Pharmacologic management of COPD

Breadth of products for encouraging a breath of air

Alex Crawley ACPR **Tessa Laubscher** MB ChB CCFP FCFP **Patricia Muddiman** MD CCFP **Lynette Kosar** MSc

Chronic obstructive pulmonary disease (COPD) is common and pernicious. About 4% of Canadians older than 35 years have been diagnosed with the disease, although this likely underestimates the true prevalence.[1,2] Chronic obstructive pulmonary disease increases mortality and has a negative effect on quality of life. It is ranked as the fifth-leading cause of death in Canada.[3] Almost half (45%) of Canadians with COPD report their overall health to be "fair or poor," while 21% report that breathing problems affect their life "quite a bit or extremely."[1]

Numerous new medications and devices for treating COPD have recently arrived on the Canadian market. Here we attempt to unravel some of the uncertainties regarding these products: their similarities, differences, advantages, and disadvantages.

Mr B.Z., a 58-year-old married plumber, has an appointment with you today to review his spirometry results. He seldom sees a physician, but 2 weeks ago he presented to the clinic with shortness of breath. He was given a prescription for a salbutamol inhaler and sent for spirometry testing. Today, further history reveals dyspnea on exertion and an associated cough; he has had production of yellowish sputum every morning for the past few years. Recently he has only been able to walk for 5 to 10 minutes before needing to stop to catch his breath. In the past 2 weeks he has used the salbutamol about 4 times daily with minimal relief of dyspnea. Mr B.Z. has smoked an average of 2 packs of cigarettes per day since the age of 15 (86 pack-years).

Upon reviewing the spirometry results, you note that Mr B.Z. has a ratio of forced expiratory volume in the first second of expiration (FEV_1) to forced vital capacity of 0.62 and an FEV_1 of 68% of the predicted value with no substantial bronchodilator effect. You make a diagnosis of moderately severe COPD based on the spirometry result, smoking history, and his symptoms.

His medical history includes a diagnosis of gastroesophageal reflux disease. Current medications are 20 mg of omeprazole daily and 500 mg of acetaminophen occasionally taken for joint pain.

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Bringing evidence on initial treatment to practice

Mr B.Z. is typical of many people with COPD in that his diagnosis is made years after onset of symptoms. Suspicion of COPD should be high in individuals older than 40 years of age with respiratory symptoms (eg, coughing, dyspnea, sputum) and at least 1 risk factor (eg, smoking, occupational exposure to lung irritants). Spirometry remains the criterion standard for diagnosis; the threshold is a postbronchodilator ratio of FEV_1 to forced vital capacity less than 0.7.

Smoking cessation remains one of the most important aspects of management, reducing the risk of mortality in COPD patients by 40%, and slowing the decline in lung function by the same amount.[4,5] Regrettably, no medication has been shown to slow the progression of COPD. Instead, the goals of therapy are to improve symptoms and quality of life, and prevent exacerbations and hospitalizations.

The initial approach to COPD therapy (**Table 1**) is bronchodilation, achieved through the use of short- or long-acting muscarinic (anticholinergic) antagonists or β-agonists. Short-acting agents can relieve dyspnea symptoms and improve quality of life. They are usually used first in mild COPD. Long-acting agents relieve dyspnea symptoms and improve quality of life, and also reduce the risk of exacerbations and hospitalizations (eg, tiotropium reduces exacerbations by 29% versus placebo, and reduces the odds of hospitalization by 66% versus ipratropium).[6,7] As COPD severity and functional status worsen, advancing therapy to long-acting agents is warranted.

Few studies are available to guide the choice between using a long-acting muscarinic agent (LAMA) or a long-acting β-agonist (LABA). Limited evidence suggests LAMAs might be superior in reducing exacerbations and might be better tolerated (eg, less discontinuation during randomized controlled trials).[8,9] Regardless of whether a LAMA or a LABA is chosen, a short-acting agent from the opposite class might be used intermittently (eg, before increased physical activity).

Despite the recent introduction of so many new agents (**Table 2**), none of the LAMAs or LABAs can claim superiority over others within their classes. This can make it difficult when deciding which one to choose.

