Chapter 6

The future of COPD

The past 10 years have seen major changes in the way we look at chronic obstructive pulmonary disease and how we manage it. At present, we still have yet to find a therapy that changes the prognosis or reverses disease progression [1], with smoking cessation being the only effective intervention to achieve this.

New bronchodilators

Bronchodilators are currently the main treatment used for the relief of breathlessness in COPD, but they do not directly affect the underlying disease process even though they are effective at reducing exacerbation rates. Long-acting bronchodilators are the preferred therapy, including the anticholinergic (anti-muscarinic) tiotropium bromide and the long-acting β_2-agonists (LABAs) salmeterol and formoterol. Importantly, there is an additive effect between tiotropium and formoterol (Figure 6.1) [2]. Thus, possibilities exist for the development of fixed-combination inhalers containing both a long-acting anticholinergic and a LABA, particularly an ultra-LABA (uLABA). This emerging combination modality is now an area of fierce competition.

The long-acting muscarinic antagonist (LAMA) aclidinium bromide was approved in the United States and Europe in July 2012 [3,4]. Glycopyrronium bromide was approved in Europe in October 2012 and an application is expected to be filed in the United States in 2014. Several other LAMAs with an action of over 24 hours are now in development, including glycopyrrolate and LAS34273 (Table 6.1) [5,6]. Currently

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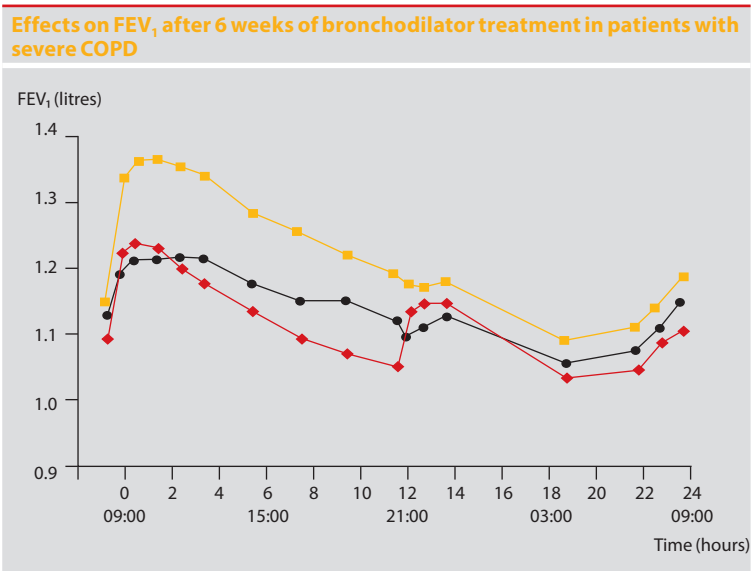

Figure 6.1 Effects on FEV_1 after 6 weeks of bronchodilator treatment in patients with severe COPD. Mean FEV_1 (adjusted for period, centre and patient within centre) before and during 24 hours after the inhalation of tiotropium once daily (●), formoterol twice daily (◆) and tiotropium plus formoterol once daily (■) at the end of the 6-week treatment period. Reproduced with permission from [2].

available LABAs need to be given twice a day, and so are not ideal for the fixed LABA/LAMA combination. Table 6.2 lists novel LABA/LAMA combinations in development [5,7]. The uLABA indacaterol was approved in Europe in 2009 and in the United States in 2011 [8,9]. Some uLABAs in development are listed in Table 6.3 [5,7,10]. Theoretically, LABA/corticosteroid combination inhalers should be more effective than LABAs or corticosteroids alone owing to increased glucocorticoid receptor translocation. This has been reflected in data from the Towards a Revolution in COPD Health (TORCH) study [11]. Primary endpoint all-cause mortality rates were 12.6% in the combination therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group and 16.0% in the fluticasone group, although the difference did not reach clinical significance. In the future, it should be feasible to put all three medications together (uLABA, LAMA and a once-daily steroid). This could further enhance any potential additive effects of these drugs.

