COPD Update: Focus on Intensifying LABA, LAMA and ICS Therapy

B.C. Provincial Academic Detailing Service **February 2017**

Background

In Canada, approximately 20 inhaled medications are approved to treat Chronic Obstructive Pulmonary Disease (COPD). Numerous clinical practice guidelines addressing the management of COPD are available. They provide treatment recommendations that involve a stepwise intensification of drug therapy in people with persistent breathlessness or exacerbations.

To provide drug information that supplements these recommendations, participants in this PAD education session will have the opportunity to discuss:

- The effect of intensifying inhaled therapies on health-related quality of life, the risk of exacerbations, and the risk of death (ie, when progressing to double or triple therapy);
- Relevant clinical considerations when prescribing and monitoring patients receiving inhaled therapies;
- Comparative efficacy and safety, dosing, and costs of inhaled therapies;
- Advantages and disadvantages of various inhaler devices.

COPD Inhaled Medications	
Class	**Medication (Brand Name, *Inhaler Device*)**
SABA	salbutamol (Ventolin HFA *MDI*, Airomir *MDI*, Ventolin *Diskus*) terbutaline (Bricanyl *Turbuhaler*)
SAMA	ipratropium (Atrovent HFA *MDI*)
SAMA+SABA	ipratropium + salbutamol (Combivent *Respimat*)
LABA	formoterol (Foradil *Aerolizer*) indacaterol (Onbrez *Breezhaler*) salmeterol (Serevent *Diskus*, Serevent *Diskhaler*)
LAMA	aclidinium (Tudorza *Genuair*) glycopyrronium (Seebri *Breezhaler*) tiotropium (Spiriva *HandiHaler*, Spiriva *Respimat*) umeclidinium (Incruse *Ellipta*)
LAMA+LABA	aclidinium + formoterol (Duaklir *Genuair*) glycopyrronium + indacaterol (Ultibro *Breezhaler*) tiotropium + olodaterol (Inspiolto *Respimat*) umeclidinium + vilanterol (Anoro *Ellipta*)
ICS+LABA	budesonide + formoterol (Symbicort *Turbuhaler*) fluticasone furoate + vilanterol (Breo *Ellipta*) fluticasone propionate + salmeterol (Advair *Diskus*)
SABA short acting beta$_2$ adrenergic agonist; **SAMA** short acting muscarinic antagonist **LABA** long acting beta$_2$ adrenergic agonist; **LAMA** long acting muscarinic antagonist **ICS** inhaled corticosteroid	

What is the applicability of the clinical trial evidence for LABA, LAMA and ICS in COPD?

- Participants in COPD clinical trials are, on average, in their early to mid-sixties, more often male than female, have moderate to severe disease determined by spirometry, and are current or former smokers.[1,2]
- People with asthma, a recent COPD exacerbation or respiratory tract infection (eg, within 4 to 6 weeks), or those receiving supplemental oxygen are commonly excluded from clinical trials.[1]

What effect does intensifying therapy in COPD have on health-related quality of life?

There is an absence of high-quality evidence regarding the effect of intensifying inhaled therapy (ie, progressing to LAMA+LABA) on health-related quality of life.

- Health-related quality of life might be measured in COPD trials using the St. George's Respiratory Questionnaire (SGRQ).[3] This patient-reported outcome measures the effect of an intervention on symptoms, activity and psychosocial impacts.[3] In this questionnaire, the total score ranges from 0 (perfect health) to 100 (most severe health status) with lower scores indicating better quality of life.[1]
- In people with persistent breathlessness, the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends the following:[4]
  1. monotherapy: LABA or LAMA (no preference stated)
  2. progression to double therapy: LAMA+LABA (addition of a second long-acting bronchodilator)
- Note, GOLD maintains a role for short-acting bronchodilators in people with occasional dyspnea.[4]

Table 1: Relevant Evidence from Cochrane Systematic Reviews: SGRQ mean difference

