Bronchodilators, Beta$_2$-Agonist Review

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Overview

Beta$_2$-agonist bronchodilators are used for the treatment and prevention of bronchospasm associated with asthma, prophylaxis of exercise-induced bronchospasm (EIB), and in the treatment of chronic obstructive pulmonary disease (COPD).

The mainstay of asthma therapy is the use of inhaled glucocorticoids and long-acting beta$_2$-agonists as controller medications. These agents lead to improvements in lung function and symptoms and reduce the need for short-acting beta$_2$-agonists for quick relief. While the corticosteroid reduces inflammation, the long-acting beta$_2$-agonist acts principally to dilate the airways by relaxing airway smooth muscle. The short-acting beta$_2$-agonists have not been shown to be beneficial as controller medications, but due to their rapid onset, they are useful for temporary relief of bronchoconstriction and the accompanying acute symptoms such as wheezing, chest tightness, and cough.[1]

Bronchodilator medications are central to the symptomatic management of COPD.[2,3,4,5] They improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance. [6] They are given either on an as needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. Regular bronchodilation with these drugs does not modify the decline of function in mild COPD or the prognosis of the disease.[7] The principal bronchodilator treatments are beta$_2$-agonists, anticholinergics, and theophylline. These are given either as monotherapy or in combination with the inhaled agents being preferred. While short-acting beta$_2$-agonists can be used on an as needed basis in mild COPD, regular treatment with a long-acting agent is required as the disease progresses.[8]

Pharmacology

Beta-agonists stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity, especially from mast cells. The beta$_2$-agonists relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, COPD, or bronchiectasis. Bronchodilation may additionally facilitate expectoration.

Although there are both beta$_1$ and beta$_2$ receptors in the heart, the latter are more predominant in the lungs, where they serve as the primary adrenergic receptors in bronchial smooth muscle. In order to reduce cardiac toxicities (e.g., tachyarrhythmias), the use of beta$_2$ specific agonists is preferred in the treatment of bronchospasm. This has minimized the use of less specific and less safe agents such as epinephrine (Primatene®) and isoproterenol (Isuprel®). To further reduce cardiac toxicities, non-systemic dosage forms given by inhalation are preferred to oral dosage forms.

FDA-Approved Indications and Dosage Forms

Generic Name	Brand Name (Manufacturer)	Dosage Forms	Reversible Bronchospasm		Prevention of EIB	COPD	Age
			Prevention and Treatment	Relief			
Short Acting Agents							
albuterol CFC MDI[9]	generic	90 mcg per actuation	X	X	X		≥4
albuterol HFA MDI[10,11]	Proventil HFA® (Schering)						
	Ventolin HFA® (GlaxoSmithKline)						
albuterol HFA MDI[12]	ProAir HFA (Ivax)	90 mcg per actuation	X	X	X		≥12
albuterol inhalation solution[13,14]	generic	2.5 mg/3 mL, 5 mg/mL		X			≥2
	Accuneb® (Dey); generic	0.63 mg/3 mL, 1.25 mg/3 mL		X			2-12
levalbuterol inhalation solution[15]	Xopenex® (Sepracor)	0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL	X				≥6
levalbuterol HFA MDI[16]	Xopenex HFA® (Sepracor)	45 mcg per actuation	X				≥4
metaproterenol inhalation solution[17]	generic	8 mg/2 mL, 5 mg/mL, 12 mg/2 mL,	X	X		X	≥6
metaproterenol MDI[18]	Alupent® (Boehringer -Ingelheim)	0.65 mcg per actuation	X			X	≥12
pirbuterol MDI[19]	Maxair Autohaler® (3M)	200 mcg per actuation	X				≥12
Oral Agents							
albuterol oral syrup[20]	generic	2 mg/5 mL		X			≥2
albuterol oral tablets[21]	generic	2 mg, 4 mg		X			≥6
albuterol extended-release oral tablets[22]	generic	4 mg, 8 mg					
metaproterenol oral syrup[23]	generic	10 mg/5 mL	X			X	≥6
metaproterenol oral tablets[24]	generic	10 mg, 20 mg		X			≥6
terbutaline tablets[25]	generic	2.5 mg, 5 mg		X		X	≥6
Long Acting Agents							
arformoterol inhalation solution[26]	Brovana® (Sepracor)	15 mcg/2 mL				X	≥18
formoterol DPI[27]	Foradil Aerolizer® (Schering)	12 mcg per inhalation	X		X		5-11
			X		X	X	≥12
salmeterol DPI[28]	Serevent Diskus (GlaxoSmithKline)	50 mcg/dose	X		X	X	≥4

