

ABSTRACT

The 2011 revision of the GOLD global strategy on COPD is a major paradigm shift in diagnosis and management of the disease. In particular, detailed assessment of current symptom control and future risk in terms of airflow limitation and exacerbation history, now allows more accurate categorisation of individual COPD patients. Pharmacological interventions are now directly linked to these categories. The recommendations for drug therapy in each of the 4 new categorical groups of COPD phenotypes reflect the accumulated knowledge base from literature. Bronchodilatation and anti-inflammatory drug therapy continue to be the main basis of drug choice and regimens.

Keywords: Chronic Obstructive Pulmonary Disease, pulmonary emphysema, inhaler, pharmacotherapy

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is an evolving global health problem, and management of this disease has progressed from one of nihilism to that which highlights a disease that is preventable and treatable, as aptly included in the definition from the Global Initiative for Chronic Obstructive Lung Disease (GOLD)¹. The GOLD committee has, since 2001, published documents on strategy for diagnosis and management of COPD, based on the available evidence from literature. The 2nd five-year revision of the GOLD document was released in late 2011. This particular revision not only incorporated the state of current knowledge but also promoted a paradigm shift in opinion on various aspects of the disease, particularly in the approach to pharmacological intervention.

FOCUS ON SYMPTOM EVALUATION INTO 4 CATEGORY CLASSIFICATION

The latest GOLD method of assessment of COPD focuses on symptom evaluation, either by the modified Medical Research Council (mMRC) dyspnoea grade or the COPD assessment test (CAT) score. For the first time, a comprehensive validated multi-symptom score (i.e. CAT) is acknowledged for clinical use. Similarly important are the determination of airflow limitation via the traditionally familiar forced expiratory volume in 1st second

(FEV₁) and a new component of exacerbation history. Exacerbations are now recognised as crucial milestones in the natural progression of COPD. It is of such significance that determination of the number of exacerbations in the last 1 year has an equal severity impact in terms of future risk as that of FEV₁. Finally, screening for and managing comorbidities take a major role in the overall care plan. The goal of therapy is now two-fold; to gain current control of symptoms and reduce future risk, mainly that of exacerbations, disease progression and mortality.

With past GOLD management strategies, drug therapies were added in stepwise fashion with each increasing stage of the disease severity as defined by airflow limitation of FEV₁. However, with better understanding of the natural history of COPD, it is clear that the unidimensional nature of FEV₁, which was used as a staging criterion, does not fully reflect the complexity and heterogeneity of the individual COPD patient². The combination of symptoms, airflow limitation and exacerbation history is now merged into a 4-category classification and treatment matrix (Figure 1). Whereas in the past, severity of symptoms and number of exacerbations did not directly impact the choice of drugs, now clinicians can better correlate assessment to treatment decisions on an individual patient level. Experts have also agreed that the current categorisation is but an initial concept change, and that further refinement can be expected with widespread use of the approach.

MATCHING PHARMACOLOGICAL MANAGEMENT TO 4-CATEGORY CLASSIFICATION

As pharmacological management of COPD now matches each of the categories, clinicians are advised on the 1st choice drug therapy for each group, together with alternatives. This is a departure from earlier practice which emphasises a progressive and somewhat conservative approach to drug therapy in COPD. Although pharmacological treatment of comorbidities³ in COPD is an area very much in need of more research, its discussion is beyond the scope of this article.

The choice of pharmacological agents within each category group depends on drug availability, cost and the patient's response. The following discussion is based on each of the 4 groups (Figure 2).

