NPS NEWS
National Prescribing Service Newsletter

58 2008

ISSN 1441-7421 June 2008

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Inhaled corticosteroids and long-acting beta$_2$ agonists in asthma and COPD

Inhaled corticosteroids and long-acting beta$_2$ agonists (LABAs) have distinct roles in asthma and chronic obstructive pulmonary disease (COPD). Managing obstructive respiratory diseases effectively relies on: choosing drugs appropriately according to a confirmed diagnosis and severity, ongoing monitoring and titration, and patient education and review.

Spirometry: the best test for reversible and irreversible airway obstruction

Post-bronchodilator spirometry is needed to confirm a diagnosis of COPD, while asthma must be diagnosed on the basis of both spirometry and clinical history (Table 1).[1,2] Symptoms of asthma and COPD often coexist: COPD with significant reversibility is as common as COPD without reversibility[3] and therefore it may not be possible to distinguish the two diagnoses in some individuals.

Table 1. Spirometry criteria for COPD and asthma[1,2]

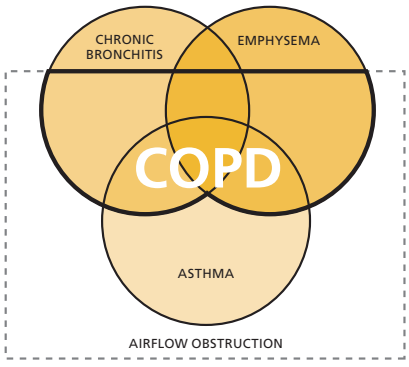
	Post-bronchodilator spirometry results	
	FEV_1	FEV_1/FVC
COPD	< 80% predicted	< 70%
Asthma	increase of > 200 mL **and** > 12% on pre-bronchodilator value	

People with symptoms of COPD but reversibility in the asthma range should be managed as for a diagnosis of asthma. Consider referring patients to a respiratory physician to exclude other diagnoses or complications, especially for irreversible obstruction in people younger than 40 years, people with a smoking history of < 10 pack–years, or people with a rapid decline in FEV_1.[1]

Spirometry also has a place in monitoring lung function during therapy. It is recommended for assessing long-term medication response in COPD and for assessing asthma control in response to treatment (see page 3).[1,2]

Chronic bronchitis, airway narrowing and emphysema may occur in various combinations in COPD. Underlying inflammation, fibrosis and remodelling of the peripheral airways result in irreversible airflow limitation. The overlap between clinical features and their relationship to airflow obstruction and COPD are shown in Figure 1. Smoking causes around 70% of COPD cases in Australia.[4]

Figure 1. Conceptual overlap of clinical features within COPD.[1]



NPS is an independent, non-profit organisation for Quality Use of Medicines, funded by the Australian Government Department of Health and Ageing.

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Select and review therapy according to the diagnosis

Current guidelines recommend inhaled corticosteroids as first-line therapy in persistent asthma, while in COPD inhaled corticosteroids should only be considered for the later stages of disease (Table 2).[1,2] Conversely, LABAs should only be added to inhaled corticosteroid therapy in asthma in response to poor asthma control, but in COPD they may be used earlier in therapy as an alternative to other bronchodilators.* Monitoring and titration also differs between conditions, reflecting differences in the course of illness and responsiveness to treatment.

* Single-ingredient inhalers containing either salmeterol (Serevent) or eformoterol (Foradile, Oxis) are not PBS listed for COPD.

Table 2. When to start inhaled corticosteroid–LABA combination therapy in asthma and COPD

Diagnosis	Current therapy	Symptoms	Recommended combination
Asthma	Low-dose inhaled corticosteroid	Inadequately controlled asthma	Low-dose inhaled corticosteroid plus LABA
COPD	Long-acting bronchodilator	$FEV_1 < 50\%$ predicted and repeated exacerbations	High-dose inhaled corticosteroid plus long-acting bronchodilator†

† Fluticasone with salmeterol (Seretide 250/25 MDI and Seretide 500/50 DPI strengths only) is PBS listed for COPD in people with $FEV_1 <$ 50% predicted who have a history of repeated exacerbations despite regular $beta_2$ agonist treatment. Budesonide with eformoterol (Symbicort) is neither TGA registered nor PBS listed for COPD.

