β-Agonists

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β-Agonists have been used in the treatment of asthma since injected epi-
nephrine was introduced in 1903. In 1924, ephedrine was found to be the
active principle in the traditional Chinese herbal medicine Ma Huang and
its use was suggested for treating asthma. In 1941, isoproterenol was intro-
duced as the first synthetic β-adrenergic bronchodilator. Since then, selective
β2-agonists have been discovered, with minimization of side effects. Cur-
tently, short-acting β2-agonists are used as rescue medications for acute
asthma, and long-acting β2-agonists are used in the prevention and control
of asthma symptoms. β2-Agonists are generally termed simply β-agonists.

Pharmacology

Adrenergic receptors

Adrenergic receptors are classified into α-receptors and β-receptors.
β-Receptors are further classified into β1, β2, and β3. Of these, β2-receptors
are the most important in the treatment of asthma. β2-Receptors are located
in virtually every tissue, but most prominent in the lung in smooth muscle,
epithelial cells, immune cells, glands, and alveolar walls. β1 is the principal
β-adrenergic receptor in the heart where stimulation leads to increases
in inotropic and chronotropic activity. β3-Receptors are found mostly in
brown adipose tissue and have not been identified in the human lung [1].

Like all adrenergic receptors, β2-receptors are members of the G protein–
coupled superfamily of cell surface receptors. After an agonist binds to the
receptor, the conformation of the coupled G protein is changed, activating
adenylate cyclase, which catalyzes the conversion of ATP to cAMP. Cyclic
AMP then affects the physiologic response, specific to cell type. In the lung,
β₂-agonists bind to β₂-receptors, activating G proteins and adenylate cyclase in smooth muscle cells, leading to activation of protein kinase A and relaxation of bronchial smooth muscle [2].

Structure and pharmacogenetics of β₂-receptors

The human β₂-receptor is encoded on chromosome 5q31-32. The primary amino acid sequence of the β₂-receptor is shown in Fig. 1. The protein crosses the cell membrane seven times. Agonists seem to bind at the pockets formed by the transmembrane-spanning domains [2].

Several genetic polymorphisms of the β₂-receptor have been identified, and these show variable function. Wild-type includes Arg16, Arg 19, Gln27, Val34, and Thr164. Known polymorphic alleles code for Gly16, Cys19, Glu27, Met34, and Ile164, respectively. Both animal and human studies have shown functional effects corresponding to these variants, including correlation with nocturnal asthma, degrees of bronchial hyperresponsiveness, increased IgE levels, and variable degrees of down-regulation or desensitization of receptors after prolonged exposure to agonist [3]. Children with certain variants have lower or higher responsiveness to albuterol [4]. Overall,
there is no difference in the prevalence of the polymorphisms between asthmatics and normal controls [5]. It seems that the polymorphisms do not cause asthma per se but may have a role in an individual’s response to β-agonist medications.

**Effects of β-agonists**

**Beneficial effects**

The major therapeutic effect of β-agonists is improvement of airway function by relaxation of bronchial smooth muscle. They may provide other benefits, however, by acting on endothelial and inflammatory cells [6]. The clinical significance of these actions is uncertain. β-Agonists do not seem to have any effect on chronic inflammation in the lung [6]. Such additional actions are discussed later.

**Actions on endothelial cells**

β-Agonists decrease vascular permeability by preventing separation of endothelial cells in postcapillary venules, thereby reducing mucosal edema [7]. They also reduce adhesion of neutrophils and eosinophils to venular endothelial cells, inhibiting their movement into the airway [8].

**Increased mucociliary clearance**

Studies have shown that β-agonists can increase the beating frequency of cilia in human bronchial tissue [9] and increase epithelial chloride and mucus secretion [10], potentially increasing mucociliary clearance.

