Chapter 12
Bronchodilators for COPD: At What Stage Should Therapeutic Intervention Be Initiated?

Takashige Kuraki

Abstract Pharmacologic therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Medications that increase the FEV_1 or change other spirometric variables, usually by altering airway smooth muscle tone, are termed bronchodilators, since the improvements in expiratory flow reflect widening of the airways rather than changes in lung elastic recoil. Such medications improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance. The extent of these changes, especially in severe and very severe patients, is not easily predictable from the improvement in FEV_1. This chapter will describe some of the information that support the use of mono- or combined bronchodilator therapy in patients with COPD.

Keywords COPD • Bronchodilator

12.1 Introduction: The Physiological Rationale for Using Bronchodilators

Medications that increase the FEV_1 or change other spirometric variables, usually by altering airway smooth muscle tone, are termed bronchodilators, since the improvements in expiratory flow reflect widening of the airways rather than changes in lung elastic recoil. Such medications improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance [1].

A schematic description of the innervation of the airways is fundamental for understanding how bronchodilators work and why they have clinical utility. Airway tone is mainly controlled by the vagus nerve, and the parasympathetic nerves

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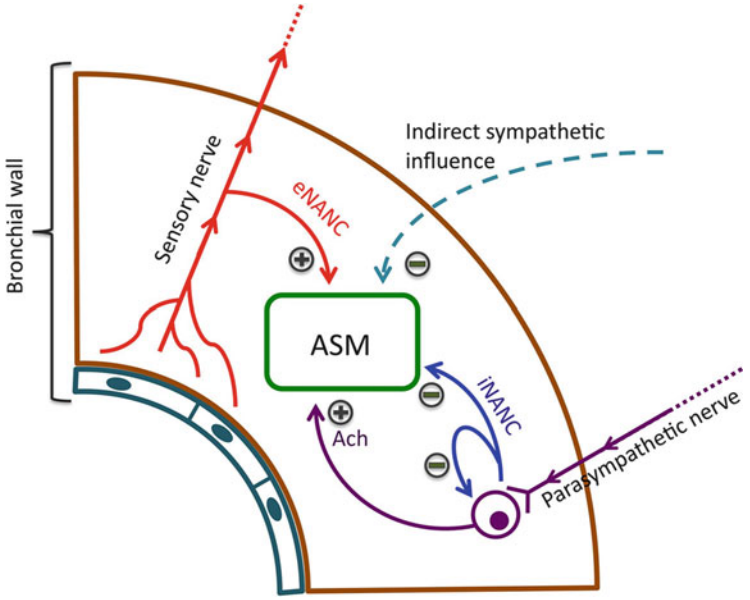


Fig. 12.1 Neural regulation of bronchial tone[2]. *eNANC* excitatory NANC, *Ach* acetylcholine. (Ref : Cazzola M, Pharmacol Rev 2012, 64:450–504.)

carried in the vagus nerve are tonically active, producing a stable, readily reversible baseline tone of the airway smooth muscle (ASM) (Fig. 12.1).

12.1.1 Cholinergic Pathway

Acetylcholine (ACh) is the "classic" neurotransmitter of the parasympathetic nervous system at both the level of ganglionic transmission and the neuroeffector junctions. ACh acts via activation of muscarinic receptors (mAChRs) that belong to the large seven-transmembrane family of G protein-coupled receptors (GPCRs). Five different subtypes of mAChRs have been identified by molecular biological techniques (M_1–M_5), but so far, a sufficient pharmacological and functional characterization has been provided for only four of them (M_1–M_4) [3]. The mAChRs are expressed in almost every cell type of the airway and lung tissue, including airway and vascular smooth muscle, different glandular and surface epithelial cells, endothelial cells, and various inflammatory cells. In humans, M_1 mAChRs seem to be expressed particularly in peripheral lung tissue and in the alveolar wall, but they have not been detected in larger airways, where M_2 and M_3 mAChRs represent the major population of mAChRs. Under "physiological" conditions, the ASM contraction induced by ACh is mediated primarily via the M_3 subtype. M_2 mAChRs couple to adenylyl cyclase via Gi in an inhibitory manner. They functionally oppose the β-AR-mediated increase in cAMP, leading to attenuation of β-AR-induced

relaxation of ASM and prevent activation of Ca_2-dependent K (KCa) channels [2, 3].

12.1.2 Adrenergic Pathway

β-ARs are present in high concentration in lung tissue, and autoradiographic mapping and in situ hybridization studies show that they are localized to several cell types. β-ARs are subdivided into three types: β_1, β_2, and β_3. They are members of the seven-transmembrane spanning family of GPCRs related to bacteriorhodopsin and are composed of 413 amino acid residues. There is a 65–70 % homology between β_1/ β_3- and β_2-ARs. Binding studies show that approximately 70 % of pulmonary β-ARs are of the β_2-AR subtype. These receptors are localized to ASM (3–4/10^4 per cell), epithelium, vascular smooth muscle, and submucosal glands [4], whereas β1-ARs in the lung are confined to glands and alveoli. There is a uniform distribution of β-ARs on the alveolar wall with a 2:1 ratio of β_1/ β_2-ARs. β_2-AR density increases with increasing airway generation, and high levels are found in the alveolar region. Computed tomography scanning has confirmed that β_2-AR distribution is greater for small rather than large airways. β_2-ARs are also expressed on many proinflammatory and immune cells, including mast cells, macrophages, neutrophils, lymphocytes, eosinophils, epithelial and endothelial cells, and type I and type II alveolar cells [2].

GPCRs are dynamic proteins that switch between an inactive state and an active conformation that can engage G proteins (Fig. 12.2). Persistent activation of a GPCR is achieved through the binding of both an agonist and a G protein at opposite ends of the receptors relative to the lipid bilayer, where the combined binding interactions reduce the energy barriers to the formation of the active state. β_2-ARs are coupled to Gs, where stimulation by a β_2-AR agonist activates adenylyl cyclase and increases cAMP levels. cAMP increases protein kinase A (PKA) activity, which phosphorylates downstream protein modulators. The overall activation of this signal transduction pathway can lead to the inhibition of phosphoinositol hydrolysis, a fall in intracellular Ca_2 levels, and the activation of large-conductance K channels. The hyperpolarization of airway smooth muscle as a result of opening K channels can lead to relaxation of airway smooth muscle. β_2-AR stimulation produces airway relaxation, but prolonged β_2-AR activation leads to a decrease in receptor responsiveness that differs depending on the cell type but is more readily demonstrable in inflammatory cells than ASM [5].

12.1.3 Non-adrenergic Non-cholinergic Pathway

Autonomic neural control of ASM tone cannot be fully explained by the functions of the cholinergic and adrenergic nervous systems alone [6]. For example, striking

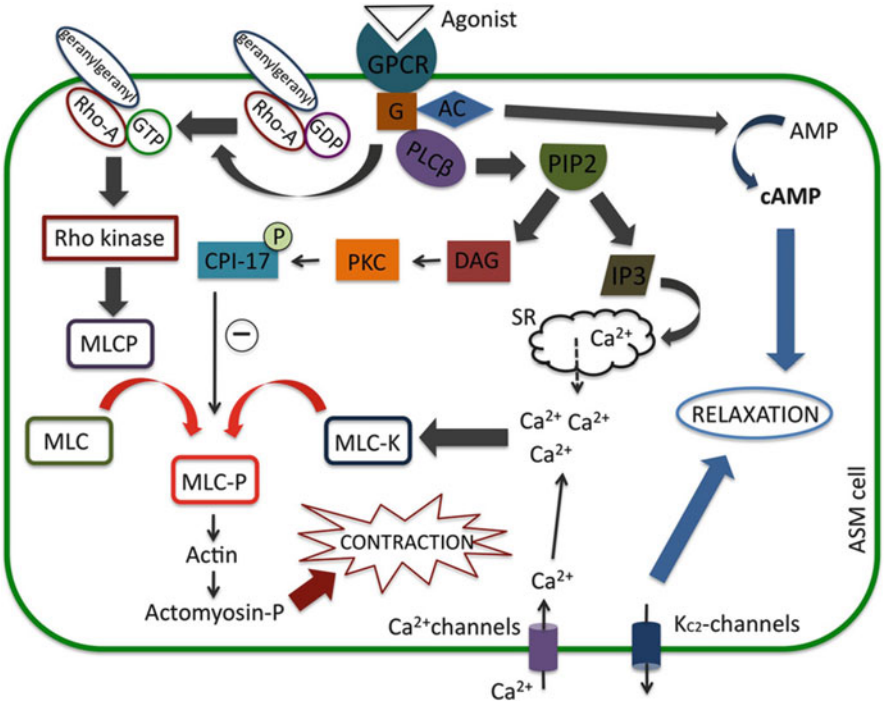


Fig. 12.2 Main intracellular pathways involved in the bronchomotor tone regulation [2] *PLC* phospholipase C-, *PIP2* phosphatidylinositol 4,5-bisphosphate, *IP3* inositol 1,4,5-trisphosphate, *DAG* diacylglycerol, *SR* sarcoplasmic reticulum, *MLCK* myosin light-chain kinase, *MLC* myosin light chain, *MLC-P* myosin light-chain phosphorylation, *CPI-17* C kinase-potentiated phosphatase inhibitor, *Rho kinase* Rho-associated serine/threonine kinase, *AC* adenylyl cyclase(Ref : Cazzola M, Pharmacol Rev 2012, 64:450–504.)

