Treatment guidelines for COPD - Going for GOLD?

Treatment guidelines for COPD – Going for GOLD?' is a consensus based article, that sets out a simple treatment pathway based on the predominant characteristics of COPD for an individual – whether symptoms or exacerbations – distilled from current guidelines. The article has been developed by a group of clinicians working with and in primary care, facilitated by integrated care consultant, Vince Mak, GPs, Duncan Keeley and Kevin Gruffydd Jones and practice nurse, Carol Stonham. Corresponding author Vince Mak, email: info@pcrs-uk.org

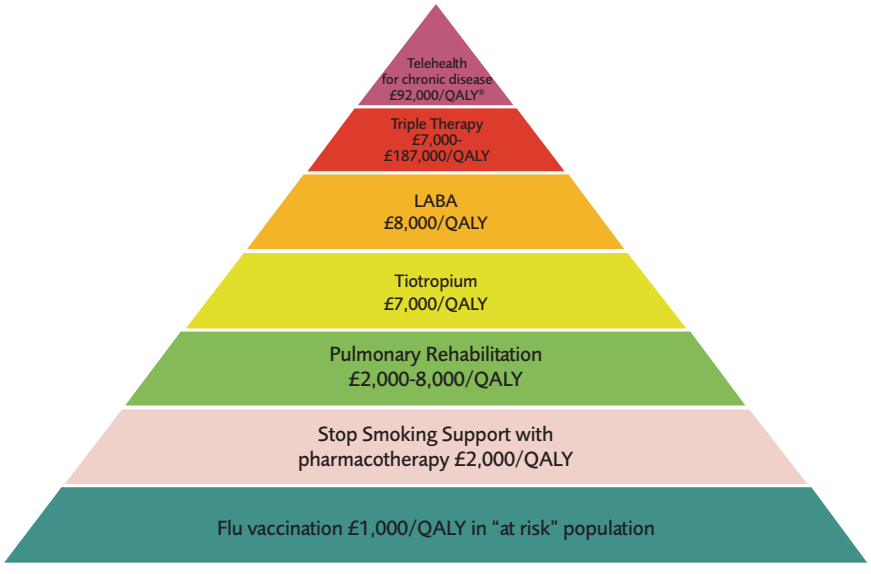
The way we manage certain conditions is usually directed by clinical guidelines. In the UK, we tend to adopt guidance either from respected specialist societies or from the National Institute of Health and Care Excellence (NICE). The guidelines are always based on the best evidence available at the time of writing, and ideally updated regularly as new research emerges.

Current guidance for COPD

The current NICE COPD Guidelines – CG101, were published in 2010,[1] so includes research up to 2009. The next iteration of NICE COPD is not due to be published until late 2018. Several new drug classes have been introduced since then and we understand more about the relative value of various interventions in the management of COPD (Figure 1).[2] The decision by NICE not to update the guideline more recently has resulted in more up-to-date guidelines being sought from other sources, and in some instances, local guidelines being devised. The GOLD (Global Initiative for Chronic Obstructive Lung Disease) Global strategy for diagnosis, management and prevention of COPD has therefore gained greater prominence.[3] Indeed, in a recent survey of PCRS-UK members, 65% of respondents used GOLD or a local variation of GOLD as their management pathway, with only 33% using NICE (PCRS-UK – data on file June 2017). However, being a member of the PCRS-UK proclaims an interest and degree of prior expertise in COPD and is therefore probably not representative of the majority of primary care clinicians who manage patients with COPD.

The length and complexity of both NICE and GOLD guidance is daunting, making an informed choice between the two very difficult for the busy clinician. There is a need for a simplified approach to the management of COPD aimed at a non-expert primary care audience. For the experienced practitioner who is already competent at COPD management, the choice should be based on which takes into account the most up to date studies.

Figure 1 London Respiratory Team COPD Value Pyramid



What is COPD?

