Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine

REVIEW

Emerging Therapeutic Options for the Management of COPD

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Abstract: Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide and is projected to be the third by 2020. COPD is characterized by chronic airflow limitation caused by airway inflammation and parenchymal destruction that is usually progressive. Inhaled bronchodilators continue to be the mainstay of the current management of COPD. Safety and efficacy data of the recently approved medications including aclidinium, glycopyrronium, roflumilast, and indacaterol are reviewed here.

Keywords: chronic obstructive pulmonary disease, COPD therapy, long-acting muscarinic agent, phosphodiesterase-4 inhibitor, long-acting β_2-agonist

Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine 2013:7 7–15

doi: 10.4137/CCRPM.S8140

This article is available from http://www.la-press.com.

Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide and is projected to be the third by 2020.[1,2] It is associated with a significant economic and social burden. In the United States, exacerbations requiring hospitalization account for the greatest proportion of the burden on the health care system, with cost of care directly related to the severity of the disease. Estimated direct costs of COPD are $29.5 billion. In developing countries, the impact of COPD on the economy, through loss of workplace and home productivity, represents a more serious threat than direct medical costs.[1]

COPD is characterized by chronic airflow limitation that is only partly reversible and is caused by airway inflammation and parenchymal destruction that is usually progressive. Exposure to noxious particles and gas through inhalation leads to the stimulation of inflammatory cells including neutrophils, macrophages, and CD8+ lymphocytes, which results in widespread destructive damage. Progressive decline in lung function as evidenced by decreased forced expiratory volume in 1 second (FEV_1) and inadequate lung emptying on expiration are the resulting features. Exacerbations and comorbidities also contribute to the disease severity.[1,3]

The Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD) guidelines recommend a stepwise approach for management of COPD, based according to the individualized assessment of disease severity, symptoms, and exacerbations. Previous versions of the GOLD treatment recommendations were based solely on spirometry; however, FEV_1 alone is a poor indicator of disease status. Classification of the severity of airflow obstruction is based on the postbronchodilator FEV_1. The four stages of severity previously described as mild, moderate, severe, and very severe are now classified as GOLD 1 ($FEV_1 \geq 80\%$ predicted), GOLD 2 ($50\% \leq FEV_1 < 80\%$ predicted), GOLD 3 ($30\% \leq FEV_1 < 50\%$ predicted), and GOLD 4 ($FEV_1 < 30\%$ predicted). In addition to spirometry, current guidelines use letter categories A through D that also take into consideration the risk of future exacerbations and current symptoms (Table 1).[1] Dyspnea severity has been shown to closely correlate with survival, while exacerbations have been shown to reduce quality of life and increase morbidity.[1,3]

The goals of pharmacological treatment are to reduce symptoms and exacerbations and improve health status and exercise tolerance. Inhaled bronchodilators continue to be the mainstay of the current management of COPD.[1]

Recent drug approvals include improved bronchodilators and phosphodiesterase-4 inhibitors (Table 2).[4] The pharmacology, pharmacokinetics, clinical efficacy, and safety of the recently approved medications are reviewed in this article.

Approved Therapies

Long-acting muscarinic agents

Mechanism of action, metabolism and pharmacokinetic profile

Antagonism of the muscarinic receptors, particularly M_3, mediates bronchodilation and smooth muscle relaxation. Two new long-acting muscarinic agents (LAMA), aclidinium and glycopyrronium, were approved by the European Union in 2012; in the

Table 1. GOLD severity/symptom/risk evaluation and recommended initial treatment.[1]

Patient category	Characteristics*	Spirometric classification	Exacerbations per year	Pharmacotherapy
A	Low risk, less symptoms	GOLD 1–2	0–1	SAMA or SABA
B	Low risk, more symptoms	GOLD 1–2	0–1	LAMA or LABA
C	High risk, less symptoms	GOLD 3–4	≥2	ICS + LABA or LAMA
D	High risk, more symptoms	GOLD 3–4	≥2	ICS + LABA or LAMA

Note: *Based on mMRC or CAT score.
Abbreviations: SAMA, short-acting muscarinic antagonist; SABA, short-acting β_2-adrenergic agonists; LAMA, long-acting muscarinic antagonist; LABA, long-acting β_2-adrenergic agonists; ICS, inhaled corticosteroid; PDE4, phosphodiesterese-4 inhibitor.