**Inhibition of inflammatory cells**

β-Agonists decrease histamine release from both basophils and mast cells [11] and prostaglandin D₂ release from mast cells [12]. They inhibit the oxidative burst and release of thromboxane and leukotriene C₄ by eosinophils [6], and cytokine release by monocytes [13] and lymphocytes [14]. β₂-Receptors on alveolar macrophages are desensitized by treatment with inhaled β-agonists [15]. Both neutrophil oxidative function and mediator release are inhibited by β-agonists [16,17].

**Interaction between corticosteroids and β-agonists**

Studies have shown a number of complementary actions between corticosteroids and β-agonists. Salmeterol and albuterol activate the glucocorticoid receptor in vitro [18]. Salmeterol enhances inhibitory activity of corticosteroids on allergen-induced blood mononuclear cell activation in vitro [19]. Glucocorticoids increase β₂-receptor transcription in the lung [20], and protect against down-regulation of β₂-receptors in lung tissue [21]. β-Agonists and glucocorticoids demonstrate synergistic inhibition of inflammatory cytokine release from human airway smooth muscle cells in vitro [22]. Such
interactions may be the basis for the benefits observed with combination therapy.

Side effects

Side effects generally result from stimulation of β2-receptors in tissues outside of the lungs, from large systemic doses. The risk for side effects can be greatly reduced by administering the β-agonists by inhalation rather than by oral or parenteral routes.

Skeletal muscle

The most common side effect is tremor secondary to stimulation of β2-receptors in skeletal muscle. Some tolerance seems to develop with chronic use [23].

Cardiac

Cardiac side effects including tachycardia and palpitations are more common with nonselective β-agonists, because of stimulation of β1-receptors, but also can result from stimulation of β2-receptors in the heart. Prolongation of the QTc interval may occur.

Metabolic

Acute metabolic effects include increased plasma glucose, lactate, pyruvate, and free fatty acids. Hypokalemia develops from stimulation of a cell membrane–associated potassium-sodium pump with increased transport of potassium into cells [24]. Some studies also show hypomagnesemia [25]. These metabolic changes diminish with chronic use [23].

Ventilation-perfusion mismatching

β-Agonists may also cause a transient decrease in arterial oxygen tension (<5 mm drop in PaO2) because of an increased ventilation-perfusion mismatch. Reversal of potential hypoxemic vasoconstriction in the pulmonary vasculature may lead to changes in blood flow distribution [26]. This decrease in PaO2 lasts less than 10 minutes and can be managed by monitoring of oxygen saturation and administering oxygen to patients with severe acute asthma receiving higher doses of β-agonists.

Tolerance

Regular use of short-acting β-agonists can result in tolerance. Tolerance develops to systemic effects including tachycardia, hypokalemia, hyperglycemia, tremor, and palpitations [23]. Tolerance may be caused by receptor desensitization, which can occur by three mechanisms: (1) receptor phosphorylation, (2) sequestration or internalization, and (3) down-regulation [1]. Down-regulation develops over days to weeks of repeated use and may
shorten the duration of bronchodilation provided by a short-acting β-agonist [27]. Tachyphylaxis to the peak immediate bronchodilatory response, however, does not develop with regular use of β-agonists in asthmatic patients [23]. The decrease in duration of effect is usually not clinically relevant when the medications are used to relieve acute symptoms [7].

Many studies have examined regular use versus as-needed use of short-acting β-agonists. Some studies have shown that the regular, continuous use of short-acting β-agonists including albuterol, terbutaline, and fenoterol can result in a small increase in bronchial hyperresponsiveness that may persist for days after cessation of therapy [28]. This effect has been observed with challenges with methacholine, histamine, or allergen [28]. It has also been shown, however, that in mild asthma, regularly scheduled short-acting β-agonists are equally as effective and no worse than on-demand β-agonists [29].

