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Modern treatment of chronic obstructive pulmonary disease

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) is a major cause of ill health and medical expenditure worldwide. Despite recent increases in the knowledge about the nature of the disease process and recognition of cytokine-mediated pathways of inflammation, current management is focussed on patient outcomes that relate to physiological measures of dysfunction.

The new Global initiative in Obstructive Lung Disease (GOLD) management guidelines are evidence-based and stress both pharmacological and nonpharmacological therapy. Effective drug therapy can help smoking cessation in motivated patients (nicotine replacement, bupropion). Bronchodilator therapy is best given by inhaler, can use either beta-agonists or anticholinergics and is more effective if long acting. Health status and exercise performance can improve without parallel changes in forced expiratory volume in one second. Inhaled corticosteroids are indicated if there is a significant bronchodilator response or the patient has more severe disease with frequent exacerbations.

Antioxidant therapy remains controversial but may reduce exacerbation number. Acute exacerbations require higher doses of bronchodilators and short courses of oral corticosteroids. New drug treatment is a major priority for chronic obstructive pulmonary disease research.
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Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and morbidity worldwide. It is a common cause of hospitalization and days lost from work, but until recently has not attracted the kind of intensive research interest devoted to other forms of obstructive lung disease, particularly bronchial asthma. This situation has changed substantially in the last decade and it is now clear that a scientific basis is present for the majority of existing treatments. In most cases these have been "borrowed" from approaches used in managing bronchial asthma [1]. The outcomes of treatment in COPD are very different and it is not appropriate to assess responsiveness in this condition by expecting changes of a similar magnitude to those seen in patients with asthma. Indeed, if they were present such patients would be considered asthmatic [2]. Nonetheless, pharmacological treatment does have an important role to play in the management of these patients. The principal goals of which are summarized in table 1.

In this article the major treatment approaches will be reviewed and the extent to which they produce improvements with individual patients will be considered. Before doing so it is worthwhile reviewing how pharmacological management is organized and what recommendations have been made to optimize COPD management.

Management guidelines in chronic obstructive pulmonary disease

Following the success in early 1990s of several national and international treatment guidelines for asthma a range of groups have developed treatment recommendations for the management of COPD. The European Respiratory Society led the way in this [3] but was subsequently followed by the American [4], British [5] and many other national bodies. All of these documents have been expert, consensus-based statements and none have tried to systematically evaluate different therapies in terms of the evidence available to support their use in COPD. In most cases an initial statement has been made but not revised and so much of the information available is now lagging behind with the rapid pace of developments in the pharmacological therapy of COPD. This has been partly addressed by the conclusion of the first stage of the Global initiative for Chronic Obstructive Lung Disease (GOLD). This programme has, as its name suggests, a global purpose and is supported by the World Health Organization (WHO) and the National Heart, Lung and Blood Institute in the USA. It has applied a standardized evidence-grading procedure to the available literature and has consulted widely to obtain the maximum amount of input to its treatment recommendations. It is likely that further revisions of

Table 1. – Therapeutic effects of bronchodilators in chronic obstructive pulmonary disease

Physiological	Clinical
Increased FEV1 and FVC	Reduce dyspnoea at rest and during exercise
Reduced resting and dynamic hyperinflation	Increase exercise capacity
Increase self-paced walking distance and $V'_{O_2,max}$	Reduce frequency of night time symptoms (LABA)
Improve respiratory muscle function secondary to better chest wall geometry (direct muscle effect with T is controversial)	Improve health status (LABA, LAIA, regular AC and T)
	Reduce the frequency of exacerbations (LABA, LAIA and possibly AC)

FEV1: forced expiratory volume in one second; FVC: forced vital capacity; $V'_{O_2,max}$: maximum oxygen consumption; LABA: long-acting inhaled beta-agonists; LAIA: long-acting inhaled anticholinergic; AC: short-acting inhaled anticholinergic; T: theophylline. When statement is not qualified it applies to all classes of drug.

the national and international societies documents will take place and preliminary discussions about the best way to achieve this and integrate this with the GOLD programme are now occurring.