Table 2. Recent approvals of novel therapies for COPD.

Generic name	Trade name(s)	Status in US and Europe
Long acting muscarinic agents		
Aclidinium bromide	Tudorza Pressair Bretaris Genuair Eklira Genuair	FDA and EU approved 2012
Glycopyrronium bromide	Tovanor Breezhaler Seebri Breezhaler	EU approved 2012
Phosphodiesterase-4 inhibitors		
Roflumilast	Daliresp Daxas Libertek	EU approved 2010 FDA approved 2011
Ultra long acting beta agonists		
Indacaterol maleate	Arcapta Neohaler Hirobriz Breezhaler Onbrez Breezhaler Oslif Breezhaler	EU approved 2009 FDA approved 2011

Abbreviations: MDI, metered dose inhaler; DPI, dry powder inhaler.

United States, aclidinium is also approved; however, glycopyrronium is still under investigation.

Aclidinium bromide is a new molecular entity that belongs to the anticholinergic class of drugs; more specifically, it is a long-acting muscarinic antagonist. It has similar affinity to the muscarinic subtypes M1 to M5. In the airways, it exhibits its effects through inhibition of the M3 receptor at the smooth muscle leading to bronchodilation. Its effect is dose dependent and lasts longer than 24 hours. Aclidinium undergoes rapid hydrolysis into two major metabolites, a carboxylic acid derivative and an alcohol derivative, which do not bind to muscarinic receptors. The estimated effective half-life of aclidinium is 5 to 8 hours, and about 0.09% of the dose is excreted in the urine. Although formal drug interactions studies were not performed, there is a low likelihood of cytochrome CYP450-related interactions.[5–13]

Similar to aclidinium, glycopyrronium bromide is also a high affinity muscarinic receptor antagonist. In vitro studies suggest that glycopyrronium's onset of action may be faster than tiotropium and is sustained over 24 hours.[13,14]

Safety and efficacy

The safety and efficacy of aclidinium bromide has been evaluated in four large Phase 3 clinical trials.[8,10,15] In the ACCLAIM/COPD trials, subjects received aclidinium 200 mcg once-daily or placebo for 1 year.[15] Aclidinium significantly improved lung function versus placebo, however at smaller magnitudes of effect than demonstrated in previous LAMA trials.[16–19] Improvements in lung function were maintained throughout the 52-week study period in both trials; mean trough FEV_1 improvements from baseline ranged from 60 to 67 mL in ACCLAIM/COPD I and 51 to 78 mL in ACCLAIM/COPD II. In contrast, previous studies with tiotropium once-daily have demonstrated trough FEV_1 improvements ranging from 100 to 150 mL. The suggested minimum clinically effective difference (MCID) is 100 to 140 mL.[20]

Subsequent trials sought to investigate twice-daily and higher-dose aclidinium.[8,10] ACCORD COPD I demonstrated significant and sustained improvements in lung function over 12 weeks with both 200 mcg and 400 mcg twice-daily versus placebo. Magnitudes of change in trough FEV_1 were 86 mL and 124 mL for the 200 mcg ($P = 0.019$) and 400 mcg ($P < 0.001$) groups, respectively. ATTAIN replicated these findings in a larger subject population over 24 weeks. Changes in trough FEV_1 were 99 mL and 128 mL for the 200 mcg and 400 mcg groups, respectively (both $P < 0.0001$).

