Optimizing the management of chronic obstructive pulmonary disease: applying the GOLD strategy

Anthony D'Urzo*

Practice Points

- Recognizing that the severity of airflow limitation alone is not sufficient to encapsulate the multiple clinical manifestations of chronic obstructive pulmonary disease (COPD), or to predict an individual patient's prognosis or response to therapy, the Global Initiative for Obstructive Lung Disease (GOLD) 2013 strategy recommends that the assessment and management of COPD should be based on a strategy incorporating severity of airflow limitation and symptoms, disease impact and the future risk of disease progression.
- Bronchodilators are the foundation of pharmacological management of COPD and are recommended for all patients with COPD (groups A–D). They are the preferred option for maintenance treatment of COPD, either alone or in combination with another bronchodilator or an inhaled corticosteroid (ICS).
- Combining bronchodilators of different pharmacological classes has the potential to provide maximal bronchodilation and decrease the risk of side effects compared with increasing the dose of a single bronchodilator.
- Once-daily long-acting β2 adrenergic agonist (LABA)/long-acting muscarinic antagonist (LAMA) fixed-dose combinations can provide improvements in bronchodilation and symptoms over and beyond what monotherapy offers. With the additional benefit of reduced dosing frequency, fixed-dose LABA/LAMA combinations may provide the benefit of adherence, resulting in an overall better control.
- Despite guideline recommendations for the use of ICS in patients with severe or very severe airflow limitation and/or or ≥2 exacerbations per year (GOLD group C and D), ICS and fixed-dose combinations containing ICS are often inappropriately prescribed earlier in the disease process to patients with more moderate COPD.

*1670 Dufferin Street, Suite 107, Toronto, ON Canada; Tel.: +416 652 9336/416 652 9870; Fax: +416 652 0218; tonydurzo@sympatico.ca

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- Given that COPD is vastly under- or mis-diagnosed, there appears to be value in early identification and treatment of COPD; maintenance treatment with long-acting bronchodilators may be effective in patients with early COPD.

SUMMARY The goals for management of stable chronic obstructive pulmonary disease (COPD) as per the latest global initiative for chronic obstructive lung disease (GOLD) 2013 revision include reducing both symptoms (modified medical research council dyspnea score and/or COPD assessment tool) and future risk (severity of airflow limitation and/or exacerbation history in the previous year). Bronchodilators remain central to the management of COPD; a combination of long-acting bronchodilators from different pharmacological classes is recommended to achieve maximal bronchodilation in patients not controlled with monotherapy alone. Presently several issues related to COPD management remain unaddressed, perhaps due to the paucity of evidence – when should bronchodilator therapy be stepped up, what is the value of early diagnosis and treatment of COPD; how appropriate is long-acting bronchodilator therapy in early disease, and what is the role of inhaled corticosteroids in COPD? The intent of this review is to address the issues highlighted above using a pragmatic and evidence-based approach that can be utilized by both primary and specialty care providers.

Burden of chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease, with significant pulmonary and extrapulmonary effects and associated comorbidities [1]. The chronic inflammatory response to noxious particles is enhanced in the airways of patients with COPD, causing narrowing of the small airways and parenchymal destruction, and leading to persistent airflow limitation and air trapping [2]. Current management options comprise both nonpharmacological and pharmacological therapies, helping to reduce COPD symptoms and exacerbations, and improve health status and exercise endurance [2]. However, convincing evidence that any of the available medications can reduce the long-term decline in lung function is lacking [2].

COPD is a cause of significant morbidity and mortality, and is increasing in incidence and prevalence; it is estimated that COPD will be the fourth leading cause of death by the year 2030 [1,3]. WHO has estimated that, globally, COPD results in an annual loss of productivity of 27,700 years (measured by disability adjusted life years) [4].

Despite the increasing burden of COPD, it continues to be under-recognized and/or -diagnosed, leading to a delay in initiating appropriate therapy and the loss of opportunities to prevent deterioration of the disease [5,6]. Globally, clinicians still face challenges in assessing patients with COPD and providing optimal therapy and management.

COPD & changing paradigms

Traditionally, COPD management plans have focused on assessing and monitoring the disease, reducing risk factors, and early identification and management of exacerbations and stable COPD [7]. However, COPD is now recognized as a multisystem disease with effects on patients beyond those arising from airflow limitation alone [8,9], necessitating a holistic assessment and management paradigm.

In December 2011, the strategy developed by the Global Initiative for Obstructive Lung Disease (GOLD) – a multidisciplinary network of healthcare professionals and scientists – underwent a major revision with the aim of providing guidance for a multidimensional approach to COPD assessment and management [1]. This revised report has since been updated based on literature published between July 2011 and December 2012, and is therefore referred to as GOLD 2013 hereafter [2].