All of these expert reviews agree that the management of stable COPD involves several clear steps: 1) Reduction of risk factor exposure and particularly cigarette smoking; 2) optimizing expiratory flow by the use of bronchodilator drugs; 3) Reducing pulmonary inflammation most commonly attempted using corticosteroids; and 4) preventing and managing acute exacerbations of COPD.

In addition there is strong evidence for the role of domiciliary oxygen treatment in patients with persistent hypoxaemia and of pulmonary rehabilitation as an added adjunctive therapy at all stages of the disease from the point when the patient develops exertional breathlessness. Surgical therapy has a role in more advanced disease or where there is a large localized bulla with compression of adjacent lung structures. Ventilatory support either acutely or chronically using noninvasive methodologies has been studied and the acute use of this therapy in patients with hypercapnia is now clearly justified [6]. In this review, the potential mechanisms of action of pharmacological therapy and the evidence for their effectiveness will be considered.

Smoking cessation

Tobacco smoking is the best recognized factor producing COPD, as continued exposure to tobacco is associated with an accelerated decline in lung function with time [7]. Conversely, there are now good data in early COPD that smoking cessation produces a small but statistically significant improvement in lung function and permits the forced expiratory volume in one second (FEV1) to decline at a more normal pace [8]. To date, there is much less direct information about the effects of smoking cessation in people with more established disease *i.e.* <50% predicted FEV1. There is a strong belief that this remains an appropriate measure even if there is evidence of persisting inflammation in those patients who have successfully stopped smoking. The complexity of inhaled tobacco smoke makes it a difficult agent to study mechanistically and to date, no specific pattern of cytokines has been attributed to specific components of this complex mixture of gases and particles. In the foreseeable future, it is most unlikely that a "safer" cigarette will be developed and hence pharmacological therapy has largely been devoted to increasing the successful cessation rate rather than reducing the impact of this important causative agent.

Until recently, most approaches to smoking cessation were behavioural and the success rate when measured objectively using exhaled carbon monoxide analysers has been disappointingly low. The recognition that cigarette smoking is specifically connected to nicotine addiction in the majority of cases, and that smoking withdrawal symptoms can be produced by providing nicotine, allowed the first pharmacological therapies to be developed. These comprised nicotine replacement treatments, which have been shown in a series of studies to be effective ways of increasing the sustained rate of quitting [9]. Nicotine delivery does not mimic the rapid absorption characteristic of inhaled nicotine but instead provides a background level of this drug, which diminishes some of the unpleasant effects associated with its cessation. Which preparation is used is as much determined by cultural norms as by the specifics of absorption. In North America, nicotine chewing gum has proven to be highly successful but this is less appropriate in European Societies were nicotine patches or nasal sprays are preferred.

The most important pharmacological development has been the chance observation that the antidepressant drug bupropion was associated with an unexpectedly high incidence of smoking cessation in patients who used this treatment whilst they were depressed. This has subsequently led to a successful research programme, which has demonstrated that this drugs properties as a dopamine antagonist within the central nervous system seem to reduce the degree of nicotine dependence. At the moment it has only been studied in populations of people who are motivated to quit and although several large studies have been presented as abstract, only two investigations in such motivated "patients" have been reported in detail [10]. These clearly show that this agent is at least equivalent to nicotine replacement and possibly superior in the short term. It increases the smoking cessation rate and also has an additive effect with nicotine replacement.

Although the one-year quit rate of approximately one third of patients might appear to be disappointing, it represents a substantial advance on any previous smoking cessation strategy. This drug is now licensed in North America and Europe and is likely to play an important role in patients with COPD although specific studies examining the smoking cessation behaviour in these patients have not yet been presented. A major side effect is insomnia, which can be limiting in some patients. Epilepsy was originally reported when used in populations of patients with significant depression but has not been an important finding in patients attending smoking cessation programmes. Future development of related agents is likely.

