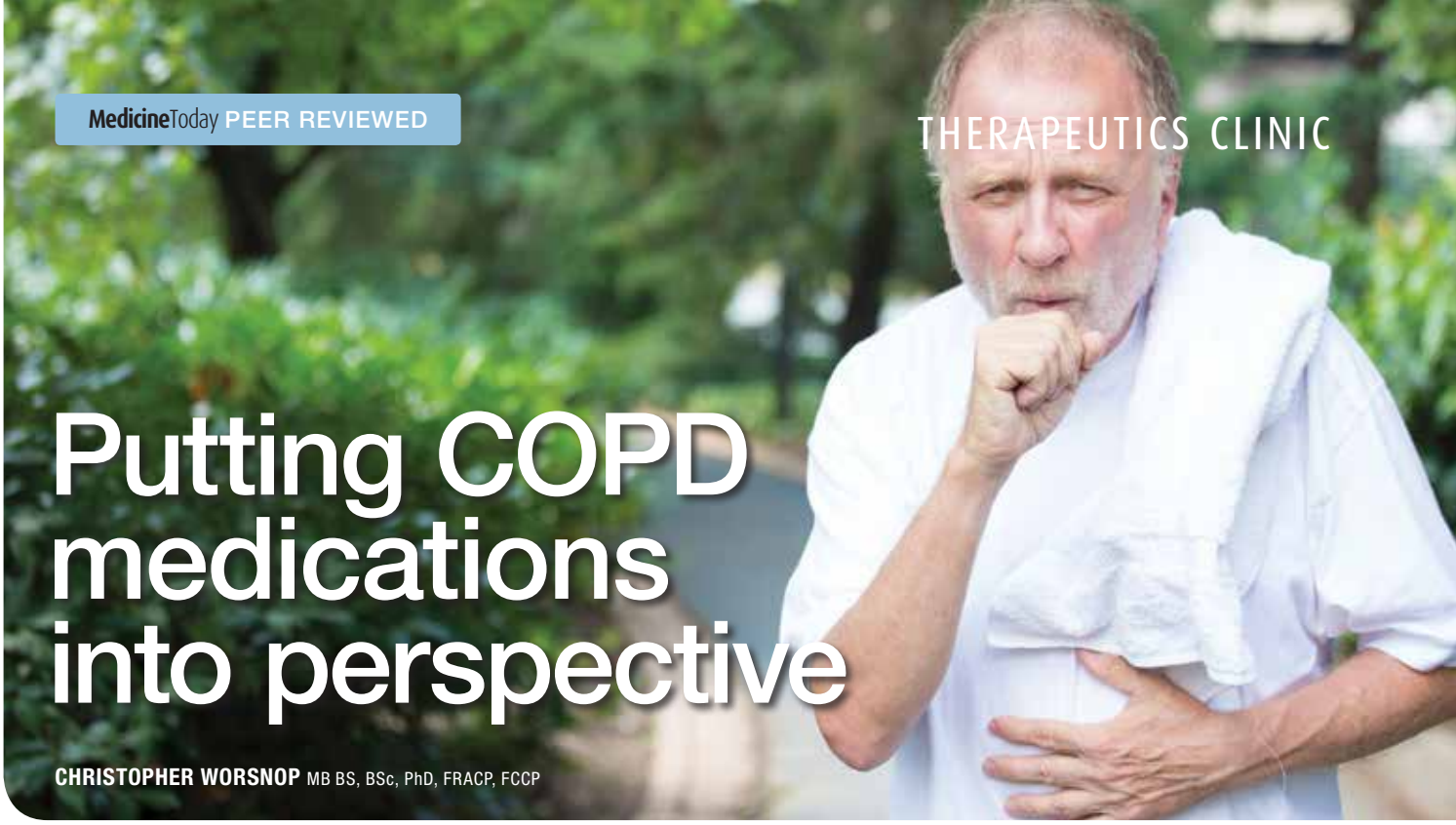

Putting COPD medications into perspective

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Over the past few years, new drugs have been added to the bronchodilators and inhaled corticosteroids used for treating COPD. There is no strong evidence to say that one drug within a class is better than another and the decision about which drugs to use is mainly about patient preference, although multiple drugs from the same class should not be used in the same patient.