LABA vs PLACEBO[5]	Effect of LABA compared to placebo		26 RCTs, N=14,939
2.32 unit improvement	95%CI 3.09 lower to 1.54 lower; 16 months	Moderate quality	17 RCTs, N=11,397
LAMA vs PLACEBO[6]	Effect of tiotropium compared to placebo		22 RCTs, N=23,309
2.89 unit improvement	95%CI 3.35 lower to 2.44 lower; 3-48 months	High quality	9 RCTs, N=13,034
LAMA+LABA vs LAMA[7]	Effect of adding LABA to tiotropium		10 RCTs, N=10,894
1.34 unit improvement	95%CI 1.87 lower to 0.80 lower; 3-12 months	Moderate quality	5 RCTs, N=6709
LAMA+LABA vs LABA[7]	Effect of adding tiotropium to LABA		4 RCTs, N=3378
1.25 unit improvement	95%CI 2.14 lower to 0.37 lower; 3-12 months	Moderate quality	4 RCTs, N=3378

Notes:
SGRQ outcome responder analyses Cochrane reviews may also report the numbers of people with ≥ 4 unit change in SGRQ score[5,6,7]
SGRQ outcome study limitations Cochrane network meta-analysis evaluated LABA, LAMA, ICS, ICS+LABA effect on SGRQ; 71 RCTs were identified (N=73,062) and 42 RCTs provided SGRQ data (N=54,613); incomplete outcome data & selective outcome reporting were judged by the Cochrane authors to be the most common RCT methodological limitations (approximately 40% of RCTs unclear or high risk of bias)[1]
Placebo other COPD medications permitted (eg, salbutamol) as long as they were not one of the randomized treatments
RCTs randomized controlled trials; **N** number of participants; **95%CI** 95% confidence interval
High quality evidence Cochrane authors are very confident that the true effect lies close to the estimate of the effect
Moderate quality evidence Cochrane authors are moderately confident that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
LAMA+LABA provided as separate inhalers;[7] LAMA+LABA provided as combination inhaler Cochrane review is at the protocol stage[8]

Making clinical decisions regarding a symptomatic response

- The 2016 GOLD COPD guideline includes the following questions which may be useful when deciding with a patient whether they have experienced a meaningful symptomatic response:[9]

> Have you noticed a difference since starting this treatment?
> If you are better:
> - Are you less breathless?
> - Can you do more?
> - Can you sleep better?
>
> Is that change worthwhile to you?

- The 2017 GOLD COPD guideline now includes recommendations for stopping therapies when there is an inadequate symptomatic response.[4] For example, if the combination of LAMA+LABA does not improve dyspnea, consider stepping down to a single bronchodilator.[4]

What effect does intensifying therapy in COPD have on the risk of exacerbation or death?

There is an absence of high-quality evidence regarding the effect of intensifying inhaled therapy (ie, progressing to LAMA+LABA and LAMA+LABA+ICS) on the risk of COPD exacerbation and death.

- In people with persistent exacerbations (defined by GOLD as: ≥ 2 exacerbations per year or 1 leading to hospitalization), the 2017 GOLD COPD guideline recommends the following:[4]
  1. monotherapy: LAMA (rather than LABA)
  2. progression to double therapy: LAMA+LABA (rather than ICS+LABA, unless asthma diagnosis)
  3. progression to triple therapy: LAMA+LABA+ICS (addition of ICS to LAMA+LABA)

Table 2: Relevant Evidence from Cochrane Systematic Reviews: Exacerbations, Total Mortality