Suitability for support programmes, nicotine replacement and bupropion is dependent on the willingness of the patient to contemplate changing their smoking habit, something which a diagnosis of COPD can often promote. Additionally, patients who are less physically dependent on nicotine *i.e.* those who do not smoke until after getting out of bed in the morning are more likely to succeed in any form of smoking cessation intervention. There are some data suggesting that higher doses of nicotine replacement may be more effective in these particularly dependent individuals and an approximate assessment of the degree of dependence, based on the time to first cigarette, is a useful agent to using these therapies.

Bronchodilator therapy

Bronchodilator drugs remain the most widely used and effective way of controlling symptoms in COPD. Their major effects are summarized in table 1. They reduce breathlessness at rest and on exertion but may also reduce the intensity of cough and episodes of wheezing. These latter effects are much less prominent than in bronchial asthma. Despite claims that cholinergic tone is specifically increased in patients with COPD [11] there is no clear evidence that this is the case when allowance is made for differences in starting airway geometry. Both beta-agonists and anticholinergic therapy are effective with no clear distinction between them, at least when assessed in terms of change in FEV_1 postbronchodilator. They appear to work by abolishing resting airway smooth muscle tone as judged by the similarity of the improvements in absolute values of FEV_1 seen irrespective of the starting value. There is evidence of a dose response relationship with both categories of drugs [12, 13] but this is relatively flat. Although the drugs operate through different mechanisms the evidence for synergy between them when given at high doses is limited. Careful studies in highly selected patients can show small improvements when combination treatments are used. In general, lower doses are adopted and in these circumstances, it is easier to show an additive effect of the components of a combination [14] which is maintained over at least three months of treatment. Inhaled therapy remains the preferred route because of significantly fewer side effects and a shorter onset of action. Concerns about the lower inspiratory flow rates, which some COPD patients develop, failing to activate dry powder devices and space valves have been realized in practise. COPD patients tend to be older than asthmatics and may have more difficulty in coordinating metered dose inhalers. Specific care and attention is required to instruct the patient if you are to obtain optimum benefits. Two important developments now influence our thinking about bronchodilator therapy in COPD.

In the last ten years there has been clear evidence that the functional benefits of inhaled bronchodilator treatment are not closely related to the changes in FEV_1 they produce. Thus, patients who meet conventional criteria for having a bronchodilator response fair no better than those who are "unresponsive" when assessed in terms of self paced walking distance, resting or end exercise breathlessness. Improvements occur after inhaling an active drug compared to a placebo irrespective of the spirometric change [15, 16]. There is now clear evidence that the improvements in breathlessness produced by any class of inhaled bronchodilators are due to a reduced tendency to develop dynamic hyperinflation during exercise [17, 18]. It is likely, but not certain that similar processes explain the reduced work of breathing previously reported in patients receiving oral theophyllines [19]. Predicting the magnitude of these changes is difficult from resting measurements and surprisingly little is known about the individual reproducibility of this form of response. The best clinical strategy is to enquire whether the patient experiences subjective benefits, as this is likely to be a better reflector of the true respiratory physiology than simply measuring forced expiratory flows.

Until recently, inhaled bronchodilators had a relatively short duration of action with ipratropium being somewhat longer than the beta-agonists, a finding which suggested that three times daily use was adequate. This has been based more on statistical rather than clinical considerations and it seems likely that most short-acting beta-agonists have their optimum effect in the 4 h after administration, with their effects measurable from around 30 min onwards. Oral agents such as the theophylline compounds clearly can be dosed over longer periods, particularly with the availability of slow release preparations. However, the unpleasant side effects, particularly those associated with phosphodiesterase (PDE) III inhibition such as the ventricular arrythmias have now made this therapy a third line option. Long-acting inhaled beta-2 agonists have now been shown to be effective in terms of increasing FEV_1 for around 12 h after a single dose [1]. This effect is sustained over weeks of treatment and unlike previous reports of short-acting bronchodilators, is associated with a clinically significant improvement in health status [20]. These findings have been established using salmeterol but currently unpublished studies with formoterol confirm these results in a wider range of subjects. There seems to be no advantage in giving higher doses of long-acting beta agonists presumably because of tremor and sleep disturbance. Four-times daily ipratropium produced a similar improvement in health status to twice daily salmeterol in one study, but this has not

