

<p>What is COPD?</p> <ul style="list-style-type: none"> Progressive, partially reversible airway limitation Damage to the walls of the airways → reduced elasticity → reduced ability of patient to exhale. 4th leading cause of death in Canada; prevalence ~5%. Primary cause (85% of cases) is smoking. An estimated 15-20% of smokers develop COPD. 	<p>Symptoms: Cardinal triad: dyspnea, chronic cough, and sputum production. Dyspnea is typically progressive, worsens with exercise, persistent; described as gasping.</p> <p>Definitions: Emphysema describes damage to the alveoli. Chronic bronchitis is defined by increased cough and sputum. Most COPD patients have features of both.</p> <p>Diagnosis: Spirometry post-bronchodilator FEV₁/FVC < 0.7</p>	<p>Indicators: symptoms (dyspnea, cough, sputum), smoking history (10-20 pack-years or more), family history of COPD, environmental exposure to dust/chemicals. Screen for α₁-antitrypsin deficiency in select patients (e.g. if atypical features, disease onset <45 years).</p> <p>Goals of therapy: ↓ dyspnea, ↑ exercise tolerance, ↑ quality of life, & ↓ complications such as exacerbations & cor pulmonale.</p> <p>Comorbidities: common, especially depression and CV disease.</p>
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Therapeutic Pearls / Nonpharmacologic Approach FOR ALL PATIENTS	
<ul style="list-style-type: none"> An estimated 50% of patients are non-adherent to COPD therapy and 50% of patients cannot demonstrate proper inhaler technique! Reassess at every visit. Establish individualized action plan e.g. www.copdactionplan.com/1408_THOR_ActionPlan_v2.pdf Pulmonary rehab has large benefits (NNT=4 to prevent one hospitalization in patients with recent exacerbation).¹² Tai Chi or yoga may also be effective.^{85,86} 	<ul style="list-style-type: none"> Encourage smoking cessation. Benefits (40% ↓ in both death & rate of lung function decline) apparent even in severe COPD ("never too late to quit!"). Annual influenza vaccine ↓ death by ≤50% and hospitalizations by ≤40%. Also give COVID-19 vaccine. Pneumococcal vaccine ↓ pneumonia (NNT=21) and ↓ exacerbations (NNT=8).³⁰ Give PNEUMOVAX-23 x 1. If age >65, consider PREVNAR-13 X ⊗, then PNEUMOVAX-23 8-52wks later.^{NACI}

An Approach to Therapy. Escalate therapy as needed to control symptoms & exacerbations, but check inhaler technique first. If no exacerbations for 2yrs and/or eosinophils <300, option to taper ICS (& follow-up).⁹³⁻⁹⁵

Pharmacotherapy		Comments and Clinical Pearls
Step 1	ipratropium, salbutamol, or terbutaline (short-acting bronchodilators)	<ul style="list-style-type: none"> See next page for available agents: short-acting bronchodilators, LAMAs, LABAs, LAMA/LABA combos, LABA/ICS combos, and LAMA/LABA/ICS combos. In general, COPD agents appear to show a class effect;³⁶ however, see Table 2 below on how to pick an agent within a class. Short-acting bronchodilators are often <u>scheduled</u> in Step 1. As therapy escalates, continue to prescribe <u>as-needed</u> for symptom relief. COMBIVENT (salbutamol + ipratropium) also a reasonable choice anytime a short-acting bronchodilator would be useful. Starting at Step 2 or Step 3 often appropriate (e.g. based on severity of symptoms or risk of exacerbation), but note that some drug plans require trials of short-acting agents before long-acting agents are covered. If history of asthma, start an ICS early (but do not use ICS monotherapy). A LABA rather than LAMA can be used for Step 2, but a LAMA has potentially ↑ efficacy & tolerability (see info box below).^{POET} Before escalating therapy, review inhaler technique. Up to 50% of patients have inappropriate technique.³¹ Consider referral to a pharmacist or COPD Educator. Teaching sheets at rxfiles.ca. Patient handouts at www.lungsask.ca/lungs/programs-support/inhaler-resources. Inhaled corticosteroids are typically added last due to ↑AE (e.g. ↑pneumonia risk ~2% per year).^{TORCH, FLAME, IMPACT} Evidence is conflicting for ICS efficacy: results of the WISDOM trial suggested ICS had little benefit; IMPACT and ETHOS showed ↓exacerbations, but had methodology issues (e.g. NNT=36,³² but 70-80% of control had ICS abruptly stopped on enrollment, and asthmatics not excluded). High-dose no better than low-dose for ↓exacerbations.^{ETHOS} When adding an ICS, consideration may be given to using an ICS-combo product approved in COPD (rather than an ICS-alone asthma product). The rationale is to prevent patients from accidentally staying adherent to only ICS monotherapy (which has ↑ mortality risk in COPD).^{TORCH}
Step 2	LAMA (or LABA) (long-acting bronchodilator)	
Step 3	LAMA + LABA ("dual therapy") ^{FLAME}	
Step 4	LAMA + LABA + ICS ("triple therapy") ^{IMPACT}	
Specialist Referral	O ₂ if severely hypoxic; ⁴² theophylline or roflumilast; azithromycin; ³⁷ noninvasive ventilation NNT=3; ⁴⁰ n-acetylcysteine NNT=8. ⁴¹	Consider specialist referral if: diagnostic uncertainties; symptoms are disproportionate to FEV ₁ ; α ₁ antitrypsin deficiency; accelerated lung function decline; symptoms and/or exacerbations are severe or recurrent; respiratory failure; onset is at < age 35; need for surgery/O ₂ /pulmonary rehab.