Novel LAMAs undergoing development

Drug	Advantages	Latest developments	Company working on this strategy
Umeclidinium bromide	Long duration of action when administered via inhalation in animal models supports the potential for use as a once-daily bronchodilator for COPD. Clinical data have not been disclosed	Phase III	GlaxoSmithKline, London, UK
TD-4208	Significant improvement in lung function versus placebo; comparable to ipratropium bromide. Rapid mechanism of action. Well tolerated; most common side effects are headache and dyspnoea	Phase IIa	Theravance, South San Francisco, CA, USA
CHF 5407	An antagonist as potent and long-acting as tiotropium on human M_3 muscarinic receptors, but significantly short-acting on M_2 receptors. Duration of action is similar to that of tiotropium	Phase I/II	Chiesi Farmaceutici, Parma, Italy

Table 6.1 Novel LAMAs undergoing development. LAMAs, long-acting anti-muscarinic antagonists; ACCLAIM: AClidinium CLinical Trial Assessing Efficacy and Safety In Moderate to Severe COPD Patients. Data adapted from [5,6].

More effective smoking cessation

Smoking cessation is a vital part of COPD management. Clinicians should be prepared to intervene in cases where patients are willing to quit; supportive strategies such as the 'five As' (ask, advise, assess, assist, arrange) can be beneficial (see Table 6.4) [12]. However, current smoking cessation strategies, including behavioural approaches, hypnosis and nicotine replacement therapy (NRT), have very low success rates, although recently it has become clear that prior use of NRT before smoking cessation can improve quit rates. One of the most effective pharmacological agents available is bupropion, but in patients with COPD the annual quit rate is only 15%. This indicates that more effective smoking cessation therapies are needed in the future. Several new classes of non-nicotinic drugs for smoking cessation are now in development (see Table 6.5). Varenicline, a partial nicotine agonist which targets the $\alpha_4\beta_2$-nicotinic acetylcholine receptor, was licensed in 2006. Despite carrying a black-box

Novel combinations of LABAs and LAMAs undergoing development

Drug(s)	Advantages	Latest developments	Company working on this strategy
Vilaterol/ umeclidinium bromide	Statistically significant improvements in lung function vs. placebo, vilaterol alone, and tiotropium. Few serious side effects	Phase III	GlaxoSmithKline, London, UK/ Theravance, South San Francisco, CA, USA
Indacaterol/ glycopyrronium bromide (QVA-149)	Superior effect on lung outcome and functions	Phase III	Novartis, Basel, Switzerland
Aclidinium/ formoterol (LAS40464)	No data presented yet. It should be established whether formoterol can be administered on a once-daily basis	Phase III	Almirall Prodesfarma, Barcelona, Spain
Olodaterol/ tiotropium	Significant improvements in lung function over 24 hours versus olodaterol alone. Safe and well tolerated. Current Phase III program (TOviTO) underway	Phase II/III	Boehringer Ingelheim, Ingelheim, Germany
Glycopyrrolate/ formoterol (PT003)	Significant improvement in peak expiratory flow rates compared with its individual components and tiotropium. Reduced albuterol usage. Safe and well tolerated.	Phase IIb	Pearl Therapeutics, Redwood City, CA, USA
GSK-961081	It is both a muscarinic antagonist and a β_2-adrenoceptor agonist. It is at least equivalent to 50 µg salmeterol b.i.d. plus 18 µg tiotropium q.d.	Phase II	GlaxoSmithKline, London, UK/Theravance, South San Francisco, CA, USA
Carmoterol/ tiotropium	No data presented yet	Phase I/II	Chiesi Farmaceutici, Parma, Italy
Formoterol/ dexpirronium	No data presented yet. It should be established whether formoterol can be administered on a once-daily basis	Phase I	Meda Pharmaceuticals, Solna, Sweden

Table 6.2 Novel combinations of LABAs and LAMAs undergoing development. LABAs, long-acting β_2-agonists; LAMA, long-acting anti-muscarinic antagonists. Data adapted from [5,7].

drug warning when the long-term results of two licensing studies were pooled (Table 6.6), varenicline more than doubled the odds of stopping smoking compared with placebo (odds ratio [OR] 2.82; 95% confidence interval [CI] 2.06–3.86) and was significantly better than bupropion (OR 1.56; 95% CI 1.19–2.06) [13,14].

