has demonstrated significant and sustained bronchodilation (opening of the airways) [45] and reduction in hyperinflation (air trapping) [46, 47]. Tiotropium also demonstrated superior and sustained improvements in lung function (FEV_1) over ipratropium bromide (a short-acting anticholinergic medication that must be taken approximately every 4 hours). Tiotropium has also demonstrated superior improvement in key parameters of lung function over salmeterol [48]. Patients treated with tiotropium compared with those treated with placebo had less activity-induced breathlessness and improved exercise endurance. They required fewer doses of rescue medications as well as fewer exacerbations and COPD-related hospitalizations [45]. In clinical trials, the most common adverse reaction reported with tiotropium was dry mouth (which was usually mild and often resolved spontaneously during treatment) [45, 49]. Tiotropium provided statistically significant improvements in health-related QoL as measured by the SGRQ ($p < 0.001$) and sustained improvements in lung function for up to 4 years ($p < 0.001$), but it did not alter the rate of decline in lung function. In the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, tiotropium use was associated with mean delay-to-first exacerbation of 4.1 months ($p < 0.001$), and a reduction in the number of exacerbations per patient year (14%, $p < 0.001$). In addition, tiotropium use significantly reduced the risk of exacerbations leading to hospitalization (hazard ratio [HR] 0.86, $p < 0.002$). Tiotropium use over 4 years resulted in a decrease in the risk of death (all cause and cardiac-related) of 6% ($p = 0.016$) [49, 50].

LABA + LAMA therapy for COPD

The 2011 GOLD guidelines recognized the importance of LABA + LAMA therapy, which had been shown to improve lung function and hyperinflation more than either drug alone [1]. The combination is only second-line therapy in GOLD 2011, but it is an important combination. Studies with

COPD patients combining a LAMA and a LABA have demonstrated greater improvements in lung function (specifically FEV₁) than either bronchodilator alone [51]. β_2 -adrenergic receptor agonists bind to β_2 adrenoreceptors on the surface of smooth muscle cells at all levels of the airways (even in the small airways involved in COPD), leading directly to relaxation of smooth muscle and subsequent bronchodilation [52, 53]. Anticholinergic agents antagonize muscarinic (M3) receptors on airway smooth muscle [52], thereby preventing smooth-muscle contraction [53]. M3 receptors mediate bronchoconstriction and mucus secretion. M3 receptors may have negative feedback on β -adrenoreceptors, which may be removed by an anticholinergic agent and thus promote the effects of the β_2 agonist [32]. Improved FEV₁ is an important outcome, but patients value many other outcomes more highly than FEV₁. FEV₁ alone does not adequately reflect the health status or QoL of a person with COPD. LABA/LAMA combination therapies demonstrate significant improvements in patient-centred outcomes such as dyspnea, symptoms, use of rescue medications and QoL compared with monotherapy with a LABA or LAMA. This information should be considered carefully when selecting COPD therapy [54].

Leukotriene modifiers

Leukotriene receptor antagonists (LTRAs) are not indicated in COPD therapy [1]. A few clinical trials have suggested that LTRAs may be an alternative to corticosteroid therapy in smokers with COPD. However, there are no data to demonstrate that LTRAs can effectively reduce the progression of inflammation in smokers with COPD [55]. Because COPD is recognized as an inflammatory disease characterized by neutrophilia (and, in some cases, eosinophilia) in sputum, hope for some role of LTRA therapy in COPD remains. Leukotriene B₄ (LTB₄), a neutrophil and T-cell chemo-attractant produced by macrophages, neutrophils and epithelial cells, is a potent inflammatory mediator. In cilia, and other sites of inflammation (not always LTB₄-driven), there are several sites where antileukotriene agents exert their action as well as at the end-organ receptors. These drugs seem to be well tolerated, but more studies are required to demonstrate their value in COPD management before they can be recommended for use outside clinical trials [56].

Methylxanthines

Methylxanthines (e.g. theophylline, aminophylline) may be enjoying a renewed role in COPD therapy. As one of the oldest classes of therapies for obstructive lung diseases, methylxanthines have gone in and out of favor for decades. Due to its toxicity at levels close to the therapeutic range, theophylline is rarely used as a first-line COPD medication. However, in low doses that preclude the need for weekly or bi-weekly monitoring of drug levels, it has been considered to be an add-on therapy in those with severe or very severe COPD. Theophylline has been used as a modestly effective bronchodilator and reported to have anti-inflammatory properties now known to be related to its role as a histone deacetylase (HDAC)2 enhancer [55].