LAMA vs PLACEBO[6]	Effect of tiotropium compared to placebo		22 RCTs, N=23,309
Exacerbations: number of people with one or more	PLACEBO = 44 per 100 vs LAMA = 38 per 100		3-48 months (range)
	OR 0.78, 95%CI 0.70-0.87 SS	High quality	22 RCTs, N=23,309
Mortality (all cause)	OR 0.98, 95%CI 0.86-1.11 NSS	Moderate quality	22 RCTs, N=23,309
LAMA vs LABA[10]	Effect of tiotropium compared to LABA		7 RCTs, N=12,223
Exacerbations: number of people with one or more	LABA = 29 per 100 vs LAMA = 26 per 100		3-12 months (range)
	OR 0.86, 95%CI 0.79-0.93 SS	Moderate quality	6 RCTs, N=12,123
Mortality (all cause)	OR 0.82, 95%CI 0.60-1.13 NSS	Very low quality	6 RCTs, N=12,123
LAMA+LABA vs LAMA[7]	Effect of adding LABA to tiotropium		10 RCTs, N=10,894
Exacerbations: number of people with one or more	RCTs were not pooled	Ungraded	3-12 months (range) 7 RCTs, N=6391
Mortality (all cause)	OR 1.24, 95%CI 0.81-1.90 NSS	Low quality	8 RCTs, N=9633
LAMA+LABA+ICS vs LAMA+LABA[11]	Effect of adding ICS to tiotropium + LABA		1 RCT, N=293
Exacerbations: number of people with one or more	LAMA+LABA = 65 per 100 vs triple = 60 per 100		12 months
	OR 0.81, 95%CI 0.51-1.30 NSS	Ungraded	1 RCT, N=293
Mortality (all cause)	OR 1.02, 95%CI 0.32-3.24 NSS	Ungraded	1 RCT, N=293

Notes:
Exacerbation outcome COPD exacerbations are not consistently defined, counted, analyzed in clinical trials which affects interpretability[12-14]
Placebo other COPD medications permitted (eg, salbutamol) as long as they were not one of the randomized treatments
RCTs randomized controlled trials; **N** number of participants; **OR** odds ratio; **95%CI** 95% confidence interval
SS statistically significant difference; **NSS** not statistically significantly different
High quality evidence Cochrane authors are very confident that the true effect lies close to the estimate of the effect
Moderate quality evidence Cochrane authors are moderately confident that the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low quality evidence Cochrane authors' confidence in the effect estimate is limited, the true effect may be substantially different
Very low quality evidence Cochrane authors have very little confidence in the effect estimate, the true effect is likely substantially different
LAMA+LABA provided as separate inhalers;[7] LAMA+LABA provided as combination inhaler Cochrane review is at the protocol stage;[8] results for the exacerbation outcome were not pooled in the LAMA+LABA vs LAMA comparison due to heterogeneity between the studies, however the number of people with exacerbations was not reduced in the 3 subgroups (formoterol, olodaterol, or salmeterol when added to tiotropium)[7]
LAMA+LABA+ICS triple therapy provided as ICS+LABA (combination inhaler) + LAMA (second inhaler);[11] Cochrane authors did not grade the quality of evidence but conclude that there were not enough patients to draw firm conclusions;[11] Cochrane review of triple therapy provided as LAMA+LABA (combination inhaler) + ICS (second inhaler) did not identify any relevant studies[15]

ICS+LABA vs LABA[16]	Effect of adding ICS to LABA		14 RCTs, N=11,794
Exacerbations: number of people with one or more	LABA = 47 per 100 vs ICS+LABA = 42 per 100		12 months (median)
	OR 0.83, 95%CI 0.70-0.98 SS	Moderate quality	6 RCTs, N=3357
Mortality (all cause)	OR 0.92, 95%CI 0.76-1.11 NS	Moderate quality	10 RCTs, N=10,681

Notes:
ICS+LABA provided as combination inhaler twice daily;[16] the exacerbation outcome does not include TORCH 2007 (N=6184) or SUMMIT 2016 (N=16,590);[17,18] the mortality outcome does not include SUMMIT 2016 (N=16,590)[18]
ICS+LABA vs LAMA+LABA Cochrane review is at the protocol stage[19]
ICS+LABA once daily vs LABA Cochrane review is at the protocol stage[20]
ICS+LABA twice daily vs tiotropium Cochrane authors conclude that the relative efficacy & safety of ICS+LABA vs tiotropium is uncertain[21]
ICS+LABA once daily vs LAMA Cochrane review is at the protocol stage[22]

Specific Considerations: Contraindications, Precautions, Adverse Events, Drug Interactions

Specific Considerations serves to emphasize current clinically relevant drug information and is not intended to replace comprehensive prescribing information accessible from Health Canada's Drug Product Database: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php.