The need for change

Spirometry has been the standard for diagnosing and monitoring the progression of COPD and the initial diagnosis of COPD is largely based on postbronchodilator spirometric assessment, specifically a reduction in the ratio of forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) below 0.70 [1]. Until recently, COPD severity was classified solely based on FEV_1, with the underlying belief that the severity of airflow limitation tracked the severity of disease. The severity of symptoms and exacerbation risk did not directly impact assessment and management of COPD [7].

However, it has been shown that airflow limitation alone does not reflect the burden of COPD on the patient [10]. While FEV_1 is a well-standardized and accepted measurement of airflow limitation [11], it is poorly correlated with patient-centered outcomes, such as dyspnea, exercise tolerance and health status impairment [8,11–13].

Respiratory symptoms are more closely related to health-related quality of life than airflow limitation (measured by FEV_1), indicating that health-related quality of life is impacted more by symptoms than by changes in FEV_1 [14,15]. Furthermore, while the degree of airflow limitation is a weak predictor of mortality and hospitalizations at a population level, a history of previously treated exacerbations is the best predictor at a patient level of having future exacerbations [16]. It follows that the assessment of COPD severity should be based on a combination of the degree of airflow limitation (measured by FEV_1), the impact of the patient's symptoms and assessment of the patient's risk of having a serious event in the future (exacerbations/death); this approach should guide identification of the appropriate management plan [1].

GOLD 2013 strategy

Diagnosis & assessment of COPD

Spirometry remains central to the diagnosis of COPD [2]. Previously, spirometry was used to support the diagnosis of COPD, which was primarily based on symptoms and a history of exposure to risk factors [17]. The GOLD 2013 strategy recommends that spirometry is a requirement for the confirmation of a diagnosis of COPD [2]. Patients with suspected COPD on the basis of symptoms, clinical and family history, and physical examination should have airflow obstruction confirmed with spirometry. As stated previously, the spirometric criterion for a diagnosis of COPD is a FEV_1/FVC ratio <0.70 when measured postbronchodilator.

GOLD 2013 strategy aims to provide a composite, patient-centered approach to the assessment of COPD [1]. Recognizing COPD as being a disease of more than just airflow limitation, the GOLD 2013 strategy offers a new assessment system that includes a composite evaluation of symptomatology, future risk of events and airflow limitation.

To evaluate the symptom burden, GOLD 2013 recommends using the modified Medical Research Council dyspnea scale [18,19] and the COPD assessment test [13]. In contrast to the modified medical research council scale, which measures perceived respiratory disability, the recently developed COPD assessment test has a broader coverage of the impact of COPD on the patients daily life and covers cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep and energy. The Clinical COPD Questionnaire, which measures the clinical control of patients with COPD, may also be used to assess symptoms [20–22].

The concept of staging COPD (stages I–IV) has now been abandoned. Instead, the spirometric classification of airflow limitation using the fixed ratio FEV_1/FVC provides four 'grades' of airflow limitation:

- GOLD 1 is mild (FEV_1 ≥80% predicted);
- GOLD 2 is moderate (50% ≤ FEV_1 < 80% predicted);
- GOLD 3 is severe (30% ≤ FEV_1 < 50% predicted);
- GOLD 4 is very severe airflow limitation (<30% FEV_1 predicted).

The rate of exacerbations varies greatly between patients [8]. Previously treated events are the best predictor of having frequent exacerbations (two or more exacerbations per year) [16]. The GOLD 2013 strategy document suggests two ways to assess the risk of exacerbations: spirometry to determine the GOLD grade (GOLD 1 and 2 are low risk, GOLD 3 and 4 indicate high risk) and assessment of the number of exacerbations in the previous year (0 or 1 indicates low risk, while 2 or more indicates high risk). If the two methods yield different risk categories, the higher risk

Figure 1. GOLD 2011 update: assessment of chronic obstructive pulmonary disease combining symptoms, spirometric classification and future risk of exacerbation.
Reproduced from [1].

should determine the category of the patient [1].

Assessment of patients in terms of the degree of airflow limitation and the symptoms they experience, together with their risk of experiencing future COPD exacerbation places them in one of the four categories:

- A (low risk, less symptoms);
- B (low risk, more symptoms);
- C (high risk, less symptoms);
- D (high risk, more symptoms) **(Figure 1)**.

Management of COPD

The recommended management of stable COPD in GOLD 2013 is a reflection of the composite assessment and is based on a strategy incorporating symptoms (disease impact) and future risk (especially of exacerbation) [1]. Bronchodilators remain central to the pharmacological management of COPD **(Figure 2)**.

Figure 2. The pharmacological management of stable COPD: summary of the GOLD 2013 strategy.
†Alternate choice medications can be used alone or in combination with first or second choice options.
SABA: Short-acting β2-agonist; SAMA: Short-acting muscarinic antagonist; p.r.n.: *pro re nata* (as needed); LABA: Long-acting β2-agonist; LAMA: Long-acting muscarinic antagonist; ICS: Inhaled corticosteroid; PDE-4-inh: PDE-4 inhibitor.
Reproduced from [1].

