Canadian Geriatrics Society

UPDATE: WHAT IS NEW IN COPD IN 2018?

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Abstract

Chronic obstructive pulmonary disease is one of the most common chronic conditions in Canada. It is encountered by clinicians on almost a daily basis however, at times, therapy can be suboptimal due to misunderstandings of the underlying condition and the increasing complexity of therapeutic options. This article reviews common presenting symptoms, the revised Global initiative for chronic Obstructive Lung Disease (GOLD) severity classification. This, in turn, is used to provide a logical selection of treatments including short acting beta agonists, long-acting beta agonists, long-acting muscarinic agonists, inhaled corticosteroids as well as combinations of these agents. The article then reviews tools to assist with formal pharmacotherapy decisions and links the reader to useful algorithms and websites to assist the clinician in day to day therapeutic decision making.

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Conflict of Interest: Co-chair of Health Quality Ontario Community management of COPD standards document.[i] Member of Health Canada Section on Allergy and Respiratory Therapeutics.
Advisory board or speakers bureau for Astra Zeneca, Boehringer Ingelheim, GSK, Johnson and Johnson, Merck, Mylan, Novartis, Pfizer, Paladin, Purdue, Sanofi, Teva, Trudell.

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Chronic Lung Disease, Pulmonary, Chronic Obstructive Pulmonary Disease, COPD

Definition of COPD

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. The familiar terms 'chronic bronchitis' and 'emphysema' are no longer used, but are now included within the COPD diagnosis. COPD is not simply a 'smoker's cough' but an under-diagnosed, life-threatening lung disease[1]. The most common symptoms of COPD include chronic and progressive breathlessness, cough, sputum production, wheezing and chest congestion. In addition to the airflow restriction and changes to the lung, COPD is associated with systemic effects and comorbidities. Systemic effects include weight loss, nutritional abnormalities and malnutrition and skeletal muscle dysfunction; while common comorbidities include ischemic heart disease, osteoporosis, respiratory infection, bone fractures, depression and anxiety, diabetes, sleep disorders, anemia, glaucoma, cataracts and cancer[2].

COPD is one of the most common chronic conditions in Canada. Data in Ontario estimates a prevalence of 9.5% in 2007[3]. Age- and sex-standardized COPD mortality in Ontario was 4.3% in 2007, translating to 32,000 deaths each year. COPD is the second most common reason for hospitalization (after deliveries), with 18% of hospitalized COPD patients readmitted during the year following their hospitalization.

Goals of Therapy

The goals of COPD care are to prevent disease progression, alleviate breathlessness and other symptoms, improve exercise tolerance and daily activity, reduce frequency and severity of exacerbations, improve health status, treat exacerbations and complications of the disease and reduce mortality[4].

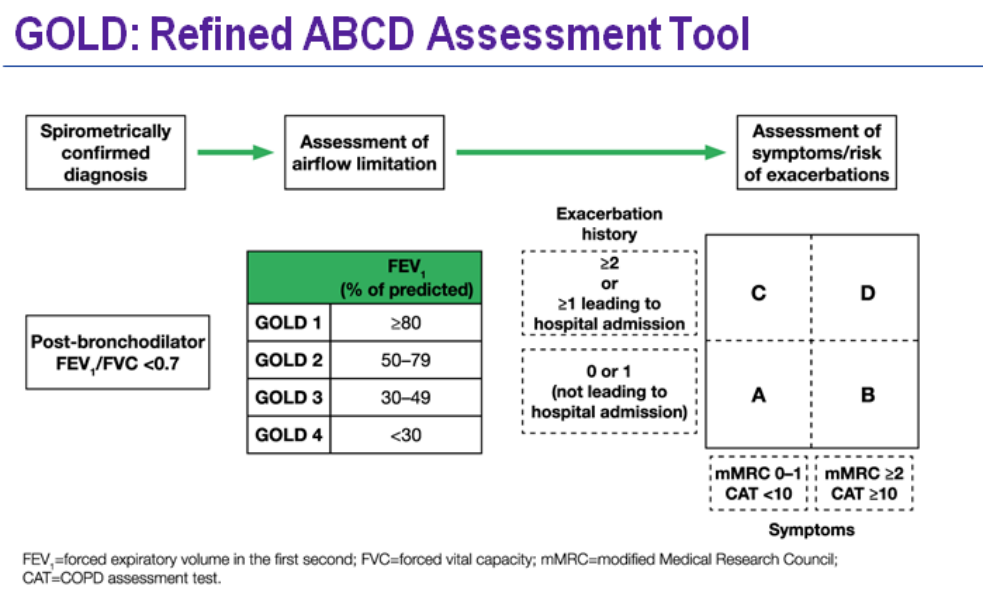
How Do We Diagnose?

