Review

Evolving therapies in chronic obstructive pulmonary disease

Anthony D D'Urzo*[,1], M Reza Maleki-Yazdi[2] & R Andrew McIvor[3]

[1]Department of Family & Community Medicine, Faculty of Medicine, University of Toronto, 500 University Avenue, 5th Floor, Toronto, ON, M5G 1V7, Canada

[2]Division of Respiratory Medicine, Women's College Hospital, University of Toronto, Toronto, ON, M5G 1N8, Canada

[3]St Joseph's Healthcare, McMaster University, 50 Charlton Avenue E, Hamilton, ON, L8N 4A6, Canada

*Author for correspondence:
Tel.: +1 416 652 9336
Fax: +1 416 652 0218
tonydurzo@sympatico.ca

Practice points

- An estimated three million people die of chronic obstructive pulmonary disease (COPD) every year, and the prevalence of COPD is increasing. By 2020, COPD is expected to become the third-leading cause of death worldwide.
- The burden of illness associated with COPD is high. Both the disease itself and common comorbidities, such as cardiovascular disease, asthma, diabetes and mental health problems, have a negative impact on the health status of patients with all disease severities.
- COPD treatment costs in primary care are substantial and due mainly to costs of medication; hospitalization represents the major cost driver in secondary and tertiary care.
- Early diagnosis and treatment of COPD may lessen the burden of disease.
- Together with smoking cessation and other nonpharmacologic approaches, optimal pharmacological treatment and correct inhaler use are important for successful therapy outcomes.
- According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy, patients should be assessed and treated according to their degree of COPD symptoms and risk of exacerbations (based on the degree of airflow limitation and history of exacerbations). In the GOLD 2014 management strategy for stable COPD, bronchodilators are the cornerstone of pharmacologic disease management.
- GOLD first- and alternative-choice treatment recommendations for patients with persistently symptomatic disease are: long-acting β_2-adrenergic agonists (LABAs), long-acting muscarinic antagonists (LAMAs) or combination therapy with a LABA/LAMA.
- Several LABA and LAMA monotherapies have well-established safety and efficacy profiles. Combining these different agents may improve clinical outcomes and decrease the risk of side effects, compared with increasing the dose of a single bronchodilator.
- Use of phosphodiesterase-4 inhibitors with long-acting bronchodilators and/or inhaled corticosteroids (ICS), or ICS/LABA combination therapy is effective in appropriate patients with severe or very severe disease at high risk of exacerbations. Triple therapy with ICS/LABA/LAMA combinations appears promising, but more data are needed to confirm the long-term risk–benefit profile of this approach.
- Other emerging COPD therapies include single-molecule muscarinic antagonist/β_2-agonists, TNF-α antagonists, *N*-acetylcysteine and its derivatives, CCR1 chemokine receptor antagonists, p38 MAP kinase inhibitors, M_3-selective muscarinic antagonists and prophylactic antibiotics. However, the roles of these agents in the treatment of COPD and their potential interaction with existing drugs have yet to be determined.

The global prevalence of chronic obstructive pulmonary disease (COPD) is rising, although the disease is often underdiagnosed or misdiagnosed as asthma. Early diagnosis and intervention in the primary care setting may improve outcomes and reduce the overall burden of COPD and its comorbidities. Bronchodilators are the mainstay of pharmacologic treatment in international and national guidelines, with long-acting agents administered alone or as part of a combination regimen

Future Medicine part of fsg

in patients who are persistently symptomatic and/or at high risk of COPD exacerbations. Here, we report results of a systematic literature search to review the evidence supporting several approved bronchodilator monotherapies, as well as dual bronchodilator treatment, combination therapy with inhaled corticosteroids plus one or two bronchodilators and other emerging COPD treatment options.

Keywords: bronchodilation • chronic obstructive pulmonary disease • cost of illness • epidemiology • Global Initiative for Chronic Obstructive Lung Disease 2014 • treatment

Chronic obstructive pulmonary disease (COPD) is characterized by chronic and progressive dyspnea, cough and mucus production, punctuated by episodic worsening of these symptoms (exacerbations). Faced with projected increases in the prevalence and burden of COPD, WHO, along with the US NIH and the National Heart, Lung, and Blood Institute, combined to form the Global Initiative for Chronic Obstructive Lung Disease (GOLD). GOLD first published their global strategy for the diagnosis, management and prevention of COPD in 2001 [1], with the aim of reducing the burden of COPD through increased awareness, and improved management and prevention. Its target audience includes physicians in primary care who typically are the first to evaluate patients with respiratory symptoms and who are in an ideal position to establish an early diagnosis of COPD. Updated yearly, the strategy document is designed as a tool for implementing effective COPD management in any clinical setting based on available healthcare systems, and can form a framework for national guidelines.

GOLD provides a variety of evidence-based recommendations for the prevention, diagnosis and management of COPD and highlights the central roles of smoking cessation, pulmonary rehabilitation, and pharmacological and nonpharmacological interventions in reducing symptoms, reducing future risk and improving patient outcomes. Many of these recommendations (e.g., smoking cessation and pulmonary rehabilitation) are extremely well established in the treatment of COPD and come with excellent track records. These interventions should be strongly promoted for adoption in primary care in a manner that emphasizes individualized patient care and the management of comorbidities.

However, in recent years there has been an explosion in the number of new pharmacological treatments available for the treatment of COPD, creating new challenges among primary care physicians related to therapeutic choices that are less well described in the primary care setting, compared with the secondary care setting. This review therefore provides an overview of these developments with a focus on treatments for patients with persistently symptomatic disease (GOLD groups B and D). We also review the epidemiology of COPD and burden of disease.

Methods

Structured PubMed searches were used to identify literature for this review, with publication dates from January 2002 to March 2013 (Table 1). All searches were limited to human studies published in English. References were also obtained from publications cited within papers identified by the PubMed searches, as well as through author expertise. The GOLD 2014 strategy document [1] was the source of most guideline information; local guidelines were quoted where appropriate.

Epidemiology

Historically, COPD has been considered to predominantly affect male smokers, particularly in North America and Europe [2]. However, in recent decades the prevalence of COPD-related mortality has grown fastest in women [2–4]. This may be due in part to changes in the epidemiology of smoking and increased use of biomass fuels in certain nations, but gender differences in the diagnosis, treatment and natural history of COPD also appear to play a role.

Prevalence

An estimated three million people die of COPD every year [5]. By 2020, COPD is expected to become the third leading cause of death worldwide [5]. In a systematic review and meta-analysis, the global prevalence of physiologically defined COPD in adults aged ≥40 years was 9–10% [6]. However, this likely underestimates the true prevalence, as COPD is frequently underdiagnosed, and COPD population studies are complicated by methodologic issues, lack of disease awareness and inconsistencies in coding for COPD [7,8]. For primary care physicians, the increasing prevalence and mortality of COPD may require development of new skills and tools for diagnosis and management, as well as new approaches for integrating COPD into chronic disease management models [9].

Burden of illness

While COPD itself creates a heavy burden at the personal and societal levels, COPD is now understood to be a multimorbid systemic disease that affects an aging population, rather than purely a lung-specific disease [1]. Comorbidities include cardiovascular disease, asthma, diabetes and its precursors (obe-

Table 1. Overview of PubMed search strategy.

Searches	Search terms
All	"Pulmonary disease, chronic obstructive" or "COPD" or "chronic obstructive pulmonary disease" or "chronic obstructive pulmonary disorder"
Epidemiology	"Epidemiology" or "epidemiol*"
Burden of illness	"Burden of illness" or "quality of life" or "QoL" or "cost of illness" or "cost-effective" or "healthcare costs" or "cost to society" or "healthcare cost" or "costs to society" or "treatment burden" or "burden" or "cost-effectiveness" or "economic burden" or "quality of life" or "life qualities" or "life quality" or "cost of Illness" or "illness cost" or "illness costs" or "cost of disease" or "costs of disease" or "sickness cost" or "disease cost" or "disease costs" or "illness burden" or "illness burdens" or "cost of sickness" or "sickness costs" or "economics, medical" or "medical economics"
	And "primary health care" or "primary care" or "primary healthcare"
New therapies[†]	And "treatment" or "therapy" or "therapies" or "therapeutic"
	And the names of drugs currently approved for treating COPD listed below:
	"AD237" or "AD 237" or "AD-237" or "Enurev" or "glycopyrrolate" or "glycopyrronium bromide" or "NVA 237" or "NVA-237" or "NVA237" or "Seebri" or "Breezhaler" or "Daliresp" or "Daxas" or "ipratropium bromide" or "Duoneb" or "Arcapta" or "indacaterol" or "Neohaler" or "Hirobriz" or "Onbrez" or "Onbrize" or "QAB149" or "QAB 149" or "QAB-149" or "acetylcysteine" or "Mucomyst" or "zambon" or "Fluimucil" or "Flumil" or "NSC 111180" or "NSC-111180" or "NSC111180" or "Rhinofluimucil" or "Rinofluimucil" or "Spiriva" or "titropium bromide" or "tiotropium bromide" or "HandiHaler" or "Tiova" or "Respimat" or "BA-679" or "BA 679" or "BA679" or "Tudorza" or "aclinidium" or "Bretaris" or "Genuair" or "KRP-AB1102" or "LAS 32471" or "LAS-32471" or "LAS32471" or "Pressair" or "aclidinium bromide" or "LAS34273" or "LAS 34273" or "LAS-34273" or "Dulera" or "mometasone furoate" or "formoterol" or "fumarate dehydrate" or "SCH418131" or "SCH 418131" or "SCH-418131" or "Zenhale" or "arformoterol" or "eformoterol" or "formoterol" or "Brovana" or "beclometasone" or "beclomethasone" or "budesonide" or "levosalbutamol" or "levalbuterol" or "albuterol" or "Xopenex" or "salbutamol" or "prednisone" or "Lodotra" or "roflumilast" or "APTA2217" or "APTA 2217" or "APTA-2217" or "B9302–107" or "B9302 107" or "B9302107" or "BY217" or "BY 217" or "BY-217" or "BYK20869" or "BYK 20869" or "BYK-20869" or "Libertek" or "salmeterol" or "Serevent" or "SN408" or "SN-408" or "SN 408" or "CHF 1535" or "CHF1535" or "CHF-1535" or "Combair" or "Formodual" or "Fostair" or "Novopulmon" or "Novolizer" or "Symbicort" or "Oxez" or "Oxis" or "Atimos" or "Tovanor" or "Innovair" or "Inuvair" or "Inuver" or "Inuxair" or "Kantos" or "Budecort" or "Tafen" or "Alenia" or "Turbuhaler" or "Oxeze" or "Foradil" or "Perforomist" or "Atrovent"

Searches were limited to human studies that were published in English between January 2002 and March 2013, except where noted.
The use of an asterisk (*) in the database search enabled retrieval of all variations of the word, regardless of the ending after the symbol.
[†]Additional/alternative search limits: meta-analyses, randomized controlled trials and reviews published from January 2006 to March 2013.
Licensed drug names were identified via the ADIS R&D Insight database.
COPD: Chronic obstructive pulmonary disease; QoL: Quality of life.

sity and metabolic syndrome), mental health problems, osteoporosis, and cognitive impairment. The presence of a comorbid condition is associated with a worse outcome compared with a single condition alone, with a cumulative risk for multiple comorbidities [10,11]. COPD and its comorbidities have a significant effect on health status in patients with all disease severities [12,13]. COPD exacerbations also have a negative impact on outcomes and quality of life [11,14,15]. An exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [1]. Despite their importance, exacerbations are often not reported [16]. Weekly assessment with a questionnaire may be used to detect unreported

exacerbations, [16] and more recently, smartphone-based diaries have been developed to monitor daily symptoms [17].