Group A – Patient with low risk of future events and few symptoms

This is the patient who is of low risk of future events and has few symptoms. There is mild or moderate airflow limitation (GOLD grade 1 – 2) and 1 exacerbation per year or less and mMRC grade 0–1 or CAT < 10. At present, literature is not robust with evidence on the effectiveness of drug treatment for patients with mild airflow obstruction, that is FEV₁ >80% predicted⁴. Short-acting bronchodilators taken as needed, are recommended due to its well-known effect on dyspnoea and improvement in

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FIGURE 1. FOUR-CATEGORY CLASSIFICATION BY SYMPTOMS AND RISK

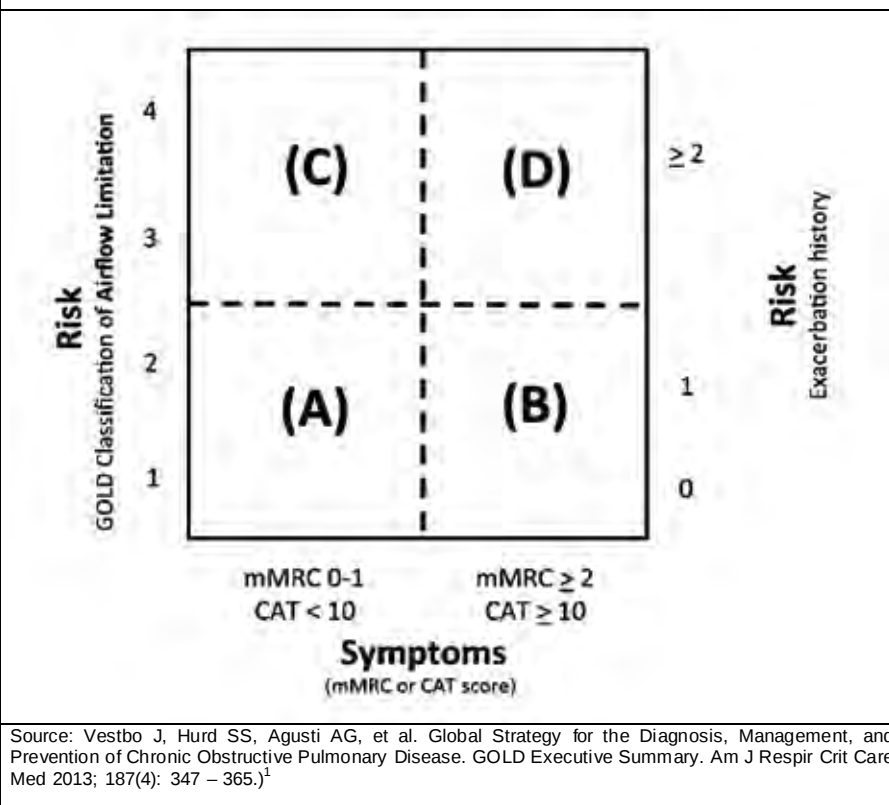
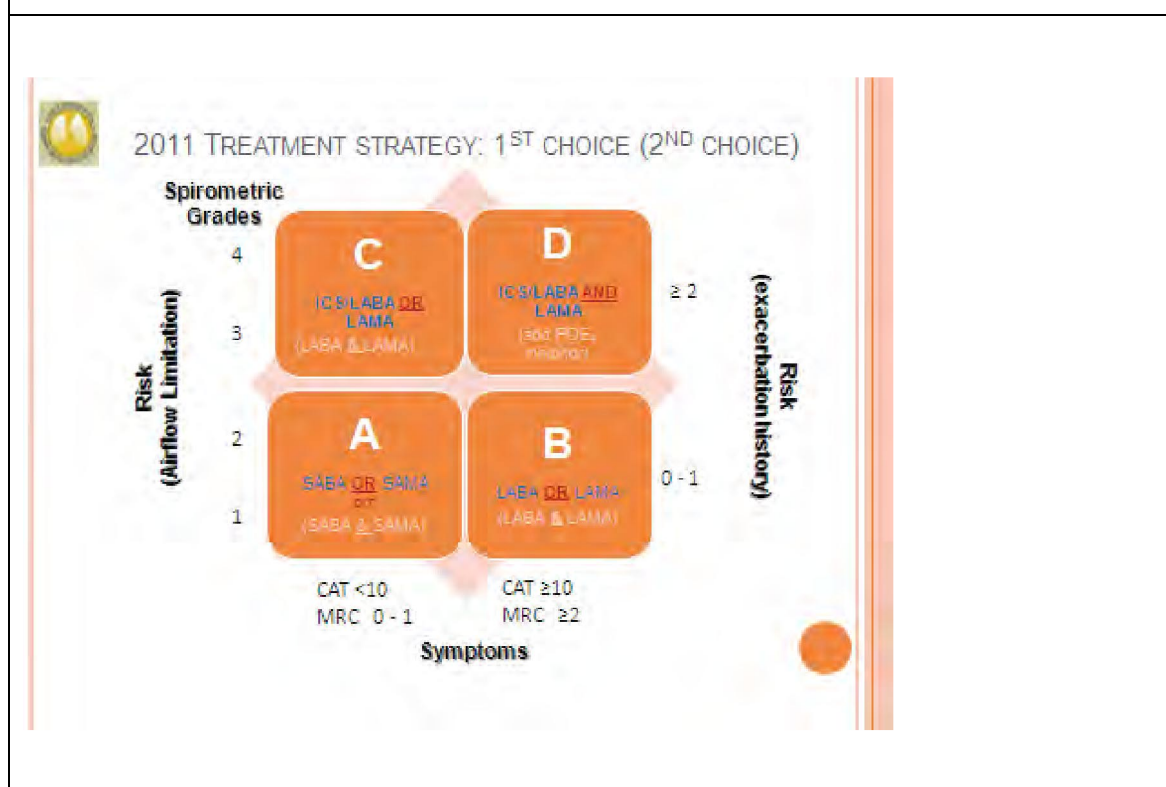