A diagnosis of COPD should be considered in patients with progressive dyspnea, chronic cough or increased sputum production with risk factors (e.g., smoking). COPD can be diagnosed with spirometry with a post-bronchodilator Forced Expiratory Rate (FEV1)/forced vital capacity (FVC) ratio of less than 0.70[4].

Classifying Severity for Treatment

The severity classification of COPD has been revised by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for 2017[5] in order to better adapt treatments to individual patient symptoms. Once the diagnosis of COPD has been confirmed by spirometry (with post-bronchodilator FEV1/FVC ratio of less than 0.70) the treatments are based on the combination of disability of the patient and exacerbation frequency (Figure 1). After an assessment of lung function (measured from GOLD 1 to Gold 4 – see Figure 1), disability in patients with COPD is measured by two tools. The mMRC or Modified Medical Research Council questionnaire measures disability from 0-4 with 0 being dyspnea on severe exertion and 4 being dyspnea on activities of daily living (see Table 2.5 page 6). The CAT tool or COPD Assessment Test has eight domains including symptoms (cough, phlegm, chest tightness and breathlessness walking up a hill) and other disability (activity limitation, confidence leaving the house, sleep and energy) (see Figure 2.3 Page 7). In the GOLD Refined ABCD Assessment Tool (Figure 1) exacerbation history is combined with symptomology (as measured by mMRC or CAT) to generate four quadrants A-D. A are those with minimal disability (CAT<10, MRC 0-1) with infrequent exacerbations. B are those with significant disability (CAT ≥10, MRC ≥2) and infrequent exacerbations. C are those with frequent exacerbations defined as two or more per year or a single hospitalization but no significant daily disability (CAT< 10, MRC 0-1). D are those with frequent exacerbations and significant disability (CAT ≥10, MRC ≥2). This allows targeting therapy at both symptom control and at exacerbation reduction appropriately.

Figure 1:



FEV1=forced expiratory volume in the first second; FVC=forced vital capacity; mMRC=modified Medical Research Council; CAT=COPD assessment test.

What are the Pharmacologic Treatments?

The GOLD guidelines recommend an approach to COPD where we assess both symptoms and risk for future exacerbations. Both lung function (FEV1) and a history of past exacerbations influence the risk of future exacerbations.

By the separate consideration of the pulmonary function on the one hand and the symptoms/exacerbations on the other hand, a more individualized treatment becomes possible. Different treatment recommendations are available for the individual severity levels. The GOLD ABCD score can be used to target therapy (see Figure 4.1 Page 23).

For patients with only occasional symptoms, a short-acting bronchodilator, either a short-acting beta-agonist or a short-acting muscarinic antagonist is recommended. For patients with persistent symptoms, either a long-acting beta-agonist (LABA) or a long-acting muscarinic antagonist (LAMA) is recommended. For patients with persistent symptoms on single bronchodilator therapy, advancement to dual therapy with a LAMA plus a LABA or combination Inhaled Corticosteroid (ICS)/LABA is recommended, with a preference given to dual-bronchodilator therapy. Dual bronchodilator therapy is now given preference based on the increased risk of pneumonia with the use of ICS in patients with COPD and the superior efficacy in preventing exacerbations and improving patient reported outcomes in the most severe category of patients with COPD when dual bronchodilator therapy is compared to ICS/LABA therapy[6]. For the most severe category of patients, triple therapy with LAMA/LABA/ICS can be used, with the addition of roflumilast if FEV1 is less than 50% and patient has persistent cough and sputum (the phenotype called chronic bronchitis).