As lung function is a poor indicator of symptom control in patients with COPD, it is worth noting secondary endpoints of health status, as measured by St. George's Respiratory Questionnaire (SGRQ) scores and rates of exacerbation and/or times to first exacerbation. Across all four studies, more treatment subjects gained clinically significant (ie, ≥4 units) improvements in SGRQ scores versus placebo up to 44 weeks, with modest treatment differences ranging from 1.53 to 2.21 units. Overall exacerbation rates were lower with aclidinium 200 mcg and 400 mcg, once- and twice-daily versus placebo. No statistically significant difference was observed in rates of moderate or severe exacerbations or time to first moderate or severe exacerbation where assessed.[8,10,15]

Aclidinium 200 mcg and 400 mcg twice-daily for 24 weeks was well-tolerated, with no differences in safety profiles between the two doses. The most commonly occurring adverse events, excluding exacerbations, in all treatment groups were headache and nasopharyngitis (8.1%–12.3%). Rates of anticholinergic adverse events were low (<1% except for urinary tract infections in 2.2% of patients on 400 mcg twice-daily aclidinium in ATTAIN). Rates of any

serious adverse event were similar across all three groups (4.3%–5.6%), none of which were attributed to the study medication.

Glycopyrronium was approved for COPD treatment in Europe this year but is awaiting approval in the United States. Published trial results include those from two large, multicenter Phase 3 trials—GLOW1 and GLOW2.[21,22] Data demonstrated that glycopyrronium 50 mcg conferred rapid (+90 mL within 5 minutes and +144 mL within 15 minutes), sustained (on day 1 and at weeks 12, 26, and 52), and clinically meaningful improvements in lung function. When compared with tiotropium, glycopyrronium 50 mcg achieved numerically greater improvements in trough FEV_1 at all time points versus placebo, although not statistically significant.

Dosing and administration

Aclidinium is indicated for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. As with tiotropium, the only other LAMA approved for use in the United States, it is not indicated for rescue therapy. Aclidinium is supplied as a dry powder inhalation formulation administered by an inhaler device at a dose of 400 mcg twice daily.[23]

Glycopyrronium is also indicated as a maintenance bronchodilator treatment and is supplied as a capsule containing 50 mcg of glycopyrronium for use in the Breezhaler device.[24]

Phosphodiesterase-4 inhibitors

Mechanism of action, metabolism, and pharmacokinetic profile

Phosphodiesterases are a superfamily of enzymes that catalyze the breakdown of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), thereby regulating the intracellular levels of these secondary messengers. Inhibition of the phosphodiesterase-4 inhibitors (PDE-4) isoenzymes, in particular, interferes with the breakdown of cAMP, leading to its intracellular accumulation. Roflumilast is currently the only PDE-4 inhibitor available, and it is available in the United States and Europe.

Following oral administration, roflumilast is rapidly metabolized by CYP3A4 and 1A2 to active roflumilast N-oxide, which displays similar potency and selectivity for PDE-4. Roflumilast N-oxide is believed to mediate the majority of the pharmacodynamic effects of roflumilast. The pharmacokinetic profile of roflumilast is linear and predictable over the dose range of 250 to 1000 mcg. Roflumilast's half-life ranges from 8 to 31 hours and steady-state concentrations of roflumilast are achieved within 3 to 4 days of oral, once-daily dosing. Roflumilast N-oxide is primarily cleared by CYP3A4 and to a lesser extent by CYP2C19 and CYP1A1. Excretion occurs primarily through renal elimination.[12,25–30]

Safety and efficacy

The safety and efficacy of roflumilast has been demonstrated in numerous large Phase 3 clinical trials.[30–33] Primary endpoints included lung function as measured by trough FEV_1 and health-related quality of life as measured by SGRQ total scores and rates of moderate or severe exacerbations. All trials enrolled patients with moderate-to-severe or severe-to-very severe COPD with or without a history of frequent exacerbations. In over 1500 subjects with severe-to-very severe COPD, Calverley et al[31] reported a modest but significant change in trough FEV_1 with roflumilast compared with placebo (+46 mL vs. +8 mL, respectively; $P = 0.0003$), a 14.9% relative risk reduction in the rate of exacerbations versus placebo (1.08 vs. 1.27 per patient per year; $P = 0.0278$), and replicated findings in a larger study of the same patient population. In two separate Phase 3 trials, Fabbri et al[32] compared roflumilast 500 mcg once-daily with placebo plus salmeterol 50 mcg twice-daily or tiotropium 18 mcg once-daily in subjects with moderate-to-severe COPD. Again, significant albeit modest improvements were reported in lung function from baseline versus placebo plus salmeterol (+39 mL vs. −10 mL; $P < 0.0001$) and versus placebo plus tiotropium (+65 mL vs. −16 mL); $P < 0.0001$). Rates of exacerbations were not as remarkable as demonstrated in the Calverley studies, which were numerically lower in the roflumilast arm than the comparator arm but did not reach statistical significance.