Another approach that may have longer term benefits is the development of a vaccine against nicotine, which stimulates the production of antibodies that bind nicotine so that it cannot enter the brain. However,

uLABAs undergoing development

Drug	Advantages	Latest developments	Company working on this strategy
Carmoterol	Binds very firmly to the β_2-adrenoceptor. Highly potent and selective. Displays fast onset and long duration of activity in both asthma and COPD at very low dosage (2–4 μg)	Launch aimed for late 2013	Chiesi Farmaceutici, Parma, Italy
Vilanterol	Potent, selective β_2-adrenoceptor agonist. Displays a long duration of activity in both asthma and COPD. Safe and well tolerated, with the most frequently reported adverse event being headache.	No plans for single launch — will concentrate on combinations	GlaxoSmithKline, London, UK/Theravance, San Francisco, CA, USA
Olodaterol	Potent β_2-adrenoceptor agonist. Seems to be equivalent to formoterol for speed of onset and efficacy, but with a longer duration of action. Displays a long duration of activity(24-h) in both asthma and COPD	Phase II/III	Boehringer Ingelheim, Ingelheim, Germany
Abediterol	24-h duration of activity in asthma	No plans for single launch — will concentrate on combinations with inhaled corticosteroids	Almirall Prodesfarma, Barcelona, Spain

Table 6.3 uLABAs undergoing development. uLABAs, ultra-long-acting β_2-agonists. Data adapted from [5,7,10].

the first nicotine vaccine to make it to that stage failed two large Phase III trials, as efficacy was found to be no different from placebo. It is unclear as to whether further development will continue.

The problem of corticosteroid resistance in COPD

In sharp contrast to patients with asthma, patients with COPD show a poor response to inhaled corticosteroids, suggesting that there is a degree of resistance to their anti-inflammatory effects. There may be several reasons for corticosteroid resistance in COPD; one of the most convincing is a reduction in the nuclear enzyme histone deacetylase 2 (HDAC2), which is recruited by the activated glucocorticoid receptor to switch off inflammatory gene transcription. There is a marked reduction

The 'five As' strategy for patients willing to quit tobacco use	
Ask	Systematically identify all tobacco users at every visit
	Implement a system that ensures that for every patient at every clinic visit, tobacco use status is queried and documented
Advise	In a clear, strong and personalised manner, urge every tobacco user to quit
Assess	Determine willingness to make a quit attempt
	Ask every tobacco user if he or she is willing to make a quit attempt at this time (ie, within the next 30 days)
Assist	Aid the patient with a quit plan
	Provide practical counselling
	Provide intra-treatment social support
	Help the patient obtain extra-treatment social support
	Recommend use of approved pharmacotherapy except in special circumstances
	Provide supplementary materials
Arrange	Schedule follow-up contact, either in person or via telephone

Table 6.4 The 'five As' strategy for patients willing to quit tobacco use. Adapted from [12].

Drugs for smoking cessation
Current therapies
Nicotine replacement
Bupropion
Varenicline
Future therapies
Gamma-aminobutyric acid B agonists
Nicotine vaccine

Table 6.5 Drugs for smoking cessation.

in HDAC2 activity in the peripheral lung, preventing corticosteroids from switching off inflammation [15]. This reduction in HDAC2 appears to be the result of oxidative and nitrative stress, both of which are increased in patients with COPD. This provides an alternative strategy for the development of new treatments. Theoretically, antioxidants should reverse corticosteroid resistance, but current drugs are not efficient. Inhibitors of nitric oxide generation should also be effective, and several potent inhibitors of inducible nitric oxide synthase are now in clinical development. Unexpectedly, low-dose theophylline seems to act as a novel HDAC activator and is able to reverse corticosteroid resistance in both animal models of smoking and cells taken from humans with COPD [16]. Two recent studies [17,18] have explored whether theophylline can

Cessation rates of two randomised controlled outcome trials

	End of treatment		One-year follow-up	
	Study 1	Study 2	Study 1	Study 2
Varenicline	44	44	22	23
Bupropion	30	30	16	15
Placebo	18	18	8	10

Table 6.6 Cessation rates of two randomised controlled outcome trials. Treatment is for 12 weeks. Numbers in table are % abstinent (weeks 9–12 in 'end of treatment'). Conventional rounding was used: 0.1–0.4, rounded down; 0.5–0.9, rounded up. Data from [13,14].

reverse steroid resistance in patients wth COPD. It is hopeful that this will lead to the development of a large clinical trial to determine whether disease progression can be halted. This would revolutionise the management of COPD. Furthermore, theophylline is inexpensive and raises no safety concerns when the low doses (~5–10 mg/L) required to increase HDAC levels are used.

New treatments for COPD

New therapies are desperately needed for COPD, particularly anti-inflammatory therapies to prevent exacerbations and disease progression [19]. Testing drugs in COPD is a major challenge. High dropout rates make it difficult to devise long-term large studies. However, proof-of-concept clinical studies are more easily performed. There is some research interest in the molecular and cell biology of COPD in order to identify novel therapeutic targets. Animal models of COPD for early drug testing are poor and focus on emphysema, rather than the small airway disease that appears to underlie the progressive loss of FEV_1 and the increasing symptoms over time that are characteristic of COPD. Better animal models that have predominantly small airway disease are urgently needed.