The costs of treating patients with COPD in primary care are high and are predicted by the presence of comorbidities, severity of airflow obstruction, frequency of previous exacerbations, health status, healthcare resource utilization and duration of work disability [18]. Medication and hospitalizations are the major cost drivers [19,20].

Reducing the burden

Primary care physicians may lessen the burden of COPD by providing early diagnosis and treatment [21]. COPD is underdiagnosed and often misdiagnosed [22–24]. The GOLD strategy document recommends that a clinical diagnosis of COPD should be considered in any adult over the age of 40 who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for COPD (particularly tobacco smoke exposure, which is the most frequent cause of the disease) [1]. Many patients accept some degree of respiratory symptoms because they smoke, are ex-smokers or are growing older, and may not recognize signs of COPD. Furthermore, because COPD develops insidiously, many patients do not perceive indications of worsening disease. Consequently, primary care providers may need to proactively ask patients about their symptoms. Patients with early or mild COPD are predominantly treated by primary care physicians, and these patients are becoming an increasingly important part of the primary care population [25].

Spirometry is essential in order to make a diagnosis of COPD. Earlier detection of COPD through use of spirometry at the primary care level would allow earlier implementation of effective management strategies and, thus, improve the chances of influencing the course of the disease. The spirometric criterion for a diagnosis of COPD is an forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <0.7 following optimal bronchodilation. Application of this fixed ratio may result in overdiagnosis in the elderly and underdiagnosis in subjects aged <45 years, and other approaches such as using the lower limit of normal value, or using the FEV_1/ forced expiratory volume in 6 seconds (FEV_6) ratio, have been proposed [26,27]. However, the potential drawbacks of using the FEV_1/FVC <0.7 ratio are outweighed by the advantages of a simple and consistent approach to diagnosis [1].

Although spirometry is essential to make a diagnosis of COPD, spirometry itself cannot rule out asthma. Careful history taking, physical examination, and assessment of respiratory symptoms also need to be considered when diagnosing and managing this disease, and in case-finding trials or programs [28,29]. Particular care must be taken in elderly patients with asthma, in whom the symptoms of fixed-airflow obstruction can appear similar to those of COPD [30]; one study reported a misdiagnosis of COPD in 20% of elderly patients with asthma [31]. However, an asthma-COPD phenotype may also be evident in patients with asthma who smoke; this overlap syndrome is associated with poor health status and worse outcomes than COPD alone [32,33]. Serum eosinophil levels and other characteristics in asthma may differ from those associated with COPD [29].

While the benefits of spirometric screening for COPD at a general population level are questionable, primary care providers have an important role in improving COPD detection rates through case finding among at-risk individuals, for example in adults aged over 45 years with an extensive smoking history and/or repeated respiratory tract infection [1,23].

In the early stages of COPD, disease impact can be reduced by smoking cessation, symptom management, and appropriate nonpharmacologic and pharmacologic management [21]. Only smoking cessation and long-term oxygen therapy in the hypoxemic patient have been shown definitively to improve survival in COPD [1,34].

Early implementation of smoking cessation programs, by removing the most common risk factor for COPD, has the greatest potential to reduce mortality in COPD [1,34]. Smoking cessation may form part of a pulmonary rehabilitation program, a multidisciplinary initiative that includes exercise training together with components such as nutrition counseling, education and exacerbation management [1,35]. Attention to optimal bronchodilation at the start of an exercise program is recommended, since it removes the limitation of dyspnea on exercise and allows an increased focus on peripheral muscle exercise [35]. Along with maximal bronchodilation, correct inhaler use is important for successful pulmonary rehabilitation and therapy outcomes [36,37].

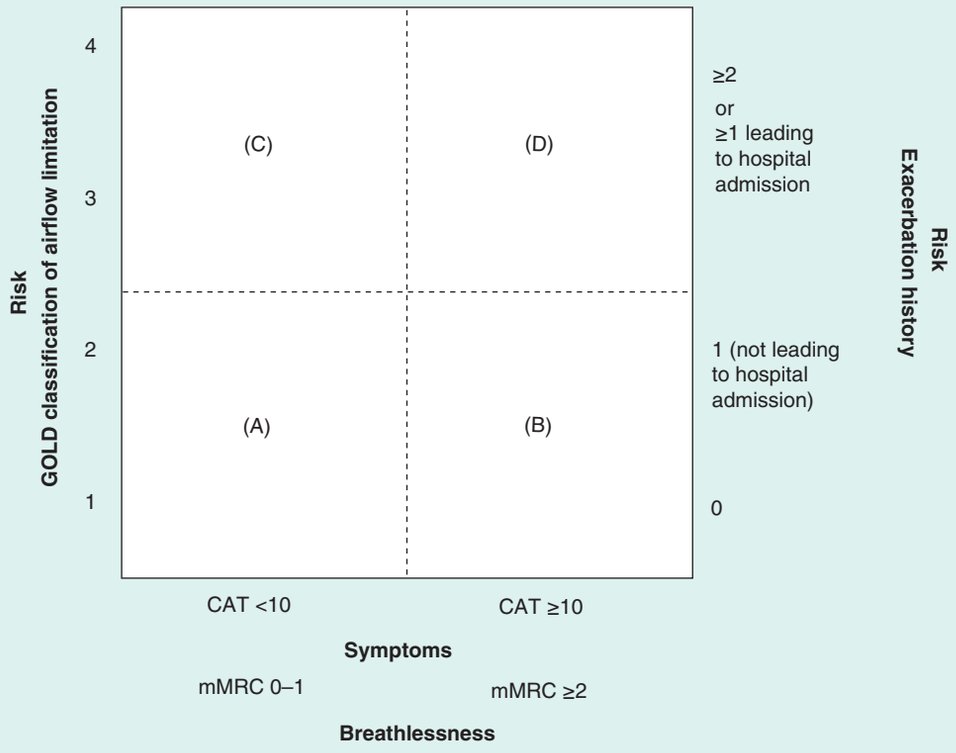
Pulmonary rehabilitation can benefit patients at all stages of the disease. An integrated approach in the primary care setting, involving optimal medication, education, physical activity and exacerbation management, has been shown to improve 1-year quality of life, compared with conventional care [38]. Practice nurses may also play a major role in reducing the burden of COPD by supporting self-management and health-behavior change [39]. However, self-management may lead to delays in seeking appropriate medi-

cal help, perhaps owing to overconfidence, and further work is needed to identify clearly those patients who are most likely to benefit from such strategies [40].

At the other end of the spectrum, for patients with severe COPD who are hypoxemic, long-term oxygen therapy has been shown to reduce mortality [1].

Pharmacological strategies

In 2011, GOLD provided a new assessment tool for evaluating the degree of COPD symptoms in combination with spirometric classification and/or risk of exacerbations (Figure 1) [1,41]. The assessment combines the patient's perception of the disease with the



Patient category	Characteristics	Spirometric classification	Exacerbations per year	CAT	mMRC
A	Low risk, less symptoms	GOLD 1–2	≤1†	<10	0–1
B	Low risk, more symptoms	GOLD 1–2	≤1†	≥10	≥2
C	High risk, less symptoms	GOLD 3–4	≥2‡	<10	0–1
D	High risk, more symptoms	GOLD 3–4	≥2‡	≥10	≥2

Figure 1. Model of symptom/risk evaluation in chronic obstructive pulmonary disease. This tool assigns patients to one of four groups lettered A through D. The CAT and mMRC scales are recommended for evaluating symptoms and breathlessness, respectively. Either the GOLD spirometric classification or patient history of exacerbations is used to assess exacerbation risk. When establishing risk, it is recommended that the highest risk according to GOLD grade or exacerbation history (≥1 hospitalizations for COPD exacerbations should be considered high risk) should be chosen. The severity of airflow limitation (in patients with forced expiratory volume in 1 second [FEV_1] /forced vital capacity <0.7) is classed as follows: GOLD 1 (mild), FEV_1 ≥80% predicted; GOLD 2 (moderate), FEV_1 50 to <80% predicted; GOLD 3 (severe), FEV_1 30 to <50% predicted; GOLD 4 (severe); FEV_1 <30% predicted.
†Not leading to hospital admission.
‡≥1 leading to hospital admission.
CAT: Chronic obstructive pulmonary disease Assessment Test; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: Modified Medical Research Council score.
Reproduced with permission from the Global Strategy for Diagnosis, Management and Prevention of COPD 2014 [1] © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved.
Available from [45].

quantification of risk, and is thought to better reflect the complexity of disease than a single FEV_1 measurement (as was previously the case) [42]. This system groups patients into one of four categories, comprising A: low risk, less symptoms; B: low risk, more symptoms; C: high risk, less symptoms; and D: high risk, more symptoms [1,41]. This approach is broadly similar to the stratification system recommended by the Canadian Thoracic Society that is based on both spirometry and the Medical Research Council dyspnea grade [43]. However, the new GOLD grouping is not without its controversies as it produces an uneven split of the COPD population, with a third of patients in group A and a third in group D [44]. Furthermore, its prognostic validity to predict time-to-death does not differ from the old GOLD staging based on spirometry criteria alone. The GOLD grouping also requires the use of questionnaires that are not widely utilized by physicians.