Recent work has shown that low doses of theophylline enhance the activity of the key corticosteroid-associated corepressor protein HDAC2, which is reduced in COPD. Reduction of HDAC2 may be the reason for the relative corticosteroid resistance seen in COPD inflammation. This may be why combination therapy with an inhaled corticosteroid (ICS) and low-dose theophylline is beneficial in late-stage COPD treatment [57–59]. Another potential role for methylxanthines may be in controlling the fibrosis characteristic of COPD. They are very early data but new information suggests that lung fibroblasts participate in the chronic inflammation in COPD by releasing interleukin (IL)-6 and IL-8. Low-dose theophylline can alleviate the production of pro-inflammatory mediators by fibroblasts. This may bring methylxanthines back for yet another round of assessment [60].

Phosphodiesterase (PDE) inhibitors

Important new additions to the potential therapies for COPD are the oral PDE inhibitors, in particular the PDE4 inhibitor roflumilast. Roflumilast is indicated for the maintenance treatment of severe COPD (FEV₁ post-bronchodilator <50% predicted, i.e. those in the new GOLD grades C and D; see Figure 1) associated with chronic bronchitis in adult patients with a history of frequent exacerbations. The benefit of an oral medication that does not require yet another new type of inhaler technique to be taught is one of the best aspects of this new medication.

Roflumilast is to be used only as adjunct therapy in people who are already on long-term bronchodilator therapy [1, 61–64]. In this specific patient population, roflumilast (500 μ g, once daily) reduces the prevalence of exacerbation and improves lung function [62–64]. The major role of roflumilast will probably be in the management of severe chronic bronchitis in patients who continue to have acute exacerbations despite aggressive treatment with inhaled long-acting bronchodilators (LABA + LAMA), inhaled corticosteroids and episodic 'burst' therapy with prednisone. These patients may receive most of their care in specialty clinics or offices.

Inhibition of PDE4 can increase the intracellular concentration of cyclic monophosphate (cAMP) by inhibiting its degradation, leading to reduced activity in inflammatory cells [65]. Inhibition of PDE4 can target three main components of COPD: bronchoconstriction, mucus hyper-secretion and airway remodeling [65–68]. PDE4 is the major cAMP metabolizing enzyme, so inhibition of PDE4 suppresses the inflammatory response [67]. Also, by suppressing over-expression of mucin 5AC by epidermal growth factor receptors, PDE4 inhibition inhibits mucus production directly [69]. Inhibition of PDE4 may also lead to minimization of airway remodeling by suppressing the release of tumor necrosis factor (TNF) α [70]. Though impressive, most of these data come from pre-clinical studies, and the long-term impact of roflumilast beyond the prevention of exacerbation has yet to be determined.

The use of roflumilast is limited by the specific targeted group for which it is indicated. The side-effect profile from

clinical trials includes significant diarrhea in 6% of users and weight loss due to the diarrhea in only 2% of users, but case reports suggest a higher prevalence [71].

Exacerbations

An exacerbation is defined by GOLD as 'an acute event characterized by worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medications' [1]. Exacerbations range in severity from transient declines in functional status to fatal events. Recurrent episodes of exacerbations are often associated with accelerated pulmonary decline [72] and decreased QoL [73]. Severe exacerbations are associated with an increase in the risk of mortality [74]. Less severe exacerbations (those that are amenable to treatment in a primary care office) appear to arise quickly and are responsive to therapy within 7 days, whereas more severe episodes require hospitalization with extended recovery periods. Some patients never return to their pre-exacerbation baseline [75]. Other studies have demonstrated a high prevalence of recurrence, and authors have labeled subgroups as 'frequent exacerbators' [13]. In people with severe COPD, exacerbations requiring hospitalizations result in high mortality [76, 77].

Bacterial and viral respiratory tract infections trigger most COPD exacerbations [78]. Additional triggers include exposure to tobacco, occupational dust, biomass fuel smoke and environmental pollution [1]. Exacerbations are more likely to recur in patient subsets with a history of exacerbations [1], patients with other independent clinical predictors (chronic cough and sputum production) [79], or in patients with physician-diagnosed concomitant asthma [80].