There are also uncertainties about how to test drugs for COPD, which may require long-term studies (over 1 year) in relatively large numbers of patients at an enormous cost. For example, the TORCH trial, which looked at the effects of drug intervention on mortality, cost several hundred million dollars. Furthermore, many patients with COPD will have comorbidities such as ischaemic heart disease and diabetes, which may exclude them from clinical trials of new therapies. There is little

information about how surrogate markers like biomarkers in the blood, sputum or breath, may help to monitor the short-term efficacy and predict the long-term potential of new treatments. Finally, it is difficult to accurately measure small airway function in patients with COPD, so there is a need to develop better tests of small airway function that are not affected by emphysema or abnormalities of large airway function [20].

Several new classes of anti-inflammatory drugs are now in clinical development for COPD. The most advanced of these new drugs are phosphodiesterase (PDE)4 inhibitors, which increase cyclic adenosine monophosphate concentrations in inflammatory cells and have a broad spectrum of anti-inflammatory effects (Figure 6.2) [21–23]. The dose has been limited by side effects, particularly nausea and gastrointestinal problems. In 2011, roflumilast was approved by the FDA as an add-on treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations [24]. More selective inhibitors (PDE4B inhibitors) and administration through inhalation (although this too has proved disappointing) are currently being investigated to try and limit side effects.

Several other broad-spectrum anti-inflammatory therapies are currently under investigation (Figure 6.2), but most of these are likely to have side effects when given systemically, so inhaled administration may be required.

Mediator antagonists

Many mediators are now implicated in COPD, including lipid mediators and cytokines [25]. Although inhibiting specific mediators, by receptor antagonists or synthesis inhibitors, is a relatively easy approach, this is unlikely to produce very effective drugs owing to the large amount of redundancy within these biological systems, an example of which is the failure of p38 blockade in rheumatoid arthritis (although this may be a useful therapy in acute exacerbations of COPD). The premise of mediator blockade is to ‘take out’ the insulting raised cytokine/chemokine (Figure 6.3) [23]. This can be achieved by small molecule inhibition (low molecular weight) or biological targeting through receptor or moiety antibody blockade (high molecular weight or so-called ‘biologics’).