GOLD's new assessment tool provides a model for pharmacologic management of stable COPD disease [1,41]. As shown in Figure 2, bronchodilators form the cornerstone of pharmacologic disease management. These agents reduce bronchoconstriction and air trapping to improve airflow limitation (Figure 3). Although inhaled corticosteroids (ICS) are a mainstay of treat-

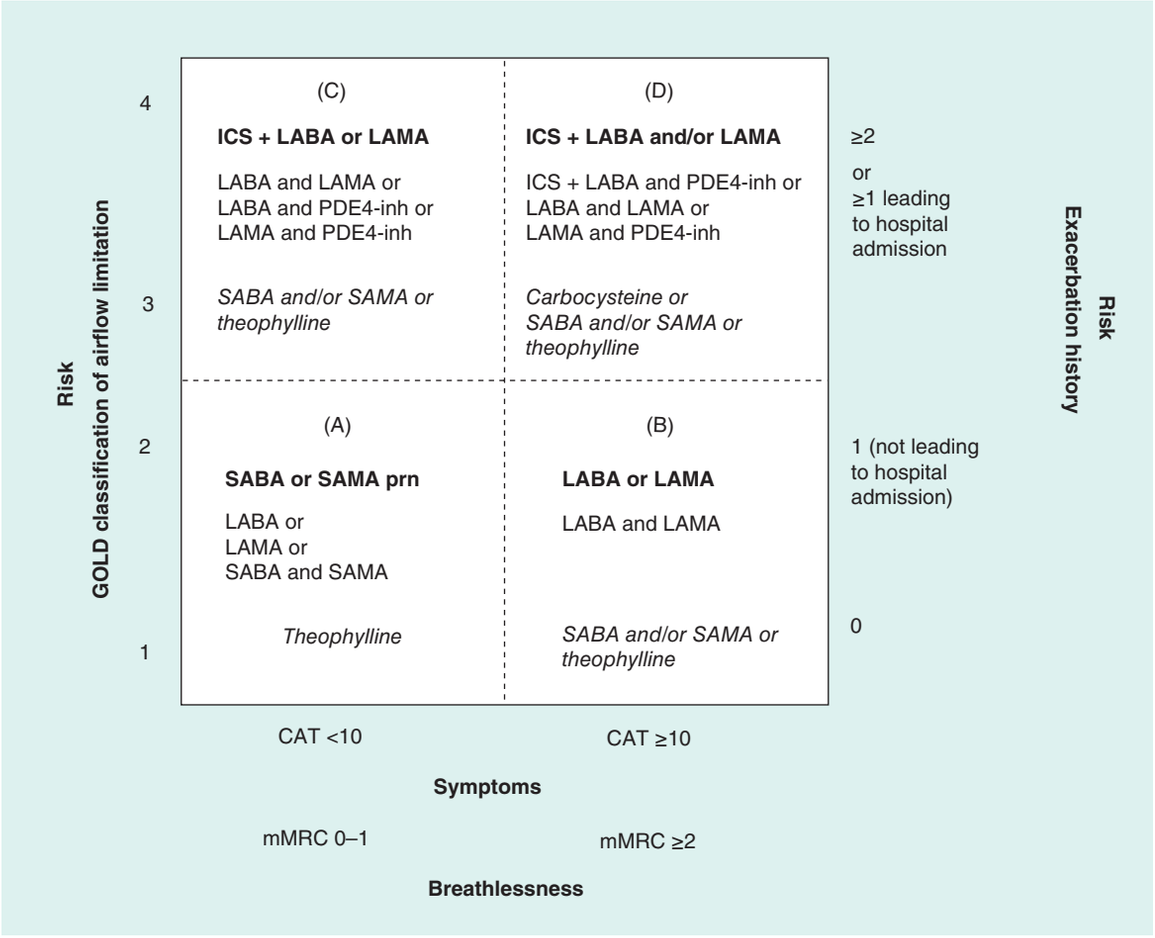


Figure 2. Global Initiative for Chronic Obstructive Lung Disease recommendations for initial pharmacologic management of chronic obstructive pulmonary disease. Recommended first choice treatments are presented in bold, alternative choices are shown in regular type and other possible treatments are presented in italics [1,49]. Other possible treatments can be used alone or in combination with other options listed as first or alternative choices. Within first choice, alternative choice and other treatment categories, medications are listed in alphabetical order and not in order of preference.
CAT: COPD Assessment Test; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: Inhaled corticosteroid; LABA: Long-acting β_2 adrenergic agonist; LAMA: Long-acting muscarinic antagonist; mMRC: Modified Medical Research Council score; PDE4-inh: Phosphodiesterase-4 inhibitor; prn: As needed (*pro re nata*); SABA: Short-acting β_2 agonist; SAMA: Short-acting muscarinic antagonist.
Adapted and reproduced from the Global Strategy for Diagnosis, Management and Prevention of COPD 2014 [1] © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved.
Available from [45].

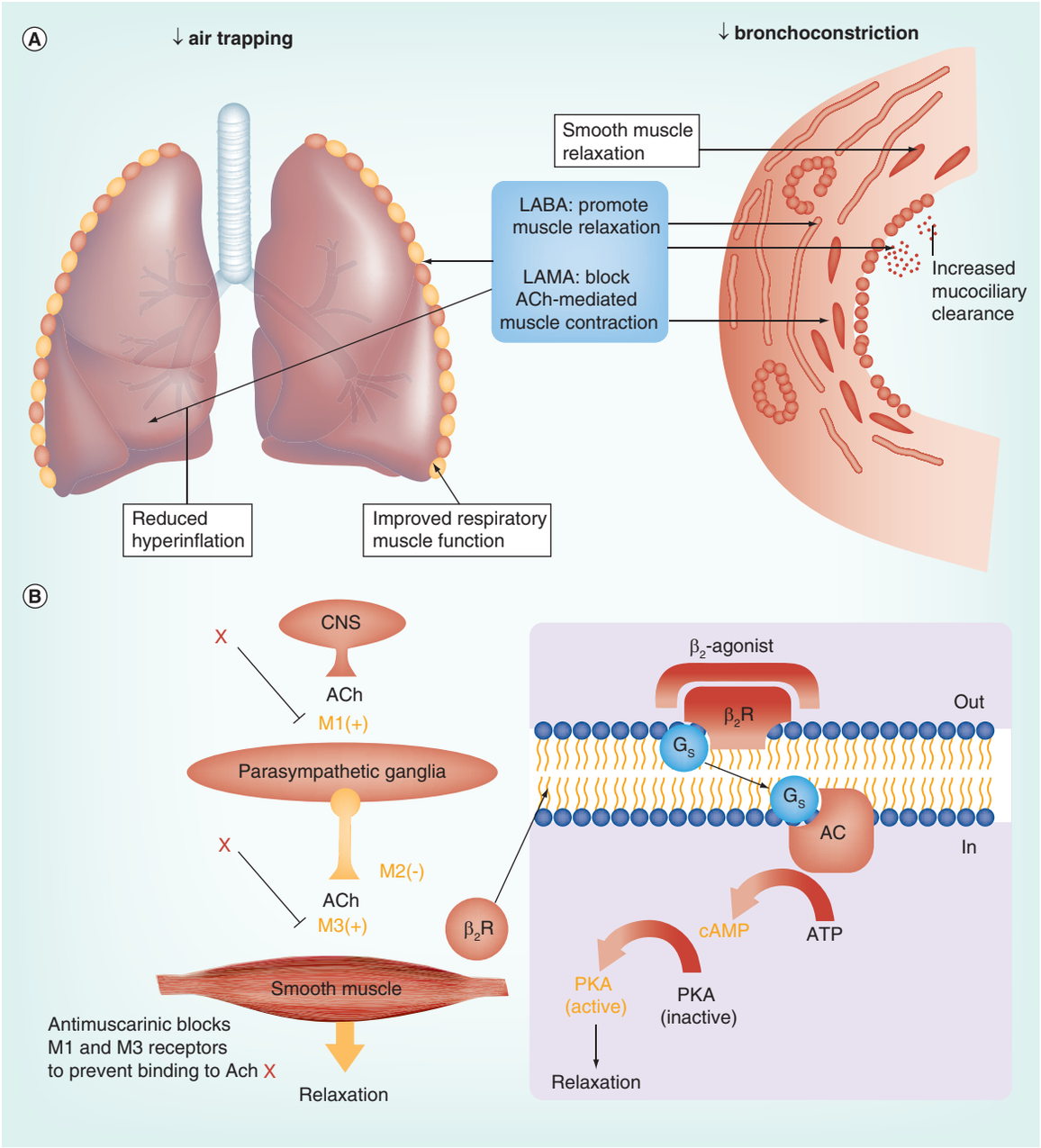


Figure 3. Mode of action of long-acting β_2 adrenergic agonist and long-acting muscarinic antagonist bronchodilators. (A) LABAs and LAMAs are bronchodilators that address airflow limitation by targeting bronchoconstriction and reducing air trapping [1,50–52]. **(B)** The mode of action for LABAs and LAMAs is different, but both provide bronchodilation via smooth muscle relaxation. Through activation of β_2 receptors on smooth muscle, β_2 agonists directly relax smooth muscle. Muscarinic antagonists inhibit the action of Ach at receptor sites in the lung, indirectly inhibiting contraction of airway smooth muscle.
β_2R: β_2 receptor; Ach: Acetylcholine; G_s: Stimulatory G-protein; LABA: Long-acting β_2 adrenergic agonist; LAMA: Long-acting muscarinic antagonist.
(B) Adapted and reprinted with permission from [50]. Copyright © Elsevier 1998.

ment for asthma, their therapeutic benefits in COPD are less clear cut. ICS monotherapy is not recommended in COPD, since it is less effective than ICS and long-acting β_2-adrenergic agonist (LABA) combinations [1]. An ICS/LABA combination was shown to be more effective than an ICS alone for all-cause mortality, COPD-related mortality and exacerbations [46]. GOLD recommends that ICS/LABA combinations are restricted to patients in GOLD group C and group D [1]. While use of ICS/LABA combinations in appropriate patients is effective [46], ICS are often prescribed inappropriately to patients with more moderate

disease [47,48]. For example, an analysis of Swiss general practitioner's adherence to COPD GOLD guidelines using the 2001 GOLD classification system showed that contrary to recommendations, 38% of patients with GOLD stage 1 and 57% of patients with GOLD stage 2 were prescribed ICS/LABA combination therapy [47]. This inappropriate use of ICS may put patients at unnecessary risk of steroid-related side effects with a low potential for therapeutic benefit [47,48].

Evolution of pharmacologic therapies

In this section, COPD therapies for patients with persistently symptomatic disease (GOLD group B and group D) are discussed, particularly the GOLD first- and alternative-choice recommendations: LABAs, long-acting muscarinic antagonists (LAMAs) and combination therapy with LABA/LAMA or ICS/LABA. Other emerging approaches are discussed briefly.