FIGURE 2. MATCHING PHARMACOLOGICAL MANAGEMENT TO 4-CATEGORY CLASSIFICATION



lung function. This can be in the form of short-acting beta-2 agonist (SABA) or short-acting anti-muscarinic agent (SAMA). The combination of the 2 classes either as separate inhalers or in a single inhaler is an alternative. The evidence for the using a long-acting bronchodilator is weak, as most studies on long-acting agents are done on subjects with at least moderate airflow limitation.

Group B – Patient with low risk but more symptoms

The patient with low risk but more symptoms (mMRC grade ≥ 2 or CAT score ≥ 10) may present frequently to healthcare professionals. Long-acting bronchodilators are recommended due to its superiority to short-acting bronchodilators⁵. Initial treatment can either be with a long-acting beta-2 agonist (LABA) or a long-acting anti-muscarinic agent (LAMA), with some early evidence favouring the latter^{6,7}. However, at present there is still no conclusive study to determine which the superior long acting bronchodilator is. In the end, the patient's perception of symptom relief may be the best deciding factor. The second choice of a combination of LABA and LAMA can be considered for those patients in this group with very severe dyspnoea. These are based on short-term studies and at least one recent meta-analysis⁸. Alternative choices include short-acting bronchodilators and theophylline, especially if long-acting bronchodilators are unavailable or unaffordable.

Group C – Patient has few symptoms and high risk of adverse events

Group C patients are typically challenging for clinicians in convincing to adhere to drug treatment. They have few symptoms but are at high risk of adverse events, including exacerbation and mortality. Patients are at GOLD grade 3 – 4 (severe or very severe airflow limitation) and/or have > 2 exacerbations per year and/or > 1 hospitalised exacerbation per year. Symptom scores are typically low with mMRC grade 0–1 or CAT score < 10 . Recommendation by GOLD is that of a LAMA or a combination of inhaled corticosteroid (ICS) with a LABA^{9–11}. The INSPIRE study¹² was the only one directly comparing these 2 treatment regimens, but did not show any difference in exacerbation rates. As a 2nd choice, the combination of LABA and LAMA is recommended as both drug classes reduce the risk of exacerbations, although good long-term studies are still lacking. A phosphodiesterase-4 inhibitor may be considered if the patient has characteristics of chronic bronchitis^{13–14}.