CFC=chlorofluorocarbon; HFA=hydrofluroalkane; MDI=metered-dose inhaler; DPI=dry powder inhaler

Pharmacokinetics

Drug	Relative ß$_2$ Specificity	Onset of Action (minutes)	Duration of Action (hours)
Short Acting Agents			
albuterol CFC MDI[29]	ß$_2$ >> ß$_1$	5-15	3-6
albuterol HFA MDI (ProAir HFA, Proventil HFA, Ventolin HFA)[30,31,32]	ß$_2$ >> ß$_1$	5.4-8.2	3-6
albuterol inhalation solution (generic, Accuneb)[33,34]	ß$_2$ >> ß$_1$	2-5	3-6
levalbuterol inhalation solution (Xopenex)[35]	ß$_2$ >> ß$_1$	10-17	5-8
levalbuterol HFA MDI (Xopenex HFA)[36]	ß$_2$ >> ß$_1$	5-10	3-6
metaproterenol inhalation solution[37]	ß$_2$ > ß$_1$	5-30	2-6
metaproterenol MDI (Alupent)[38]	ß$_2$ > ß$_1$	5-30	1-5
pirbuterol MDI (Maxair)[39]	ß$_2$ > ß$_1$	≤ 5	5
Oral Agents			
albuterol extended-release tablets (Vospire ER)[40]	ß$_2$ >> ß$_1$	30	12
albuterol syrup, tablets[41,42]	ß$_2$ >> ß$_1$	30	4-8
metaproterenol syrup, tablets[43,44]	ß$_2$ > ß$_1$	30	≥4
terbutaline tablet[45]	ß$_2$ >> ß$_1$	30	4-8
Long Acting Agents			
arformoterol inhalation solution (Brovana)[46]	ß$_2$ >>> ß$_1$	7-20	12
formoterol DPI (Foradil)[47]	ß$_2$ >>> ß$_1$	5-15	12
salmeterol DPI (Serevent Discus)[48]	ß$_2$ >>> ß$_1$	30-48	12

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled comparative trials are considered the most relevant in this category. Criteria for study inclusion in this review are the following: English language, human studies, analyze the data consistently with the study question, randomly allocate participants to comparison groups, include follow-up (endpoint assessment) for at least 80 percent of those entering the investigation, and have clearly stated, predetermined outcome measure of known or probable clinical importance. Studies were determined to be free of bias. Unbiased studies

were then reviewed for validity and importance. The majority of clinical drug trials are sponsored and/or funded by pharmaceutical manufacturers. While objective criteria were used to ensure that the studies included are free of bias, the potential influence of manufacturer sponsorship/funding must be considered.

albuterol MDI and formoterol DPI (Foradil)

Formoterol DPI 12 mcg twice daily was compared to albuterol MDI 180 mcg four times daily and placebo in a total of 1,095 patients with mild-to-moderate asthma in two twelve-week, multicenter, randomized, double-blind, parallel group studies.[49] The results of both studies showed that formoterol inhalation powder resulted in significantly greater postdose bronchodilation, as measured by serial forced expiratory volume in one second (FEV_1) for 12 hours postdose, throughout the study period. Compared with placebo and albuterol, patients treated with formoterol demonstrated improvement in the secondary efficacy endpoints of improved combined and nocturnal asthma symptom scores, fewer nighttime awakenings, fewer nights in which patients used rescue medication, and higher morning and evening peak expiratory flow (PEF).