In clinical trials, roflumilast 500 mcg once-daily was generally well-tolerated. The most common adverse effects were gastrointestinal—diarrhea (9.5%) and nausea (4.7%)—and attributed with the most common cause for discontinuation. Other notable adverse effects that occurred in >2% of the 4359 roflumilast-treated patients included weight loss (7.5%),

headache (4.4%), back pain (3.2%), insomnia (2.4%), dizziness (2.1%), and decreased appetite (2.1%). Psychiatric adverse events, including insomnia, anxiety, depression, suicidal ideation, and a suicide were also reported to have occurred more commonly in the roflumilast-treated patients versus placebo.

Dosing and administration

Roflumilast is available as a 500 mcg round tablet. The recommended dosage for patients with moderate-to-severe COPD is one 500 mcg tablet daily, which may be administered with or without food. Although it has shown only modest benefits in improving lung function, its oral dosage form may be preferable in patients who have difficulty with proper inhalation technique.[34]

Ultralong-acting beta agonists

Mechanism of action, metabolism, and pharmacokinetic profile

β_2-agonists activate the β_2 receptors on the smooth muscle cells, which stimulate protein G activating adenylcyclase. This in turn produces cAMP, which results in muscle relaxation. The long-acting β_2-agonists (LABA), salmeterol and formoterol, provide 12 hours of bronchodilation. Novel ultralong-acting β_2-agonists with longer half-lives than other currently available LABAs may offer once daily dosing. Indacaterol is currently the only ultralong-acting β_2-agonist available in both the United States and Europe.

Indacaterol is a chirally pure R-enantiomer that behaves as a near full agonist. In preclinical trials, indacaterol demonstrated 73% agonistic activity compared to 38% by salmeterol. Following inhalation, indacaterol's onset of bronchodilation occurs within 5 minutes and is prolonged for 24 hours, which allows for once daily dosing. Maximum serum concentrations of indacaterol are achieved within 15–60 minutes of dosing. It does not appear to antagonize the bronchodilator effect of a SABA. Indacaterol is lipophilic and dissociates slowly from lung tissue. Less than 1% of the drug is eliminated renally.[12,13,35,36]

Safety and efficacy

The safety and efficacy of indacaterol has been demonstrated in four randomized, double-blind, placebo-controlled trials, including head-to-head trials of indacaterol versus placebo alone,[37] tiotropium,[38] salmeterol,[39] and formoterol.[40] Trial duration ranged from 12 weeks[37] to one year[40] and together comprised over 4800 subjects with moderate-to-severe COPD. In addition to assessing change in trough FEV_1 from baseline, postbronchodilator FEV_1 was also assessed as a measure of onset of action (an outcome of interest as investigators purported it may impact medication adherence in practice). Secondary endpoints of interest included breathlessness as measured by the transition dyspnea index (TDI), use of as-needed salbutamol, exacerbations, and SGRQ score. In superiority studies, only indacaterol and tiotropium exceeded the prespecified MCID trough FEV_1 of +120 mL. Both indacaterol 150 mcg and 300 mcg proved statistically superior to tiotropium. Indacaterol 150 mcg was superior to salmeterol, and indacaterol 300 mcg was superior to formoterol. The efficacy of indacaterol was sustained for the studies' duration of 6 months to 1 year. Additionally, indacaterol demonstrated a quick onset of action; mean post bronchodilator FEV_1 was significantly greater than placebo (by a difference of 110–130 mL; $P < 0.001$), tiotropium (by a difference of 70 mL; $P < 0.001$), and salmeterol (by a difference of 60 mL; $P < 0.001$).