FEV ₁	mMRC	COPD Stage	Symptom/Disability	Table 1. Should I choose a LAMA or a LABA?
≥ 80%	0	At Risk	Not troubled by breathlessness except with strenuous exercise.	Both will improve symptoms; LAMAs (tiotropium) may be superior in ↓ exacerbations (but unclear if this applies to newer agents). LAMAs may also be better tolerated than LABAs (↓ withdrawal in RCTs). ⁸ Often in clinical practice, LAMAs are the preferred starting point.
	1	Mild	Short of breath when hurrying on the level or walking up a slight hill.	
50-79%	2	Moderate	Walks slower than most people of the same age on the level because of breathlessness, or has to stop for breath when walking at own pace on the level.	Table 2. Which LAMA / which LABA should I choose? ① Consider available devices. Some require more inspiratory effort; some are more difficult to manipulate. See page 208 & Geri-Rxfiles: Hands vs Lungs . ② Consider adherence (e.g. once vs twice daily regimens). ③ Consider onset of action (see next page). If a patient frequently makes mistakes, re-educate or choose an alternate device.
	3		Stops for breath after walking about 100 meters (~ 1 block) or after a few minutes on the level.	
30-49%	4	Severe	Too breathless to leave the house, or breathless when dressing or undressing.	
< 30%		Very Severe		

Table 3. Management of AECOPD: acute worsening of symptoms over >48 hours. DECAF score: predicts hospital mortality (useful calculator at mdcalc.com).		
<p>① Initiate scheduled salbutamol +/- ipratropium.³⁵ Long-acting inhalers can be continued but should not replace short-acting bronchodilators.</p>	<p>② Initiate prednisone 30-50mg po daily x 5 REDUCE to 10 days. Consider a longer duration & taper if ≥ 3 steroid courses in last year.⁹⁷</p>	<p>③ Add antibiotic x 5-7 days if both change in sputum purulence (colour) AND at least one of increased sputum volume or increased dyspnea vs baseline. Antibiotics should also be strongly considered if pt requires hospitalization. Some early evidence suggests patients with a CRP level <20mg/L may not benefit from antibiotics.³⁸ Antibiotic choice <u>for low risk pts</u>: amoxicillin, doxycycline, TMP/SMX, clarithromycin, azithromycin, cefuroxime, or cefprozil; <u>for high risk pts</u>: amoxi-clav, levofloxacin, or moxifloxacin (high risk = severe COPD, CAD, chronic steroids, ≥ 4 exacerbations/yr, home oxygen, or recent antibiotics).</p>

Table 4. Prevention of AECOPD.
Optimization and adherence to meds; vaccinations (influenza, pneumococcal); avoid environmental triggers ; ⁹⁶ smoking cessation; pulmonary rehab .