GOLD 2013 offers a first, second and alternate choice of initial pharmacological management options for each group (A–D). Short-acting bronchodilators are recommended as the first and second choice options only in group A, alone or in combination, in conjunction with nonpharmacologic methods for reducing risk factors (smoking cessation, maintenance of physical activity and influenza and pneumococcal vaccination). They may be offered as alternate choices in groups B–D.

Long-acting inhaled bronchodilators are convenient and more effective at producing sustained symptom relief compared to short-acting bronchodilators. Regular treatment with one or more long-acting bronchodilators, including long-acting β_2-adrenergic agonist (LABA) and long-acting muscarinic antagonist (LAMA), may be offered in conjunction with nonpharmacologic therapy (including pulmonary rehabilitation) for patients in groups B–D. Roflumilast, an oral PDE-4 inhibitor, has been recommended in combination with a LAMA as second choice in group D and as an alternative choice in group C. Combining bronchodilators of different pharmacologic classes may improve efficacy and decrease the risk of side effects as opposed to increasing the dose of a single bronchodilator [1].

Inhaled corticosteroids (ICS) are recommended as a regular treatment option in combination with a LABA or LAMA for patients in group C or D – i.e., for those who have had frequent exacerbations in the previous year (≥2 exacerbations) and/or FEV_1 <50% predicted.

Rationale for pharmacological management of COPD

The GOLD 2013 strategy observes that as a general principle for bronchodilators, long-acting bronchodilators are preferable to short-acting formulations, if symptoms are not improved by monotherapy, combination treatment is recommended, and inhaled bronchodilators are preferred over oral bronchodilators. It proposes a model for the pharmacological management of COPD based on the individualized assessment of airflow limitation, symptoms and exacerbation risk **(Figure 2)**.

Patients in group A have few symptoms and are at a low risk of exacerbations. There is relatively little evidence for the efficacy of pharmacological treatment for patients in this category.

Short-acting bronchodilators are recommended as first choice, with the combination of two short-acting bronchodilators, or the use of a long-acting bronchodilator (either LAMA or LABA) as second choice. The evidence for short-acting bronchodilator combinations and long-acting bronchodilators in this group of patients with COPD is limited [23,24].

Patients in group B have more symptoms, but are still at a low risk of exacerbations. Long-acting bronchodilators (LABAs or LAMAs) are superior to short-acting bronchodilators in providing sustained relief from symptoms and are recommended [23,24]. There is no evidence to indicate the superiority of one class over the other. In patients whose symptoms are not controlled with LABA or LAMA monotherapy, a second choice of a LABA plus LAMA combination is offered [25–31]. Theophylline and short-acting bronchodilators are alternative choices; theophylline may be useful when inhaled bronchodilators are not available or not affordable.

Group C patients have few symptoms but a high risk of exacerbations. A fixed-dose combination of ICS/LABA or a LAMA is offered as first choice [24,32–34]. There is limited data comparing these treatments [35]. LABA plus LAMA is offered as second choice. PDE-4 inhibitors may be of value in patients with COPD who have bronchitis, and this option is therefore included as an alternate choice [36,37]. Alternative choices offered are short-acting bronchodilators, theophylline and PDE-4 inhibitors (especially if the patient has chronic bronchitis) [36].

Group D patients have more symptoms and are at a high risk of future exacerbations. As with group C, risk reduction is an important consideration in this group of patients and a ICS/LABA fixed-dose combination or a LAMA is offered as first choice. Several options are presented as second choice, including a combination of ICS, LAMA and LABA [38], the addition of PDE-4 inhibitor to the first choice treatment (if the patient has bronchitis) [36,37], and LABA plus LAMA or LAMA plus ICS combinations. Alternative choices include short-acting bronchodilators, theophylline or carbocysteine [39].

Bronchodilation in COPD: the evidence

LABAs

LABAs currently approved for the treatment of COPD include salmeterol, formoterol and indacaterol. Formoterol and salmeterol have 12-h durations of action and are therefore generally inhaled twice daily in COPD. Compared with placebo, other β_2-agonists, anticholinergics and theophylline, formoterol and salmeterol have demonstrated significant improvements in lung function, symptoms and health status, with a decreased need for rescue medication use and have also been shown to reduce the rate of COPD exacerbations [40,41].

Figure 3. The spirometry interpretation algorithm from the Primary Care Respiratory Alliance of Canada.
Reproduced from [86].

Indacaterol, a 24-h LABA, offers the convenience of once-daily dosing; the efficacy of indacaterol has also been demonstrated in several studies. Indacaterol 150 µg and 300 µg has been shown to provide improved lung function, breathlessness, health status and rescue medication use versus placebo [42–45], and 24-h bronchodilation, improvement in breathlessness and health status, and reduction in rescue medication use, at least as effective as tiotropium [46–48]. Indacaterol 150 µg provided an improvement in lung function, health status and rescue medication use that was statistically superior to salmeterol 50 µg [45,49] and the 300-µg dose demonstrated superior improvements in lung function, symptoms and rescue medication use versus formoterol 12 µg [43].

