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UNSOLICITED REVIEW

Current controversies in the stepping up and stepping down of inhaled therapies for chronic obstructive pulmonary disease at the patient level

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Abstract

The implementation of potential new step-up or step-down treatment recommendations in response to current guidelines is one of the main challenges currently faced in actual daily practice settings. In the present narrative review, we aim to discuss the relevance of these step-up and step-down proposals at the patient level in daily clinical practice. In particular, we aim to review the challenges associated with inhaled maintenance therapy for COPD in four clinical scenarios. First, we discuss the step up from single to double bronchodilation, including current controversies regarding the addition of a second bronchodilator vs. initial treatment with two bronchodilators. Second, we discuss the step up from double bronchodilation to triple therapy while challenging current indications for inhaled steroid therapy and discussing triple therapy designs. Third, we discuss the step down from triple therapy to double bronchodilation while evaluating the effect of this downshift in risk categories on the patient according to the new classifications. Finally, we discuss the step down from double to single bronchodilation, with a special focus on safety. We believe this review will help to highlight the most relevant discussion points regarding the treatment of COPD in a manner that will stimulate and guide related clinical research.

Key words: COPD; inhaled therapies, pharmacological treatment, step-up, step-down

Short title: stepping up and down COPD therapies

Abbreviations

ACO: asthma and COPD overlap

COPD: chronic obstructive pulmonary disease

ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points

FEV_1: forced expiratory volume in the first second

GOLD: Global Initiative for Obstructive Lung Disease

ICS: inhaled corticosteroid

LABA: long-acting $ß_2$ agonist

LABD: long-acting bronchodilators

LAMA: long-acting muscarinic antagonist

SPIROMICS: Subpopulations and Intermediate Outcomes in COPD Study

WISDOM: Withdrawal of Inhaled Steroids During Optimised bronchodilator Management

1. Introduction

In recent years, an increased understanding of chronic obstructive pulmonary disease (COPD) and a considerable expansion of therapeutic options have contributed to significant changes in the management of affected patients. This increased understanding has led to the greater acceptance of two strategies for disease management. The strategy proposed by the Global Initiative for Obstructive Lung Disease (GOLD) is based on the three main variables of pulmonary function, symptoms, and exacerbations[1]. By contrast, the algorithm underlying the Spanish proposal (which has since been extended to other countries) is based on clinical phenotypes[2]. Both approaches have similarities and differences, as well as advantages and disadvantages[3, 4]. The 2017 updates of both strategies reveal progressive approaches[5, 6], and both share the goal of increased treatment individualization with the aim of further advances.

In this context, although several reports have underscored the importance of various pharmacological response factors, such as sex-related effects[7, 8], biological–functional behavior[9], or COPD etiology[10, 11], clinicians may face a range of truly challenging clinical scenarios when stepping up or down in different patient populations, with a significant degree of uncertainty in the clinical decision-making process.

In the present narrative review, we aim to focus on these step-up and down proposals and to discuss their relevance and main controversies at the patient level in daily clinical practice. In particular, we aim to review the challenges of inhaled maintenance therapy for COPD in four clinical scenarios: 1) a step up from single to double bronchodilation; 2) a step up from double bronchodilation to triple therapy; 3) a step down from triple therapy to double bronchodilation, and 4) a step down from double to single bronchodilation. Of note, patient-level characteristics may clearly influence the therapeutic response. Unfortunately, a comprehensive picture is not yet available;

however, it is probable that “omics” and systems biology approaches will finally help us understand individual responses in the coming years. At present, we believe that our following discussion and arguments will highlight current needs to encourage patient-centered clinical research.

2. Step up from single to double bronchodilation

Studies in recent decades have established long-acting bronchodilators (LABDs) as the mainstay of treatment for COPD[1, 2]. The recommendations to step up to double bronchodilation have led to three key issues that must be clarified: the indications for a step up to double bronchodilation, the indications for first-line treatment with double bronchodilation, and the potential modulatory role of pulmonary rehabilitation. Additionally, the potential adverse effects of increasing bronchodilator therapy should also be considered (see the step down from double to single bronchodilation section).

2.1. When to step up from single to double bronchodilation

Currently, an overwhelming amount of scientific evidence supports the recommendations in favor of double bronchodilator therapy for COPD[12]. According to a recent systematic review[13], at least 26 clinical trials with 24,338 patients have used different inhaled therapies and objectives to conduct detailed investigations of the efficacy and safety of double bronchodilation. Consequently, current recommendations suggest starting with monotherapy and progressing to dual therapy in patients who remain symptomatic, or starting with double bronchodilator therapy for patients with severe breathlessness[1]. Notably, we must remember that these trials have been designed to compare the average improvements achieved by patients at the cohort level. However, at the patient level, the responses vary considerably[13], and only a few studies have used a patient-based analysis to evaluate individual responses to treatment and identify the responders.

In this light, one of the most relevant reports was published by Donohue et al.[14]. The authors evaluated the functional response to double bronchodilation (umeclidinium/vilanterol) as a function of the response to single bronchodilation, using an increase of >12% and >200 mL in the trough forced expiratory volume in the first second (FEV_1) as a marker of a positive response. They found that approximately one-third of patients responded positively to both LABD, another third responded positively only to one agent, and the remainder did not respond positively to either LABD. Interestingly, the former third of patients also had stronger responses to double bronchodilation.

The above observation of different responses to LABD, either alone or in combination, lead to the hypothesis that the response to single bronchodilation may be used to identify candidates for double bronchodilation. This is idea is interesting, since we could potentially identify patients by evaluating bronchodilator responses in a bronchodilator test. Unfortunately, studies regarding the ability of the response to this test to predict a response to LABD have reported conflicting results[15-18].