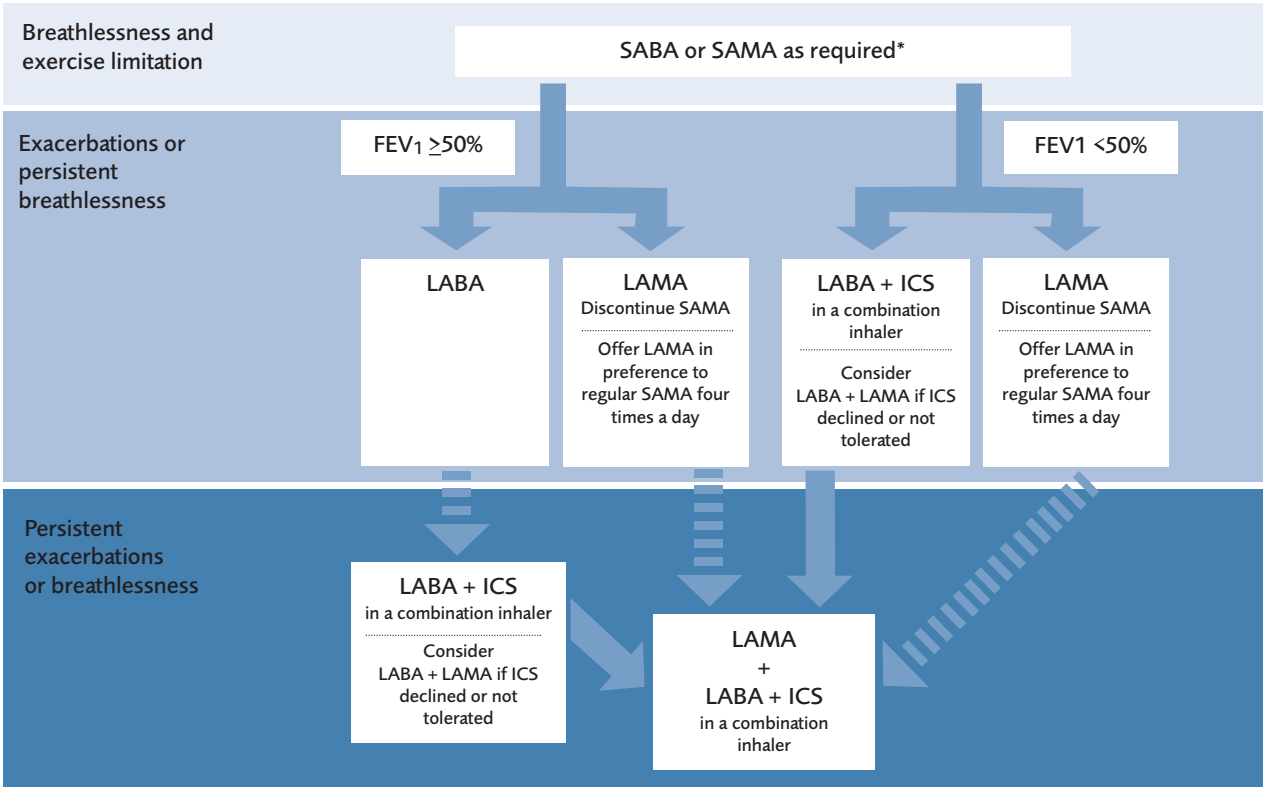
One major caveat needs to be highlighted first; COPD is not actually a disease. COPD is an umbrella term that encompasses a range of disorders; chronic bronchitis, emphysema and chronic asthma[4] and describes poorly reversible chronic obstruction of the airways. When the term "COPD" was first coined, there were limited treatment options, so combining all causes of chronic airflow obstruction into a single condition made diagnosis and treatment simpler. However, with the advent of more treatment modalities for each subgroup of COPD, the utility of a blanket term of "COPD" becomes questionable (for instance, how can chronic asthma with fixed airflow obstruction be treated in the same way as the same level of airflow obstruction caused by emphysema?). In addition, interpretation of studies of "COPD" patients becomes more difficult if we realise that it is not a homogenous disease.

Although all guidelines highlight the importance of differentiating COPD from asthma, there is a grey area where patients may have both chronic poorly reversible obstruction and asthma. More up to date guidelines now recognise that there are differences between patients and GOLD does this by distinguishing different subsets on the basis of symptoms and frequency of exacerbations. However, this leads to 4 different potential treatment pathways (excluding asthma-COPD overlap). Some guidelines attempt to differentiate many potential subsets of COPD which then add to complexity.[5]

The NICE algorithm

NICE primarily uses lung function (measured by FEV_1) as the first step to assess severity and then guide treatment. However, with either increasing symptoms or exacerbations, all treatment pathways lead to triple therapy (LAMA+LABA+ICS) regardless of FEV_1 (Figure 2). Thus patients with continuing breathlessness (a common symptom in COPD) may end up on triple therapy. However, evidence supports the use of inhaled corticosteroids in COPD mainly in the prevention of exacerbations.[6,7] Currently, inhaled steroids are used inappropriately across the severity stages of COPD[8,9] causing waste and potential harm from side effects.