AECOPD=acute exacerbation of COPD COPD=chronic obstructive pulmonary disease CRP=C-reactive protein DPI=dry powder inhaler FEV₁=forced expiratory volume in 1 second FVC=forced expiratory vital capacity ICS=inhaled corticosteroid LABA=long-acting Beta2-Agonist LAMA=long-acting muscarinic antagonist mMRC=modified Medical Research Council dyspnea scale NIV=noninvasive ventilation SABA=short-acting Beta2-Agonist SAMAs=short-acting muscarinic antagonist TMP/SMX=trimethoprim/sulfamethoxazole

	Generic/TRADE	Usual Dose [Max Daily Dose]	Comments / Adverse Events AE / Drug Interactions DI / Monitoring M	\$/30 day	
Anticholinergics	Short-Acting Muscarinic Antagonist (SAMA): binds unselectively to pulmonary muscarinic receptors, reducing smooth muscle contraction. Duration 4-6 hours. Option in mild COPD, or as prn add-on to LAMAs/LABAs.				
	Ipratropium ATROVENT 20mcg MDI; 250 mcg/1mL, 500 mcg/2mL nebs; inhalation soln (for dilution)	MDI: 40mcg (2 puffs) inhaled TID-QID [12 puffs/day] Neb: 500mcg (1 neb) inhaled TID-QID [2000mcg]	<ul style="list-style-type: none"> Improves COPD symptoms; does not reduce exacerbations. Onset <20 min. AE similar to LAMA; ↓ incidence of dry mouth vs tiotropium (less potent). Avoid eye contact (can precipitate acute glaucoma) – especially with nebs. DI: OATP1B1/1B3 (see pg 219) 	\$ 49 \$ 116 neb	
	Long-Acting Muscarinic Antagonist (LAMA): slow to dissociate from pulmonary M ₃ receptors = long-lasting ↓ in smooth muscle contraction. For mod-sev COPD, or after SABA +/- SAMA failure. Tiotropium, glycopyrronium: may accumulate in renal impairment; clinical significance unknown. Acridinium, umeclidinium: not renally eliminated. (USA: Revenfenacin YUPELRI 175ug neb daily, Glycopyrrolate LONHALA MAGNAIR 25 mcg neb bid)				
	Tiotropium SPIRIVA 18mcg cap; 2.5mcg soft mist	HandiHaler: 18mcg (1 cap) inhaled once daily SWALLOW UPLIFT Respimat: 5mcg (2 puffs) inhaled once daily	<ul style="list-style-type: none"> Tiotropium: may ↓ COPD exacerbations by 20-30%/yr. Other LAMAs appear similar. AE: dry mouth, cough, constipation, urinary retention, headache. 	\$ 69 \$ 69	
	Acridinium TUDORZA 400mcg DPI	Genuair: 400mcg (1 puff) inhaled BID ASCENT-COPD: NS for cardiovascular events	Avoid eye contact. Rinse mouth after inhalation to ↓ dry mouth AE.	\$ 68	
	Glycopyrronium SEEBRI 50mcg cap	Breezhaler: 50mcg (1 cap) inhaled once daily SWALLOW GLOW	Glycopyrronium < dry mouth vs tiotropium, but URTI and UTI. GLOWS	\$ 68	
Umeclidinium INCRUSE 62.5mcg DPI	Ellipta: 62.5mcg (1 puff) inhaled once daily	• Fastest onset: glycopyrronium (<15 min).	\$ 65		
Sympathomimetics	Short-Acting Beta₂-Agonist (SABA): binds to β ₂ pulmonary receptors, which ↑ cAMP; cAMP responsible for the relaxation of bronchial smooth muscle. Option in mild COPD, or as prn add-on to LAMAs/LABAs.				
	Salbutamol VENTOLIN, g 100mcg MDI; 200mcg DPI X ▼; 1.25, 2.5, & 5 mg/2.5mL nebs; inhal'n soln	MDI: 100-200mcg (1-2 puffs) inhaled QID prn [800mcg] Diskus: 200mcg (1 puff) inhaled QID prn [800mcg] Neb: 2.5mg inhaled QID prn [15mg]	<ul style="list-style-type: none"> Improves COPD symptoms; does not reduce exacerbations. Useful as "rescue" therapy due to short onset (salbutamol <5 min; faster than SAMA). AE: tremor, ↑ nervousness, ↑ HR (esp. neb), ↑QT, headache. 	\$ 17 \$ 34 \$ 58 neb	
	Terbutaline BRICANYL 500mcg DPI	Turbuhaler: 500mcg (1 puff) inhaled QID prn [3000mcg]	At high doses: ↓ K ⁺ , ↑ insulin secretion	\$ 22	
