

Combination long-acting bronchodilators for COPD

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A number of long-acting bronchodilators are now available as fixed-dose combination inhalers for treatment of patients with COPD. What is their place in therapy and what common prescribing mistakes should be avoided?

Inhaled long-acting bronchodilators have long been used in the management of chronic obstructive pulmonary disease (COPD), either as monotherapy (e.g. tiotropium) or in combination with inhaled corticosteroids (e.g. eformoterol plus budesonide, salmeterol plus fluticasone and vilanterol plus fluticasone). The number of long-acting bronchodilators available has expanded considerably in recent years, with a variety of new long-acting muscarinic antagonists (LAMAs) and long-acting beta-2 agonists (LABAs) approved by the PBS for use in patients with COPD. Although additional medications give additional choices to prescribers, they also bring added complexity and a need to understand which inhalers can and cannot be used in combination.

A number of fixed-dose LAMA/LABA combinations are now listed on the PBS, as outlined in the Table. Randomised controlled trials consistently report that these LAMA/LABA combinations improve expiratory flow rates to a greater extent than LAMA monotherapy or LABA monotherapy.¹⁻⁸ In regard to patient-related outcomes, the benefits of LAMA/LABA combinations vary across different clinical trials. Some studies report modest improvements in dyspnoea, exercise tolerance and quality of life relative to LAMA monotherapy or LABA monotherapy.^{1,2,6,8} However, this is not a universal finding, and there is an ongoing need to better identify

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those patients who will benefit from combination therapy and those who can be managed with monotherapy. Evidence is emerging that LAMA/LABA combinations may reduce the frequency of COPD exacerbations compared with LAMA monotherapy.^{8,9}

When is it appropriate to use LAMA/LABA combinations in COPD?

All the combination inhalers listed in the Table are available for patients with COPD via a PBS streamlined authority, providing patients have been stabilised on a combination of a LAMA and a LABA before being prescribed a fixed-dose combination inhaler. LAMA/LABA combinations are not currently approved for use in asthma.

All these drugs have flat dose-response curves, and there is little to be gained from higher doses or more frequent administration than recommended. Fixed-dose combinations with once-daily dosing have the advantage of reduced medication burden and improved compliance, whereas agents with twice-daily dosing may be preferred by patients who experience nocturnal symptoms.

Adverse events are generally mild and predictable. LAMAs may cause dry mouth, but ocular problems and bladder outflow obstruction seem uncommon. All LABAs may cause tachycardia and tremor. Ongoing studies are assessing the risks of cardiac

TABLE. COMBINATION LAMA/LABA INHALERS AVAILABLE IN AUSTRALIA

LAMA	LABA	Trade name	Frequency of use
Acclidinium	Eformoterol	Brimica Genuair	Twice daily
Glycopyrronium	Indacaterol	Ultibro Breezhaler	Once daily
Tiotropium	Olodaterol	Spiolto Respimat	Once daily
Umeclidinium	Vilanterol	Anoro Ellipta	Once daily

Abbreviations: LABA = long-acting beta-2 agonist; LAMA = long-acting muscarinic antagonist.

Green tick indicates therapies that can be used together

		SABA	SAMA	LAMA	LABA	LABA/LAMA	ICS/LABA
SABA	• salbutamol (Ventolin™, Airomir™, Asmol™) • terbutaline (Bricanyl™)	✓	✓	✓	✓	✓	✓
SAMA	• ipratropium (Atrovent™)	✓	✓	✓	✓	✓	✓
LAMA	• tiotropium (Spiriva™) • glycopyrronium (Seebri™) • aclidinium (Bretaris™) • umeclidinium (Incruse™)	✓	✓	✓	✓	✓	✓
LABA	• salmeterol (Serevent™) • eformoterol (Oxis™, Foradile™) • indacaterol (Onbrez™)	✓	✓	✓	✓	✓	✓
LABA/LAMA	• indacaterol/glycopyrronium (Ultibro™) • umeclidinium/vilanterol (Anoro™) • tiotropium/olodaterol (Spiolto™) • aclidinium/eformoterol (Brimica™)	✓	✓	✓	✓	✓	✓
ICS/LABA	• fluticasone propionate/salmeterol (Seretide™) • budesonide/eformoterol (Symbicort™) • fluticasone furoate/vilanterol (Breo™)	✓	✓	✓	✓	✓	✓

Figure. Guide to addition of therapies for patients with COPD.

Abbreviations: ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting beta-2 agonist; SAMA = short-acting muscarinic antagonist.

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arrhythmias in patients with COPD treated with LAMAs and LABAs. As patients with COPD often have underlying ischaemic heart disease, it is wise to be cautious and to monitor the serum potassium level, especially in those with a history of arrhythmias. At this stage there is no evidence that dose adjustment is required in patients with renal or liver disease.

Beware inappropriate drug combinations

The most common prescribing error seen with the new LAMA/LABA combinations is the inadvertent use of two long-acting bronchodilators from the same class. There is nothing to be gained by prescribing two LAMAs together, or two LABAs together, but there is a greater risk of adverse events. For this reason, LAMA/LABA fixed-dose combinations should not be used in conjunction with inhaled corticosteroid/LABA fixed-dose combination inhalers. Short-acting bronchodilators (e.g. salbutamol) can continue to be used for temporary relief of worsening dyspnoea, but patients may experience more tachycardia and tremor if already taking a LABA. Lung Foundation Australia has compiled a guide that highlights the different drug classes and inappropriate combinations (Figure).

Other issues to consider in managing patients with COPD

- Spirometry is important for accurate diagnosis of COPD.
- Drug therapy is just one part of optimal management.
- Tobacco smoking, marijuana smoking and other environmental exposures should be addressed.
- Patients should be encouraged to undertake a graded exercise program, and referral to a local pulmonary rehabilitation program should be considered.
- Medication adherence and inhaler technique should be reviewed before a second long-acting bronchodilator is added.
- Most long-acting bronchodilators have similar therapeutic effects. The choice of agent is often determined by the inhaler device and its ease of use. Prescribing multiple inhaler devices for a patient is likely to produce confusion.

- The diagnosis should be reviewed if symptoms do not improve despite apparently optimal treatment. Referral to a respiratory physician should be considered if the diagnosis is in doubt or the patient has persistent symptoms despite optimal therapy.

Unresolved issues

- Are LAMA/LABA combinations cost effective and do they reduce healthcare utilisation?
- Which patients with COPD should receive LAMA/LABA combinations, and which require only monotherapy?
- What is the place of LAMA/LABA combinations in COPD in relation to inhaled corticosteroids? Concern about pneumonia risk in patients treated with high-dose inhaled corticosteroids has led to a re-evaluation of their role in COPD management. In our view, not all patients with COPD need inhaled corticosteroid treatment, although this treatment should be seriously considered in patients with severe airflow obstruction and a history of frequent COPD exacerbations, and in those with a history of previous asthma.

Conclusion

Long-acting bronchodilators improve lung function and symptoms in many patients with COPD. If the clinical response is inadequate with monotherapy, some patients will benefit from a combination of a LAMA plus a LABA. Fixed-dose combination products given via a single inhaler offer practical advantages and may improve adherence. They may also reduce the frequency of COPD exacerbations.

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References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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This article is for general information purposes only, and the full product information should be consulted before prescribing any of the mentioned medications.

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