Pharmacological treatment of stable chronic obstructive pulmonary disease

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Funding information
National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC)

Series Editors: Christine Jenkins and Pascal Chanet

Abstract
Pharmacological treatment for chronic obstructive pulmonary disease (COPD) aims to alleviate symptoms and reduce the future risk of events such as exacerbations, disease progression and death. The heterogeneity of COPD results in variable responses to pharmacological interventions. COPD treatment has evolved towards a precision medicine approach, incorporating clinical and biomarker information in order to optimize treatment decisions for each individual. The evidence supporting the use of blood eosinophil counts to predict responses to inhaled corticosteroids (ICS) in COPD patients has led to the adoption of this biomarker for use in clinical practice. The development of novel double and triple inhaled combination treatments containing long-acting bronchodilators with or without ICS has involved some landmark randomized controlled trials in COPD patients. These studies have provided valuable evidence to direct the use of different classes of combination treatments. However, there are still some unresolved questions and debates. This review article describes the advances in the pharmacological treatment of COPD, particularly the personalization of treatment. The evidence base for current recommendations is discussed, and controversial issues are dissected.

KEYWORDS
bronchodilator agents, chronic obstructive pulmonary disease, eosinophil

INTRODUCTION
The aims of pharmacological treatment for chronic obstructive pulmonary disease (COPD) are to improve symptoms and reduce the risk of adverse clinical outcomes including exacerbations, disease progression and death.1 Targeting symptoms enables improvements in exercise tolerance and quality of life. Risk assessment in COPD patients commonly focuses on exacerbations, and is performed by using the history of exacerbations in the previous year to predict future exacerbation risk.2 A historical focus on using forced expiratory volume in 1 s (FEV1) to guide pharmacological treatment has been replaced by this more individualized approach towards symptoms and exacerbations, introduced by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2012 report.3 The concept of treatable traits has also become prominent in recent years; these are disease components which can be individually targeted for treatment.4

The GOLD 2019 report highlighted the need for pharmacological treatment to target dyspnoea and exacerbations, easily recognizable treatable traits that enable an individualized approach to alleviating symptoms and reducing risk.5 COPD is both complex, encompassing many different abnormalities of pathophysiology, and heterogeneous, with considerable variation between individuals with regard to the presence and severity of pathophysiological abnormalities which give rise to clinical characteristics.6 Disease heterogeneity causes variable responses to pharmacological interventions. Precision medicine is an individualized approach which integrates clinical and biological information in order to better predict prognosis or response to treatment.4,5 Biomarkers allow the presence or activity of biological processes to be assessed, thus identifying individuals with distinct pathophysiological mechanisms suitable for tailoring pharmacological therapy.7 Considerable evidence now shows that blood eosinophil counts predict...
responses to inhaled corticosteroids (ICS) in COPD patients when combined with clinical information.\textsuperscript{5,8} GOLD 2019 recommended that this biomarker is used in patients with a history of exacerbations to help direct the appropriate use of ICS,\textsuperscript{5} marking the implementation of precision medicine in COPD.

The development of inhaled combination treatments containing two long-acting bronchodilators (LABDs; a long-acting beta-agonist [LABA] with a long-acting muscarinic antagonist [LAMA]) or triple therapy (ICS/LABA/LAMA) involved a number of large randomized controlled trials (RCTs) to evaluate the effects on lung function, symptoms and exacerbations.\textsuperscript{5,8–10} These RCTs have provided evidence to help identify which COPD patients would benefit most from ICS containing combination treatments, although there are still uncertainties and controversies regarding their use in clinical practice.

GOLD provides recommendations regarding pharmacological management based on scientific evidence.\textsuperscript{5} GOLD does not provide cost-effectiveness analysis. Regional variations in the availability and costs of medicines mean that local or national guidelines are often used, with many incorporating GOLD recommendations.\textsuperscript{11} Furthermore, the American Thoracic Society (ATS) has recently published a clinical practice guideline for the pharmacological management of COPD focusing on six important questions,\textsuperscript{12} while the European Respiratory Society (ERS) has also published a short guideline concerning ICS withdrawal.\textsuperscript{13} The presence of GOLD recommendations coupled with national, ATS and ERS guidelines provides a plethora of useful information for practising clinicians, but also runs the danger of information overload. In addition, while conflicting recommendations can lead to healthy debate, they may also cause confusion with regard which recommendation to follow.

