Australian Prescriber
VOLUME 40 : NUMBER 1 : FEBRUARY 2017

ARTICLE

Drugs for chronic obstructive pulmonary disease

SUMMARY

Chronic obstructive pulmonary disease is a complex disease, with both pulmonary and systemic manifestations. There is an increased risk of serious comorbidity and mortality.

Although chronic obstructive pulmonary disease is most often progressive, both pharmacological and non-pharmacological interventions significantly ameliorate the severity and impact of symptoms, and reduce the frequency of exacerbations.

Stopping smoking and pulmonary rehabilitation are key interventions.

Mild symptoms are managed with short-acting inhaled bronchodilators. One or two long-acting bronchodilators are added if symptoms persist. The role of inhaled corticosteroids is being questioned as they may not benefit all patients.

Optimal therapy includes reviewing patients' inhaler use, and ensuring they have a self-management plan that enables them to promptly start treatment of infection and exacerbations. In future, treatment is likely to combine a multidimensional management approach with tailored treatment and clinical phenotyping.

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Keywords
antimuscarinics, beta agonists, COPD (chronic obstructive pulmonary disease), corticosteroids

Aust Prescr 2017;40:15–9
http://dx.doi.org/10.18773/austprescr.2017.003

Introduction

The optimal management of chronic obstructive pulmonary disease (COPD) requires a multifaceted approach which incorporates non-drug as well as drug-management strategies. It is a complex disease, with both pulmonary and systemic manifestations, and an increased risk of serious comorbidity and mortality. For most patients, it has a major impact on lifestyle and quality of life. Although it has not been studied systematically, early treatment is likely to help sustain lung function.

Assessment

There is a wide variability in symptom severity and this correlates relatively poorly with lung function as measured by the forced expiratory volume in one second (FEV_1). Generally symptoms worsen over time.[1,2] Patients' symptoms should be assessed in their own right to guide management, rather than relying on the FEV_1 which is an insensitive measure of disease impact.[3] A multidimensional approach to assessment has been advocated by guidelines in recent years. This gives objective targets for assessing symptoms and their response to treatment. The Australian COPD-X guidelines[4] recommend a thorough assessment of the patient for the impact of day-to-day symptoms such as breathlessness, cough and sputum, the frequency of exacerbations and their prevention, and the presence of comorbidities.

Patients with COPD often have comorbid conditions beyond those that can be explained by the common pathway of cigarette smoking, including cardiovascular disease, osteoporosis, diabetes, anxiety and depression. They also have comorbidities related to their lung disease such as lower respiratory tract infections. These problems greatly increase the risk of hospitalisation and worsen the quality of life for patients. Hence the identification and management of comorbidities is a crucial aspect of treatment. It is important for these patients to have pneumococcal and influenza immunisation, but reductions in exacerbation rates have only been shown for influenza. In a Cochrane review, influenza vaccination in patients with COPD significantly reduced total exacerbations per vaccinated person compared to those who received placebo.[5]

It is frequently said that patients do not become symptomatic until they have lost approximately 50% of their lung function, but recent evidence from the UK shows that patients present on many occasions to primary care in the 10 years before a formal diagnosis. They often present with episodes of lower respiratory tract infection and persisting productive cough after viral infection.[6] These episodes in smokers and ex-smokers should be regarded as red flags, alerting clinicians to the possibility of COPD.[7]

The diagnosis is confirmed by finding an FEV_1 under 80% of the predicted value and an FEV_1/FVC (forced vital capacity) ratio less than 0.7, in a patient with

a consistent history of smoking or dust and fume exposure. An objective assessment of symptoms based on functional impact should be made, ideally using a validated symptom score such as Medical Research Council (MRC) or COPD assessment test (CAT).[8]

Non-drug therapy

Non-drug interventions are as important as pharmacotherapy in maximising quality of life and minimising the impact of symptoms, risk of exacerbations, and loss of functional capacity.[9] The most important intervention is smoking cessation as it improves the quality of life, reduces the risk of declining lung function and reduces mortality.[10-12]

Pulmonary rehabilitation is a crucial intervention to maximise exercise capacity and quality of life. Although frequently incorporating education, symptom control and self-management strategies, the vital component of pulmonary rehabilitation is a structured exercise program. This is usually implemented by regular participation for eight weeks, under the supervision of a physiotherapist skilled in this area. It is associated with reduced hospital admissions and exacerbations, particularly when it is part of an integrated care approach.[13] Patients with COPD of all severities are suitable for pulmonary rehabilitation and should be actively encouraged to participate.