Two additional studies have evaluated differences in responses to double bronchodilation according to sex[8] or the baseline disease severity, as measured by the COPD Assessment Test[19]. Interestingly, the authors of the latter article observed a greater response to double bronchodilation among patients with more severe disease impact, thus supporting the recommendation of GOLD to administer double bronchodilator therapies to more symptomatic patients. In general, the identification of treatment response to double bronchodilation constitutes one the current challenges that clinicians face.

2.2. When to administer double bronchodilation as a first-line therapy

The existing guidelines recommend that a patient be initially treated with a single LABD, with a step up to two LABDs if symptoms or exacerbations persist[20].

Additionally, the GOLD recommendations suggest a first-line double LABD strategy for highly symptomatic patients. Although the threshold has not been clearly established, this approach of increased treatment intensity in response to disease impact is reasonable; however, it can be challenged with an alternative reasoning.

This alternative reasoning can be attributed to the *Understanding Potential Long-Term Impacts on Function with Tiotropium* (UPLIFT) trial[21], which aimed to evaluate the impact of tiotropium on the rate of FEV_1 decline. Despite the overall negative outcome, the subgroup analyses revealed that those with less-advanced lung disease[22-25] appeared to obtain the benefit of reducing FEV_1 decline, supporting the relevance of early treatment [26]. This idea is compelling, as later studies found that the FEV_1 decline may be more rapid during early stages[27-31]. Therefore, if our objective is to alter the natural course of the disease by reducing the rate of FEV_1 decline, then the approach should comprise double bronchodilator treatment during the early stages of disease to slow progression, followed by either single or double bronchodilator therapy during more advanced stages according to the need for symptom control. We note that clinical trials have not yet addressed the long-term effects of double LABD therapy in terms of the FEV_1 decline and therefore this hypothesis cannot be confirmed to date. An UPLIFT-like trial with two LABD would allow us to confirm or discard this hypothesis and is therefore strongly needed. To make things more complex, a recent clinical trial comparing two double bronchodilation combinations highlighted the fact that individual patients may respond differently to different bronchodilators [32], confirming the individualized response observed by others [14]. Therefore, future trials should evaluate the long-term impact of double bronchodilation in different patient types.

2.3. Double bronchodilation and pulmonary rehabilitation

Interestingly, the GOLD document recommends the addition of a second bronchodilator as the logical step-up to single-agent bronchodilation[1]. However,

respiratory rehabilitation has been shown to yield relevant clinical benefits to patients with a good efficacy/safety profile [33-38]. These findings have led clinicians to debate whether an increase to a second LABD or implementation of a respiratory rehabilitation program would be the best strategy for a patient with persistent symptoms. Even considering the limitations of pulmonary rehabilitation in practice, i.e. the availability of resources, the percentage of responders and the maintained effect in the long term [39, 40], knowing the impact of exercise programs as compared to double bronchodilation would probably help advance individualized therapy at the patient level. Unfortunately, no clinical trial has yet addressed this issue, establishing another area for research.

3. Step up from double bronchodilation to triple therapy

Scaling to triple therapy is increasingly a source for debate, especially with the advent of triple therapy in a single inhaler. According to the 2017 GOLD document, the combination of a long-acting muscarinic antagonist (LAMA), a long-acting ß$_2$ agonist (LABA), and an inhaled corticosteroid (ICS) would most commonly involve the addition of an ICS for patients experiencing frequent exacerbations despite correct bronchodilator treatment, as well as in cases of asthma and COPD overlap (ACO)[1]. Here, the appropriateness of these indications, the role of peripheral blood eosinophil counts as a predictive biomarker for the use of ICS[41], the design of a triple therapy regimens[42], and the role of comorbidities deserves a comment.

3.1. Indication of ICS for the treatment of frequent exacerbators

The evaluation of patients experiencing frequent exacerbations have revealed two main controversies. First, the concept of a frequent exacerbator requires reevaluation. This was largely based on the findings of the *Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points* (ECLIPSE) study, a large observational, prospective, cohort study following 2138 patients over three years, which identified one group of patients experiencing persistent exacerbations during a three-year period,

despite receiving active treatment[43]. However, current guidelines have simplified the concept by limiting the evaluation to only the prior year, regardless of treatment status. Consequently, this restriction may lead to the misclassification of patients. This was recently shown in the *Subpopulations and Intermediate Outcomes in COPD Study* (SPIROMICS) [44], another prospective cohort following up 2981 patients for three years. By using a prospective evaluation, the authors were able to show an inconsistent exacerbation pattern in 41% of the cohort. Similarly, the ECLIPSE cohort presented an inconsistent exacerbation pattern in 65% of the cases [43]. Interestingly, in the ECLIPSE cohort, 17% of patients changed from infrequent to frequent exacerbators and 39% from frequent to infrequent between years 1 and 2 of follow-up [45]. Notably, when ECLIPSE tried to identify the clinical predictors of exacerbations during the following year at the patient level, the researchers were unable to identify a clinical trait that clearly predicts an imminent change in exacerbation frequency category [45]. In other words, although the number of previous exacerbations is a good predictor of subsequent exacerbations at a cohort level[43], this parameter does not seem to support therapeutic decisions at the patient level. Therefore, it remains unknown whether a patient who experiences two exacerbations within 1 year is experiencing a punctual increase as part of the natural, variable presentation of the disease or if the episodes represent a true worsening of COPD, that would require reevaluation of the treatment strategy[46].

Second, even if we accept the frequent exacerbator concept, the notion that ICS must be added to the treatment regimen of a patient with persistent exacerbations despite receiving double bronchodilation must be revisited[47]. A patient with persistent exacerbations despite receiving appropriate medical treatment, using a correct inhalation technique, and exhibiting good treatment adherence, presents a significant challenge. These persistent exacerbators[47] may have one or more of several potentially treatable extrapulmonary comorbidities associated with exacerbations.