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There are four main components in the long-term management of patients with chronic obstructive pulmonary disease (COPD): smoking cessation, regular exercise with or without pulmonary rehabilitation, medications, and influenza and pneumococcal vaccinations. This article focuses on medications, but this does not imply that they are more important than the other components. In fact, smoking cessation is the most important aspect of COPD management as it is the only treatment that has been convincingly shown to slow the progressive decline in lung function in those who continue to smoke. Indeed, when patients participate in a full pulmonary rehabilitation program the benefits are at least as great as with use of the full range of medications.

Each of the four components should be applied simultaneously. COPD medications have benefits in both past and current smokers, and also have added benefits when combined with regular exercise. This article addresses the long-term management of patients with COPD; it does not cover the management of acute exacerbations.

INHALED VERSUS ORAL MEDICATIONS

The vast majority of people being treated for COPD will be using inhaled medications. Doses of these drugs given by the inhaled route can be much smaller than if they were given systemically. Many of these drugs have little systemic absorption from the lungs and little or no absorption from the gastrointestinal tract, and there is a high level of systemic degradation when some of the dose is swallowed or if the drug is mistakenly taken orally. These factors lead to a very good benefit to side effect ratio, with many of the drugs having little in the way of systemic effects.

The use of oral medications such as long-term prednisolone, theophylline and long-term antibiotics is not part of the routine

1. TREATING COPD WITH MEDICATIONS*

- *Start with*
  - LAMA or LABA:
    tiotropium or glycopyrronium or aclidinium or umeclidinium (LAMAs) or indacaterol (LABA)
- *Progress to*
  - LAMA and LABA:
    tiotropium or glycopyrronium or aclidinium or umeclidinium and indacaterol
    OR glycopyrronium/indacaterol combination or umeclidinium/vilanterol combination

  OR in more severe COPD with a history of exacerbations
  - LAMA and LABA and ICS:
    tiotropium or glycopyrronium or aclidinium or umeclidinium *AND* fluticasone propionate/salmeterol 500/50 µg twice daily or budesonide/eformoterol 400/12 µg twice daily or fluticasone furoate/vilanterol 100/25 µg once daily

ABBREVIATIONS: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting antimuscarinic agent.

* Medications listed in chronological order of availability on PBS (oldest first). There is little to distinguish between drugs within a class.

management of COPD. These medications will, therefore, not be discussed further here, other than to say that the lack of efficacy compared with the inhaled medications and the much greater tendency for side effects precludes their chronic use in most patients.

CLASSES OF INHALED MEDICATIONS

The inhaled medications used in patients with COPD are bronchodilators and corticosteroids. None of these can cure COPD and there is little evidence to show that they can alter the course of the disease process. The main purpose of their use therefore is to make patients feel better; that is, to reduce symptoms such as breathlessness, improve exercise capacity, improve quality of life and reduce exacerbations. This is important to remember as the medications do not have a role in patients with COPD who really are not limited in their activities, have no symptoms and no exacerbations.

The treatment of COPD with medications is outlined in Box 1 and the drug classes used are discussed below.

Inhaled bronchodilators

First-line drug treatment for patients with COPD is with inhaled bronchodilators, of which there are two classes, the anticholinergic agents and the β_2-agonists. These medications relax the bronchial smooth muscle in the airways, thereby increasing the airway diameter. As the resistance of the airways is inversely related to the radius to the power of four, a small increase in the radius can lead to a marked drop in airway resistance.

Breathlessness in patients with COPD is related to hyperinflation of the chest. The reduced resistance allows more air to be breathed out, which reduces hyperinflation and so reduces dyspnoea and enables greater exercise tolerance. The symptoms in COPD do not correlate with forced expiratory volume in one second (FEV_1), and changes in FEV_1 do not predict improvement in symptoms or even health-related quality of life with the use of long-term bronchodilators. Thus, even though spirometry is essential in diagnosing COPD, it has less of a role in predicting response to treatment or in monitoring response to bronchodilators in COPD than in asthma.

Smooth muscle contraction is only one component of the airway narrowing in patients with COPD as there are also inflammatory and structural changes in the airways. Thus bronchodilators may have limited or no benefit. As it is not possible to predict which patients with COPD will benefit, a trial of treatment is needed to see if the symptoms improve.

It is common for patients with COPD to have low levels of activity to avoid the uncomfortable feeling of dyspnoea. Therefore, when a patient is prescribed a bronchodilator, they need to be encouraged to try to be more active to feel the benefits of the medication.