Maintenance of physical activity is very important for sustaining the benefit and is probably a bigger challenge for many patients than an eight-week course of pulmonary rehabilitation alone. Patients with COPD are markedly inactive compared to age- and sex-matched peers. Nevertheless higher levels of physical activity even in moderate to severe disease are associated with substantially better outcomes in exacerbation risk, hospital admissions and mortality.[14,15]

Drug therapy

Apart from oxygen, no drug has been shown to reduce the increased risk of death in patients with COPD. For this reason drugs are prescribed predominantly to reduce symptoms, improve functional capacity, and prevent and treat exacerbations. Drugs are prescribed in a stepwise fashion.[16] Mild symptoms can be managed with an inhaled short-acting beta agonist (SABA), taken when needed either before exercise or for the relief of exertional breathlessness.[17] Patients who need inhalations several times a week are likely to benefit from adding a long-acting muscarinic antagonist (LAMA) or a long-acting beta agonist (LABA).[18,19]

The choice of second-line drug depends on the patient's response and preference.[18,20,21] While there are few clinically important differences between the LAMAs,[22] there are differences between LABAs which may be more obvious to patients, and are important in affecting their choice.[23] Most importantly, formoterol, indacaterol and vilanterol have a relatively fast onset of action, of 5–10 minutes, while salmeterol has a 30-minute onset. These differences may not be important once patients are taking long-acting bronchodilators regularly. Like salmeterol, formoterol and indacaterol, the newly available LABAs vilanterol and olodaterol have statistically and clinically significant effects on lung function, exercise tolerance, SABA use, dyspnoea, quality of life and exacerbations.[24] LABAs are well tolerated and there are negligible differences between them in relation to adverse effects.[25] Tremor and tachycardia appear to occur less commonly with LABAs than SABAs.

LAMAs include tiotropium, umeclidium, glycopyrronium and aclidinium. There are only small differences between them in efficacy.[26] The duration of action of aclidinium is shorter and therefore it is the only LAMA prescribed in a twice-daily regimen.[27] These drugs have adverse effects which include urinary retention in patients with prostatic enlargement, worsening of glaucoma and atrial arrhythmias. While these effects had a very low prevalence in clinical trials,[28] most studies have excluded patients at risk,[19,27] so it is difficult to know the true prevalence of these adverse effects in the general population of patients with COPD. In a large safety study of tiotropium with cardiac end points, there was no increased mortality or major adverse cardiac effects with tiotropium 5 microgram or 2.5 microgram inhaled daily for a median of one year.[29]

Combination therapy

Guidelines have recommended the addition of inhaled corticosteroids to long-acting bronchodilators when the FEV_1 is less than 50% predicted and the patient has had more than one exacerbation in the previous 12 months.[4,17] In the stepwise management of stable COPD, combination inhaled corticosteroids/LABA therapy is recommended for this group of patients.[16] Many patients will already have been taking a LAMA, so they will be stepping up from a single long-acting bronchodilator to 'triple therapy'. The availability of dual bronchodilators, LABA and a LAMA combined in a single device, has changed this paradigm.

Although there is debate regarding the clinical value of LAMA plus LABA together, compared to either alone, in randomised controlled trials, the combination is generally superior to either drug alone.[18,30-32] Most recently dual bronchodilators have been shown not only to improve lung function, exercise capacity, dyspnoea and reduce the use of short-acting bronchodilators, compared to either LABA or LAMA alone, but also to reduce COPD exacerbations.[33,34]

Since exacerbation reduction is the most important effect of inhaled corticosteroids, the question has arisen whether the addition of inhaled corticosteroids is still the most appropriate step for all patients who have frequent exacerbations. Several studies have tested this using different designs – either withdrawal of inhaled corticosteroids or a comparison of LAMA plus LABA with inhaled corticosteroids plus LABA.[35,36] In one study in which patients took placebo or inhaled corticosteroid during a progressive drop in the dose of inhaled corticosteroids over 12 weeks, the corticosteroid withdrawal was not associated with an increased risk of exacerbations.[35] Patients on placebo lost slightly more lung function than those who received inhaled corticosteroids, but subsequent analysis suggests that this effect plateaus and lung function is not lost at a faster rate in the long term. More studies are required to verify this.