Indacaterol also improved scores of breathlessness, similar to (with 150 mcg dose) or greater (with 300 mcg dose) than tiotropium, and a greater effect than formoterol and salmeterol. Improvements in breathlessness versus placebo were sustained at 12 weeks, 6 months, and 1 year. Subjects treated with indacaterol used an as-needed rescue inhaler significantly less than those receiving placebo or any of the other study treatments, experienced fewer exacerbations (but not of statistical significance) and improved health status compared with placebo and the other two LABAs.

Furthermore, two recent trials (INTRUST-1, INTRUST-2) have demonstrated that combination indacaterol 150 mcg and tiotropium is superior to tiotropium alone, with compelling treatment differences in trough FEV_1 of 70 to 80 mL ($P < 0.001$). Changes in trough FEV_1 from baseline at week 12 were 190 and 230 mL for indacaterol plus tiotropium, and 150 and 110 mL for tiotropium alone.[41]

Indacaterol was generally well-tolerated in clinical trials. Adverse events occurred at similar rates in the indacaterol and placebo treatment groups. The most common adverse events were symptoms of worsen-

ing COPD (eg, respiratory tract infections) and not attributed to the medication itself. Mild, transient cough was also reported in approximately 20% of all indacaterol-treated patients but did not affect drop-out rates.

Dosing and administration

Indacaterol joins two other long-acting β_2-agonists, salmeterol and formoterol, both of which are dosed twice daily. Indacaterol is approved for use in Europe at doses of 150 and 300 mcg daily; however, safety concerns prompted the United States Food and Drug Administration to approve only the 75 mcg dose. Although no head-to-head studies have been conducted, indacaterol appears to be comparable with salmeterol in terms of safety and efficacy. Its once daily dosing may improve adherence in those patients who have difficulty adhering to a regimen requiring more than one dose per day, although its utilization will likely be low until a combination with an inhaled steroid is available. It is available as a capsule for inhalation use only with the Neohaler device.[42]

Conclusions

COPD continues to be a major global health problem. The economic burden is substantial and likely to continue to increase as the elderly population continues to grow. The focus of pharmacologic therapy (Table 3) has been to control symptoms, reduce exacerbations, improve health status, and increase exercise tolerance. Recent drug developments include a novel drug class and improved bronchodilators. It remains to be seen the clinical advantage that aclidinium may have, if any, in medical practice. Initial studies failed to demonstrate compelling improvements in lung function with once-daily dosing. Later studies with aclidinium suggested that patients may achieve significant improvements in lung function that meet the MCID but required twice-daily dosing to do so. The niche for glycopyrronium in COPD treatment is also unknown at this point as more studies elucidating its safety and efficacy against commercially available COPD therapies (including indacaterol, tiotropium, and salmeterol/fluticasone) are yet to be published and well awaited. Roflumilast has a clearer advantage in that it is the only orally administered medication for COPD; however, its approved use is restricted to patients with moderate-to-severe COPD, it confers only modest benefits, and is associated with gastrointestinal and psychiatric adverse events. Indacaterol has the potential to offer considerable advantages over the commercially available LABAs, including convenient once-daily dosing. Additionally, the concurrent use of this once-daily LABA plus once-daily tiotropium may confer additional benefits without compromising convenience and thus quality of life. The choice of agent should be individualized and take into consideration expected adverse events, cost, ease of use, and patient preference. Agents with prolonged duration of action should be considered because of the added convenience of once- or twice-daily dosing which may serve to improve medication adherence.

Author Contributions

Wrote the first draft of the manuscript: DR, NP. Contributed to the writing of the manuscript: DR, NP. Agree with manuscript results and conclusions: DR, NP. Jointly developed the structure and arguments for the paper: DR, NP. Made critical revisions and approved final version: DR, NP. All authors reviewed and approved of the final manuscript.

Funding

Authors disclose no funding sources.