LABAs

Salmeterol and formoterol are well-established twice-daily therapies for COPD and have been shown to improve lung function, quality of life and rates of disease exacerbations [53]. Indacaterol is the most recently approved LABA and provides 24-h improvement in lung function with once-daily dosing [54].

FEV_1 with indacaterol is significantly improved compared with placebo [54], and is similar to that provided by the LAMA tiotropium (Table 2) [55–57]. Indacaterol also significantly improves dyspnea and health status, compared with placebo [55] and tiotropium [57], as well as providing superior improvements in lung function [54,58–59], rescue medication use [58,59] and dyspnea [58,59] versus the LABA salmeterol (Table 2). In a 1-year study in patients with severe COPD and a history of exacerbation in the past year, tiotropium was more effective than indacaterol in reducing exacerbations; effects on dyspnea and health status were similar [60]. Furthermore, European-based analyses have shown that indacaterol is cost effective versus tiotropium and salmeterol [61,62]. Other LABAs in development include olodaterol (BI-1744 CL), carmoterol, vilanterol trifenatate (GW642444M) and PF-00610355 [53].

LAMAs

LAMAs licensed for COPD treatment include tiotropium, and in some countries, glycopyrronium, aclidinium and umeclidinium. Once-daily tiotropium was compared with placebo in the 4-year UPLIFT trial and significantly improved lung function and health status relative to placebo (Table 3) [63]. Secondary analyses of UPLIFT found that tiotropium appeared to slow disease progression in maintenance therapy-naive patients [64] and reduced the rate of decline of postbronchodilator FEV_1 and health status, as well as increasing time to first exacerbation and time to first exacerbation requiring hospitalization in patients with moderate COPD (GOLD stage 2) [65]. These findings suggest that COPD bronchodilator treatment should be considered at an early stage of disease. Tiotropium is also effective in patients with moderate to very severe COPD, as shown in the POET-COPD trial (Table 3) [66]. Compared with salmeterol, tiotropium significantly increased time to first exacerbation and decreased the annual rate of severe exacerbations. Furthermore, this effect was independent of concomitant ICS use, suggesting that bronchodilator treatment alone may be sufficient, even in patients with severe disease. In addition, a subgroup analysis of POET-COPD in patients with GOLD stage 2 disease or who were maintenance therapy naive found that tiotropium significantly prolonged time to first exacerbation, compared with salmeterol [67].

The once-daily LAMA glycopyrronium was evaluated in the GLOW series of clinical studies (Table 3) [68–70]. GLOW1 showed that glycopyrronium had a fast onset of action, maintained improvement in lung function over 26 weeks, and improved dyspnea, health status and use of rescue medication, as well as significantly reducing the risk of moderate-to-severe COPD exacerbations versus placebo [68]. In GLOW2, glycopyrronium had a faster onset of action than tiotropium following the first dose, as measured by FEV_1 ($p < 0.01$ at all time points from 5 min to 4 h post-dose vs tiotropium) [69]. Differences between glycopyrronium and placebo, and between tiotropium and placebo were comparable for outcomes over 52 weeks, including lung function, dyspnea, health status, exacerbations and use of rescue medication [69]. The 3-week GLOW3 study showed that glycopyrronium produced immediate and significant improvement in exercise tolerance versus placebo from day 1, among other related clinical benefits [70].

Aclidinium, a recently approved addition to the available LAMAs, is administered twice daily and has shown benefits in lung function, health status and dyspnea, compared with placebo (Table 3) [71,72]. Improvement in lung function over 6 weeks was similar with aclidinium and tiotropium [74]. Aclidinium was also effective and well tolerated during extended therapy of up to 1 year (Table 3) [73].

Umeclidinium was recently approved in the EU, Canada and USA for the once-daily treatment of COPD. Improvements in lung function and patient-reported outcomes (dyspnea, health status and exacerbations) with umeclidinium 62.5 µg once daily compared with placebo have been reported in studies of up to 6 months in duration (Table 3) [75,76].

Table 2. Selected trials of long-acting β_2 adrenergic agonist bronchodilator therapy in chronic obstructive pulmonary disease.

Study (year)	Trial design	Patients (n)	Key efficacy results	Ref.
Donohue *et al.* (2010)	INHANCE: randomized, 26-week study of indacaterol (150 and 300 μg o.d.) vs placebo (double blind) or open-label tiotropium (18 μg o.d.) in moderate-to-severe COPD	1683	Indacaterol and tiotropium increased trough FEV_1 significantly vs placebo at week 12 At week 26, indacaterol significantly increased TDI total score and significantly decreased SGRQ total score vs placebo At week 26, tiotropium significantly improved TDI total score but not SGRQ total score, compared with placebo	[55]
Vogelmeier *et al.* (2010)	Randomized, double-blind, 14-day, three-period crossover study of indacaterol (150 and 300 μg o.d.) vs tiotropium (18 μg o.d.) and placebo in moderate-to-severe COPD	169	Trough FEV_1 after 14 days was comparable for both active treatments	[56]
Korn *et al.* (2011)	INSIST: randomized, double-blind, double-dummy, 12-week study of indacaterol (150 μg o.d.) vs salmeterol (50 μg b.i.d.) in moderate-to-severe COPD	1123	At week 12, FEV_1 $AUC_{(5\ min–11\ h\ 45\ min)}$, 24-h trough FEV_1, 24-h FEV_1 and 24-h FVC were significantly higher for indacaterol vs salmeterol Week 12 TDI total score and the percentage of patients with a clinically relevant change from baseline were statistically superior for indacaterol vs salmeterol Patients on indacaterol used significantly fewer puffs/day of rescue medication and had a significantly greater percentage of days with no rescue medication use vs salmeterol	[58]
Buhl *et al.* (2011)	INTENSITY: randomized, blinded, 12-week study of indacaterol (150 μg o.d.) vs tiotropium (18 μg o.d.) in moderate-to-severe COPD	1598	At week 12, overall effects on trough FEV_1 were comparable with indacaterol and tiotropium Week 12 TDI and SGRQ total scores were statistically superior for indacaterol vs tiotropium Indacaterol-treated patients were significantly more likely to experience clinically relevant improvement in TDI or SGRQ scores, compared with tiotropium-treated patients	[57]
Laforce *et al.* (2011)	INTEGRAL: randomized, double-blind, 14-day, three-period crossover study of indacaterol (300 μg o.d.) vs placebo or open-label salmeterol (50 μg b.i.d.) in moderate-to-severe COPD	68	At day 14, trough FEV_1 was significantly higher with indacaterol than salmeterol or placebo At days 1 and 14, indacaterol significantly improved FEV_1 vs salmeterol or placebo at multiple time points	[54]
Kornmann *et al.* (2011)	INLIGHT-2: randomized, double-blind, 6-month study of indacaterol (150 μg o.d.) vs salmeterol (50 μg b.i.d.) or placebo in moderate-to-severe COPD	1002	At week 12, trough FEV_1 was significantly increased with indacaterol vs salmeterol or placebo Both indacaterol and salmeterol significantly improved SGRQ and TDI total scores vs placebo throughout the study At week 12, SGRQ and TDI total scores were significantly improved with indacaterol vs salmeterol	[59]

Studies listed in order of publication date.
AUC: Area under the concentration–time curve; b.i.d.: Twice daily; COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; o.d.: Once daily; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnea Index.

Table 3. Selected trials of long-acting muscarinic antagonist bronchodilator therapy in chronic obstructive pulmonary disease.

Study (year)	Trial design	Patients (n)	Key efficacy results†	Ref.
Tashkin *et al.* (2008)	UPLIFT: randomized, double-blind, 4-year study of tiotropium (18 μg o.d.) vs placebo in moderate-to-very-severe COPD	5993	No significant between-group differences in rate of decline in FEV_1 or FVC pre- or post-bronchodilator, from day 30 to end of treatment Mean absolute FEV_1 improved significantly with tiotropium vs placebo throughout the trial SGRQ total score was significantly improved with tiotropium vs placebo at each time point Tiotropium was associated with a reduced risk of exacerbations, exacerbation-related hospitalizations and respiratory failure	[63]
Vogelmeier *et al.* (2011)	POET-COPD: randomized, double-blind, double-dummy, 1-year study of tiotropium (18 μg o.d.) vs salmeterol (50 μg b.i.d.) in moderate-to-very severe COPD	7376	Tiotropium significantly increased time to first exacerbation vs salmeterol Tiotropium significantly increased time to first severe exacerbation and reduced the annual number of severe exacerbations vs salmeterol	[66]
D'Urzo *et al.* (2011)	GLOW1: randomized, double-blind, 26-week study of glycopyrronium (50 μg o.d.) vs placebo in moderate-to-severe COPD	822	Glycopyrronium produced significant improvements vs placebo in: • Trough FEV_1 from the end of day 1, sustained through to week 26 • FEV_1 throughout the 24-h period on day 1, at week 12 and week 26, and at all other visits and time points • TDI total score and SGRQ total score at week 26 Significant reduction in the risk of first moderate/severe COPD exacerbation and use of rescue medication vs placebo	[68]
Kerwin *et al.* (2012)	GLOW2: randomized, double-blind, 52-week study of glycopyrronium (50 μg o.d.) vs placebo and open-label tiotropium (18 μg o.d.) in moderate-to-severe COPD	1066	Significant results vs placebo for: • Increase in trough FEV_1 for glycopyrronium and tiotropium at week 12 • Improvements in TDI total score and SGRQ total score for glycopyrronium • Reduction in the risk of moderate-to-severe COPD exacerbations and the use of rescue medication for glycopyrronium	[69]
Beeh *et al.* (2012)	GLOW3: randomized, crossover exercise tolerance study of glycopyrronium (50 μg o.d.) or placebo for 3 weeks in moderate-to-severe COPD	108	Significant results vs placebo for: • Increase in endurance time with glycopyrronium, from day 1 through to day 21 • Clinically relevant improvements in dynamic IC at exercise isotime and trough FEV_1, from day 1 and throughout the study • Decrease in leg discomfort on day 21 and exertional dyspnea on days 1 and 21	[70]
Kerwin *et al.* (2012)	ACCORD COPD 1: randomized, double-blind, 12-week study of aclidinium (200 or 400 μg b.i.d.) and placebo in moderate-to-severe COPD	561	Compared with placebo, both aclidinium doses produced significant improvements in trough and peak FEV_1, SGRQ, TDI and almost all COPD symptom scores	[71]

Studies listed in order of publication date.
†Safety data are reported for trials that included safety or tolerability as a primary objective.
AUC: Area under the concentration–time curve; b.i.d.: Twice daily; COPD: Chronic obstructive pulmonary disease; E-RS: EXAcerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; IC: Inspiratory capacity; o.d.: Once daily; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnea Index; TEAE: Treatment-emergent adverse event.

