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Review of the American Thoracic Society guidelines on the pharmacological management of patients with chronic obstructive pulmonary disease

This article summarises the recommendations of the new American Thoracic Society guidelines on the pharmacological management of chronic obstructive pulmonary disease, comments on how they differ from other guidelines, and considers the research needs and unanswered questions posed.

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Introduction

New American Thoracic Society guidelines on the pharmacological management of chronic obstructive pulmonary disease provide targeted recommendations addressing common clinical scenarios. These cover the use of combination bronchodilator inhalers, inhaled corticosteroids, blood eosinophils as biomarkers for predicting response to inhaled corticosteroids, oral steroids, and opiates. However, they are not comprehensive and therefore need to be supplemented by other resources for chronic obstructive pulmonary disease management. This article summarises the guidelines' recommendations and comments on how they differ from other guidelines, and the research needs and unanswered questions posed.

Summary of recommendations

The American Thoracic Society has recently released guidelines on the pharmacological management of chronic obstructive pulmonary disease (Nici et al, 2020). These provide focused guidance on six scenarios facing clinicians managing patients with chronic obstructive pulmonary disease, covering the use of inhaled therapies in various combinations, oral steroids and opiates.

The scenarios selected by the guidelines panel will strike a chord with the broader community. Those less accustomed to the American Thoracic Society format of specific clinical scenarios and questions and recommendations may feel lost without a scheme for categorising patients and a flow chart or treatment ladder for guiding management, as is common practice elsewhere.

The evidence for each recommendation is referenced, with full systematic reviews and meta-analyses currently under review and due to follow. Only one recommendation is considered 'strong', highlighting the weaknesses of the existing evidence base.

The first recommendatoin, while not explicitly about choice of treatment in a newly diagnosed patient, concludes strongly in support of dual inhaled bronchodilator therapy with a long-acting muscarinic antagonist (LAMA) and long-acting β2 agonist (LABA) over monotherapy with either agent, and can therefore be considered a recommendation for initial inhaled therapy. This is supported by a meta-analysis within the guideline showing that treatment with a combination LABA/LAMA inhaler reduces exacerbations and hospital admissions compared to monotherapy.

Three of the following questions deal with the thorny issue of inhaled corticosteroids for chronic obstructive pulmonary disease. Regimens containing inhaled corticosteroids (such as inhaled corticosteroids plus LABA, or 'triple therapy' with inhaled corticosteroids, LAMA and LABA) are known to reduce exacerbation frequency but also increase the risk of pneumonia compared to those without inhaled corticosteroids (Agusti et al, 2018). In patients with frequent exacerbations, the benefit outweighs the increased but still relatively small risk of pneumonia, confirmed again in these guidelines.

However, it is likely that there are subgroups of patients who do and do not respond to inhaled corticosteroids. The challenge lies in identifying these patients. The finding that

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raised blood eosinophil counts are associated with an increased exacerbation frequency in some (but not all) cohort studies has led to investigation of their potential as biomarkers, although thus far only in post hoc analyses of trials that included a therapy that contained inhaled corticosteroids (Rabe et al, 2017). An increased response is seen in those with eosinophilia, suggesting this can be used to guide treatment with inhaled corticosteroids, albeit that the threshold eosinophil count remains unclear and such an approach has not been tested in a prospective study. The guideline correspondingly recommends triple therapy in those with eosinophilia and a history of exacerbations, quoting thresholds of ≥2% eosinophils or ≥150 eosinophils per microlitre, but not eosinophilia alone.

For those on triple therapy who have not experienced an exacerbation in the past year, there is a conditional recommendation for withdrawal of inhaled corticosteroids based on two trials where withdrawal of inhaled corticosteroids did not alter the rates of exacerbations, pneumonia or all-cause mortality.

Long-term treatment with oral corticosteroids is not advised, even in those with frequent and severe exacerbations, owing to a lack of evidence of benefit and high rates of adverse effects. The inclusion of this question seems odd given oral corticosteroids have long been out of favour as a maintenance treatment.

Finally, the guidelines advocate considering opiates in patients with 'advanced refractory dyspnoea', albeit noting that much of the evidence comes from small trials predating modern treatments. The accompanying editorial in the same issue as the guidelines queries the wisdom of this, particularly given that opioids induce tachyphylaxis.