Table 2. – Treatment or chronic obstructive pulmonary disease (COPD)

Treatment of stable COPD	
Smoking cessation	Nicotine replacement±bupropion
Bronchodilator drugs	Other short-acting beta agonists or anticholinergic as needed initially. If symptoms are persistent regular therapy using drugs singly or in combination. Long-acting inhaled therapy is probably better than regular short-acting drugs. Theophylline and/or nebulized bronchodilators help some severe cases as third line treatment
Anti-inflammatory therapy	Inhaled corticosteroids in moderate dose (800 mg budesonide/100 mg fluticasone daily) is indicated if: the postbronchodilator FEV_1 increases by 200 mL and 12% baseline after a therapeutic trial; or the FEV_1 is <50% predicted and the patient has frequent exacerbations
Other	Antioxidant therapy with *N*-acetyl cysteine may reduce exacerbation frequency. Annual influenza vaccination is protective.
Treatment of exacerbations of COPD	
Increased bronchodilators	Increase the frequency of existing bronchodilator use, add another drug or give in high dose *via* a nebulizer
Anti-inflammatory	Oral corticosteroid (30 $mg \cdot day^{-1}$) for 10–14 days
Antibiotics	Prescribe broad spectrum drug if dyspnoea worse and increased amounts if green sputum present.

FEV_1: forced expiratory volume in one second.

been confirmed using a different questionnaire in a larger investigation. There is some tantalizing evidence that the time between exacerbations can be increased by using long-acting inhaled beta-agonists [21]. Although further prospective studies are required to establish this definitely.

The development of once daily therapy with tiotropium bromide represents a further advance. This is an exceptionally long-acting inhaled anticholinergic drug which produces significant improvements in pulmonary function over three months compared with placebo and ipratropium [22]. Data in abstracts suggest that this also improves health status and there are clear questions to be answered about its relationship with the long-acting inhaled beta-agonists and with a further combination therapy will be the optimum way of providing maintenance bronchodilitation. There still seems to be a role for short-acting bronchodilator treatment to help with acute symptoms and high doses are often administered by wet nebulizer to patients with severe end-stage disease. The evidence that this is more beneficial than lower doses for a spacer device is limited and almost certainly requires a more detailed physiological approach than that currently used in the literature.

Anti-inflammatory therapy

The recognition of COPD is characterized by persistent airway inflammation and that as the disease advances there are an increased number of neutrophils in the alveolar structures which makes anti-inflammatory therapy both a logical and attractive approach to managing this condition. In practice this has meant using either oral or inhaled corticosteroids, and data about other forms of intervention has not, so far, extended to man. The experimental evidence in support of corticosteroid therapy in COPD, as opposed to asthma, is conflicting. Some studies report reductions in neutrophil chemotaxis and reduced numbers in induced sputum [23, 24] while others using a variety of oral and inhaled interventions have found no effect on important sputum markers such as interleukin-8 and tumour necrosis factor-α [25]. Unpublished biopsy data suggests there may be a small reduction in the number of mast cells in airway biopsies from COPD patients treated with inhaled corticosteroids but overall the pattern of other inflammatory markers, and in particular T-lymphocytes, is unaffected.

Empirical observations initially suggested a survival benefit for patients treated with inhaled corticosteroids [26] and early reports pointed to a substantial improvement in patients managed this way compared with those treated with bronchodilators alone [27]. However, these data included large numbers of people who would in other circumstances be classified as having bronchial asthma. Data studying the change in FEV_1 over time was again initially encouraging with a significant improvement in prebronchodilator FEV_1 [28] a finding confirmed on a subsequent meta-analysis of European studies [29]. Subsequent prospective investigations have used a number of inhaled corticosteroids as this route was preferred to oral therapy due to the high incidence of side-effects and evidence for corticosteroid myopathy which may contribute to mortality [30].