Table 1. Stepwise approach to COPD pharmacotherapy

STEP AND ACTION	PHARMACOTHERAPY	COMMENTS
Step 1: Start short-acting agents	• SAMA with or without SABA (scheduled or as needed)	Start at step 1 if • COPD is mild, or • there are cost barriers to LAMA or LABA use Expected benefit: • relieves symptoms but might not decrease AECOPD and hospitalizations
Step 2: Reassess inhaler technique and start long-acting agents	• LAMA with SABA as needed, or • LABA with SABA as needed with or without SAMA as needed	Start at step 2 if • COPD is moderate to severe Move to step 2 if • there is treatment failure in step 1 Expected benefit: • relieves symptoms; decreases AECOPD and hospitalizations • LAMA is often preferred
Step 3: Reassess inhaler technique and optimize long-acting agents	• LAMA with LABA and with SABA as needed • LAMA and LABA-ICS and SABA as needed (if there is poor symptom control despite LAMA with LABA, or if there is frequent AECOPD)	Move to step 3 if • there is treatment failure in step 2 Expected benefit: • limited evidence vs LAMA alone; addition of LABA might further relieve symptoms; addition of LABA-ICS might decrease AECOPD and possibly improve symptoms

AECOPD—acute exacerbation of COPD, COPD—chronic obstructive pulmonary disease, ICS—inhaled corticosteroid, LABA—long-acting β-agonist, LAMA—long-acting muscarinic antagonist, SABA—short-acting β-agonist, SAMA—short-acting muscarinic antagonist.

However, it should be noted that the LAMA tiotropium, especially when delivered by the HandiHaler device, has a large body of evidence and experience supporting its use in reducing exacerbations and hospitalizations versus placebo and versus LABAs.[8,10] For this reason tiotropium might still be considered the criterion standard.

Inhaler technique is very important to ensure adequate drug delivery to the lungs, and should be assessed regularly; 50% to 59% of patients use their inhalers incorrectly.[11,12] Patients can be referred to a pharmacist or COPD educator for assistance with device selection, for initial device training, and for reassessing inhaler technique. Links to teaching tools are provided in **Box 1**.

All patients with COPD should receive a yearly influenza vaccine, which reduces COPD mortality by 50% and the risk of hospitalizations by 40%.[13] At least 1 pneumococcal vaccine should also be given (evidence is unclear as to whether a second pneumococcal vaccine booster provides additional benefit). Another nonpharmacologic intervention is pulmonary rehabilitation (COPD education plus supervised exercise), which has been shown to reduce dyspnea and anxiety associated with COPD, improve quality of life, and decrease hospitalizations for acute exacerbations.

Box 1. Links to tools and resources

The following websites offer some useful tools and resources:

- Teaching sheets: **www.RxFiles.ca**
- Patient handouts: **sk.lung.ca/health-professionals/resources/resptrec-resources**
- Pulmonary rehabilitation programs: **www.lung.ca/lung-health/get-help**

Treating newly diagnosed COPD for Mr B.Z.

When you talk to Mr B.Z. about the benefits of smoking cessation, you determine that he is in the contemplative stage of change. While he is currently not ready to quit smoking, he should be encouraged to seek help if he does decide to quit, and smoking cessation should be discussed at COPD review visits.

Mr B.Z. has moderate-severity COPD and is getting suboptimal relief from salbutamol. Prescribing either a LAMA or a LABA is reasonable, assuming he can afford it. After a telephone call to Mr B.Z.'s pharmacist, you find out that tiotropium is covered under his provincial drug plan. You prescribe 18 µg of inhaled tiotropium via HandiHaler once daily, and continue his previously prescribed 100-µg salbutamol inhaler at a dose of 1 to 2 puffs up to 4 times daily if needed. You ask Mr B.Z.'s pharmacist to provide instruction on correct inhaler technique.

Mr B.Z. receives annual influenza immunizations and is willing to be given the pneumococcal vaccine today.

You ask Mr B.Z. to make an appointment with you in 3 months to assess how well the tiotropium is working and you encourage him to return earlier if he would like help quitting smoking.