Table 3. Selected trials of long-acting muscarinic antagonist bronchodilator therapy in chronic obstructive pulmonary disease (cont.).

Study (year)	Trial design	Patients (n)	Key efficacy results†	Ref.
Jones *et al.* (2012)	ATTAIN: randomized, double-blind, 24-week study of aclidinium (200 or 400 μg b.i.d.) and placebo in moderate-to-severe COPD	828	Compared with placebo, both doses produced significant improvements in trough and peak FEV_1, and SGRQ and TDI total scores at week 24	[72]
D'Urzo *et al.* (2013)	52-week extension to core ACCORD COPD I trial to evaluate long-term safety. Patients with moderate-to-severe COPD receiving aclidinium in core trial continued on same treatment, whereas patients originally on placebo were randomized 1:1 to aclidinium (200 or 400 μg b.i.d.)	291	Both doses had similar incidences of TEAEs with a low incidence of anticholinergic or cardiac TEAEs Improvements in lung function were greatest for patients who received continuous aclidinium treatment (i.e., from core study) and those who were randomized from placebo to 400 μg during the extension	[73]
Beier *et al.* (2013)	Randomized, double-blind, 6-week trial of aclidinium (400 μg b.i.d.), tiotropium (18 μg o.d.) or placebo in moderate-to-severe COPD	414	Aclidinium and tiotropium significantly improved FEV_1 $AUC_{0–24h}$ and FEV_1 $AUC_{12–24h}$ vs placebo at week 6 Significant improvements in E-RS total scores were numerically superior for aclidinium vs placebo ($p < 0.0001$) and for tiotropium ($p < 0.05$) vs placebo Specific scores for early morning cough, wheeze and shortness of breath, phlegm and night-time symptoms were improved by aclidinium compared with placebo, but not by tiotropium	[74]
Trivedi *et al.* (2014)	Randomized, double-blind, 12-week trial of umeclidinium 62.5 and 125 μg o.d. or placebo in moderate-to-very severe COPD (FEV_1 47% predicted)	246	Umeclidinium 62.5 and 125 μg significantly improved lung function, dyspnea and health status compared with placebo, and were well tolerated	[75]

Studies listed in order of publication date.
†Safety data are reported for trials that included safety or tolerability as a primary objective.
AUC: Area under the concentration–time curve; b.i.d.: Twice daily; COPD: Chronic obstructive pulmonary disease; E-RS: EXAcerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; IC: Inspiratory capacity; o.d.: Once daily; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnea Index; TEAE: Treatment-emergent adverse event.

LABA/LAMA combination therapy

LABAs and LAMAs have differing modes of action, and combining bronchodilators of different pharmacologic classes may improve efficacy and decrease the risk of side effects, compared with increasing the dose of a single bronchodilator [1,77–78], owing to their complementary modes of action (Figure 3) [79]. Both the Japanese Respiratory Society and the Canadian Thoracic Society Guidelines concur with this view and recommend the use of LABA/LAMA combinations in patients with moderate COPD with persistent symptoms [43,80]. The Japanese Respiratory Society guidelines recommend LAMAs as first-line therapy for the management of stable COPD, followed by LABA plus LAMA combination therapy. Recommendations from the Canadian Thoracic Society are similar, in that LAMA or LABA monotherapy is recommended first-line for the treatment of moderate COPD with infrequent (<1/year) acute exacerbations, followed by LAMA plus LABA combination therapy [43,80]. Most of the currently available data on this treatment approach are from free-combination studies of the LAMA tiotropium with the LABAs formoterol, salmeterol or indacaterol [53,77]. Dual bronchodilation with indacaterol and tiotropium was superior to tiotropium alone in two identical, double-blind studies of patients with moderate-to-severe COPD (Table 4) [77]. These findings support GOLD treatment recommendations for the use of bronchodilators with different mechanisms of action in patients with severe breathlessness, such as those in group B and group D [1].

The first fixed-dose LABA/LAMA combination licensed for use in COPD was QVA149, a once-daily

Table 4. Selected trials of bronchodilator combination therapy in chronic obstructive pulmonary disease.

Study (year)	Trial design	Patients (n)	Key efficacy results	Ref.
Dual therapy				
Calverley *et al.* (2007)	TORCH: randomized, double-blind, 3-year study comparing SFC (50/500 μg b.i.d.) vs either agent alone and vs placebo in patients with COPD (<60% prebronchodilator FEV_1)	6112	Combination regimen significantly reduced annual rate of exacerbations and improved both SGRQ total score and FEV_1 vs placebo Reduction in death from all causes in the combination therapy group vs placebo did not reach predetermined level of statistical significance	[46]
Wedzicha *et al.* (2008)	INSPIRE: randomized, double-blind, double-dummy 2-year study comparing SFC (50/500 μg b.i.d.) vs tiotropium (18 μg o.d.) in patients with severe or very severe COPD (postbronchodilator FEV_1 <50%)	1323	No significant difference in effect on exacerbation rate; SFC was associated with lower mortality and better health status but more cases of pneumonia compared with tiotropium (all differences significant)	[81]
Mahler *et al.* (2012)	INTRUST 1 and 2: two identically designed randomized, double-blind, 12-week studies of tiotropium (18 μg o.d.) plus either indacaterol (150 μg o.d.) or placebo in moderate-to-severe COPD	1134 and 1142	Dual therapy increased FEV_1 and trough IC significantly, compared with monotherapy	[77]
Vogelmeier *et al.* (2012)	ILLUMINATE: randomized, double-blind, double-dummy, 26-week study of QVA149 (indacaterol 110 μg plus glycopyrronium 50 μg o.d.) vs SFC (50/500 μg b.i.d.) in moderate-to-severe COPD	523	FEV_1 $AUC_{0–12h}$ significantly higher with QVA149 vs SFC at week 26 • TDI total score increased significantly with QVA149 vs SFC at week 26	[82]
Bateman *et al.* (2013)	SHINE: randomized, double-blind, 26-week study of QVA149 (indacaterol 110 μg plus glycopyrronium 50 μg o.d.), single bronchodilator therapy (indacaterol 150 μg o.d., glycopyrronium 50 μg o.d. or open-label tiotropium 18 μg o.d.) and placebo in moderate-to-severe COPD	2144	Trough FEV_1 at week 26 was improved significantly with QVA149 vs indacaterol, glycopyrronium, tiotropium or placebo QVA149 significantly improved TDI and SGRQ scores vs placebo and tiotropium at week 26	[78]
Mahler *et al.* (2013)	BLAZE: randomized, blinded, double-dummy, three-period crossover study of QVA149 (indacaterol 110 μg plus glycopyrronium 50 μg o.d.), placebo and tiotropium (18 μg o.d.) in moderate-to-severe COPD	247	Compared with tiotropium and placebo, QVA149 produced significantly higher: • TDI total score at week 6 • $FEV_1AUC_{0–4h}$ post-dose at day 1 and week 6 • Rescue medication use significantly lower with QVA149 vs placebo and tiotropium	[83]
Wedzicha *et al.* (2013)	SPARK: randomized, double-blind, 64-week study of QVA149 (indacaterol 110 μg plus glycopyrronium 50 μg o.d.), glycopyrronium (50 μg o.d.) or open-label tiotropium (18 μg o.d.) in patients with severe to very severe COPD and ≥1 moderate COPD exacerbation in the past year	2224	Compared with tiotropium and glycopyrronium, QVA149 significantly: • Reduced the rate of all exacerbations improved trough $FEV_1$and SGRQ score • Improved trough FEV_1 and SGRQ score	[84]

Studies listed in order of publication date.
AUC: Area under the concentration–time curve; b.i.d.: Twice daily; COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in 1 second; IC: Inspiratory capacity; o.d.: Once daily; SFC: Salmeterol/fluticasone; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnea Index.

Table 4. Selected trials of bronchodilator combination therapy in chronic obstructive pulmonary disease (cont.).

Study (year)	Trial design	Patients (n)	Key efficacy results	Ref.
Triple therapy				
Aaron *et al.* (2007)	OPTIMAL: randomized, double-blind, 12-month study of tiotropium (18 μg o.d.) plus placebo, tiotropium (18 μg o.d.) + salmeterol (25 μg b.i.d.), or tiotropium (18 μg o.d.) plus SFC (250/25 μg b.i.d.) in moderate-to-severe COPD	449	No significant differences between treatment groups in exacerbation rates Compared with tiotropium alone, tiotropium plus SFC (but not tiotropium plus salmeterol) significantly improved FEV_1 and reduced exacerbation-related and all-cause hospitalizations Both combination treatments significantly improved SGRQ scores vs tiotropium alone	[85]
Welte *et al.* (2009)	CLIMB: randomized, double-blind, 12-week study of budesonide/formoterol (320/9 μg b.i.d.) or placebo added to tiotropium (18 μg o.d.) in moderate-to-severe COPD	660	Budesonide/formoterol plus tiotropium significantly increased pre- and post-dose FEV_1 vs tiotropium alone Time to first severe exacerbation, frequency of severe exacerbations and SGRQ total, morning symptoms and morning activities scores significantly improved with budesonide/formoterol + tiotropium vs tiotropium alone	[86]

Studies listed in order of publication date.
AUC: Area under the concentration–time curve; b.i.d.: Twice daily; COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in 1 second; IC: Inspiratory capacity; o.d.: Once daily; SFC: Salmeterol/fluticasone; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnea Index.

dual bronchodilator consisting of indacaterol and glycopyrronium that is currently approved in Europe and Japan. Other compounds in development include glycopyrrolate/formoterol, tiotropium/olodaterol and vilanterol/umeclidinium [87]. As extensive data are available for these and other fixed-dose LABA/LAMA combination treatments, we will focus on QVA149 as an example of this drug class.

Recently, findings from the SHINE QVA149 trial have been published in patients with GOLD stage 2–3 disease, showing that this agent provides rapid and sustained bronchodilation with significant improvements in lung function versus the monocomponents glycopyrronium and indacaterol (Table 4) [78]. QVA149 also improved dyspnea and health status versus tiotropium. In the BLAZE study, superior improvements in patient-reported dyspnea and lung function were seen with QVA149 versus placebo and tiotropium, as well as improvements in other symptoms and a decrease in rescue medication use (Table 4) [83].