A study compared the efficacy and tolerability of formoterol DPI 12 mcg and 24 mcg twice-daily with albuterol MDI 180 mcg four times daily and placebo.[50] A total of 484 adolescents and adults (ages 12-75 years) with mild-to-moderate asthma completed this 12-week, multicenter, double-blind, double-dummy, placebo-controlled, parallel-group study. For the primary efficacy variable, FEV_1, both formoterol 12 and 24 mcg were statistically superior to placebo at all time points on all test days ($p \leq 0.017$) and to albuterol at most time points on all test days ($p \leq 0.001$). The onset of improvement in FEV_1 was rapid, with 15 percent increase within five minutes in 57, 71, and 65 percent of formoterol 12 mcg, formoterol 24 mcg, and albuterol patients, respectively. Formoterol was also superior to placebo and albuterol in terms of secondary efficacy variables: FEV_1, AUC, percentage of predicted FEV_1, forced vital capacity (FVC), asthma symptom scores, and peak expiratory flow rate (PEFR). Formoterol and albuterol were both well-tolerated.

Eighteen patients with EIB were randomized in a double-blind, placebo-controlled, four-way, crossover study.[51] Each patient received, in random sequence, a single dose of formoterol DPI 12 or 24 mcg, albuterol MDI 180 mcg, or placebo at intervals of three to seven days. Pulmonary function measurements were taken before and after exercise challenge tests at 15 minutes postdose and at four, eight, and 12 hours postdose. Both doses of formoterol produced significantly greater protection against EIB than placebo at all time points ($p \leq 0.016$). The two doses of formoterol were not significantly different from one another at any time. Protection against EIB with albuterol was clinically significant only at the 15 minute postdose time point and was statistically superior to placebo at 15 minutes and four hours. Rescue medication was used substantially less with either dose of formoterol, compared with albuterol or placebo. All treatments were well tolerated. Two-hour postdose electrocardiograms (ECGs) and vital signs were unremarkable for all study treatments.

In a double-dummy, four-way crossover study, 17 adult and adolescent asthmatic patients received single doses of formoterol DPI 12 and 24 mcg, albuterol MDI 180 mcg, and placebo.[52] Exercise challenge tests were conducted at 15 minutes and at four, eight, and 12 hours postdose. Compared with placebo, both doses of formoterol produced significantly greater inhibition of FEV_1 decreases at all time points ($p<0.01$). There were no significant differences in efficacy measures between the two formoterol doses throughout the study. The exercise-induced decrease in FEV_1 after albuterol treatment was significantly reduced compared with

placebo only at 15 minutes after dosing ($p<0.05$). Formoterol and albuterol exhibited a similar rapid onset of action (<15 minutes), but formoterol continued to protect patients against EIB for at least 12 hours ($p<0.01$), whereas albuterol was no longer clinically effective by the four hour exercise challenge test.

albuterol MDI, formoterol DPI (Foradil), and salmeterol DPI (Serevent) in COPD

A cross-over, randomized, double-blind, placebo-controlled study was carried out on 20 COPD patients.[53] Patients underwent pulmonary function testing and dyspnea evaluation in basal condition and five, 15, 30, 60 and 120 minutes after bronchodilator (albuterol, formoterol, or salmeterol) or placebo administration. The results indicated that in COPD patients with decreased baseline inspiratory capacity, there was a much greater increase of inspiratory capacity after bronchodilator administration, which correlated closely with the improvement of dyspnea sensation at rest. On average, formoterol elicited the greatest increase in inspiratory capacity than the other bronchodilators used, though the difference was significant only with salmeterol.

formoterol DPI (Foradil) and salmeterol DPI (Serevent) in COPD

Researchers compared the effects of single doses of formoterol DPI 12 and 24 mcg and salmeterol DPI 50 and 100 mcg in a randomized, double-blind, placebo-controlled, crossover study of 47 patients with moderate-to-severe COPD.[54] The primary efficacy parameter was the area under curve of FEV_1 in the first hour after drug inhalation in the morning. The estimates of treatment difference in absolute terms (0.086 L; $p=0.0044$) and percentage change from predose baseline (7.8 percent; $p=0.0021$) were greater for formoterol than for salmeterol.

