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Treatments for COPD

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Summary The multicomponent nature of chronic obstructive pulmonary disease (COPD) has provided a challenging environment in which to develop successful treatments. A combination of pharmacological and non-pharmacological approaches is used to combat this problem, and an overview of these approaches and their possible future direction is given.

Bronchodilators are the mainstay of COPD treatment and can be combined with inhaled corticosteroids for greater efficacy and fewer side effects. A new generation of pharmacotherapeutic agents, most notably phosphodiesterase-4 inhibitors, which are already in the advanced stages of clinical development, and leukotriene B_4 inhibitors (in early clinical development), may shape future treatment as further insight is gained into the pathological mechanisms underlying COPD.

Non-pharmacologic treatments for COPD include long-term oxygen therapy (LTOT), nasal positive pressure ventilation (nPPV), pulmonary rehabilitation and lung-volume-reduction surgery (LVRS). Apart from smoking cessation, LTOT is the

Abbreviations: ATS, American Thoracic Society; COPD, chronic obstructive pulmonary disease; CXCR1/CXCR2, chemokine receptors 1 and 2; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; IL-8, interleukin-8; INPV, intermittent negative pressure ventilation; LABA, long-acting β_2-agonist; LTB_4, leukotriene B_4; LTOT, long-term oxygen therapy; LVRS, lung-volume-reduction surgery; NAC, *N*-acetylcysteine; NETT, National Emphysema Treatment Trial; NF-κB, nuclear factor-kappa B; nPPV, nasal positive pressure ventilation; PDE_4, phosphodiesterase-4; QoL, quality of life; SFC, salmeterol/fluticasone propionate combination; SGRQ, St. George's Respiratory Questionnaire; TNF-α, tumour necrosis factor-alpha; V'/Q', ventilation/perfusion ratio

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only treatment to date which has been shown to modify survival rates in severe cases; thus its role in COPD is well defined. The roles of nPPV and LVRS are less clear, though recent progress is reported here.

In the future, it will be important to establish the precise value of the different treatments available for COPD—evaluating both clinical and physiological endpoints and using the data to more accurately define candidate patients accordingly. The challenge will be to develop this base of knowledge in order to shape future research and allow clinicians to deliver tailored COPD management programmes for the growing number of patients afflicted with this disease.
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Introduction

Chronic obstructive pulmonary disease (COPD) is a multicomponent disease with inflammation at its core, in which patients experience progressively worsening lung function, disease symptoms and quality of life (QoL), as well as increasing exacerbations.[1] The therapeutic difficulty presented by COPD arises from the need to target all components of the disease. To this end, a clinician's paradigm for COPD management has been introduced—Global Initiative for Chronic Obstructive Lung Disease 2003 (GOLD 2003).[1,2] Current management options can be divided into pharmacologic and non-pharmacologic categories. Pharmacologic treatments include bronchodilators, inhaled corticosteroids (ICS), combination therapies and long-term oxygen therapy (LTOT). Non-pharmacologic interventions include smoking cessation, optimising nutrition, pulmonary rehabilitation, mechanical ventilation and lung-volume-reduction surgery (LVRS). Novel medications such as selective phosphodiesterase-4 (PDE_4) inhibitors are already in the advanced stages of clinical development; leukotriene B_4 (LTB_4) inhibitors also show potential for shaping future therapy, although they are only in the early stages of clinical development. Apart from smoking cessation, LTOT is the only treatment to date that has been shown to modify survival rates in severe COPD; thus it has a clear role to play in patients with COPD and chronic respiratory failure. The aim of this article is to provide an overview of the current and future treatment options available in COPD management.

Pharmacotherapeutic agents in COPD

Bronchodilators

Optimising treatment response

Bronchodilators are central to the symptomatic management of COPD and come in several forms—short-acting bronchodilators, including the β_2-agonist salbutamol and the anticholinergic ipratropium bromide, and long-acting bronchodilators, including the β_2-agonists salmeterol and formoterol, the anticholinergic tiotropium and theophylline. A fixed-dose combination of salbutamol/ipratropium (Combivent®) is also available.

Current guidelines recommend the inhaled delivery of long-acting bronchodilators as the preferred method of therapy. Several facts should be considered when choosing a bronchodilator for treatment of COPD. First, the lack of acute response to one class of bronchodilator does not necessarily imply non-responsiveness to another. Donohue[3] reported that 73% of 813 COPD patients increased their forced expiratory volume in 1 s (FEV_1) by $>12\%$ or 200 mL following long-term salmeterol treatment. However, 11% of patients showed a similar increase in FEV_1 following acute administration of ipratropium, 27% following salbutamol and 35% with both drugs combined. A second consideration is that a patient's FEV_1 response to acute bronchodilator therapy does not predict long-term response to bronchodilator therapy and may vary from day to day. Calverley et al.[4] performed acute bronchodilator testing using salbutamol, ipratropium bromide or a combination of the two on 660 COPD patients who had been classified according to both European Respiratory Society (ERS) and American Thoracic Society (ATS) spirometric criteria.[5,6] Over the 2-month study period, 55% of patients classified as irreversible under ATS criteria changed to reversible status on at least one of the visits.

In summary, the acute response to short-acting bronchodilators is of limited value in deciding future response to long-acting agents. Furthermore, while improvement in FEV_1 is important in assessing response to bronchodilator therapy, other outcome measures such as improvements in lung volumes, symptoms, exercise capacity, QoL and exacerbations may be of greater value in assessing the long-term response. The effects of commonly used bronchodilators on clinical outcomes in COPD are listed in Table 1.

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