In contrast to short-acting β-agonists, long-acting β-agonists are recommended for regular use, despite evidence of tolerance to some of the beneficial effects. Continuous use of salmeterol can result in a decrease in the bronchoprotective effect against exercise [30], or bronchial challenge with allergen [31] or methacholine [32]. This effect appears within 1 week of regular use and may be evident after just two doses [33]. Corticosteroids do not protect against the loss of bronchoprotection [34,35]. Continuous use of salmeterol does not result in a reduction of bronchodilation achieved after each dose [32] and does not decrease response to albuterol [36]. Continuous use of formoterol has also been shown to decrease bronchoprotection to methacholine challenge and may also decrease the duration of bronchodilation [37]. The clinical significance of these changes has yet to be shown because regular use of long-acting β-agonists is associated with improved asthma control [38].

Safety

The main safety concerns relate to an association of short-acting β-agonists with increased mortality among asthmatics in the 1960s and again in the 1970s to 1980s. The first epidemic occurred in the mid-1960s in England, Wales, Scotland, Ireland, New Zealand, Australia, and Norway [39]. Time trend data analysis revealed an association with high doses of isoproterenol forte, which contained a concentration of isoproterenol two to eight times greater than the standard formulation available in countries not affected by the epidemic [28,39]. The second epidemic began in the mid-1970s in New Zealand. Three case-control studies [40–42] and time-trend data [43] showed an association with use of fenoterol packaged in a high-dose formulation. The data were not consistent with other factors being the cause of mortality, such as class effect of β-agonists, asthma severity, under-use of inhaled corticosteroids, or socioeconomic factors. Asthma mortality rates declined after restricting the use of isoproterenol forte and fenoterol. A case-control study from Saskatchewan was designed to address whether the increased mortality was an effect of fenoterol alone or a class effect of β-agonists [44,45]. This
study did show an association between increased death or near death with the regular use of inhaled fenoterol or (to a lesser degree) albuterol. Debate still exists, but most experts believe that the higher use of short-acting β-agonists in fatal asthma is a marker for severe, acute, undertreated asthma, rather than a cause of it.

Methods of delivery

β-Agonists may be administered orally, by injection, or by inhalation. Oral β-agonists are not generally recommended as first-line therapy. Studies comparing the oral route with inhalation show that oral formulations have decreased onset and duration of action and increased side effects [46]. Injectable epinephrine may be used for severe, acute bronchospasm in the setting of anaphylaxis.

Inhalation delivery devices

Metered dose inhalers

The metered dose inhaler (MDI) is the most widely used inhalation device. It contains micronized drug in suspension or solution and a propellant pressurized within a canister. A surfactant lubricates the metering valve mechanism. The patient must coordinate actuation of the device with slow, deep inhalation. Most patients require careful, repeated instruction and coaching to use inhaler devices properly. For patients who have difficulty with hand-lung coordination, technique and drug delivery can be improved with breath-actuated inhalers [47] or spacer devices. Spacers come in a variety of styles. By slowing aerosol velocity and increasing transit time and distance, they produce smaller drug particles. This effect decreases oropharyngeal deposition and improves delivery to the lung periphery [48].

A small number of patients may experience paradoxical bronchospasm, a sudden onset or exacerbation of bronchospasm, after use of the MDI [49]. This most often occurs on first use of a new canister, may be related to the nonmedication components in the MDI, and can usually be managed by changing canisters or switching to a different product. Most MDIs contain chlorofluorocarbon propellants. Because of environmental concerns, MDIs using nonchlorofluorocarbon propellants, such as hydrofluoroalkane, are now available.

Dry powder inhalers

The dry powder inhaler (DPI) is a breath-actuated device that contains powdered drug. As the patient inhales, drug particles disaggregate into micronized particles. Because DPIs do not contain propellant, they are considered environmentally friendly. They can be used without a spacer and require minimal coordination. Some devices must be loaded before each use; others are preloaded with multiple doses. The main disadvantage is the
required inspiratory rate of approximately 60 L/min, which may be difficult for a patient with active bronchospasm. In fact, the amount of delivered drug can vary greatly with inspiratory rate. Careful instruction on appropriate technique is necessary.

Nebulizers

Nebulizers are inefficient, retaining a large proportion of medication inside the device [50]. Other disadvantages include equipment cost and maintenance, higher medication costs, and increased time to administer the medication. The main advantage is that they require minimal coordination or cooperation by the patient. Nebulizers are generally not recommended for home use for most adult patients but are recommended for acute asthma in the emergency setting and for very small children and infants.