Olodaterol and vilanterol are LABAs currently in development (at Boehringer Ingelheim and GlaxoSmithKline, respectively) for the treatment of COPD.

LAMAs

The first LAMA approved for COPD management was once-daily tiotropium. Tiotropium 18 µg is established as a well-tolerated and effective therapy for COPD, and has been shown

to improve lung function, exercise tolerance and health status, and reduce dyspnea and exacerbations versus placebo [32,50–52].

Other LAMAs recently approved in several regions are glycopyrronium (NVA237; the EU, Japan and Canada, among others) and aclidinium (the EU and the USA, among others). Once-daily glycopyrronium has demonstrated significant improvements in lung function, dyspnea, health status and exacerbations and exercise tolerance, and reduction in rescue medication use versus placebo [53–55], with efficacy similar to that of tiotropium [55]. Twice-daily aclidinium has been shown to improve lung function, dyspnea, health status, rescue medication use, and exercise endurance compared with placebo [56,57]. LAMAs in various stages of development include umeclidinium and glycopyrrolate (being developed by GlaxoSmithKline and Pearl Therapeutics, respectively.

■ Long-acting bronchodilator combinations

Combining bronchodilators of different classes is a preferred approach in patients with COPD symptoms not sufficiently controlled by monotherapy. Since LABAs and LAMAs target different but complementary pathways (sympathomimetic and anticholinergic, respectively), combining agents from the two classes may help to maximize bronchodilation and address the inter- and intra-patient variability in response to treatment [58]. Achieving maximal bronchodilation is important as improvements in lung function correlate with improvements in other COPD outcomes including dyspnea, health status, exacerbations [59] and exercise endurance [60].

Free combinations of LABAs and LAMAs have demonstrated improvements in lung function, symptoms, health status and rescue medication use [26–31]. While the majority of the evidence is centered around the free combination of the LAMA tiotropium with the LABAs formoterol, salmeterol or indacaterol, several fixed-dose LABA/LAMA combinations to be dosed once-daily are under development, such as (indacaterol/glycopyrronium [QVA149], vilanterol/umeclidinium, formoterol/aclidinium, formoterol/glycopyrrolate and olodaterol/tiotropium).

Recent results from Phase III studies with indacaterol/glycopyrronium have reported significant and sustained improvements in lung function versus placebo, tiotropium, salmeterol/fluticasone, and versus the monocomponents indacaterol and glycopyrronium (ILLUMINATE and SHINE studies) over 26 weeks, with significant symptomatic benefits [25,61]. Preliminary results from four pivotal Phase III studies for once-daily umeclidinium/vilanterol have also reported superior improvements in lung function with the combination versus the monocomponents, and versus placebo and tiotropium [62]. The combination of olodaterol/tiotropium is currently in Phase III development; recent data from a Phase II study has demonstrated that olodaterol/tiotropium significantly improved lung function over 24 h in patients with COPD, compared with olodaterol alone [63].

Once-daily fixed-dose LABA/LAMA combinations have the potential to offer maximal bronchodilation, with the added benefit of simplifying the treatment regimen and, hence, may foster better adherence and improved clinical outcomes in COPD.

Triple therapy is an emerging area of interest in the management of COPD. Triple therapy with a LABA, LAMA and an ICS may help to maximize therapeutic benefit in patients with COPD with frequent exacerbations [64]. Although there is limited evidence for this approach, studies investigating triple therapy have demonstrated therapeutic benefit with formoterol/budesonide/tiotropium and salmeterol/fluticasone/tiotropium versus monobronchodilator therapy in patients with COPD [38,65,66]. Coformulation of a LABA, LAMA and ICS could be an important step towards simplifying treatment regimens in patients with severe disease, which could have beneficial effects on adherence. However, long-term studies are needed to assess the extent of the benefits that can be achieved with triple therapy.

■ Nonselective phosphodiesterase inhibitors & selective PDE-4 inhibitors

Theophylline, an oral nonselective PDE inhibitor, is a weak bronchodilator and has now been superseded by inhaled muscarinic antagonists and β_2-agonists. At higher doses, theophylline has been shown to be an effective bronchodilator, but has the potential for toxicity. At lower doses, theophylline reduces COPD exacerbations, but does not improve lung function [1]. In the GOLD 2013 strategy document, theophylline is

offered as an alternative in all four categories [1].