formoterol DPI (Foradil), salmeterol DPI, (Serevent) and terbutaline MDI

Twenty-five subjects with asthma and a history of EIB were enrolled in a double-blind, double-dummy, placebo-controlled, randomized, four-period crossover study.[55] Exercise challenge was performed after 12 days at five, 30, or 60 minutes after inhalation of a single dose of formoterol DPI 12 mcg, salmeterol DPI 50 mcg, terbutaline MDI 500 mcg, or placebo. Exercise-induced bronchoconstriction did not differ significantly between the active treatments at five, 30, or 60 minutes postdose. In contrast, the onset of bronchodilation was slower after salmeterol compared to terbutaline ($p<0.05$) and formoterol ($p<0.05$), both of which showed a similar time course. At all time points between five and 60 minutes, formoterol provided significantly greater bronchodilation than salmeterol ($p<0.05$).

albuterol inhalation solution and levalbuterol inhalation solution (Xopenex)

In a randomized, double-blind, placebo-controlled, crossover study, 20 adults with mild to moderate asthma received single doses of levalbuterol inhalation solution (0.31, 0.63, and 1.25 mg) and albuterol inhalation solution (2.5 mg).[56] All doses of active treatment produced a significantly greater degree of bronchodilation (measured by change in FEV_1) than placebo, and there were no significant differences between any of the active treatment arms. The bronchodilator response of levalbuterol 1.25 mg and albuterol 2.5 mg were clinically comparable over the six hour evaluation period, except for a slightly longer duration of action after administration of levalbuterol 1.25 mg. Systemic beta adrenergic adverse effects were observed with all active doses. Levalbuterol 1.25 mg produced a slightly higher rate of systemic beta adrenergic adverse effects than the albuterol 2.5 mg dose.

A multicenter, randomized, double-blind, placebo- and active-controlled study was conducted in 316 children with mild to moderate asthma.[57] Following a one week placebo run-in, subjects were randomized to nebulized levalbuterol 0.31 or 0.63 mg, albuterol 1.25 or 2.5 mg, or placebo given three times daily for three weeks. Efficacy, measured by mean peak change in FEV_1, was demonstrated for all active treatment regimens compared with placebo. The onset and duration of effect of levalbuterol were clinically comparable to those of albuterol.

A randomized, double-blind, controlled trial was conducted in children age one to 18 years (n=482) in the emergency department (ED) and inpatient asthma care unit of an urban tertiary children's hospital.[58] Patients received a nebulized solution of either 2.5 mg racemic albuterol or 1.25 mg levalbuterol every 20 minutes (maximum six doses). Patients admitted to the asthma care unit were treated in a standardized fashion by using the same blinded drug assigned in the ED. Hospitalization rate was the primary outcome. Hospitalization rate was significantly lower in the levalbuterol group (36 percent) than in the racemic albuterol group (45 percent, p=0.02). The adjusted relative risk of admission in the racemic group compared with the levalbuterol group was 1.25 (95 percent confidence interval, 1.01 - 1.57). Hospital length of stay was not significantly shorter in the levalbuterol group (levalbuterol, 44.9 hours; racemic albuterol, 50.3 hours; p=0.63). No significant adverse events occurred in either group.

comparison of MDI propellant

Since the signing of the Montreal Protocol in 1987, new propellants, such as hydrofluoroalkane (HFA), for use in pressurized metered-dose inhalers that are non-ozone-depleting have been developed. Several randomized, double-blind, placebo-controlled, crossover studies have shown that albuterol MDI pressurized by HFA are equivalent, in terms of efficacy and tolerability, to the original chlorofluorocarbon (CFC) albuterol MDI in both adolescents and adults.[59,60,61,62] This equivalence was shown for both the treatment and prophylactic (EIB) indications of albuterol.

comparison of inhaler systems

The American College of Chest Physicians (ACCP) and the American College of Allergy, Asthma, and Immunology (ACAAI) have issued joint evidence-based guidelines for selecting aerosol delivery devices for use in asthma or COPD.[63] The authors compared the efficacy and adverse effects of treatment using nebulizers versus pressurized MDIs with or without a spacer/holding chamber versus DPIs as delivery systems for beta$_2$-agonists, anticholinergic agents, and corticosteroids in several commonly encountered clinical settings and patient populations. The authors conclude that devices used for the delivery of bronchodilators and steroids can be equally efficacious.