changes in ASM tone can be induced even in the presence of an anticholinergic agent (atropine) and a β-AR antagonist (propranolol). There is substantial evidence of contractile and relaxant NANC smooth muscle responses in mammalian airways. In fact, inhibitory NANC (iNANC) innervation is considered the primary neural mechanism mediating ASM relaxation. iNANC relaxation is thought to be generated by a combined effect of vasoactive intestinal peptide (VIP), VIP structure-related peptides (e.g., peptide histidine methionine), and nitric oxide (NO). Indeed, VIP, VIP-like peptides, and NO synthase have been identified in the parasympathetic ganglia and nerve fibers innervating ASM. Furthermore, endogenously released VIP-like and NO-like substances can attenuate ASM contraction induced by ACh. However, the precise anatomical pathways of iNANC innervation of human ASM are not clear. There is also a potent excitatory effect on the ASM involving the “efferent” functions of a specific subtype of bronchopulmonary sensory nerves containing tachykinins (e.g., substance P and neurokinin A) in guinea pig airways, although this is less evident in human airways. When these afferent endings are activated, the impulses trigger the release of tachykinins either

locally or propagating antidromically to other peripheral branches via the axonal ramifications. These sensory neuropeptides can activate neurokinin-1 and -2 receptors located on the ASM membrane and produce intense and sustained bronchoconstriction [2, 7].

12.2 Muscarinic Acetylcholine Receptor Antagonists

12.2.1 History

Inhaled mAChR antagonists have been used as treatments for respiratory diseases for centuries. The smoking of plant alkaloids was recommended as a therapy for asthma in the literature of Ayurvedic medicine as early as the seventeenth century. *Atropa belladonna* and *Datura stramonium* are rich in anticholinergic alkaloids such as atropine and stramonium [8]. Unfortunately, atropine, which is a tertiary ammonium compound, is well absorbed into the systemic circulation and penetrates the blood–brain barrier. As a result, it has multiple systemic side effects that limit its clinical usefulness. However, a renewed interest in anticholinergic drugs as therapy for respiratory diseases has been sparked by the development of safe yet effective quaternary anticholinergic compounds (Fig. 12.3). Chemical modifications of the atropine molecule, in particular by making its nitrogen atom pentavalent, have yielded a number of synthetic congeners that are very poorly absorbed from mucosae and cross the blood–brain barrier with difficulty. When given by inhalation, these agents are as effective as atropine at improving lung function but longer acting and much less prone to side effects [9].

12.2.2 Short-Acting Muscarinic Acetylcholine Receptor Antagonists

As well as atropine methonitrate, ipratropium bromide and oxitropium bromide are effective short-acting quaternary anticholinergic drugs that have been used in the treatment of respiratory diseases. Their duration of action is approximately 6–8 h, but compared with SABAs, they have a slower onset of action, although probably a longer duration of action [9].

12.2.2.1 Atropine Methonitrate

Atropine methonitrate, a quaternary ammonium congener of atropine, seems to be a more potent bronchodilator agent than its parent compound, atropine sulfate. In patients with asthma, atropine methonitrate produces a peak bronchodilator effect

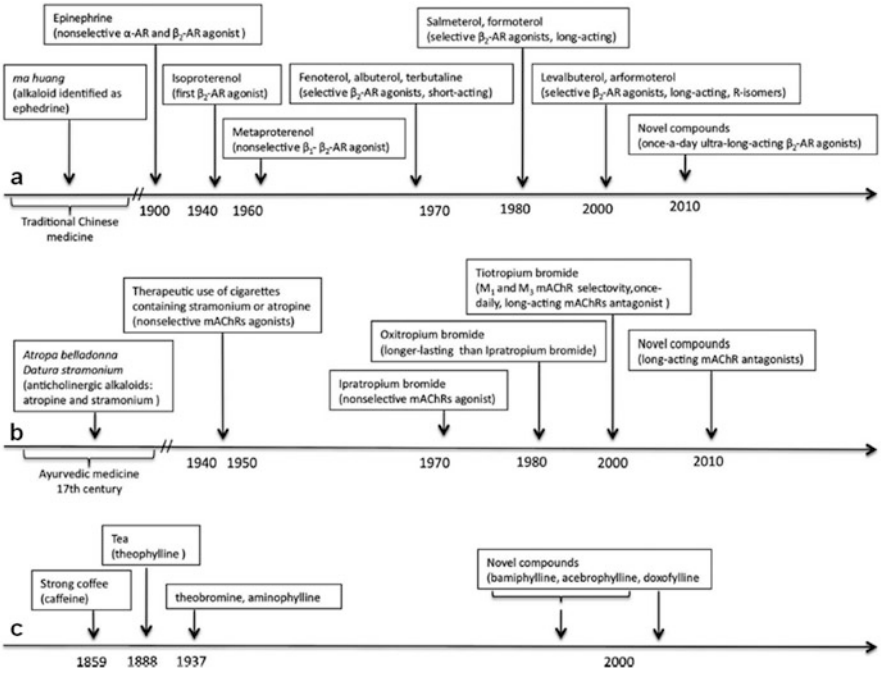


Fig. 12.3 Milestone development of β_2-AR agonists (**a**), antimuscarinics (**b**), and xanthines (**c**) (Ref : Cazzola M, Pharmacol Rev 2012, 64:450–504.) [2]

similar to that of albuterol, both administered in doses that produced close to maximum bronchodilation for the drug concerned, but the effect of atropine is more prolonged, the response being significantly greater at 4 and 6 h than with albuterol [10].

12.2.2.2 Ipratropium Bromide

Ipratropium bromide is unlike atropine; it has low lipid solubility and does not pass the blood–brain barrier. Ipratropium bromide is poorly absorbed by the oral and nasal mucosa, and the swallowed drug is poorly absorbed from the gastrointestinal tract. It is a nonselective antagonist of M_1, M_2, and M_3 mAChRs. Serum ipratropium bromide concentrations are extremely low after inhalation of the drug, peak serum concentrations being achieved at approximately 3 h after administration. The elimination half-life is 3.2–3.8 h, and ipratropium metabolites have little or no anticholinergic activity. Ipratropium bromide starts to act within 15–30 min, but maximal bronchodilation may take up to 90 min in patients with COPD. The duration of action is approximately 6 h, so in comparison with β_2-AR agonists, its broncholytic effect is slower in onset and probably longer in duration.

On the basis of the duration of action, ipratropium bromide is given four times daily, and the maximum number of doses (40 μg) per day should not exceed 12 [11].

12.2.2.3 Oxitropium Bromide

Oxitropium bromide is another quaternary anticholinergic compound but is based on the scopolamine molecule instead of atropine. The peak bronchodilation of oxitropium bromide may take 60–90 min, and its duration is 5–8 h. Oxitropium bromide is considered to have twice the strength of ipratropium bromide per dose. In patients with severe COPD, the FEV_1 and forced vital capacity (FVC) plateau attained at a total cumulative dose of 600 μg of oxitropium bromide was slightly higher than the plateau achieved with 280 μg of ipratropium bromide [12].

