PSA MEMBER BENEFIT

Chronic Obstructive Pulmonary Disease

ESSENTIAL CPE

Continuing Education from the Pharmaceutical Society of Australia

APRIL 2008

CPD&PI Pharmaceutical Society of Australia

Endorsement

The content of this distance learning module on Chronic Obstructive Pulmonary Disease is endorsed as being current and best-practice at the time of printing by The Australian Lung Foundation. The Australian Lung Foundation recognises that:

- COPD is characterised by an accelerating loss of lung function, which can constrain patients' independence and restrict them from living an active life
- As COPD progresses, symptoms gradually worsen and exacerbations occur with increasing frequency, which causes the disease to accelerate and further diminishes quality of life
- COPD is however preventable and treatable
- COPD and asthma are different diseases that require different treatment approaches
- Pharmacists have an important role to play in identifying at-risk patients and referring them early to their general practitioner.
- Pharmacists can play a pivotal role in improving health outcomes for patients by taking an active role in patient education, encouraging adherence to medication, assisting with prevention strategies and participating in the overall management plan.

THE AUSTRALIAN LUNG FOUNDATION

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Learning objectives

Upon completion of this *Essential CPE* module and assessment, the pharmacist will be able to:

- Explain the clinical aspects of COPD and related conditions
- Identify the signs and symptoms associated with COPD and how it is diagnosed in order to appropriately advise and refer patients
- Describe spirometry and relevant ventilatory indices used in the diagnosis of COPD
- Identify the risk factors of COPD
- Outline the clinical course of COPD
- Explain the complications and co-morbid conditions commonly associated with COPD
- Differentiate between COPD and asthma
- Recognise the health and financial impact of COPD
- Describe exacerbations and their impact on the clinical course of COPD
- Discuss the risks of smoking with patients and advise them on smoking cessation strategies
- Recognise treatment guidelines for COPD
- Outline the pharmacological actions of medications and complementary therapies used in COPD
- Summarise the potential risks and benefits of pharmacological treatments
- Advise and train patients in the correct use of respiratory devices for airway diseases
- Identify clinically significant potential or actual drug-related problems related to pharmacological treatments (including interactions)
- Evaluate the place of the various pharmacological treatments in therapy
- Provide advice appropriately to patients, carers and other health professionals regarding the overall management of COPD.

Pharmacists can self-assess their abilities against the competency standards relevant to their role to determine areas in which further development is needed.

This COPD Essential CPE module addresses the following competencies:

Functional area 1: ***Practise pharmacy in a professional and ethical manner***
- Unit 3: Pursue life-long professional learning and contribute to the development of others (Elements 1 & 2)

Functional area 3: ***Promote and contribute to the optimal use of medicines***
- Unit 1: Participate in therapeutic decision making
- Unit 2: Provide ongoing pharmaceutical management

Functional area 4: ***Dispense medicines***
- Unit 2: Evaluate prescribed medicines (Element 1)
- Unit 3: Supply prescribed medicines (Element 3)

Functional area 6: ***Provide primary health care***
- Unit 1: Assess primary health care needs (Element 2)
- Unit 2: Address primary health care needs of patients (Elements 1, 2 & 5)
- Unit 3: Promote good health in the community

Functional area 7: ***Provide medicines and health information and education***
- Unit 1: Retrieve information (Element 5)
- Unit 2: Evaluate and synthesise information (Element 3)
- Unit 3: Disseminate information

How to earn credit points

CPD&PI

This module is recognised under the CPD&PI Program (Group 2 activity). To obtain six credit points, carefully read through the module, complete the assessment sheet, and submit it to PSA National Office within eight weeks of receipt. Credit points are allocated to members who achieve 80% of questions correct.

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If posting your assessment, please photocopy your assessment sheet for your own records. Should you require your assessment sheet to be returned to you, please enclose a stamped, self-addressed envelope.

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CONTENTS

Learning objectives 3
- Competencies 3

What is COPD? 6
- Chronic bronchitis 6
- Emphysema 7
- Prevalence 7
- Aetiology and natural history 7
- Symptoms 8

How is COPD diagnosed? 9
- Spirometry 9
- Performing spirometry 10
- Other investigations 11
- COPD severity 11

Differences between COPD and asthma 12

Exacerbations 14
- Triggers of exacerbations 14
  - Viral causes 14
  - Bacterial causes 14
  - Pollution 15
- Impact of exacerbations 15
- Prevention of exacerbations 15
- Treatment of exacerbations 15
  - Antibiotics 15
  - Bronchodilators 16
  - Glucocorticoids 16
  - Controlled oxygen therapy 16

Systemic effects of COPD 17
- Weight loss and poor nutrition 17
- Skeletal muscle dysfunction 17
- Cardiovascular disease 17
- Pulmonary hypertension and cor pulmonale 17
- Depression 18
- Osteoporosis 18
- Other aggravating factors 19
  - Insomnia and sleep apnoea 19
  - Gastro-oesophaegeal reflux 19
  - Aspiration 19
  - Dental health 19
  - Alcohol and sedatives 19

CONTENTS (cont)

Revision of pharmacology 20
The autonomic nervous system 20

COPD treatment 22
Stable COPD 22
Bronchodilators 22
Anticholinergics 22
Beta-2 agonists 23
Theophylline 24
Corticosteroids 24
Combination Products 25
Suggested treatment algorithm 26
Other considerations for long term treatment 26
Pulmonary rehabilitation 26
Smoking cessation 27
Influenza vaccination 29
Pneumococcal vaccination 30
Antibiotics 30
Mucolytics 30
Antitussives 30
Statins 30
Nutritional support 30
Advice on travel 30
Benefits of treatment 31

COPD guidelines 32

References 33

Glossary 35

What is COPD

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterised by airway inflammation and airflow limitation that is not fully reversible[1]. The airflow limitation is usually associated with an abnormal inflammatory response of the lung to noxious particles or gases[2].

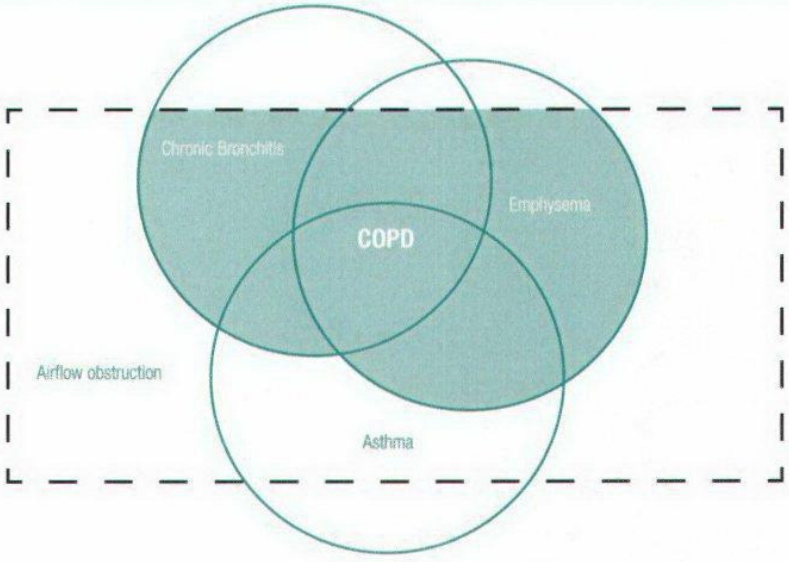
COPD is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. The lack of full reversibility of the airways is a means of distinguishing between COPD and asthma, although many patients have features of both.[3] COPD is often considered an 'umbrella' term for chronic bronchitis and emphysema. The overlap between chronic bronchitis, emphysema and asthma and their relationship to airflow obstruction and COPD are illustrated below in figure 1.

Chronic bronchitis

Chronic bronchitis, an epidemiological diagnosis, is an obstructive airway disease characterised by excessive mucus secretion that causes daily sputum production for at least three months of the year for two or more consecutive years.[1] Key changes in the airways of patients suffering from bronchitis leading to obstruction of the bronchioles include:

- Increased production of excess mucus
- Impaired clearance of mucus due to damaged cilia
- Increased bronchomotor tone
- Increased inflammation
- Increased risk of bronchial infection.

Figure 1. The overlap* of COPD *(Courtesy of COPDX Guidelines)*



The shaded region within the black dotted line represents COPD.
* *Non-proportional*

Chronic inflammation is also related to an airway remodelling process, associated with goblet cell hyperplasia, metaplasia of the epithelium, increased airway wall thickness and narrowing of the airway lumen.[4]

Emphysema

Emphysema is a pathological diagnosis, and consists of alveolar dilatation and destruction.[1] Key changes in the airways of patients suffering from emphysema lead to increased work of breathing and the inability to perform activities without experiencing distressing breathlessness and include:

- Alveolar destruction
- Loss of lung elasticity
- Airway collapse during expiration
- Dynamic hyperinflation
- Airway narrowing
- Impaired gas exchange.

Prevalence

COPD, a growing cause of morbidity and mortality worldwide, is still often unrecognised and under-diagnosed.[1] The current misdiagnosis, misclassification and masking of COPD by other illness are thought to contribute to a major underestimate of the economic burden.[5-6]

COPD was estimated to be the fifth leading cause of death worldwide in 2001 and is predicted to be the third leading cause of death by 2020.[7-8] In Australia, COPD is the fifth leading cause of death[9] and third leading cause of disease burden[10-12] with recent evidence indicating the prevalence of moderate to severe disease in Australians over the age of 40 being 10.8%.[3]

Aetiology and natural history

COPD is a progressive, disabling disease with serious complications. Impairment increases as the disease progresses, but may not be recognised because of the slow pace of the disease.[1] Patients tend to maintain their activity levels within their own symptomatic limits, and adopt strategies to avoid undue shortness of breath.[1]

Tobacco smoke remains the most important aetiological factor in the development of COPD,[1] yet not all smokers develop COPD, suggesting that it is an interaction between environmental exposures (such as tobacco smoke, air pollutants) and host factors (genetics, early lung growth, race, sex) that determines an individuals susceptibility to COPD.[13] Previous studies estimated that around 15% of smokers would go on to develop COPD; however recent evidence suggests that as many as 50% have been noted to develop COPD.[13-14]

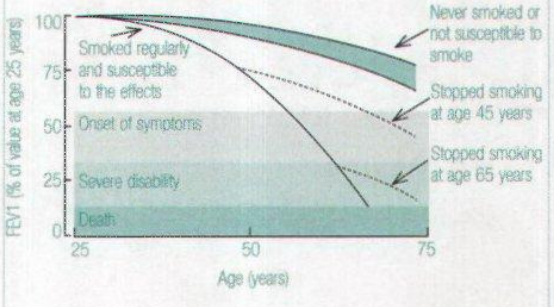
Active smoking causes a premature onset of an accelerated age-related decline in lung function with a decrease in FEV_1 (forced expiratory volume in one second), of 50-100mL/year,[15] compared with the expected rate of decline of <30mL/year in the general population of never smokers without respiratory symptoms or conditions.[16] As the amount of cigarette smoking increases, and ageing advances, the rate of decline increases. For some smokers, the increased rate of decline eventually results in dyspnoea and limitation of activities; which is when the clinical diagnosis of COPD is usually made,[17] by which stage as much as half the original lung function has already been lost.

Tobacco associated risk for developing COPD is measured in 'pack years' of smoked cigarettes. Twenty pack years or more of smoking has been identified as being a predictor of COPD.[1]

$$\text{Number of pack years} = \frac{\text{Number of years smoking} \times \text{cigarettes smoked per day}}{20}$$

Smoking cessation has been shown to slow the accelerated decline in lung function seen in COPD and extend survival.[1] It is therefore a critical step in managing the condition and preventing deterioration (see Figure 2).

Figure 2. Natural history of COPD and rate of decline of forced expiratory volume in one second (FEV_1). *(Courtesy of COPDX Guidelines: Adapted from Fletcher C and Peto R; BMJ 1977; 1:1645-1648).*



Other risk factors[1,2] which may contribute to the development of COPD include:

- Occupational dust, vapour and fume exposure
- Indoor and outdoor air pollutants
- Environmental tobacco smoke
- Ageing (lung function which reaches its peak level in young adults, starts to decline in the third and fourth decades of life[1,8])
- Genetic factors (namely a deficiency of the serine protease α1 antitrypsin (AAT), which arises in 1-3% of patients[1,9])
- Infections (play an important role in development and progression of COPD)
- Bronchial hyperresponsiveness
- Socioeconomic and related factors
- Recurrent respiratory tract infections in childhood.

Poverty is regarded as a surrogate measure for many factors that subsequently increase the risk of COPD such as poor nutrition, exposure to pollutants including high work exposures and smoking rates, poor access to health care and early respiratory tract infections.[2]

Pharmacist tip:

Pharmacists can provide counselling on avoidance of risk factors such as passive tobacco smoke or airborne pollutants.