An oral PDE-4 inhibitor, roflumilast, was recently approved in several regions including Canada, the EU and the USA for maintenance treatment of COPD associated with chronic bronchitis and a history of frequent exacerbations [67]. Roflumilast has been shown to reduce moderate and severe exacerbations treated with corticosteroids by 15–20% in patients with severe-to-very severe COPD, bronchitis, and a history of exacerbations [36]. When added to long-acting bronchodilators, roflumilast also produces an effect on lung function [36], however its impact on patient-reported outcomes is controversial [68].

Other considerations

■ COPD & the role of ICS

Although treatment with ICS is a cornerstone of controller therapy in asthma, they have a limited impact in COPD, with their principle role being the reduction in the risk of exacerbations [69]. However, there is some evidence that the combination of a twice-daily LABA with an ICS improves a range of parameters, including lung function, symptoms, risk of exacerbations and rescue medication use [33,34,70,71]. Evidence from small studies has indicated that LABA combined with an extra fine formulation of ICS may reduce airway narrowing and improve symptoms in patients with COPD [72,73], but further research is needed [74].

GOLD 2013 recommends that the use of ICS should be limited to high-risk patients with severe or very severe airflow limitation and/or ≥2 exacerbations per year (GOLD group C and D) [1]. The use of ICS is associated with significant local and systemic side effects, including pneumonia, diabetes, bone fractures and nontuberculosis mycobacteriosis [75–79]. For example, ICS use was associated with a significantly higher incidence of pneumonia when compared to LABA use in a recent systematic review of the literature [80], and a meta-analysis of 16 randomized controlled trials and seven observational studies found that long-term exposure to ICS significantly increased the risk of bone fracture in a dose-dependent manner [77]. Despite guideline recommendations and the risk of adverse effects, the use of ICS is widespread in patients with moderate COPD (group A and B) [81].

■ When should therapy be stepped-up?

Although the GOLD 2013 strategy offers a second choice of pharmacological treatment and recommends that a second bronchodilator may be added if the patient remains symptomatic on monotherapy, the unanswered question of when to step-up treatment remains. As mentioned earlier, data from several studies indicate that improved bronchodilation can be achieved with the combination of long-acting bronchodilators of different pharmacological classes. This is supported by the Japanese and Canadian Respiratory Society guidelines, which recommend the use of LABA/LAMA combinations in patients with moderate COPD with persistent symptoms [82,83].

■ Early identification & treatment of COPD

COPD is vastly under- and mis-diagnosed [5,84]. Both asthma and COPD are obstructive respiratory disorders characterized by airflow limitation and inflammation. However, the pathogenesis, treatment models, progression and outcomes of both diseases are distinct [85]. Diagnostic spirometry, when offered to all patients with respiratory symptoms and risk factors in whom the diagnosis of COPD cannot be excluded, will help in the early diagnosis of COPD and can assist in the differentiation from asthma.

Although COPD is considered to be a disease characterized by largely irreversible airflow limitation, some patients exhibit significant improvement in FEV_1 (despite a FEV_1/FVC ratio <0.70), which is comparable in magnitude to the improvement seen in some patients with asthma [32]. This improvement in FEV_1 reversibility between COPD and asthma is a drawback in using the method to differentiate between the conditions. A new spirometry interpretation algorithm currently promoted in primary care in Canada aims to address this issue [86]. The new algorithm focuses on the FEV_1/FVC ratio before and after bronchodilator challenge as a means of identifying acute or persistent airflow obstruction **(Figure 3)**. This approach, when used in conjunction with historical and physical examination data helps to exclude a diagnosis of COPD if the FEV_1/FVC ratio returns to normal after bronchodilator challenge. The distinction between asthma and COPD is crucial since first-line maintenance therapy for COPD (LABA)

is contraindicated as monotherapy in asthma management.

Furthermore, in the early stages of the disease, symptoms may occur primarily upon exertion. During increased activity, the lungs fail to empty adequately, giving rise to dynamic hyperinflation and an increased sensation of dyspnea, which ultimately contributes to exercise intolerance. Interventions aimed at an early stage in the disease may help to improve the capacity for physical activity, and thus slow down the rate of symptom progression [87]. Significant decreases in activity are seen even in patients with mild COPD [88], and can potentially impact their productivity and quality of life. Subgroup, *post-hoc* evidence from the TORCH and UPLIFT studies indicates that patients in group A may benefit from long-acting bronchodilator therapy, LABAs or LAMAs, upon diagnosis [32,89,90]. The initiation of maintenance treatment with long-acting bronchodilators early in the course of the disease has been shown to result in greater improvements in lung function, exacerbations, quality of life and mortality, compared with control [83].

Conclusion

The GOLD 2013 strategy is a comprehensive document that aims to drive international guidelines for the management of COPD. It recognizes that the assessment and management of COPD must follow a multidimensional approach, taking into account the current disease state and future risk. Bronchodilators are the mainstay of pharmacological treatment of COPD [1]. Treatment with long-acting bronchodilators (LABAs/LAMAs) given once daily is efficacious and convenient, provides the benefit of sustained bronchodilation and has the potential to impact adherence to therapy [1]. Once-daily LABA/LAMA fixed-dose combinations can provide improvements in bronchodilation and symptoms over and beyond what monotherapy offers, an approach that fulfills the mandate of maximal bronchodilation without exposure to additional side effects. With the additional benefit of reduced dosing frequency, fixed-dose LABA/LAMA combinations may promote improved adherence, resulting in better, overall, day-to-day disease control.