12.2.3 Long-Acting Muscarinic Acetylcholine Receptor Antagonists

12.2.3.1 Tiotropium Bromide

Tiotropium bromide is a once-daily, long-acting mAChR antagonist (LAMA) with high potency and kinetic selectivity at the mAChRs. It displays a 6- to 20-fold higher affinity for mAChRs than does ipratropium bromide. Although tiotropium bromide binds to all three mAChRs, it dissociates much faster from the M_2 mAChRs, which results in a more selective antagonist action for M_1 and M_3 mAChR subtypes. Its prolonged pharmacologic activity is the result of its slow dissociation from M_1 and M_3 mAChRs. The half-life of the tiotropium bromide M_3 mAChR complex is approximately 35 h, compared with 0.3 h for ipratropium bromide. The mechanism allowing for the long residency of tiotropium bromide at M_3 mAChRs is not completely known. The increased duration of binding at the M_3 mAChRs results in prolonged improvement in lung function, allowing a once-daily dose compared with the three to four doses per day previously necessary with ipratropium bromide. Tiotropium bromide is rapidly absorbed into the circulation with a peak plasma concentration within 5 min followed by a rapid fall within an hour to a steady state and a terminal half-life of 5–6 days that is independent of dose. The peak onset of bronchodilation with tiotropium bromide occurs between 1 and 3 h with improvements in FEV1 for more than 24 h [13].

12.2.3.2 Glycopyrronium Bromide

Glycopyrronium bromide is a mAChR antagonist that has a dissociation half-life from the human M_3 mAChR that is significantly shorter than tiotropium bromide or aclidinium bromide. In line with this finding, in isolated human bronchi,

glycopyrronium bromide elicits a duration of action intermediate between that produced by tiotropium bromide and that of ipratropium bromide. Clinical studies have shown that glycopyrronium bromide has a fast onset of effect that is sustained over 24 h, although another recent study with nebulized glycopyrronium bromide shows that this was probably shorter acting, at least at doses below 50 μg. The safety and efficacy of glycopyrronium bromide have been documented in patients with moderate-to-severe COPD. Glycopyrronium bromide is well tolerated at doses of up to 100 μg in this patient population [14].

12.2.3.3 Aclidinium Bromide

Preclinical studies have demonstrated that aclidinium bromide exhibits M_3/M_2 mAChR kinetic selectivity. This mAChR antagonist dissociates from humanM_3 mAChRs at a rate that was similar to that of ipratropium bromide and 2.6 times faster than that of tiotropium bromide. On the contrary, it dissociates from the same receptors slightly faster than tiotropium bromide and, in line with these findings, is equivalent to ipratropium bromide for speed of onset but with a longer duration. However, in human isolated bronchi, aclidinium bromide has a faster onset and shorter duration of action than tiotropium bromide [15]. Aclidinium bromide has the advantage of rapid hydrolytic inactivation once absorbed into the plasma, thereby enhancing its safety profile.

12.2.3.4 Umeclidinium Bromide

This agent umeclidinium is a novel high-affinity-specific mAChR antagonist. It has similar affinity to the subtypes of muscarinic receptors M_1–M_5. In the airways, it is a potent agent that demonstrates slow functional reversibility at cloned humanM_3 mAChRs and at endogenous mAChR in isolated human bronchus. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical in vitro as well as in vivo studies, prevention of methacholine- and acetylcholine-induced bronchoconstrictive effects was dose dependent and lasted longer than 24 h. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of umeclidinium is predominantly a site-specific effect [16].

12.2.4 Novel Long-Acting Muscarinic Acetylcholine Receptor Antagonists

Several other mAChR antagonists are also under development. Unfortunately, the available public information on these bronchodilators is still limited. New agents

like CHF 5407, inhaled trospium (ALKS27), and PF-4522971 are under development in 2016 now [2].

12.2.5 Oral Muscarinic Acetylcholine Receptor Antagonists

It is believed that oral anticholinergics are not a treatment option for COPD because of unacceptable side effects [11], whereas inhaled anticholinergics have virtually no systemic absorption. Mepenzolate bromide is one of the oral anticholinergics but has high affinity to M_3 muscarinic acetylcholine receptor and is under redevelopment of COPD.

12.2.6 Side Effects

Anticholinergic drugs are poorly absorbed which limits the troublesome systemic effects seen with atropine. But all of the currently approved inhaled mAChR antagonists have a very wide therapeutic margin and are very well tolerated, in part because they are very poorly absorbed after inhalation. However, if any of these agents makes inadvertent contact with the eye, they can cause papillary dilation.

In older men, who may have prostatic hyperplasia, mAChR antagonists should be used with caution because they can cause urinary retention. Men using both short- and long-acting inhaled mAChR antagonists had a significantly higher risk of acute urinary retention compared with nonusers. Patients with moderate-to-severe renal impairment (creatinine clearance of < 50 ml/min) under treatment with tiotropium bromide should be closely monitored, because tiotropium bromide is predominantly excreted by the kidneys through active secretion.

Paradoxical bronchoconstriction to ipratropium bromide has been reported in humans. It is possible that this results from blockade of prejunctional M_2 mAChRs on airway cholinergic nerves, which normally inhibit ACh release; when the drug is given by nebulizer, however, it is largely explained by the hypotonicity of the nebulizer solution. Paradoxical bronchoconstriction may also occur with other mAChR antagonists.

Concerns have been raised about possible associations of mAChR antagonists with cardiovascular morbidity and mortality. However, the results of the UPLIFT trial and a robust and extensive analysis of more than 19,000 patients participating in placebo-controlled clinical trials with tiotropium bromide indicate that there is no real increased risk for death or cardiovascular morbidity during treatment with this inhaled anticholinergic agent in patients with COPD [13, 17, 18].

12.3 β-Adrenergic Receptor Agonists

12.3.1 History

In traditional Chinese medicine, the botanical ma huang (the plant *Ephedra equisetina*), from which the active material, an alkaloid identified as ephedrine, is extracted, was used for more than 2000 years for the short-term treatment of respiratory symptoms. Beginning at the turn of the last century, the nonselective α-AR and β-AR agonist epinephrine was introduced into clinical practice and administered by the subcutaneous route for the treatment of acute asthma [19]. In the 1940s, the nonselective β-AR agonist isoproterenol was introduced for the treatment of airway disease and became the standard-of-care bronchodilator, although its use was complicated by adverse effects that were due to activation of the β_1-AR in the heart, which elicits tachycardia and predisposes patients to cardiac dysrhythmias. Metaproterenol, a noncatechol resorcinol derivative of isoproterenol, was subsequently developed in the early 1960s. It was an effective bronchodilator when inhaled but also did not discriminate between β_1- and β_2-ARs and thus produced cardiac side effects [20].

The noncatecholamine β_2-AR agonists such as fenoterol, albuterol, and terbutaline differ in their substitutions in the amine group and benzene ring. These structural modifications, conferring resistance to metabolism by COMT, result in a longer half-life and also reduce their potency for β_1-ARs, making them relatively more selective for β_2-ARs (Fig. 12.3). A major limitation of the β_2-AR agonists in use during the 1960s and 1970s was their short duration of action, typically 4 to 6 h. Therefore, the next advance in the development of β_2-AR agonists was the development of the long-acting drugs salmeterol and formoterol, the duration of action of which is approximately 12 h, which made their use for maintenance treatment. A pure *R*-isomer of albuterol, levalbuterol, and the *R*,*R*-enantiomer of formoterol, arformoterol, have been developed. It is claimed that they have a better safety profile than the racemic mixture because they do not have the *S*-enantiomer, which, at least for (*S*)-albuterol, is now known to have unwanted effects in the lung. At present, several once-a-day ultra-long-acting β_2-AR agonists are in different stages of clinical development [2].

12.3.2 Short-Acting Agents

The principal action of β_2-agonists is to relax airway smooth muscle by stimulating β_2-AR, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. The bronchodilator effects of short-acting β_2-agonists usually wear off within 4–6 h. Regular and as-needed use of short-acting β-agonists improve FEV_1 and symptoms. There is little difference in the time course of fenoterol, albuterol, and terbutaline, although there is some evidence that fenoterol

might have a slightly longer duration of action. The use of high doses of short-acting β_2-agonists on an as-needed basis in patients already treated with long-acting bronchodilators is not supported by evidence, may be limited by side effects, and cannot be recommended. For single-dose, as-needed use in COPD, there appears to be no advantage in using levalbuterol over conventional bronchodilators [1, 21].