Medications

β-Agonist medications are best classified by the duration of effect. The two classes, short- and long-acting, have different clinical applications. Structures of β-agonists currently used in the United States are pictured in Fig. 2 and dosages and delivery devices are listed in Table 1. The medications are reviewed in detail next and their role in therapy is discussed in the next section.

Short-acting β-agonists

Albuterol

Albuterol is available in a generic or branded MDI with or without chlorofluorocarbon propellant. The single-dose DPI (Ventolin Rotacaps) is less convenient for most patients. Racemic albuterol by nebulization is the first-line treatment for acute asthma in the emergency setting, but should be used infrequently for chronic treatment. Onset of bronchodilation occurs in 2 to 3 minutes, peaks at 30 to 60 minutes, and lasts 5 hours [51].

Bitolterol, metaproterenol, and pirbuterol

These medications have similar activity to albuterol. Comparison studies have shown some differences in duration but for the most part, all short-acting β-agonists act within minutes, peak in 30 to 60 minutes, and last 4 to 6 hours [51–54]. An advantage of pirbuterol is its packaging as Maxair Autohaler, which is a breath-actuated MDI. Bitolterol and metaproterenol are available as MDIs and solution for nebulization.

Levalbuterol

Levalbuterol is the R-enantiomer of racemic albuterol. It is available as Xopenex for nebulization. Because some studies have shown that regular use of albuterol can lead to tolerance and subsensitivity, the isomers of albuterol were studied. Levalbuterol, or R-albuterol, seems to be responsible for
Fig. 2. Structures of β-agonists.
bronchodilation, whereas S-albuterol may increase airway hyperresponsiveness. Levalbuterol given alone provides greater bronchodilation than an equivalent amount given as part of racemic albuterol, suggesting a negative effect of S-albuterol on therapeutic benefit. Because S-albuterol is more slowly metabolized, accumulation of S-albuterol may be the source of the decreased asthma control seen in some studies of regular use of racemic albuterol. Adverse effects, such as increased heart rate and metabolic effects, are equivalent for equal doses of levalbuterol and racemic albuterol. Because levalbuterol is a more potent bronchodilator when given alone, patients may be able to use lower doses to achieve the same benefit as higher doses of racemic albuterol [55,56].

Long-acting β-agonists

Long-acting β-agonists are more lipophilic than short-acting β-agonists and have extended hydrophobic side chains. Their prolonged duration of action stems from different mechanisms for each medication. The adverse effects of long-acting β-agonists are similar to those of short-acting bronchodilators.

Salmeterol

Salmeterol is available in MDI and DPI formulations. Bronchodilation begins at 10 to 15 minutes following inhalation, peaks at 1 to 3 hours, and lasts at least 12 hours [57]. The side chain of salmeterol binds with high affinity to a specific domain within the β_2_ receptor allowing for prolonged activation [58].

Formoterol

Formoterol is available as a DPI. Onset of bronchodilation is more rapid than with salmeterol, occurring in 2 to 3 minutes, with similar peak bronchodilation in 1 to 3 hours [57,59] and duration of action of at least 12 hours [57]. Formoterol enters the lipid bilayer of the cell membrane and is gradually released, providing prolonged stimulation of the β_2_-receptor [60].

Long-acting β-agonist combined with corticosteroids

Advair combines fluticasone and salmeterol in a single DPI delivery device available in three dosage forms with varying doses of fluticasone and a standard dose of salmeterol. Because long-acting β-agonists are an add-on therapy to inhaled corticosteroids, a combined medication device may increase adherence and reduce the chance of a patient preferentially using either medication alone.