QVA149 is effective in patients with severe disease: the SPARK study enrolled patients with GOLD Stage 3–4 COPD and found that QVA149 was superior in preventing all COPD exacerbations, compared with glycopyrronium, with accompanying improvements in lung function and health status (Table 4) [84]. This suggests a benefit of dual bronchodilation over LAMA monotherapy in patients with severe to very severe disease. Additionally, in the ILLUMINATE study QVA149 provided significant improvements in lung function and dyspnea, compared with the LABA/ICS salmeterol/fluticasone (SFC) in patients with GOLD stage 2–3 COPD (Table 4) [82].

ICS combination therapy

Treatment with a fixed-dose combination of a LABA (salmeterol) and an ICS (fluticasone propionate) was compared with placebo and monocomponents in the 3-year TORCH study (Table 4) [46]. Although combination therapy improved exacerbations, quality of life, and lung function compared with placebo, and was more cost effective than monocomponent therapy [88], improvement in overall mortality (the primary endpoint) was numerically but not statistically significantly ($p = 0.052$) greater than with placebo [46]. Furthermore, the incidence of pneumonia was significantly higher among patients receiving medications containing fluticasone propionate than among those in the non-ICS treatment arms. A *post hoc* analysis of the data from this study suggested that the ICS/LABA combination and its separate constituents all reduced the rate of decline in lung function over the 3 years compared with placebo [89]. This finding remains to be prospectively confirmed.

The 2-year INSPIRE study compared the fluticasone/salmeterol combination with tiotropium in patients with severe or very severe COPD and found no difference in overall exacerbation rate; the ICS/LABA combination was associated with a greater improve-

ment in health status and lower mortality (3 vs 6% of patients), but gave rise to more cases of pneumonia than tiotropium (8 vs 4% of patients) (Table 4) [81]. The findings of pneumonia in the TORCH and INSPIRE studies did not require radiologic confirmation. However, the approximate doubling in the risk of pneumonia in INSPIRE was still observed when the analysis was confined to radiologically confirmed events [90], and a similar pattern was seen with the newer furoate salt of fluticasone, both with and without radiological confirmation [91], in comparison with non-ICS treatments. Studies and analysis with budesonide and mometasone suggest that the association between fluticasone and pneumonia may not be shared by other ICS [92–94].

More recently, the PATHOS observational study examined patient records between 1999 and 2009 from 9893 patients with physician-diagnosed COPD and revealed that patients treated with budesonide/formoterol had significantly lower exacerbation rates than those treated with SFC [95]. There were also lower COPD-related hospitalization rates, greater reductions in days spent in hospital, fewer emergency visits and fewer oral steroid and antibiotic courses in the budesonide/formoterol group than in the SFC group [95]. Additionally, significantly fewer adverse events were reported with budesonide/formoterol than SFC, including the incidence of pneumonia and both hospital admissions and mortality related to pneumonia [96]. However, the incidence of all-cause mortality was comparable between the groups. These observations require confirmation in a prospective, double-blinded study.

The extent of the incremental improvement to be obtained with an ICS/LABA compared with a LABA alone has been questioned, and the use of the combination may be best reserved for the patients who are most likely to benefit: those with a history of frequent exacerbations and those with a syndrome of overlapping COPD and asthma [97]. The benefits of ICS need to be weighed carefully against the risks in terms of side effects that have been reported in individual studies, as mentioned above, and in observational studies and systematic reviews. Those risks include pneumonia, tuberculosis (particularly in endemic populations) and bone fractures [97].

Triple therapy with tiotropium and an ICS/LABA combination was investigated in the CLIMB [86] and OPTIMAL [85] studies (Table 4). In CLIMB, budesonide/formoterol plus tiotropium provided rapid and sustained improvements in lung function, health status, morning symptoms and morning activities, and reduced severe exacerbations requiring systemic corticosteroid treatment or hospitalization versus tiotropium alone [86]. SFC plus tiotropium (but not tiotropium plus salmeterol) significantly improved lung function and disease-specific quality of life, and reduced hospitalizations versus tiotropium plus placebo, but there were no differences in the numbers of patients experiencing an exacerbation [85]. Moreover, 40% of patients receiving tiotropium plus placebo or tiotropium plus salmeterol discontinued the study prematurely or switched to open-label ICS or LABA therapy, implying a benefit of ICS treatment [85]. However, a Cochrane review concluded there is uncertainty regarding the long-term benefits and risks of treatment with ICS/LABA plus tiotropium triple therapy as there are so few studies (and consequently insufficient data) from which to formulate a robust assessment [98].

Other emerging therapies

Other emerging therapies in the treatment of COPD include PDE-4 inhibitors, single-molecule muscarinic antagonist/β_2-agonists (MABAs), TNF-α antagonists, *N*-acetylcysteine and its derivatives, CCR1 chemokine receptor antagonists, p38 MAPK inhibitors, M3-selective muscarinic antagonists, bifunctional muscarinic antagonist–β_2 agonists, and prophylactic antibiotics. Theophylline, a nonspecific PDE inhibitor, has been used as an orally active bronchodilator for many years [99]. Owing to its poor therapeutic index, however, treatment with theophylline is not recommended unless long-term inhaled bronchodilators are unavailable or unaffordable [1]. Its potential anti-inflammatory activity at low doses as an adjunct to ICS has been investigated in preliminary studies in patients with COPD [100]. The PDE-4 inhibitor roflumilast has been shown to improve lung function versus placebo when given in combination with long-acting bronchodilators, and to reduce the rate of moderate-to-severe exacerbations as monotherapy versus placebo [101]. GOLD recommends using roflumilast (in combination with a long-acting bronchodilator) to reduce exacerbations in patients with chronic bronchitis, severe and very severe COPD, and frequent exacerbations inadequately controlled by long-acting bronchodilators [1]. A recent analysis of roflumilast data released by the US FDA assessed the benefits (reducing the risk of exacerbations) and harms (gastrointestinal, psychiatric and neurological symptoms or disorders) and found that the only patient group to receive a net benefit was those at a high (>22%) risk of severe COPD exacerbations [102], which is in line with the GOLD recommendations.

Several MABAs, bifunctional single molecules combining the properties of a LAMA and LABA, are being developed. The bronchodilator efficacy of an inhaled MABA has been reported in dose-ranging studies in patients with COPD [103,104]. The TNF-α antagonist etanercept is being explored as an anti-inflammatory treatment for acute exacerbations, but in a recent study it did not prove any more effective than prednisone [105].

The p38 MAPK inhibitor losmapimod also proved disappointing, with no effect on lung function or exercise tolerance in patients with COPD [106]. Drugs such as *N*-acetylcysteine and its derivatives may have a role in patients with recurrent exacerbations [1], but study results are variable [107,108]. Added to usual therapy, the mucolytics *N*-acetylcysteine and carbocystine were reported to reduce exacerbations in patients with COPD [109,110]. Finally, initial studies of AZD9164, an M_3-selective muscarinic antagonist, showed that it produced greater bronchodilator effects than tiotropium, but also induced immediate, transient and dose-related bronchoconstriction, which is of concern and requires further investigation [111].

Conclusion

Despite widespread underdiagnosis and misdiagnosis of COPD, the prevalence of this disease is on the increase. COPD is associated with a significant burden of disease, and even in patients with mild airway obstruction, has a marked impact on quality of life. Bronchodilation continues to be the mainstay of COPD therapy, and new treatment options and guidelines are continuing to evolve hand in hand. Maximizing bronchodilation with LABA or LAMA monotherapies, or once-daily, fixed-dose LABA/LAMA combinations, plays an important role in the management of this disease. Further studies are needed to evaluate the long-term impact of LABA/LAMA combinations and other new pharmacologic treatments on the disease course of COPD.

Future perspective

The worldwide prevalence of COPD is increasing. In the next decade we will likely be facing a new epidemic of the disease in developing countries, due to exposure to biomass fuels, pollution, and smoking. Further, COPD continues to be poorly recognised and diagnosed. However, more sensitive and specific biomarkers of COPD activity and severity may aid early detection and prevention of symptoms and exacerbations, as well as providing targeted therapy for specific COPD phenotypes in the future. The development of pragmatic strategies to identify COPD phenotypes in primary care in a timely manner is a key challenge. In addition, integrated care approaches to COPD management are needed to provide improved patient access to diagnostic tests, education, and specialist assessments. Public health campaigns to reduce tobacco consumption and encourage exercise in elderly populations, as well as the adoption of screening spirometry, may help to decrease the prevalence of COPD, intervene with effective management strategies, and slow disease progression. The future also promises to bring new vaccinations and treatments for respiratory viruses, as well as novel medications and delivery systems for COPD therapies.

Author contributions

All the authors contributed to the conception and design of this work, reviewed the literature search strategy, identified relevant publications for inclusion and critically reviewed the manuscript. All authors reviewed and approved the final version of the manuscript.

Financial & competing interests disclosure

AD D'Urzo has received research, consulting and lecturing fees from Almirall SA, Altana, AstraZeneca, Forest Laboratories, GlaxoSmithKline, KOS Pharmaceuticals, Methapharm, Ono Pharmaceuticals, Novartis, Schering Plough and Sepracor. MR Maleki-Yazdi has contributed to Continuing Medical Education (CME) projects, received research grants and attended advisory boards for the following pharmaceutical companies: AstraZeneca, Boehringer-Ingelheim, Forest Laboratories, GlaxoSmithKline, Merck, Novartis, Pfizer, Ono Pharmaceuticals and Takeda. RA McIvor has participated in CME activities and attended advisory boards for pharmaceutical companies comprising AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Merck, Novartis, Pfizer and Takeda. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing assistance was utilized in the production of this manuscript. The authors were assisted in the preparation of the manuscript by M Heitz and C McDonnell, professional medical writers contracted to CircleScience (Tytherington, UK). Writing support for this article was funded by Novartis Pharma AG (Basel, Switzerland).

Open access

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Global initiative for chronic Obstructive Lung Disease (GOLD 2014). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2014. www.goldcopd.org/uploads/users/files/GOLD_Report_2014.pdf

•• **Provides a global strategy for chronic obstructive pulmonary disease (COPD) diagnosis, management and prevention.**

2 Kirkpatrick DP, Dransfield MT. Racial and sex differences in chronic obstructive pulmonary disease susceptibility, diagnosis, and treatment. *Curr. Opin. Pulm. Med.* 15(2), 100–104 (2009).