Exacerbations have been classified based on the number and severity of symptoms such as breathlessness, increased production of sputum and increased purulence of sputum [81], or graded based on requirements for healthcare resources such as care at home, in hospital or in the intensive care unit due to respiratory failure [82]. The numbers of exacerbations increase and become more severe with increasing COPD severity [83]. Exacerbation rates have been estimated to be 0.85 per person per year for patients with GOLD Stage 2, 1.34 for patients with GOLD Stage 3, and 2.00 for patients with GOLD Stage 4 COPD [84]. Overall, 22% of patients with Stage 2 disease, 33% of patients with Stage 3 disease and 47% of patients with Stage 4 disease had frequent exacerbations (≥ 2 in the first year of follow-up) [83]. Frequent COPD exacerbators may require different approaches than patients whose exacerbations increase in frequency based solely on increasing disease severity. Those approaches are not well outlined other than initiation of ICS earlier than usually recommended [1].

It is better to prevent exacerbations than to treat them. Smoking cessation remains the most useful approach to exacerbation prevention. In addition, avoiding environmental pollution and interaction with individuals who have viral or bacterial respiratory infections as well as appropriate immunizations (see below) are important. If patients have asthma as well as COPD, they should avoid allergic triggers such as pollen and pets [85].

Formoterol has been shown to have some significant beneficial effects compared with placebo upon outcomes defining milder exacerbations, with little difference compared with placebo for more severe exacerbations. In the large, 3-year Towards a Revolution in COPD Health (TORCH) study, salmeterol significantly reduced the rate of all grades of exacerbations relative to placebo, including those requiring hospitalization [21]. Most other studies showed similar effects between active and placebo treatment or numerical reduction with salmeterol over placebo. In the UPLIFT trial, tiotropium was shown to decrease the time-to-first exacerbation and the number of exacerbations per year compared with placebo [49]. In a 1-year trial comparing treatment with tiotropium (18 μg , once daily) with 50 mg of salmeterol (b.i.d.) in patients with moderate-to-very-severe COPD (the POET study), tiotropium was more effective than salmeterol in preventing exacerbations [86]. Indacaterol treatment was associated with significant or numerical reductions in exacerbations compared with placebo.

ICS are commonly prescribed to patients with COPD, with reported usage ranging from 39 to 50% of patients in the USA [87, 88], 67% in Canada [89] and 35–75% of patients in various European countries [90–93]. COPD management strategy [1] recommends ICS treatment in patients classed as being at high risk of exacerbations, which is defined by a history of frequent exacerbations (≥ 2 /year) and/or severe airflow limitation ($\text{FEV}_1 < 50\%$ predicted). However, the use of ICS in COPD is associated with several side-effects [94], and the risk of these side-effects may be increased by patient factors that are common in COPD, such as increasing age and multiple comorbid conditions [95]. Arguably the most serious side-effect is the increased incidence of pneumonia, which has been observed among patients with COPD in controlled clinical trials [21, 96, 97] and case-control studies [98], with an excess risk that was more pronounced with high ICS doses ($\geq 1000 \mu\text{g}/\text{day}$) [98–100]. The use of ICS without prior exacerbations appears to have an unacceptable cost-to-benefit ratio, and therefore should be used only after the risk of exacerbations has been established [101, 102].

After an exacerbation, the need for pharmacotherapy as well as pulmonary rehabilitation may change. Therefore, one must consider reassessing spirometry and inhaler technique and ascertain if the patient can cope with his/her usual environment, understands the recommended treatment regimen and/or requires long-term oxygen therapy or a home nebulizer [1].

Problems in COPD management

Often the management of COPD is suboptimal, and poor inhaler technique is one of the prime reasons for this [103–106]. Physicians frequently prescribe inhaler devices based on available/preferred drugs, without ascertaining if the patient/caregiver can use them effectively [106]. Most COPD occurs in older adults who may have comorbid conditions, such as tremor, poor eyesight, arthritis and cognitive problems that may aggravate effective inhaler device use. Therefore, device

selection must be based on COPD severity, the physical and cognitive abilities of the patient and caregiver, the insurer's classification and requests for prior authorization, and cost-saving requests from the patient.

All types of inhaler devices have similar efficacy if tested under strict clinical-trial conditions. However, in real life, each inhaler has distinct characteristics that can become advantages or disadvantages for individual patients that affect outcome, patient satisfaction (and therefore adherence for use) [104, 107, 108]. For individual patients, ‘inhalers’ should not be viewed as equivalent, and device type must become an important variable to consider when planning optimal COPD management [109].