Interestingly, of these comorbid conditions, only the overlap with asthma is treated with ICS. Therefore, cases of persistent exacerbation constitute a form of complex COPD (Figure 1) and must be approached systematically by a specialized respiratory medicine department to determine the conditions influencing the incidence of exacerbations and thus administer the correct preventive treatment. Additionally, other disease features such as FEV_1 decline, lifestyle and coping, medication adherence, or symptoms may also contribute to disease complexity. The correct systematic diagnostic approach toward identifying the best treatment for these patients must be defined in the near future.

3.2. Indication of ICS for overlapping asthma and COPD

Although ACO is another relevant indication for ICS use[1, 2], at least three controversial aspects should be considered. First, the concept of ACO is poorly defined. ACO could encompass four different situations (Figure 2) and may indicate either the presence of both diseases in one patient or a single disease with a peculiar clinical presentation. This distinction is beyond semantic, as a patient with two diseases could potentially be treated with agents for both conditions if indicated (e.g., biological therapy or phosphodiesterase inhibitors). However, therapeutic decisions become more controversial for a patient with a single disease with a peculiar clinical presentation, as new clinical trials would be needed for this specific indication. The most recent Spanish proposal, although controversial, encompasses both concepts associated with ACO[48].

Second, the identification of ACO remains controversial. Several biomarkers have been associated with ACO, including a positive bronchodilator test, bronchial hyper-responsiveness, or peripheral blood or sputum eosinophilia. Although several observational studies have indicated interrelationships among these biomarkers at the cohort level[49, 50], multiple studies have indicated mismatches among these biomarkers

at the patient level[51-53]. Consequently, the biomarkers needed to identify this specific population remain unknown.

Third, the treatment of ACO remains controversial. The asthma component has led clinicians to assume that all affected patients should receive ICS therapy. Despite the likely truth of this assumption, supportive evidence from clinical trials is not available because of the lack of a consensus definition or a method of patient identification. In fact, an earlier observational study highlighted potential controversies regarding the role of ICS for ACO[54, 55].

In summary, despite the clinical reality of ACO, these different disease concepts of ACO based on varying diagnostic criteria[56-58] strongly underscore the need for clarification and research on this issue. This condition must be adequately defined at the individual patient level, and a consensus must be reached on diagnostic criteria and patient identification before clinical trials can be conducted to determine the optimal treatment.

3.3. Peripheral blood eosinophils as a marker of responsiveness to ICS

At least 4 post-hoc analyses of major clinical trials[59-63] have identified blood eosinophils as a potential biomarker for ICS response. However, three controversies must be addressed at the patient level. First, the stability of the blood eosinophil population over time remains to be determined. A novel marker of ICS treatment should be sufficiently stable to reflect the disease status over time. However, the results of several studies are controversial, and a recent long-term follow-up study reported that this stability decreased over time and appeared to be significantly affected by age and sex[64].

Second, the accuracy of the blood eosinophil population as a surrogate marker of the corresponding airway population remains a challenge. Although some studies suggested a relationship[65], further data analysis revealed a weak correlation[53, 66] and a poor diagnostic profile[67].

Third, an understanding of eosinophil physiology may be more important than a simple count. The eosinophil is an immune cell with a complex physiology that involves different activation marker pathways and interactions with other types of immune cells[68]. Interestingly, a recent publication described new subtypes of eosinophils that exert a regulatory, rather than effector, role and are indistinguishable in a simple blood cell count analysis[69]. Therefore, future studies will need to evaluate blood eosinophils along with activation markers in specific clinical scenarios to finally determine their role in patient management[70].

3.4. Triple therapy design

The introduction of double bronchodilation provides a new option to build triple therapy comprising a fixed LABA/LAMA combination with an ICS in a second inhaler. This has led to questions regarding the most appropriate strategy. Given the lack of clinical trials that directly compare both possible triple therapies, a recent opinion piece suggested the potential benefits of using LABA/ICS+LAMA for asthma and LABA/LAMA+ICS for COPD[42]. This scenario will likely change in the near future once triple therapies are available in a single inhaler, as clinically, combined treatments have been associated with improved adherence and subsequent clinical and economic benefits[71]. Recently the TRIBUTE study, a randomized clinical trial comparing triple therapy with formoterol / glycopyrronium / beclomethasone vs double bronchodilator therapy with indacaterol / glycopyrronium provided further evidence on the improvements of stepping up to triple therapy[72]. Additionally, the IMPACT trial comparing fluticasone furoate / umeclidinium / vilanterol versus fluticasone furoate / umeclidinium or umeclidinium / vilanterol over a 52-week treatment period was been recelntly published[73]. Nonetheless, the potential risks of over prescribing more intense therapies in a single inhaler may also to lead to overtreatment. Therefore, treatment decisions should be patient-tailored.

3.5. The role of comorbidities.

Finally, there are a number of comorbidities described that should probably be considered when evaluating stepping up to triple therapy, e.g., previous pneumonia or osteoporosis. The debate of pneumonia and ICS prescription would need an ad-hoc review. Briefly, from the publication of the results of the TOwards a Revolution in COPD Health (TORCH) trial[74], several studies have shown a consisting relationship between lower-respiratory tract infections and the use of ICS. This relationship is under study, since it seems to be influenced by several factors, including the molecule, the dose, or specific clinical features [75-77]. Interestingly, the TRIBUTE study did not find a significant relationship between both treatment arms and the incidence of pneumonia[72], but the IMPACT trial showed a higher incidence of of pneumonia in the ICS containing regimens and an increased risk of pneumonia as assessed in the time-to-first event analysis[73]. To make things more complex, corticosteroids, either systemic or inhaled, have been associated with a better prognosis of pneumonia[78, 79] and the reason why ICS reduce exacerbations (the majority of which are related to an infective cause) but increase pneumonia has not been fully elucidated[47].