12.3.3 Long-Acting β2-Adrenergic Receptor Agonists

Long-acting inhaled β_2-AR agonists show duration of action of 12 or more hours [22]. The duration of action of β_2-AR agonists in the human bronchus is in the following order: salmeterol $>>$ formoterol $>$ albuterol $>$ terbutaline $>$ fenoterol. Formoterol and salmeterol significantly improve FEV_1 and lung volumes, dyspnea, health-related quality of life, and exacerbation rate, but have no effect on mortality and rate of decline of lung function. A systematic review of trials of salmeterol and formoterol showed a significant reduction in the numbers of patients requiring treatment for exacerbations and the number requiring hospitalization [23, 24]. Salmeterol reduces the rate of hospitalization. Although formoterol and salmeterol are both potent and effective β_2-AR agonists, their different chemical structures confer markedly different pharmacological characteristics.

12.3.3.1 Formoterol

Formoterol is a full agonist of β_2-ARs and has been shown to provide a rapid-onset bronchodilating effect that occurs within minutes after inhalation. A number of studies have shown a comparable clinical effect of formoterol compared with the SABAs albuterol and terbutaline in stable patients with asthma [2]. But an oral formulation of formoterol did not seem to offer a clear advantage to albuterol. In effect, formoterol has a long duration of action when given by inhalation but not when given orally. A dose–response comparison of formoterol in patients with asthma suggested that after inhalation and 50 times more potent after oral administration [25].

12.3.3.2 Salmeterol

Salmeterol is a drug resulting from a specific research program designed to achieve prolonged duration of action by molecular modification of albuterol. Salmeterol is a partial agonist with ~60 and 85 % of the efficacy of isoprenaline, respectively. In contrast to its effects on β_2-ARs, at cardiac β_1-ARs, salmeterol is >10,000-fold weaker than isoprenaline and has a very low efficacy (4 %). The onset of action of salmeterol on ASM is slower than that of other β_2-AR agonists, such as albuterol and formoterol, but it seems to be inherently long acting, in that its effects are

independent of concentration as a result of exosite binding, whereas albuterol, fenoterol, and formoterol have shorter durations of action, but this can be prolonged by increasing the concentration of the β_2-AR agonist applied to the tissue [26].

12.3.4 Ultra-Long-Acting β2-Adrenergic Receptor Agonists

A variety of β_2-AR agonists with longer half-lives are currently in development, with the hope of achieving once-daily dosing. These agents include indacaterol, olodaterol, vilanterol, carmoterol, PF-610355, and AZD-3199, the structure of which has not yet been disclosed.

12.3.4.1 Indacaterol

Indacaterol is the first ultra-long-acting β_2-agonist approved for the treatment of COPD that allows for once-daily administration. It is rapidly acting, with an onset of action in 5 min, like salbutamol and formoterol but with a sustained bronchodilator effect, that lasts for 24 h, like tiotropium. In long-term clinical studies in patients with moderate-to-severe COPD, once-daily indacaterol improved lung function significantly more than placebo, and improvements were significantly greater than twice-daily formoterol and noninferior to once-daily tiotropium bromide. Indacaterol was well tolerated at all doses and with a good overall safety profile. These findings suggest that indacaterol can be a first choice drug in the treatment of the patient with mild/moderate stable COPD [27].

12.3.4.2 Olodaterol

Olodaterol is a new long-acting β_2-agonist for COPD. Olodaterol statistically significantly improved lung function in people with moderate to very severe COPD compared with placebo over 24 weeks and was not statistically significantly different from formoterol. Although olodaterol appears to improve lung function as well as formoterol, little evidence is available comparing it directly with other LABAs and LAMAs for COPD, particularly in terms of patient-oriented outcomes such as exacerbations, breathlessness, and quality of life. Olodaterol was often coadministered with tiotropium and ICS and only limited data support its use alone [28].

12.3.4.3 Vilanterol

Vilanterol is a potent, selective β_2-AR agonist in human functional cellular assays. Vilanterol produced rapid bronchodilation in patients with COPD that was

maintained over 24 h at all doses. After dosing with vilanterol, there were no serious adverse events or withdrawals due to adverse events. Vilanterol in patients with COPD significantly improved FEV_1 in a dose-dependent manner. Clinically relevant treatment differences of >130 ml in mean FEV_1 were observed. Clinical doses of vilanterol were associated with a low incidence of treatment-related side effects. Vilanterol was often co-administered with umeclidinium and ICS, and only limited data support its use alone [29].

12.3.4.4 Carmoterol

Carmoterol has been demonstrated to be a highly potent and selective β_2-AR agonist. Carmoterol has a similar onset of action compared with albuterol and formoterol and a faster onset of action compared with salmeterol. The duration of tracheal smooth muscle relaxation is longer for carmoterol compared with both formoterol and salmeterol. In COPD, a single use of carmoterol had an effect on 24 h trough FEV_1 that was better than that of two uses of salmeterol given 12 h apart. After a 2-week treatment period, once-daily doses of 2 and 4 μg of carmoterol resulted in placebo-adjusted improvements compared with baseline in trough FEV_1 of 94 and 112 ml [30].

12.3.4.5 LAS100977, PF-610355, and AZD-3199

Abediterol (LAS100977), PF-610355, and AZD-3199 are novel, selective, potent, once-daily LABA in development for treatment of asthma and chronic obstructive pulmonary disease.

12.3.5 Intravenous β2-Adrenergic Receptor Agonists

An interesting new option is the development of a β_2-AR agonist to be administered intravenously. Bedoradrine (MN-221) is a novel, highly selective β_2-adrenoceptor agonist under development for the treatment of acute exacerbation of asthma and COPD. A preliminary small trial showed that bedoradrine added to standard therapy for severe acute asthma exacerbations was safe and provided additional clinical benefit [31].

In a small group of patients with COPD, bedoradrine seemed to improve lung function at all dose levels and reached statistical significance at both 600 and 1200 μg compared with placebo [32].

12.3.6 Transdermal β2-Adrenergic Receptor Agonists

Tulobuterol is the first bronchodilator to be available as a transdermal patch. This drug delivery system ensures that the time at which the peak drug concentration in the blood is reached coincides with the morning dip in respiratory function. The use of the patch also prevents excessive increase in blood drug concentrations, thereby reducing the incidence of systemic adverse reactions. But the efficacy and potentials are not fully recognized, and the tulobuterol patch has been used in the limited regions in the world [33].

12.3.7 Side Effects of β2-Adrenergic Receptor Agonists

Stimulation of β_2-AR can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in susceptible patients, although these seem to have remarkably few clinical implications. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of β_2-agonists, whatever the route of administration, and this limits the dose that can be tolerated. Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics [34], and oxygen consumption can be increased under resting conditions [35], these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO_2 can occur after administration of both short- and long-acting β_2-agonists, but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago related to β_2-agonists in the management of asthma, further detailed study has found no association between β_2-agonist use and an accelerated loss of lung function or increased mortality in COPD [1].

12.4 Methylxanthines

12.4.1 History

One of the earliest reports of the efficacy of methylxanthines in asthma was published in 1859, where Henry Hyde Salter, himself an asthmatic, described his experience that “one of the commonest and best reputed remedies of asthma... is strong coffee.” The first analysis of a xanthine derivative extracted from tea leaves was accomplished by Kossel, who was able to extract not only caffeine but also another xanthine derivative, a dimethylxanthine. The name theophylline was then applied to a compound that has two methyl groups (1,3-dimethylxanthine) (Fig. 12.3). Until 1930, xanthine derivatives were used in clinical practice only because of their diuretic and cardiotonic properties. Years later, a combination of theophylline and aminophylline was used intravenously as an effective

bronchodilator in acute asthma. Since then, several other xanthines have been synthesized and are used clinically in various parts of the world [2].