Warnings

In August 2003, the FDA updated the safety information for products containing salmeterol. The new labeling for these products contains a boxed warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma related deaths observed in patients taking salmeterol in the large, placebo-controlled Salmeterol Multicenter Asthma Research Trial (SMART). In this prematurely stopped study, only the single component agent, Serevent, was administered. Post-hoc analysis indicates that the risk of these serious reactions was significantly higher in African-Americans. The FDA did indicate that the benefits of salmeterol in patients with COPD or asthma outweigh the risks.[64]

On November 18, 2005, FDA alerted health care professionals and patients that several long-acting bronchodilator medicines have been associated with possible increased risk of worsening

wheezing (bronchospasm) in some people, and requested that manufacturers update warnings in their existing product labeling. Since March 2, 2006, the product labeling for all of the long acting beta agonists have included this update in their labeling. Arformoterol inhalation (Brovana) also has the same warnings in the labeling.[65]

*Adverse Effects**

Drug	Headache	Nausea/ Vomiting	Nervousness	Palpitations	Tachycardia	Tremor
Short Acting Agents						
albuterol CFC MDI[66]	0 - 27	2 - 15	1 - 20	<1 - 10	1 - 10	<1 -24.2
albuterol HFA MDI (Proventil HFA, Ventolin HFA, ProAir HFA)[67,68,69]	7-20	7 - 10	7	<3	<3 - 7	2-7
albuterol inhalation solution (generic, Accuneb)[70,71]	3 - 27	1.4 - 4	4 - 8.1	<1	1 - 2.7	2.7 - 20
levalbuterol inhalation solution (Xopenex)[72]	0 - 11.9	<2	2.8 - 9.6	<2	2.7 - 2.8	0 - 6.8
levalbuterol HFA MDI (Xopenex HFA)[73]	--	10.5	reported	--	reported	reported
metaproterenol inhalation solution[74]	3.3	7.7 - 14	14.1	<1	2.5 – 16.6	2.5 - 33
metaproterenol MDI (Alupent)[75]	1 - 4	1 - 4	6.8	1 - 4	<1	1 - 4
pirbuterol MDI (Maxair)[76]	1.3 - 2	0 - 1.7	4.5 – 6.9	1.3 - 1.7	1.2 - 1.3	1.3 - 6
Oral Agents						
albuterol extended release tablets (Vospire ER)[77]	18.8	4.2	8.5	2.4	2.7	24.2
albuterol syrup[78]	4	<1 - 2	9 - 15	<1	1 - 2	10
albuterol tablets[79]	7	2	20	5	5	20
metaproterenol syrup[80]	1.1	1.3	4.8	<1	6.1	1.6
metaproterenol tablets[81]	7	0.8 - 3.6	20.2	3.8	17.1	16.9
terbutaline tablets[82]	7.8 - 10	1.3 - 10	<5 - 31	≤23	1.3 - 3	<5 - 38
Long Acting Agents						
arformoterol inhalation solution (Brovana)[83]	<2	--	<2	<2	<2	--
formoterol DPI (Foradil)[84,85,86]	<1 - 4.3	<1 - 1.4	<1 - 6	<1	<1 - 2	<1 - 2.9
salmeterol DPI (Serevent Discus)[87]	13 - 17	1 - 3	1 - 3	reported	reported	reported

***** Reported as a percentage. Each drug's adverse events are reported from pooled studies, different age groups, and product package information and therefore, should not be directly compared.