Role of β-agonists in the treatment of asthma

The publication Guidelines for the Diagnosis and Management of Asthma produced by the National Institutes of Health classifies asthma into four
<table>
<thead>
<tr>
<th>Product</th>
<th>Supplied as</th>
<th>Suggested adult dosage</th>
<th>Route</th>
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<tbody>
<tr>
<td><strong>Short-acting</strong></td>
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<tr>
<td>Albuterol</td>
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<tr>
<td>Generic</td>
<td>90 µg/puff</td>
<td>2 puffs q 4–6 h</td>
<td>MDI containing CFC</td>
</tr>
<tr>
<td>Proventil, Ventolin</td>
<td>90 µg/puff</td>
<td>2 puffs q 4–6 h</td>
<td>MDI containing CFC</td>
</tr>
<tr>
<td>Proventil HFA</td>
<td>90 µg/puff</td>
<td>2 puffs q 4–6 h</td>
<td>MDI containing HFA</td>
</tr>
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<td>Ventolin Rotacaps</td>
<td>200 µg/inhalation</td>
<td>1–2 inhalations q 4–6 h</td>
<td>Inhalation with Rotahaler</td>
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<td>Airet, Proventil</td>
<td>0.083%</td>
<td>1 unit dose q 6–8 h</td>
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<td>Proventil, Ventolin</td>
<td>0.5%</td>
<td>0.5 mL/2.5 mL saline q 6–8 h</td>
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<td>2 mg/5 mL</td>
<td>2–4 mg q 6–8 h</td>
<td>Oral syrup</td>
</tr>
<tr>
<td>Proventil, Ventolin</td>
<td>2 mg, 4 mg</td>
<td>2–4 mg q 6–8 h</td>
<td>Tablet</td>
</tr>
<tr>
<td>Proventil Repetabs</td>
<td>4 mg</td>
<td>4–8 mg q 12 h</td>
<td>Tablet, extended release</td>
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<tr>
<td>Volmax</td>
<td>4 mg, 8 mg</td>
<td></td>
<td></td>
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<tr>
<td>Bitolterol</td>
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<td>Tomalate</td>
<td>370 µg/puff</td>
<td>2 puffs q 8 h</td>
<td>MDI</td>
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<td>0.2%</td>
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<td>Levalbuterol</td>
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<td>Xopenex</td>
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<td>1 unit dose q 6–8 h</td>
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<td>Xopenex</td>
<td>1.25 mg/3 mL</td>
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<td>Metaproterenol</td>
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<td>Alupent, Prometa</td>
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<td>Arm-a-Med</td>
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<td>5%</td>
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<tr>
<td>Alupent</td>
<td>10 mg/5 mL</td>
<td>20 mg q 6–8 h</td>
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<td>Metaprel syrup</td>
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<tr>
<td>Alupent</td>
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<td>20 mg q 6–8 h</td>
<td>Tablet</td>
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<td>Pirbuterol</td>
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<td>Maxair</td>
<td>200 µg/puff</td>
<td>1–2 puffs q 4–6 h</td>
<td>MDI</td>
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<tr>
<td>Maxair autohaler</td>
<td>200 µg/puff</td>
<td>1–2 puffs q 4–6 h</td>
<td>Breath-actuated MDI</td>
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<td>Terbutaline</td>
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</tr>
<tr>
<td>Brethaire</td>
<td>200 µg/puff</td>
<td>2 puffs q 4–6 h</td>
<td>MDI</td>
</tr>
<tr>
<td>Brethine Oral</td>
<td>2.5 mg, 5 mg</td>
<td>2.5–5 mg q 6 h</td>
<td>Tablet</td>
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<td>Long-acting</td>
<td>Salmeterol</td>
<td>Serevent</td>
<td>25 μg/puff</td>
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<tr>
<td></td>
<td>Serevent Diskus</td>
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<td>1 inhalation bid</td>
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<td>Formoterol</td>
<td>Foradil aerolizer</td>
<td>12 μg/inhalation</td>
<td>1 inhalation bid</td>
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<td>Combinations</td>
<td>Fluticasone/Salmeterol</td>
<td>Advair Diskus</td>
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<td></td>
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<td>250 μg/50 μg</td>
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<td></td>
<td></td>
<td>500 μg/50 μg</td>
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<td>Combivent</td>
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<td>Systemic</td>
<td>Epinephrine</td>
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<td>Epi-Pen Jr</td>
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<td>Terbutaline</td>
<td>Brethine injection</td>
<td>1 mg/mL</td>
<td>0.25 mg SC q 15–30 min prn</td>
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<td>Bricanyl injection</td>
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levels of severity: (1) mild intermittent, (2) mild persistent, (3) moderate persistent, and (4) severe persistent [61]. These guidelines recommend a stepwise approach to managing asthma with medications, which are classified as quick-relief medications or long-term control medications.