Future perspective

The management of COPD continues to evolve, as demonstrated by the many therapies in development. What is still lacking are data that describe how prolonged bronchodilation with once-daily LABA/LAMA combinations will influence the natural history of COPD and important outcomes such as exacerbations, hospitalizations and mortality, compared with monotherapy and with once- or twice-daily LABA/ICS combinations. Data comparing combinations of once-daily LABA/LAMA/ICS to LABA/LAMA on relevant outcomes will also be needed to better understand how we might individualize therapy to reflect the need for current control and future risk reduction. Based on the data available to date, it appears that initiating therapies that promote maximal bronchodilation will offer the greatest benefit to patients, including those with early disease.

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References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Global Initiative for Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. *www.goldcopd.com* (2011).

2 Global Initiative for Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. *www.goldcopd.com* (2013).

▪▪ **The Global Initiative for Obstructive Lung Disease (GOLD) guidelines, for the first time, incorporate a multidimensional strategy for achieving current control and reducing future risk in patients with chronic obstructive pulmonary disease (COPD).**

3 Lopez AD, Mathers CD. Measuring the global burden of disease and epidemiological transitions: 2002–2030. *Ann. Trop. Med. Parasitol.* 100(5–6), 481–499 (2006).

4 WHO. *Global Surveillance, Prevention and Control of Chronic Respiratory Diseases: a Comprehensive Approach.* Bousquet J, Khaltaev N (Eds.) WHO Press, Geneva, Switzerland (2007).

5 Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. *Proc. Am. Thorac. Soc.* 4(7), 502–506 (2007).

6 Takahashi T, Ichinose M, Inoue H, Shirato K, Hattori T, Takishima T. Underdiagnosis and undertreatment of COPD in primary care settings. *Respirology* 8(4), 504–508 (2003).

▪ **Underlines the need to establish more effective diagnostic approaches at the primary care level. The delay in timely and accurate diagnosis of COPD limits the opportunity to translate relevant knowledge into day-to-day practice.**

7 Global Initiative for Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. *www.goldcopd.com* (2010).

8 Agusti A, Calverley PM, Celli B *et al.* Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir. Res.* 11, 122 (2010).

9 Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur. Respir. J.* 33(5), 1165–1185 (2009).

10 Celli BR, Cote CG, Marin JM *et al.* The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N. Engl. J. Med.* 350(10), 1005–1012 (2004).

▪ **Highlights the importance of utilizing a composite score for evaluating the impact of COPD on patient-centered factors.**

11 Cazzola M, MacNee W, Martinez FJ *et al.* Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur. Respir. J.* 31(2), 416–469 (2008).

12 Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 320(7245), 1297–1303 (2000).

13 Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline LN. Development and first validation of the COPD assessment test. *Eur. Respir. J.* 34(3), 648–654 (2009).

14 Schlecht NF, Schwartzman K, Bourbeau J. Dyspnea as clinical indicator in patients with chronic obstructive pulmonary disease. *Chron. Respir. Dis.* 2(4), 183–191 (2005).

15 Voll-Aanerud M, Eagan TM, Wentzel-Larsen T, Gulsvik A, Bakke PS. Respiratory symptoms, COPD severity, and health related quality of life in a general population sample. *Respir. Med.* 102(3), 399–406 (2008).

▪ **Highlights how COPD impacts on patient-related factors in ways that are often inadequately captured by measurements of lung function.**

16 Hurst JR, Vestbo J, Anzueto A *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N. Engl. J. Med.* 363(12), 1128–1138 (2010).

▪▪ **Provides evidence for the important link between previously treated exacerbations and the risk of future exacerbations.**

17 Global Initiative for Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. *www.goldcopd.com* (2010).

18 Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 54(7), 581–586 (1999).

19 Mahler DA, Ward J, Waterman LA, McCusker C, Zuwallack R, Baird JC. Patient-reported dyspnea in COPD reliability and association with stage of disease. *Chest* 136(6), 1473–1479 (2009).

20 Reda AA, Kotz D, Kocks JW, Wesseling G, van Schayck CP. Reliability and validity of the clinical COPD questionniare and chronic respiratory questionnaire. *Respir. Med.* 104(11), 1675–1682 (2010).

21 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).

22 van der MT, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the clinical COPD questionnaire. *Health Qual. Life Outcomes* 1, 13 (2003).

23 Appleton S, Poole P, Smith B, Veale A, Lasserson TJ, Chan MM. Long-acting β2-agonists for poorly reversible chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* (3), CD001104 (2006).