12.4.2 Aminophylline

Aminophylline is the ethylenediamine salt of theophylline with higher solubility at a neutral pH. In vivo intravenous aminophylline has an acute bronchodilator effect in patients with asthma that is most likely to be due to a relaxant effect on ASM. Aminophylline also increases diaphragmatic contractility and reverses diaphragm fatigue. However, side effects such as nausea and vomiting are common, and the benefit/risk ratio is unknown. Aminophylline is also widely used for the treatment of acute exacerbations of COPD despite a lack of evidence to support this practice. It remains possible that aminophylline confers a small but clinically significant benefit when added to standard therapy. However, it was unable to find evidence for any clinically important additional effect of aminophylline treatment when used with high-dose nebulized bronchodilators and oral corticosteroids in patients with nonacidotic COPD exacerbations [36].

12.4.3 Theophylline

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. Changes in inspiratory muscle function have been reported in patients treated with theophylline, but whether this reflects changes in spirometry or a primary effect on the muscle is not clear. Despite its extensive use in the treatment of respiratory disease, the precise molecular actions of theophylline have not been fully elucidated. Its efficacy in the treatment of patients with COPD or asthma has traditionally been attributed to nonselective phosphodiesterase (PDE) inhibition, resulting in an increase in cAMP by inhibition of PDE_3 and PDE_4 and an increase in cGMP by inhibition of PDE_5. All studies that have shown efficacy of theophylline in COPD were performed with slow-release preparations.

Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable. However, there is evidence for a modest bronchodilator effect compared with placebo in stable COPD. There is also some evidence of symptomatic benefit compared to placebo. Addition of theophylline to salmeterol produced a greater improvement in FEV_1 and breathlessness than salmeterol alone. Low-dose theophylline reduces exacerbations but does not improve post-bronchodilator lung function [37, 38].

Theophylline can also act as a respiratory stimulant. Moreover, theophylline is able to improve diaphragmatic contractility and has anti-inflammatory properties. There is good evidence for inhibitory effects of theophylline on airway inflammation in patients with asthma and COPD, and these effects are seen at plasma concentrations below 10 mg/l [39].

12.4.4 Novel Xanthine

The positive clinical effects of theophylline in airway disease, combined with its advantageous oral bioavailability, has spurred the development of other xanthines, such as bamifylline, acebrophylline, and doxofylline, for the treatment of respiratory disease, with the anticipation that such drugs would have greater efficacy than theophylline but with an improved side effect profile.

12.4.5 Side Effects

Toxicity is dose related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given. Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of 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 theophylline. These medications also have significant interactions with commonly used medications such as digitalis, Coumadin, etc. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental) [1].

12.5 Novel Classes of Bronchodilators

Novel classes of bronchodilators have proved difficult to develop, but there is still a continued interest in generating new classes of bronchodilators that act via emerging targets, particularly given the recent concerns over the selective phosphodiesterase inhibitors.

There are some pathways to release the ASM constriction like K channel openers, VIP analogs, Rho kinase inhibitors, neuropeptides, and NO donors (Fig. 12.2).

12.5.1 Selective Phosphodiesterase Inhibitors

The principal action of selective phosphodiesterase-4 inhibitors is to reduce inflammation by inhibiting of the breakdown of intracellular cyclic AMP. It is a once-daily oral medication with no direct bronchodilator activity, although it has been shown to improve FEV_1 in patients treated with salmeterol or tiotropium [40, 41].

Roflumilast reduces moderate and severe exacerbations treated with corticosteroids by 15–20 % in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations. The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators. There are no direct comparisons or add-on studies of roflumilast and inhaled corticosteroids. Phosphodiesterase-4 inhibitors should always be used in combination with at least one long-acting bronchodilator.

As an alternative to oral administration, a number of groups are now investigating the topical application of PDE4 inhibitors as a possible way to improve their efficacy in the treatment of inflammatory airway diseases while minimizing side effects. A non-emetic mixed PDE3/PDE4 has already successfully undergone a number of phase 2 clinical trials in patients with either COPD or asthma. And there are also some recent pilot data showing that PDE5 inhibitors such as sildenafil can have bronchodilator activities.

12.5.2 Other Types of Bronchodilators

12.5.2.1 K_ Channel Openers

In ASM cells, K channels, such as large-conductance, voltage-dependent Ca_2-activated K channels (K_{Ca}), or the ATP-dependent K potassium channels (K_{ATP}), play an important role in modulating contractile activity. Activation of these channels will cause cell hyperpolarization that should oppose Ca_2 entry through voltage-dependent Ca_2 channels, leading to smooth muscle relaxation. Consequently, K channel modulators may be of value in the treatment of chronic airway disorders. However, K_{ATP} openers, although effective in relaxing human airways in vitro, are not effective in treating asthma or COPD because they are more potent as vasodilators, which limits the dose that can be administered safely [42].

12.5.2.2 Vasoactive Intestinal Peptide Analogs

VIP, one of the major peptide transmitters in the central and peripheral nervous systems, is abundantly present in the normal human lung, and VIP-immunoreactive nerves are found in the smooth muscle layer and glands of the airway and within the

walls of pulmonary and bronchial vessels. The bronchodilatory effect of VIP in human bronchi is almost 100 times more potent than adrenergic dilation induced by isoproterenol. VIP is subject to degeneration by proteases present in the lung lining fluid [43]. As a consequence, several peptidase-resistant VIP analogs have been developed.

12.5.2.3 Rho Kinase Inhibitors

There is now substantial evidence that Rho kinase (RhoK) is involved in bronchoconstriction [44]. RhoK can modulate smooth muscle contraction by multiple mechanisms. Considering that Rho/RhoK signaling is thought to be involved in various processes that contribute to chronic airway diseases, the use of RhoK inhibitors in asthma and COPD therapy clearly holds promise. Inhibition of RhoK reduces contractile responses induced by spasmogens. Indeed, the RhoK inhibitor (Y-27632) has been shown to relax human isolated bronchial preparations. Several analogs of Y-27632 exist that have similarly high inhibitory constants for RhoK and similar smooth muscle relaxant properties.

12.5.2.4 Brain Natriuretic Peptide and Analogs

It is well known that the guanylyl cyclase/cGMP second messenger system has a parallel role to the adenylyl cyclase/cAMP system in ASM, regulating its contractile and proliferative functions. Therefore, it is not surprising that agents activating this signaling pathway bronchodilate in vivo and relax ASM in vitro [45]. Particulate guanylyl cyclases act as plasma membrane receptors for natriuretic and related peptides. Some of them serve as receptors for the natriuretic peptides, a family of peptides that includes atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide, three peptides known to play important roles in renal and cardiovascular physiology. There is evidence that ANP relaxes human ASM in vitro. Moreover, in humans, exogenous ANP reverses airway hyperresponsiveness when given intravenously or by inhalation in high doses.

12.5.2.5 Nitric Oxide Donors

Exogenous NO has the ability to exert bronchodilatory effects in patients with bronchial asthma [46], and NO has been used in the treatment of preterm children to improve lung capacity. The augmented availability of NO in the lungs may represent a plausible approach for the treatment of asthma and COPD. Nitrates, NO, and NO donors relax ASM in vitro and in guinea pigs and humans, and inhaled NO exerts bronchodilatory effects against methacholine-induced bronchoconstriction in vivo. Studies in bronchial and tracheal smooth muscle have shown that a major target of NO is the enzyme soluble guanylyl cyclase,

although NO is also a very active agonist at inducing vascular smooth muscle relaxation. There is therefore a need for suitable NO donors that have minimal effects on the vasculature. The main prototypes of NO donors traditionally used, such as sodium nitroprusside and nitroglycerine, have several well-known adverse effects, such as rapid tachycardia, high toxicity, and rapid induction of tolerance. Likewise, sydnonimines, another well-known class of NO donor drugs, have a characteristically low therapeutic index (because of cyanide toxicity).

At present, a number of groups are designing and synthesizing various chemical compounds capable of modulating NO metabolism for therapeutic purposes that also possess an improved therapeutic index [47]. Specifically, various new classes of NO donors are under intense pharmacological investigation, each characterized by a particular PK and PD profile. The most important obstacle in the field of new NO donor drugs seems to be carefully targeting NO release to lungs at an optimal concentration to achieve a beneficial action and to limit possible adverse effects, particularly on the cardiovascular system.

NO budesonide and ruthenium complex (NO_3) are novel compounds, currently in development for the treatment of chronic respiratory disorders.