	Long-Acting Beta₂-Agonist (LABA): slow to dissociate from pulmonary β ₂ receptors, resulting in long-lasting bronchodilation. For mod-severe COPD, or use after SABA +/- SAMA failure.				
	Formoterol OXEZE, FORADIL 12mcg caps ♀ ♀; 6mcg, 12mcg DPI ♀ ♀	Turbuhaler: 6-12mcg inhaled BID [48mcg] Aerolizer: 12mcg (1 cap) inhaled BID SWALLOW	<ul style="list-style-type: none"> LAMA vs LABA: both first line COPD therapy, but often use LAMA first. Tiotropium shown to have greater reduction in exacerbations than salmeterol. POET unclear whether this is a class effect. LAMAs may have ↑ tolerability vs LABAs (less discontinuation). 	\$ 69 \$ 63	
	Salmeterol SEREVENT 50mcg DPI ♀ ♀	Diskus: 50mcg (1 puff) inhaled BID	• AE: tremor, ↑ HR. Similar AE to SABAs, but less substantial. Indacaterol: 18% incidence of cough following inhalation; INLIGHT may lessen after 1 week.	\$ 78 \$ 61	
Indacaterol ONBREZ USA: Arcapta Neohaler 75mcg cap ♀ ♀	Breezhaler: 75mcg (1 cap) inhaled once daily SWALLOW	• Fastest onset: indacaterol, formoterol, olodaterol, and vilanterol (<5 min).	USA only		
Olodaterol STRIVERDI 2.5mcg soft mist X ⊗	Respimat: 5mcg (2 puffs) inhaled once daily				
Combinations	SAMA + SABA combination: useful as prn therapy in any stage of COPD, and for management of acute exacerbations of COPD (see Table 3).				
	Ipratropium + Salbutamol COMBIVENT 0.5+2.5mg/2.5mL nebs; 20+100mcg soft mist	Respimat: 20/100mcg (1 puff) inhaled QID prn [6 puffs] Neb, g: 0.5/2.5mg (1 neb) inhaled QID prn [4 nebs]	<ul style="list-style-type: none"> In AECOPD: use high dose; may continue long-acting agents; ^{GOLD 2023} limited evidence for combination over a single agent (but commonly used) 	\$ 44 \$ 116 neb	
	LAMA + LABA combination: aka "Dual Therapy". Decreased cost & ↑ convenience vs using a LAMA + LABA in separate inhalers. {Glycopyrrolate + Formoterol} ^{Besvespi} FDA: 2 MDI inhalations BID				
	Acridinium + Formoterol DUAKLIR 400+12mcg DPI ♀ ▼	Genuair: 400/12mcg (1 puff) inhaled twice daily	<ul style="list-style-type: none"> Choose LAMA+LABA over LABA+ICS: ↓ exacerbations & ↓ pneumonia. FLAME Escalating to dual therapy reasonable if poorly controlled on a single agent (although may not be significantly better than LAMA alone).²⁵ 	\$ 76	
	Glycopyrronium + Indacaterol ULTIBRO 50+110mcg DPI ♀ ▼	Breezhaler: 50/110mcg (1 cap) inhaled daily SWALLOW USA: Utilibron		\$ 98	
	Tiotropium + Olodaterol INSPIOLTO 2.5+2.5mcg soft mist ♀ ▼	Respimat: 5/5mcg (2 puffs) inhaled once daily. USA: Stiolto		\$ 77	
	Umeclidinium + Vilanterol ANORO 62.5+25mcg DPI ♀ ▼	Ellipta: 62.5/25mcg (1 puff) inhaled once daily		\$ 99	
	LABA + Inhaled Corticosteroid (ICS) combination: useful as part of triple therapy in severe COPD with frequent exacerbations; withdrawal of ICS an option in some. ^{WISDOM} If using LABA/ICS, ensure LAMA also on board.				
	Formoterol + Budesonide SYMBICORT 6+100, 6+200 mcg DPI ♀ ♀	Turbuhaler: 12/400mcg (2 puffs) inhaled BID [24/800mcg]	<ul style="list-style-type: none"> Inhaled corticosteroids are typically added last in COPD due to risk of AE. LAMA/LABA superior to LABA/ICS. FLAME LAMA as good as LABA/ICS. INSPIRE Avoid ICS monotherapy: increases mortality NNH=87/yr vs LABA+ICS. TORCH Some suggestion that pts with blood eosinophils ≥ 300 may receive greatest benefit from ICS, but evidence limited to subgroup analyses and limited testing in RCTs. ³² CORTICO-COP 	\$ 114	