Figure 2 NICE COPD guideline 101 (2010) treatment algorithm



Abbreviations
SABA - Short-acting beta agonist; SAMA - Short-acting muscarinic antagonist; LABA - Long-acting beta agonist; LAMA - Long-acting muscarinic antagonist; ICS - inhaled corticosteroid; * SABA (as required) may continue at all stages

Offer therapy (strong evidence) Consider therapy (less strong evidence)

GOLD - assessment and algorithm

The GOLD strategy is based on consensus using up to date evidence rather than the grading of evidence, based on rigorous GRADE methodology that is used by NICE. NICE also looks at cost effectiveness whereas GOLD is based on a review of clinical evidence and a consensus of expert clinical opinion.

GOLD previously used lung function (measured by FEV_1) as a guide to severity and treatment, but in its 2017 update, GOLD relegated the use of FEV_1 on the basis that there is poor correlation between lung function and severity.[10] Instead, GOLD now mainly uses a combination of symptoms (determined by either the modified MRC (mMRC) score or CAT score) and exacerbation frequency to assess a patient. This classifies the patient into one of 4 quadrants; ABC or D (Figure 3). Drug treatment options are then proposed for each quadrant giving 4 treatment pathways. As there are several alternatives for some quadrants, this adds to complexity (Figure 4).

In search of a simpler solution – clinical phenotypes

The development of different options for pharmacological and non-pharmacological treatments for patients with COPD has led to the understanding that clinical response differs according to the characteristics of the disease. The concept of phenotype (defined as the observable characteristics of a subject as determined by the interaction of its genotype with the environment) applied to COPD has resulted in the definition of different groups of COPD patients with prognostic and therapeutic significance.