Symptoms

The symptoms of COPD are generally non-specific and may be found in other disease states (see Table 1). The main symptoms are breathlessness, cough and sputum production.[1] Patients often attribute breathlessness to ageing or lack of fitness, and limit their activities to avoid dyspnoea. A persistent cough, typically worse in the mornings with mucoid sputum is common in smokers.[1] Other symptoms such as chest tightness, wheezing, recurrent infective bronchitis and airway irritability are common.[1]

Physical features in more advanced disease that are commonly found include hyperinflation of the chest, reduced chest expansion, hyperresonance to percussion, soft breath sounds and a prolonged expiratory phase.[1] Fatigue, poor appetite and weight loss are also more common in advanced disease.[1]

Table 1: Summary of key indicators for COPD

Chronic cough	Present intermittently or every day Often present throughout the day; seldom only nocturnal
Chronic sputum production	Present for many years, worse in winter. Initially mucoid – becomes purulent with exacerbation
Dyspnoea that is	Progressive (worsens over time) Persistent (present every day) Described by patients as "increased effort to breathe" or "gasping for breath". Worse with activities Worse during respiratory infections
Acute bronchitis	Repeated episodes
History of exposure to risk factors	Tobacco smoke (personal and environmental) Occupational dusts and chemical smoke from home cooking and heating fuel Indoor and outdoor pollution.

In mild-to-moderate COPD physical examination alone is not helpful for diagnosis as physical signs are not usually present until significant impairment of lung function has occurred.[1] Many patients also adopt strategies to avoid symptoms and do not discuss this with their doctor.

How is COPD diagnosed?

Chronic cough, sputum production or dyspnoea are usually absent in the early stages of COPD, and most patients seek help from a general practitioner at a stage of breathlessness when COPD may already be moderate or severe.[20]

The major differential diagnosis is between COPD and asthma; however other conditions involved include:[21]

- Congestive heart failure
- Bronchiolitis
- Bronchiectasis
- Tuberculosis
- Cystic fibrosis.

Where the diagnosis is uncertain, or when the disease is interfering with daily life, review by a respiratory physician is recommended.

Physical examination or peak expiratory flow measurements (PEF) alone are not diagnostic. PEF is not a sensitive measure of airway function in COPD patients, as it is effort dependent, has a wide range of normal values and may be normal despite significant airflow obstruction.[1]

Spirometry

Spirometry is a type of lung function test which measures the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled and is the gold standard for diagnosing, assessing and monitoring COPD.[1] Spirometry also identifies patients at risk; an early indicator of COPD is when FEV_1 is >80% but FEV_1/FVC is <70%, and discovering this abnormality has been shown to motivate patients to stop smoking.[20] Most spirometers provide predicted ('normal') values obtained from healthy population studies, and derived from formulae based on height, age, sex and ethnicity.[1] The results are reliable as long as maximal patient effort is obtained, standards for performing the test are adhered to and there is good quality control of equipment.

Spirometry should be considered in:[20]

- All smokers and ex-smokers over 35 years old
- Any patient with a risk factor or one or more symptoms including:
  - Breathlessness
  - Chronic cough
  - Regular sputum production
  - Wheezing
  - Recurrent infective bronchitis.

The measures obtained from spirometry mainly include:[1]

- **FEV_1** – Forced expiratory volume in one second; the volume expired in the first second of maximal expiration after a maximal inspiration and is a useful measure of how quickly full lungs can be emptied.
- **FEV_6** – Forced expiratory volume in six seconds: the volume expired in the first six seconds of maximal expiration after a maximal inspiration
- **FVC** – Forced vital capacity; the volume of air that can be forcibly expelled from the lungs from a position of full inspiration, with no limit to the duration of expiration. It is the total volume of air which can be exhaled from the lungs
- **FEV_1/FEV_6** – FEV_1 expressed as a percentage of FEV_6 which gives a clinically useful index of airflow limitation.
- **FEV_1/FVC** – FEV_1 expressed as a percentage of VC or FVC which gives a clinically useful index of airflow limitation. This may also see expressed as **FEV_1/FEV_6**.

COPD patients have a reduced FEV_1, FEV_6, FEV_1/FEV_6 and FEV_1/FVC – that is COPD patients have difficulty exhaling air from their lungs; air becomes trapped in the lungs as a result.

FVC is an essential element of the test used to diagnose airway obstruction and rule out a restrictive process, however the measurement requires the patient to empty his or her lungs completely; a process that may take up to 20 seconds and that can be physically exhausting for older or impaired individuals or those with severe respiratory diseases.[23]

The FEV_6, forced expiratory volume in six seconds, has the practical advantage of simplifying test procedures, reducing test variability and possibly improving accuracy in the diagnosis of airway obstruction, and is considered an acceptable surrogate for FVC.[23]

To distinguish between asthma and COPD, apart from the patient history, the degree of reversibility of airflow obstruction following inhalation of a short-acting beta-2 agonist should be measured. Airflow limitation in asthma is substantially reversible either spontaneously or in response to treatment. By contrast, airflow obstruction in COPD is not completely reversible. Reversible airflow limitation can be detected by spirometry before and about 15 minutes after bronchodilator administration (at least 200 micrograms of salbutamol).

There is presently no universal agreement on the definition of significant bronchodilator reversibility. According to the Thoracic Society of Australia and New Zealand the criterion for significant reversibility in adults is:[1]

- ≥12% improvement in FEV_1 (or FVC) and an absolute improvement of ≥0.2L (or 200mL)**

This degree of reversibility is not diagnostic of asthma and is frequently seen in COPD patients. The diagnosis of asthma relies on an appropriate history and complete or at least substantial reversibility of airflow limitation.[1]

** The degree of improvement is calculated using the following formula:

$$\% \text{ Improvement} = 100 \times \frac{FEV_1 \text{ (post-bronchodilator)} - FEV_1 \text{ (baseline)}}{FEV_1 \text{ (baseline)}}$$

Airflow limitation is not-fully reversible, and COPD is diagnosed, when after administration of bronchodilator medication:

- FEV_1 remains <80% of the predicted value and
- The ratio of FEV_1 to FVC remains <0.7.

Performing spirometry

Spirometry is best performed when the patient is seated with their feet firmly on the floor. Patients should be clinically stable and free of respiratory infections, and the following medications should be withheld as indicated prior to testing:

- Short acting bronchodilators – withhold six hours prior to testing
- Long acting beta-agonists – withhold 12 hours prior to testing
- Sustained-release theophyllines – withhold 24 hours prior to testing
- Tiotropium – withhold at least 24 hours prior to testing.

During the spirometry test the patient must:

1. Breathe in fully
2. Seal their lips around the mouthpiece
3. Force air out of the chest as hard and as fast as they can until their lungs are completely 'empty' *
4. Breathe in again and relax.

** Exhalation must continue until no more air can be exhaled, must be at least six seconds, and can take up to 15 seconds or more.*[24]

Like any test, spirometry results will only be of value if the expirations are performed satisfactorily and consistently. At least three technically acceptable manoeuvres should be obtained, ideally with less than 0.2L variability for FEV_1 (and FVC) between the highest and second highest result.

Figure 3 summarises the process used in assessing pre- and post-bronchodilator spirometry.

Figure 3. Flow chart of assessment of pre and post bronchodilator spirometry

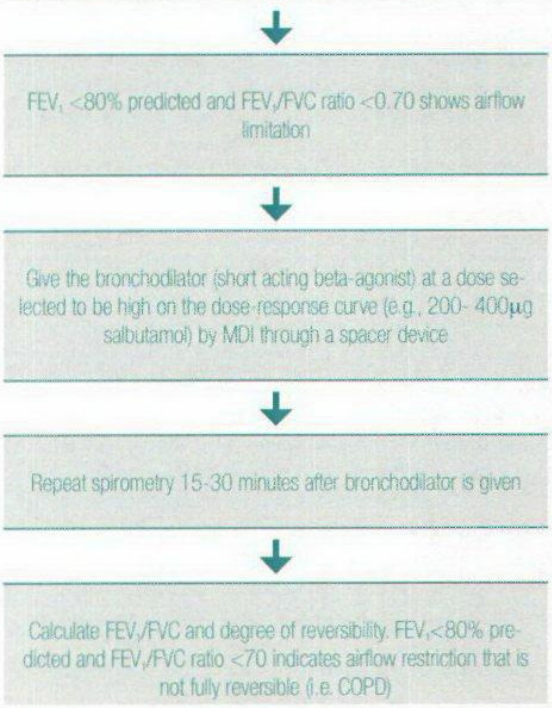


Table 2: Classification of severity of COPD*			
	Mild	**Moderate**	**Severe**
Spirometry findings post-bronchodilator	FEV_1 60-80% predicted	FEV_1 40-59% predicted	FEV_1 <40% predicted
Functional assessment (Activities of daily living)	• Few symptoms • No effect on daily activities • Breathless on moderate exertion	• Increasing dyspnoea • Breathless on the flat • Increasing limitation of daily activities	• Dyspnoea on minimal exertion • Daily activities severely curtailed • Severely impaired quality of life • Life threatening exacerbations/ complications

** Adapted from The COPD-X Plan: Australian and New Zealand Guidelines for the management of COPD*

Other investigations

Other investigations to aid diagnosis or management include:[1]

- Chest x-ray (helps to exclude other conditions such as lung cancer)
- Arterial blood gas measurement (performed in patients with severe disease, an FEV_1 ≤1.0L or <40% predicted, if there are signs of respiratory failure or cor pulmonale and those with breathlessness out of proportion to their clinical status to determine the concentrations of CO_2, O_2, bicarbonate and the pH of the blood).
- Full blood count (to identify anaemia or polycythaemia)
- Alpha-1 antitrypsin deficiency screening.

Exercise testing may be useful to differentiate between breathlessness resulting from cardiac and respiratory disease, and may be helpful to identify other causes of exercise limitation (e.g. hyperventilation, musculoskeletal disorders).

COPD severity

The percentage of predicted FEV_1 is used to determine severity of COPD and reflects prognosis. Spirometry in addition to clinical examination, improves the diagnostic accuracy of COPD compared to clinical examination alone.[25] Table 2 provides a classification of severity of COPD that is used in Australia and New Zealand.

Pharmacist tip:

Pharmacists can aid in the early detection of COPD by identifying at risk patients and referring them to their doctor for assessment. Any patients aged ≥ 35 years of age should be referred if they:

- Are current or past smokers or
- Have a family history of bronchitis or emphysema or
- Have been exposed to environmental tobacco smoke, dusts, chemicals, indoor or outdoor pollutants
- Have a history of repeated episodes of bronchitis or respiratory infections
- Patients with a diagnosis of asthma who do not respond to treatment as expected

  And

- Have dyspnoea, chronic cough or sputum
- Are not experiencing symptoms but avoid daily activities to limit their breathlessness
- Attribute breathlessness to ageing or poor fitness.

It is important to consider COPD in all at-risk patients as early diagnosis and treatment improves outcomes. Early detection may motivate patients to stop smoking sooner, which may help slow disease progression and prevent long-term complications.

Differences between COPD and asthma

Even though there is some overlap between asthma and COPD and they share many common symptoms, they are usually easy to differentiate. Spirometry is the key in establishing diagnosis. Whilst the pathological features of asthma are chronic, symptoms typically run a variable course and are sometimes modifiable by eliminating relevant triggers. Airflow limitation in asthma is substantially, if not completely reversible either spontaneously or in response to treatment. COPD runs a more progressive course, with a typically late onset of symptoms and airflow obstruction that is not completely reversible.[48]

Although there is an inflammatory component in COPD, it is markedly different to that in asthma,[63] and thus the treatment approaches between asthma and COPD differ.

Table 3 summarises the differences in clinical features and pathophysiology between asthma and COPD.[50,63,64]

Table 3: Differences between COPD and asthma

	COPD	Asthma
Pathophysiological features		
Typical stimuli	Smoke Infections	Allergens (e.g. pollen, dust etc.) Infections
Inflammatory cascade	CD8+ T-lymphocytes Neutrophils Large increase in macrophages	CD4+ T-lymphocytes Eosinophils Small increase in macrophages
Airway epithelium	Squamous metaplasia Neutrophil infiltrate	Marked epithelial cell shedding
Airway lumen	Narrowed (consistently) Serous/mucus excess	Narrowed (variably) Mucus plugging
Mucus glands and goblet cells	Hyperplasia	Hypersecretion Hyperplasia
Smooth muscle	Small airway remodelling	Hyper-responsive
Lung parenchyma	Emphysematous	Normal
Clinical features		
Age at onset of symptoms	Normally > 40 years	Typically early in life but can occur at any stage
Smoking	Usually smokers or ex-smokers	Non-smokers and smokers affected
Atopic features	Irrelevant	Common
Disease progression	Chronic, progressive disease leading to disability and death	Usually able to be well controlled, rarely fatal
Symptoms	Progressively worse with time Dyspnoea consistent, limiting exercise Wheeze less prominent Cough productive (especially in the morning)	Vary from day to day Dyspnoea variable, post-exercise Wheeze prominent and variable Cough typically dry
Lung function	Airflow limitation is not fully reversible	Airflow limitation is fully reversible
Past history	Less likely atopic No childhood complaints	Atopic conditions Childhood croup, bronchitis, asthma
Spirometry	Consistent airflow limitation No or minor reversibility	Variable airflow limitation Complete or substantial reversibility

Pharmacist tip:

Pharmacists should be aware that COPD is often misdiagnosed as asthma. This is an important distinction to be made as the two diseases, although similar in some ways, have very different treatment requirements. For example, important aspects of asthma treatment are avoidance of triggers and regular use of inhaled corticosteroids, whereas some important aspects of COPD treatment include vaccinations, smoking cessation, tiotropium, pulmonary rehabilitation and oxygen therapy.