As the bronchoconstriction is present most of the time, it makes sense to use long-acting bronchodilators rather than short-acting ones such as the anticholinergic ipratropium and the β_2-agonists salbutamol and terbutaline.

Anticholinergic agents

Anticholinergics block muscarinic receptors in the airway smooth muscle, causing the muscle to relax. Four long-acting antimuscarinic agents (LAMAs) are available in Australia on the PBS for COPD (Box 2). Tiotropium has been available for many years in Australia for COPD. It is used once daily with a dry powder inhaler device that needs to be loaded by the patient just before each use. The three newer LAMAs are glycopyrronium and umeclidinium, which are taken once daily, and aclidinium, which is taken twice daily.

There is no evidence to indicate if one LAMA is better than another. However, there is some controversy over whether once daily or twice daily dosing is preferable in patients with COPD because once daily is more convenient but twice daily may better deal with patients' symptoms. There are no comparative data to settle this issue so the choice should be left to discussion with the patient.

As LAMAs have minimal side effects they are dosed to produce maximal clinical benefit, so all four are only available

2. USING INHALED BRONCHODILATORS AND CORTICOSTEROIDS PBS-LISTED FOR COPD*

To avoid doubling up within a class of drug for COPD, do not use more than one drug/drug combination from each column at a time

LAMAs†
- Tiotropium
- Glycopyrronium
- Aclidinium
- Umeclidinium
- Glycopyrronium/indacaterol
- Umeclidinium/vilanterol

LABAs†
- Indacaterol
- Glycopyrronium/indacaterol
- Umeclidinium/vilanterol
- Fluticasone propionate/salmeterol 500/50 µg
- Budesonide/eformoterol 400/12 µg
- Fluticasone furoate/vilanterol 100/25 µg

ICS
- Fluticasone propionate/salmeterol 500/50 µg
- Budesonide/eformoterol 400/12 µg
- Fluticasone furoate/vilanterol 100/25 µg

ABBREVIATIONS:
COPD = chronic obstructive pulmonary disease;
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LAMA = long-acting antimuscarinic agent.

* Medications listed in chronological order of availability on PBS (oldest first). There is little to distinguish between drugs within a class.
† Combination products (with other classes) included. The LABA vilanterol is only available as a combination therapy for COPD; the LABAs eformoterol and salmeterol are generally not used as monotherapies for COPD.

in one dose. (Although some patients develop a dry mouth with these drugs, LAMAs do not produce other side effects more than placebo in clinical trials.) There is no benefit in using more than one LAMA at a time, including during exacerbations. There are no data on changing the patient's LAMA to the short-acting antimuscarinic ipratropium during an exacerbation. Some clinicians will simply keep the patient on the LAMA as long as the patient can still use the relevant inhaler. If ipratropium is used during an exacerbation then the LAMA should be stopped because there is no evidence that using more than one antimuscarinic drug at a time adds any benefit and there is the potential to increase the risk of side effects when more than one is used at the same time.

Beta$_2$ agonists

Beta$_2$ agonists bind to and stimulate β_2-receptors causing airway muscle relaxation. Indacaterol is the only long-acting β_2-agonist (LABA) available as monotherapy on the PBS for COPD in Australia (Box 2). It is given once per day, and is available in two doses, 150 µg and 300 µg; the 150 µg dose will be used in most patients, but patients with more severe disease may be prescribed the 300 µg dose. A few people cough a couple of times after inhaling indacaterol, but as its systemic absorption is very low, side effects such as tremor and tachycardia are no greater than with placebo.

As β_2-agonists used without inhaled corticosteroids (ICS) in asthma have been shown to make asthma worse and even increase mortality, there is a concern about the patient with COPD who also has asthma. Indacaterol should not be used in patients with both COPD and asthma without an ICS being used as well.

Vilanterol, another once-daily LABA, is only available as combination therapies (with the LAMA umeclidinium and with the ICS fluticasone furoate).

Salmeterol has an indication for COPD but is not on the PBS as monotherapy for use in patients with COPD. Eformoterol does not have an indication as a single agent for COPD in Australia. These drugs are generally not used as monotherapies for COPD.