Another problem is the adverse effects of corticosteroids. There is a substantial database and evidence from randomised controlled trials that high-dose inhaled corticosteroids (>500 microgram/day fluticasone propionate or equivalent) are associated with an increased risk of pneumonia in patients with COPD.[37-39]

Effect of eosinophilia

Adding to the controversy regarding the role of inhaled corticosteroids are recent studies suggesting that they are more effective in patients with peripheral blood eosinophilia.[40-42] Although the threshold for this effect has not been verified, a count greater than 300–400/microlitre or 3–4% is the likely cut point. Although systematic reviews suggest that inhaled corticosteroids reduce the risk of exacerbation in COPD by around 25% across all study participants,[43,44] there is significant heterogeneity of effect.[45] Compared to LABA alone, the greatest benefit of inhaled corticosteroids was seen when the peripheral count was more than 400/microlitre.[42] The evidence is therefore accumulating that inhaled corticosteroids are most effective in a particular subgroup of patients and do not confer benefit in others.[46,47] In view of the adverse effects of corticosteroids, it is likely in the future that they will not be prescribed for all patients with COPD and frequent exacerbations.

Patients without eosinophilia may not benefit from inhaled corticosteroids but will still be at risk of adverse effects.[48,49] Further randomised controlled trials are required to verify that corticosteroids should not be prescribed to these patients.

Future developments

Classification of COPD either by the presence or absence of eosinophilia, exacerbation phenotype (infrequent or frequent) or clinical presentation (chronic bronchitis or mucus hypersecretion vs emphysema vs asthma COPD overlap) is now beginning to guide treatment decisions and clinical trials.[50-52] The results of these trials should be of great value in tailoring COPD management, as much of the evidence suggesting that phenotypic classification is helpful comes from retrospective studies. The most convincing data for treating the chronic bronchitis phenotype come from studies of roflumilast (not currently available in Australia), a phosphodiesterase-4 inhibitor which has significant benefit in reducing COPD exacerbations in patients with COPD and mucus hypersecretion.[53] Finally, careful attention to comorbidities, especially co-existing cardiovascular and metabolic disease, is likely to reduce hospital admissions and complications of exacerbations. Future trials are awaited, particularly of cardioselective beta blockers in COPD, as retrospective analyses suggest they are safe but their efficacy in COPD has not yet been tested in randomised controlled trials.

Drug delivery

The marketing of new inhaled drugs for COPD has brought with it a plethora of new devices.[16] It is essential that clinicians familiarise themselves with these and tailor the drug and the device to the patient. Simplifying the regimen is of no value if the new device is not appropriately used. Every new treatment should be considered in the light of the device in which it is delivered and its suitability for each patient. The number of devices per patient should be minimised to help maintain adherence and good inhaler technique. Device use must be demonstrated carefully, and reviewed regularly.

Conclusion

The impression of COPD as a disease with a bleak outlook and minimal benefit from treatments, is no longer appropriate. Major advances in drug therapy and a recognition of the importance of non-drug interventions have dramatically improved the patients' quality of life, symptom severity and exacerbation frequency. Approaching patients with an understanding of the multiple impacts of the disease, assessing and managing comorbidities, and tailoring treatment while assisting them in optimal use of their inhalers is likely to deliver sustained benefits in well-being and disease control. ≺

Christine Jenkins contributes to many educational programs and symposia for government, non-government organisations and the pharmaceutical industry. She is a member of national and international advisory boards and steering committees for AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim and Novartis.

Q:

SELF-TEST QUESTIONS

True or false?

1. High doses of inhaled corticosteroids increase the risk of pneumonia in patients with chronic obstructive pulmonary disease.
2. If a patient with chronic obstructive pulmonary disease needs to use a short-acting bronchodilator several times a week, an inhaled corticosteroid should be added to their treatment.

Answers on page 41

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