Pharmacists should also be aware that a small percentage of patients do have co-existing COPD and asthma, and patients with worsening symptoms despite their current treatment should be referred to their doctor for assessment.

Exacerbations

An exacerbation in a patient with underlying COPD is considered as an event characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication.[26]

The duration of an exacerbation can vary greatly – usually lasting from days to weeks. People with COPD should watch closely for any changes in their condition that might signal an exacerbation so they can seek timely medical attention. Patients with COPD have, on average, two to three acute exacerbations per year,[27] although most of these are relatively mild and uncommonly need hospital care.

Figure 4. Triggers of COPD exacerbations and associated pathophysiological changes[26]
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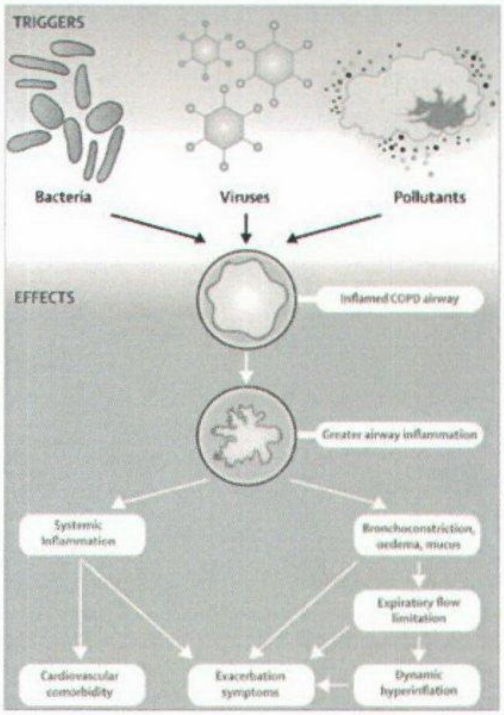


Bacteria, pollutants and viruses are the main triggers of COPD exacerbations causing airway oedema, bronchospasm, and increased sputum production leading to worsening airflow limitation and development of dynamic hyperinflation (refer Figure 4). Dynamic hyperinflation is the main cause of dyspnoea and has other effects including modulating gas exchange, mechanical and cardiovascular effects.[26]

Exacerbations often lead to increased:

- Physician visits
- Emergency department visits
- Hospitalisations.

Triggers of exacerbations

Viral causes

COPD exacerbations are frequently triggered by upper respiratory tract infections, and these are more severe and are associated with longer recovery times than those triggered by other factors.[26] The most common viruses isolated are human rhinoviruses, influenza, parainfluenza, syncytial virus and adenovirus.[26] Since the widespread introduction of influenza immunisation for patients with chronic lung disease, the virus has become a less prominent cause of exacerbations.

Bacterial causes

The precise role of bacteria in COPD exacerbations has been difficult to assess, because bacteria that colonise airways in the stable state are the same as those isolated during exacerbations including *Haemophilus influenzae, Streptococcus Pneumoniae, Moraxella catarrhalis, Staphylococcus aureus and Pseudomonas aeruginosa.*[28]

COPD exacerbations associated with purulent sputum are more likely to produce positive bacteria cultures than those where sputum production is mucoid.[26] The use of antibiotics thus shows a greater benefit in patients presenting with increased sputum volume and purulence as well as dyspnoea.[26]

Pollution

COPD patients may experience increased exacerbations and hospital admissions with increasing environmental pollution.[28] People who work in an industry where they are exposed to harmful dusts, chemicals or gases (e.g. in farming and mining) should follow appropriate safety procedures to minimise their exposure to harmful pollutants.

Impact of exacerbations

Exacerbations become both more frequent and more severe as the severity of the underlying COPD increases.[29] Patients with a history of frequent exacerbations have worse quality of life than patients with a history of fewer exacerbations, increased risk of hospital admission and greater mortality.[28] Frequent exacerbations play a part in the progression of the disease, and produce a more rapid decline in lung function, estimated to be around 25% of the total decline in lung function.[30]

Acute exacerbations of COPD often require hospital admission for treatment of respiratory failure, so preventing exacerbations and detecting and managing exacerbations early can prevent deterioration and reduce hospital admissions.[1]

Box 1 summarises the impacts of exacerbations on COPD.

Box 1: Impact of exacerbations on COPD

- Accelerated decline in lung function
- Increased morbidity
- Progressive loss of independence
- Increase mortality rates
- Hospitalisation
- Poorer quality of life

Prevention of exacerbations

There are several measures that can be taken to prevent acute exacerbations, including smoking cessation, annual influenza immunisation and current pneumococcal vaccination. Influenza vaccinations reduce the relative risk of exacerbations, hospitalisation and death by 50%.[1]

Preventing exacerbations is important as patients may never return to their previous lung function after an exacerbation and once an exacerbation has been experienced, the patient is likely to experience more.

Current evidence does not support the long-term use of antibiotics to prevent exacerbations in COPD. Tiotropium 18 µg daily is the only pharmacological treatment that has been shown to reduce exacerbations in all COPD severity levels (mild, moderate and severe).[30] Tiotropium decreases associated healthcare resource utilisation as indicated by significant reductions in the use of concomitant respiratory medication, antibiotics, oral steroids, the number of unscheduled physician contacts[31] and frequency of hospitalisations.[30]

Inhaled corticosteroids reduce the number of exacerbations compared to placebo, but only with high doses and in moderate to severe COPD.[32] Fluticasone with salmeterol has been shown to reduce exacerbations more than either fluticasone or salmeterol given alone in moderate to severe COPD,[33,34] however there is no current indication in Australia for the prevention of COPD exacerbations for either the combination therapy or fluticasone or salmeterol given alone.[35]

Pulmonary rehabilitation in conjunction with long term maintenance exercise programs and optimised medical treatment can lead to significant reductions in the frequency of acute exacerbations, hospitalisations and premature mortality.[1]

Treatment of exacerbations

Treatment is directed at reducing airflow limitation, excess sputum production, airway inflammation, infection, hypoxia, hypercarbia and acidosis.[1]

Antibiotics

Exacerbations with clinical signs of infection (increased volume and change in the colour of sputum and/or fever, leukocytosis and/or raised inflammatory markers such as C-reactive protein) benefit from antibiotic therapy, which reduce the volume and purulence of sputum,[36] as well as hasten recovery.

When antibiotics are indicated the *Respiratory Therapeutic Guidelines 2005* recommend using:

- Amoxycillin 500mg orally, 8-hourly for five days OR
- Doxycycline 100mg orally, twice daily for five days.*

A response is usually seen within three to five days, and a change of antibiotic should be considered if the response is unsatisfactory. In more severe COPD, however, 10-day courses are often required for complete recovery.

** It is important to note that many respiratory physicians are cautious with the standard doxycycline therapy mentioned above, and tend to advise doxycycline 100mg twice-daily for the first day and then 100mg daily thereafter to minimise the potential for gastrointestinal intolerances.*

Macrolides are much less likely than other antibiotics to suppress *H. influenzae* and are more likely to result in early relapse — they are therefore not recommended unless

H. influenzae infection has been excluded. Antibiotics other than amoxycillin or doxycycline (e.g. macrolides, cephalosporins, and amoxycillin+clavulanate) have not been shown to be superior and are not recommended.[36] These antibiotics have not been shown to be inferior and could therefore be recommended where there has been antibiotic failure or known resistance to standard antibiotics.

Bronchodilators

Inhaled salbutamol or terbutaline (combined with the patients' regular COPD medication) can be given at higher doses and/or frequencies than used in the management of patients with stable COPD or can be given via a spacer or nebuliser. Nebulised therapy should be used if symptoms are not controlled with a spacer.[22] For an initial treatment of an acute exacerbation of COPD use:[36]

- salbutamol 100µg MDI up to 8 to 10 inhalations (preferably via a large-volume spacer), repeated as required OR
- terbutaline 500µg DPI, 1 to 2 inhalations repeated as required.

It is inappropriate to cease regular maintenance therapy (such as tiotropium), and replace with ipratropium for acute exacerbations (as ipratropium does not provide any additional benefit to salbutamol in this setting, and tiotropium is more effective than ipratropium in every clinical parameter). See ***Anticholingerics***.

If symptoms are severe or poorly controlled, combine either salbutamol or terbutaline with ipratropium at the doses indicated above. Use of an MDI via spacer is as effective as nebulisation for the delivery of beta-2 agonists in managing episodes of acute airflow obstruction. The dose interval is titrated to the response and can range from hourly to six-hourly,[1] however it is recommended that patients seek medical attention if bronchodilators are needed more than three hourly.[36]

Glucocorticoids

Oral corticosteroids reduce the severity of exacerbations, shorten recovery from acute exacerbations and reduce the likelihood of relapse.[1,20,37] Up to two weeks therapy with prednisolone (30-50mg) is adequate, as longer courses add no further benefit and have an increased risk of adverse effects such as hyperglycaemia and bone density loss.[38]

Tapering of glucocorticoid therapy is not necessary after short-term administration. However, patients who have taken glucocorticoids for more than three consecutive weeks may have adrenal suppression,[31,39] and their glucocorticoid therapy should not be ceased abruptly.

Patients on long-term oral steroid therapy (≥7.5 mg prednisolone daily for more than six months) are at risk of developing osteoporosis. Prevention and treatment of steroid-induced osteoporosis should be considered.[1]

Controlled oxygen therapy

This is indicated in patients with hypoxia, with the aim of improving oxygen saturation to over 90% (PaO_2 >50mmHg, or 6.7kPa), and is usually given in the ambulance or emergency department to patients.[36] Patients with moderate to severe COPD are at an increased risk of developing hypercapnia if they breathe high-inspired oxygen concentrations, thus nasal prongs (e.g., 2-4 LPM maximum) , which deliver controlled flow rates of oxygen should be used rather than Hudson masks which deliver high-flow uncontrolled oxygen.[36]

Systemic effects of COPD

The systemic side effects of COPD described to date include:[40-41]

- weight loss
- poor nutrition
- skeletal muscle dysfunction
- cardiovascular disease
- hypertension and cor pulmonale
- depression
- osteoporosis.

Weight loss and poor nutrition

Unexplained weight loss occurs in about 50% of patients with severe COPD, but it can also be seen in about 10 to 15% of patients with mild to moderate disease.[39,40] Patients with COPD have an increased basal metabolic rate which may be due to the increased work of breathing that characterises the disease, tissue hypoxia, systemic inflammation or drugs that are commonly used in the treatment of COPD (beta-2 agonists).[39,40] Weight loss in COPD is mostly due to skeletal muscle atrophy and a low body mass index (BMI<21) and low fat-free mass (which reflects muscle mass) have been associated with a significant increase in the risk of mortality.[42] The BODE index represents a multidimensional approach in assessing mortality risk as it considers several systemic consequences of COPD including BMI (B), the degree of airflow obstruction (O), dyspnoea (D) and exercise capacity (E).[43]

Alternatively, excessive weight increases the work of breathing and predisposes patients to sleep apnoea.[1]

Malnutrition is a common problem in COPD patients, and is largely caused by an imbalance between low-energy intake and high-energy requirements, leading to muscle wasting and dysfunction.[44] Patients with COPD should not eat large meals as this can increase dyspnoea. Several small nutritious (high energy, high protein) meals are better tolerated. Snacks may provide a useful addition to energy and nutrient intake. Referral to a dietician for individual advice may be beneficial.

Skeletal muscle dysfunction

Skeletal muscle dysfunction occurs and loss of muscle mass is common in patients with severe COPD and contributes significantly to limited exercise capacity and reduced quality of life.[41] Improving nutrition and encouraging regular activity or pulmonary rehabilitation with specific strength-building and/or endurance training can reduce or prevent skeletal muscle weakness. Anabolic agents have shown inconsistent benefits and significant adverse effects, and are not currently recommended.[1,2]

Cardiovascular disease

More patients with COPD die of cardiovascular causes and lung cancer than respiratory causes, and patients with COPD have a high morbidity and mortality from stroke and coronary heart disease.[45-47] COPD increases the risk of cardiovascular disease by two to three fold.[41]

The biological mechanisms responsible for the association between COPD and cardiovascular disease are poorly understood. Smoking is a well recognised risk factor for both COPD and cardiovascular disease, however recent evidence has shown that patients with COPD also have increased arterial stiffness and higher blood pressure independent of smoking status.[48]

Increased awareness and targeted treatment of cardiovascular risk and hypertension has the potential to reduce morbidity and improve prognosis in COPD.

Pulmonary hypertension and cor pulmonale

Pulmonary hypertension in COPD is likely the result of multiple factors including pulmonary vasoconstriction due to local hypoxia and vasoconstrictor peptides produced by inflammatory cells.[49] Whilst this initially more precisely matches lung perfusion to areas of better ventilated lung and therefore helps to maintain blood gases, right

ventricular hypertrophy (cor pulmonale) and right heart failure result as an adaptive response to long-term increased pressure. The development of pulmonary hypertension and peripheral oedema is a poor prognostic sign in COPD, and if left untreated, the five year survival is around 30%.[49]

Besides optimising COPD management, treatment may include the use of long-term oxygen therapy to partially relieve pulmonary vascular constriction,[50] diuretics to reduce fluid retention and ACE inhibitors such as captopril and enalapril may also be useful.[51] While calcium antagonists have short-term beneficial effects, their long-term benefits balanced against adverse effects have not been confirmed.[52]

Depression

Depression, anxiety and panic are frequent complications of chronic disabling breathlessness, with dependence and social isolation being common.[53] The natural progression of COPD results in functional constraints and limitations in completing activities of daily living, and as a consequence, patients enter a cycle of inactivity that leads to physical deconditioning. This is associated with the development of dyspnoea at lower exercise intensities and significant deterioration of health status.[54]

Factors such as limitations in daily activities, the need to change jobs or consider early retirement and the restriction of recreational interests, result in progressive and significant depression.