3 Han MK, Postma D, Mannino DM *et al.* Gender and chronic obstructive pulmonary disease: why it matters. *Am. J. Respir. Crit. Care Med.* 176(12), 1179–1184 (2007).

4 Cote CG, Chapman KR. Diagnosis and treatment considerations for women with COPD *Int. J. Clin. Pract.* 63(3), 486–493 (2009).

5 Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 349(9064), 1498–1504 (1997).

6 Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur. Respir. J.* 28(3), 523–532 (2006).

7 Salvi SS, Manap R, Beasley R. Understanding the true burden of COPD: the epidemiological challenges. *Prim. Care Respir. J.* 21(3), 249–251 (2012).

8 Marcus P, Braman SS. International classification of disease coding for obstructive lung disease: does it reflect appropriate clinical documentation? *Chest* 138(1), 188–192 (2010).

9 Yawn BP, Keenan JM. COPD – the primary care perspective: addressing epidemiology, pathology, diagnosis, treatment of smoking's multiple morbidities and the patient's perspective. *COPD* 4(1), 67–83 (2007).

10 Miller J, Edwards LD, Agusti A *et al.* Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. *Respir. Med.* 107(9), 1376–1384 (2013).

11 Divo M, Cote C, de Torres JP *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 186(2), 155–161 (2012).

12 Jones PW, Brusselle G, Dal Negro RW *et al.* Health-related quality of life in patients by COPD severity within primary care in Europe. *Respir. Med.* 105(1), 57–66 (2011).

13 Sundh J, Stallberg B, Lisspers K, Montgomery SM, Janson C. Co-morbidity, body mass index and quality of life in COPD using the Clinical COPD Questionnaire. *COPD* 8(3), 173–181 (2011).

14 Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 57(10), 847–852 (2002).

15 Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 157(5 Pt 1), 1418–1422 (1998).

16 Trappenburg JC, Touwen I, de Weert-van Oene GH *et al.* Detecting exacerbations using the Clinical COPD Questionnaire. *Health Qual. Life Outcomes* 8, 102 (2010).

17 Johnston NW, Lambert K, Hussack P *et al.* Detection of COPD exacerbations and compliance with patient-reported daily symptom diaries. *Chest* 144(2), 507–514 (2013).

18 de Miguel Diez J, Carrasco GP, García CM *et al.* Determinants and predictors of the cost of COPD in primary care: a Spanish perspective. *Int. J. Chron. Obstruct. Pulmon. Dis.* 3(4), 701–712 (2008).

19 Chan FW, Wong FY, Yam CH *et al.* Risk factors of hospitalization and readmission of patients with COPD in Hong Kong population: analysis of hospital admission records. *BMC Health. Serv. Res.* 11, 186 (2011).

20 Maleki-Yazdi MR, Kelly SM, Lam SY, Marin M, Barbeau M, Walker V. The burden of illness in patients with moderate to severe chronic obstructive pulmonary disease in Canada. *Can. Respir. J.* 19(5), 319–324 (2012).

21 Price D, Freeman D, Cleland J, Kaplan A, Cerasoli F. Earlier diagnosis and earlier treatment of COPD in primary care. *Prim. Care Respir. J.* 20(1), 15–22 (2011).

22 Peña VS, Miravitlles M, Gabriel R *et al.* Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. *Chest* 118(4), 981–989 (2000).

23 Hill K, Goldstein RS, Guyatt GH *et al.* Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. *CMAJ* 182(7), 673–678 (2010).

24 Pearson M, Ayres JG, Sarno M, Massey D, Price D. Diagnosis of airway obstruction in primary care in the UK: the CADRE (COPD and Asthma Diagnostic/management REassessment) programme 1997–2001. *Int. J. Chron. Obstruct. Pulmon. Dis.* 1(4), 435–443 (2006).

25 Radin A, Cote C. Primary care of the patient with chronic obstructive pulmonary disease-part 1: frontline prevention and early diagnosis. *Am. J. Med.* 121(7 Suppl.), S3–S12 (2008).

26 Bhatt SP, Kim YI, Wells JM *et al.* FEV/FEV to diagnose airflow obstruction: comparisons with computed tomography and morbidity indices. *Ann. Am. Thorac. Soc.* 11(3), 335–341 (2014).

27 Swanney MP, Ruppel G, Enright PL *et al.* Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 63(12), 1046–1051 (2008).

28 Lam DC, Hui CK, Ip MS. Issues in pulmonary function testing for the screening and diagnosis of chronic obstructive pulmonary disease. *Curr. Opin. Pulm. Med.* 18(2), 104–111 (2012).

29 Yawn BP. Differential assessment and management of asthma vs chronic obstructive pulmonary disease. *Medscape. J. Med.* 11(1), 20 (2009).

30 Di Lorenzo G, Mansueto P, Ditta V *et al.* Similarity and differences in elderly patients with fixed airflow obstruction by asthma and by chronic obstructive pulmonary disease. *Respir. Med.* 102(2), 232–238 (2008).

31 Bellia V, Battaglia S, Catalano F *et al.* Aging and disability affect misdiagnosis of COPD in elderly asthmatics: the SARA study. *Chest* 123(4), 1066–1072 (2003).

32 Menezes AM, Montes de OM, Perez-Padilla R *et al.* Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest* 145(2), 297–304 (2014).

33 Miravitlles M, Soriano JB, Ancochea J *et al.* Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respir. Med.* 107(7), 1053–1060 (2013).

34 Godtfredsen NS, Lam TH, Hansel TT *et al.* COPD-related morbidity and mortality after smoking cessation: status of the evidence. *Eur. Respir. J.* 32(4), 844–853 (2008).

35 Spruit MA, Singh SJ, Garvey C *et al.* An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am. J. Respir. Crit. Care Med.* 188(8), e13–e64 (2013).

36 Thomas M, Decramer M, O'Donnell DE. No room to breathe: the importance of lung hyperinflation in COPD *Prim. Care Respir. J.* 22(1), 101–111 (2013).

37 Yawn BP, Colice GL, Hodder R. Practical aspects of inhaler use in the management of chronic obstructive pulmonary disease in the primary care setting. *Int. J. Chron. Obstruct. Pulmon. Dis.* 7, 495–502 (2012).

38 Chavannes NH, Grijsen M, van den Akker M *et al.* Integrated disease management improves one-year quality of life in primary care COPD patients: a controlled clinical trial. *Prim. Care. Respir. J.* 18(3), 171–176 (2009).

39 Fletcher MJ, Dahl BH. Expanding nurse practice in COPD: is it key to providing high quality, effective and safe patient care? *Prim. Care Respir. J.* 22(2), 230–233 (2013).

40 Nici L, Bontly TD, Zuwallack R, Gross N. Self-management in chronic obstructive pulmonary disease. Time for a paradigm shift? *Ann. Am. Thorac. Soc.* 11(1), 101–107 (2014).

41 Global Initiative for Chronic Obstructive Lung Disease (GOLD 2011). Global strategy for diagnosis, management, and prevention of COPD. www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf

42 Agusti A, Hurd S, Jones P *et al.* FAQs about the GOLD 2011 assessment proposal of COPD: a comparative analysis of four different cohorts. *Eur. Respir. J.* 42(5), 1391–1401 (2013).

43 O'Donnell DE, Hernandez P, Kaplan A *et al.* Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update – highlights for primary care. *Can. Respir. J.* 15 (Suppl. A), 1A–8A (2008).

44 Soriano JB, Alfageme I, Almagro P *et al.* Distribution and prognostic validity of the new Global initiative for chronic Obstructive Lung Disease grading classification. *Chest* 143(3), 694–702 (2013).

45 Global Initiative for Chronic Obstructive Lung Disease. www.goldcopd.org

46 Calverley PM, Anderson JA, Celli B *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N. Engl. J. Med.* 356(8), 775–789 (2007).

- **In this large 3-year study, combination therapy with fluticasone propionate/salmeterol (SFC) did not significantly reduce all-cause mortality relative to placebo or long-acting β_2 adrenergic agonist monotherapy, although SFC improved exacerbation rates, health status and spirometric measures. This was the first report to link use of fluticasone propionate with an increased risk of pneumonia in patients with COPD.**

47 Jochmann A, Neubauer F, Miedinger D *et al.* General practitioners' adherence to the COPD GOLD guidelines:baseline data from the Swiss COPD Cohort Study. *Swiss Med. Wkly* 140, W13053 (2010).

48 de Miguel-Díez J, Carrasco-Garrido P, Rejas-Gutierrez J *et al.* Inappropriate overuse of inhaled corticosteroids for COPD patients: impact on health costs and health status. *Lung* 189(3), 199–206 (2011).

49 D'Urzo A. Optimizing the management of chronic obstructive pulmonary disease: applying the GOLD strategy. *Clin. Pract.* 10(4), 481–492 (2013).

50 Roux E, Molimard M, Savineau JP, Marthan R. Muscarinic stimulation of airway smooth muscle cells. *Gen. Pharmacol.* 31(3), 349–356 (1998).

51 Cazzola M, Page CP, Rogliani P, Matera MG. β_2-agonist therapy in lung disease. *Am. J. Respir. Crit. Care Med.* 187(7), 690–696 (2013).

52 O'Donnell DE, Laveneziana P, Webb K, Neder JA. Chronic obstructive pulmonary disease: clinical integrative physiology. *Clin. Chest Med.* 35(1), 51–69 (2014).

53 Tashkin DP, Fabbri LM. Long-acting beta-agonists in the management of chronic obstructive pulmonary disease: current and future agents. *Respir. Res.* 11, 149 (2010).

54 Laforce C, Aumann J, de Teresa PL *et al.* Sustained 24-hour efficacy of once daily indacaterol (300 µg) in patients with chronic obstructive pulmonary disease: a randomized, crossover study. *Pulm. Pharmacol. Ther.* 24(1), 162–168 (2011).

55 Donohue JF, Fogarty C, Lötvall J *et al.* Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. *Am. J. Respir. Crit. Care Med.* 182(2), 155–162 (2010).

56 Vogelmeier C, Ramos-Barbon D, Jack D *et al.* Indacaterol provides 24-hour bronchodilation in COPD: a placebo-controlled blinded comparison with tiotropium. *Respir. Res.* 11, 135 (2010).

57 Buhl R, Dunn LJ, Disdier C *et al.* Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. *Eur. Respir. J.* 38(4), 797–803 (2011).

58 Korn S, Kerwin E, Atis S, Amos C, Owen R, Lassen C. Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12-week study. *Respir. Med.* 105(5), 719–726 (2011).

59 Kornmann O, Dahl R, Centanni S *et al.* Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. *Eur. Respir. J.* 37(2), 273–279 (2011).