24 Barr RG, Bourbeau J, Camargo CA, Ram FS. Inhaled tiotropium for stable chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* (2), CD002876 (2005).

25 Bateman ED, Ferguson GT, Barnes N. Benefits of dual bronchodilation with QVA149 once daily versus placebo, indacaterol, NVA237 and tiotropium in patients with COPD: The SHINE study. Presented at: *European Respiratory Society*.

▪▪ **This pivotal study examined the effects of once-daily indacaterol/glycopyrronium bromide (QVA149) versus placebo, indacaterol, glycopyrronium (NVA237) and tiotropium in patients with COPD, demonstrating that the long-acting β2-adrenergic agonist/long-acting muscarinic antagonist combination is superior to monotherapy without an attendant increase in side effects.**

26 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 study to document the superiority of combining a long-acting β2-adrenergic agonist (indacaterol) and a long-acting muscarinic antagonist (tiotropium) on relevant COPD outcomes compared with tiotropium alone.**

27 Cazzola M, Di MF, Santus P *et al.* The pharmacodynamic effects of single inhaled doses of formoterol, tiotropium and their combination in patients with COPD. *Pulm. Pharmacol. Ther.* 17(1), 35–39 (2004).

28 Cazzola M, Centanni S, Santus P *et al.* The functional impact of adding salmeterol and tiotropium in patients with stable COPD. *Respir. Med.* 98(12), 1214–1221 (2004).

29 Rabe KF, Timmer W, Sagkriotis A, Viel K. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. *Chest* 134(2), 255–262 (2008).

30 Tashkin DP, Donohue JF, Mahler DA *et al.* Effects of arformoterol twice daily, tiotropium once daily, and their combination in patients with COPD. *Respir. Med.* 103(4), 516–524 (2009).

31 van Noord JA, Aumann JL, Janssens E *et al.* Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur. Respir. J.* 26(2), 214–222 (2005).

32 Tashkin DP, Rennard SI, Martin P *et al.* Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. *Drugs* 68(14), 1975–2000 (2008).

33 Calverley P, Pauwels R, Vestbo J *et al.* Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 361(9356), 449–456 (2003).

34 Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur. Respir. J.* 22(6), 912–919 (2003).

35 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).

36 Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 374(9691), 685–694 (2009).

37 Fabbri LM, Calverley PM, Izquierdo-Alonso JL *et al*. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long acting bronchodilators: two randomised clinical trials. *Lancet* 374(9691), 695–703 (2009).

38 Singh D, Brooks J, Hagan G, Cahn A, O'Connor BJ. Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. *Thorax* 63(7), 592–598 (2008).

39 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).

40 Steiropoulos P, Tzouvelekis A, Bouros D. Formoterol in the management of chronic obstructive pulmonary disease. *Int. J. Chron. Obstruct. Pulmon. Dis.* 3(2), 205–215 (2008).

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

42 Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B. Long-term safety and efficacy of indacaterol, a long-acting β(2)-agonist, in subjects with COPD: a randomized, placebo-controlled study. *Chest* 140(1), 68–75 (2011).

43 Dahl R, Chung KF, Buhl R *et al*. Efficacy of a new once-daily long-acting inhaled β2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax* 65(6), 473–479 (2010).

44 Feldman G, Siler T, Prasad N *et al*. Efficacy and safety of indacaterol 150 microg once-daily in COPD: a double-blind, randomised, 12-week study. *BMC Pulm. Med.* 10, 11 (2010).

45 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).

46 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).

47 Donohue JF, Fogarty C, Lotvall 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).

48 Rodrigo GJ, Neffen H. Comparison of indacaterol with tiotropium or twice-daily long-acting β-agonists for stable COPD: a systematic review. *Chest* 142(5), 1104–1110 (2012).

49 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).

50 Casaburi R, Mahler DA, Jones PW *et al*. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur. Respir. J.* 19(2), 217–224 (2002).

51 Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. *Chest* 124(5), 1743–1748 (2003).

52 Donohue JF, van Noord JA, Bateman ED *et al*. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 122(1), 47–55 (2002).

53 Beeh KM, Singh D, Di SL, 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).

54 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, 156 (2011).

55 Kerwin E, Hebert 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).

56 UK Medicine Information. Aclidinium bromide. *www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=4515* (2012).

57 Vestbo J, Vogelmeier C, Creemers J, Falques M, Ribera A, Gil EG. Onset of effect of aclidinium, a novel, long-acting muscarinic antagonist, in patients with COPD. *COPD* 7(5), 331–336 (2010).

58 Cazzola M, Molimard M. The scientific rationale for combining long-acting β2-agonists and muscarinic antagonists in COPD. *Pulm. Pharmacol. Ther.* 23(4), 257–267 (2010).

