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Review

Recommendations based on guidelines on the management of mild to moderately severe chronic obstructive pulmonary disease: some practical applications in primary care

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A variety of clinical guidelines on the management of asthma have appeared over the last ten years.[1-6] Guidelines for the management of chronic obstructive pulmonary disease (COPD) have also been published,[6-13] but these are mainly drawn up by thoracic societies and some parts are less relevant for patients with milder forms of COPD or those treated in primary care. The aim of this paper is to provide recommendations (evidence-based where possible) to guide primary care professionals in their management of adult patients with COPD.

A Medline search has been performed over the past 10 years with the combined MESH headings 'COPD' and 'guidelines'. In total 32 published papers were found. Only guidelines for the managment of COPD which were published in English were selected. Only 10 publications met these criteria[6-16] and none of them were specifically aimed at patients treated in primary care. Based on these publications and on the consensus of the authors, the following guidelines for the management of mild to moderate COPD in primary care are suggested.

In drawing up a plan for the management of patients with COPD, there are a number of important considerations. Firstly, the treatment of the patients should be based on the underlying pathophysiology mechanisms. In this respect there are significant differences between COPD and asthma that have obvious consequences for treatment.[6] COPD is a generic term for chronic bronchitis, emphysema and a disorder of the peripheral airways, of which chronic progressive irreversible airflow obstruction is the

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Table 1: Diseases that may lead to chronic irreversible airflow obstruction

Chronic bronchitis Chronic bronchiolitis (small airways disease) Emphysema	COPD
Chronic asthma	
Bronchiectasis	
Primary ciliary dyskinesia	
Cystic fibrosis	
Pulmonary tuberculosis	
Sarcoidosis	
Obliterative bronchiolitis	

common hallmark. Asthma, on the other hand, is characterised by episodes of reversible airflow obstruction. As there are mixed forms it is sometimes difficult to make a distinction between adult asthma and COPD, especially in the early onset of the diseases which often present in primary care. In addition, chronic airflow obstruction occurs in several other diseases (Table 1), which also hampers a clear diagnosis of COPD. By the nature of their discipline, general practitioners focus mainly on the presentation of symptoms, which often do not give a clear distinction between asthma and COPD. Therefore, we have recently proposed pragmatic (partly symptom-based) primary care definitions of asthma and COPD.[17] COPD was defined as chronic cough and/or chronically increased sputum production and/or effort dyspnoea combined with chronic airflow obstruction with little or no reversibility.[17]

A treatment plan for patients with chronic airflow obstruction has to be adapted for each patient. The ideas for management formulated here are based on COPD in its narrowest sense, namely where the chronic airflow obstruction is caused by an airway component and/or emphysema mostly due to smoking. Even the group that is defined in this way is heterogeneous. Although cigarette smoking is strongly associated with its development, COPD may also incidentally occur in those who never smoke. Moreover, COPD may manifest itself in different clinical patterns. In one patient chronic cough and excessive mucus production may be prominent (chronic bronchitis), whereas in another symptoms of dyspnoea associated with the destruction of lung parenchyma (emphysema) are present. The factors determining these differences are not yet fully understood. Respiratory and skeletal muscle weakness (probably related to loss of muscle mass) might be considered as well as lung function impairment in the presence of impaired exercise tolerance.[18]

In this paper we present an agreed treatment plan for patients with stable, mild and moderately severe COPD (Table 2). Patients with a forced expiratory volume in one second (FEV_1) of more than approximately 50% of the predicted value[19] and with normal arterial blood gases at rest and on submaximal exercise are considered as patients with moderately severe COPD. In severe COPD other aspects are involved, which will not be covered in these recommendations. We suggest that patients with severe COPD or recurrent severe exacerbations should be under the management of a specialist. Given the chronic and gradually progressive nature of COPD, not only does pharmacological treatment of the condition at organ level play an important part, but treatment should also be directed at preventing and/or delaying the development of functional limitation and handicap. An extensive discussion of this non-pharmacological treatment is beyond the scope of this paper.

Table 2: Classification of the severity of COPD, based on FEV_1

Mild	FEV_1 60-80% predicted
Moderate	FEV_1 40-59% predicted
Severe	FEV_1 <40% predicted

AIMS OF TREATMENT

Treatment of COPD is generally aimed at:
- reducing symptoms and improving quality of life;
- optimising lung function;
- avoiding unnecessary use of medication;
- preventing and treating exacerbations;
- reducing the annual decline in lung function;
- secondary (and tertiary) prevention of impaired functional health.