Group D – Patient has severe symptoms and high risk of poor outcomes

These are COPD patients at high risk of poor outcomes, with GOLD grade 3 – 4 (severe or very severe airflow limitation) and/or > 2 exacerbations per year / > 1 hospitalised exacerbation per year. They also have significantly severe symptoms (mMRC grade ≥ 2 or CAT score ≥ 10). Intuitively, this group of patients accounts for a considerable burden of healthcare resource and some are eventually transitioned to a palliative care approach¹⁵. Although the initial therapy maybe begin with that as for patients in group C, clinicians should consider the early use of a combination of all three classes of drugs (ICS + LABA +

LAMA)^{16–17} in order to reduce the risk of exacerbation. Again, evidence need to address the lack of long-term studies and cost-effectiveness analysis, and some inconsistent findings¹⁸. Similarly, in those with symptoms of chronic bronchitis, adding a phosphodiesterase-4 inhibitor is an option.

There is evidence that the phosphodiesterase-4 inhibitor roflumilast may reduce exacerbations for patients with chronic bronchitis, FEV₁ $\leq 50\%$ predicted, and frequent exacerbations that are not adequately controlled by long acting bronchodilators. This is a specific subset of COPD patients with chronic cough and sputum production. Roflumilast is an example of targeted therapy for COPD. Experience from Europe¹⁹ show a modest but sustained improvement in lung function and reduction in exacerbation rates in those with severe disease. Common adverse events were diarrhea, nausea, and headache, which usually subsided during continued treatment. However, roflumilast resulted in more withdrawals within the first 3 to 4 weeks of administration. Nevertheless, this class of drugs still hold promise as additional treatment in the most severe COPD patient.

ADVICE FROM GOLD 2011 UPDATE

The GOLD committee continues to provide general recommendations for pharmacological therapy¹. In particular, there is strong recommendation that LABA and LAMA are preferred over its short-acting counterparts; and inhaled bronchodilators are safer and more effective than oral bronchodilators. Weaker recommendations are listed for the combined use of SABA or LABA and antimuscarinics if symptoms are not improved with single agents. Of particular relevance in Asia, treatment with theophylline is not recommended based on evidence of relatively low efficacy and more side effects, unless LABA or LAMA are unavailable or unaffordable.

Strong recommendations are noted on corticosteroid usage. There continues to be no evidence for a short-term therapeutic trial with oral corticosteroids in patients with COPD to identify those who will respond to inhaled corticosteroids. Maintenance therapy with ICS is recommended for patients with FEV₁ $< 50\%$ predicted and/or frequent exacerbations that are not adequately controlled by long-acting bronchodilators. As such, optimal and maximal bronchodilatation still remains the cornerstone of COPD pharmacotherapy. Long-term monotherapy with oral corticosteroids is not recommended in COPD and long-term monotherapy with ICS is also not recommended in COPD because it is less effective than the combination of ICS plus LABA.

CONCLUSION

The revised GOLD strategy document places assessment of symptoms and future risk at the core of individualised therapeutic decision. Pharmacotherapy can now be targeted

toward the heterogeneity of COPD phenotypes to relieve symptoms, reduce exacerbations, improve exercise tolerance and health-related quality of life. Bronchodilatation is an essential therapy in all categories and anti-inflammatory therapy with ICS is effective for those at high risk. Although at present, none of the approved drug therapies are able to conclusively modify the long-term decline in lung function, there is hope that with every new GOLD standard, COPD sufferers and their caregivers can look forward to a better future ahead.

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LEARNING POINTS

- **The 2011 revision of the GOLD global strategy on COPD is a major paradigm shift in diagnosis and management of the disease – It places assessment of symptoms and future risk at the core of individualised therapeutic decision.**
- **Detailed assessment of current symptom control and future risk in terms of airflow limitation and exacerbation history, now allows more accurate categorisation of individual COPD patients into 4 categories.**
- **Pharmacological interventions are now directly linked to these 4 categories.**
- **Bronchodilatation and anti-inflammatory drug therapy continue to be the main basis of drug choice and regimens.**
- **Although at present, none of the approved drug therapies are able to conclusively modify the long-term decline in lung function, there is hope that with every new GOLD standard, COPD sufferers and their caregivers can look forward to a better future ahead.**