Use fixed-dose combinations only when both components are appropriate

The place of fixed-dose combination inhalers containing an inhaled corticosteroid and a LABA (i.e. Seretide and Symbicort) follows the guidelines for the individual constituents (see Table 3 for dose categories).[2,5]

In asthma, a LABA should always be used together with an inhaled corticosteroid because of an association between LABA monotherapy and asthma-related hospital admissions and deaths.[6–9] Consistent with this advice, 95% of PBS LABA prescriptions in 2007 across all indications were for inhaled corticosteroid–LABA fixed-dose combination products.[10]

While fixed-dose combination inhalers may be more convenient, combination therapy using two single-ingredient inhalers allows for more flexibility in titrating the inhaled corticosteroid dose up and down or stopping one of the two drugs. A further alternative in asthma is the maintenance and reliever regimen for the budesonide with eformoterol dry powder inhaler (Symbicort Turbuhaler) — see page 4.

Monitor inhaled corticosteroid response and minimise adverse effects

Inhaled corticosteroids have a long-acting anti-inflammatory effect that reduces exacerbations in asthma and moderate to severe COPD.[11–15] However, effectiveness varies between patients and also over time, while adverse effects follow a clear dose–response relationship. For example, in a 2-year study of inhaled fluticasone the incidence of oral candidiasis was 2% at 200 micrograms/day but 14% at 1000 micrograms/day.[16]

In mild to moderate asthma, increasing the dose of inhaled fluticasone beyond 500 micrograms/day has little additional benefit.[17] On the other hand, high-dose inhaled corticosteroids have a place in COPD‡ but they should be reviewed and discontinued 4–8 weeks after initiation if there is no response (see page 3). Using a high-dose inhaled corticosteroid continuously can cause serious adverse effects. Trials of inhaled corticosteroids in COPD patients show an increased incidence of pneumonia[18], but no statistically significant effect on mortality.[15]

Finding the correct dose of inhaled corticosteroid for people with asthma requires regular monitoring and titration (see page 3). Once asthma control is attained, the inhaled corticosteroid should be back-titrated to the lowest effective dose.[2]

‡ Inhaled corticosteroids are not approved by the TGA for COPD. They are listed on the PBS general schedule as unrestricted benefits and prescribers may write prescriptions in line with their clinical judgment.

Educate patients about inhaled medications

PBS prescribing data strongly suggest that few people with asthma or COPD use their prescribed inhaled corticosteroid or combination inhaler on a daily basis.[19] One factor associated with irregular use of inhaled corticosteroids may be the lack of an immediate, noticeable effect.[20] People with asthma may also believe inhalers are unnecessary when they are asymptomatic, or they may be wary of side effects.[20]

Explain the purpose of daily maintenance dosing, and that regular review is the best way to achieve a good balance of benefits and side effects. Provide patients with an asthma or COPD action plan and ensure they understand what to do if symptoms flare.

Clarification: *NPS News 56*

NPS News 56 guide to initiating insulin suggested adjusting insulin by 6 to 8 units for patients with mean FBG levels ≥ 8 mmol/L. We have received feedback that this varies from other local guidelines.

This guidance is just one way to initiate and titrate insulin. Prescribers concerned about the risk of hypoglycaemia can adjust insulin in increments up to 4 units (every 3–4 days, according to mean FBG), rather than 6 or 8 units. Alternatively, they can follow RACGP (adjust by increments of 10% to 20%) or local guidelines.

Patient review — the key to optimising therapy

Asthma[2]

Review every 6–12 weeks. Children with intermittent asthma and adults with good asthma control may only require yearly review.

Ask about symptoms, for example:

1. On average, how often are you woken by your asthma during the night?
2. On average, how bad are your asthma symptoms when you wake up in the morning?
3. In general, how limited are you in your activities because of your asthma?
4. In general, how much shortness of breath do you experience because of asthma?
5. In general, how often did you wheeze over the past few weeks or since the last visit?
6. On average, how many puffs of short-acting beta$_2$ agonist (SABA) 'reliever' do you use each day?
7. How much work/school has been missed due to asthma?