The most important symptoms of COPD are breathlessness and coughing. Breathlessness impedes the patient in everyday life; therefore, improving lung function, in the short as well as the long-term, is of great importance. However, there is not a good correlation between the presence of dyspnoea and the severity of airflow obstruction. For diagnosis and therapy, repeated lung function measurements are indispensable. In COPD, peak expiratory flow (PEF) provides insufficient information about the diameter of the smaller airways, a much better index of the severity and progression of COPD is the FEV_1 value.[17] Treatment should be aimed at reaching a FEV_1 value that is as high as possible and therefore requires repeated assessment.

TREATMENT STRATEGY

Lifestyle changes are at the core of successful treatment in COPD. In particular, stopping smoking and avoidance of other inhaled irritants are very important. Nicotine chewing gum, skin patches or spray might be helpful. It is important to pay repeated attention to smoking cessation as prevention of infections and pharmacotherapy are probably much more efficacious following cessation. Pharmacological treatment of COPD includes:
1. dilation of the airways by using bronchodilators;
2. supressing the inflammatory component in the airways by using anti-inflammatory therapy;
3. increasing protection with antioxidants, because the balance may be disturbed due to an increased amount of free radicals in the airways.

The clinical efficacy of anti-inflammatory and antioxidant treatment is still under study. Therefore, a treatment plan for COPD is less evidence-based than for asthma. A step-wise treatment plan of mild and moderately severe COPD is summarised in Table 3.

Step 1: Preventive measures

To prevent further damage to the airways and alveoli, preventive measures should be advised first. It is of utmost importance for patients to stop smoking. Once smoking has stopped, symptoms of bronchitis in the form of coughing and sputum production will usually decrease after some time. The effect of smoking on the progressive decline in lung function is of greater

importance. Following smoking cessation, the annual rapid decline of the FEV_1 is usually reduced, sometimes to the level of non-smokers.[20] The presence of air pollution caused by substances other than smoke in the patient's immediate environment may also contribute to a deterioration of symptoms and an increased decline in the FEV_1.[21] Avoidance of such stimuli – including in the workplace – is therefore of great importance.

Recurrent exacerbations caused by viral and/or bacterial respiratory infections are a frequent problem in patients with COPD. An annual influenza vaccination is associated with a substantial reduction of severe morbidity and mortality.[22]

Step 2: Treatment with bronchodilators
Bronchodilators diminish bronchial obstruction by relaxation of airway smooth muscle. Even without a clear increase in FEV_1 dyspnoea may decrease, possibly because of a reduction of dynamic hyperinflation during exercise.

Bronchodilator medication may be divided in three types: anticholinergic drugs, $ß_2$-agonists and theophylline. Start preferably with inhaled anticholinergics or $ß_2$-agonists. Patients with mild COPD may use bronchodilators regularly, since this does not adversely influence the course of lung function,[20,23] as was previously observed in rapid progressive asthma and COPD.[24]

Anticholinergic drugs
If used, the anticholinergic drug, ipratropium bromide, has to be taken three to four times daily; oxitropium bromide may be used twice daily. A disadvantage of anticholinergic drugs is that the bronchodilator effect begins about 30 minutes after administration. To promote reliable inhalation of these drugs, it should be pointed out to the patient that these drugs differ from $ß_2$-agonists (which reach their maximum effect after five to 15 minutes). In some studies, maximally attainable bronchodilation is greater after anticholinergics than after $ß_2$-agonists;[25-27] in others, however, a similar response to the two types of bronchodilators is seen.[28,29] Where the first prescribed bronchodilator has insufficient effect, it can be changed, e.g. from ipratropium bromide to a $ß_2$-agonist or vice versa. Compared to placebo, an additional favourable effect of ipratropium bromide relates to a decrease in the frequency and severity of coughing, combined with a reduction of the amount of sputum, yet without negative effects on mucociliary clearance.[30]

$ß_2$-agonists
Inhaled $ß_2$-agonists are also effective in COPD. Short-acting $ß_2$-agonists, such as salbutamol, terbutaline sulphate and fenoterol hydrobromide, have to be used three to four times daily. Although little is known about the effect of the inhaled long-acting $ß_2$-agonists, eformoterol fumarate and salmeterol in COPD, these drugs may be useful, particularly for the treatment of morning dyspnoea. Several studies have shown beneficial effects of salmeterol on symptoms and peak expiratory flow measurements in patients with COPD.[31,32] Quality of life especially seems to improve during use of long-acting $ß_2$-agonists.[32]