Depression occurs in 51-74% of patients with COPD.[53] Various studies have shown that less than 40% of anxiety or depressive disorders in COPD patients are recognised, and only 30% of patients with depression or anxiety and only a slightly higher percentage of those with severe anxiety and/or depression are being treated.[55]

General support, specific behavioural training and the use of appropriate antidepressant medication may enhance quality of life for the patient as well as the spouse or carer.[1]

Pharmacist tip:

Pharmacists should be aware of the signs and symptoms of depression and refer patients to their doctor for assessment.

Patients taking anti-depressant medications should be counselled using the CMI and encouraged to discuss any concerns about adverse effects, mood changes or thoughts about suicide with their GP. Pharmacists should monitor potential interactions and provide clear instructions to patients when switching anti-depressant therapies.

Osteoporosis

There is a high prevalence of accelerated bone loss in the COPD patient population, which is often undiagnosed.[56] Patients with COPD have high rates of bone fracture (11-14%) and bone mineral density (BMD) an average of 10% lower compared with control patients, which equates to a 2.6 fold increase in fracture risk.[1]

One of the most obvious cases of osteoporosis in these patients is treatment with both systemic and inhaled glucocorticoids. A cross sectional study, predominantly in females, showed a prevalence of osteopenia and osteoporosis in 68% of patients with COPD, which concluded that steroid use alone was insufficient to explain the high prevalence.[56]

Risk factors for low BMD in patients with COPD include:[1,56]

- periods of immobilisation or hospitalisation
- low FEV_1
- use of oral corticosteroids
- decreased weight-bearing activity
- smoking
- low calcium intake
- low BMI/poor nutrition
- alcohol abuse
- hypogonadism.

Pharmacist tip:

Pharmacists can encourage patients to reduce risk factors for osteoporosis, such as smoking and regular and excessive alcohol use. Refer patients on long-term high dose corticosteroids to their doctor for a bone mineral density test and thorough assessment, as fracture risk is related to the severity of reduction in bone density and the duration of exposure to corticosteroids.

Patients should be encouraged to exercise and to attend a pulmonary rehabilitation program (depending on the severity of their COPD) and patients should be referred to a dietician for nutritional assessment. Encourage patients to maintain adequate calcium intake (>1000mg/day) and vitamin D (400-800 units/day) intake[57,58] and obtain supplements in consultation with their doctor and pharmacist if needed.

Pharmacists can assist with minimising the risk of falls for patients by encouraging them to wear correct footwear, improve lighting, remove objects that may cause falls and have their eyes checked regularly.

Intervention should be targeted at men and women who are taking more than 7.5-15mg daily of prednisolone or have several of the risk factors and whose BMD is <1.5 standard deviations below the young adult mean.[1]

All patients who take corticosteroids should be advised to undertake regular weight-bearing exercise. Oral bisphosphonates are effective in both the prevention and treatment of glucocorticoid induced osteoporosis with the best current data supporting alendronate and risedronate.[57] Other agents that have been used with some success in patients with respiratory disease include calcium, calcitonin, Vitamin D and medroxyprogesterone acetate[1]. A calcium intake of at least 1000mg daily is recommended in all patients receiving glucocorticoids.[57]

Other aggravating factors

Insomnia and sleep apnoea

It is believed that more than 50% of COPD patients have sleep complaints characterised by longer latency falling asleep, more frequent awakenings, or generalised insomnia, which tend to be more severe with advancing disease and contribute to decreased quality of life.[59]

Some of the factors that contribute to poor sleep in COPD patients include:[60]

- delayed sleep onset
- symptoms that disturb sleep (eg: cough, sputum or dyspnoea)
- hypoventilation
- disturbed gas exchange
- medications (e.g. corticosteroids or theophylline can cause insomnia, and beta-agonists may produce sufficient adrenergic stimulation to interfere with initiating and maintaining sleep[61])
- depression.

If the patient also has sleep apnoea, the following measures should be considered:[36,60]

- weight reduction (10-15% has been associated with significant reductions in upper airway obstruction)
- smoking cessation
- avoidance of night-time alcohol and drugs causing sedation
- treatment of nasal congestion
- good sleep hygiene (eg: avoid caffeine, avoid prolonged daily naps, exercise in the day etc.)
- relaxation techniques
- change in sleep position.

Some of these generic measures can be factored into the overall treatment of any COPD patient (regardless of whether they have sleep apnoea).

Pharmacological treatments for insomnia such as benzodiazepines and non-benzodiazepine hypnotics should be avoided in COPD,[62] as they are associated with respiratory depression, hypoxaemia, an increased risk of pneumonia and can worsen sleep-related hypoventilation.[60] Generally, if a hypnotic agent is needed for insomnia, a short-acting agent is preferred and potential benefits must be weighed against the risks.[62]

Gastro-oesophaegeal reflux

Hyperinflation, coughing and the increased negative intrathoracic pressures of inspiration may predispose patients to reflux, especially during reclining or sleeping. The presence of gastroesophageal reflux symptoms appears to be associated with increased exacerbations in COPD[26]. Lifestyle changes such as smoking cessation, reduction of caffeine and alcohol consumption, weight loss and exercise should be discussed, and consider trialling H_2-antagonists or a proton pump inhibitor in patients who still complain of symptoms[49].

Aspiration

COPD patients are more prone to aspiration because of impaired swallowing efficiency. Hyperinflation impairs lower oesophageal sphincter efficiency and the upper oesophageal sphincter relaxes during REM sleep resulting in a high risk of aspiration. Patients with aspiration are more likely to develop pneumonia and have reduced ventilatory reserve.[49] Treatment involves re-training in safe swallowing techniques; therefore patients ideally should be assessed by a dietician and speech pathologist.[49]

Dental health

There is a weak association between poor oral health and COPD, and dental decay and poor oral hygiene has been identified as a potential risk factor for pneumonia.[63]

There is good evidence that improved oral hygiene and regular professional oral health care reduces the progression or occurrence of respiratory disease, in particular the progression or occurrence of pneumonia.[63]

Alcohol and sedatives

Prolonged and heavy exposure to alcohol impairs mucociliary clearance[64] and hypnotics are associated with respiratory depression, hypoxaemia, hypoventilation and an increased risk of pneumonia, and so should be avoided.[59]

Revision of pharmacology

The autonomic nervous system

The autonomic nervous system is responsible for maintaining and controlling the involuntary effects of the human body. The autonomic nervous system regulates the contraction and relaxation of smooth muscle thus controlling the diameter of the bronchioles, the rate of breathing and regulating the rate of airflow.[57]

The autonomic nervous system is further divided into the sympathetic nervous system and parasympathetic nervous system (as well as the *enteric nervous system*). In the respiratory system, the sympathetic and parasympathetic systems have opposing actions. Stimulation of the sympathetic nervous system (SNS) causes the smooth muscle of the bronchi and bronchioles to relax, causing bronchodilation, whereas stimulation of the parasympathetic nervous system (PNS) causes smooth muscle to contract, leading to bronchoconstriction. Table 4 provides a summary of the neurotransmitters involved in the SNS and PNS and their primary receptor subtypes.[57]

Adrenergic receptor subtypes include:[57]

- Alpha adrenergic (α_1 & α_2): these have several functions including vasoconstriction of the arteries the heart and veins, as well as effects on the motility of smooth muscle in the gastrointestinal tract and will not be discussed here.
- Beta adrenergic (β_1 & β_2):
  - β_1 – Have a number of different locations and functions centred around heart rate and contractility of the heart muscle, and thus will not be discussed here
  - β_2 – Also have a number of different functions; however, stimulation results in smooth muscle relaxation resulting in bronchodilation.

Muscarinic receptor subtypes with different functions have been found in human airways:[58]

- **M_1 receptors** facilitate ganglionic transmission and enhance cholinergic reflex bronchoconstriction (blocking M_1 receptors would cause bronchodilation)
- **M_2 receptors** are located on cholinergic nerve endings and act as feedback inhibitors of acetylcholine release (blocking M_2 receptors would result in an increase in ACh and ultimately bronchoconstriction)
- **M_3 receptors** are located in the smooth muscle of the airways, submucosal glands and, endothelial cells and epithelium. They mediate bronchoconstriction and mucus secretory response to ACh and cholinergic nerve stimulation (blocking M_3 receptors would cause bronchodilation).

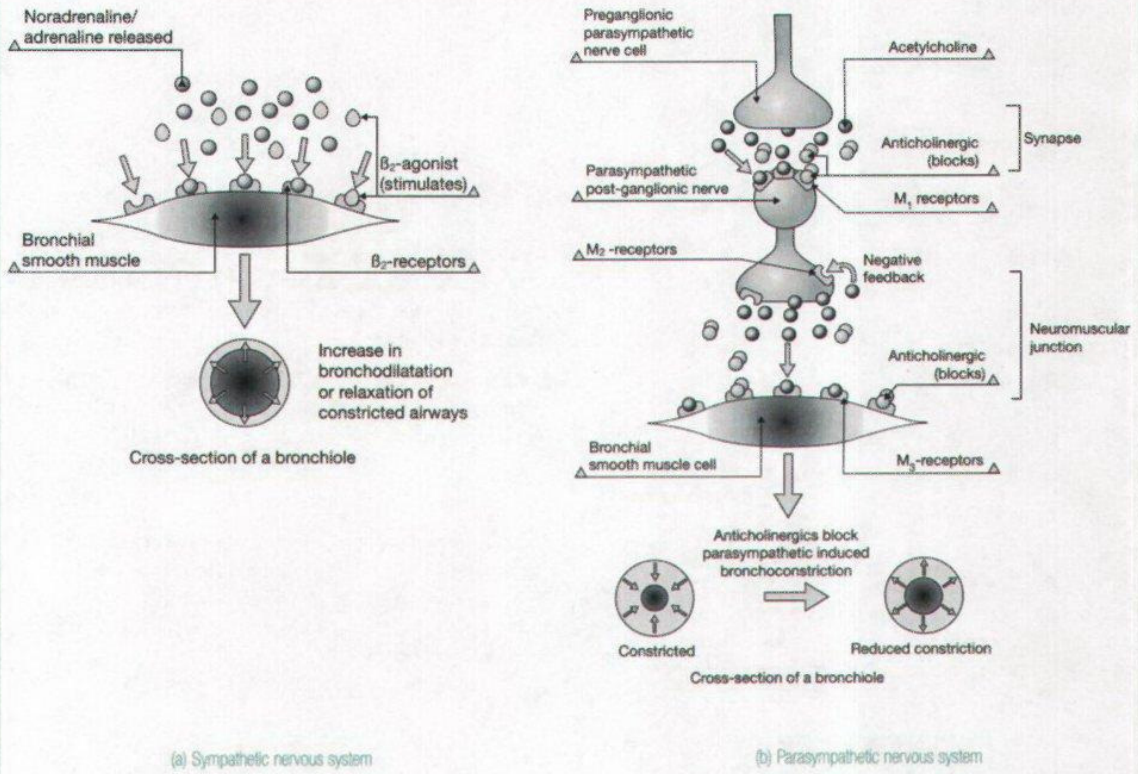
M_4 and M_5 receptors are expressed in human tissues but have not been detected in human airways.

Figure 5. (a) & (b) illustrates the effects of β_2 agonists and anticholinergic agents on airway smooth muscle.

Table 4: Neurotransmitters and receptors of the sympathetic and parasympathetic nervous systems

	Sympathetic nervous system	Parasympathetic nervous system
Pre and post ganglionic neurons	Adrenergic or noradrenergic	Cholinergic
Primary types of neurotransmitters	Noradrenaline and adrenaline	Acetylcholine (Ach)
Primary types of receptors	Alpha adrenergic (α1 & α2) Beta adrenergic (β1 & β2)	Muscarinic (M1, M2, M3 ...etc) Nicotinic
Result of stimulation	Airways dilated and reduced airflow obstruction Bronchodilation	Airways constricted and increased airflow obstruction Bronchoconstriction

Figure 5. (a) Mode of action of β2 agonists on airway smooth muscle by stimulation of the sympathetic nervous system; (b) Mode of action of acetylcholine in the parasympathetic nervous system.



Impaired lung function in COPD is caused by structural narrowing of the airways combined with the effects of cholinergic vagal bronchoconstrictive tone and decreased elastic recoil.[51] Bronchodilators improve the airflow limitation observed in patients with COPD by producing airway smooth muscle relaxation, although β_2 agonists and anticholinergics achieve this effect through different mechanisms.[68]

COPD treatment

Stable COPD

The aims of treatment are to:

- Minimise risk factors
- Improve symptoms
- Prevent disease progression
- Prevent future exacerbations
- Delay death
- Improve quality of life.