59 Jones PW, Donohue JF, Nedelman J, Pascoe S, Pinault G, Lassen C. Correlating changes in lung function with patient outcomes in chronic obstructive pulmonary disease: a pooled analysis. *Respir. Res.* 12, 161 (2011).

60 O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 160(2), 542–549 (1999).

61 Vogelmeier C, Bateman ED, Pallante J. Once-daily QVA149 significantly improves lung function and symptoms compared to twice-daily fluticasone/salmeterol in COPD patients: The ILLUMINATE study. Presented at: *European Respiratory Society*. Vienna, Austria, 1–5 September 2012

62 GlaxoSmithKline. GSK and Theravance announce positive results from four pivotal Phase III studies for once-daily LAMA/LABA (UMEC/VI) in COPD. *http://investor.theravance.com/releasedetail.cfm?releaseid=688175* (2013).

63 Aalbers R, Maleki-Yazdi MR, Hamilton A *et al*. Dose-finding study for tiotropium and olodaterol when administered in combination via the Respimat® inhaler in patients with COPD. *Eur. Respir. J.* 40(Suppl. 56), P2882S (2012).

64 Cazzola M, Matera MG. Emerging inhaled bronchodilators: an update. *Eur. Respir. J.* 34(3), 757–769 (2009).

65 Jung KS, Park HY, Park SY *et al*. Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. *Respir. Med.* 106(3), 382–389 (2012).

66 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).

67 UK Medicine Information. *www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=3320* (2010).

68 Rabe KF. Update on roflumilast, a phosphodiesterase 4 inhibitor for the

treatment of chronic obstructive pulmonary disease. *Br. J. Pharmacol.* 163(1), 53–67 (2011).

69 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).

70 Hanania NA, Darken P, Horstman D *et al*. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. *Chest* 124(3), 834–843 (2003).

71 Mahler DA, Wire P, Horstman D *et al*. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 166(8), 1084–1091 (2002).

72 Corda L, Bertella E, La Piana GE, Boni E, Redolfi S, Tantucci C. Inhaled corticosteroids as additional treatment in β-1-antitrypsin-deficiency-related COPD. *Respiration* 76(1), 61–68 (2008).

73 Tatsis G, Kotsifas K, Filaditaki V, Makrantoni G, Boulia S. Efficacy of beclomethasone dipropionate HFA 200 microg once daily in chronic obstructive pulmonary disease and bronchial asthma. *J. Int. Med. Res.* 35(3), 361–373 (2007).

74 Stewart JI, Criner GJ. The small airways in chronic obstructive pulmonary disease: pathology and effects on disease progression and survival. *Curr. Opin. Pulm. Med.* 19(2), 109–115 (2013).

75 Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N. Engl. J. Med.* 337(1), 8–14 (1997).

76 Guillot B. Adverse skin reactions to inhaled corticosteroids. *Expert Opin. Drug Saf.* 1(4), 325–329 (2002).

77 Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. *Thorax* 66(8), 699–708 (2011).

78 Sin DD, McAlister FA, Man SF, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease: scientific review. *JAMA* 290(17), 2301–2312 (2003).

79 Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *Am. J. Med.* 123(11), 1001–1006 (2010).

80 Spencer S, Evans DJ, Karner C, Cates CJ. Inhaled corticosteroids versus long-acting β(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* (10), CD007033 (2011).

81 Suissa S, Barnes PJ. Inhaled corticosteroids in COPD: the case against. *Eur. Respir. J.* 34(1), 13–16 (2009).

82 Koichiro T. Pharmacotherapy options in COPD according to the new guidelines of the Japanese Respiratory Society. *Jap. Med. J.* 54(2), 105–109 (2011).

83 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).

84 Bellamy D, Smith J. Role of primary care in early diagnosis and effective management of COPD. *Int. J. Clin. Pract.* 61(8), 1380–1389 (2007).

85 Price DB, Yawn BP, Jones RC. Improving the differential diagnosis of chronic obstructive pulmonary disease in primary care. *Mayo Clin. Proc.* 85(12), 1122–1129 (2010).

86 D'Urzo AD, Tamari I, Bouchard J, Jhirad R, Jugovic P. New spirometry interpretation algorithm: primary care respiratory alliance of Canada approach. *Can. Fam. Physician* 57(10), 1148–1152 (2011).

■ **Highlights the importance of understanding the spirometric overlap between asthma and COPD and describes a new spirometric interpretation algorithm designed to minimize disease misclassification.**

87 O'Donnell DE, Laveneziana P. Physiology and consequences of lung hyperinflation in COPD. *Eur. Respir. Rev.* 15, 61–67 (2006).

88 Troosters T, Sciurba F, Battaglia S *et al*. Physical inactivity in patients with COPD, a controlled multi-center pilot-study. *Respir. Med.* 104(7), 1005–1011 (2010).

89 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).

90 Jenkins CR, Jones PW, Calverley PM *et al*. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. *Respir. Res.* 10, 59 (2009).