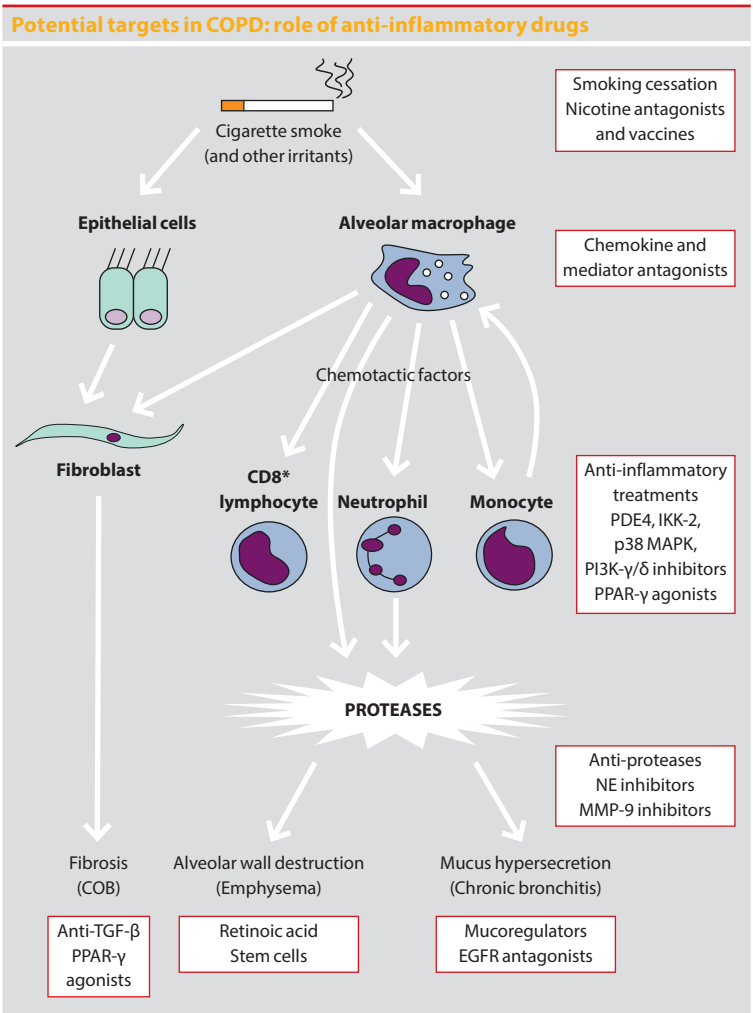

Figure 6.2 Potential targets in COPD: role of anti-inflammatory drugs. Cigarette smoke and other irritants activate macrophages in the respiratory tract that release multiple chemotactic factors that attract neutrophils, monocytes and T-lymphocytes (particularly CD8* cells). Several cells also release proteases, such as neutrophil elastase (NE) and matrix metalloproteinase-9 (MMP-9), which break down connective tissue in the lung parenchyma (emphysema) and also stimulate mucus hypersecretion (chronic bronchitis). CD8* may also be involved in alveolar wall destruction. This inflammatory process may be inhibited at several stages (shown in boxes). PDE, phosphodiesterase; IKK, inhibitor of nuclear factor-κB kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide-3-kinase; PPAR, peroxisome proliferator activated receptor; COB, chronic obstructive bronchitis; TGF, transforming growth factor; CB, cannabinoid; EGFR, epithelial growth factor receptor. Reproduced with permission from [23].

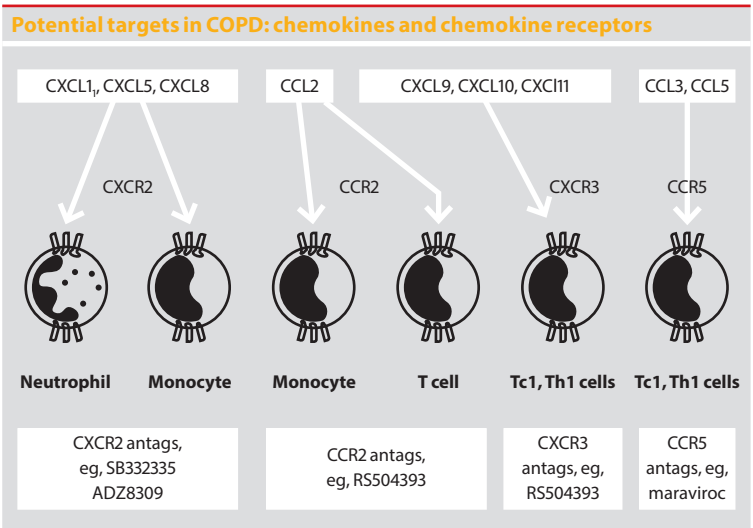

Figure 6.3 Potential targets in COPD: chemokines and chemokine receptors. Several chemokines and chemokine receptors are involved in the inflammation of COPD. Chemokines released from epithelial cells and macrophages in the lung recruit inflammatory cells (Tc1 CD8* T lymphocytes, neutrophils and monocytes) from the circulation. Small molecule chemokine receptor agtagonists are now in development (shown in boxes). Reproduced with permission from [23].

Further engineering of these molecules can improve efficacy, eg, the development of nanobodies and diabodies. Anti-TNF antibodies are currently used to treat patients with severe rheumatoid arthritis and inflammatory bowel disease, but so far these appear to be disappointing in COPD. An IL-8-blocking antibody has also proved to be largely ineffective in COPD. Although other biological targets are being pursued, it remains to be seen whether the efficacy of these products can be measured in an acceptable timeframe.

Protease inhibitors

Several proteases, particularly elastases, have been implicated in alveolar destruction, and are a target for therapy in patients with COPD and emphysema. Proteases may be inhibited by administering their endogenous antiproteases, such as α_1-antitrypsin, or small molecule inhibitors. So far, no clinical studies have demonstrated that these approaches have any effect in COPD.

Lung repair

COPD is largely irreversible, but it is possible that efforts to enhance the remodelling process may restore lung function. There has been particular interest in retinoic acid, which is able to reverse experimental emphysema in rats; however, this is unlikely to work in humans, whose lungs do not have the same regenerative capacity. There are now small mediators that have been specifically implicated in restorative functions, eg, resolvins, and these may be of interest in the future. Another novel approach that is being actively explored is the use of stem cells (distil airway stem cells expressing p63/Krt5) to regenerate epithelial/alveolar cells within the lung, though the possibility of unchecked cellular division could lead to an unacceptable increase in solid tumour growth.