Four studies are now available which have addressed the role of inhaled corticosteroids in the long-term management of COPD. Each has studied rather different groups of patients and their baseline characteristics are summarized in table 2. In all the studies the rate of decline of FEV_1 with time has been the primary end-point and the postbronchodilator FEV_1 has been chosen as the most reproducible measurement to assess this. In two of the studies patients with relatively early disease or those where it was not unduly severe were tested in the hope of preventing disease progression [31, 32]. In the remaining studies other end-points related to the symptoms of the disease could be considered. All the studies are in agreement in finding no beneficial effect of any of the inhaled steroids (budesonide, fluticasone

propionate and triamcinolone) on the rate of decline of FEV_1 with time. In two studies [32, 33] there was a small but statistically significant improvement in postbronchodilator FEV_1 evident by three months and persistent throughout the study and this varied between 60 and 100 mL. In the Lung Health Study II there was a reduction in the number of the cases complaining of new onset breathlessness and attending for additional medical attention related to their chest problems [34], a surrogate for exacerbation in this group of moderately severe COPD patients. In the Inhaled Steroids and Obstructive Lung Disease (ISOLDE) study [33] where the patients were sicker and were already attending hospital clinics inhaled corticosteroids reduced the number of exacerbations by ~25% with most of this benefit residing in patients with an FEV_1 <50% pred. This study also showed a reduction in the rate of decline in health status with time indicating that although all patients got worse, the extent of deterioration in important clinical symptoms was substantially less in those treated with inhaled corticosteroids.

In the three studies where it was reported, skin bruising occurred in ~5% of individuals treated with the active drug. There were no clinically significant differences in serum cortisol measurement and data about bone mineral density is conflicting, with the studies using budesonide finding no ill effects but the Lung Health Study using triamcinolone suggesting some deterioration in femoral neck bone density with time. Local side effects such as oral candidiasis and hoarse voice occurred with a frequency similar to that seen in bronchial asthma.

Current guidance incorporated in the GOLD report suggest that inhaled corticosteroids should be considered in patients with an FEV_1 <50% pred who have at least one exacerbation per year. Additionally, there are data suggesting that ~10% of individuals will show significant spirometric improvement after oral corticosteroids, which can be sustained with time [35]. GOLD suggests that patients who show such an improvement in post bronchodilator FEV_1 also merit inhaled corticosteroid therapy although the robustness of this particular recommendation still requires testing.

Management of acute exacerbations

COPD is characterized by periodic worsening of the symptoms sustained for more than 48 h commonly described as an exacerbation. This can occur at all stages of the disease and vary from a troublesome increase in cough and sputum production to severe breathlessness and respiratory failure. The therapy offered is dictated by the severity of the symptoms and the background severity of the COPD but falls broadly under four headings.

Treatment of the precipitating factor

Viral or bacterial infection are thought to be the most common precipitants of exacerbation and antimicrobial therapy is indicated in patients in whom there is an increase in breathlessness accompanied by an increase in sputum volume purulence [36]. The evidence in favour of treating less severe episodes is scant although new anti-viral therapies are available, they have not been fully evaluated in terms of COPD patients and in particular whether they shorten the duration of exacerbations. This could be a potentially important intervention for the various neuraminidase inhibitors, which have now been licensed for use in North America and Europe. Preventing exacerbations is clearly important and there is indirect, but powerful evidence that regular influenza vaccination based on the prevailing strain can do this. In contrast, the benefits of immunization against the pneumococcus is much more controversial, with conflicting data from North America and Western Europe. At present, this is not routinely recommended.

