Current Drug Treatment, Chronic and Acute

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KEYWORDS

• Bronchodilators • Inhaled corticosteroids • COPD and exacerbations

KEY POINTS

- Increasing the dose or number of bronchodilators together with a short course of oral corticosteroids reduces the severity of chronic obstructive pulmonary disease (COPD) exacerbation.
- Supplementary methylxanthine treatment adds nothing to exacerbation management except risk for patients.
- Long-acting antimuscarinics should be given once daily as a first-line treatment of COPD, although new once daily long-acting beta-agonists may prove equally effective.
- Adding inhaled corticosteroids to a long-acting beta-agonist prevents exacerbations in severe disease and seems to be effective in some once daily combination treatments.
- Pneumonia is seen with all treatments containing fluticasone-related drugs, but appears to be less evident with budesonide. Once-daily tiotropium seems safe when given as a dry power, but there are concerns about its use when inhaled from a soft mist system.

INTRODUCTION

The appropriate management of chronic obstructive pulmonary disease (COPD) involves more than taking prescription medicines. The key components have been set out in detail in many treatment guidelines, both national and international.[1–3] They include the avoidance of identified risk factors, especially tobacco smoking, and the optimization of daily physical activity, topics covered elsewhere in this volume.

For a few patients with severe disease, noninvasive ventilation can be a lifesaving treatment in the acute episode,[4] although not all patients benefit.[5] There is a role for long-term domiciliary oxygen treatment, which is widely used in the United States and can reduce mortality and even improve exercise performance.[6,7] However, the effectiveness of ambulatory oxygen has been challenged[8]; the use of oxygen to relieve breathlessness after exercise having been shown to be ineffective when compared with room air.[9] These considerations do not seem to have dented the popularity of this treatment, with patients and their physicians indicating the limits of evidence-based clinical practice. However for many patients with COPD, a key part of their care remains the drugs their doctors prescribe and in recent years both the choice of treatment and the evidence for its effectiveness has improved.

This article reviews the key components of the pharmacologic treatment of COPD, both acute and chronic, with an emphasis on those recent studies, which are likely to change practice in the next few years.

DRUG TREATMENT IN ACUTE EXACERBATIONS

Acute exacerbations of COPD drive the morbidity and cost associated with this disease and the markers of an increased risk of dying, especially after the patients have been hospitalized.[10] In patients with more severe COPD and those attending

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the emergency department, breathlessness is the dominant symptom; there are good data showing that this results from a mixture of static and dynamic hyperinflation and consequent restriction on tidal volume.[11,12] Worsening lung mechanics leads to the deterioration in ventilation-perfusion matching and an increase in dead space, producing hypoxemia with or without hyperpnoea. Hence, the management of the acute episode focuses on reversing or limiting these physiologic abnormalities. The distress and ill health of the hospitalized patient makes the conduct of randomized control trials difficult or risky and so we have almost no clinical trial data to support the use of oxygen to either reduce breathlessness or improve outcomes in COPD. We do know that oxygen-induced hypercapnia can be dangerous,[13] but for physicians to take the opposite view and not prescribe oxygen to critically ill patients would seem to be perverse.

Similar considerations apply to drug treatment, but here there is at least some direct physiologic evidence of benefit resulting from studies conducted over the last decade.

Inhaled bronchodilators are the key components of management. For good practical reasons related to the speed of onset of action and the risk of adverse effects, the inhaled route is preferred for both acute and chronic treatment, and the main drug classes are beta-agonists (BA) and antimuscarinic (MA), which are also known as anticholinergic drugs.

There is little evidence for a dose-response effect with either BA or MA in COPD, although some data for unstable disease suggest a potential benefit of high doses of ipratropium.[14] However, many physicians prescribe nebulized BA, usually salbutamol in doses of 2.5 to 5.0 mg or MA such as ipratropium 250 to 500 mcg alone, or in combination with each other, to reduce symptoms in hospitalized patients with exacerbations. Adding ipratropium to salbutamol did not change the rate of recovery of forced expiratory volume in the first second of expiration (FEV_1) in one small UK study,[15] which did not examine other markers of lung mechanics or symptoms. However, there is evidence that even at high doses of BA, adding another drug of a different class can produce physiologically important reductions in end expiratory lung volumes,[16] changes similar to those observed after combination bronchodilators in acutely ill patients with COPD.[12]

There are no good studies to indicate when this high-dose treatment should be discontinued; this decision is usually an empiric one, made by the attending physician. Patients often think high-dose nebulized drugs during an exacerbation should be continued during their chronic care; but the evidence for this is lacking and is confused by the facial cooling effects of the nebulized mist, which can decrease acute breathlessness.[17] Other considerations related to the reimbursement of nebulized drugs may also be potent reasons why these agents are considered. The most common adverse events are tachycardia and palpitations with high doses of BA while hypokalemia is not a problem in normal clinical practice. MA drugs are well tolerated, although there is a risk of inducing glaucoma if mist from a facial mask enters the eyes of susceptible patients.

Intravenous aminophylline was used as the primary treatment of hospitalized acute COPD exacerbations long before safer inhaled bronchodilators were available, and it is still often added to the treatment of patients with severe breathlessness caused by acute COPD. However, xanthenes are weak bronchodilators and only effective at near-toxic doses.[18] Data from Rice and colleagues[19] suggested that it was ineffective when used acutely. This finding was confirmed in a large randomized controlled trial that showed that aminophylline reduced arterial carbon dioxide slightly but made no difference to the rate of recover, symptoms, lung function, or to the time spent in hospital.[20] Given the toxicity of this therapy, it should not be used in hospitalized patients with COPD. A trial of the acute effects of the phosphodiesterase IV inhibitor roflumilast in acute exacerbations of COPD is currently being conducted; but until these data are available, this drug is not recommended for acute use.

Acute exacerbations are characterized by an increase in inflammation,[21] triggered by infections and/or environmental insults, which produce the acute deterioration in lung mechanics noted earlier. Two therapies have been applied to reduce inflammation and shorten the acute episode.

High-dose enteral or parenteral corticosteroids have been tested in a limited number of studies. With one exception, patients were recruited from the emergency department (ED) or had been hospitalized; in these settings, corticosteroid treatment delayed the time to relapse (including relapses occurring within 30 days of an ED visit), reduced the number of treatment failures related to the primary event, and accelerated the rate at which lung function improved (**Fig. 1**), thereby reducing the hospital stay.[22–24] Lower doses of oral prednisolone (approximately 30 mg/d) were as effective as large doses of methylprednisolone. Although the large trials gave treatment for 10 to 14 days, most of the benefit accrues in the first week; one small study has shown that 10 days of treatment is better than 3 days.[25]