If the effect of one of these medicines alone is insufficient, they can be used in combination. It may be appropriate to consider a long-acting $ß_2$-agonist twice daily in combination with ipratropium bromide (or oxitropium bromide) twice daily, or a short-acting $ß_2$-agonist with ipratropium bromide both three to four times daily, possibly in a combined preparation.[33]

Theophylline
Theophylline has a clear bronchodilator effect, although it is weaker than inhaled bronchodilators. Theophylline is effective in serum concentrations between 5 and 16 µg/ml. When theophylline is used, regular determinations of the serum concentration are necessary. Stable serum concentrations can only be achieved using sustained-release preparations; administered once or twice daily. Theophylline is considered as a third-line bronchodilator in moderately severe COPD, it is used more often in patients with severe COPD (FEV_1 < 40% predicted) and in this case very often in addition to a $ß_2$-agonists and/or ipratropium bromide. The efficacy in such patients is possibly due to other, non-bronchodilator effects of theophylline, such as a central stimulant effect on respiration and possibly an improvement in respiratory muscle function.[34]

Assessing the effect of a bronchodilator
After a patient has started using bronchodilators, it is important to assess the effect on dyspnoea, FEV_1 and exercise tolerance, at least every six months.

Step 3a: Consider an inhaled steroid trial
Many patients with COPD are treated with inhaled corticosteroids; this is controversial because of differences in the pathogenesis and pathophysiology of asthma and COPD.[35,36] A number of studies in patients with COPD have indeed shown no effect, or only a limited effect, of inhaled corticosteroids on symptoms and course of lung function.[37-40] However, these studies were either short-term,[37-39] uncontrolled,[40] or used protocols without distinction between asthma or COPD.[41] The effect of long-term treatment is currently being investigated in several studies. The following considerations may be important in prescribing a trial of treatment:

1. in COPD patients with features of asthma (such as symptoms of hyper-responsiveness), administering inhaled corticosteroids seems to be useful, given the underlying pathophysiologic process;[42]
2. if there is a rapid decline in lung function, a trial treatment with corticosteroids may be considered.[40]

When a trial of inhaled steroids is started (beclomethasone dipropionate, budesonide or fluticasone propionate), it is important they are prescribed in a sufficiently high dose, e.g. 800 µg daily. Evaluation of the effect is advised after six months on the basis of symptoms, exacerbation rate and lung function. In the meantime, inhalation technique and compliance with therapy should be assessed. Depending on the effect, inhaled steroids can either be continued or stopped. The safety of inhaled steroids is considered acceptable at these doses; a routine check of adrenal function or bone metabolism is not currently advised in adults.

Another possibility is to start with a burst of oral prednisolone in a dosage of 30-40 mg daily over at least two to four weeks. A meta-analysis demonstrated that approximately 10% of patients with stable COPD treated

with oral steroids had an increase in the FEV_1 of approximately 20% of baseline.[43] If FEV_1 improves, continuation with inhaled steroids may be considered, however, this does not automatically imply that inhaled steroids will be beneficial. It is important to evaluate the contribution of their use at each checkup.

Step 3b: Consider a trial of treatment with N-acetylcysteine (NAC) in recurrent exacerbations