Several studies have demonstrated that errors in inhaler use are common amongst patients with COPD [110, 111] (Table 3). One study estimated that while 76% of pMDI users and 49–55% of DPI users made at least one error, fortunately only 28% and 11–32% of pMDI and DPI users, respectively, made errors that compromised the clinical benefits of their medications [110]. Reasons for poor inhaler use may be divided into issues related to the device, patient, physician and healthcare professionals, practice, and cost issues leading to failure to obtain the inhalers. Multiple issues may affect any single patient.

The importance of correct use of inhaler devices in achieving optimum management of COPD cannot be over-emphasized. Understanding the practical aspects of inhaler use (including device selection, correct inhalation techniques and adherence to treatment) are key to the early and successful management of COPD in the primary care setting [112]. Successful COPD management will be achieved by improving device selection based on individual patient need together with education and training of the patient, high-quality physician–patient communication and regular monitoring.

To make inhalers more patient-friendly, new inhalers continue to be produced. Indacaterol uses a new DPI that is very similar to the one used for formoterol, which can be used in

individuals with very low inspiratory flow rates and which is preferred by some individuals because they feel assured they receive a ‘new’ dose each time [43]. One of the most recent is Respimat[®], and is reported to have a much ‘gentler’ spray that patients prefer [113]. The aerosol cloud of Respimat has a high fine-particle ratio, and the low velocity of the cloud and long ‘hang’ time of the aerosol can result in a larger portion of the dose being deposited in the lungs when compared with aerosols from pMDIs and DPIs. Therefore, drug formulations using Respimat may use only one-half or one-quarter of the dose delivered by a pMDI. The long duration of the spray may benefit patients who have difficulty in coordinating inhalation and device activation [114].

Unfortunately, all of the new inhalers are limited to 1–2 drugs, making it necessary for patients to continue to have multiple inhalers. Multiple inhaler types add to the problems of poor inhaler technique and unintentional poor adherence to treatment.

Immunization: the forgotten pharmacotherapy

Management of COPD includes efforts to relieve symptoms, prevent disease progression, prevent and treat exacerbations, improve exercise tolerance and improve overall QoL. Ensuring that patients with COPD are up-to-date with recommended immunizations is a primary prevention strategy that can reduce the risk for exacerbations and thereby help to improve overall QoL. Recommendations are made and updated annually by the Advisory Committee on Immunization Practices (ACIP) [115] in the USA for vaccines indicated for adults based on conditions such as COPD. Similar indications are recommended by GOLD [1, 116]. Unfortunately, significant gaps remain in immunization coverage for those with COPD. For example, in the USA, the coverage for influenza is less than 75% [117].

Table 3. Critical inhaler errors.

Critical error	pMDI	Multi-dose DPI Diskus [™] /Turbuhaler [™]	Single-dose DPI Handihaler [™] /Aerolizer [™]
Did not remove cap	×	×	×
Holding inhaler upside down	×	×	×
Did not load dose		×	×
Did not pierce capsule			×
Blowing into device		×	×
A tight seal with the lips is not made		×	×
Inhalation and actuation not synchronized	×		
Too weak or too slow an inhalation		×	×

Abbreviations

DPI, dry-powder inhaler; pMDI, pressurized metered-dose inhaler

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COPD exacerbations are often triggered by viral and bacterial respiratory infections. Therefore, the importance of influenza and pneumococcal immunizations for patients with COPD cannot be overemphasized. These vaccinations are recommended in COPD guidelines and included in clinical performance measures for COPD [1]. One dose of influenza vaccine is recommended annually for all adults, including those with COPD [115]. The influenza strains for the 2012–2013 season are A/California/7/2009(H1N1), A/Victoria/361/2011 (H3N2) and B/Wisconsin/1/2010 [115]. Trivalent inactivated influenza vaccine (TIV) is appropriate for all adults; a high-dose formulation is approved for persons aged 65 years or older and an intramuscular formulation is approved for those aged 18–64 years. The live attenuated influenza vaccine (LAIV) (intranasal) is seldom used for those with COPD and is approved only for adults aged up to 49 years [115].

A single dose of pneumococcal polysaccharide vaccine (PPSV23) is recommended for all adults with COPD [1]. One-time revaccination with PPSV23 is recommended for those aged 65 years and older who received a dose of PPSV23 five or more years previously and were less than 65 years of age at the time of primary vaccination. Pneumococcal conjugate vaccine (PCV13) is approved for adults in several countries, including in the USA [118], where it is recommended only as an add-on to PPSV23 vaccine for those who are immunocompromised [119].