Osteoporosis and the use of ICS poses another challenge. In the last decade, different observational studies have shown a relationship between the use of ICS and an increased risk for low bone mineral density or fractures[80]. However, well-designed prospective randomized trials have failed to find such association[74]. To make things more complex, it has been described that the progression of COPD does not correlate with the progression of annual change in bone mineral density[81]; and a potential preventive role of ICS for osteoporosis has been proposed[82, 83]. This relationship is complex and there are several hypotheses and confounding factors[84, 85] that should be carefully evaluated in an ad-hoc study in the future.

Although the mentioned comorbidities are not formally considered full contra-indications for treatment strategies at present, it is likely that in the future we shall be able to identify data at the patient level, which would then influence treatment selection in specific cases.

4. Step down from triple therapy to double bronchodilation

ICS discontinuation may be encountered in two main clinical scenarios.

4.1. First scenario: uncontrolled exacerbations

The first clinical scenario involves patients in whom the number of exacerbations could not be controlled with ICS. As discussed earlier, several comorbidities present an increased risk of worsening exacerbations (Figure 1) and of these, only ACO is treated with ICS. Accordingly, the GOLD 2017 guidelines recognize that patients with persistent exacerbations despite LABA/LAMA/ICS treatment may discontinue ICS, given the reported lack of efficacy, elevated risk of adverse effects (including pneumonia), and evidence showing no significant harm from withdrawal[1]. Strictly speaking, this scenario has only been evaluated in the *Withdrawal of Inhaled Steroids During Optimised bronchodilator Management* (WISDOM) trial[86], in which the authors found that the risk of moderate or severe exacerbation was similar among those who did and did not discontinue ICS[86], with a slight decrease in lung function that did not worsen over the course of the study[87]. Therefore, evidence regarding the safety of ICS withdrawal in patients with persistent or increasing exacerbations despite receiving triple therapy is limited.

At the patient level, however, the key clinical challenge involves the identification of patients whose conditions would worsen after ICS discontinuation. A previous study identified a several sub-groups of patients prone to worsening exacerbations after ICS discontinuation, including women, elderly patients, smokers, and patients with higher concomitant bronchodilator use[88]. Additionally, the time of the year was also identified

as relevant to the discontinuation of ICS[89]. Interestingly, the WISDOM data revealed that a blood eosinophil count might predict a deleterious response to ICS withdrawal[90]. Despite the ongoing debate on the general use of blood eosinophils as a biomarker for treatment selection (see above), the utility of this population in this specific clinical context should be explored further.

4.2. Second scenario: low-risk patients

Since the 2017 version of the GOLD document, patients are stratified by separating lung function from symptoms and exacerbations. The immediate consequence of this change is that patients who were considered high risk due to lung function alone under the GOLD 2016 criteria would now be considered low risk. Interestingly, when analyzing the distribution of patients according to GOLD 2016, the great majority of high-risk patients were classified as such according to lung function[91]. Therefore, the GOLD 2017 classification would be expected to shift a considerable number of previously high-risk patients to the low-risk category[92]. A quantitative analysis of data from previous cohort studies supports this expectation (Figure 3).

The implications for this change in patient status are obvious. The number of patients over-exposed to ICS[93, 94] may now increase, as many patients receiving high-risk treatment would now be considered low-risk and would not be indicated to use ICS[1]. Fortunately, at least 4 studies of different designs have reported about the safety of ICS withdrawal among low-risk patients[95-98]. Taken together, the evidence suggests ICS discontinuation is safe for current low-risk patients. Further studies will need to identify specific patient types through a patient-based analysis to fill in the details.

5. Step down from double to single bronchodilation

The transition from double to simple bronchodilation deserves a specific comment in two clinical scenarios. First, the 2017 GOLD guidelines recommend that for patients in group B, treatment could be stepped down to single bronchodilation if the addition of a

second bronchodilator did not improve symptoms[1]; although this may be a difficult thing to explore in patients with limited exercise tolerance. In such cases, the possibility of symptoms related to comorbidities should be investigated[99]. Second, a low-symptomatic patient receiving double bronchodilator therapy may need to determine whether to maintain this regimen or to step down to a single LABD. Although common sense suggests against a change in therapy if the symptoms are controlled, no clinical trials have evaluated this type of treatment switch at the patient level.

One aspect that may lead clinicians to rethink a possible step down from double to single bronchodilation is safety. Two relevant safety analyses have been recently published. The first included 31,174 patients from the UK Clinical Practice Research Datalink[100], which found that the addition of a second LABD was not associated with an increased risk of myocardial infraction, stroke, or arrhythmia; however, an elevated risk of heart failure was observed with double therapy (hazard ratio = 1.16; 95% confidence interval = 1.03–1.30). Nonetheless, this was a retrospective database analysis and it has not been borne out in any of the randomized controlled trials of LAMA/LABA therapy. Therefore, this finding warrants further investigations of safety.

The second was a retrospective, observational cohort study of health insurance claims data from which 19,067 patients who received LABA/LAMA or LABA/ICS for COPD were identified[101]. Cardiovascular events in the LABA/LAMA cohort were lower in the LABA/ICS group, with no significant difference in the risk of cerebrovascular events. Therefore, LABA/LAMA fared well vs. LABA/ICS in a comparison of safety.

6. Conclusions

As reflected in this review, changes to the management of COPD that address some of the stated challenges at the patient level are underway. Although numerous large clinical trials have aimed to address a range of clinical objectives, in many clinical situations, common sense and the available evidence should be used to make the best

possible decision at the patient level. In our present review, we have discussed only inhaled treatments. However, another review may discuss oral treatments, such as methylxanthines[102], phosphodiesterase inhibitors[103], mucolytics[104], or antibiotics[105], which have also been the subject of controversy. We hope that this review will help to highlight the most relevant discussion points regarding the treatment of COPD in a manner that will stimulate and guide related research.