This article provides an overview of COPD pharmacological management, covering current recommendations, precision medicine and current controversies.

PHARMACOLOGICAL MANAGEMENT AT INITIAL DIAGNOSIS

GOLD recommends that an assessment of symptoms and exacerbation risk is performed at initial diagnosis, using the ABCD grouping system; C and D patients have a history of ≥2 moderate exacerbations (requiring antibiotic and/or oral corticosteroid treatment) or one severe exacerbation (hospitalization) in the previous year, which are predictors of increased future exacerbation risk.\textsuperscript{5} B and D patients have higher symptom scores, measured using the COPD assessment test score (>10) or modified British Medical Research Council Questionnaire (≥2). The principle of the ABCD grouping is to separate patients according to both the level of symptoms and risk of exacerbations, in order to tailor pharmacological treatment appropriately. Few RCTs of inhaled treatments have specifically enrolled newly diagnosed patients, or those who are treatment naïve, so the evidence base for treatment recommendations in this group is sparse.

Short-acting bronchodilator treatment alone may be used as initial treatment for COPD patients with a relatively low symptom burden. However, many COPD patients have symptoms that require regular maintenance treatment with LABDs to enable prolonged smooth muscle relaxation and hence improved airflow. LABD monotherapy improves lung function, symptoms, quality of life and exercise performance.\textsuperscript{14,15} These wide ranging benefits make LABD monotherapy an attractive initial treatment option. LABDs can also prevent exacerbations, with LAMAs having a greater effect than LABAs demonstrated in studies such as POET (11% difference in exacerbation rate reduction).\textsuperscript{16} GOLD recommends LABD monotherapy as a possible initial treatment option for all patients, but with LAMA preferred for groups C and D due to the superior effect on exacerbations compared to LABA (summarized in Figure 1).\textsuperscript{5} ICS treatment (as ICS/LABA combination) features only as an option for group D patients with higher blood eosinophil counts.

LABDs can be combined due to the different mechanisms of action that cause bronchodilation; LAMAs attenuate acetylcholine signalling at muscarinic receptors, while LABAs upregulate cAMP signalling.\textsuperscript{15,17} RCTs have demonstrated that LAMA/LABA combinations improve lung function, symptoms and quality of life to a greater extent than LABD monotherapies; the mean treatment differences are usually over 100 ml for peak FEV\textsubscript{1} and in the range 50–100 ml for trough FEV\textsubscript{1}, up to 0.5 units for the transition dyspnoea index and approximately 1.5 units for the St George’s Respiratory Questionnaire.\textsuperscript{12,17–20} These mean treatment differences have fallen short of suggested minimal clinically important difference values, causing debate regarding the validity of these values and whether using different thresholds or individual responder analysis is a more appropriate method to analyse the results.\textsuperscript{6} Regardless, the overall weight of evidence including acceptable safety supported a strong recommendation in the ATS clinical practice guideline for the use of LAMA/LABA combination treatments over LABD monotherapy for patients with dyspnoea or exercise intolerance.\textsuperscript{12}

A controversy is whether dual bronchodilator (LAMA/LABA) combination treatments should be used as initial pharmacological treatment, and whether there is a patient subgroup in whom this strategy is most appropriate.\textsuperscript{21,22} Most RCTs comparing LAMA/LABA versus LABD were not performed in treatment-naïve individuals, and many patients were allowed to continue pre-existing ICS treatment after randomization,\textsuperscript{22} meaning that triple therapy was compared to ICS + LABD treatment in a proportion of the study population. Furthermore, the magnitude of benefit of LAMA/LABA over LABD monotherapy varies considerably between individuals,\textsuperscript{23} arguing in favour of starting treatment with one LABD, assessing the response and adding the second LABD to allow any further benefit in real life to be assessed.\textsuperscript{5,21} On the other hand, post hoc subgroup analysis of treatment-naïve individuals has reported larger effects for dual bronchodilator combinations compared to LABD.
monotherapies on lung function and patient reported outcomes, although the smaller sample sizes (in subgroup analysis) contribute to less power to achieve statistical significance. Furthermore, a recent study of LAMA/LABA versus LABD monotherapies in COPD patients who were either maintenance treatment naïve or using LABD monotherapy before study entry reported superiority for dual bronchodilator treatment for lung function and symptoms. Overall, there are arguments for and against using LAMA/LABA combinations as first-line therapy, and GOLD suggests that these combination treatments can be considered as initial treatment in individuals with a higher symptom burden (Figure 1), which is a practical recommendation rather than the one supported by RCT evidence.