12.5.2.6 E-Prostanoid Receptor 4 Agonists

Inhaled prostaglandin E_2 (PGE_2) has been shown to be a bronchodilator in subjects with asthma or COPD. However, PGE_2 itself has the potential to cause the adverse effects of cough and retrosternal burning when inhaled by humans, particularly in subjects with asthma. Moreover, PGE_2 also stimulates other prostaglandin-like receptors having inhibitory and stimulatory activity on the intrinsic tone of the airway smooth muscle. PGE_2 acts predominantly via specific E-prostanoid (EP) receptors.

Whereas it has been established that PGE_2-induced sensory nerve activation and cough are mediated via the EP_3 receptor [48], the EP_4 receptor seems to be the predominant receptor responsible for PGE_2-induced relaxation of human ASM in vitro. Thus, highly potent EP_4 subtype-selective receptor agonists have been suggested to have therapeutic potential without side effects [49].

12.5.2.7 Bitter Taste Receptor Agonists

Bitter taste receptors work as chemoreceptors that interact with taste stimuli to initiate an afferent signal to the brain, where it becomes taste perception. Stimulation of the taste 2 receptors is responsible for the bitter taste. These receptors were recently found on airway smooth muscle. When activated, they caused relaxation through a calcium-dependent mechanism. Agonists to these receptors may make up a new class of useful direct bronchodilators for treating obstructive lung disease, but because they are members of the G protein-coupled receptor superfamily, they may undergo desensitization.

Saccharin, chloroquine, denatonium, aristolochic acid, strychnine, quinine, colchicine, and yohimbine were used in the preclinical studies. Aristolochic acid, strychnine, and yohimbine are probably too toxic to be considered for human use. Perhaps it is worth considering developing an inhalation preparation of quinine for testing in humans with asthma [50].

12.6 Combination Therapy

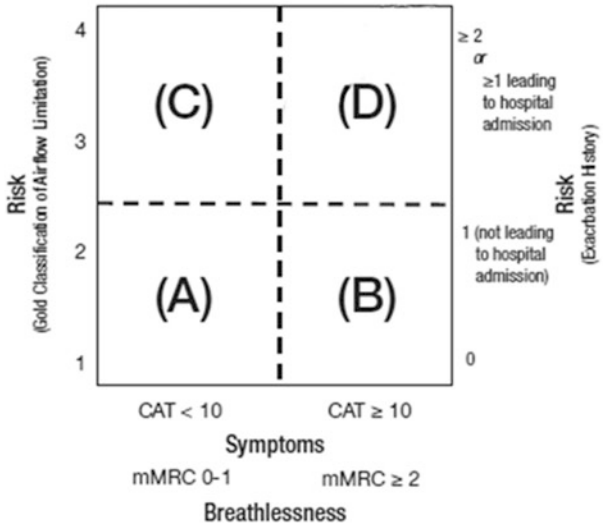
12.6.1 Pharmacologic Rationale for Combination

GOLD guidelines recommend combination therapy involving two long-acting bronchodilators with differing modes of action in patients whose COPD is not sufficiently controlled with monotherapy (Fig. 12.4). In fact, it seems reasonable to postulate that targeting bronchoconstriction through two distinct mechanisms should maximize the bronchodilator response and help to overcome inter- and intrapatient variability in bronchomotor tone associated with airway obstruction [51]. Moreover, combining two or more classes of molecules allows the use of lower doses to achieve the same efficacy while decreasing adverse effects. Combination therapy with a LABA and an ICS is considered an important approach for treating patients suffering from asthma and patients with severe COPD who have frequent exacerbations [52]. In addition, combination therapy with a LAMA and an ICS seems to be intriguing, although the clinical effects of such combination are largely unknown.

12.6.2 Combining β2-Adrenergic Receptor Agonists and Muscarinic Acetylcholine Receptor Antagonists

12.6.2.1 Pharmacologic Rationale

Airway tone is regulated by both the parasympathetic and sympathetic nervous systems. The complete nature of interactions between the two physiological systems is not yet fully understood, but there is enough evidence to suggest that combining β_2-AR agonists and mAChR antagonists is pharmacologically reasonable for two reasons. First, the addition of a β_2-AR agonist decreases the release of ACh through the modulation of cholinergic neurotransmission by prejunctional β_2-ARs and thereby amplifies the bronchial smooth muscle relaxation induced by the mAChR antagonist. Second, the addition of a mAChR antagonist can reduce bronchoconstrictor effects of ACh, the release of which has been modified by the β_2-AR agonist, and thereby amplify the bronchodilation elicited by the β_2-AR agonist through the direct stimulation of smooth muscle β_2-ARs [53]. Another possibility is the fact that the mAChR antagonist and not the β_2-AR agonist can



Patient Category	Characteristics	Spirometric Classification	Exacerbations per year	CAT	mMRC
A	Low Risk, Less Symptoms	GOLD 1-2	≤1	< 10	0-1
B	Low Risk, More Symptoms	GOLD 1-2	≤1	≥ 10	≥ 2
C	High Risk, Less Symptoms	GOLD 3-4	≥ 2	< 10	0-1
D	High Risk, More Symptoms	GOLD 3-4	≥ 2	≥ 10	≥ 2

Fig. 12.4 Model of symptom/risk of evaluation of COPD [1]
(From the Global Strategy for Diagnosis, Management, and Prevention of COPD 2016, Global Initiative for Chronic Obstructive Lung Disease (GOLD), http://www.goldcopd.org
COPD chronic obstructive lung disease, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *mMRC* modified Medical Research Council, *CAT* COPD Assessment Test)

suppress mucus/fluid secretions; hence, surface tension changes that would normally collapse the airways are less likely to occur [54].

12.6.2.2 Clinical Use

Fixed combinations of LABA/LAMA appeared to show a greater degree of improvement in trough FEV_1 when compared with the respective single components. Analysis of synergism on clinical indices including quality of life, exacerbation rates, and disease progression was not possible because dose–response relationships for the single-component drugs were not available, but carefully designed and sufficiently powered studies could help evaluate these missing important efficacy data. Therefore, while FEV_1 may be a relatively poor predicator of

improvements in symptom scores, either the dose–response relationship for these phenomena is different or more sensitive measures of small airway caliber (e.g., forced oscillatory techniques) might offer greater predictability. It is therefore likely that the combination therapy provides a complimentary coverage of airway smooth muscle relaxation with a suppression of mucus secretions which benefits the patient provided this is not at the expense of more adverse effects [55]. It remains to be seen whether any purported synergy would allow a dose reduction of both component drugs while still affording clinical meaningful bronchodilation over a 24 h period.

Umeclidinium/vilanterol, glycopyrrolate/indacaterol, and aclidinium/formoterol (available in Canada) are dry-powder inhalers. Tiotropium/olodaterol is a soft mist inhaler. LABA/LAMA combination seems to play an important role in maximizing bronchodilation studies to date indicating that combining different classes of bronchodilators results in significantly greater improvements in lung function and other outcomes compared with individual drugs used alone and that these combinations are well tolerated in patients with moderate-to-severe COPD [56, 57].

12.6.3 Combining β2-Adrenergic Receptor Agonists and Inhaled Corticosteroids

The addition of LABA therapy with ICS has been suggested to improve the efficacy of ICS effects, and a number of molecular interactions between corticosteroids and β_2-ARs have been described [58].

The LABA/ICS combination is now increasingly recommended in patients with COPD because the addition of LABA to ICS provides additional benefits. Several large-scale studies in patients with moderate-to-severe COPD have demonstrated that treatment with salmeterol/fluticasone and formoterol/budesonide leads to significantly greater improvements in lung function, exacerbations, health status, and breathlessness compared with placebo or monotherapy with the component drugs. Compared with placebo, the LABA/ICS combination therapy leads to a significant reduction of a quarter in exacerbation rates. Compared with monocomponent ICS therapy, the LABA/ICS combination significantly reduces morbidity and mortality in COPD. There is a significant reduction in all-cause mortality with the addition of data from the Towards a Revolution in COPD Health (TORCH) study, although in the TORCH study regular treatment with salmeterol/fluticasone narrowly failed to demonstrate a statistically significant benefit on the reduction in all-cause mortality over 3 years [59]. In addition, in the TORCH study, the LABA/ICS combination reduced the rate of decline in FEV_1 in patients with moderate-to-severe COPD by 16 ml/year compared with placebo. However, this improvement was also observed in the LABA-only and ICS-only groups. Moreover, the superiority of combination inhalers should be viewed against the increased risk of side effects, particularly pneumonia in patients with COPD [60].