In order to manage disease progression, at risk patients should be identified and referred early to their general practitioner or specialist for appropriate treatment. There are a number of different treatments used in managing stable COPD, which are aimed at reducing symptoms and/or complications.

Clinical trials are currently investigating possible treatments which may have an impact on slowing disease progression; however there are no current pharmacological treatments that have been shown to slow the decline in lung function significantly over a long period of time.

A stepwise treatment approach should be undertaken for stable COPD which is dependant on symptoms and disease severity.

Bronchodilators

Bronchodilators are the mainstay of pharmacological therapy for COPD, and are recommended by current and international guidelines as first line therapy in symptomatic patients and those with demonstrated airflow limitation.[68] Inhaled short acting bronchodilators are currently recommended for the rescue of symptoms, whereas inhaled long-acting bronchodilators (in particular long acting anticholinergics) are recommended as first-line agents for maintenance therapy in patients with mild, moderate or severe disease.[69] This is mainly due to the fact that increased cholinergic tone is important in the pathogenesis of COPD and contributes both to increased bronchial smooth muscle tone and mucus hypersecretion.[69]

There is some evidence that anticholinergic drugs can have effects on inflammatory cells including neutrophils, macrophages and T-lymphocytes, raising the possibility that anticholinergics might also have some anti-inflammatory effects,[65] although to date this has not been confirmed in patients with COPD.

When symptoms are not sufficiently controlled by the use of one long-acting bronchodilator, combining bronchodilators of different classes is a more effective approach.

Anticholinergics

Anticholinergics are the bronchodilators of choice in the management of COPD. Cholinergic tone is the major reversible component of airway obstruction in COPD, and anticholinergics promote bronchodilation by inhibiting cholinergic bronchomotor tone.[70] Two anticholinergic agents are currently available in Australia:

1. Ipratropium (*Atrovent*) – short acting anticholinergic
2. Tiotropium (*Spiriva*) – long acting anticholinergic

Generally, there is no significant systemic absorption and anticholinergic side effects are uncommon, even with nebulised drugs.[68] The most common side effect is dry mouth (occurs in 14-16%), which is mild in the majority of cases and tends to occur in the first three to five weeks of treatment.[69]

Concomitant use of ipratropium and tiotropium is not recommended because of the potential for an increase in systemic anticholinergic adverse effects. Anticholinergics should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

Pharmacist tip:

Pharmacists can advise patients to rinse their mouth with water after using their medication to minimise the risk of adverse effects.

Ipratropium

Ipratropium is short acting bronchodilator which acts on all three muscarinic receptors (M_1, M_2 and M_3), and has long been used as maintenance therapy in COPD. Its duration of action is approximately six to eight hours so it requires dosing four times a day.[72] The onset of action is ~30-60 minutes; therefore it is not suitable for use as a reliever medication.[72]

Ipratropium has a significantly greater effect on lung function compared to short-acting β_2 agonists, in addition to improving quality of life and decreasing the need for oral corticosteroid treatment.[1] Its use is being superseded by tiotropium, as tiotropium taken once daily is more effective than the standard ipratropium dose in every clinical parameter.[65] The formulations of ipratropium available that are indicated for bronchodilator maintenance treatment of bronchospasm associated with COPD, are the metered aerosol (MDU) and unit dose vials (UDV) for inhalation.[72]

Pharmacist tip:

For patients switching from ipratropium to tiotropium, one strategy has been to discontinue ipratropium and use a short acting β_2 agonist on an as needed basis while waiting to reach the peak effect with tiotropium.

Tiotropium

Tiotropium has become first-line therapy in COPD.[73] It is a long acting anticholinergic drug which has similar binding affinity for the M_1, M_2 and M_3 receptors, however dissociates more slowly from M_1 and M_3 receptors and more rapidly from M_2 receptors. When compared to ipratropium, tiotropium dissociates much more slowly from the M_3 receptor resulting in a longer duration of activity and a once daily dose (see Table 5 below).[70]

Table 5: Dissociation of ipratropium and tiotropium from muscarinic receptors

Muscarinic receptor subtypes	Ipratopium	Tiotropium
M_1	0.11h	14.6h
M_2	0.035h	3.6h
M_3	0.26h	34.7h

Current evidence suggests that tiotropium is more effective than LABAs.[74] Tiotropium has been shown to improve lung function; even in patients with COPD not previously on any maintenance treatment,[75,76] and sustained improvements in lung function have been demonstrated over a year.[77] The current UPLIFT trial (Understanding Potential Long-term Impacts on Function with Tiotropium) is a four year trial designed to study the potential for tiotropium to slow the decline in lung function and reduce symptom progression in patients with COPD.[43] Results are expected to be available in late 2008. Tiotropium has been demonstrated to improve airflow, reduce air trapping and breathlessness, increase activity, and improve quality of life in patients with COPD.[74]

Tiotropium is the only long-acting bronchodilator subsidised on the PBS for all severities of COPD, being PBS listed for the long-term maintenance treatment of bronchospasm and dyspnoea associated with COPD.[35] The dose of tiotropium is inhaled once daily via a *HandiHaler* device. It is not intended as a rescue medication and therefore should not be used for the initial treatment of acute episodes of bronchospasm. Tiotropium is also the only treatment indicated for the prevention of exacerbations.

Pharmacist tip:

Pharmacists should advise patients to replace their *HandiHaler* every 12 months. An improved version of the *HandiHaler* is now available which has been redesigned for ease of use.

Beta-2 agonists

Beta-2 agonists stimulate β_2 adrenoreceptors which causes relaxation of bronchial smooth muscles through the activation of adenylate cyclase pathways. Although the major action of beta-2 agonists on airways is smooth muscle relaxation, they may also have other effects on inflammatory mediator release, mucociliary transport and airway smooth muscle cell proliferation.[66] There are two main categories of beta-2 agonists:

1. SABAs (short acting β_2 agonists)
2. LABAs (long acting β_2 agonists).

SABAs are generally well tolerated, however may cause episodes of tremor and tachycardia.[66] Serious hypokalaemia may occur with high doses of beta-2 agonists which may be worsened by theophyllines, corticosteroids, diuretics and hypoxia.[36] They should be used with caution in patients with underlying cardiac disorders, including ischaemic heart disease.[69]

SABAs

SABAs have a rapid onset of action (5-15 minutes) and are useful for obtaining prompt relief of symptoms.[36,72] Due to their short duration of action (3-6 hours), they must be given four times daily to achieve sustained bronchodilation and are thus not used as maintenance treatment in COPD – they are prescribed for use as rescue medication (i.e: for relief of breathlessness).[36,38,69]

SABAs currently available include:

- Salbutamol (*Ventolin; Asmol*)
- Terbutaline (*Bricanyl*).

LABAs

LABAs have a long duration of action (>12 hours), are dosed twice daily and are useful in COPD for those patients who remain symptomatic despite treatment with short acting bronchodilators. LABAs have been shown to significantly improve lung function, health status and symptom reduction compared with placebo and ipratropium.[69]

LABAs currently available include:

- Salmeterol (*Serevent*)
- Eformoterol (also known as formeterol) (*Oxis; Foradile*).

The efficacy of eformoterol 12μg bd is comparable to salmeterol 50μg bd and superior to ipratropium 40μg qid in improving lung function, controlling COPD symptoms, and reducing the need for rescue medications.[78] Long-acting beta-2 agonists are not currently listed on the Pharmaceutical Benefits Schedule (PBS) for use in patients with COPD; however, mono-therapy with a LABA has been shown to reduce the frequency of exacerbations compared with placebo.[38]

LABAs (long acting β_2 agonists), may have additional bronchodilator effects and may be added successfully to inhaled anticholinergic therapy.[69]

Pharmacist tip:

Pharmacists can identify poorly controlled patients by monitoring the use of 'rescue medication'. Patients with regular symptoms, who require rescue medication >2 times per week should be on maintenance treatment, so should be referred to their GP for assessment and add-on therapies.

Turbuhaler devices are not ideal for use during exacerbations as they are breath activated and require a deep inhalation.

Theophylline

Theophylline is a non-selective phosphodiesterase inhibitor that acts both as a weak bronchodilator and a respiratory stimulant, and has some anti-inflammatory properties.[69]

The use of theophylline has declined in recent years as it has been superseded by inhaled anticholinergics and beta-2 agonists, and is considered third line therapy, when symptoms persist despite optimal bronchodilator therapy,[65] or when patients are unable to use inhaled therapy.[36] Another reason for the decline in theophylline use is due to its narrow therapeutic window, requiring monitoring of plasma theophylline levels and the potential for drug interactions and adverse effects (such as gastro-oesophageal reflux).[36,38] Theophylline is available as conventional (*Brondecon Elixir; Brondecon Expectorant; Nuelin Syrup*) and controlled release oral formulations (*Nuelin SR*).[72] Use of conventional oral formulations is associated with a high incidence of adverse effects due to rapid absorption.[38]

Corticosteroids

Corticosteroids reduce bronchial mucosal inflammation possibly as a result of direct binding of the activated glucocorticoid receptor (GR) to glucocorticoid response elements (GREs) in the promoter region of target genes or indirectly via the ability of the GR to interact with other nuclear transcription factors thereby enhancing or suppressing their effects.[79]

Whereas corticosteroids have a well established role in the treatment of asthma, and have become first line preventer treatment in people with persistent disease, their place in the treatment of COPD is less clear.[80] COPD is characterised by a type of airway inflammation different from that seen in asthma and appears to be relatively resistant to treatment with corticosteroids.[80]

Oral corticosteroids

The long term use of systemic corticosteroids in COPD is not recommended.[1,66] Studies indicate that only 20-30% of all patients with COPD show improvement in lung function with steroid treatment.[81]

Oral corticosteroid reversibility tests do not predict response to inhaled corticosteroids and thus should not be used to identify which patients should be prescribed inhaled corticosteroids.[36] The response to glucocorticoids should be assessed with spirometry and measures of performance status and/or quality of life.[1]

Oral glucocorticoids are used during exacerbations as controlled trials have shown that their use in patients who are admitted to hospital with an acute exacerbation have a reduced rate of treatment failure, improvement in FEV, within 24 hours and shortened hospital stay.[1] Tapering of glucocorticoids is not necessary following short-term administration;[1] however in some patients with very severe COPD, oral corticosteroids cannot be withdrawn after an exacerbation without deterioration in the patient's condition. In these patients, oral corticosteroid should be continued at the lowest possible dose and preventative pharmacotherapy for osteoporosis should be considered.[22,33,37]

Inhaled corticosteroids

Inhaled corticosteroids (ICS) have been shown to reduce the number of exacerbations, but only with high doses in moderate to severe, not mild COPD.[37]

Regular treatment with ICS does not modify the long-term decline of FEV_1 in patients with COPD. The recent TORCH study concludes otherwise, but is open to interpretation. High-dose Inhaled corticosteroids are indicated only in patients with severe disease who have frequent exacerbations.[70] This treatment has been shown to reduce the frequency of exacerbations and thus improve health status. Guidelines recommend adding inhaled corticosteroids to long acting bronchodilators in patients with severe COPD (FEV_1 ≤50%) and frequent exacerbations (two or more exacerbations a year).[38]

Only high-dose inhaled corticosteroids are effective in moderate to severe COPD, and high doses increase the risk of the following adverse effects:[33]

- Oropharyngeal candidiasis and dysphonia
- Adrenal impairment, skin thinning and bruising, osteoporosis, cataracts and glaucoma, particularly in older people
- Pneumonia.

A recent cohort study of patients with COPD found that current inhaled corticosteroid use was associated with a significant 70% increase in the risk of being hospitalised for pneumonia.[80] In this study the use of inhaled corticosteroids was associated with an excess risk of pneumonia hospitalisation and of pneumonia hospitalisation followed by death within 30 days among elderly patients which COPD.[80] Withdrawal from inhaled corticosteroids should be undertaken with care as sudden cessation can lead to an exacerbation in some cases.[38]

Pharmacist tip:

To minimise oropharyngeal candidiasis and systemic absorption of inhaled corticosteroids, patients should be advised to rinse their throat and mouth with water and spit out after inhalation. Patients using an MDI should also be advised to use a spacer to lessen the risk of the above and also dysphonia.[38]

Combination products

Inhaled corticosteroids combined with long-acting beta-2 agonists (ICS + LABA), are more effective than the individual components. Fluticasone and salmeterol have been shown to improve FEV_1 more than either fluticasone or salmeterol alone in people with moderate to severe disease.[33] ICS + LABA combination products have been shown to improve lung function, symptoms, health status and reduce exacerbations in patients with moderate to severe COPD.[69]

Currently, there are two long-acting beta-2 agonists plus inhaled corticosteroid combination products available:[72]

1. Salmeterol plus fluticasone (*Seretide*)
2. Eformoterol plus budesonide (*Symbicort*)

Symbicort is not indicated for COPD. Seretide is indicated for the symptomatic treatment of COPD, where the FEV_1 is less than 50% predicted normal and there is a history of repeated exacerbations with significant symptoms despite regular beta-2 agonist bronchodilator therapy.[35] This listing only applies to fluticasone with salmeterol 250/25 MDI and 500/50 dry powder inhaler (DPI); it is not indicated for the initiation of bronchodilator therapy in COPD.[33]

Fluticasone with salmeterol has been shown to improve FEV_1 and reduce exacerbations more than either fluticasone or salmeterol given alone in moderate to severe COPD.[33] The combination of fluticasone with salmeterol has no statistically significant effect on mortality.[46]

Only patients who show a clear and clinically significant benefit should continue combined therapy, so response to treatment should be assessed by monitoring symptoms and FEV_1, and stopped if there is no significant response after 4-8 weeks.[33]

Pharmacist tip:

It is estimated that up to 70% of patients have poor inhaler technique[36] which results in sub-optimal delivery of medication. Pharmacists can play an active role in counselling the patient on the correct technique and storage and care of medication and delivery devices.[81]

Using the product CMI plus physical demonstration significantly improves patient technique.[81] Patients with COPD may have trouble generating a deep breath, especially when sitting down. Patients should be encouraged to stand when using their inhalers. Encourage the patient to demonstrate the appropriate technique at the time of consultation to check correct use.