Dosages

Drug	Usual Adult Dosage	Prevention of EIB	Usual Pediatric Dose
Short Acting Agents			
albuterol CFC MDI[88]	2 inhalations every 4-6 hrs as needed	2 inhalations 15 minutes prior to exercise	1 inhalation every 4-6 hrs as needed
albuterol HFA MDI (Proventil HFA, Ventolin HFA, ProAir HFA)[89,90,91]	2 inhalations every 4-6 hrs as needed	2 inhalations 15-30 minutes prior to exercise	Ages 12 and up (ProAir HFA) Ages 4 and up (Proventil HFA and Ventolin HFA): 1 or 2 inhalations every 4-6 hrs as needed
albuterol inhalation solution (generic, Accuneb)[92,93]	2.5 mg every 6-8 hrs as needed	--	Ages 2 to 12 years (Accuneb only): 0.63-1.25 mg TID-QID as needed
levalbuterol inhalation solution (Xopenex)[94]	0.63-1.25 mg TID	--	Ages 6 to 11 years: 0.31-0.63 mg TID
levalbuterol HFA MDI (Xopenex HFA)[95]	1 or 2 inhalations every 4-6 hrs as needed	--	Ages 4 and up: 1 or 2 inhalations every 4-6 hrs as needed
metaproterenol inhalation solution[96]	10-15 mg TID-QID	--	5-10 mg TID-QID
metaproterenol MDI (Alupent)[97]	2-3 inhalations every 3-4 hrs	--	--
pirbuterol MDI (Maxair)[98]	1-2 inhalations every 4-6 hrs	--	--
Oral Agents			
albuterol oral syrup[99]	2-4 mg every 6-8 hrs	--	0.1-0.2 mg/kg every 8 hrs
albuterol oral tablets[100]	2-4 mg every 6-8 hrs	--	2 mg every 6-8 hrs
albuterol extended-release tablets (Vospire ER)[101]	4-8 mg every 12 hrs	--	4 mg every 12 hrs
metaproterenol oral syrup[102]	20 mg TID-QID	--	10 mg TID-QID
metaproterenol oral tablets[103]			
terbutaline tablets[104]	2.5-5 mg TID	--	2.5 mg TID
Long Acting Agents			
arformoterol inhalation for solution (Brovana)[105]	15 mcg BID	--	--
formoterol DPI (Foradil)[106]	1 inhalation every 12 hrs	1 inhalation 15 minutes prior to exercise	Ages 5 and up: 1 inhalation every 12 hrs
salmeterol DPI (Serevent Diskus)[107]	1 inhalation every 12 hrs	1 inhalation 30 minutes before exercise	Ages 4 and up: 1 inhalation every 12 hrs

Summary

Due to its rapid onset of action, relative lack of adverse systemic effects, and availability of multiple dosage forms, albuterol remains the "gold standard" among the short acting beta$_2$-agonist bronchodilators. Albuterol nebulizer solution is available generically in both unit dose (2.5 mg/3 mL) and concentrate (5 mg/mL), the latter of which is easily diluted to lower doses that may be indicated for younger children. As a result, the inclusion of low strength, unit dose albuterol (Accuneb) on the PDL is of little consequence from a clinical standpoint. Albuterol CFC MDIs are available generically. Schering (Proventil HFA), Ivax (ProAir HFA) and GlaxoSmithKline (Ventolin HFA) produce equivalent inhalers using HFA propellant. Although HFA is more environmentally friendly than CFC, there appears to be no difference in tolerability or efficacy between the two MDI types.

A systematic review of pertinent randomized, controlled, clinical trials was undertaken using MEDLINE, EmBase, and the Cochrane Library databases to determine if a difference in efficacy and adverse effects exists between the various aerosol delivery devices (MDI vs. DPI vs. nebulizers) used in the management of asthma and COPD exacerbations.[108] A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested beta$_2$-agonists) proved to have useable data. None of the pooled meta-analyses showed a significant difference between devices in any efficacy outcome in any patient group for each of the clinical settings that was investigated. The adverse effects that were reported were minimal and were related to the increased drug dose that was delivered. Each of the delivery devices provided similar outcomes in patients using the correct technique for inhalation. When selecting an aerosol delivery device for patients with asthma and COPD, the following should be considered: device/drug availability; clinical setting; patient age and the ability to use the selected device correctly; device use with multiple medications; cost and reimbursement; drug administration time; convenience in both outpatient and inpatient settings; and physician and patient preference.