PHARMACOLOGICAL MANAGEMENT DURING FOLLOW-UP

GOLD recommends that pharmacological treatment is targeted towards the need to (further) treat dyspnoea and/or exacerbations during follow-up clinic visits. A management cycle incorporating the review (of dyspnoea and exacerbations) coupled with assessment of inhaler technique and adherence plus non-pharmacological management is suggested prior to making any decisions regarding adjusting treatment; review—assess—adjust. This management cycle serves to ensure that essential components of management are conducted before any change (adjust) in pharmacological treatment is made. The options to adjust include switching device or molecules are relevant, for example, if a patient has difficulty with a particular device or cannot tolerate a particular molecule. Adjustment may involve treatment escalation or de-escalation (if there is no benefit or there are unacceptable side effects) and the subsequent clinical response reviewed. The dyspnoea and exacerbation pathways in the GOLD report allow patients to be switched between pathways as appropriate during long-term follow-up.

Dyspnoea pathway

The intensification of treatment for dyspnoea involves the addition of more LABD treatment if possible. For patients already treated with LABD monotherapy, GOLD and the ATS guideline recommend escalation to LAMA/LABA combination treatment on the basis of the evidence already discussed. If there is no clinical benefit from this escalation, GOLD suggests switching device or molecules, or de-escalation to LABD monotherapy. For patients already treated with an ICS/LABA combination, the addition of a LAMA is recommended; this is supported by RCTs showing benefits on lung function, symptoms and quality of life for triple therapy versus ICS/LABA. This route to triple therapy is possible in patients who required ICS/LABA initially for exacerbation prevention, and then the subsequent addition of LAMA for dyspnoea. Alternatively, some patients may have been started on ICS/LABA treatment inappropriately (i.e., there was no clinical history of exacerbations), and here switch to LAMA/LABA treatment is recommended by GOLD.

One of the difficult situations in clinical practice is the treatment of dyspnoea and exercise intolerance in patients already established on LAMA/LABA combination treatment, as there are no further pharmacological escalation steps supported by clinical evidence. In these situations, the review cycle provides opportunities to address inhaler technique and compliance, non-pharmacological management (e.g., pulmonary rehabilitation) and management of comorbidities, as these often contribute significantly to symptoms.

Exacerbation pathway

For patients already treated with LABD monotherapy, intensification of treatment for exacerbations may involve escalation to a double combination (ICS/LABA or LAMA/LABA) or triple therapy. Considering RCTs performed in patients who are at increased risk of exacerbations (i.e., a history of
≥1 exacerbation in the last year), there is plenty of evidence that ICS/LABA is superior to LABA monotherapy, with approximately 25% fewer exacerbations observed on average (although this varies with baseline eosinophil counts—discussed later). However, the comparison of ICS/LABA versus LAMA showed no difference for exacerbations. These different results in ICS/LABA versus LABD monotherapy RCTs are likely due to the greater effect of LAMA compared to LABA on exacerbation prevention. On a similar theme, two large RCTs comparing LAMA/LABA versus LAMA (tiotropium) showed reductions of 7% (p = 0.0498; not meeting the 0.01 level set for significance), 12% (p = 0.038) and 10% (p = 0.096) for moderate/severe exacerbations. These results suggest only modest additional effects of adding LABA to LAMA treatment for exacerbation prevention, again reflecting the lower influence of LABA compared to LAMA on exacerbation prevention. However, COPD patients with persistent exacerbations often also require further symptomatic treatment, supporting the case to add LABA to existing LAMA treatment. Another option for patients already on LAMA treatment is to escalate directly to triple therapy without using a double combination, as triple therapy reduced exacerbations by 20% compared to LAMA monotherapy. Adding LAMA to LABA treatment for exacerbation prevention has not been evaluated, but one can reasonably speculate that LAMA/LABA would be more effective based on other RCTs of LAMA addition. Nevertheless, the actual RCT evidence for exacerbation prevention (from populations at increased exacerbation risk) supports (1) escalation from LABA to ICS/LABA (with the benefit related to eosinophil counts as discussed in the next section), (2) only a small benefit for escalation from LAMA to LAMA/LABA in comparison to (3) a greater benefit for escalation from LAMA to triple therapy (see Figure 2 for a summary of inhaled treatment escalation steps supported by RCT evidence).