LONG ACTING BETA$_2$ AGONISTS (LABA)

- **Health Canada COPD LABA indication** maintenance bronchodilator treatment; not indicated for relief of acute symptoms in COPD[1-10]
- **2016 comparative effectiveness review** no consistent differences identified in benefit or harm outcomes within the LABA class[11]
- **discontinue regularly scheduled short-acting bronchodilator** use a short-acting bronchodilator (ie, SABA) as needed for acute symptoms[1-10,12]
- **dose response** relatively flat dose-response curve for bronchodilation (FEV_1 change) in stable COPD[13]
- **sympathomimetic effects** emphasis on dosage limits in people vulnerable to cardiovascular or central nervous system effects (eg, increased heart rate, cardiac contractility, tremor) in conditions such as ischemic heart disease, coronary insufficiency, cardiac arrhythmias, hypertension, convulsive disorders, thyrotoxicosis[1-10]
- **QTc interval prolongation** formoterol, olodaterol, salmeterol, vilanterol listed by CredibleMeds® as Drugs to Avoid in Congenital Long QT Syndrome (indacaterol not yet assessed);[14] caution concomitant use of other medications known to prolong QT interval, see https://www.crediblemeds.org/[14]
- **electrolytes** may decrease serum potassium, caution with medications that potentiate effect of potassium loss[1-7,9,10]
- **cough (indacaterol)** sporadic cough within 15 seconds of inhalation typically lasting for 5 seconds (14% of patients)[2]
- **selected drug interactions** strong cytochrome P450 3A4 inhibitors+salmeterol (including specific anti-retrovirals, azole antifungals, macrolides);[15] beta blockers Cochrane review of cardioselective beta blockers (eg, acebutolol, atenolol, bisoprolol, metoprolol) did not identify an adverse effect on FEV_1 response in people with COPD receiving inhaled beta$_2$ agonists[16]

LONG ACTING MUSCARINIC ANTAGONISTS (LAMA)

- **Health Canada COPD LAMA indication** maintenance bronchodilator treatment; not indicated for relief of acute symptoms in COPD[1-9]
- **2016 comparative effectiveness review** no consistent differences identified in benefit or harm outcomes within the LAMA class[10]
- **discontinue regularly scheduled short-acting bronchodilator** use a short-acting bronchodilator (ie, SABA) as needed for acute symptoms[1-9,11]
- **dose response** relatively flat dose-response curve for bronchodilation (FEV_1 change) in stable COPD[12]
- **antimuscarinic (anticholinergic) effects** dry mouth, blurred vision, gastrointestinal motility disorders; caution in patients with urinary retention, narrow-angle glaucoma (avoid contact with eyes)[1-9]
- **cardiovascular effects** atrial fibrillation, tachycardia; caution in patients with unstable ischemic heart disease, arrhythmia, heart failure[1-5]
- **tiotropium: mortality, exacerbations and inhaler device**
  - mortality: tiotropium versus placebo (Cochrane review subgroup analysis by inhaler device)[13]
    - tiotropium dry powder inhaler versus placebo: OR 0.92, 95%CI 0.80 to 1.05 (19 RCTs; 16,787 participants)
    - tiotropium soft mist inhaler versus placebo: OR 1.47, 95%CI 1.04 to 2.08 (3 RCTs; 6522 participants)
  - mortality & exacerbations: tiotropium soft mist inhaler versus tiotropium dry powder inhaler (TIOSPIR; 17,183 participants; no placebo group)[14]
    - tiotropium 2.5 mcg and 5 mcg soft mist inhaler non-inferior for risk of death versus tiotropium 18 mcg dry powder inhaler
    - tiotropium 5 mcg soft mist inhaler not superior for risk of exacerbation versus tiotropium 18 mcg dry powder inhaler
    - 2014 U.S. Food and Drug Administration advisory committee mixed vote (9 yes, 4 no) that the TIOSPIR trial adequately addresses potential adverse safety signal including mortality for tiotropium soft mist inhaler[15]
- **renal** glycopyrronium caution eGFR <30 mL/min, ESRD (Seebri Breezhaler, Ultibro Breezhaler);[2,7] tiotropium caution CrCl ≤50 mL/min (Spiriva HandiHaler, Spiriva Respimat, Inspiolto Respimat)[3,4,8]
- **selected drug interactions** antimuscarinics (anticholinergics) avoid co-administration with LAMA[16]

