Chronic obstructive pulmonary disease (COPD) is a serious, progressive and disabling condition that limits airflow in the lungs. It includes emphysema and chronic bronchitis. People with COPD are prone to severe episodes of shortness of breath, with fits of coughing. Smoking is the most important risk factor in the development of COPD.

The condition mainly affects older people. More than 1 in 20 Australians aged 55 and over have COPD (5.7%). In 2012 COPD was the fifth leading cause of death in Australia.

**Signs and symptoms**
The main symptoms of COPD are breathlessness, cough and sputum production. Other symptoms such as chest tightness, wheezing and airway irritability are common. Signs and symptoms of COPD include:

- Breathlessness
- Cough and sputum production
- Chest tightness
- Dyspnoea
- Wheezing
- Reduced exercise tolerance
- Decreased health-related quality of life
- Acute exacerbations

**Treatment**
The goal of therapy is to prevent and control symptoms, reduce frequency and severity of exacerbations, and improve exercise tolerance. COPD cannot be cured, and usually progresses with age. Additional medications will be required as disease worsens. Management of stable COPD should centre on supporting patients to quit smoking. Encouraging physical activity and maintenance of a normal weight range are also important. Pulmonary rehabilitation is recommended in symptomatic patients.

Bronchodilators include short-acting beta₂ agonists (SABAs) and long-acting beta₂ agonists (LABAs) as well as short-acting muscarinic antagonists (SAMAs) and long-acting muscarinic antagonists (LAMAs). Both LAMAs and LABAs have been shown to reduce exacerbations and hospitalisations in patients with COPD.

Inhaled corticosteroids (ICS) are recommended in addition to long-acting bronchodilators for patients with moderate to severe COPD, especially in those with recurrent exacerbations. ICS give additional benefits of reduced exacerbations and improved quality of life.

**Fixed-dose combination products**
Various fixed-dose combination inhalers are available on the Pharmaceutical Benefits Schedule (PBS) in Australia. Current PBS rules state the patient must have been stabilised on a combination of a LAMA and LABA before commencing a combination LAMA/LABA product, and LAMA/LABAs are not indicated for the initiation of bronchodilator therapy in COPD. Similarly ICA/LABAs are not indicated for the initiation of bronchodilator therapy in COPD.

Fixed-dose combination products are grouped as ICS/LABAs and LAMA/LABAs.

**LAMA/LABAs include:**
- Eformoterol /aclidinium (Brimica Genuair)
- Indacaterol/glycopyrronium (Ultibro Breezhaler)
- Olodaterol/tiotropium (Spiolto Respimat)
- Vilanterol/umeclidium (Anoro Ellipta)

LAMA/LABAs yield a greater improvement in trough forced expiratory volume in one second (FEV₁), and quality of life and dyspnoea scores than monotherapies. Combination therapy with LAMAs and LABAs is the most effective strategy in improving lung function, quality of life, symptom scores and moderate-to-severe exacerbation rates. Safety outcomes and severe exacerbations are similar with combination therapy when compared with monotherapies.

**ICS/LABAs include:**
- Budesonide/eformoterol (Symbicort Rapihaler and Turbuhaler)
- Fluticasone propionate/salmeterol (Seretide Inhaler and Accuhaler)
- Fluticasone propionate /eformoterol (Flutiform Inhaler)
- Fluticasone furoate/vilanterol (Breo Ellipta)

**TRIPLE THERAPY FOR COPD**

February 2016
Fluticasone propionate/efomterol and fluticasone furoate/vilanterol are not indicated or PBS-subsidised for bronchodilator therapy in COPD.

A systematic review of 19 randomised controlled trials involving 10,400 patients with COPD of combined ICS and LABAs in one inhaler found that, compared with placebo, both fluticasone/salmeterol and budesonide/formoterol reduced the rate of exacerbations. Combined treatments also improved health status to a small extent and improved lung function. Increased risk of pneumonia was observed with combined treatments compared with placebo; however hospitalisations or deaths did not increase.

The Lung Foundation Australia guidelines recommends ICS/LABA combination therapy (fluticasone propionate/salmeterol or budesonide/efomterol) only when FEV₁ is less than 50% predicted AND the patient has had 2 or more exacerbations in the previous 12 months.

**Triple therapy**

Triple therapy with LABAs, LAMAs, and ICS is efficacious in patients with more severe COPD, such as those with frequent exacerbations and predominant chronic bronchitis. Emerging evidence supports the addition of ICS to LAMA/LABA therapy in people with COPD who have had two or more exacerbations or one hospitalization for a flare-up in a 12-month period and have FEV₁ below 50% of the predicted level.

The recently published Australian GLISTEN study showed an advantage of adding a LAMA to a combination of an ICS and a LABA. In this study a once-a-day LAMA (glycopyrronium or tiotropium) was added to salmeterol/fluticasone propionate (via Accuhaler) twice-daily therapy, with improvements shown in lung function, quality of life and use of rescue medication compared to salmeterol/fluticasone propionate therapy. Glycopyrronium (Seebri Breezhaler) was just as effective as tiotropium (Spiriva Handihaler). This is the first time the superiority of using LAMA plus LABA/ICS over using a LABA/ICS alone has been effectively demonstrated.

Improvements in lung function can also be achieved through combining triple therapy with pulmonary rehabilitation in patients with advanced COPD.

ICS/LAMA/LABA combination is also indicated for patients with a long history of asthma in addition to COPD (asthma and COPD overlap syndrome) to manage both the asthma and COPD components of the disease.

No single product is currently available in Australia containing all three classes of medication. A variety of triple combinations are currently under development. So for now, an ICS can be added to a LAMA/LABA or a LAMA added to a ICS/LABA combination product when indicated for selected patients. Duplication of medicines within a class (i.e. ICS, LAMA, LABA) is not appropriate. It is preferable, although not always possible, to use the same devices to administer the three medications.

**Pneumonia risk**

Long-term use of the inhaled corticosteroid, fluticasone, and to a lesser extent budesonide, increases the risk of community-acquired pneumonia. The increased risk of pneumonia and hospitalisation from pneumonia appears to be dose-related. However increase does not appear to affect mortality rates in these patients, suggesting that the episode is of reduced severity.

Budesonide (Pulmicort Turbuhaler) appears to be a safer option compared to fluticasone (Flixotide Inhaler or Accuhaler) in terms of significant reduction of the risk of pneumonia and pneumonia-related mortality in COPD patients.

These concerns need to be balanced with the known benefits of ICS including fewer exacerbations, improved lung function and quality of life.

**Summary**

Combining inhaler therapies from different classes of medicines for COPD is commonly recommended. Triple therapy (LAMA+LABA/ICS) is superior in terms of lung function, health status and rescue medication use in patients compared to LABA/ICS. Triple therapy is indicated only in people with moderate-to-severe COPD and frequent flare-ups or hospitalisation, as well as people with asthma and COPD overlap syndrome.

**References**

COPD-X Guidelines – Version 2.43 (September 2015)
Thorax 2015;0:1–9.