There are little data to support the use of oral albuterol except in children who are unable to effectively use an MDI and whose asthma is not severe enough to warrant nebulizer therapy. Oral dosage forms of albuterol are less desirable than the inhaled forms due to systemic beta-adrenergic stimulation of the former, especially in patients sensitive to these effects, such as those with cardiovascular disease. The extended-release forms of albuterol have fewer side effects than immediate-release dosage forms, although they are also less effective than inhaled beta$_2$-agonists.

Metaproterenol is neither as beta$_2$ selective nor as long acting as albuterol, therefore should not be considered for first-line therapy. Another beta$_2$-agonist, terbutaline, is more beta$_2$ selective than metaproterenol but is available only as oral tablets. The short duration of action of terbutaline reduces its value in the treatment of bronchoconstriction, although it is of some benefit in its more common use of inhibiting uterine contraction in premature labor. Pirbuterol (Maxair) is similar in both efficacy and safety to the generically available albuterol CFC inhalers, although it is somewhat less beta$_2$ selective.

Levalbuterol (Xopenex) is the R-enantiomer form of albuterol. This inhalation solution is touted as having equivalent efficacy with fewer adverse effects when given in equivalent doses to albuterol inhalation solution. The data supporting this claim are contradictory, however. The FDA denied an additional pediatric indication for children as young as two years of age due to safety concerns. Levalbuterol is most appropriately reserved for second line therapy in patients with documented intolerance to albuterol inhalation solution.

Formoterol (Foradil) and salmeterol (Serevent) are the two long acting, inhaled, beta$_2$-agonist bronchodilators. The main difference between the two is that formoterol has an earlier onset of action. A recent study indicates that, while both of these long-acting agents attenuate the response to short-acting beta$_2$-agonists, salmeterol may have a more pronounced effect.[109] Whether this translates to a clinical significant effect is unknown. The black box warning recently added to all long acting beta agonists may discourage the use of these agents, especially in the African-American population. More data are needed to verify the significance of this warning. Additionally, a recent meta-analysis of 19 trials with 33,826 patients examined the effects of LABAs in patients with asthma.[110] Although the meta-analysis suggested a 3.5-fold greater risk for asthma-related deaths in patients using LABAs, it did not distinguish the impact of baseline asthma severity, medication adherence or pharmacogenomics. This meta-analysis is also criticized because 78 percent of the study population came from the SMART trial where only 47 percent of the patients were receiving an inhaled corticosteroid. Long-acting beta$_2$-agonists are more appropriate for routine use than the short-acting agents.

Arformoterol (Brovana) is the newest agent in this category. It is the first and only approved long-acting beta agonist for nebulization indicated for the twice-daily, long-term maintenance treatment of bronchoconstriction in patients with COPD, which includes chronic bronchitis and emphysema. This nebulized form may prove beneficial for patients who have difficulty synchronizing breath and actuation using the other existing long-acting beta agonists available as dry powder inhalers (Foradil and Serevent). There are no comparative data to suggest that arformoterol is superior in efficacy or safety to the other agents. Also, arformoterol has not been demonstrated to have an impact on the progression of disease or survival of patients with COPD.

In November 2006, the GINA guidelines for asthma management were updated to reflect a change in focus from asthma severity to asthma control.[111] Asthma control is defined as no or minimal daytime symptoms; no limitations of activity; no nocturnal symptoms; no or minimal need for rescue medications; normal or near normal lung function; and no exacerbations. A five-step treatment approach is introduced in this guideline that offers flexibility to step up treatment if control is loss or step down treatment when asthma is controlled. These new guidelines suggest treatment with short acting beta-$_2$ agonists only on an as-needed basis particularly if patients experience only occasional daytime symptoms of short duration. When symptoms are more frequent and/or worsen periodically, patients require regular controller therapy.

In December 2006, the updated GOLD guidelines were released and state that beta$_2$ agonist bronchodilators are among the principal treatments for symptomatic management of COPD.[112] The guidelines also state that regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators.

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