What are these new drugs?

There are basically six classes of inhaled therapeutics for COPD management, which include SABD (short-acting bronchodilators), LABA, LAMA, ICS/LABA, LABA/LAMA and coming soon triple therapy with LABA/LAMA/ICS all in one device (which will not be discussed as they are not currently available). They have differences in formulation, device and dosing frequency with mild differences in efficacy and potential safety.

There are three types of inhalers: metered dose inhalers (MDIs), dry powder inhalers (DPIs) and soft mist inhalers (SMIs).

A. Short-Acting Bronchodilators

These are used for breakthrough symptoms as needed and include short-acting beta-agonists (SABA): Salbutamol (Ventolin) via MDI or Diskus and Terbutaline (Bricanyl) via Turbuhaler as well as short-acting muscarinic antagonist (SAMA): anticholinergic Ipratropium (Atrovent) via MDI. There is a combination of SABA/SAMA of salbutamol and ipratropium called Combivent, which is delivered via a soft mist inhaler called Respimat.

B. Long-Acting Bronchodilator or Combinations

Long-Acting Muscarinic Agents

Tiotropium[7] or Spiriva is available in two formats, either the Handihaler at a dose of 18 ug once daily or the Respimat device at a dose of 5 ug: two puffs of 2.5 ug daily. This is the oldest drug in this market with a plethora of data behind it, including uniquely in the class, exacerbation reduction. The Tiospir[8] trial showed that the drug delivered via either device is equivalent in terms of effect and safety, only differing by the device and patient/physician preference[9].

Glycopyrronium[10] or Seebri is delivered via the Breezhaler device at a dose of 50 ug once daily. It has a faster onset of action than Tiotropium.

Aclidinium[11] or Tudorza is delivered via the Genuair device at a dose of 400 ug bid. It also has a faster onset of action than Tiotropium, but is given twice daily. The twice daily dosing strategy may be better for those with worsened nighttime and first morning symptoms.

Umeclidinium[12] or Incruse is delivered via the Ellipta device at a dose of 62.5 ug daily. It also has a rapid onset of action and may actually outperform other agents in the class with respect to trough FEV1.

The most common side effects of all drugs in this class is dryness of mouth. The most significant concern for clinicians is the potential to induce urinary retention in men with benign prostatic hypertrophy.

Figure 2: Long-Acting Muscarinic Agents (formerly called Long-Acting Anticholinergics) LAMAs

Long-Acting Beta-Agonists (LABAs)

Salmeterol or Serevent[13] is delivered by the Diskus device at a dose of 50 ug bid. It has a slow onset of action relative to all other LABAs.

Formoterol[14] currently available as Oxeze via Turbuhaler or Foradil via Aerolizer at a dose of 6 ug two doses/12 ug bid.

Indacaterol[15] or Ombrez delivered by the Breezhaler device at a dose of 75 ug once daily.

Figure 3: Long-Acting Beta-Agonists (LABAs)

CLASS	INHALER NAME	BRAND NAME / GENERIC NAME
LABA	DPI Diskus 	Serevent® (salmeterol)
	DPI Aerolizer  	Foradil® Oxeze® (formoterol)
	DPI Breezhaler 	Onbrez® (indacaterol)

Inhaled Corticosteroid/LABA Combinations

Salmeterol/Fluticasone Propionate or Advair[16] is available in the Diskus or MDI device in a variety of dosing based on low, medium and high dose ICS; 100, 250 or 500 ug along with Salmeterol for a total dose of 50 ug given twice daily.

Formoterol/Budesonide or Symbicort[17] is available in the Turbuhaler device given bid with three dose strengths of the budesonide, 100, 200 and 400 ug.

Vilanterol/Fluticasone Furate[18] or Breo is available in the Ellipta device in a dose of 50 ug/100 ug given once daily. Vilanterol onset of action is rapid like the LABAs above other than Salmeterol. There is also a 50/200 ug dose that has an indication for asthma.