The FLAME study reported a 17% exacerbation rate reduction for LAMA/LABA treatment compared to ICS/LABA. In contrast, the IMPACT and ETHOS studies reported the opposite pattern; ICS/LABA had a 10% and 11% greater effect on exacerbation prevention, respectively. These variations can mostly be explained by the different exacerbation risks of the study populations; the FLAME population consisted mostly of patients with one exacerbation in the previous year, while the IMPACT and ETHOS populations specifically recruited higher risk individuals with the majority of the patients having ≥2 moderate exacerbations in the previous year or a history of hospitalization. Overall, it appears that the benefit of ICS is increased in patients with higher exacerbation risk; this is supported by a subgroup analysis of IMPACT showing similarity of these double combinations in patients with one moderate exacerbation in the year prior to study entry while ICS/LABA was superior in patients with ≥2 exacerbations in the previous year. There have been other debates surrounding the design and patient populations of these large RTCs, such as the differences in the run-in periods and different exclusion criteria concerning current and past history of asthma. While these issues undoubtedly influence the results, the important point for clinical practice is that there are different levels of exacerbation risk, that is, patients with one moderate exacerbation compared to higher risk patients with ≥2 exacerbations or a hospitalization, and that the relative clinical benefits of double combination inhalers change with this risk. Accordingly, GOLD suggests ICS/LABA is more suitable for higher exacerbation risk patients.

The use of triple therapy as an escalation step from double combinations to prevent exacerbations is supported by the ETHOS and IMPACT studies, and the TRILOGY and TRIBUTE studies where triple therapy was compared to ICS/LABA and LAMA/LABA, respectively; the exacerbation rate reductions vary from 13% to 25% in the various analysis in favour of triple therapy. Subgroup analysis shows that a benefit was observed regardless of previous exacerbation history, although it should be noted that individuals with a lower rate of exacerbations prior to study entry also have a lower rate of exacerbations over the course of the study regardless of the randomized treatment.
Blood eosinophils: A biomarker to guide ICS use

There has been considerable debate about the therapeutic index (toxicity vs. efficacy) of ICS in COPD, as these drugs may cause adverse effects including osteoporosis, pneumonia and cataracts.5,37 Blood eosinophil counts have emerged as a practical biomarker that can be used with the clinical history of exacerbations to help predict which patients are most likely to gain benefit, thus helping to optimize the benefit versus risk ratio.5

RCTs reported that COPD patients with higher sputum eosinophil counts demonstrated greater clinical responses to corticosteroid treatment.38,39 Subsequent work focused on blood eosinophils as a more accessible biomarker. Post hoc and pre-specified analyses of RCTs that investigated the effects of ICS containing combination treatments on exacerbation prevention have reported greater effects in COPD patients with higher blood eosinophil counts at baseline; this has been demonstrated for ICS/LABA versus LABA,40–42 and triple therapy versus LAMA/LABA.10,35,43 Data modelling has generally shown that the benefit of ICS treatment on exacerbation rate reduction is apparent at ≥ approximately 100 eosinophils/μl.40,43 A continuous relationship is observed between blood eosinophil counts and ICS benefit, with greater effects observed at higher eosinophil counts as shown in Figure 3, with approximately 50% exacerbation rate reduction at >300 eosinophils/μl. Two of these analysis have noted that ICS benefits were reduced in current smokers, thus right-shifting the threshold where a benefit on exacerbation rate reduction is observed to approximately 200 eosinophils/μl.40,43 However, the GOLD recommendations for the use of inhaled treatments to prevent exacerbations use a precision medicine strategy based on exacerbation history and blood eosinophil counts,5 without incorporating current smoking status. These recommendations highlight approximately 100 eosinophils/μl as a threshold above which it is more likely that a beneficial ICS response is observed, while higher eosinophil counts (e.g., >300 cells/μl) further increase the chance of treatment success (Figure 2). It is interesting to compare the GOLD recommendations alongside the RCT evidence in Figure 2; the treatment escalation steps in GOLD align to the evidence, except there is no distinction between LAMA or LABA used as monotherapy, and stepwise escalation is used in GOLD (i.e., no leap from LABD monotherapy to triple).