You can also use a validated asthma control tool such as the Asthma Score or Asthma Control Questionnaire.

COPD[1]

Review 4–8 weeks after changing or adding a medication.

Ask about symptoms, difficulty with daily activities and exercise capacity. Functional limits can be graded using the Medical Research Council (MRC) dyspnoea scale (see below).

MRC dyspnoea scale

Grade	Symptom
1	"I only get breathless with strenuous exercise"
2	"I get short of breath when hurrying on the level or walking up a slight hill"
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"
4	"I stop for breath after walking about 100 yards or after a few minutes on the level"
5	"I am too breathless to leave the house" or "I am breathless when dressing"

Check inhaler technique

Ask the patient to demonstrate use of their inhaler. Ability to use an inhaler can decline within 2 months of first instruction.[21]

Ask about medication use

Some example questions[22] that may help elicit information about adherence:

- How is the treatment plan going? Let's go over it. Are you experiencing any difficulties?
- How often do you forget your medications?
- Are there times when you are more likely to forget your medications?
- How do you usually remember? What can we do to help you to remember?

Check pre- and post-bronchodilator lung function by spirometry

Reduce inhaled corticosteroid dose if asthma is well-controlled. With some inhalers this can be achieved by reducing the number of puffs per day; otherwise prescribe a lower strength. **Step up** treatment if persistent symptoms and/or poor lung function after ruling out a lack of adherence or incorrect inhaler technique.

Discontinue the new medication if lung function or functional capacity not improved after initiating an inhaled corticosteroid and/or long-acting bronchodilator and **try an alternative therapy** (see *NPS News 45: Managing COPD and preventing progression*).

Ask about smoking status and give brief counselling. Refer to *NPS News 45: Managing COPD and preventing progression* for more information about interventions for smoking cessation.

Educate patients about their disease, how to monitor their own symptoms and the purpose of the medication they are receiving.

Table 3. Daily adult inhaled corticosteroid dose equivalents*

	Low	Medium	High
beclomethasone dipropionate (CFC-free)	100–200 micrograms	200–400 micrograms	> 400 micrograms
budesonide	200–400 micrograms	400–800 micrograms	> 800 micrograms
ciclesonide	80–160 micrograms	160–320 micrograms	> 320 micrograms
fluticasone propionate	100–200 micrograms	200–400 micrograms	> 400 micrograms

* Doses as labelled: ex-actuator dose for ciclesonide, and ex-valve dose for others.[2]

A 'SMART' way to treat asthma?

An alternative dosing regimen for the budesonide with eformoterol dry powder inhaler (Symbicort Turbuhaler) was introduced in 2007, under the name Symbicort Maintenance and Reliever Therapy (SMART). It can be used by people who have frequent asthma symptoms despite receiving conventional combination therapy or corticosteroids alone.

The maintenance and reliever regimen is not recommended for children under 12 years[23] and there is no evidence to support its use in COPD. The regimen is registered only for the lower-strength inhalers (100/6 and 200/6).

The regimen uses the Symbicort inhaler for both maintenance dosing and on-demand in response to acute asthma symptoms. Patients must stop using a short-acting beta$_2$ agonist 'reliever' inhaler completely — the Symbicort inhaler provides bronchodilation just as quickly.[24] Some people who perceive airway obstruction poorly or who habitually overuse relievers may be unsuitable candidates for the new regimen because of the risk that they will receive too much or too little inhaled corticosteroid.[25]

Double-blind trials found that the maintenance and reliever regimen reduced severe asthma exacerbations compared with a conventional regimen.[26–29] The new regimen is not recommended for patients who have good asthma control, however.

Patients must receive a matching asthma action plan (AAP). Suitable AAP templates are available online at www.nationalasthma.org.au/html/management/action_plans/ap005.asp and are also included in Medical Director prescribing software. The templates detail the maximum number of on-demand puffs and how to respond to increases in on-demand use.

Fluticasone with salmeterol (Seretide) cannot be used in a maintenance and reliever regimen, because salmeterol has too slow an onset of action.[24]

For further information see *NPS RADAR*.

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The opinions expressed do not necessarily represent those of the reviewers.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence.
Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.

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Amended August 2008