While not specifically recommended for people with COPD, pertussis (whooping cough) immunization may be beneficial. More than 25,000 cases of pertussis were reported in the USA in 2010, and notable outbreaks have continued in several US states into 2012 [120]. Pertussis can cause serious illness in young children, teens and adults; most deaths are in infants and the elderly. Clearly, the '100-day pertussis cough' would be an unfavorable development for someone with COPD. All adults who have not received the Tdap (diphtheria, tetanus and pertussis) vaccine previously should receive a one-time dose of Tdap. Tdap can be administered regardless of the interval since the last Td (diphtheria) vaccine.

Pulmonary rehabilitation

Pulmonary rehabilitation is an important and inadequately used part of COPD therapy [1, 121]. Programs should be a minimum of 6 weeks, with follow-up support, and typically include exercise training, nutrition counseling and COPD education. Pulmonary rehabilitation does not directly improve FEV₁ but does address the many systemic effects of COPD. Pulmonary rehabilitation has been shown to improve exercise performance and reduce dyspnea and fatigue in COPD patients at all levels of severity. It has been shown to be especially effective if combined with tiotropium, which improves ventilation mechanics [122]. The combination results in higher exercise tolerance [1].

Long-term oxygen therapy

Chronic hypoxemia (defined as an arterial partial pressure of oxygen ≤ 55 mmHg or increase in oxygen saturation $\leq 88\%$) occurs with worsening airflow limitation [1]. In these patients, long-term oxygen therapy (>15 hours per day) increases the chances of survival. Typically introduced at GOLD Stage 4 (very severe), long-term oxygen therapy may be appropriate for patients with less severe disease who have resting hypoxemia (e.g. those in category D) [1]. The benefits of long-term oxygen therapy for the hypoxic COPD patient include a mortality benefit, stabilization of pulmonary hypertension, improved mental status, reduced stay in hospital, increased exercise capacity and improved health-related QoL [1].

Patient compliance with oxygen therapy tends to be poor. Support includes education on how and why to use oxygen, and ways to overcome the self-consciousness of using a treatment that is very conspicuous [1]. Successful long-term oxygen therapy is dependent (at least in part) upon coping skills, motivation and a supportive family influence [123].

Exacerbation treatment

Exacerbations may be treated at home, in the office, in the Emergency Room, or in hospital. Home-based therapy for COPD exacerbations typically involves an increase in the dose and frequency of the existing short-acting bronchodilator therapy (especially short-acting β_2 -adrenergic bronchodilators) [1]. Albuterol is the short-acting β_2 -adrenergic bronchodilator of choice for COPD exacerbations. Levalbuterol is more expensive and does not confer additional efficacy [1]. A short-acting anticholinergic bronchodilator or a combination of short-acting bronchodilators may be used for symptom control.

Most exacerbations lasting more than a few hours require systemic glucocorticosteroids [1]. Systemic glucocorticosteroids increase the rate of recovery of lung function and improve FEV₁. They may also reduce the chance of treatment failure, length of hospital stay and the risk of early relapse. Typically, prednisone (30–40 mg, p.o.) is administered daily for 7–10 days. Prolonged treatment is not recommended because it increases the risk of side-effects while not providing additional efficacy [1, 13]. Tapering of the corticosteroid dose is usually not required with short bursts lasting 10 days or less.

Respiratory infections are the most common cause of an exacerbation. There is strong evidence that patients experiencing a COPD exacerbation with signs of airway infection (e.g. increased sputum purulence) benefit from antibiotic treatment. The infectious agents in COPD can be viral or bacterial. *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Moraxella catarrhalis* are the most common bacterial pathogens involved in COPD exacerbations.

Antibiotic selection in COPD exacerbations is important in light of evidence that inappropriate initial antimicrobial treatment contributes to exacerbations associated with mul-

tidrug-resistant bacteria [1]. Commonly used antibiotics for treating a COPD exacerbation include β -lactams (e.g. penicillin, amoxicillin), tetracycline, doxycycline, trimethoprim/sulfamethoxazole, macrolides (e.g. azithromycin, clarithromycin), second- or third-generation cephalosporins and fluoroquinolones (e.g. levofloxacin, moxifloxacin). Clinicians should base their choice of antibiotics on local resistance patterns (antibiogram), and therapy should be given for 3–7 days [124]. Antibiotics are used for exacerbations with any of the following criteria: increased sputum volume; increased sputum purulence; any exacerbation requiring hospitalization [1].