60 Decramer ML, Chapman KR, Dahl R *et al.* Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. *Lancet Respir. Med.* 1(7), 524–533 (2013).

61 Price D, Gray A, Gale R *et al.* Cost-utility analysis of indacaterol in Germany: a once-daily maintenance bronchodilator for patients with COPD. *Respir. Med.* 105(11), 1635–1647 (2011).

62 Price D, Asukai Y, Ananthapavan J, Malcolm B, Radwan A, Keyzor I. A UK-based cost-utility analysis of indacaterol, a once-daily maintenance bronchodilator for patients with COPD, using real world evidence on resource use. *Appl. Health Econ. Health Policy.* 11(3), 259–274 (2013).

63 Tashkin DP, Celli B, Senn S *et al.* A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N. Engl J. Med.* 359(15), 1543–1554 (2008).

•• **Randomized, double-blind, placebo-controlled UPLIFT study providing information on the natural course of COPD. Although tiotropium did not reduce the rate of lung-function (forced expiratory volume in 1 second) decline in the overall study population, a secondary analysis by Troosters *et al.* [64] found that bronchodilator treatment reduced disease progression in maintenance therapy-naive patients, indicating that bronchodilator treatment should be considered at an early stage of disease.**

64 Troosters T, Celli B, Lystig T *et al.* Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT trial. *Eur. Resp. J.* 36(1), 65–73 (2010).

65 Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet* 374(9696), 1171–1178 (2009).

66 Vogelmeier C, Hederer B, Glaab T *et al.* Tiotropium versus salmeterol for the prevention of exacerbations of COPD *N. Engl. J. Med.* 364(12), 1093–1103 (2011).

67 Vogelmeier C, Fabbri LM, Rabe KF *et al.* Effect of tiotropium vs. salmeterol on exacerbations: GOLD II and maintenance therapy naive patients. *Respir. Med.* 107(1), 75–83 (2013).

68 D'Urzo A, Ferguson GT, van Noord JA *et al.* Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. *Respir. Res.* 12(1), 156 (2011).

69 Kerwin E, Hébert J, Gallagher N *et al.* Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. *Eur. Respir. J.* 40(5), 1106–1114 (2012).

• **A 52-week study showing that glycopyrronium had a fast onset of action, provided sustained 24-h efficacy, was well tolerated and had a comparable efficacy profile to tiotropium.**

70 Beeh KM, Singh D, Di Scala L, Drollmann A. Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW3 trial. *Int. J. Chron. Obstruct. Pulmon. Dis.* 7, 503–513 (2012).

71 Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Garcia GE, Caracta CF. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). *COPD* 9(2), 90–101 (2012).

72 Jones PW, Singh D, Bateman ED *et al.* Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. *Eur. Respir. J.* 40(4), 830–836 (2012).

73 D'Urzo A, Kerwin E, Rennard S, He T, Gil EG, Caracta C. One-year extension study of ACCORD COPD I: safety and efficacy of two doses of twice-daily aclidinium bromide in patients with COPD. *COPD* 10(4), 500–510 (2013).

74 Beier J, Kirsten AM, Mróz R *et al.* Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled Phase IIIb study. *COPD* 10(4), 511–522 (2013).

75 Trivedi R, Richard N, Mehta R, Church A. Umeclidinium in patients with COPD: a randomised, placebo-controlled study. *Eur. Respir. J.* 43(1), 72–81 (2014).

76 Celli B, Crater G, Kilbride S *et al.* Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: a randomized, controlled study. *Chest* doi:10.1378/chest.13-1579 (2014) (Epub ahead of print).

77 Mahler DA, D'Urzo A, Bateman ED *et al.* Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. *Thorax* 67(9), 781–788 (2012).

•• **First trial to show that including long-acting β_2 adrenergic agonist/long-acting muscarinic antagonist combination therapy significantly improved COPD outcomes compared with long-acting muscarinic antagonist monotherapy.**

78 Bateman ED, Ferguson GT, Barnes N *et al.* Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *Eur. Respir. J.* 42(6), 1484–1494 (2013).

• **In this pivotal randomized, double-blind study, dual indacaterol/glycopyrronium therapy provided significant benefits over treatment with either long-acting bronchodilator alone, with a comparable safety profile.**

79 Barnes PJ. Distribution of receptor targets in the lung. *Proc. Am. Thorac. Soc.* 1(4), 345–351 (2004).

80 Koichiro T. Pharmacotherapy options in COPD according to the new guidelines of The Japanese Respiratory Society. *JMAJ* 54(2), 105–109 (2011).

81 Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am. J. Respir. Crit. Care Med.* 177(1), 19–26 (2008).

82 Vogelmeier CF, Bateman ED, Pallante J *et al.* Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respir. Med.* 1(1), 51–60 (2012).

83 Mahler DA, Decramer M, D'Urzo A *et al.* Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: BLAZE study. *Eur. Respir. J.* doi:10.1183/090300124013 (2013) (Epub ahead of print).

84 Wedzicha JA, Decramer M, Ficker JH *et al.* Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir. Med.* 1(3), 199–209 (2013).

85 Aaron SD, Vandemheen KL, Fergusson D *et al.* Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann. Intern. Med.* 146(8), 545–555 (2007).

86 Welte T, Miravitlles M, Hernandez P *et al.* Efficacy and tolerability of budesonide/formoterol added to tiotropium in

patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 180(8), 741–750 (2009).

87 Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. *Respir. Res.* 14, 49 (2013).

88 Briggs AH, Glick HA, Lozano-Ortega G *et al.* Is treatment with ICS and LABA cost-effective for COPD? Multinational economic analysis of the TORCH study. *Eur. Respir. J.* 35(3), 532–539 (2010).

89 Celli BR, Thomas NE, Anderson JA *et al.* Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am. J. Respir. Crit. Care Med.* 178(4), 332–338 (2008).

90 Calverley PM, Stockley RA, Seemungal TA *et al.* Reported pneumonia in patients with COPD: findings from the INSPIRE study. *Chest* 139(3), 505–512 (2011).

91 Dransfield MT, Bourbeau J, Jones PW *et al.* Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir. Med.* 1(3), 210–223 (2013).

92 Halpin DM, Gray J, Edwards SJ, Morais J, Singh D. Budesonide/formoterol vs. salmeterol/fluticasone in COPD: a systematic review and adjusted indirect comparison of pneumonia in randomised controlled trials. *Int. J. Clin. Pract.* 65(7), 764–774 (2011).

93 Sin DD, Tashkin D, Zhang X *et al.* Budesonide and the risk of pneumonia: a meta-analysis of individual patient data. *Lancet* 374(9691), 712–719 (2009).

94 Tashkin DP, Doherty DE, Kerwin E *et al.* Efficacy and safety characteristics of mometasone furoate/formoterol fumarate fixed-dose combination in subjects with moderate to very severe COPD: findings from pooled analysis of two randomized, 52-week placebo-controlled trials. *Int. J. Chron. Obstruct. Pulmon. Dis.* 7, 73–86 (2012).

95 Larsson K, Janson C, Lisspers K *et al.* Combination of budesonide/formoterol more effective than fluticasone/salmeterol in preventing exacerbations in chronic obstructive pulmonary disease: the PATHOS study. *J. Intern Med.* 273(6), 584–594 (2013).

- **Budesonide/formoterol provided superior efficacy and safety, compared with fluticasone/salmeterol in this observational, retrospective study of over 9800 patients.**

96 Janson C, Larsson K, Lisspers KH *et al.* Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting b2 agonist: observational matched cohort study (PATHOS). *BMJ* 346, f3306 (2013).

97 Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD *Prim. Care Respir. J.* 22(1), 92–100 (2013).

98 Karner C, Cates CJ. Combination inhaled steroid and long-acting beta$_2$-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* 3, CD0085322011).

- **This independent review of triple therapy with inhaled corticosteroids, long-acting β2 adrenergic agonists, and long-acting muscarinic antagonists concluded that more information is needed on the long-term risks and benefits of this therapeutic approach.**

99 Barnes PJ. Theophylline. *Am. J. Respir. Crit. Care Med.* 188(8), 901–906 (2013).

100 Ford PA, Durham AL, Russell RE, Gordon F, Adcock IM, Barnes PJ. Treatment effects of low-dose theophylline combined with an inhaled corticosteroid in COPD. *Chest* 137(6), 1338–1344 (2010).

101 Oba Y, Lone NA. Efficacy and safety of roflumilast in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Ther. Adv. Respir. Dis.* 7(1), 13–24 (2013).

102 Yu T, Fain K, Boyd CM *et al.* Benefits and harms of roflumilast in moderate to severe COPD. *Thorax* doi:10.1136/thoraxjnl–2013–204155 (2013) (Epub ahead of print).

103 Bateman ED, Kornmann O, Ambery C, Norris V. Pharmacodynamics of GSK961081, a bi-functional molecule, in patients with COPD. *Pulm. Pharmacol. Ther.* 26(5), 581–587 (2013).

104 Wielders PL, Ludwig-Sengpiel A, Locantore N, Baggen S, Chan R, Riley JH. A new class of bronchodilator improves lung function in COPD: a trial with GSK961081. *Eur. Respir. J.* 42(4), 972–981 (2013).

105 Aaron SD, Vandemheen KL, Maltais F *et al.* TNF-α antagonists for acute exacerbations of COPD: a randomised double-blind controlled trial. *Thorax* 68(2), 142–148 (2013).

106 Watz H, Barnacle H, Hartley BF, Chan R. Efficacy and safety of the p38 MAPK inhibitor losmapimod for patients with chronic obstructive pulmonary disease: a randomised, double-blind, placebo-controlled trial. *Lancet Respir. Med.* 2(1), 63–72 (2014).

107 Sadowska AM, Verbraecken J, Darquennes K, De Backer WA. Role of *N*-acetylcysteine in the management of COPD. *Int. J. Chron. Obstruct. Pulmon. Dis.* 1(4), 425–434 (2006).

108 Schermer T, Chavannes N, Dekhuijzen R *et al.* Fluticasone and *N*-acetylcysteine in primary care patients with COPD or chronic bronchitis. *Respir. Med.* 103(4), 542–551 (2009).

109 Zheng JP, Kang J, Huang SG *et al.* Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. *Lancet* 371(9629), 2013–2018 (2008).

110 Tse HN, Raiteri L, Wong KY *et al.* High-dose *N*-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. *Chest* 144(1), 106–118 (2013).

111 Bjermer L, Bengtsson T, Jorup C, Lötvall J. Local and systemic effects of inhaled AZD9164 compared with tiotropium in patients with COPD *Respir. Med.* 107(1), 84–90 (2013).