A next-generation, the ultra-LABA/ICS combination consisting of vilanterol and fluticasone furoate is another combination, had greater improvements than placebo in trough FEV_1 with a good safety and tolerability profile.

12.6.3.1 Combining Muscarinic Acetylcholine Receptor Antagonists and Inhaled Corticosteroids

Experimental evidence has also suggested an influence of corticosteroids on mAChRs, signifying the potential of a LAMA/ICS combination for the treatment of asthma and COPD.

Very few studies published to date have been designed specifically to evaluate the effect of LAMA and ICS combinations on clinical outcomes, and this is an area that warrants future study. Treatment with tiotropium bromide and budesonide in patients with COPD has led to significant improvements in the quality-of-life status according to SGRQ, measuring both dyspnea and lung function, and a reduction of the number of exacerbations of treatment in patients with COPD and chronic asthma [61].

12.6.4 Triple Combination Therapies

Triple therapy with LAMA plus LABA/ICS has also been investigated, demonstrating benefits over monotherapy on lung function. Additionally, a pilot study of patients with advanced COPD reported that triple therapy combined with pulmonary rehabilitation provided a benefit in terms of lung function. Some reports also suggest that triple therapy can provide additional benefits, such as reduction in exacerbation rate and mortality, although a recent systematic review concluded that further, longer-term studies are required to determine the benefits of tiotropium plus LABA and ICS or the additional benefit of ICS on top of LAMA/LABA combinations [56].

12.6.5 Bifunctional Muscarinic Acetylcholine Receptor Antagonists and β2-Adrenergic Receptor Agonists (MABA)

There is another approach that is the design and development of dual-acting agents that combine both mAChR antagonist and β_2-AR agonist pharmacology in a single molecule [54]. This approach may offer several advantages over combination therapy of two separate drug entities. These include the benefit of delivering a fixed ratio into every region of the lung, reducing the complexity of combination

inhalers. These agents are known as dual-acting mAChR antagonist–β_2-AR agonist (MABA) bronchodilators. All MABA compounds disclosed so far have an M_3 mAChR antagonist part and a β_2-AR agonist part connected by a linker, the potential synergistic interaction between a LABA and LAMA. It might not be unreasonable to suggest that MABAs are inherently synergistic in terms of their pharmacological effect on airway caliber. A change from baseline trough FEV_1 was 215 and 277 mL with a once-daily dose of 400 and 800 mg GSK961081. A change that was of a similar magnitude to fixed-dose combinations of LABA/LAMA was shown in this analysis to be synergistic. The selectivity of the β_2-agonist and muscarinic antagonist components of the MABA was assumed to be 1:1; the analysis suggests that a threefold lower dose of the MABA is required to produce an equi-effective response with either component acting alone.

12.7 The Role of Bronchodilators in the Management of COPD

In 2011, we saw a substantial revision of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for diagnosis, management, and prevention of COPD, which has recently been updated [1]. Recommendations for treatment are no longer based primarily on categorization ("staging") by spirometric assessment, but on categorization by existing symptoms (using validated modified Medical Research Council and COPD Assessment Test questionnaires) and risk (based on severity of airflow limitation and history of exacerbations). This approach acknowledges the importance of consideration of both short- and long-term outcomes when making treatment decisions (Fig. 12.4). The classes of medications commonly used in treating COPD are shown in Tables 12.1, 12.2, 12.3 and 12.4. The choice within each class depends on the availability of medication and the patient's response. A proposed model for initial pharmacological management of COPD according to the individualized assessment of symptoms and exacerbation risk is shown in Table 12.5 [56].

Group A patients have few symptoms and a low risk of exacerbations. Specific evidence for the effectiveness of pharmacologic treatments is not available for patients with $FEV_1 > 80$ % predicted (GOLD 1). However, for all Group A patients, a short-acting bronchodilator used as needed is recommended as first choice based on its effect on lung function and breathlessness. An alternative choice is a combination of short-acting bronchodilators or the introduction of a long-acting bronchodilator. The evidence for this step-up is weak; few studies of the combination exist, and most trials of therapy with long-acting bronchodilators have been performed in patients with more severe airflow limitation.

Group B patients have more significant symptoms but still a low risk of exacerbations. Long-acting bronchodilators are superior to short-acting bronchodilators

Table 12.1 Formulations and typical doses of COPD medications[a] (anticholinergics)

Drug	Inhaler (μg)	Solution for nebulizer (mg/ml)	Duration of action (hours)
Short acting			
Ipratropium bromide	20, 40 (MDI)	0.25–0.5	6–8
Oxitropium bromide	100 (MDI)	1.5	7–9
Long acting			
Tiotropium	18 (DPI), 5 (SMI)		12
Glycopyrronium bromide	44 (DPI)		24
Aclidinium bromide	322 (DPI)		24
Umeclidinium	62.5 (DPI)		24

MDI metered-dose inhaler, *DPI* dry-powder inhaler, *SMI* soft mist inhaler
[a]Not all formulations are available in all countries; in some countries, other formulations may be available

(taken as needed, or prn) and are therefore recommended. There is no evidence to recommend one class of long-acting bronchodilators over another for initial treatment. In the individual patient, the choice should depend on the patient's perception of symptom relief. For patients with severe breathlessness, the alternative choice is a combination of long-acting bronchodilators. Other possible treatments include short-acting bronchodilators and theophylline, the latter of which can be used if inhaled bronchodilators are unavailable or unaffordable.

Group C patients have few symptoms but a high risk of exacerbations. As first choice, a fixed combination of inhaled corticosteroid/long-acting β_2-agonist or a long-acting anticholinergic is recommended. As an alternative choice, a combination of two long-acting bronchodilators or the combination of inhaled corticosteroid/long-acting anticholinergic can be used. Both long-acting anticholinergic and long-acting β_2-agonist reduce the risk of exacerbations, and although good long-term studies are lacking, this principle of combination treatment seems sound. The recommendation for a combination of inhaled corticosteroid/long-acting anticholinergic is not evidence based, but this lack of evidence seems to be the result of lack of interest from the pharmaceutical industry rather than doubts about the rationale. A phosphodiesterase-4 inhibitor used in combination with at least one long-acting bronchodilator could be considered if the patient has chronic bronchitis. Other possible treatments include short-acting bronchodilators and theophylline if long-acting inhaled bronchodilators are unavailable or unaffordable.

Group D patients have many symptoms and a high risk of exacerbations. The first choice of therapy is inhaled corticosteroid plus long-acting β_2-agonist or long-acting anticholinergic. As second choice, a combination of all three classes of drugs (inhaled corticosteroids/long-acting β_2-agonist/long-acting anticholinergic) is recommended. It is also possible to add a phosphodiesterase-4 inhibitor to the treatment chosen as first choice, provided the patient has chronic bronchitis. A

Table 12.2 Formulations and typical Doses of COPD medications[a] (β2-agonist)

Drug	Inhaler (μg)	Solution for nebulizer (mg/ml)	Oral	Vials for injection (mg)	Patch (transdermal)	Duration of action (hours)
Short acting						
Fenoterol	100–200 (MDI)	1	0.05 % (syrup)			4–6
Levalbuterol	45–90 (MDI)	0.21, 0.42				6–8
Salbutamol (albuterol)	100, 200 (MDI and DPI)	5	5 mg (pill), 0.024 % (syrup)	0.1, 0.5		4–6
Terbutaline	400, 500 (DPI)		2.5, 5 mg (pill)			4–6
Long acting						
Formoterol	4.5–12 (MDI and DPI)	0.01[b]				12
Arformoterol		0.0075				12
Salmeterol	25–50 (MDI and DPI)					12
Ultra-long acting						
Indacaterol	75–300 (DPI)					24
Olodaterol	5 (SMI)					24
Tulobuterol					0.5,1,2 mg	24

MDI metered-dose inhaler, *DPI* dry-powder inhaler, *SMI* soft mist inhaler
[a]Not all formulations are available in all countries; in some countries, other formulations may be available
[b]Formoterol nebulized solution is based on the unit dose vial containing 20 mcg in a volume of 2.0 ml