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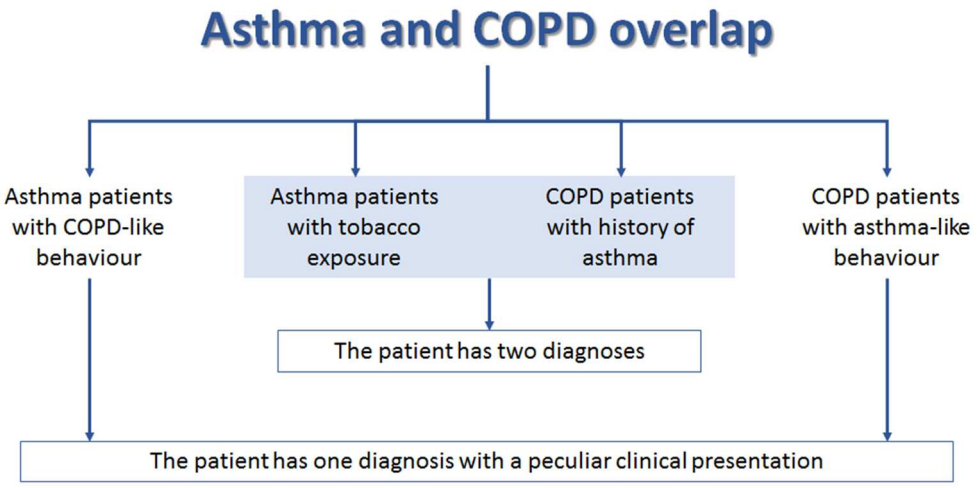
Figure 1. Identification of complex COPD patients solely based on exacerbation persistence and some of the potential causes.

ACOS: asthma and COPD overlap syndrome, GERD: gastro-esophageal reflux disease

Figure 2. Possible profiles of patients presenting with asthma and COPD overlap

Figure 3. Changes in patient stratification according to the Global Initiative for Obstructive Lung Disease (GOLD) 2017 criteria relative to the GOLD 2017 criteria in a) the Copenhagen City Studies [106], b) COPDGene study [107], and c) ECLIPSE study [91].



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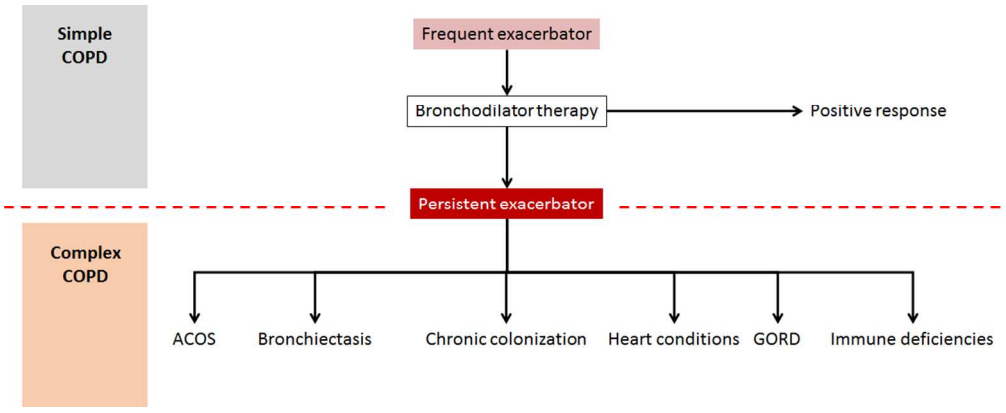

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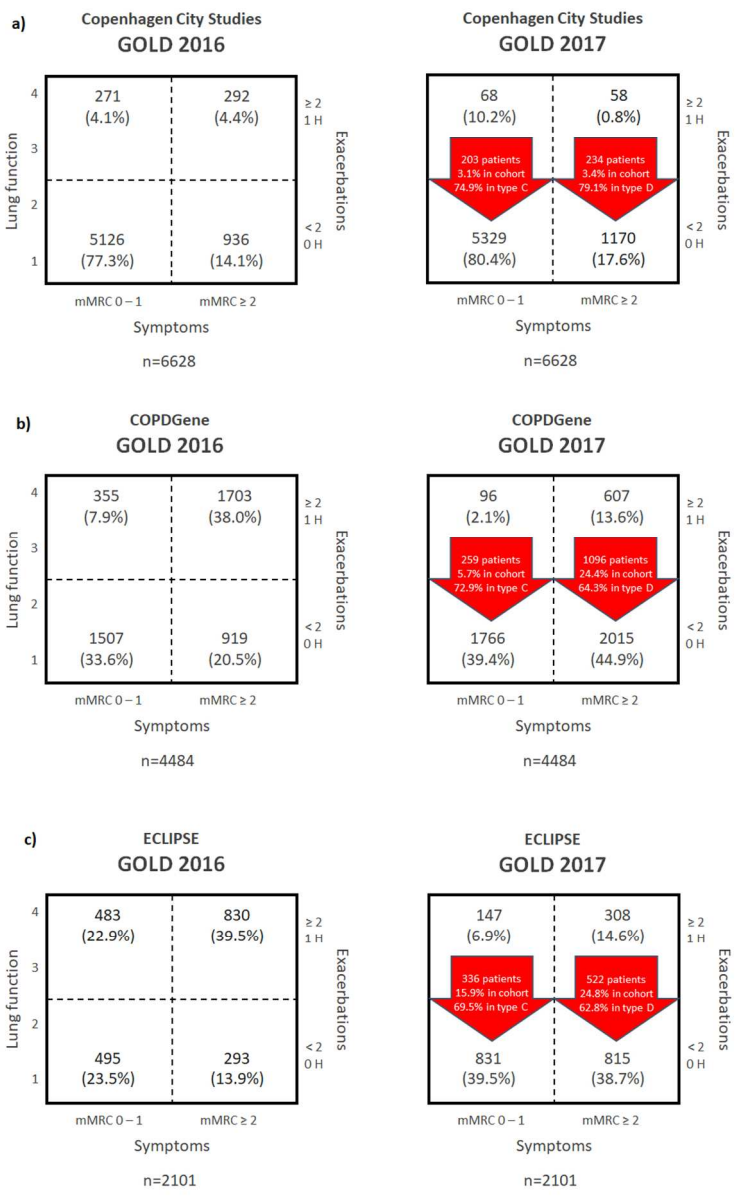