Combined inhaled bronchodilators

There is no evidence to indicate whether a LAMA or LABA should be tried first. When LAMAs and LABAs are combined they produce increased benefits in terms of better lung function, fewer symptoms, better quality of life and increased exercise capacity, although not double the effects of each alone. Patients often use both a LAMA and a LABA because of the greater reduction in symptoms provided.

Some LAMAs and LABAs are now available packaged in the same inhaler, making the combined use more convenient, namely glycopyrronium/indacaterol and umeclidinium/vilanterol (Box 2).

Inhaled corticosteroids

ICS have been shown to reduce exacerbations in patients with COPD, particularly those with more severe COPD. However, they are not thought to control the underlying disease process as they have minimal effect on the predominantly neutrophilic inflammation present in COPD. They therefore should not be regarded as a drug of first choice in patients with COPD or be used routinely in such patients. ICS are less effective in current smokers.

In Australia, the ICS inhalers that contain only ICS (i.e. those for fluticasone proprionate, budesonide and ciclesonide) do not have an indication for COPD. However, if asthma is also present then their use should be considered. Inhalers containing several

ICS/LABA combinations are indicated for use in patients with COPD, as discussed below.

Combined inhaled bronchodilators and corticosteroids

Clinical trials have shown that ICS have greater benefits in patients with COPD when combined with a LABA. The ICS/LABA combinations that have been used in Australia for many years for patients with COPD are fluticasone propionate/salmeterol 500/50 µg twice daily and budesonide/eformoterol 400/12 µg twice daily (Box 2). These corticosteroid doses are large and may produce side effects in some patients (e.g. oral thrush, dysphonia and skin bruising). Thus the potential benefits should be balanced against the occurrence of side effects.

There is now a new ICS/LABA combination, fluticasone furoate/vilanterol. This has been developed for both asthma and COPD. Its COPD indication is for those patients with severe COPD (i.e. those having a FEV_1 less than 50% predicted) and who are experiencing exacerbations. The combination is taken just once daily and comes in two strengths: only the 100/25 µg dose is indicated for COPD, and there is no advantage in using the higher dose (200/25 µg, which is only indicated for asthma) in patients with COPD.

It is now well accepted that there is an increased risk of pneumonia in patients with COPD on ICS, especially with the high dose formulations approved for use in COPD in Australia. The benefits of ICS outweigh this risk when ICS are used in patients who have experienced multiple exacerbations, but it is important to educate patients about seeking prompt medical attention when they develop a chest infection.

THE INHALERS FOR COPD

As the new inhaled medications have been developed for patients with COPD, new inhaler devices have also been developed for their use.

There is now an increasing range of dry powder devices specifically designed for use by patients with COPD. With the correct use of these devices, the drugs should be deliverable to the airways of even those patients with severe COPD (a FEV_1 less than 50% predicted). Some devices require a capsule to be loaded each time they are used, and some are preloaded. Clinicians should be familiar with these so that sensible decisions can be made about which device is best for each individual patient. Of course, it is imperative that patients are educated about how to use the devices correctly and have their techniques reviewed regularly.

When metered dose inhalers (MDI) are used, it is preferable that spacers are also used.

CONCLUSION

The management of patients with COPD is not simply prescribing drugs. Providing advice about smoking cessation, regular exercise, and influenza and pneumococcal vaccinations are at least as important.

The first-line medications are inhaled bronchodilators, either a LAMA or a LABA. A LAMA and a LABA may be used together if further clinical effect is needed. An ICS may be added in patients with severe COPD who are experiencing exacerbations or in those with coexisting asthma. Over the past few years, new drugs have been added to these three classes. There is no strong evidence to say that one drug within a class is better than another. It is important though to be aware of the class to which each of the drugs belongs so that multiple drugs from the same class are not used in the same patient. The decision about which drugs to use is mainly about which inhaler device is preferred by the patient, and whether once-daily or twice-daily dosing is preferred. MT

FURTHER READING

Abramson M, Frith P, Yang I, et al. COPD-X: concise guide for primary care. Brisbane: Lung Foundation Australia; 2014. Available online at: http://lungfoundation.com.au/wp-content/uploads/2014/11/LFA-COPD-X-V3.01.pdf (accessed February 2015).

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD 2015. GOLD; 2015. Available online at: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015.pdf (accessed February 2015).

COMPETING INTERESTS: Dr Worsnop has presented talks on COPD drugs for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Menarini and Novartis.

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