Table 12.3 Formulations and typical doses of COPD medications[a] (xanthines and PGE4 inhibitors)

Drug	Oral	Vials for injection (mg)	Duration of action (hours)
Methylxanthines			
Aminophylline	200–600 mg (pill)	240	up to 24
Theophylline (SR)	100–600 mg (pill)		up to 24
Phosphodiesterase-4 inhibitors			
Roflumilast	500 mcg (pill)		24

MDI metered-dose inhaler, *DPI* dry-powder inhaler, *SMI* soft mist inhaler
[a]Not all formulations are available in all countries; in some countries, other formulations may be available

Table 12.4 Formulations and typical doses of COPD medications[a]

(Combination of β2-agonist plus anticholinergic in one inhaler)			
Drug	Inhaler (mg)	Solution for nebulizer (mg/ml)	Duration of action (hours)
Short-acting β2-agonist plus anticholinergic			
Fenoterol/ipratropium	200/80 (MDI)	1.25/0.5	6–8
Salbutamol/ipratropium	100/20 (SMI)		6–8
Long-acting β2-agonist plus anticholinergic			
Formoterol/aclidinium	12/340 (DPI)		12
Indacaterol/ glycopyrronium	85/43 (DPI)		24
Olodaterol/tiotropium	5/5 (SMI)		24
Vilanterol/ umeclidinium	25/62.5 (DPI)		24

MDI metered-dose inhaler, *DPI* dry-powder inhaler, *SMI* soft mist inhaler
[a]Not all formulations are available in all countries; in some countries, other formulations may be available

phosphodiesterase-4 inhibitor is effective when added to a long-acting bronchodilator, whereas evidence of its benefit when added to inhaled corticosteroid comes from less valid secondary analyses. Other possible treatments include short-acting bronchodilators and theophylline or carbocisteine, which can be used if long-acting inhaled bronchodilators are unavailable or unaffordable [1].

12.8 Route of Drug Delivery to the Airway

12.8.1 Inhaled Route

Inhalation is the preferred mode of delivery of many drugs with a direct effect on airways, particularly for asthma and COPD. The major advantage of inhalation is the delivery of drugs to the airways in doses that are effective with a much lower risk of systemic side effects. This is particularly important with the use of inhaled corticosteroids (ICS), which largely avoids systemic side effects. In addition, inhaled bronchodilators have a more rapid onset of action than when taken orally (Fig. 12.5).

Table 12.5 GOLD guidelines (2016): initial pharmacological management of COPD[a]

Patient group	Recommended first choice	Alternative choice	Other possible treatments[b]
A	SAMA prn. or SABA prn.	LAMA or LABA or SABA + SAMA	Theophylline
B	LAMA or LABA	LAMA + LABA	SABA and/or SAMA
			Theophylline
C	ICS + LABA or LAMA	LAMA+ LABA or LAMA + PDE-4 I or LABA + PDE-4 I	SABA and/or SAMA
			Theophylline
D	ICS + LABA and/or LAMA	ICS + LABA + LAMA or ICS + LABA + PDE-4 I or LAMA + LABA or LAMA + PDE-4 I	Carbocisteine
			N-acetylcysteine
			SABA and/or SAMA
			Theophylline

[a]Medications in each box are mentioned in alphabetical order and therefore not necessarily in order of preference

[b]Medications in this column can be used alone or in combination with other options in the recommended first choice and alternative choice columns

From the Global Strategy for Diagnosis, Management and Prevention of COPD 2016, Global initiative for chronic Obstructive Lung Disease (GOLD), http://www.goldcopd.org

Medications in each box are mentioned in alphabetical order and, therefore, not necessarily in the order of preference

prn as needed, *SABA* short-acting β2-agonist, *LABA* long-acting β2-agonist, *SAMA* short-acting muscarinic antagonist, *LAMA* long-acting muscarinic antagonist, *ICS* inhaled corticosteroid, *PDE4I* phosphodiesterase-4 inhibitor

12.8.1.1 Particle Size

The size of particles for inhalation is of critical importance in determining the size deposition in the respiratory tract. The optimum size for particles to settle in the airways is 2–5 μm mass median aerodynamic diameter (MMAD). Larger particles settle out in the upper airways, whereas smaller particles remain suspended and are therefore exhaled. There is increasing interest in delivering drug particles of ~1 μm MMAD, which is now possible using drugs formulated in hydrofluoroalkane (HFA) propellant and soft mist inhaler as Respimat device [63].

12.8.1.2 Pharmacokinetics

Of the total drug delivered, only 10–50 % enters the lower airways with a conventional pressurized metered-dose inhaler. Drugs are absorbed from the airway lumen and have direct effects on target cells of the airway. Drugs may also be absorbed into the bronchial circulation and then distributed to more peripheral airways.

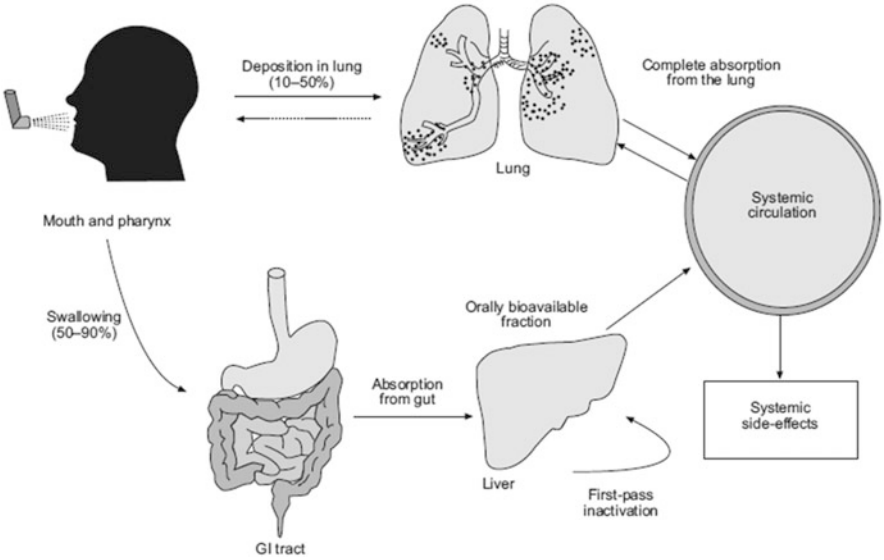


Fig. 12.5 Deposition of inhaled drugs
Inhalation therapy deposits drugs directly, but not exclusively, in the lungs. Distribution between lungs and oropharynx depends mostly on the particle size and the efficiency of the delivery method. Most material will be swallowed and absorbed, entering systemic circulation after undergoing the first-pass effect in the liver. Some drug will also be absorbed into the systemic circulation from the lungs. Use of a large-volume spacer will reduce the amount of drug deposited on the oropharynx, thereby reducing amount swallowed and absorbed from the GI tract, thus limiting systemic effects (From Eur Respir J 2006; 28: 1042–1050)[62]

Drugs with higher molecular weights tend to retain to a greater extent in the airways. Nevertheless, several drugs have greater therapeutic efficacy when given by the inhaled route. More extensive pulmonary distribution of a drug with a smaller MMAD increases alveolar deposition and thus is likely to increase absorption from the lungs into the general circulation resulting in more systemic side effects.

12.8.2 Oral Route

Drugs for treatment of pulmonary diseases may also be given orally. The oral dose is much higher than the inhaled dose required to achieve the same effect (typically by a ratio of ~20:1), so that systemic side effects are more common. When there is a choice of inhaled or oral route for a drug, the inhaled route is always preferable, and the oral route should be reserved for the few patients unable to use inhalers. Xanthine is ineffective by the inhaled route; it must be given systemically.

12.8.3 Parenteral Route

The intravenous route should be reserved for delivery of drugs in the severely ill patient who is unable to absorb drugs from the GI tract. Side effects are generally frequent due to the high plasma concentrations.

12.8.4 Transdermal Route

The transdermal route should be reserved for delivery of drugs in the severely ill patient who is unable to use inhalers.

12.9 Conclusion

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are anticholinergics, β_2-agonist, and methylxanthines used as monotherapy or in combination. Therapeutic intervention should be initiated on categorization by symptoms and risk.

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