transdermal patches, bupropion, and varenicline, may provide additional benefit.

Pharmacologic Therapies

After COPD is established, therapy is directed at avoiding complications such as exacerbations, relieving airflow obstruction through use of bronchodilators, and providing supplemental oxygen to patients with hypoxemia. Commonly used inhaled bronchodilators include sympathomimetic agents (β_2-adrenoreceptor agonists) and anticholinergic agents. Ipratropium bromide, a short-acting anticholinergic agent, is effective at decreasing dyspnea and improving FEV_1 in COPD (level 1 evidence). Albuterol is the most commonly used β_2-agonist; its bronchodilator effect is rapid in onset and relatively short lived. In practice, a combination of albuterol and ipratropium is frequently prescribed because these agents produce greater benefits when used in combination than individually.

Short-acting agents are typically prescribed for patients with mild disease or intermittent symptoms on an as-needed basis. Short-acting bronchodilators can be delivered by metered-dose inhaler (MDI) or by nebulizer. The MDI offers advantages of portability and ease of administration and convenience. When used correctly with a spacer, MDIs are as effective as nebulizers in delivering the drug. Nebulization has no advantage over the use of MDIs in the long-term management of obstructive lung disease except in patients who are unable to use an MDI properly.

Long-acting bronchodilators are effective for maintenance therapy in patients who have at least moderate COPD. Long-acting agents include the long-acting β_2-agonists (LABAs), which are available in once- or twice-daily formulations, and the long-acting anticholinergic/muscarinic antagonists (LAMAs), which are administered once daily. Both the LABAs and the LAMAs provide effective bronchodilation with resultant improvements in FEV_1 and symptoms (level 1 evidence). Tiotropium, a LAMA, as well as salmeterol, indecaterol, and formoterol, all LABAs, have been shown to reduce exacerbation rates in COPD (level 1). Initiation of either a LABA or a LAMA is reasonable for patients with COPD who require a long-acting bronchodilator. Tachycardia, hypokalemia, and tremor are potential adverse effects of LABAs, whereas dry mouth and urinary retention may occur with LAMA administration. In more advanced disease, there is some evidence (level 2) of additional benefits from the combination of a LABA and a LAMA.

Current data suggest that the chronic use of inhaled corticosteroids improves symptoms and decreases the frequency of exacerbations (level 1). Inhaled long-acting corticosteroids (e.g., beclamethasone, budesonide, fluticasone propionate) should be considered for individuals with COPD and a history of exacerbations but should not be used as monotherapy. Inhaled corticosteroids are less clearly effective in COPD than in asthma, and pneumonia occurs more frequently in patients with COPD treated with inhaled corticosteroids (level 1). Inhaled corticosteroids can be combined with LABAs; the combination salmeterol with fluticasone in patients with moderate to severe COPD was shown to improve health-related quality of life and to reduce exacerbations to a greater extent than either component alone (level 2).

Systemic use of corticosteroids is indicated during acute exacerbations, and intravenous corticosteroids are useful in the acute setting. Intravenous corticosteroids have also proved effective for the management of acute exacerbations of most obstructive lung diseases, including asthma (Fig. 16-4). Patients with acute exacerbations are usually transitioned from intravenous to oral steroids within 72 hours, with a subsequent tapering of the oral steroid dose over 2 weeks, although shorter courses may also be effective. Other agents with anti-inflammatory capabilities, such as leukotriene inhibitors, are not indicated for treatment of COPD.

Theophylline, a methylxanthine, is a weak systemic sympathomimetic agent with a narrow therapeutic window. It is not a first-line drug in the treatment of COPD, although long-acting derivatives with improved safety profiles have been developed. Theophylline preparations have some anti-inflammatory activity and may provide additional bronchodilation in patients with COPD who do not respond adequately to inhaled β-agonists. When these preparations are used, blood concentrations should be maintained in the lower end of the therapeutic range (between 8 and 12 μg/mL). Toxicity is common at concentrations higher than 20 μg/mL. The metabolism of theophylline is decreased by many commonly used drugs (e.g., erythromycin), and toxic serum concentrations of theophylline can be reached quickly when these other drugs are administered unless the theophylline dose is adjusted appropriately. Toxic effects of theophylline may be observed in the gastrointestinal, cardiac, and neurologic systems. Severe theophylline toxicity can be fatal, and treatment with charcoal hemoperfusion may be required.

Phosphodiesterase type 4 (PDE4) inhibitors have been investigated for the treatment of COPD, and an oral PDE4 inhibitor was recently approved as add-on therapy for treatment of severe COPD with chronic bronchitis and a history of exacerbations. PDE4 inhibitors act to inhibit breakdown of cyclic adenosine monophosphate (cAMP), resulting in a weak bronchodilator effect (approximately 50 mL improvement in FEV_1); they should not be used as acute bronchodilators. However, roflumilast was demonstrated to reduce exacerbation rates in patients who had severe COPD with chronic bronchitis and a history of exacerbation in the prior year and were not using inhaled corticosteroids (level 2 evidence). Adverse effects include weight loss, nausea and loss of appetite, and an increase in psychiatric adverse reactions including suicidality.

Oxygen Therapy and Mechanical Ventilation

Continuous oxygen therapy has been shown to improve survival in patients with COPD and hypoxemia (level 1 evidence). Oxygen supplementation is recommended once the partial pressure of oxygen in arterial blood (Pao_2) drops below 55 mm Hg or the hemoglobin oxygen saturation decreases to 88%. Oxygen supplementation is indicated at higher levels of Pao_2 if end-organ damage, such as pulmonary hypertension, is present.

Oxygen therapy is frequently necessary for treatment of acute exacerbations of obstructive lung disease. In patients who hypoventilate chronically and therefore have an elevated $Paco_2$, elevating the inspired oxygen content may acutely worsen hypercarbia by inhibiting the hypoxic ventilatory drive and by promoting the dissociation of carbon dioxide from oxygenated hemoglobin (the Haldane effect). High-flow oxygen has been