Short-acting β-agonists fall in the category of quick-relief medications. All patients with asthma should have a short-acting β-agonist for quick relief to be used as needed. The usual dose is two puffs by MDI, four times daily as needed. The need for the short-acting β-agonist is a marker of asthma control and helps to define level of severity. Patients whose asthma is well controlled use little as needed bronchodilator, whereas patients with poorly controlled asthma or with an asthma exacerbation may use short-acting bronchodilators several times a day or night. Increased use of bronchodilators should alert the physician that an adjustment in therapy may be warranted.

Long-acting β-agonists fall in the category of long-term control medications along with inhaled corticosteroids. Other controller medications include cromolyn, nedocromil, theophylline, and leukotriene-modifying agents. Their roles are not discussed here. Inhaled long-acting β-agonists should not be used for rescue or quick relief of asthma symptoms. They should not be used as a single controller agent because they exert little, if any, anti-inflammatory effect. The recommended dose is two puffs twice a day for salmeterol MDI and one puff twice a day for salmeterol or formoterol DPI.

**Stepwise approach**

**Mild-intermittent asthma**

Patients with mild intermittent asthma have symptoms no more than 2 days per week, no more than 2 nights per month, a forced expiratory volume in one second (FEV₁) greater than or equal to 80% predicted, and peak flow variability less than 20% [61]. They require no daily medication and may use a short-acting β-agonist as needed.

**Mild-persistent asthma**

These patients have symptoms 3 to 6 days per week, 3 to 4 nights per month, an FEV₁ of greater than or equal to 80%, and peak flow variability of 20% to 30% [61]. They should be prescribed a daily controller anti-inflammatory medication, specifically a low-dose inhaled corticosteroid. They should continue to use the short-acting β-agonist as needed.

**Moderate-persistent asthma**

At this level of severity, patients have symptoms daily and at least 5 nights per month. The FEV₁ ranges from 60% to 80% predicted and peak flow variability is greater than 30% [61]. Treatment options include increasing the inhaled corticosteroid or adding a long-acting β-agonist to low or moderate doses of inhaled corticosteroid. A meta-analysis of nine trials
comparing these two options showed that combination therapy resulted in greater improvement in symptoms and pulmonary function than inhaled corticosteroids alone, even at high doses [62]. In fact, addition of a long-acting \( \beta \)-agonist twice daily may allow a reduction in daily dose of inhaled corticosteroid. In a study of patients with asthma suboptimally controlled with triamcinolone therapy who then achieved control after the addition of salmeterol, the dose of inhaled steroid could be reduced by 50\% (but not totally eliminated) without a significant loss of asthma control [36]. The use of a long-acting \( \beta \)-agonist does not mask worsening asthma or change the character of asthma exacerbations, which are decreased in frequency [38]. The combination can be administered by two separate inhalers, or by the fluticasone-salmeterol combination product. Again, patients should continue the short-acting \( \beta \)-agonist as needed.

**Severe-persistent asthma**

Patients with severe-persistent asthma have continual symptoms, frequently at night; an FEV\(_1\) no greater than 60\%; and peak flow variability of greater than 30\% [61]. Severe asthma uncontrolled by high-dose inhaled corticosteroids is improved by the addition of a long-acting \( \beta \)-agonist [63,64]. This combination may obviate the need for maintenance oral corticosteroid therapy [65]. The combination of inhaled long-acting \( \beta \)-agonists and inhaled corticosteroids is considered the treatment of choice for severe asthma. The short-acting \( \beta \)-agonist as needed should be continued.