Biomarkers of COPD

Predicting disease susceptibility to the effects of cigarette smoke is perhaps the most important potential use of any biomarker in COPD. Efforts in this area in particular genetic analysis of single nucleotide polymorphisms using gene-chip technology, have yet to make a breakthrough. Whilst the search continues for useful disease indicators, the use of pro-calcitonin in the prognostication of exacerbation severity has shown some promise. Tools are being developed which help predict exacerbations, such as the EXACT-PRO model advocated by the FDA and the DOSE Index [26,27]. Ultimately, these may be made available to patients via PDA (personal digital assistant) platforms. Sensitive measures of small airway function are now being more widely used, such as X5 (reactance) using impulse oscillometry and the older technique of multiple breath nitrogen washout. New imaging techniques, such as MRI scanning with radiolabelled helium and xenon, also offer promise as they do not involve large amounts of ionising radiation, a problem with high-resolution computed tomography. The use of the apparent diffusion coefficient within this context shows promise. Utilizing autofluoresence to directly image cells within the alveoli/terminal airways also has a great deal of potential [28]. Induced sputum is still employed in many proof-of-concept trials. It is now widely accepted that sputum neutrophils and IL-8 are good valid measures of airway inflammation if used correctly.

Routes of drug delivery

Traditionally, drugs for airway diseases are given by inhalation, but inhaler devices usually target larger airways, such as those implicated in asthma. In COPD, the inflammation is mainly in the smaller airways and the lung parenchyma, suggesting that inhalers which deliver drugs more peripherally may be more useful. Small particle inhalers, such as hydrofluoroalkane–beclomethasone propionate, used for asthma control, may be attractive in COPD because the inhaled drug would reach the lung periphery. Small volume nebulisers, eg, Respimat® Soft Mist™ inhaler, may also prove more effective, through low flow and a reduced particle size via a 'mist' formulation. Recent studies comparing the Handihaler and Respimat inhalers showed equivalent efficacy, measured by trough FEV_1 (5 μg Respimat SMI tiotropium versus 18 μg HandiHaler [29,30]). Oral therapy may treat systemic complications such as muscle wasting, weight loss and osteoporosis, which are a problem in patients with severe disease, although this carries an increased risk of side effects. Another experimental approach could exploit specific cell uptake mechanisms in target cells, such as macrophages.

Nonpharmacological treatments

Several nonpharmacological treatments are increasingly used as a complement to drug therapy. Nutritional supplements may have some benefit, but most research has focused on pulmonary rehabilitation (PR). This has been shown to improve exercise performance and health status in patients with COPD [31]. Pulmonary rehabilitation also reduces the utilisation of healthcare resources. Future PR programmes are likely to be community-based and consist of highly focused interactive sessions. Ongoing care taking place after the initial PR programme, including telephone calls, could be beneficial and may improve the long-term outcome, although this has not been studied systematically. An important area of development is the positive interaction between PR and current pharmacological therapies, particularly bronchodilators. Also, non-invasive ventilation in patients with severe ventilatory limitation appears to enhance the effects of exercise training.

In the future, better predictors of response are required, together with strategies that combine PR with other therapies such as treatments

to enhance muscle strength. Unfortunately, one of the major barriers to the implementation of PR is the availability of trained staff. An organised integrated PR programme should be available to all patients seen at any tertiary referral unit.

Integrated care

It is now apparent that COPD is a highly complex disease with several systemic manifestations as well as associations with severe comorbidities, particularly cardiovascular disease. This means that a multidisciplinary approach is needed, with the participation of respiratory specialists, GPs, specialist nurses, physiotherapists and others (Figure 6.4) [32]. There will be a trend towards evaluating not only airflow limitation, but also systemic effects and comorbidities to optimise QOL.

COPD in the developing world

As Western governments impose smoking bans and legislate against smoking advertising, tobacco companies are increasingly turning their attention to the developing world. Higher levels of cigarette smoking correlates well with greater prosperity. Thus, not only will the burden of COPD increase but also the prevalence of other smoking-related diseases, leading to more premature deaths. For example, Central and Eastern Europe have the highest lung cancer rates in the world for men [33]. Low birth weight and the burning of biomass fuels also amplify the risks of cigarette smoke exposure. Emerging economies need the support of the developed world in order to prevent a forthcoming epidemic of COPD and smoking-related diseases. The developed world must set the agenda for change and lead by example. The countries of Eastern Europe, India and China are at risk of repeating all of the mistakes made in Western Europe and the United States in the 1960s and 1970s.