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Article title: Current controversies in the stepping up and stepping down of inhaled therapies for chronic obstructive pulmonary disease at the patient level

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Signature	Jose Luis Lopez-Campos

Date	December 10th, 2017

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Editor comments

This review discusses the clinically important topic of personalised pharmacotherapies for COPD by stepping up or down. In such, it could provide a descriptive rationale for the most recent GOLD approach. It is well-written by a group of well-known authors. In addition to the comments of the two expert reviewers, these are my personal ones.

RESPONSE: We thank the editor for the positive evaluation. We have responded to each one of the comments below.

General comments:

* While your review aims to discuss indications for step-up and step-down at a patient level, the relevance of important patient-specific characteristics is not discussed, such as gender, BMI, age, severity of airflow limitation. For example: risk of pneumonia with ICS in elderly underweight severe patients.

RESPONSE: We agree with the editor that patient-specific characteristics are key to advancing personalized medicine. In the second paragraph of the Introduction, we highlight this concept. In the present review, we would like, however, to focus on current controversies in stepping-up and down rather than analyzing all potential variables that could influence treatment response. That would be a different review, in which there are some promising markers (as the editor mentions), but we do not have a comprehensive picture yet. In the coming years, "omics" and systems biology approaches will probably finally help us understand individual responses. In the present review, we would like to stimulate discussion and arguments that highlight current needs, to encourage patient-centered clinical research in this area. We have added a comment in the Introduction to make this clear.

* Instead of focussing on indications, there should be some discussion on patient level contra-indications for the various treatment strategies, such as previous pneumonia, osteoporosis and so on or the impact of comorbid heart failure on preferred treatment.

RESPONSE: This is an extremely interesting comment. Although the mentioned comorbidities are not formally considered full contra-indications for treatment strategies at present, it is also true that these should be considered when deciding upon treatment selection. Of note, there is considerable controversy and ongoing research for many of these comorbidities. We have reviewed the document and added a few comments in different sections to highlight current controversies at the patient level. Additionally, we have added a new section on comorbidities on page 13.

* The recently published TRIBUTE study (Papi, Lancet 2018) should be incorporated in this review.

RESPONSE: Indeed. We have included a mention of the TRIBUTE and IMPACT trials on pages 12-13.

* The rationale for Figure 1 is unclear. Why call frequent exacerbators 'simple COPD' and the conditions below 'complex COPD' This is a very personal view of the authors, not taking into account important disease characteristics such as FEV1 (decline), lifestyle and coping, medication adherence, symptoms and so on. I believe this figure must be carefully revised or removed.

RESPONSE: The editor is correct, and we appreciate the opportunity to clarify this issue. As indicated, complex COPD should be defined based on different relevant aspects of the disease. Here, we wanted to highlight that a patient with frequent exacerbations despite the correct inhaled therapy represents a challenge for clinicians, which is complex to evaluate and resolve. As the editor knows, exacerbations are part of these variables that define complexity in COPD.

We have changed the text and the figure title to highlight this perspective. If the editor is not convinced, we can remove it.

Reviewer: 1

Current Controversies in Stepping up & Stepping down inhaled therapies for chronic obstructive pulmonary disease at educational level. This is a valiant, well constructed, thoughtful review of some very important clinical problems. By way of background however I must point out the idea of stepping up and stepping down inhaled therapies generally regarded as more pertinent issue in asthma where there is more pronounced seasonal variation in the severity of the disease. Therefore a much higher likelihood of over and under treatment using static inhaler regimes that are not adjusted to clinical symptoms compared to COPD. I believe the major controversy in terms of over treatment or under treatment revolves around the use of the steroid inhaler component of the inhaler regimes to treat COPD. This review has decided to focus on bronchodilation as well as inhaled steroid therapy despite the paucity of data available to make recommendations about the optimal approach to bronchodilation.

RESPONSE: We thank the reviewer for the positive comments and we fully agree. As compared to asthma, stepping up and down in COPD represents a challenge for clinicians precisely due to the paucity of data available to make strong recommendations. We agree with the reviewer that this is a relevant debate and we would like to ensure that the ultimate goal of this review highlights current needs and encourages patient-centered clinical research, rather than giving specific recommendations for which there is no evidence.

Paragraph 2.1 deals with the step up from single to dual bronchodilation. The authors suggest those patients who respond well to single bronchodilation may also be the patients that respond better to dual bronchodilation but ultimately conclude that data supporting this approach is ambiguous at best. This suggests to me that the authors agree with the suggestion by the GOAL guidelines to start with monotherapy and progress to dual therapy in patients who remain symptomatic. This should be clarified in the review.

RESPONSE: The reviewer is correct in underlining some of the controversies regarding stepping up from single to double bronchodilation. As the reviewer indicates, current recommendations suggest starting with monotherapy and progressing to dual therapy in patients who remain symptomatic, or starting with double bronchodilator therapy for patients with severe breathlessness. This is mentioned in subsection 2.2, and we have now acknowledged that in subsection 2.1 as well, as per the suggestion.