Table 2. Medications for COPD currently available in Canada

MEDICATION	DEVICE	USUAL DOSE
SABAs		
• Salbutamol	Metered-dose inhaler	1-2 puffs inhaled 4 times daily as needed
	Diskus	1 puff inhaled 4 times daily as needed
	Nebule	2.5 mg inhaled 4 times daily as needed
• Terbutaline	Turbuhaler	1 puff inhaled 4 times daily as needed
SAMA		
• Ipratropium	Metered-dose inhaler	2 puffs inhaled 4 times daily as needed
	Nebule	500 µg inhaled 4 times daily as needed
Combination SABA and SAMA		
• Salbutamol and ipratropium	Nebule	1 ampoule inhaled 4 times daily as needed
	Respimat	1 puff inhaled 4 times daily as needed
LAMAs		
• Tiotropium	HandiHaler	1 capsule inhaled once daily
	Respimat	2 puffs inhaled once daily
• Aclidinium	Genuair	1 puff inhaled twice daily
• Glycopyrronium	Breezhaler	1 capsule inhaled once daily
• Umeclidinium	Ellipta	1 puff inhaled once daily
LABAs		
• Salmeterol	Diskus	1 puff inhaled twice daily
• Formoterol	Aerolizer	1 capsule inhaled twice daily
	Turbuhaler	6-12 µg inhaled twice daily
• Indacaterol	Breezhaler	1 capsule inhaled once daily
• Olodaterol	Respimat	2 puffs inhaled once daily
Combination LAMA and LABA		
• Umeclidinium and vilanterol	Ellipta	1 puff inhaled once daily
• Glycopyrronium and indacaterol	Breezhaler	1 puff inhaled once daily
• Tiotropium and olodaterol	Respimat	2 puffs inhaled once daily
• Aclidinium and formoterol	Genuair	1 puff inhaled twice daily
Combination LABA and ICS		
• Formoterol and budesonide	Turbuhaler	12 µg and 400 µg inhaled twice daily
• Salmeterol and fluticasone	Diskus	50 µg and 250 µg inhaled twice daily
• Vilanterol and fluticasone	Ellipta	1 puff inhaled once daily

COPD—chronic obstructive pulmonary disease, ICS—inhaled corticosteroid, LABA—long-acting β-agonist, LAMA—long-acting muscarinic antagonist, SABA—short-acting β-agonist, SAMA—short-acting muscarinic antagonist.

Four years later, Mr B.Z. is 62 years old and his COPD has progressed. He now feels short of breath after walking only short distances, resulting in a marked reduction in his physical activity and ability to work. You rate his functional status at grade 3 using the Modified Medical Research Council Dyspnea Scale, and a recent spirometry test shows an FEV_1 of 59%. Fortunately, Mr B.Z. successfully quit smoking 2 years ago and has not had any COPD exacerbations in the past year. His current medications are 18 µg of inhaled tiotropium daily, 100 µg of salbutamol inhaled as needed, 20 mg of omeprazole daily, 40 mg of citalopram daily added recently to treat depression, and 650 mg of acetaminophen 4 times daily for osteoarthritis in his hands and knees. Mr B.Z. uses salbutamol 4 times a day most days, but this does not provide much benefit. His osteoarthritis makes it challenging to load the small tiotropium capsules into the inhaler. Beyond this issue, he demonstrates good inhaler technique.

Bringing evidence on treating disease progression to practice

Combining a LABA and a LAMA might provide a modest benefit in COPD versus a single long-acting agent, and it is recommended in those with poor symptom control and infrequent COPD exacerbations (less than

1 per year). In clinical trials, combined LABA and LAMA therapy did not change hospitalization or exacerbation rates compared with LAMA therapy alone.[14] Trials showed a statistically significant, although perhaps not clinically meaningful, improvement in lung function and quality of life.[14] Despite these disappointing outcomes, it should be noted that this situation is relatively unstudied. Anecdotally, some patients report an improvement in symptoms with combination therapy, while others do not.

Adding a LABA and inhaled corticosteroid (ICS) to a LAMA might also provide a modest benefit, with the risk of adverse effects. In a large clinical trial, combined LABA and ICS therapy did reduce exacerbations compared with LABA therapy alone.[15] However, this was associated with an increase in pneumonia (number needed to harm of 16 during 3 years) and it is also unclear if exacerbations can be reduced with LABA-ICS therapy when a LAMA is already being taken.[15] Current recommendations are to reserve the use of LABA-ICS combinations for patients with frequent exacerbations (1 or more per year) or whose COPD is uncontrolled when taking combined LAMA and LABA therapy with maximal nonpharmacologic management, including pulmonary rehabilitation, COPD education, optimal use of inhalers, treatment of obstructive sleep apnea, and supplemental oxygen if appropriate.[2]

One benefit of the novel inhalers on the market is additional drug combinations and delivery devices to choose from. New combination LAMA-LABA products have cost and convenience advantages. Some of the new devices are easy to use and have advantages in patients with poor hand dexterity. A complete overview of device-specific advantages and disadvantages is available at **CFPlus**.*

Treating disease progression for Mr B.Z.

Mr B.Z., who has not had an exacerbation in the past year, is a candidate for addition of a LABA rather than addition of a LABA-ICS combination. Further, Mr B.Z. might find a new type of delivery device easier to use than the tiotropium HandiHaler.