Formoterol/Mometasone or Zenhale is available in Canada in three dose strengths but does not have an indication for COPD.

Figure 4: Inhaled corticosteroid/LABA combinations

LABA/LAMA Combinations

Glycopyrronium/Indacaterol or Ultibro is delivered via the Breezhaler device in an effective dose of 50/150 ug in a once daily dose. It has been shown to be superior to both LAMA monotherapy[19] and ICS/LABA[20] in improving dyspnea in symptomatic group D and/or B patients. Furthermore, in the SPARK study, the LABA/LAMA fixed combination provided a further reduction in the exacerbation rate in high-risk C-D patients versus LAMA alone, and this was accompanied by improvements in health status versus comparators[21].

Umeclidinium/Vilanterol or Anoro is delivered via the Ellipta device in a dose of 62.5/25 ug in a once daily dose.

Aclidinium/Formoterol or Duaklir is delivered via the Genuair device in a dose of 400/12 ug in a twice daily dosing schedule.

Tiotropium/Olodaterol or Inspiolto is delivered via the Respimat device in a dose of 2.5/5 ug two sprays once daily.

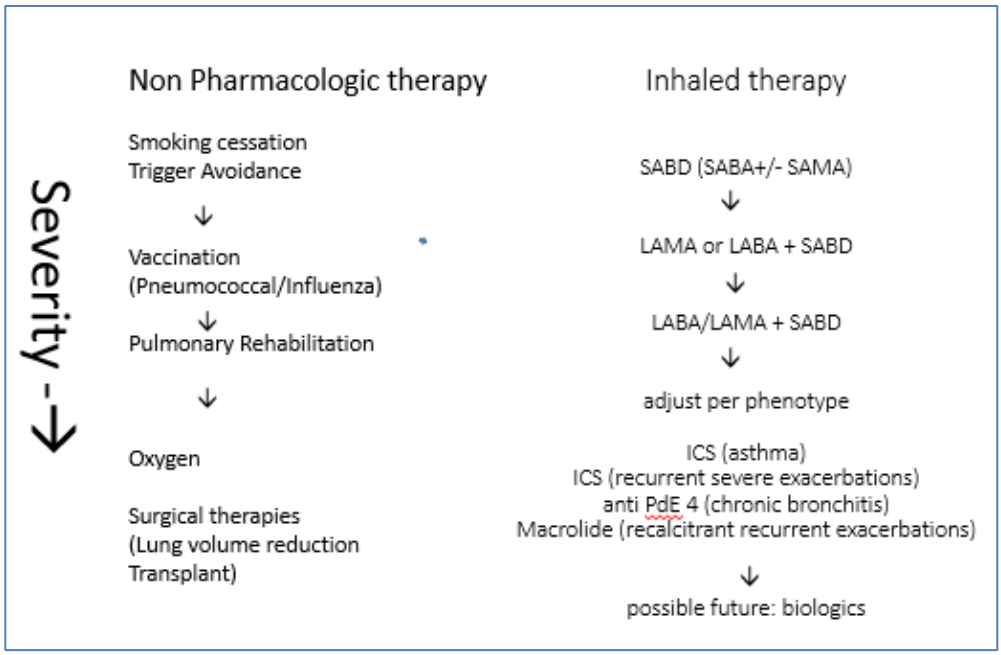
Figure 5: LABA/LAMA Combinations

Overall, the strategy for management is to first optimize bronchodilator therapy for improving quality of life and lung function. While not definitive, it appears that beginning with a LAMA may be preferable, at least with respect to exacerbations per the POET trial[22]. Some LABAs (indacaterol), however, may perform as well as LAMA with respect to lung function[23], but not with respect to exacerbations[24]. Controversy remains as to whether to start with one class of long-acting agent versus the other, or in fact begin with the combination of LABA/LAMA.

So, how do we use all of these new medications?