Competing Interests

Authors disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

Table 3. Drug therapy options for COPD.[1,24,43]

Drug	Formulation	Dosage	Common adverse reactions
Bronchodilators			
Beta$_2$-agonists			
Short acting			
Albuterol	MDI 90 mcg/actuation	1–2 inhalations every 4–6 hours as needed	Nausea, tachyarrhythmia, throat irritation, rhinitis, upper respiratory infection, hypokalemia
	Solution 2.5 mg/3 mL (0.083%)	2.5 mg nebulized solution inhaled over 5–15 minutes, 3–4 times daily as needed	
Levalbuterol	Solution 0.63 mg/3 mL, 1.25 mg/3 mL	0.63–1.25 mg nebulized solution inhaled three times daily	Rhinitis, sinusitis, viral infection
Terbutaline	Oral tablet 2.5 mg, 5 mg	2.5–5 mg by mouth three times daily	Palpitations, tachyarrhythmia, headache, seizure, tremor, nervousness
Long acting			
Salmeterol	DPI 50 mcg/actuation	1 inhalation twice daily	Headache, nasal congestion, musculoskeletal pain
Formoterol	12 mcg inhalation capsule via Aerolizer device	1 inhalation twice daily	Palpitations, nausea, diarrhea, tremor
	Solution 20 mcg/2 mL	20 mcg nebulized solution inhaled twice daily	
Arformoterol	Solution 15 mcg/2 mL	15 mcg nebulized solution inhaled twice daily	Chest pain, peripheral edema, rash, backache, sinusitis
Ultralong acting			
Indacaterol	75 mcg inhalation capsule via Neohaler device	1 inhalation once daily	Cough, headache, nasopharyngitis
Anticholinergics			
Short acting			
Ipratropium	MDI 17 mcg/actuation	2 inhalations four times daily	Bronchitis, xerostomia, dry nasal mucosa, sinusitis
	Solution 500 mcg/2.5 mL (0.02%)	500 mcg nebulized solution inhaled 3–4 times per day	
Long acting			
Tiotropium	18 mcg inhalation capsule via HandiHaler device	1 inhalation daily	Xerostomia, pharyngitis, sinusitis, upper respiratory infection, constipation
Aclidinium	DPI 400 mcg/actuation	1 inhalation twice daily	Headache, nasopharyngitis, cough
Glycopyrronium	DPI 44 mcg/actuation	1 inhalation daily	Xerostomia, insomnia, nasopharyngitis
Combination anticholinergic/short-acting beta$_2$-agonist			
Ipratropium/ albuterol	MDI 1.8 mcg/ actuation-90 mcg/actuation	1 inhalation 4 times daily	Headache, bronchitis, dyspnea, upper respiratory infection
	Inhalation spray 20 mcg/ actuation-100 mcg/actuation	1 inhalation 4 times daily	
	Solution 0.5 mg/ 3 mL-3 mg/3 mL	3 mL nebulized solution inhaled 4 times daily	
Corticosteroids			
Beclomethasone	MDI, DPI, solution	40 to 320 mcg twice daily	Headache, upper respiratory tract infection, sinusitis
Budesonide	DPI 90 mcg/actuation, 180 mcg/actuation	90–360 mcg twice daily	
Fluticasone	MDI, DPI 44 mcg/actuation, 110 mcg/actuation, 220 mcg/actuation	44–220 mcg twice daily	
Prednisone	Oral	5–60 mg daily	Hypertension, fluid retention, hypernatremia, GI upset, muscle weakness, impaired wound healing, infection
Methylprednisolone	Oral	4–80 mg orally in divided doses	

(*Continued*)

Table 3. (*Continued*)

Drug	Formulation	Dosage	Common adverse reactions
Combination corticosteroid/long acting beta$_2$-agonist			
Budesonide/ formoterol	MDI 80 mcg/actuation-4.5 mcg/actuation, 160 mcg/actuation-4.5 mcg/actuation	2 inhalations twice daily	Oral candidiasis, stomachache, headache, nasopharyngitis, throat pain, sinusitis, upper respiratory tract infections
Mometasone/ formoterol	MDI 100 mcg/ actuation-5 mcg/actuation, 200 mcg/actuation-5 mcg/ actuation	2 inhalations twice daily	Headache, nasopharyngitis, sinusitis
Fluticasone/ salmeterol	MDI, DPI 100 mcg/ actuation-50 mcg/actuation, 250 mcg/actuation-50 mcg/ actuation, 500 mcg/ actuation-50 mcg/actuation	1 inhalation twice daily	Nausea, oral candidiasis, musculoskeletal pain, headache, throat irritation, upper respiratory tract infection
Phosphodiesterase-4 inhibitors			
Roflumilast	Oral tablet 500 mcg	500 mcg once daily	Diarrhea, weight loss, nausea, headache, insomnia, decreased appetite
Methylxanthines			
Aminophylline	Oral, injection	380–760 mg/day in divided doses every 6–8 hours	Nausea, vomiting, dizziness, diuresis, restlessness
Theophylline	Oral	IR and elixir: 300–600 mg/ day in divided doses every 6–8 hours ER: 300–600 mg daily	Nausea, vomiting, headache, tremor, restlessness