Furthermore, this is a little problematic when it comes to making the contrary argument for using dual bronchodilation as first line therapy (Paragraph 2.2). The authors reference the UPLIFT trial as showing that patients with relatively well preserved FEV1 tend to have the most profound decline in FEV1 if left untreated. Hence the rationale for using dual bronchodilation as first line therapy. However, the problem is that there are no studies that show that bronchodilation arrests the progression of decline in FEV1 that are statistical significant. In fact exacerbation frequency was the primary outcome in the UPLIFT trial. This needs to be addressed by the authors. The paragraph ultimately concludes with the suggestion that more clinical trials are required but that is a standard refrain. The authors need to provide insights and opinion on whether they would in fact recommend starting with dual bronchodilation in any patient population.

RESPONSE: We fully agree with the reviewer. The impact of two LABDs on FEV1 decline in mild-moderate COPD patients has not been explored in any clinical trial or observations study. Therefore, this hypothesis cannot be confirmed to date. Therefore, the need for an ad-hoc

clinical trial for this issue is not simply a standard refrain, but a clear research objective. Until evidence becomes available, we should comply with the GOLD recommendations. To make matters more complex, a recent clinical trial comparing two double bronchodilation combinations highlighted the fact that individual patients may respond differently to different bronchodilators. Therefore, future trials should evaluate the long-term impact of double bronchodilation in different patient types. We have added a comment to reflect this debate.

In Paragraph 2.3 they suggest the possibility of pulmonary rehabilitation as a possible step up alterative to dual bronchodilation from monotherapy. While this is a clever idea (which I'm sure has some validity). However, in real life practice, it is very unlikely that we will ever have the kind of access to pulmonary rehabilitation that would make it a viable alternative to a therapy as readily available as an inhaler and therefore does not add much to the review.

RESPONSE: We fully agree with the reviewer. Since a main goal of this review is to put forward potential research initiatives, we believe that this is an interesting aspect to explore. Even considering the limitations of pulmonary rehabilitation in real life, i.e., the availability of resources, the percentage of responders, and the maintained effect over the long term, knowing the impact of exercise programs as compared to double bronchodilation would probably help advance individualized therapy at the patient level. We have commented further in the text to provide a more complete view of the arguments from the reviewer.

Paragraph 3.1 indication of ICS for the treatment of frequent exacerbations, the authors have highlighted the concern about using the ECLIPSE data which covers a three year period and simplifying it to the number of exacerbations over the past twelve months. The authors cite a study (reference 41) that showed that this leads to misclassification of patients as exacerbators. The review needs to expand on the techniques used by reference 41 to show this misclassification. Another study cited by the authors Reference 42. This study apparently shows the eclipse trial investigators were unable to reproduce their overall findings with regards to exacerbations at an individual patient level but again the review does not provide details as to how that study was conducted. The sentence "Researchers were unable to identify such a clinical trait" is confusing. I assume it means that exacerbations, when assessed in isolation, did not identify itself as a poor prognostic trait. The notion that exacerbations while providing guidance to populations as a whole, may not be applicable to individual patients, I think is a well expected limitation of evidence based medicine and I am not sure why this limitation is particularly pertinent to the case of ICS inhalers in COPD patients. This needs to be clarified.

RESPONSE: We thank the reviewer for the cogent comment and for providing us an opportunity to clarify this issue. In section 3.1, the two main studies cited are the ECLIPSE and SPIROMICS cohort studies. We have included a short sentence summarizing the methodology of these two studies, as per the suggestion. We apologize for not being clear in our previous text. We have modified it in an effort to be more clear and specific.

The review next addresses the notion of adding an ICS to patients who are already on maximum bronchodilation i.e. dual bronchodilation and still exacerbating. The authors suggest that other causes need to be identified. But in the absence of an alternate cause being identified I am not sure what the recommendation here is with regards to which patient should receive an ICS if they continue to exacerbate on dual bronchodilation. The authors should attempt to answer the question they posed irrespective of the lack of an evidence base.

RESPONSE: The reviewer poses a relevant question here. One of the problem with evidence-based medicine is that if there is no evidence, then there is no recommendation. This is where the knowledge of experts in the field is valuable and this is what we wanted to stress by showing these gaps in knowledge. Of course, since it is not evidence based, we may disagree, but this is exactly what we wanted with this review, to promote debate and highlight research

needs. Regarding this comment, we wanted to highlight that persistent exacerbators represent a complex problem and that future research should help build a diagnostic algorithm to correctly diagnose these patients, in order to determine the best potential therapy.

In the next paragraph they examined the indication for ICS for overlying asthma and COPD. It certainly highlights some of the problems. My concern here lies with this notion of a patient having both COPD and asthma at the same time. In my mind COPD represents fixed airflow obstruction, asthma represents reversible airflow obstruction, and while I can understand the notion of someone having a hybrid condition, the idea of somebody having both fixed and reversible airflow obstruction simultaneously, it is difficult for me to understand. Furthermore, the use of the phrase "at the patient level", it needs to be replaced by the phrase "at an individual patient level"

RESPONSE: Again, we must agree with the reviewer. As we reflect in the manuscript, the concept of ACOS is confusing from the definition to the current use. Although it is a clinical reality, the key aspects for identifying it are controversial. As acknowledged by the asthma GINA document, non-reversible asthma exists. Additionally, as acknowledged by the COPD GOLD document, partially reversible COPD exists. Taken together, we may find subjects that fulfill diagnostic criteria for both conditions. The problem is how to identify these patients. The number of criteria is so great that we have suggested that ACOS should stand for "Another Confusing Obstructive Syndrome", as we mentioned in another recent article (Lopez-Campos JL, Centanni S. COPD 2018). Notably, we will not be able to conduct ad-hoc clinical trials until there is a consensus definition. We have now modified the term, as per the suggestion.

Paragraph 3.3 looks at the notion of peripheral eosinophils as a marker of responsiveness to ICS. The weakness of this approach is cleverly highlighted in the review. The phrase "at a patient level" being applied to the idea that blood eosinophils lack stability over time is ignoring the fact that it will limit their utility in patient populations as well as in individual patients. So the phrase "at a patient level" could be removed. This also applies to the assertion that magnitude of the cell biology effects of eosinophils may not be captured by simply measuring eosinophil counts is surely true of large cohorts as well as individual patients.

