

Combination bronchodilator therapy. Although monotherapy with long-acting β_2 -agonists appears to be safe^{411, 412}, combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. For example, a combination of a short-acting β_2 -agonist and an anticholinergic produces greater and more sustained improvements in FEV₁ than either drug alone and does not produce evidence of tachyphylaxis over 90 days of treatment^{126,147,148} (**Evidence A**).

The combination of a β_2 -agonist, an anticholinergic, and/ or theophylline may produce additional improvements in lung function^{126,146-151} and health status^{126,152}. Increasing the number of drugs usually increases costs, and an equivalent benefit may occur by increasing the dose of one bronchodilator when side effects are not a limiting factor. Detailed assessments of this approach have not been carried out.

Glucocorticosteroids

The effects of oral and inhaled glucocorticosteroids in COPD are much less dramatic than in asthma, and their role in the management of stable COPD is limited to specific indications. The use of glucocorticosteroids for the treatment of acute exacerbations is described in *Component 4: Manage Exacerbations*.

Inhaled glucocorticosteroids. Regular treatment with inhaled glucocorticosteroids does not modify the long-term decline of FEV₁ in patients with COPD^{98-100, 161}. However, regular treatment with inhaled glucocorticosteroids has been shown to reduce the frequency of exacerbations and thus improve health status¹⁴⁰ for symptomatic COPD patients with an FEV₁ < 50% predicted (*Stage III: Severe COPD* and *Stage IV: Very Severe COPD*) and repeated exacerbations (for example, 3 in the last 3 years)¹⁶²⁻¹⁶⁵ (**Evidence A**) and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients¹⁶⁶. Treatment with inhaled glucocorticosteroids increases the likelihood of pneumonia and does not reduce overall mortality⁴¹¹.

The dose-response relationships and long-term safety of inhaled glucocorticosteroids in COPD are not known. Only moderate to high doses have been used in long-term clinical trials. Two studies showed an increased incidence of skin bruising in a small percentage of the COPD patients^{98,100}. One long-term study showed no effect of budesonide on bone density and fracture rate^{98,170}, while another study showed that treatment with triamcinolone acetonide was associated with a decrease in bone density¹⁶¹. The efficacy and side effects of inhaled glucocorticosteroids in asthma are dependent on the dose and type of glucocorticosteroid¹⁷¹. This pattern can also be expected in COPD and needs documentation in this patient population. Treatment with inhaled glucocorticosteroids can be recommended for patients with more advanced COPD and repeated exacerbation.

Combination inhaled glucocorticosteroid/bronchodilator therapy: An inhaled glucocorticosteroid combined with a long-acting β_2 -agonist is more effective than the individual components in reducing exacerbations and improving lung function and health status^{162,164,165,168,169,411,422} (**Evidence A**). Combination therapy increases the likelihood of pneumonia and a large prospective clinical trial failed to demonstrate statistically significant effects on mortality⁴¹¹.

Oral glucocorticosteroids: short-term. Many existing COPD guidelines recommend the use of a short course (two weeks) of oral glucocorticosteroids to identify COPD patients who might benefit from long-term treatment with oral or inhaled glucocorticosteroids. This recommendation is based on evidence¹⁵³ that short-term effects predict long-term effects of oral glucocorticosteroids on FEV₁, and evidence that asthma patients with airflow limitation might not respond acutely to an inhaled bronchodilator but do show significant bronchodilation after a short course of oral glucocorticosteroids.

There is mounting evidence, however, that a short course of oral glucocorticosteroids is a poor predictor of the long-term response to inhaled glucocorticosteroids in COPD^{38,100}. For this reason, there appears to be insufficient evidence to recommend a therapeutic trial with oral glucocorticosteroids in patients with *Stage II: Moderate COPD*, *Stage III: Severe COPD*, or *Stage IV: Very Severe COPD* and poor response to an inhaled bronchodilator.

Oral glucocorticosteroids: long-term. Two retrospective studies^{154,155} analyzed the effects of treatment with oral glucocorticosteroids on long-term FEV₁ changes in clinic populations of patients with moderate to very severe COPD. The retrospective nature of these studies, their lack of true control groups, and their imprecise definition of COPD are reasons for a cautious interpretation of the data and conclusions.

A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy¹⁵⁶⁻¹⁵⁸, which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced COPD. In view of the well-known toxicity of long-term treatment with oral glucocorticosteroids, prospective studies on the long-term effects of these drugs in COPD are limited^{159,160}.

Therefore, based on the lack of evidence of benefit, and the large body of evidence on side effects, long-term treatment with oral glucocorticosteroids is not recommended in COPD (**Evidence A**).