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of COPD (GOLD) 2013. *Global Initiative for Chronic Obstructive Lung Disease*. http://www.goldcopd.org. Updated 2013. Accessed February 18, 2013.
2. Soriano JB, Lamprecht B. Chronic obstructive pulmonary disease: a worldwide problem. *Med Clin North Am*. 2012;96(4):671–80.
3. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *The Lancet*. 2012;379(9823):1341–51.
4. Seifart C, Vogelmeier C. Emerging drugs in chronic obstructive pulmonary disease. *Expert Opin Emerg Drugs*. 2009;14(1):181–94.
5. Casarosa P, Bouyssou T, Germeyer S, et al. Preclinical evaluation of long-acting muscarinic antagonists: comparison of tiotropium and investigational drugs. *J Pharmacol Exp Ther.* 2009;330(2):660–8.
6. Gavaldà A, Miralpeix M, Ramos I, et al. Characterization of aclidinium bromide, a novel inhaled muscarinic antagonist, with long duration of action and a favorable pharmacological profile. *J Pharmacol Exp Ther.* 2009;331(2):740–51.
7. Singh D, Magnussen H, Kirsten A, et al. A randomised, placebo- and active-controlled dose-finding study of aclidinium bromide administered twice a day in COPD patients. *Pulm Pharmacol Ther.* Jun 2012;25(3): 248–53.
8. Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: The ATTAIN study. *Eur Respir J*. 2012;40(4):830–6.
9. Lasseter K, Dilzer S, Jansat JM, Garcia Gil E, Caracta CF, Ortiz S. Safety and pharmacokinetics of multiple doses of aclidinium bromide administered twice daily in healthy volunteers. *Pulm Pharmacol Ther.* 2012;25(2):193–9.
10. Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Garcia Gil E, Caracta CF. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). *COPD.* 2012;9(2):90–101.
11. Sims MW, Panettieri RA. Profile of aclidinium bromide in the treatment of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2011;6:457–66.
12. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev*. 2012;64(3):450–504.
13. Mak G, Hanania NA. New bronchodilators. *Curr Opin Pharmacol*. 2012; 12(3):238–45.
14. Ulrik CS. Once-daily glycopyrronium bromide, a long-acting muscarinic antagonist, for chronic obstructive pulmonary disease: a systematic review of clinical benefit. *Int J Chron Obstruct Pulmon Dis*. 2012;7:673–8.
15. Jones PW, Rennard SI, Agusti A, et al. Efficacy and safety of once-daily aclidinium in chronic obstructive pulmonary disease. *Respir Res*. 2011;12:55.
16. Tonnel AB, Perez T, Grosbois JM, et al. Effect of tiotropium on health-related quality of life as a primary efficacy endpoint in COPD. *Int J Chron Obstruct Pulmon Dis*. 2008;3(2):301–10.
17. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med*. 2005; 143(5):317–26.
18. Dusser D, Bravo ML, Iacono P. The effect of tiotropium on exacerbations and airflow in patients with COPD. *Eur Respir J*. 2006;27(3):547–55.
19. Casaburi R, Conoscenti CS. Lung function improvements with once-daily tiotropium in chronic obstructive pulmonary disease. *Am J Med*. 2004; 117(Suppl 12A):33S–40.
20. Donohue JF. Minimal clinically important differences in COPD lung function. *COPD*. 2005;2(1):111–24.