It is important to reinforce correct technique when the patient is reviewed and at any time there is an acute exacerbation or evidence of disease deterioration as inhaler technique may begin to decline two months after patient education.[36]

Figure 6. Suggested treatment algorithm for stable COPD

			Add an inhaled corticosteroid * # ^ϕ **Continue regular maintenance therapy and long acting β_2 agonist + short acting β_2 agonist prn**
	Start maintenance therapy and continue short acting β_2 agonist prn	**Add long acting β_2 agonist** **Continue regular maintenance therapy and short acting β_2 agonist prn**	
Short acting bronchodilator prn Salbutamol 100-200µg MDI prn up to qid OR Terbutaline 500µg prn up to qid OR Ipratropium bromide 40-80µg prn up to qid+	Tiotropium bromide 18µg once daily + Salbutamol 100-200µg MDI prn	Tiotropium bromide 18µg once daily + Eformoterol 12µg bd OR salmeterol 50µg bd	Tiotropium bromide 18µg once daily + Eformoterol 12µg bd OR salmeterol 50mg bd + Fluticasone 250-375µg bd OR Budesonide 800µg bd or beclomethasone diproprionate 300-400µg bd
Intermittent symptoms COPD not confirmed	**Mild COPD** FEV_1 60-80% predicted	**Moderate COPD** FEV_1 40-59% predicted	**Severe COPD** FEV_1 <40% predicted

* Treatment should be initiated with single ingredient preparations of fluticasone and salmeterol to allow assessment of response and dose adjustment of each drug as recommended by the guidelines.

May substitute individual ICS and LABA with combination product (250/50µg bd increasing to 500/50µg fluticasone/salmeterol bd if necessary).

^ Combination fluticasone and salmeterol should be considered for people with COPD who have FEV_1<50% of predicted normal and symptoms that are poorly controlled despite regular β2 agonist therapy.

+ Avoid combination with tiotropium.

ϕ No single ingredient inhaled corticosteroids have a COPD indication.

Suggested treatment algorithm

Pharmacological management is dependent on symptoms and disease severity. The principle goals of therapy are to optimise lung function with medications and pulmonary rehabilitation, and to prevent or treat aggravating factors and complications.[1] Figure 6 summarises a suggested treatment algorithm for COPD patients which has been established based on a review of randomised controlled trials.[36,68]

Other considerations for long term treatment

Pulmonary rehabilitation

Pulmonary rehabilitation is a multidisciplinary program of care for patients with chronic respiratory impairment and is one of the most effective interventions in COPD.[83]

Comprehensive pulmonary rehabilitation programs may be hospital or community-based and typically incorporate exercise training, patient education/self management and psychosocial support to help patients reach and maintain a good level of functioning in the community. The aims of pulmonary rehabilitation are to:[1]

- Improve cardiovascular fitness, muscle function and exercise endurance
- Enhance patient self confidence and coping strategies
- Improve medication adherence and use of respiratory treatment devices
- Improve mood by controlling anxiety and panic, decreasing depression and reducing social impediments
- Aid in smoking cessation.

Pulmonary rehabilitation has been shown to reduce dyspnoea, anxiety and depression, and improve exercise capacity and quality of life.[1] It is mainly offered to patients with moderate to severe COPD, but is also relevant to patients with milder disease.[84]

Pulmonary rehabilitation reduces anxiety and depression by:[1,84]

- Enhancing the patients self-confidence and coping strategies
- Improving mood by controlling anxiety and panic, decreasing depression and reducing social impediments.

Short intensive group pulmonary rehabilitation programs should run for at least six weeks (the longer the program the greater the response), and patients should be encouraged to continue prescribed as well as casual exercise; 30 minutes per day is suggested.[36]

Patients may be referred to pulmonary rehabilitation by their general practitioner, specialists and/or pharmacist, and many programs accept patients who contact them directly. The Australian Lung Foundation maintains a comprehensive national database of programs and can supply contact details for programs Australia wide. For more information visit www.lungnet.org.au or phone 1800 654 301.

Smoking cessation

Smoking cessation should be encouraged at every opportunity and is the single most important intervention to prevent or slow the progression of COPD, decreasing lung function decline by 50%.[38]

Before starting treatment, a history of smoking habits should be obtained, including the number of cigarettes smoked per day, how soon after waking patients smoke a cigarette, previous attempts to stop quitting, as well as confidence and motivation to quit smoking.

The level of smoking dependence can be determined as described in Table 6.
Treatment choice should depend upon the smoker's preference, needs and tolerance, and should be combined with regular counselling and support in order to aid motivation, provide behavioural skills to enable continued abstinence and increase the chances of quitting.[1]

Table 6: Determining smoking dependence[38]

Level of dependence	Number of cigarettes smoked per day	Need to smoke in relation to sleep/ waking
High	> 30	Waking at night to smoke or smoking within the first 5 minutes after waking
Moderate	20-30	Smoking within 30 minutes after waking
Low-to-moderate	10-20	Not needing to smoke within the first 30 minutes after waking
Low	<10	Not needing to smoke in the first hour after waking

Non-pharmacological treatment is focused around counselling and behavioural techniques to aid and encourage smoking cessation, support services (e.g. Quitline), nutritional advice and an exercise program which may prevent or reduce weight gain.

Pharmacotherapy in addition to counselling and support should be offered to motivated patients who smoke more than 10 cigarettes per day.[38] There is no evidence that drug treatment will benefit people who smoke <10 cigarettes daily and these patients may become dependent on nicotine replacement therapy (NRT) if used.[22,37]

The aims of NRT is to replace some of the nicotine from cigarettes without the harmful constituents found in tobacco smoke, as well as reduce withdrawal symptoms associated with nicotine addiction.[85] NRT produces lower peak levels of nicotine than active smoking, and is safe in patients with stable cardiac disease.[1] NRT is available in a variety of formulations including gum, inhaler, lozenge, patch or sublingual tablet, and almost doubles the chance of quitting for a year compared with placebo (only six-months data for lozenges).[85] There is no evidence that one form of NRT is more effective than another, but higher strength preparations are more suitable for heavy smokers.[38]

Bupropion, which was originally developed as an antidepressant, has been shown to double the chance of quitting in comparison to placebo, but has only been assessed when combined with regular counselling, in subjects who were highly motivated to quit, and smoked an average of 15 or more cigarettes per day.[38] Bupropion may be offered to patients who relapse while using nicotine products and should be started at least seven days before the quit date and continued for seven to nine weeks.[38] Unlike NRT, bupropion can cause serious (rare) adverse effects, and has the potential to affect the metabolism of a number of drugs.

Table 7 is adapted from the *Smoking Cessation Guidelines for Australian General Practice* and the *COPDX Guidelines*, and summarises the advantages and disadvantages of pharmacological treatments for smoking cessation.[1,38,72,85,86]

There is only one study that compares bupropion and NRT for smoking cessation, where bupropion was found to be more effective than treatment with a nicotine patch, however further studies are needed to confirm overall benefit compared with other forms of NRT.[86] Smokers with severe nicotine dependence and those who have made many unsuccessful attempts to stop, may benefit from combining patches, and 2mg gum, or bupropion.[38]

The tricyclic anti-depressant nortryptyline has been shown to increase long-term quit rates, but should only been considered when other pharmacotherapies are contraindicated or not tolerated due to its adverse effect profile.[33,37,66]

Varenicline (*Champix*) is a nicotinic acetylcholine receptor partial agonist that aids smoking cessation by relieving nicotine withdrawal symptoms and reducing the rewarding properties of nicotine.[66] In clinical trials of generally healthy, motivated smokers, more people using varenicline (23%) had quit smoking at one year compared with those using bupropion (15%) or placebo (10%).[86]

Table 7: Advantages and disadvantages of pharmacological treatments for smoking cessation

Treatment	Advantages	Disadvantages	Practice points
Nicotine patch *(Available in 16hr and 24hr patches)*	Easy to use Discreet Few compliance problems	Mild local skin irritation may occur (especially if application site is not rotated). Some sleep disturbances with the 24 hour patch.	Apply patch to dry non-hairy skin above the waist Rotate site of application Remove the patch at night if sleep disturbance occurs or use 16 hour patch 24 hour patch is useful for those who need to smoke shortly after waking but is more likely to cause vivid dreams. After removal, nicotine absorption continues for up to two hours from nicotine already in the skin There is no difference in effectiveness between the 16hr and 24hr patch Eight weeks of patch therapy is as effective as longer courses and there is no evidence that tapered therapy is better than abrupt withdrawal
Nicotine gum	Provides oral substitute for smoking.	Correct chewing technique is important so need to spend time explaining correct use. Gum is commonly under-used so may have a negative impact on successful smoking cessation. Dependence may occur. Cannot be used in people with dentures.	There is evidence that 4mg gum results in higher cessation rates than 2mg gum in more dependent smokers (>20 cigarettes/day). Patient should be instructed to chew slowly (about 15 chews) until a peppery taste or tingling sensation is noticed, then park the gum in the cheek or tongue for 1-2 minutes or until the taste disappears. Repeat this cycle for 30 min. Three months of use is recommended by manufacturers followed by a period of tapering.
Nicotine lozenges	Easy to use Alternative to gum in denture wearers No special technique required	May cause hiccups in some patients	Allow to dissolve in the mouth for around 20 min without chewing or swallowing it whole If a patient smokes their first cigarette within half an hour of waking then the 4mg dose is suggested.
Nicotine inhaler	Mimics hand-to-mouth behaviour of cigarette smoking	May cause mild throat irritation, cough and occasionally taste disturbance Low nicotine levels Poor compliance	Typically 6-12 cartridges inhaled daily, according to craving or withdrawal symptoms for eight weeks, then gradually reduced over four weeks to zero. Aimed at those smokers that miss the hand to mouth action of smoking. 20 min of intense use removes all available nicotine from a cartridge.
Nicotine sublingual tablet	Easy to use – no need to chew Discrete	Number need to use and frequency of use	1-2 tablets should be placed under the tongue and allowed to dissolve slowly for about 30min (~every hour according to craving or withdrawal symptoms) for 8-12 weeks. Reduce use gradually over next four weeks to zero. Avoid chewing or swallowing the tablet

Table 7: Advantages and disadvantages of pharmacological treatments for smoking cessation (cont.)

Treatment	Advantages	Disadvantages	Practice points
Bupropion	Non-nicotine Can be used with patch Reduces urge to smoke and withdrawal symptoms.	Common side effects include insomnia and dry mouth. Other rare but serious side effects include seizures and tachyphylaxis. May affect mental alertness Check contraindications and specific considerations. Alcohol co-administration can increase the risk of fits and other unpleasant effects.	Start at least a week before stopping smoking as it takes about eight days of regular administration to reach steady state. Dose is initially 150mg once daily in the morning for three days, then 150mg twice daily for at least seven to nine weeks. Swallow whole - do not crush or chew tablets. Take in the morning when starting treatment to reduce the risk of sleep disturbance. Assess progress after seven weeks of treatment; stop drug if a marked reduction in smoking has not been achieved.
Varenicline	Non-nicotine Higher quit and continuous abstinence rates than bupropion	Nausea is a common side effect (~30%) and the most common reason for treatment withdrawal Possible psychiatric adverse events Treatment withdrawal can cause irritability, an urge to smoke, depression and sleep disturbances in up to 3% of people. New drug, so may be side effects which are not yet know.	Patients should start varenicline 1-2 weeks before their quit date and titrate the dose by taking 0.5mg daily for days 1-3; increasing to 0.5mg twice-daily for days 4-7; and continuing with 1mg twice-daily from day 8 to the end of the 12 week course. Patients should take varenicline with food and a full glass of water to reduce nausea. Dosage adjustments are necessary in renal impairment. Combination with NRT is not recommended due to an increase in nausea, headache, dyspepsia, fatigue and dizziness.