In some studies it has been demonstrated that treatment with 600 mg/day of NAC in patients with COPD may lead to an improvement of symptoms such as the frequency of coughing and the amount and viscosity of the sputum.[44,45] The exacerbation rate and the number of sick days has been shown to decrease during daily use over a period of six months.[44-47] The effects of NAC do not seem to be explained by the mucolytic property of the preparation, because such effects were not found during treatment with iodinated glycerol, a mucolytic without antioxidant action.[48] These effects are probably explained by the antioxidant action of NAC. In the gastrointestinal tract cysteine is separated from NAC. Cysteine is a precursor of glutathione, a non-enzymatic antioxidant which plays an essential role in the metabolic protection against reactive oxygen species ('free radicals'). In vitro, NAC reduces the increased production of reactive oxygen species by alveolar macrophages in response to cigarette smoke.[49] Beneficial effects were also found with regard to the function of neutrophilic granulocytes, fibroblasts and epithelial cells.[50] There are indications that in patients with COPD, maintenance treatment with NAC reduces the number of bacterial colonies in the lower airways, which results in a decrease in the exacerbation rate.[51] In addition, NAC prevents oxidative inactivation of α_1-proteinase inhibitor (α_1-PI), the most important protector of the lower airways against neutrophil elastase.[52] This is important, as this inactivation of α_1-PI is thought to play an essential role in the development and progression of emphysema.[53] Recently the results of an open study showed that NAC in a dosage of 600 mg/day over a period of two years slowed the decrease in FEV_1 in patients with COPD, compared to a reference group of similar patients without NAC.[54] Both groups were treated with inhaled bronchodilators. However, the favourable effect was only significantly different in patients aged over 50. Based on the above-mentioned findings, a trial treatment with NAC may be considered in patients with recurrent exacerbations, although controlled studies with respect to the long-term effects of NAC are urgently needed. We recommend NAC (*not licensed in UK – Editor*) in a dosage of at least 600 mg/day over six months in order to assess the effect; the effect of treatment will determine whether or not to continue this medication.

Table 3: Maintenance treatment of mild and moderately severe COPD

Step 1: Preventative measures
- stop smoking,
- if possible, remove sensitisers from the environment,
- annual vaccination against influenza.

Step 2: Treat with bronchodilators
- anticholinergics or β_2-agonists,
- if effect is insufficient use other bronchodilator(s) or in combination,
- if insufficient response consider theophylline,
- if insufficient improvement consider **STEP 3A** and/or **3B.**

Step 3A: Trial treatment with inhaled corticosteroids
- assess effect and evaluate after six months.

Step 3B: Trial treatment with N-acetylcysteine in case of recurrent exacerbations
- assess effect and evaluate after six months.

Table 4: Indications for specialist referral (based on BTS Guidelines)[13]

Reason	Purpose
Suspected severe COPD.	To confirm diagnosis & optimise treatment.
Onset of cor pulmonale.	To confirm diagnosis & optimise treatment.
Assessment for O_2 therapy.	To measure blood gases.
Assessment in accordance with nebuliser guidelines.	To exclude inappropriate prescriptions.
Bullous lung disease.	To identify & assess candidates for surgery.
COPD in patient less than 40 years.	To identify α_1-antitrypsin deficiency, consider therapy & screen family.
Symptoms disproportionate to lung function deficit.	To look for other explanations.
Frequent infections.	To exclude bronchiectasis.

Checking compliance with therapy and inhalation technique before changing medication

The efficacy of all medication should be assessed repeatedly. It should be ascertained that there is optimal compliance with therapy and inhalation technique before any type of medication is changed or added.

Treatment of exacerbations

Exacerbations are mostly caused by viral and/or bacterial respiratory infections. They are accompanied by an increase in dyspnoea, a change in cough pattern and in the nature and production of the sputum. Exacerbations should be treated by intensifying the bronchodilator therapy, supplemented with a burst of oral corticosteroids if necessary. Corticosteroids are indicated for a decrease in FEV_1 by 40% or more compared to personal best, or where there is marginal lung function. With severe disorders of lung function, blood gas monitoring may be indicated. Antibiotics are only indicated in the case of bacterial respiratory infections, if treatment with bronchodilators and corticosteroids has insufficient effect (or had insufficient effect in the past).

Referral to hospital specialist

There are several reasons for a referral to a hospital specialist at different stages of the disease. In Table 4 we have summarized the most important reasons (and their purpose) based on the BTS guidelines.[13]

SUMMARY

Treatment of patients with mild and moderately severe COPD is schematically represented in Table 3.
- Preventive measures include stopping smoking, avoiding inhalation of sensitisers and annual vaccination against influenza.
- Treatment is primarily directed at reducing dyspnoea and recurrent exacerbations. Optimal lung function should be aimed for, in the short and long-term.
- Bronchodilators should be administered to reduce chronic airflow obstruction.
- In COPD the efficacy of inhaled corticosteroids has to be proven. A favourable effect on airflow obstruction can be expected in patients with an asthmatic component. A trial of treatment should evaluate the effectiveness.
- In the case of recurrent exacerbations chronic use of NAC may have a favourable effect. A trial of treatment might be considered.
- In the case of insufficient treatment effect after six months, other determining factors of respiratory symptoms (impaired diffusion capacity, respiratory or skeletal muscle weakness) have to be considered.■

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