The pharmacologic management of COPD can be simplified into a few steps. First of all, bronchodilate your patient to allow deflation and relieve dyspnea. This can mean just a short-acting bronchodilator if symptoms are mild or moving up to dual bronchodilation, the combination of both LABA and LAMA in those with more severe symptoms. From there, additional therapy is added to deal with phenotypic drivers. If there is a concern about concomitant asthma or eosinophilic inflammation, use of ICS would be advised. For those where there are frequent exacerbations, especially if severe, ICS have been traditionally added. For those with the phenotype of chronic bronchitis and exacerbations, roflumilast can be added. For those who despite therapy are still frequently exacerbating consider macrolide therapy. Continue short-acting bronchodilators for your patient to use as rescue therapy for intermittent symptoms. Remember to vaccinate (covered in another article in this edition) and consider oxygen in those who are hypoxic. Smoking cessation pharmacotherapy can also be of value. See the algorithm below for this concept.

Figure 6:



What else is new in COPD pharmacotherapy decisions in management?

The role of ICS in ICS/LABA was always felt to reduce exacerbations in patients with COPD. This goes back many years to landmark trials such as TORCH, which showed a reduction in exacerbations in a population compared with LABA alone[25]. This study was done in a population not on LAMA and subsequent studies have shown a reduction in exacerbations due to LAMA comparable to ICS/LABA[26]. Side effects of ICS in patients with COPD have become more appreciated and include local effects such as thrush and dysphonia and systemic side effects such as osteoporosis and fracture, increased risk of diabetes and progression to insulin, cataracts, glaucoma and increased risk of pneumonia[27]. As such studies have looked at reducing ICS doses in patients with COPD felt to not have asthma (in patients without a primary diagnosis of asthma and a blood eosinophil count of <600). The Wisdom trial[28] showed that a reduction of dose of ICS to low dose had no adverse effects on lung function or exacerbations and complete removal of ICS had only a minimal effect on lung function (~45 cc) and no real statistical difference in exacerbation frequency. Subsequently, the Flame study compared use of LABA/LAMA versus ICS/LABA in exacerbations as the previous endpoints (as previous trials had already definitely proven superiority in lung function and dyspnea). Again, in those patients who did not have asthma and had a blood eosinophil count <600 had fewer exacerbations with the LABA/LAMA than with ICS/LABA. As of now, there are no published trial comparing triple therapy to LABA/LAMA. The new triple therapies of ICS/LABA/LAMA have been found superior to ICS/LABA alone[29, 30] or to LAMA alone[31]; albeit initial results released of the IMPACT[32] trial of triple vs LABA/LAMA appear to indicate an improvement in lung function and health related quality of life[33].

Algorithms have been created to attempt to assist physicians to progressively and safely reduce the ICS dose in the not uncommon situation of patients with COPD who may not be needing/benefiting from the ICS component of therapy[34]. See: Applying the wisdom of stepping down inhaled corticosteroids in patients with COPD: a proposed algorithm for clinical practice.

What else can/should we do for our COPD patients?

While the focus of this article was on what is new in pharmacotherapy, we must recognize that this is only part of patient care. The care of the COPD patient requires a holistic approach to non-pharmacologic therapies that include smoking cessation, vaccination for influenza and pneumonia (covered in another article in this edition), nutritional advice and pulmonary rehabilitation. In addition, mortality is frequently related to other conditions, so evaluation and management of comorbidities such as cardiovascular disease, hyperlipidemia, diabetes and osteoporosis can improve outcomes. Screening for, and managing mood and anxiety can improve patients' quality of life considerably; all beyond just the management of the lung disease.

Conclusion

The plethora of new therapies available has created some confusion for clinicians. While there are many choices, two basic premises remain for pharmacotherapy. Give sufficient bronchodilation be it a short acting, long acting or two long-acting medications. Attempt to reduce exacerbation frequency by appropriate additional anti-inflammatory therapies with ICS or Roflumilast. Learn how to use the new devices, and take the time to give your patients a choice, because patient comfort with their devices improves adherence[35] and subsequently outcomes. For patient resources go to the Ontario Lung Association website.

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