The effectiveness of varenicline on long-term abstinence rates beyond one year has not been studied and its safety and efficacy in smokers with serious medical or psychiatric illness has not been established. Varenicline is subsidised on the PBS for one 12 week course of treatment per patient per year.[35] The period between starting a course of varenicline and a course of bupropion for smoking cessation must be at least six months, and nicotine replacement therapies should not be avoided whilst taking varenicline.[86]

Influenza vaccination

All COPD patients should be vaccinated annually for influenza, as this reduces the development of severe respiratory complications and hospitalisation or death from respiratory disease and all causes by approximately 50%.[1]

Clinical trial evidence shows that influenza vaccination has a clinically important protective effect on influenza related exacerbations, and probably an effect on the total number of exacerbations in COPD patients.[88]

The NHMRC recommends that influenza vaccination be provided in early autumn, in anticipation of influenza outbreaks in winter.[89] Influenza vaccines normally contain the three recommended strains of purified inactivated virus; two current influenza A subtypes and influenza B, representing the circulating viruses.[89] Currently available influenza vaccines confer protection for about a year so in order to provide continuing protection, annual vaccination with the most recent strains is necessary. The influenza vaccination can be given at the same visit as the pneumococcal vaccination.[89]

Pharmacist tip:

Pharmacists can provide brief counselling to increase the chance of smoking cessation. Even a brief three minute period of counselling to urge a smoker to quit can be effective. Provide counselling using the **5As** strategy:[22,37,86,87]

- **A**SK and identify all smokers at every visit
- **A**DVISE smokers on the risks of smoking and the benefits of quitting
- **A**SSESS the willingness and motivation to attempt to quit
- **A**SSIST the patient to quit by providing counselling, pharmacotherapy and resources
- **A**RRANGE follow up visits within a week of the quit date and one month after

Provide brief counselling on the correct use of pharmacotherapies and the expected recommended duration of use.

Pneumococcal vaccination

Pneumococcal vaccination is known to be highly effective in the prevention of pneumococcal pneumonia and bacteraemia in previously healthy individuals as well as certain groups of patients at high risk of developing pneumococcal infections, but may be less effective in elderly or immunosuppressed patients.[1,90] There is no evidence that pneumococcal vaccination provides any protection against acute exacerbations, however protection against pneumonia remains an important treatment goal.[91]

Revaccination is recommended five years after the first dose for non-indigenous adults >65 years, and it should not be given within three years of the previous dose, because of an increased risk of local reactions.[89]

Antibiotics

Antibiotics should be used in exacerbations (see ***Exacerbations: Treatment***); however prophylactic antibiotics in COPD do not have a place in routine treatment because of concerns about the development of antibiotic resistance and the possibility of adverse effects.[1]

Mucolytics

Drugs that modify the physiochemical properties of sputum to assist expectoration may play a useful role in COPD. Mucolytic therapy may improve symptoms of COPD, and may reduce the frequency of exacerbations and the risk of rehospitalisation in some patients. It should be considered in patients with COPD who have a chronic cough productive of sputum that is difficult to expectorate and should be continued if there is a symptomatic response to treatment.[1] Bromhexine is an oral mucolytic available over the counter in Australia.

Antitussives

Antitussive therapy should not be used in the management of stable COPD. Antitussive therapy may suppress breathing and induce hypercapnia, and can be counterproductive by causing sputum retention and increasing the risk of bacterial infection.[48]

Statins

A recent prospective analysis has indicated that statin use is associated with slower rates of lung function decline in the elderly;[92] however there were several limitations to the study and further randomised controlled trials are needed to confirm any potential benefit.

Nutritional support

Randomised controlled trials of nutritional support in COPD have not shown significant improvements in nutrition, exercise capacity or other outcomes,[93] but referral to a dietician may educate COPD patients on nutrition, diets and supplements specific to the needs of the individual.

Advice on travel

Altitude changes during flying causes a decrease in oxygen saturation which increases the risk of hypoxaemia, so patients with moderate to severe COPD should be referred to be assessed for their fitness to fly, particularly those recovering from an acute exacerbation or on long term oxygen therapy.[1]

Pharmacist tip:

Pharmacists can advocate the importance of vaccination for influenza and pneumococcal to COPD patients in reducing exacerbations and should refer patients who are not immunised to their GP. This does not need to be restricted to the over 65-year-olds.

Benefits of treatment

Generally, patients can expect the following benefits from specific combinations of both pharmacological and non-pharmacological treatments:

- Improvements in lung function
- Reduced dyspnoea
- Improved exercise tolerance
- Reduced number of exacerbations
- Reduced number of hospitalisations and health resource utilisation
- Improved health status and quality of life
- Reduced need for rescue medication.

Most patients with COPD report that their breathlessness with activities increases over time.

Treatment can significantly improve dyspnoea which improves exercise tolerance and increases a patient's ability to carry out daily activities. The Medical Research Council (MRC) dyspnoea scale is an instrument used to measure the impact of breathlessness on daily activities and may be useful in monitoring a patient's progress over time[94] (Box 2), as well as being an important step in initial assessment when determining the severity of disease.

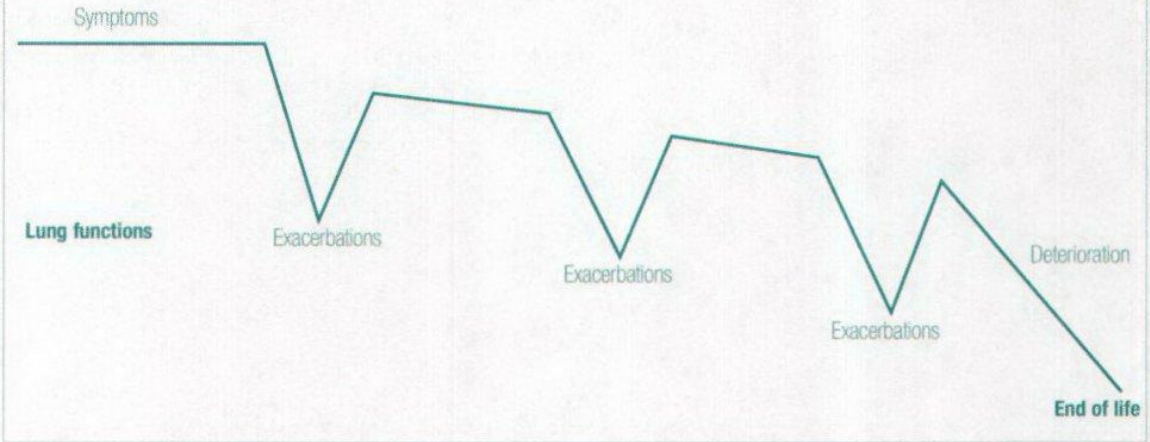
Box 2: MRC grading of functional limitation due to dyspnoea

GRADE 1:	'I only get breathless with strenuous exercise'
GRADE 2:	'I get short of breath when hurrying on the level or walking up a slight hill'
GRADE 3:	'I walk slower than most people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level'
GRADE 4:	'I stop for breath after walking about 100 yards or after a few minutes on the level'
GRADE 5:	'I am too breathless to leave the house' or 'I am breathless when dressing'

It is incorporated within the BODE score, and is an independent determinant of risk of death.

Many patients perceive no benefit when initially starting their inhaled maintenance medications and it is important to educate patients that continued maintenance treatment is expected not only to improve lung function, but importantly to prevent exacerbations and deterioration and have a positive impact on their ability to perform daily activities and their overall quality of life. Figure 8 illustrates the potential trajectory of deterioration should patients not be compliant with maintenance therapy and experience repeated exacerbations.

Figure 8. Potential lung function decline in patients with frequent exacerbations



COPD guidelines

The COPDX guidelines are the outcome of a joint project between the Thoracic Society of Australia and New Zealand, and The Australian Lung Foundation as part of The Australian Lung Foundation's national COPD program. The guidelines are based upon the Global initiative for Obstructive Lung Disease (GOLD) and are updated quarterly using the latest evidence from systematic reviews and large RCTs. The COPDX guidelines are recognised as best practice in the treatment and management of COPD in Australia.

The four key areas of the COPDX guidelines are:[1]

C Confirm diagnosis

O Optimise lung function

P Prevent deterioration

D Develop a support network and self-management plan

X Manage eXacerbations

For a full version of the COPDX guidelines visit www.copdx.org.au . The Australian Lung Foundation is the premier COPD patient and advocacy organisation in Australia and information and a number of resources on COPD for both patients and health care professionals. For more information visit www.lungnet.org.au or phone toll free 1800 654 301, for patient and health care professional information.

Pharmacist tip:

Pharmacists can play a pivotal role in improving health outcomes for patients by taking an active role in patient education and encouraging adherence to medications and the overall management plan. A clear explanation of the purpose of the drug and its intended effects may improve adherence to treatment.

Patient education can play a role in improving skills and the ability to cope with illness and should incorporate strategies to help minimise dyspnoea, advice about where to seek help and self management skills. Pharmacists can also play a role in conjunction with the patients GP to develop a COPD action plan outlining the patients overall management and important steps during an exacerbation.

Pharmacists can refer patients to patient support groups and pulmonary rehabilitation programs through The Australian Lung Foundation.

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Glossary

AAT: Alpha-1 antitrypsin; a glycoprotein produced in the liver which functions to protect the lungs from the neutrophil elastase enzyme. Normal blood levels of alpha-1 antitrypsin are 1.5-3.5g/L. In its absence, neutrophil elastase is free to break down elastin (which contributes to the elasticity of the lungs), resulting in respiratory complications such as emphysema and COPD.

Acetylcholine: Abbreviated (Ach); a direct acting cholinergic neurotransmitter.

Acidosis: Acidosis is an increased acidity of the blood plasma. Acidosis is said to occur when arterial pH falls below 7.35.

Adrenergic: Pertaining to the sympathetic nerve fibres of the autonomic nervous system that liberate noradrenaline at a synapse where a nerve impulse passes.

Alveoli: Tiny air sacs located at the ends of the smallest airways within the lungs, where the exchange of oxygen and carbon dioxide takes place.

Apnoea: Temporary cessation of breathing from any cause, formally defined as a reduction in nasal air flow to less than 30% of normal for more than 10 seconds.

Aspiration: The entry of secretions or foreign material into the trachea and lungs.

Atherosclerosis: Hardening of the arteries which is specifically due to an atheromatous plaque.

Atrophy: The partial or complete wasting of a part of the body.

Autonomic nervous system: Abbreviated (ANS); a subdivision of the peripheral nervous system. The ANS regulates involuntary function including the activity of the cardiac muscle, smooth muscles (including airway smooth muscle) and glands. It is further divided into the sympathetic and parasympathetic nervous systems.

Bronchiectasis: Widening of the bronchi or their branches. It may be congenital or may result from infection or obstruction. Pus may form in the widened bronchus so that the patient coughs up purulent sputum, which may contain blood.

Bronchiolitis: Inflammation of the small airways in the lungs due to infection by viruses, usually respiratory syncytial virus.

Bronchomotor tone: Tone of the bronchial muscles which may cause a change in the calibre, dilation or contraction of bronchioles.

Cholinergic: Pertaining to the parasympathetic nerve fibres of the autonomic nervous system that liberate acetylcholine at a synapse where a nerve impulse passes.

COPD: Chronic obstructive pulmonary disease; a progressive disease characterised by airflow limitation which is not fully reversible and is usually associated with an abnormal inflammatory response of the lung to noxious particles or gases.

Cor pulmonale: An enlargement of the right ventricle of the heart resulting from disease of the lungs or pulmonary arteries.

CRP: C-reactive protein; is an acute phase plasma protein produced by the liver and by adipocytes. Its levels rise dramatically during inflammatory processes occurring in the body and elevated levels of CRP are associated with increased cardiovascular risk.

Cyanosis: A bluish coloration of the skin due to the presence of deoxygenated hemoglobin in blood vessels near the skin surface. It occurs when the oxygen saturation of arterial blood falls below 85%.

Cystic fibrosis: A hereditary disease affecting cells of the exocrine glands. The abnormality results in the production of thick mucus, which obstructs the intestinal glands, pancreas, and bronchi. Respiratory infections, which may be severe, are a common complication.

Deconditioning: To lose or cause decline from a condition of physical fitness.

Dynamic hyperinflation: Hyperinflation (increased lung volume) resulting from a decreased expiratory flow.

Dysphonia: Any abnormality in the speaking voice such as hoarseness.

Dyspnoea: Shortness of breath; breathlessness.

Expiratory Reserve Volume: The extra volume of air that can be expired with maximum effort beyond the level reached at the end of a normal, quiet expiration (functional residual capacity). Common abbreviation is **ERV**.

FEF25-75%: Forced expiratory flow at 50% or 75% FVC; average expired flow over the middle half of the FVC manoeuvre and is regarded as a more sensitive measure of small airways narrowing than FEV_1. FEF 25-75% has a wide range of normality, is less reproducible than FEV_1, and is difficult to interpret in the VC (or FVC) is reduced or increased.

FET: Forced expiratory time; the time required to perform the FVC manoeuvre (usually less than 5-6 seconds in adults).

FEV_1/FVC: FEV_1 expressed as a percentage of VC or FVC. Gives a clinically useful index of airflow limitation; may also see expressed as FEV_1/FEV_6.

FEV_1: Forced expiratory volume in one second; the volume expired in the first second of maximal expiration after a maximal inspiration and is a useful measure of how quickly full lungs can be emptied.

FEV_6: Forced expiratory volume in six seconds; the volume expired in the first six seconds of maximal expiration after a maximal inspiration; considered as a surrogate for FVC.

Functional Residual Capacity: This is the lung volume at the end of a normal expiration, when the muscles of respiration are completely relaxed. The tendency of the lungs to collapse is exactly balanced by the tendency of the chest wall to expand. Also known as **FRC** or **TGV** (Thoracic gas volume).