Figure 3 The refined ABCD assessment tool

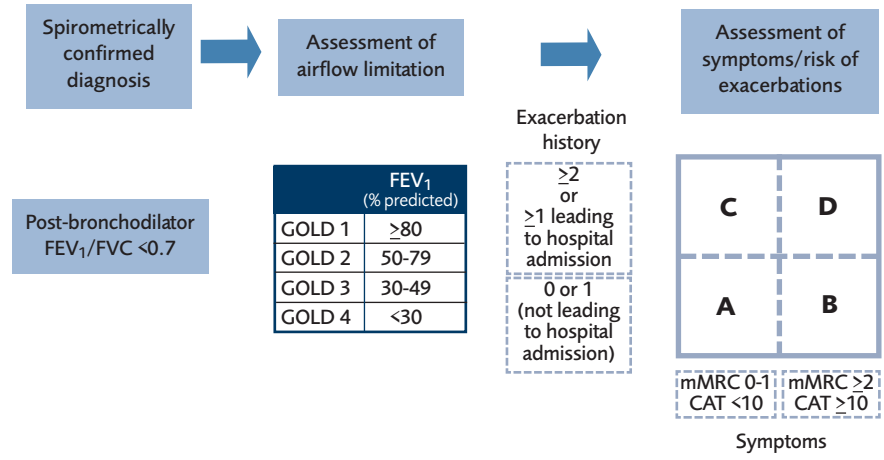


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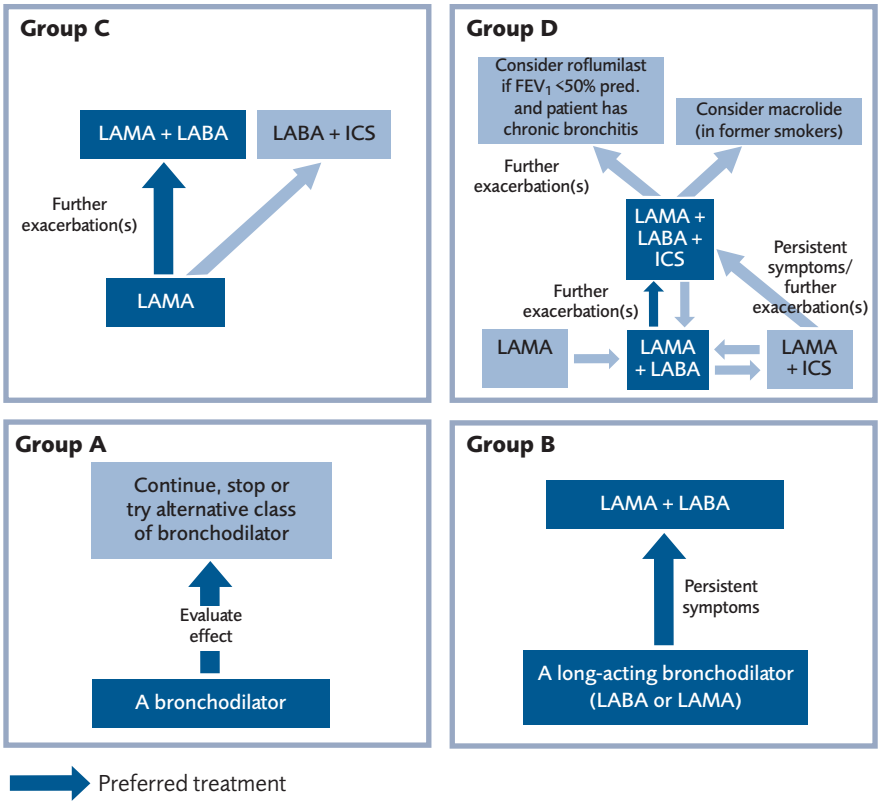
Figure 4 Pharmacologic treatment algorithms by GOLD Grade (dark blue boxes and arrows indicate preferred treatment pathways)



In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted.

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There is a move towards better characterisation of patients using their phenotype[11] rather than just by their underlying disease. In this way, we take a more personalised approach to treatment, not necessarily according to just the severity of the disease, but also modified by the clinical phenotype. From a clinical viewpoint, a COPD phenotype should separate patients into distinct groups that can differentiate their prognosis and response to treatment.

There are many potential COPD phenotypes, and there is no consensus currently. Potential classifications can be based on disease attributes such as symptoms,[12] prognosis[13] or combining different features.[14] Several excellent recent reviews have covered the extensive literature around phenotyping[15,16] and there have been guidelines developed based on clinical phenotypes.[5] However, for a classification of subgroups of COPD to be clinically useful, it should be simple for the primary care clinician to apply, and be potentially responsive to different therapeutic interventions (so called "treatable traits").

Three basic phenotypes based on the predominant symptom profile have been proposed as a possible simple classification:[17,18]

- Predominantly breathlessness
- Predominant frequent exacerbations
- COPD with features of asthma

This phenotypic classification may be useful as the predominant characteristic helps determine the main therapeutic options.

Predominant breathlessness phenotype

The key feature of this phenotype is that the main symptom is breathlessness on exertion but patients may not have frequent exacerbations (≥2 exacerbations/year requiring treatment with oral steroids and/or antibiotics).

The patient usually has a significant smoking history and full lung function shows reduced gas transfer capacity (DL_{CO}) and hyperinflation (increased RV/TLC ratio) suggestive of underlying emphysema. Many studies have demonstrated that breathlessness,[19] reduced exercise[20] and hyperinflation[21] predict mortality independent of FEV_1 defined severity.[22] The cause of breathlessness and reduced exercise tolerance may be due to hyperinflation causing increased work of breathing rather than just airflow obstruction. Therefore, reduction in hyperinflation and gas trapping may be a more relevant therapeutic target than just improvement in FEV_1. Non-drug treatments such as pulmonary rehabilitation[18,23,24] and education on breathing techniques[25] are aimed at reducing hyperinflation.

Hyperinflation can be reduced by bronchodilation with only minor improvements to airflow.[26,27] Hyperinflation is also improved by Long-Acting Muscarinic Antagonists (LAMA)[28] and a Long-Acting B_2-Agonist (LABA).[29] This strategy may have additional benefits in terms of improvement in FEV_1 and improvement in quality of life, particularly when used together.[30-33] Therefore, long acting bronchodilators should be the cornerstone of pharmacological treatment of patients with COPD with breathlessness.

Predominant frequent exacerbations phenotype

The frequent exacerbation phenotype can be defined as a patient with fixed airflow obstruction who has two or more exacerbations per year (with the exacerbations at least four weeks apart) or one hospitalised exacerbation.[10]

The risk of an exacerbation is poorly correlated with the severity of disease as classified by FEV_1, but highly correlated with having had previous exacerbations.[34] The importance of exacerbations is threefold: exacerbations adversely affect the patient's quality of life, they risk deterioration to the extent the patient may need more frequent hospital treatment, but also, they damage the lungs such that they may never return to pre-exacerbation levels (seen as a rapid decline in FEV_1). With advanced disease, the frequency of exacerbations increases,[35] so targeting treatment to reduce exacerbation frequency and severity will have beneficial long term effects on the rate of decline in lung function, morbidity and mortality.