You look up the available LAMA-LABA combination options (**Table 2**) and note that formulations are available for the Ellipta, Genuair, Respimat, and Breezhaler devices. The Breezhaler device requires a similar technique to the HandiHaler; therefore, it is a poor choice for Mr B.Z. You call Mr B.Z.'s pharmacy and find that of the remaining options only the Genuair and Ellipta devices are covered for him. As the medications within the Ellipta device are taken once a day, while Genuair is taken twice a day, you choose the Ellipta option for increased convenience. You prescribe Mr B.Z. the LAMA-LABA combination of umeclidinium and vilanterol at a dose of 1 inhalation per day. You also arrange for his pharmacist to teach him how to use his new device, and to review technique at his next refill. Salbutamol is continued as needed.

Mr B.Z. has a resting oxygen saturation of 94% on room air and no symptoms of obstructive sleep apnea. He agrees to a referral to the local pulmonary rehabilitation program.

One year later, Mr B.Z. comes into your office with a worsening of dyspnea over the past 10 days. He reports increased cough and fatigue, but no change in his sputum. His breathlessness has forced him to take time off work. You diagnose Mr B.Z. with an acute exacerbation of COPD (AECOPD). Heavy smoke from forest fires in the area is thought to be a contributing factor. This is his third exacerbation in the past 6 months. He is still taking umeclidinium-vilanterol once daily and salbutamol as needed.

Bringing evidence on treating AECOPD to practice

In AECOPD, 30 to 50 mg of oral prednisone daily for 5 days will decrease the duration of the exacerbation, the risk of hospitalization, and the risk of repeat exacerbation. Recent evidence supports the use of short courses (eg, 5 days) of prednisone instead of long courses (eg, 14 days).[16] No taper is required. High doses of short-acting bronchodilators are also needed to treat the acute symptoms of AECOPD.

Antibiotics are not always required to treat AECOPD. Evidence suggests that a change in sputum colour (eg, to yellow or green) and volume can be predictive of which AECOPD patients might benefit from antibiotics.[17,18] Some current guidelines recommend prescribing antibiotics only to patients with both a change in sputum colour and at least 1 other symptom (increased sputum volume or increased dyspnea).[19]

There is strong evidence that pulmonary rehabilitation is beneficial if started within the first 30 days after an exacerbation. Following AECOPD, only 4 patients need to be treated with 25 weeks of pulmonary rehabilitation to prevent 1 hospitalization.[20] A link in **Box 1** provides program locations for pulmonary rehabilitation.

Treating AECOPD for Mr B.Z.

You prescribe Mr B.Z. 50 mg of prednisone daily for 5 days. You also ask him to increase his inhaled salbutamol dose to 2 puffs 4 times daily for the next few days, and to decrease once symptoms improve. You do not prescribe antibiotics because he has not had a change

*__A complete overview of device-specific advantages and disadvantages__ is available at **www.cfp.ca**. Go to the full text of this article and click on **CFPlus** in the menu at the top right-hand side of the page.

in his sputum quality. You ask him to follow up with you in 1 to 2 weeks.

At follow up, you add an ICS to his regimen in light of his recent exacerbation history. As Mr B.Z. has demonstrated good technique with the Ellipta device, you switch him to umeclidinium (a LAMA) and vilanterol-fluticasone (a LABA-ICS combination). You check first with his pharmacy to make sure these products are covered under his drug plan; fortunately, they are.

Mr B.Z. admits that he did not attend pulmonary rehabilitation the last time you referred him because his COPD symptoms lessened after starting the combination LAMA-LABA. However, he is now willing to attend after hearing the potential benefits of improved quality of life, reduced exacerbations, and reduced hospitalizations.

Conclusion

In most cases a stepwise approach to COPD therapy is advised. Consider starting with short-acting agents, followed by a LAMA (often tiotropium), then dual LAMA and LABA therapy, and finally triple therapy with LAMA and a LABA-ICS combination. Acute exacerbation of COPD is treated with prednisone, with or without an antibiotic, and high doses of short-acting agents. Patients with COPD should be encouraged to stop smoking, receive their immunizations, and engage in regular exercise or a pulmonary rehabilitation program. Adherence to medications and inhaler technique should be regularly assessed; an inhaler device that works for the patient should be chosen. Newer COPD agents and devices might offer advantages in cost, convenience, or ease of use; however, drug coverage might be a challenge.

Mr Crawley is a pharmacist for the RxFiles Academic Detailing Program. **Dr Laubscher** is Clinical Associate Professor of Academic Family Medicine at the University of Saskatchewan in Saskatoon. **Dr Muddiman** is a practising family physician in Prince Albert, Sask, and Clinical Assistant Professor in the Department of Academic Family Medicine at the University of Saskatchewan. **Ms Kosar** is Information Support Pharmacist for the RxFiles Academic Detailing Program.

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Correspondence
Mr Alex Crawley; e-mail **alex.crawley@usask.ca**

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