21. D'Urzo A, Ferguson GT, van Noord JA, et al. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: The GLOW1 trial. *Respir Res*. 2011;12:156.
22. Kerwin E, Hebert J, Gallagher N, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: The GLOW2 study. *Eur Respir J*. 2012;40(5):1106–14.
23. Tudorza Pressair (aclidinium) [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc; 2012.
24. Seebri Breezhaler: glycopyrronium bromide. European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002430/human_med_001580.jsp&mid=WC0b01ac058001d124. Updated Oct 17, 2012. Accessed Dec 11, 2012.
25. Giembycz MA, Field SK. Roflumilast: First phosphodiesterase 4 inhibitor approved for treatment of COPD. *Drug Des Devel Ther*. 2010;4:147–58.
26. Gross NJ, Giembycz MA, Rennard SI. Treatment of chronic obstructive pulmonary disease with roflumilast, a new phosphodiesterase 4 inhibitor. *COPD*. 2010;7(2):141–53.
27. Halpin DMG. ABCD of the phosphodiesterase family: Interaction and differential activity in COPD. *Int J Chron Obstruct Pulmon Dis*. 2008;3(4):543–61.
28. Hatzelmann A, Morcillo EJ, Lungarella G, et al. The preclinical pharmacology of roflumilast—a selective, oral phosphodiesterase 4 inhibitor in development for chronic obstructive pulmonary disease. *Pulm Pharmacol Ther*. 2010;23(4):235–56.
29. Rabe KF. Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease. *Br J Pharmacol*. 2011;163(1):53–67.
30. Rabe KF, Bateman ED, O'Donnell D, Witte S, Bredenbröker D, Bethke TD. Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*. 2005;366(9485):563–71.
31. Calverley PM, Rabe KF, Goehring UM, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: Two randomised clinical trials. *Lancet*. 2009;374(9691):685–94.
32. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: Two randomised clinical trials. *Lancet*. 2009;374(9691):695–703.
33. Calverley PM, Sanchez-Toril F, McIvor A, Teichmann P, Bredenbroeker D, Fabbri LM. Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;176(2):154–61.
34. Daliresp (roflumilast) "Prescribing Information" http://www.frx.com/products/ Updated September 2011. Accessed February 18, 2013. St. Louis, MO: Forest Pharmaceuticals, Inc; 2011.
35. Malerba M, Radaeli A, Morjaria JB. Therapeutic potential for novel ultra long-acting β2-agonists in the management of COPD: Biological and pharmacological aspects. *Drug Discov Today*. 2012;17(9–10):496–504.
36. Ray SM, McMillen JC, Treadway SA, Helmer RS, Franks AS. Indacaterol: a novel long-acting β2-agonist. *Pharmacotherapy*. 2012;32(5):456–74.
37. Feldman G, Siler T, Prasad N, et al. Efficacy and safety of indacaterol 150 microg once-daily in COPD: a double-blind, randomised, 12-week study. *BMC Pulm Med*. 2010;10:11–2466–10–1.
38. Donohue JF, Fogarty C, Lotvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: Indacaterol versus tiotropium. *Am J Respir Crit Care Med*. 2010;182(2):155–62.
39. Kirsten A, Watz H, Kretschmar G, et al. Efficacy of the pan-selectin antagonist bimosiamose on ozone-induced airway inflammation in healthy subjects—a double blind, randomized, placebo-controlled, cross-over clinical trial. *Pulm Pharmacol Ther*. 2011;24(5):555–8.
40. Gross NJ. Novel antiinflammatory therapies for COPD. *Chest*. 2012;142(5):1300–7.
41. Mahler DA, D'Urzo A, Bateman ED, et al. Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. *Thorax*. 2012;67(9):781–8.
42. Arcapta (indacaterol) "Prescribing Information" http://pharma.us.novartis.com/product/pi/pdf/arcapta.pdf. Updated September 2012. Accessed February 18, 2013. East Hanover, NJ: Novartis Pharmaceuticals; 2012.
43. DRUGDEX® System Internet database. http://www.micromedexsolutions.com. Accessed February 18, 2013. Greenwood Village, CO: Thomson Reuters (Healthcare) Inc.