Details of inpatient therapy and surgical therapies [125] are beyond the scope of this review. However, a few important points should be stressed. Hospitalization may be required for therapy and control of severe resting dyspnea or new signs of severe lung impairment such as cyanosis on room air. However, hospital care may also be required due to significant exacerbations due to comorbid complications (e.g. CAD, congestive heart failure, or poorly controlled diabetes mellitus), newly occurring arrhythmias, diagnostic uncertainty (such as a need to exclude pulmonary embolism), older age and insufficient home support.

Summary

COPD is a treatable disease and therapy can improve QoL, the level of symptoms, functionality and life expectancy. Primary therapy remains removal of the toxic agent (in most cases, tobacco smoke). Additional therapy includes bronchodilators (β -adrenergic and antimuscarinic classes). ICS are used to prevent exacerbations and, in carefully selected patients, may have additional benefits due to exacerbation prevention. Long-acting bronchodilators also reduce the risk of exacerbations. Pulmonary rehabilitation, immunizations and, in very severe COPD, long-term oxygen therapy are the conventional COPD therapies. However, COPD is a systemic disease and often requires therapy of its protean-associated morbidities from depression to osteoporosis and muscle-wasting. Despite pessimism from several quarters, COPD is treatable.

Research needs (author's opinion)

As with all common chronic diseases, the opportunities to improve the understanding and management of COPD are numerous. We have limited understanding of COPD with regard to inflammatory cells, inflammatory triggers; the role of each step in the inflammatory cascade; the physiology of parenchyma destruction, hyperinflation and formation of blebs and bullae; and the role of genes, epigenetics and phenotypes.

Some large and lengthy randomized controlled trials have been completed, but they identified almost as many questions as they answered. It remains unclear whether it is better to begin LABAs or LAMAs or a combination of the two, or if therapy should be targeted to the few phenotypes we have identified to date. The recommended medication hierarchy in the GOLD guidelines relies on research evidence from very short-term 12-week studies and significant expert opin-

ion. That expert opinion is usually from pulmonologists and respirologists who treat the later stages of COPD. Their perspectives may not reach the same level of 'expertise' for less severe COPD seen in primary-care practices.

Opportunities for clinical research in primary care are also numerous. Tools recommended in the GOLD guidelines designed to help convert recommendations into everyday practice give preference to the mMRC and CAT without explaining why tools developed and validated in primary care have been excluded [126]. 'Natural history' studies are required to help determine the optimal frequency for COPD assessment with tools such as the BODE index, the mMRC and spirometry.

Researchers have yet to demonstrate the outcome benefits of early diagnosis in asymptomatic COPD or how to best recognize symptomatic COPD prior to significant changes in functional status. Do we screen for COPD and, if so, how? We have not had long-term studies that assessed whether specific inhaler types improve outcomes or even if once-daily medications are associated with better outcomes than those requiring multiple daily doses.

Reporting of the high prevalence of multiple morbidities in people with COPD has outlined several new areas of investigation. Are there clusters or 'phenotypes' of COPD associated with specific clusters of morbidities? Guidelines exist for COPD and most of the individual morbidities, but how should those guidelines be modified for people with multiple conditions? The 2011 GOLD guidelines began the discussion but made limited progress [1]. How is the systemic inflammation of COPD related to comorbidities such as osteoporosis, muscle-wasting and depression? What protects the one-third to one-half of chronic smokers who never develop COPD? Can we identify who will and will not develop COPD? Can we use this knowledge to help prevent COPD in others who are susceptible?

The opportunities do not stop with biomedical researchers, scientists and clinical/health services researchers. We need workers in biophysics and bioengineering sectors to design better drug-delivery devices, delivering new and old drugs more effectively to the lungs (and perhaps even to the sub-sections of the lungs). Additional devices and delivery systems are needed to introduce one-way valves to deflate large areas of hyperinflation. Imaging techniques are advancing, but many methods introduce larger doses of radiation than is optimal for already damaged lungs.

The opportunities are unlimited but the funds are not. As COPD moves into third place amongst the most common causes of death in the world, the need for new basic-science information, therapies and delivery systems will increase. For now we have to work with the information and therapies we have, knowing that the understanding and management of COPD has improved significantly in the past 10 years, but we still have a long way to go.

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