FVC: *See Vital capacity (VC).*

Hypercarbia: The physical condition of having the presence of an abnormally high level of carbon dioxide in the circulating blood.

Hyperplasia: An abnormal increase in the number of goblet cells on the tracheobronchial surfaces leading to excess mucus production.

Hyperresonance: Sounds that are louder and lower pitched than normal resonant sounds. Hyperresonant sounds are usually heard when percussing the chest of children, very thin adults, or lungs hyperinflated with such as in COPD.

Hypoxia: Hypoxia is a pathological condition in which the body as a whole (generalised hypoxia) or region of the body (tissue hypoxia) is deprived of adequate oxygen supply.

ICS: Inhaled corticosteroids.

Inspiratory Capacity: The maximum volume of air that can be inspired after reaching the end of a normal, quiet expiration. It is the sum of the tidal volume and the inspiratory reserve volume. Common abbreviation is **IC**. It is a measure of the person's room to breath.

Inspiratory Reserve Volume: This is amount of air that can be forcibly inspired at the end of normal inspiration; it is the amount of air which can be inspired on top of the tidal volume. Common abbreviation is **IRV**.

LABAs: Long acting β_2 agonists.

Metaplasia: An adaptive response to chronic irritation or inflammation which causes ciliated respiratory epithelium to be replaced with stratifies squamous epithelium.

Morbidity: The state of being diseased; the degree or severity of a disease.

Mortality: The incidence of death in the population in a given period.

Mucoid: Related to or resembling mucus.

Neurotransmitter: Any one of numerous chemicals that modify or result in the transmission of nerve impulses between synapses.

Noradrenaline: An adrenergic hormone which stimulates the sympathetic nervous system.

Norepinephrine: See *noradrenaline*.

Oedema: The abnormal accumulation of fluid in interstitial spaces of tissues.

Parasympathetic nervous system: Abbreviated (PNS); a division of the autonomic nervous system. The actions of the PNS are mediated by the release of acetylcholine and primarily involve the protection, conservation and restoration of body resources. When stimulated it causes bronchoconstriction.

PEF: Peak expiratory flow; the maximal expiratory flow achieved (rate at which a person can exhale air from the lungs) and this occurs very early in the forced expiratory manoeuvre.

Percussion: An assessment technique which produces sounds by the examiner tapping on the patients' chest wall. It helps to determine whether the underlying tissues are filled with air, fluid or solid material.

PIF: Peak inspiratory flow; the maximal inspiratory flow achieved. Unlike the PEF, the PIF occurs at about 50% FVC.

Plasma fibrinogen: Fibrinogen is the major plasma protein coagulation factor. Low plasma fibrinogen concentrations are associated with an increased risk of bleeding. Fibrinogen is an independent predictor of coronary heart disease events.

Polycythaemia: An excess of red blood cells in the blood which may occur as a primary disease or as a secondary condition in association with various respiratory or circulatory disorders. It is often accompanied by an increase in white blood cells and platelets.

Pulmonary rehabilitation: Structured, usually multi-disciplinary programs that aim to reduce the symptoms, disability and handicap arising from long-term respiratory disorders and to help patients reach and maintain a good level of functioning in the community.

Purulent: Forming, consisting of, or containing pus.

Residual Volume: This is the volume remaining in the lungs after maximal expiration. Common abbreviation is **RV**.

Rhinovirus: Any one of a group of RNA-containing viruses that cause respiratory infections resembling the common cold.

SABAs: Short acting β_2 agonists.

Sleep apnoea: A sleep disorder characterised by pauses in breathing during sleep which includes a minimum 10 second interval between breaths with either a neurological arousal or a blood oxygen desaturation of 3-4% or greater, or both. Clinically significant levels of sleep apnoea are defined as 5 or more events of any type per hour of sleep time.

Slow vital capacity: The volume of gas measured on a slow, complete expiration after or before a maximal inspiration, without forced or rapid effort. Often the SVC is significantly larger than FVC, which indicates to some degree the existence of air-trapping. (It may be less than normal due to the collapse of airways due to lack of support.) Also known as **SVC**.

Spirometer: A device used to measure timed expired and inspired volumes and comes in several different varieties. From this one can calculate how effectively and how quickly the lungs can be emptied and filled.

Static hyperinflation: Hyperinflation (increased lung volume) resulting from a loss of lung elastic recoil.

Sympathetic nervous system: Abbreviated (SNS); a division of the autonomic nervous system which is always active at a basal level and becomes more active during times of stress. Its action during the stress response comprises the flight-or-fight response. When stimulated it causes bronchodilation.

Tachyphylaxis: A phenomenon where repeated administration of some drugs results in a marked decrease in effectiveness.

Tidal Volume: This is the volume of a normal inspiration (or expiration) during quiet breathing and averages about 500mL. Common abbreviations are **TV** or $\mathbf{V_t}$.

Total lung volume/capacity: The total volume of gas contained in the lungs including the residual volume (ie: the total volume of air in the lungs after maximum inspiration). Also known as **TLV** or **TLC**.

Tuberculosis: An infectious disease caused by the bacillus *Mycobacterium tuberculosis* and characterised by the formation of nodular lesions (tubercles) in the tissues. Most common form is pulmonary tuberculosis.

Vital Capacity: The volume of air that can be expelled from the lungs from a position of full inspiration, with no limit to the duration of expiration, it is equal to the inspiratory capacity plus the expiratory reserve volume. This is the difference between Total Lung Capacity and Residual Volume

PSA's CPD&PI Program

CPD&PI Pharmaceutical Society of Australia

Watch for this logo.

The achievement of optimal health outcomes is influenced by both the competence of the professional delivering the health service and the quality of the system through which that service is delivered. Thus, PSA has developed the Continuing Professional Development (CPD) and Practice Improvement (PI) Program so pharmacists can address both of these aspects.

The CPD component recognises continuing education and other activities intended to enhance the knowledge, skills and attributes associated with maintaining or enhancing professional competence.

The PI component encompasses quality assurance or quality improvement activities directed at enhancing the processes or systems through which pharmacists deliver professional services.

Overall, the Program recognises a wide range of learning experiences, with credit points allocated to activities based on the potential of the activity to impact on behaviour change and improve clinical practice, rather than just the quantity of the activity undertaken. The achievement of a specified number of credit points is an indicator of the pharmacist's commitment to their ongoing professional development and practice improvement.

Online tools are available free to members to guide and support them in developing a personal learning plan: identifying where improvement is needed, planning how to achieve improvement, taking action, and evaluating the outcomes.

For further information on PSA's CPD&PI Program, education and practice support activities, or membership of PSA, visit www.psa.org.au or contact the following:

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ST LEONARDS NSW 1590
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CPD&PI

Pharmaceutical Society of Australia

THE AUSTRALIAN LUNG FOUNDATION

6 October 2009

Pharmacist
Pharmacy
Address

Dear xxxx

I am writing to provide you with information about a research project[1] that is being conducted in the Newcastle/Hunter Valley area and to invite your participation.

The Australian Lung Foundation is conducting a research project entitled *A collaborative screening, referral and management process to improve health outcomes in Chronic Obstructive Pulmonary Disease (COPD)*. This project aims to raise awareness of COPD, identify people at risk of COPD for early referral by pharmacy to their general practitioner for assessment and management, and to involve community pharmacy in the ongoing management of COPD patients. Please see attached for a more complete overview of the program.

Fifteen pharmacies have been recruited to participate in this project. As one of these pharmacies is XXX Pharmacy in your area, we thought it important to provide you with information.

COPD is a growing cause of morbidity and mortality worldwide. It is largely unrecognised and under-diagnosed. Patients often only seek treatment once airflow limitation has become moderate to severe. Patients often pass off symptoms of breathlessness as "normal" signs of ageing or side-effects of smoking. Early diagnosis is important in altering the clinical course of the disease and improving health outcomes.

At the Australian Lung Foundation we have been interested in the role that community pharmacy might play in raising awareness of COPD amongst their patient group and referring at-risk patients to their general practitioner for full assessment and diagnosis.

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[1] The Australian Lung Foundation is leading a collaborative team of researchers that includes Dr Bandana Saini from the Faculty of Pharmacy at The University of Sydney and Ms Simone Diamandis, Dr Geraldine Peterson-Clark, Dr Guy Gavagna and Mr David Marshall from Boehringer Ingelheim Pty Ltd. The Pharmacy Guild of Australia is funding the project as part of the Guild's Research and Development program under the Fourth Community Pharmacy Agreement.

The program and how it could affect you

- **Other than providing an indication on the GP Report Form of the outcome of the patient assessment, GPs will not be asked to fill out any lengthy paperwork nor will you be asked to provide anything other than usual care for your patients.**
- Patients will complete an initial screening questionnaire in the pharmacy to identify whether they are at risk of COPD. Those at risk of COPD may be patients with a smoking history, who have had exposure to risk factors and those presenting with symptoms. Chronic asthmatics over 35 who are not responding to treatment, patients seeking smoking cessation products and patients who have been treated for upper respiratory tract infections more than twice over the past 12 months may also be invited by the pharmacist to complete the questionnaire. Those who are identified as being "at risk" will then be invited to complete a lung function screening test using the PiKo-6 screening device.
- Those patients whose PiKo-6 lung function screening result indicates a potential obstruction will be referred to their local GP for full assessment and diagnosis. Participating pharmacists will fill out a pink GP Referral Form to provide the GP with important information gathered at the pharmacy.
- Patients will be encouraged to make an appointment with their GP and to bring the GP Referral Form with them to their appointment.
- The GP will assess patients and conduct clinically appropriate diagnostic tests.
- The GP is asked to complete a yellow GP Report Form to indicate whether or not COPD was diagnosed. The pharmacist will give the patient this form to bring with them to their GP consultation. We ask that the GP fax the completed form to the referring pharmacist.
- GPs will provide appropriate care to the patient.
- Pharmacists are encouraged to liaise with the GP as required, and may initiate contact with you.
- At the end of the 6 month trial, pharmacists, patients and GPs will be interviewed to provide their feedback about the program.

If the program is successful and the collaboration between pharmacists and GPs is of benefit to both parties, the Australian Lung Foundation would consider rolling this program out on a wider scale.

Shortly you can expect to be contacted directly by XXX Pharmacy. In the meantime, if you have any questions and or suggestions, or would like more information, please do not hesitate to contact Phoebe Kearey by emailing phoebe@lungnet.com.au or calling 0418 886 186.

Yours sincerely

Heather Allan (Chief Investigator)
Executive Director – COPD National Program

Cc: Phoebe Kearey
Bandana Saini
Simone Diamandis

MEDIA RELEASE

Date: 13 November 2008

Pharmacists to support GPs in identifying those at risk of COPD

The Australian Lung Foundation, in collaboration with the University of Sydney is running a research program in the Hunter Valley to assess the feasibility of lung function screening as a tool for identifying those at risk of Chronic Obstructive Pulmonary Disease (COPD). The program is funded by the Australian Government Department of Health and Ageing as part of the Fourth Community Pharmacy Agreement managed by the Pharmacy Guild of Australia.

Chief Investigator, Heather Allan, of The Australian Lung Foundation, said that community pharmacists were well placed to support General Practitioners diagnose COPD in patients that might not be presenting on their own to general practice with concerns about their lung health.

"Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of death and hospitalisation in Australia", said Ms Allan. "Of particular alarm to the Lung Foundation however, is the fact that it also remains largely unrecognised and under-diagnosed.

"Symptoms of COPD, such as shortness of breath and persistent cough, are often passed off by the patients themselves as "normal" signs of aging or side-effects of smoking. Consequently, patients often do not seek advice from their doctor until their condition has become moderate to severe."

Ms Allan said that the research program will work with pharmacists to identify patients who may be at risk of COPD and give them a lung function screening test using a device called the Piko 6. For those whose results indicate possible COPD, they will be referred to their GP for full assessment and diagnosis.

If COPD is diagnosed, the GP will be asked to fill out a simple form indicating the diagnosis and to return the form to the pharmacist. The GP will provide usual care and the pharmacist will support the GP by providing smoking cessation advice and proper use of medicines advice.

"We have recruited 15 pharmacists in the Newcastle/Hunter Valley area. So we expect that the GPs who are physically close to the participating pharmacies will be affected", said Ms Allan.

"We hope that this program will raise awareness about COPD and encourage earlier diagnosis for those patients might not be speaking to their GPs about their breathlessness", said Ms Allan. "As we all know, early detection and management can make a significant difference to the quality of life of people with COPD and to their longer term health."

What does it mean for GPs?

- 15 pharmacists in the Newcastle / Hunter Valley have been recruited
- Participating pharmacists will contact their local GPs by mail to alert them to their participation in the program
- Patients whose lung function screening test indicates a problem will be referred to their GP
- GPs will provide usual full assessment and diagnosis
- If COPD diagnosed, GP will be asked to fill in a referral form and return to the referring pharmacist for follow-up for smoking cessation and proper use of medication advice
- GP provides usual care

Ms Allan said that The Australian Lung Foundation has several resources GPs can use to support diagnosis and management of COPD, including the COPDX Management Guidelines, COPD Checklist and COPD Action Plan. These and other resources are available on the Lung Foundation Web site (www.lungnet.com.au).

For further information on the program contact Phoebe Kearey at phoebe@lungnet.com.au or 0418 886 186.