Treatment modalities focused on exacerbation reduction such as flu vaccination, stopping smoking and pulmonary rehabilitation are the cornerstones in the management of this phenotype.[23,36] In terms of medications, both LAMAs[37,38] and LABAs[39,40] have been shown to reduce the risk of exacerbations by about 25%. The addition of inhaled corticosteroids (ICS) therapy has also been shown to be beneficial,[6,41] and most current COPD guidelines only recommend the use of ICS in combination with a LABA.

COPD with asthma phenotype

This phenotype is the most controversial and is creating significant discussion. Some patients may have features of both asthma and COPD, so called Asthma-COPD overlap (ACO).[42,43] Current estimates suggest that depending on age, between 10-52% (pooled estimate 27%) of patients classified as having COPD may actually have a mixed COPD with asthma phenotype.[42,44] This can come about from asthmatics who have smoked heavily, or who have had lifelong chronic asthma with airways remodelling. Alternatively, a heavy smoker with COPD may develop adult onset asthma.

The importance of determining which patients have a COPD with asthma phenotype is that they may benefit from early inhaled corticosteroid (ICS) treatment.[45,46] Consensus currently is that patients who have COPD with asthma should be treated early with a combination of LABA + ICS. Monotherapy with ICS alone is not recommended.[47] Not surprisingly perhaps, patients who have significant bronchodilator reversibility seem to do better with ICS.[48,49] With more widespread use of FeNO measurement, a marker of eosinophilic inflammation in lung tissue, together with the evolving work on the presence of mild eosinophilia, it may become easier to identify those who have an asthmatic element which should respond to ICS.

What else could it be?

Multi-morbidity is very common in people with COPD and these conditions can also be a cause of breathlessness, fatigue and mimic exacerbations. This includes lung cancer, bronchiectasis and heart failure. A change in inhaler pharmacotherapy is not the treatment in these situations so we need to STOP, THINK and TAKE STOCK each time we initiate inhaled pharmacotherapy.

Stepping up treatment tends to happen at regular reviews and after exacerbations. Both of these situations should trigger a symptom cause reassessment. If the result of this review leaves you in doubt about COPD as the predominant cause and whether COPD pharmacotherapy is the best next choice, then consider whether advice and guidance from a colleague with an appropriate special interest in the additional suspected problems is required.

Keeping it simple

Defining specific phenotypes is a more patient centred approach as we are considering the presenting problem rather than some measure of lung function. In addition, phenotypes with treatable characteristics can guide more appropriate management. However, many patients exhibit more than one characteristic so the most predominant element should be identified to prioritise treatment.

To classify the patient into the most appropriate phenotype, accurate diagnosis is key. The first step is determining if the patient has chronic airflow obstruction ($FEV_1/FVC<0.70$), and then if there are any features of asthma. It they do have features of asthma then management can be modified from current asthma guidance[50]:

For patients with COPD with Asthma:

1. SABA plus LABA/ICS
2. If continuing exacerbations – SABA plus LABA/ICS plus LAMA or consider referring to specialist

If asthma is deemed unlikely, simple assessment of whether the patient is troubled mainly by breathlessness or exacerbations (or both), will determine their treatment pathway. If they have more than 2 moderate exacerbations a year (or one moderate exacerbation and one severe exacerbation requiring hospitalisation), they fall into the predominant frequent exacerbation phenotype and treatment should prioritise reduction of exacerbations.