Increased bronchodilator therapy

In general bronchodilator therapy has increased in intensity particularly in patients where breathlessness is prominent. Thus, patients with mild disease who become breathless can be treated by regular inhaled bronchodilators or the introduction of long-acting therapy, while those already receiving this treatment due to more severe background disease may need one or more days of nebulized bronchodilators. There is no clear advantage to initiating therapy with the beta agonist or an anticholinergic when nebulized drugs are used and it has been argued, based on FEV_1 criteria, that adding in ipratropium to salbutamol is not beneficial during the clinical course of patients who are hospitalized [37]. Despite this, it is common practice to use combination bronchodilators in the early stages of exacerbations of severe COPD and more data are needed about the appropriateness of this and the physiological benefits. Nebulizers tend to be used because they do not need patient cooperation and they provide therapy high on the dose-response relationship. Side effects such as tremor with beta-agonists are much more common, particularly in elderly patients were caution should also be used in those with a history of glaucoma when they are given anticholinergic drugs.

Anti-inflammatory therapy

Unlike the situation in chronic disease, there is now clear evidence that oral corticosteroids increase the rate of resolution of acute exacerbations of COPD and shorten hospital stay [38, 39]. This has been shown in outpatients and in two large studies of inpatients where similar effects were produced despite substantially different doses and duration′s of oral corticosteroid therapy. In general, medication with 0.6 $mg \cdot kg^{-1}$ of prednisolone (usually equivalent of 30 mg taken once daily) for 10 days appears to produce equivalent benefit to larger doses and mostly for longer periods. Whether oral corticosteroids are useful in patients with less severe symptoms is

not yet established. There is no benefit in giving this medication intravenously and it can be stopped without complications in most cases. Caution is needed in patients who have had recurrent causes of oral corticosteroids where a reducing dose may be required to prevent corticosteroid withdrawal effects.

Other medications

A wide range of other therapies have been developed for treatment in COPD, of these the most promising are the mucolytic drugs, although initial assumptions that they would improve the troublesome cough and sputum that characterizes mild-to-modern disease have not been well founded. Indeed it has been difficult to demonstrate any objective benefit in many of the studies conducted where outcomes such as lung function symptoms or health status have been examined. However, there is an increasing body of data, which has been collated by a good meta-analysis and has a selective review of the literature [40] to support the view that these agents reduce the number of exacerbations of chronic bronchitis symptoms experienced by COPD patients. Most of these data are driven by studies involving *N*-acetyl cysteine, which is more properly described as an antioxidant drug. There are attractive theoretical grounds for believing that this drug could be effective although the levels of air within the airways and alveoli appear to be very low on current oral dosing regimes. There are no data using currently available leukotriene antagonists or enzyme inhibitors to support a role in COPD although a substantial number of prescriptions with this indication are issued in North America. Antagonism of leukotriene B-4 may have a role in reducing the number of exacerbations and specific inhibitors are in clinical trial. There appears to be no role for nedocromil or related agents nor is there good evidence for benefits from current cough suppressants although these are often purchased by patients.

Intravenous aminophylline is frequently used in the management of acute COPD although there are no good clinical trials to demonstrate its benefit in patients who have received adequate doses of nebulized bronchodilators. It can accentuate the toxicity in patients who are already receiving oral therapy and should be used with caution, ideally with the availability of plasma theophylline levels. Respiratory failure can be managed by giving parental respiratory stimulants with doxapram hydrochloride being the favourite drug. Reports over 30 years ago suggest that this might improve blood gas tensions, but more recent studies have found it inferior to noninvasive positive pressure ventilation in the management of significant hypercapnic exacerbations of COPD [41].

Conclusions

There is now substantial evidence that through good clinical practice in the management of chronic obstructive pulmonary disease patients it is possible to lessen the symptoms and intervene positively for these patients. Further progress will be dependent on the ability to understand and categorize the processes which underline chronic obstructive pulmonary disease both in terms of its progression and the patients symptoms. As this knowledge accumulates more rational therapy will be possible. Until then, the steps outlined in table 2, which summarizes current treatment, remain the best validated way of using pharmacological agents in this disease

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