

Theophylline, the most commonly used methylxanthine, is metabolized by cytochrome P450 mixed function oxidases. Clearance of the drug declines with age. Many other physiological variables and drugs modify theophylline metabolism. Enhanced inspiratory muscle function has been reported in patients treated with methylxanthines,⁽⁹³⁶⁾ but whether this reflects a reduction in gas trapping or a primary effect on the respiratory skeletal muscles is not clear. All studies that have shown efficacy of theophylline in COPD were performed with sustained-release preparations.

There is evidence for a modest bronchodilator effect compared with placebo in stable COPD.⁽⁹³⁹⁾ Addition of theophylline to salmeterol produces a greater improvement in FEV1 and breathlessness than salmeterol alone.^(940,941) Earlier studies reported contradictory evidence regarding the effect of low-dose theophylline on exacerbation rates.^(942,943) A study that investigated the effectiveness of adding low-dose theophylline to ICS in COPD patients at increased risk of exacerbation showed no difference compared with placebo in the number of COPD exacerbations over a one-year period.⁽⁹⁴⁴⁾ A large placebo-controlled trial showed no effect of oral theophylline alone or in combination with prednisolone 5 mg daily on exacerbations of severe COPD.⁽⁹⁴⁵⁾

Adverse effects

Toxicity is dose-related, which is a particular problem with xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given.^(937,939) Methylxanthines are non-specific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include atrial and ventricular arrhythmias (which can prove fatal) and *grand mal* convulsions (which can occur irrespective of prior epileptic history). Other side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum levels of theophylline. These medications have significant interactions with commonly used medications such as erythromycin (but not azithromycin), certain quinolone antibiotics (ciprofloxacin, but not ofloxacin), allopurinol, cimetidine (but not ranitidine), serotonin uptake inhibitors (fluvoxamine) and the 5-lipoxygenase inhibitor zileuton.

Combination bronchodilator therapy

Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation with a lower risk of side-effects compared to increasing the dose of a single bronchodilator.^(946,947) Combinations of SABAs and SAMAs are superior compared to either medication alone in improving FEV1 and symptoms.⁽⁹⁴⁸⁾ Treatment with formoterol and tiotropium in *separate inhalers* has a bigger impact on FEV1 than either component alone.⁽⁹⁴⁹⁾ There are numerous combinations of a LABA and LAMA in a *single inhaler* available (**Figure 3.18**). These combinations improve lung function compared to placebo;⁽⁹⁴⁶⁾ this improvement is consistently greater than long-acting bronchodilator monotherapy effects although the magnitude of improvement is less than the fully additive effect predicted by the individual component responses.⁽⁹⁵⁰⁾ Single inhalers improve adherence to treatment.⁽⁹⁵¹⁾ In studies where patient reported outcomes (PROs) are the primary endpoint or in pooled analyses, combination bronchodilators have a greater impact on PROs compared to monotherapies.⁽⁹⁵²⁻⁹⁵⁵⁾ In one clinical trial, combination LABA+LAMA treatment had the greatest improvement in quality of life compared to placebo or its individual bronchodilator components in patients with a greater baseline symptom burden.⁽⁹⁵⁶⁾ A clinical trial showed that LABA+LAMA improved lung function and symptoms versus long-acting bronchodilator monotherapy in symptomatic patients with low exacerbation risk and not receiving inhaled corticosteroids.⁽⁶⁹⁵⁾ The LABA+LAMA combination demonstrated favorable improvements compared with the monotherapies for the majority of outcomes irrespective of baseline HRQoL.⁽⁹⁵⁷⁾ These clinical trials deal with group mean data, but symptom responses to LABA+LAMA combinations are best evaluated on an individual patient basis. A lower dose, twice daily regimen for a LABA+LAMA has also been shown to improve symptoms and health status in COPD patients⁽⁹⁵⁸⁾ (**Figure 3.19**). These findings have been shown in people across different ethnic groups (Asian as well as European).⁽⁹⁵⁹⁾

Most studies with LABA+LAMA combinations have been performed in patients with a low rate of exacerbations. One study in patients with a history of exacerbations indicated that a combination of long-acting bronchodilators is more