	Formoterol + Mometasone ZENHALE DULERA 5+50; 5+100, 5+200 mcg MDI ♀ asthma ♀ asthma	MDI: 10/200mcg (2 puffs) inhaled BID Not officially approved for COPD	<ul style="list-style-type: none"> AE of ICS: thrush 5% & hoarseness 5% (dose related: rinse mouth [swish & spit] after use; add a spacer when using an MDI), ↑ risk of pneumonia ~2%/yr see Online Extras , may ↑ risk of tuberculosis,⁴⁶ may ↑ osteoporosis/fractures, ~cataracts/glaucoma.⁴⁵ BREO: fluticasone furoate = more potent/longer lasting vs fluticasone propionate. 	\$ 132	
Salmeterol + Fluticasone propionate ADAIR 50+100, 50+250, 50+500 mcg DPI ♀ ♀	Diskus, g: 50/250mcg (1 puff) inhaled BID [100/1000mcg] (ADVAIR MDI 25+125, 25+250mcg not officially COPD approved)	\$ 66-89 g \$ 128-177			
Vilanterol + Fluticasone furoate BREO 25+100mcg DPI ♀ ♀ (25+200 mcg asthma ♀ ♀)	Ellipta: 25/100mcg (1 puff) inhaled once daily SUMMIT	\$ 108			
LABA + LAMA + ICS combination: aka "Triple Therapy". Reserve use for failure of Dual Therapy. May also use LAMA + LABA/ICS combo (agents above). Withdrawal of ICS an option in some ^{WISDOM}					
Umeclidinium + Vilanterol + Fluticasone furoate TRELEGY 62.5+25+100mcg DPI ♀ ♀	Ellipta: 62.5/25/100 mcg ^{62.5/25/200 mcg X ⊗} (1 puff) once daily	• ↑ risk of pneumonia vs LAMA/LABA combo (NNH=34/yr). ³²	\$ 160		
Glycopyrronium + Formoterol + Budesonide BREZTRI 8.2+5.8+182mcg MDI ♀ ♀	Aerosphere: 16.4/11.6/364 mcg (2 Inhalations) twice daily	• New	\$ 150		
Other	Other Agents Usually via specialist referral in severe or unresponsive COPD. Agents which are recommended in patients who are otherwise optimized: roflumilast (if chronic bronchitis & exacerbations, but expensive & many AE), n-acetylcysteine (if chronic bronchitis & exacerbations, but unpleasant smell), azithromycin e.g. 250mg 3x/week (if exacerbations, but potential hearing loss, ↑ QT & microbial resistance). ^{CTS 2019} Theophylline suggested to be unhelpful (low dose did not ↓ exacerbations). ^{TWCS}				
	Roflumilast DAXAS 500mcg tab X ⊗	500mcg po once daily	AE: diarrhea (NNH=15). ⁴⁸ nausea, HA, abd pain, ↓wt. Rare: depression/suicide, ↑AST. DI: ^{3A4,1A2} CBZ, phenobarb, phenytoin	\$ 90	
	Theophylline LA/SR, ER, UNIPHYL, THEO 100, 200, 300, (400, 600mg) UNIPHYL ER tabs	200-400mg ER po daily	Infrequently used due to AE/toxicity/DI. AE: ↑ HR, nausea, tremor M: HR, CNS effects (insomnia , irritability), serum levels (<83 μmol/L)	DI: CYP 3A4,1A2: ↓theo: CBZ, phenytoin, rifampin, smoking ↑theo: allopurinol, cimetidine , ciprofloxacin, erythromycin, febusostat, flvoxamine, norfloxacin, verapamil. Also alcohol & propranolol.	\$ 17-22
	N-Acetylcysteine (NAC) 500, 600, 900, 1000mg tab ^{OTC X ⊗, \$12-40 Health Stores} ; 600mg po BID ^{\$100}		AE: Well-tolerated. GI 2-6% (N/V/D, epigastric pain), headache, joint pain, hives. DI: nitroglycerin (can cause hypotension, severe headache).		

⊗=Do not ♀=EDS X=Non Formulary Sask ♀=prior approval NIHB ⊗=not covered by NIHB AECOPD=acute exacerbation of COPD CNS=central nervous system COPD=chronic obstructive pulmonary disease DPI=dry powder inhaler FEV₁=forced expiratory volume in 1 second HA=headache HR=heart rate inhal'n soln=inhalation solution MDI=metered dose inhaler PDE=phosphodiesterase URTI=upper respiratory tract infection UTI=urinary tract infection