The ATS clinical practice guideline made a conditional recommendation with moderate certainty to add ICS treatment to LABD treatment in patients with a history of ≥1 exacerbation and blood eosinophil counts ≥150 cells/μl (this threshold was chosen as it was used in the selected studies).12 A pooled analysis of six studies using this threshold showed that ICS addition in this population reduced exacerbation risk by 30%.

The mechanistic explanation for the association between blood eosinophil counts and ICS response is probably related to a skewing towards T2 inflammation in COPD patients with higher eosinophils.44–47 This association between eosinophil counts and T2 airway inflammation is present even after the careful exclusion of patients with asthma.44 T2 inflammation is corticosteroid sensitive in asthma, and blood eosinophil counts likely identify COPD patients with ICS-sensitive T2 inflammation. It has also been reported that COPD patients with higher sputum eosinophil counts have less colonizing bacteria in the lungs and greater bacterial diversity,48,49 while blood eosinophil counts <100 cells/μl are associated with a higher risk of chronic bacterial airway infection and pneumonia.50 Overall, these findings implicate interactions between eosinophilic inflammation and the microbiome that influence ICS response.51,52

Multiple studies have demonstrated statistically significant associations between blood and lung eosinophil counts, but the strength of the relationship has been weak to moderate.8 Technical issues such as the quality of sputum slides can negatively impact this relationship.

A highly debated topic is whether blood eosinophil counts are stable over time.8,52,53 Repeated blood eosinophil counts show a good to excellent correlation over time when analysed using intra-class correlation coefficient, ranging from 0.64 to 0.89 for repeated measurements up to 5 years.8,54,55 It has been noted that these intra-class correlation coefficient (ICCs) for blood eosinophil counts are highly similar to those for cholesterol and glycated

** Figure 3 ** Relationship between blood eosinophil counts (x-axis: cells/μl) and probability of inhaled corticosteroid benefit on exacerbation rate reduction (y-axis) in chronic obstructive pulmonary disease patients

![Graph showing relationship between blood eosinophil counts and probability of ICS benefit on exacerbation rate reduction](image-url)
haemoglobin Hb. Some studies have assessed stability by evaluating how many measurements move across a threshold. The interpretation of these results should consider these key points: (1) movement across a threshold is more likely in individuals whose measurement was near to the threshold value; such variation is often minor day-to-day fluctuation rather than a change in the underlying disease state; (2) GOLD 2020 states that the 100 and 300 cells/μl thresholds are ‘estimates, rather than precise cut-off values’, which caution against over-interpretation of small changes across a threshold value; and (3) there is lower variability in patients with lower blood eosinophil counts, suggesting persistently low levels of eosinophil-associated inflammation in a subgroup of patients is associated with reduced/no benefit with ICS treatment.

**CONTROVERSIES WITH TRIPLE THERAPY**

The IMPACT (n = 10,355) and ETHOS (n = 8,509) RCTs were conducted in similar populations at high risk of exacerbations. Both studies compared triple therapy versus LAMA/LABA and ICS/LABA. All-cause mortality was a pre-specified endpoint in both IMPACT and ETHOS; 42% and 46% lower mortality rates, respectively, were reported with triple therapy versus LAMA/LABA in the primary publications, with no differences versus ICS/LABA, indicating that this mortality benefit was principally due to the ICS component of triple therapy. Interestingly, a lower ICS dose used in the ETHOS study did not demonstrate a benefit on mortality, but showed similar effects to the higher dose triple therapy on other clinical outcomes including exacerbations. The reasons for these differences in mortality but not in other endpoints remains unclear. Nevertheless, the reduction in moderate and severe exacerbations with triple therapy versus LAMA/LABA in both studies is likely to be a dominant reason for this mortality benefit, as exacerbations are associated with increased mortality. Ideally, mortality studies should be conducted with mortality as the primary endpoint. Here, we have two large RCTs with similar designs in high exacerbation risk populations providing similar results regarding mortality, increasing confidence that this mortality effect is not a false positive, despite mortality not being the primary endpoint of these studies.