Differences from other guidelines

In only setting out to tackle six specific questions, focused on pharmacological management in stable disease, these guidelines are narrower in scope than many others on chronic obstructive pulmonary disease. This has the benefit of making them succinct and targeted, but the limitation of being of little assistance in clinical situations where none of these questions apply. Most notably, this includes the options (other than opiates) for patients with symptoms refractory to standard inhaled therapy, who represent a large and growing group of patients in secondary care. Specifically, the role of pharmacological treatments such as macrolides, theophyllines, phosphodiesterase 4 inhibitors (eg roflumilast), mucolytics and nebulised therapy, as well as surgical or endobronchial interventions (eg lung volume reduction, transplantation), long-term oxygen therapy and non-invasive ventilation, is not discussed. The lack of a partner guideline on non-pharmacological management of chronic obstructive pulmonary disease particularly jars, not least given the authors' acknowledgement that smoking cessation is proven to affect mortality and disease progression, whereas pharmacotherapy, the subject of the guideline, is not.

Another key difference is the absence of criteria for classifying patients, to tailor treatment accordingly. The widely used Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines use a somewhat complicated grid resulting in four groupings (ABCD) and corresponding treatment initiation strategies (Global Initiative for Chronic Obstructive Lung Disease, 2020). Compliance with this is poor (Price et al, 2014), perhaps owing to the complexity of the scheme. That said, the treatment recommendations are broadly aligned across the two guidelines, albeit single bronchodilator therapy is permitted under Global Initiative for Chronic Obstructive Lung Disease (2020) guidance.

GOLD has also adopted the use of blood eosinophil counts as a biomarker for predicting response to inhaled corticosteroids, but uses cut-offs of <100 and >300 eosinophils per microlitre (with an indeterminate zone in the middle) to determine those least and most likely to benefit from inhaled corticosteroids. The different thresholds in use introduce the potential for confusion.

Research needs and unanswered questions

As with all guidelines, compliance should be assessed through audit. It will be interesting to see whether these shorter, more targeted recommendations engender better compliance than the far longer, more complex GOLD guidelines, which are poorly adhered to (Price et al, 2014).

Treatments that were outside of the scope of the guidelines have already been mentioned. How to manage patients on legacy treatments, such as single bronchodilator therapy or a combination inhaled corticosteroid/LABA inhaler, is also missing from the recommendations.

The guidelines' authors themselves comment that the evidence base is largely derived from clinical trials that exclude a number of patient groups. For example those over 80 years old, those with multiple comorbidities including asthma, current smokers, and those with no history of exacerbations (at least in the last year) are under-represented at best. Evidence on the relatively efficacy of the various treatments in these groups could lead to more tailored approaches.

Further research on phenotyping would also advance the trend towards personalised medicine. This should include prospectively assessing the value of eosinophils in guiding inhaled corticosteroid treatment, as well as further interrogation of frequent exacerbators. Better management of the latter is a pressing need given the burden they place on healthcare resources (Dhamane et al, 2015).

Conclusions

These new succinct guidelines provide welcome direction for six common clinical scenarios. However, they are far from comprehensive, with several more advanced therapies not reviewed. This is particularly relevant for cases at the more severe end of the spectrum that form an increasing part of the patient load in secondary centres. Future research should seek to enrol patient groups neglected by trials (eg the elderly) and develop means for better phenotyping patients.

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Key points

- New American Thoracic Society guidelines on the pharmacological management of chronic obstructive pulmonary disease provide targeted recommendations addressing six common clinical scenarios.
- These include a strong recommendation for dual over single bronchodilator therapy.
- Triple therapy, including inhaled corticosteroids, is advised for those who exacerbate despite dual bronchodilator therapy, particularly if they have a raised blood eosinophil count.
- Opiates should be considered, in discussion with patients, for those with refractory breathlessness.
- For the various scenarios not covered by these succinct American Thoracic Society guidelines, particularly affecting patients with advanced chronic obstructive pulmonary disease already on optimal therapy, more comprehensive guidelines should be sought (such as those published by the Global Initiative for Chronic Obstructive Lung Disease).
- Research priorities include extending the evidence base to populations commonly excluded from clinical trials, such as the elderly and comorbid, and further delineation of clinically-relevant phenotypes.

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