RESPONSE: We thank the reviewer for the positive comment and have made the suggested modification.

Paragraph 3.4: Triple therapy design - It is an interesting concept. The paragraph needs to highlight in more detail the potential dangers of single inhaler device containing triple therapy changing prescribing patterns irrespective of the lack of a supporting evidence base in the literature. Triple therapy being easier to prescribe may to lead overtreatment and not to improved patient outcomes.

RESPONSE: We agree with this comment and have added it, as per the suggestion.

Next the review addresses the step down from triple therapy to double bronchodilation. This is divided into two categories: high risk and low risk patients. The paragraph regarding high risks patients may reveal my own lack of insight with regards to this particular topic. My interpretation of the WISDOM trial was that in patients with at least one exacerbation in the past year, the withdrawal of the steroid component of triple therapy to lama/laba combination did not significantly increase the risk of exacerbation in the next twelve months. It is slightly different from suggesting that the clinical trial supports the withdrawal of ICS therapy in patients with increasing exacerbations on triple therapy. I am not sure what the rate of exacerbations were in the twelve months prior to the start of the WISDOM trial compared to the twelve months monitored during the trial period. This may need to be modified.

RESPONSE: The reviewer is correct. The WISDOM trial showed that that in patients with at least one exacerbation in the previous year, the withdrawal of the steroid component of triple

therapy to LABA/LAMA combination did not significantly increase the risk of exacerbation in the following twelve months. We agree with the arguments given by the reviewer; that is why we state that the evidence regarding the safety of ICS withdrawal in patients with persistent or increasing exacerbations, despite receiving triple therapy, is limited.

Paragraph 4.2: Provide clever insight into the reclassification of high risk and low risk patients by removing the FEV1 is a determinant of risk. A lot of patient that were previously high risk have now become low risk and as a consequence those patients are now deemed to be suddenly over treated if they are on an ICS inhaler according to the most recent iteration of the goal guidelines. The review points out that the reclassification is probably appropriate given the lack of adverse effects to patients (now reclassified as low risk as the 2017 guidelines) that are removed from ICS.

RESPONSE: We thank the reviewer for the comment. We fully agree.

The last part of the review addresses step down from double to single bronchodilation by reiterating that the goal guidelines suggest stepping down from dual to single bronchodilation if the patient is not having an improvement in symptoms with dual therapy as compared to monotherapy. It should be noted that this is often a very hard thing to assess in patients who have limited exercise tolerance or limited inclination to exercise. With regards to the safety, they have identified a clinical database that suggests that dual therapy may increase the risk of heart failure but it should be noted by the authors that this is a retrospective database analysis and it hasn't been borne out in any of the randomised controlled trials of LAMA/LABA therapy. The second study that is quoted, it compares lama/laba to laba and ICS. I am not sure that that is relevant to argument of stepping down from dual bronchodilation to monotherapy as ICS would not form part of that decision making.

RESPONSE: These are interesting points for debate, and we would like to thank the reviewer for providing an opportunity to clarify. We agree that stepping down from double to single bronchodilation is controversial and may be difficult to evaluate. Although this is what GOLD recommends, we agree with the reviewer and have added this comment in the text. We also agree with the comment on the safety study of one or two bronchodilators and have added that comment to the text. The reviewer is correct about the last study that compares LABA/LAMA vs LABA/ICS. Therefore, we cannot analyze step down to ICS alone, or any treatment. We have provided it just to complete the picture of recent safety studies.

Minor issues – Page 5/Line 25 – use different molecules and objectives. I think it would be better if rephrased as "Different inhaled therapies and outcomes".

RESPONSE: We have made that change, as per the suggestion.

Page 6/Line 6 – Led is spelled LED as opposed to LEAD.

RESPONSE: We thank the reviewer for noticing these mistakes. We have reviewed the whole manuscript for typos.

Page 6/Line 6 - the line interestingly the authors deserved a greater response to double bronchodilation among patients with more severe disease impact. That needs to be re-written as I don't understand what it means.

RESPONSE: We have revised the text to make it clearer.

In summary, my feeling is that this is a well written and well researched review. The sections have focused on dual bronchodilation versus monotherapy either stepping up or stepping down therapy are not supported by much in the way of evidence because of a paucity that exists in the literature. I still think those sections should be re-written to give the readers a stronger recommendation, irrespective of the lack of evidence, in whom we should consider

stepping up and stepping down therapy. This should be based on the authors own insights and expertise as this is an area they obviously have a particular interest in. It is too easy to conclude that more evidence is required as very often clinical decisions have to made without a supporting evidence base. The areas regarding triple therapy stepping up and stepping down have a better evidence base and this is well delineated in the review.

RESPONSE: We thank the reviewer for the positive evaluation. We have tried to answer all the insightful comments, which have helped us improve the manuscript.

Reviewer: 2

Jose Luis Lopez-Campos et al. propose a narrative review aimed at discussing the approach to inhalation therapy in COPD. I think the topic of the review is very important and the approach used (different scenarios of daily clinical practice) is original. The review is comprehensive and well done. I have only a few comments:

I suggest the addition of a Figure which underlines the suggested approach for the deferent scenarios proposed. Even if we still miss the full papers, which are very important to analyze in a serious way the trials, a press release regarding two megatrials comparing LABA/LAMA FDC with triple therapy is already available (and the study design has been published). I think that a "simple" comment to this aspect would be useful for the present narrative review.

RESPONSE: We thank the reviewer for the positive evaluation. The reviewer is correct. The TRIBUTE study has already been published and we have a press release from the IMPACT trial. We have added a comment on page 12, as per the suggestion.