ICS combination treatments are often prescribed inappropriately to COPD patients without a history of exacerbations. GOLD supports ICS withdrawal from either ICS/LABA or triple therapy in such cases. Other clinical scenarios to consider ICS withdrawal include adverse effects, including pneumonia, and lack of treatment response. The risk of pneumonia in COPD patients increases with age, lower FEV1, lower BMI and a previous history of pneumonia episodes. Ultimately, decisions to withdraw ICS due to side effects should be made on an individual basis weighing risks and benefits. Such decisions are made easier when there is a clear lack of positive treatment response to ICS intervention.

The ATS guidelines made a conditional recommendation with moderate certainty that ICS can be withdrawn from triple therapy if the patient had no exacerbations in the last year. The recommendations utilized two RCTs, WISDOM and SUNSET (with the latter recruiting mainly patients with no exacerbations in the previous year). However, there are other issues to note; first, previous treatment response in clinical practice should be central to decisions regarding whether to continue or discontinue a medicine, and it would be illogical to withdraw ICS when a patient has reported a clinical benefit; second, while the overall study populations (of WISDOM and SUNSET) showed no increase in exacerbation rates, subanalysis of both studies showed more exacerbations in patients with higher eosinophil counts. This underpins the GOLD recommendation to be cautious when withdrawing ICS if blood eosinophil counts are >300 cells/μl, while the ERS guideline on ICS withdrawal provides a strong recommendation to continue ICS if eosinophil counts are >300 cells/μl, regardless of exacerbation history.

**ORAL TREATMENTS**

Roflumilast is a phosphodiesterase 4 inhibitor that exerts a wide range of anti-inflammatory effects, and reduces exacerbation rates by approximately 15%–20% in the COPD subset with chronic bronchitis, severe airflow obstruction and a history of exacerbations. RCTs have shown that roflumilast improves FEV1 by up to approximately 80 ml but without benefits on symptoms. A problem in clinical practice is that the common side effects of roflumilast include nausea, gastrointestinal disturbance and weight loss, although all of these side effects appear to be less problematic if a lower dose is used for the first month. Consequently, this drug is usually prescribed after inhaled treatments have been started. Interestingly, an RCT focused on the mechanism of action showed that roflumilast reduced bronchial biopsy eosinophil counts without a clear effect on other inflammatory cell types, while a post hoc analysis showed that roflumilast effects on exacerbations were greater in COPD patients with higher blood eosinophil counts; these results suggest greater efficacy of roflumilast on eosinophilic inflammation in COPD. GOLD currently recommends roflumilast as an add-on treatment to LAMA/LABA or triple therapy for the further management of exacerbations. RCTs have shown that long-term macrolide treatment can reduce exacerbation rates in COPD patients. Macrolides exert both anti-inflammatory and antimicrobial effects. A post hoc analysis suggests that the effects of macrolides are greater in ex-smokers, giving rise to the GOLD recommendation that macrolides are considered as add-on treatment to LAMA/LABA or triple combination for exacerbation prevention in ex-smokers. Macrolide use is associated with hearing loss and QTc interval
elongation, in addition to concerns about developing antibiotic resistance.\textsuperscript{71}

There is some evidence to support the use of mucolytics to prevent exacerbations, although the results of RCTs have been inconsistent.\textsuperscript{73} Theophylline causes small improvements in lung function, but RCTs have shown no benefit on exacerbations.\textsuperscript{74,75}

**CONCLUSIONS**

There has been a steady evolution of COPD treatment towards finding the optimum treatment for each individual based on both clinical characteristics and biomarker information. The introduction of blood eosinophils to guide treatment decisions regarding ICS use marked the beginning of the precision medicine era in COPD,\textsuperscript{5} but more biomarkers are needed to improve the degree of precision (e.g., biomarkers of disease activity).\textsuperscript{7}

Recent triple combination treatment studies have demonstrated clinically meaningful benefits on a range of endpoints including hospitalizations and mortality.\textsuperscript{9,10} However, there remain considerable gaps in the armoury available to treat COPD; for example, there are no effective pharmacological treatments to slow emphysema progression. There has been much progress, but there is still much to do.

**ACKNOWLEDGEMENT**

Dave Singh is supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC).

**CONFLICT OF INTEREST**

Dave Singh has received sponsorship to attend and speak at international meetings, honoraria for lecturing or attending advisory boards, from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, GlaxoSmithKline, Glenmark, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Teva, Therevance and Verona.

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**How to cite this article:** Singh D. Pharmacological treatment of stable chronic obstructive pulmonary disease. Respirology. 2021;26:643–651. https://doi.org/10.1111/resp.14046