For patients with COPD with frequent exacerbations and breathlessness:

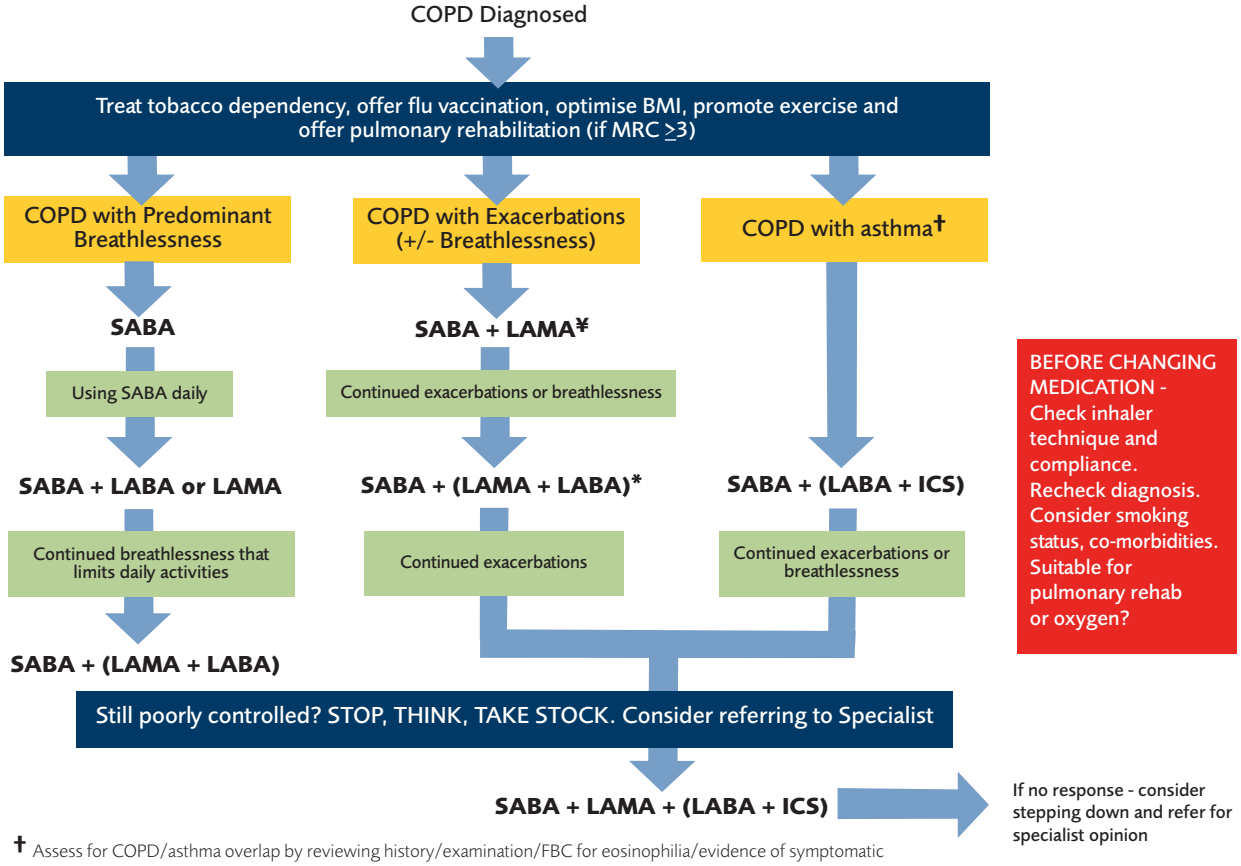
1. Intermittent exacerbations – SABA plus LAMA or LABA
2. If persistent exacerbations – SABA plus LAMA/LABA combination*
3. If continuing exacerbations – SABA plus LABA/ICS combination + LAMA or consider referring to specialist

If the patient does not have frequent exacerbations, they may have the predominant breathlessness phenotype and treatment should be focused on maximising bronchodilation and reduction in hyperinflation.

For patients with COPD and breathlessness (but no asthma):

1. Intermittent breathlessness – SABA
2. If persistent breathlessness – SABA plus LAMA or LABA
3. If still getting persistent breathlessness – SABA plus LABA/LAMA combination

Figure 5 Keeping it simple approach



* Whilst the use of LAMA and LABA in combination is recommended as an option by both GOLD and NICE for patients with exacerbations of COPD, this is not a licensed indication

This is summarized in Figure 5. These treatment options still follow what is recommended by both NICE and GOLD, but bases decisions on the predominant problem of the patient and simplifies the choices that can be made.

Conclusions

For the non-specialist primary care practitioner, currently available treatment guidelines for COPD may not reflect current practice or appear dauntingly complicated. These guidelines may not take into account adequately that COPD is not a homogenous disease but contains a collection of different clinical phenotypes. There is a need for a simple strategy that is patient centred and easy to apply. We have proposed a simple treatment pathway based on the predominant symptoms of the patient distilled from current guidelines that will hopefully make management of the patient sitting in front of us more straightforward.

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