Conclusions

Over the next 10 years, there are likely to be various developments that will improve the management of COPD. Combination long-acting bronchodilators are the treatment of choice for symptom relief and reduce exacerbation rates, but there is a pressing need for effective anti-inflammatory

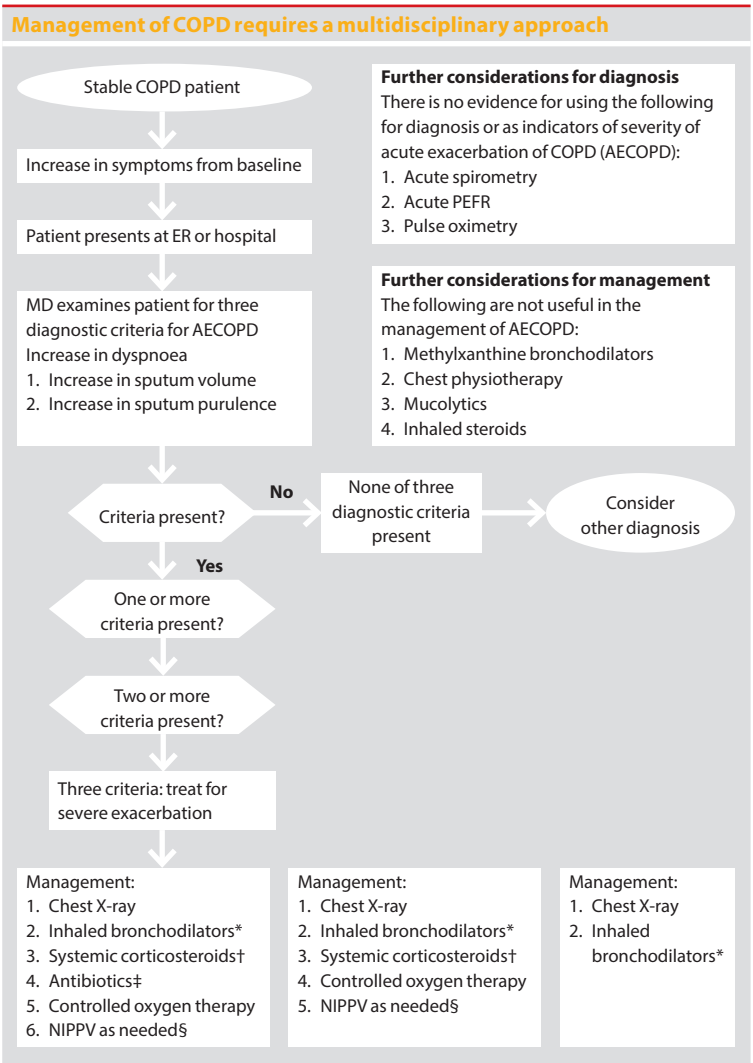

Figure 6.4 Management of COPD requires a multidisciplinary approach. *Use anticholinergic bronchodilators first, once at maximum dose, then add β_2-agonist bronchodilators. †Dosing regimen used in the SCOPE trial: 3 days intravenous methylprednisolone, 125 mg every 6 hours followed by oral prednisolone, taper to complete the 2-week course (60 mg/day on days 4–7, 40 mg/day on days 8–11, and 20 mg/day on days 12–15). ‡Use narrow-spectrum antibiotics: the agents favoured in the trials were amoxicillin, trimethoprim–sulphamethoxazole and tetracycline. §Non-invasive positive pressure ventilation should be administered under the surpervision of a trained physician. There are multiple components of COPD that need to be taken account in the management of this complex disease. This requires integrated care and a multidisciplinary approach. ER, emergency room; NIPPV, noninvasive positive pressure ventilation; PEFR, peak expiratory flow rate; URTI, upper respiratory tract infection. Adapted from [32].

treatments, particularly in patients who have ceased smoking. It is hoped that this will prevent disease progression. Various biomarkers are being developed to monitor pulmonary inflammation in COPD. Pulmonary rehabilitation is now well established and could be delivered more in the community in the future. In short, COPD is a multidimensional disease that requires an integrated multidisciplinary approach.