**Exercise-induced asthma**

Both inhaled short- and long-acting \( \beta \) agonists are indicated for prophylaxis of exercise-induced asthma [61]. A short-acting \( \beta \)-agonist, such as albuterol, should be taken 5 to 60 minutes before exercise, preferably as close to the start of exercise as possible [61]. The effects should last 2 to 4 hours [66] but may be lost in less than 2 hours [67]. The long-acting \( \beta \)-agonists offer longer-lasting protection and are better suited for prolonged activity. Salmeterol should be taken at least 30 minutes before exercise, whereas formoterol may be taken minutes before exercise. The long-acting \( \beta \)-agonist effects last 10 to 12 hours; they may be taken hours before anticipated exercise. Continuous use of inhaled long-acting \( \beta \)-agonists can lead to diminished bronchoprotection against exercise [30]. Such loss of bronchoprotection may be manifested by a shortening of the duration of effect to 6 to 8 hours [68]. In the maintenance treatment of asthma, an increase in long-term control medications may be appropriate if exercise-induced symptoms are a frequent problem.

**Nocturnal asthma**

Intuitively, long-acting agents are better suited for overnight control than short-acting agents. Both slow-release oral \( \beta \)-agonists and inhaled long-acting \( \beta \)-agonists have been recommended in the treatment of nocturnal
asthma. Comparison studies have shown similar efficacy between the two modalities measured by changes in pulmonary function, nighttime awakenings, and use of rescue albuterol, and similar incidence of adverse effects [69,70]. During the open label phase of one comparison study, more patients preferred the inhaled long-acting β-agonist because of fewer side effects, greater symptom relief, and less need for rescue β-agonist [70]. The National Institutes of Health guidelines recommend inhaled long-acting β-agonists as the preferred choice [61]. Increasing nocturnal symptoms are a sign that asthma is poorly controlled; an adjustment of daily controller medication may be in order.

**Chronic obstructive pulmonary disease**

Chronic obstructive pulmonary disease (COPD) is a separate disease entity from asthma; however, the obstruction in COPD may include a significant reversible component [71]. Bronchodilators are a key component in the treatment of COPD. Short-acting β-agonists may produce less bronchodilation than in asthma, but do produce a significant improvement in symptoms [71]. They do not alter the progression of COPD and are used as a symptom reliever. They may be used as needed or on a regular schedule combined with the anticholinergic ipratropium [71]. Long-acting β-agonists have a role in maintenance therapy. Studies show that salmeterol improves lung function and decreases dyspnea and other symptoms of COPD [72,73]. It may be more effective than ipratropium [72] or theophylline [73] as a first-line bronchodilator, and has shown greatest efficacy when used in combination with theophylline [73].

**Summary**

β-Agonists are a mainstay of asthma treatment. Short-acting β-agonists are the most effective bronchodilators for rescue or quick relief of symptoms. Long-acting β-agonists have a key role in long-term control when added to inhaled corticosteroid therapy, and are especially useful in the control of nocturnal asthma. Both types of β-agonists may be used in the prophylaxis of exercise-induced asthma with long-acting β-agonists providing more prolonged protection. β-Agonists have minimal side effects and are safe when used appropriately.

**References**


Shrewsbury S, Pyke S, Britton M. A meta-analysis of increasing inhaled steroid or adding salmeterol in symptomatic asthma. BMJ 2000;320:1368–73.

Jenkins C, Woolcock AJ, Saarelainen P, et al. Salmeterol/fluticasone propionate combination therapy 50/250 $\mu$g twice daily is more effective than budesonide 800 $\mu$g twice daily in treating moderate to severe asthma. Respir Med 2000;94:715–23.


Higgs CMB, Laszlo G. The duration of protection from exercise-induced asthma by inhaled salbutamol, and a comparison with inhaled reproterol. Br J Dis Chest 1983;77:262–9.