References

1 Barnes PJ, Stockley RA. COPD: current therapeutic interventions and future approaches. Eur Respir J 2005; 25:1084–1106.
2 van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Respir J 2005; 26:214–222.
3 Tudorza Pressair [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2012.
4 European Medicines Agency. Summary of product characteristics for Eklira Genuair. Available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002211/WC500132661.pdf. Last accessed October 2012.
5 Cazzola M, Matera MG. Emerging inhaled bronchodilators: an update. Eur Respir J 2009; 34:757-769.
6 Villetti G, Pastore F, Bergamaschi M, et al. Bronchodilator activity of (3R)-3-[[[(3-fluorophenyl)[(3,4,5-trifluorophenyl)methyl]amino] carbonyl]oxy]-1-[2-oxo-2-(2-thienyl)ethyl]-1-azoniabicyclo[2.2.2]octane bromide (CHF5407), a potent, long-acting, and selective muscarinic M3 receptor antagonist. J Pharmacol Exp Ther 2010; 335:622-635.
7 Cazzola M, Calzetta L, Matera MG. β_2-adrenoreceptor agonists: current and future direction. Br J Pharmacol 2011; 163:4-17.
8 European Medicines Agency. Summary of product characteristics for Onbrez Breezhaler. Available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001114/WC500053732.pdf. Last accessed October 2012.
9 Arcapta Neohaler [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011.
10 van Noord JA, Smeets JJ, Drenth BM, et al. 24-hour bronchodilation following a single dose of the novel β_2-agonist olodaterol in COPD. Pulm Pharmacol Ther 2011; 24:666-672.
11 Calverly PM, Anderson JA, Celli B, et al; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007; 356:775–789.
12 The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. JAMA 2000; 283:3244–3254.
13 Gonzales D, Rennard SI, Nides M, et al; Varenicline Phase 3 Study Group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006; 296:47-55.
14 Jorenby DE, Hays JT, Rigotti NA, et al; Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006; 296:56-63.
15 Barnes PJ. Reduced histone deacetylase in COPD: clinical implications. Chest 2006; 129:151–155.
16 Barnes PJ. Theophylline in chronic obstructive pulmonary disease: new horizons. Proc Am Thorac Soc 2005; 2:334–339.

17 Ford PA, Durham A, Russell RE, et al. Treatment effects of low dose theophylline combined with an inhaled corticosteroid in COPD. Chest 2010;137:1338–1344.
18 Cosio BG, Iglesias A, Rios A, et al. Low-dose theophylline enhances the anti-inflammatory effects of steroids during exacerbations of COPD. Thorax 2009; 64:424-429.
19 Barnes PJ, Hansel TT. Prospects for new drugs for chronic obstructive pulmonary disease. Lancet 2004; 364:985–996.
20 Sturton G, Persson C, Barnes PJ. Small airways: an important but neglected target in the treatment of obstructive airway diseases. Trends Pharmacol Sci 2008; 29:340-345.
21 Fan CK. Phosphodiesterase inhibitors in airways disease. Eur J Pharmacol 2006; 533:110–117.
22 Barnes PJ. New therapies for chronic obstructive pulmonary disease. Med Princ Pract 2010; 19:330-338.
23 Barnes PJ. Frontrunners in novel pharmacotherapy of COPD. Curr Opin Pharmacol 2008; 8:300-307.
24 Daliresp [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2011.
25 Barnes PJ. Mediators of chronic obstructive pulmonary disease. Pharm Rev 2004; 56:515–548.
26 Leidy NK, Wilcox TK, Jones PW, et al; for the EXACT-PRO Study Group. Development of the EXAcerbations of Chronic Obstructive Pulmonary Disease (EXACT): a Patient Reported Outcome (PRO) measure. Value Health 2010; 13:965-975.
27 Jones RC, Donaldson GC, Chavannes NH, et al. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE Index. Am J Respir Crit Care Med 2009; 180:1189-1195.
28 Thiberville L, Salaün M, Lachkar S, et al. Human in vivo fluorescence microimaging of the alveolar ducts and sacs during bronchoscopy. Eur Respir J 2009; 33:974-985.
29 van Noord JA, Cornelissen PJ, Aumann JL, et al. The efficacy of tiotropium administered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients. Respir Med 2009; 103:22-29.
30 Asakura Y, Nishimura N, Maezawa K, et al. Effect of switching Tiotropium HandiHaler® to Respimat® Soft Mist™ Inhaler in patients with COPD: the difference of adverse events and usability between inhaler devices. J Aerosol Med Pulm Drug Deliv 2012; epub ahead of print.
31 Rosenberg SR, Kalhan R. An integrated approach to the medical treatment of chronic obstructive pulmonary disease. Med Clin North Am. 2012; 96:811-826.
32 Bach PB, Brown C, Gelfand SE, et al; American College of Physicians–American Society of Internal Medicine; American College of Chest Physicians. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Ann Intern Med 2001; 134:600–620.
33 Ferlay J, Shin H-R, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127:2893-2917.