INHALED CORTICOSTEROIDS (ICS)

- **Health Canada COPD ICS+LABA indication** maintenance treatment,[1-3] moderate to severe COPD,[1] patients with persistent symptoms[1] and a history of exacerbations;[1,2] not indicated for the relief of acute symptoms in COPD[1-3]
- **2016 comparative effectiveness review** no consistent differences identified in benefit or harm outcomes between ICS+LABA combinations[4]
- **dose response**
  - fluticasone furoate+vilanterol (Breo Ellipta) → Health Canada COPD dose 100/25 mcg once a day, no additional benefit with 200/25 mcg dose[2]
  - fluticasone propionate+salmeterol (Advair Diskus, Advair MDI) → Health Canada COPD dose 250/50 mcg or 500/50 mcg twice daily, but U.S. Food and Drug Administration COPD dose only 250/50 mcg twice daily[3,5]
- **pneumonia** 2016 European Medicines Agency review of ICS and risk of pneumonia in people with COPD: affects between 1 and 10 patients in 100;[6] no conclusive evidence for difference in risk between ICS products;[6] inconsistent evidence for relationship to ICS dose[6]
  - risk factors for pneumonia: COPD exacerbation in previous year, FEV_1 <50% predicted, prior pneumonia, lower body mass index <25 kg/m^2, advancing age, and current smoker[2,7,8]
- **infection** caution in patients with fungal, bacterial, parasitic, tuberculosis infections of respiratory tract or ocular herpes simplex[1-3]
- **candidiasis** oral, pharyngeal, laryngeal;[1-3] may be helpful to rinse mouth & gargle with water (without swallowing), cleanse dentures[1-3]
- **esophageal** hoarseness, dysphonia, irritation[1-3]
- **ophthalmologic** increased intraocular pressure, glaucoma, cataracts[1-3]
- **fractures** Cochrane review of ICS versus placebo found no increase in risk of fractures in clinical trials of one year duration or longer: OR 1.00, 95%CI 0.75 to 1.32 (4 RCTs; 5226 participants);[9] Health Canada fluticasone furoate+vilanterol (Breo Ellipta) prescribing information reports increased risk of fracture in 12 month clinical trials (2 RCTs; 3255 participants): 2% of patients receiving ICS+LABA versus <1% of patients receiving LABA[2]
- **selected drug interactions** strong cytochrome P450 3A4 inhibitors (including specific anti-retrovirals, azole antifungals, macrolides): case reports of hypothalamic-pituitary-adrenal suppression secondary to increased corticosteroid systemic exposure[1-3,10]

Table 3: COPD Medication Inhaler Devices: Therapeutic Tips and Select Device Features[1-6]

- ✓ Whether developments in inhaler device technologies affect clinical outcomes is uncertain[1]
- ✓ Consider patient preference & ability to use (eg, cognition, manual dexterity, inspiratory effort)[2,3]
- ✓ Aim to keep the numbers of different devices to a minimum[4]
- ✓ Prescriptions should indicate medication name & strength, device name, numbers of inhalations per dose, and inhalation frequency[3]
- ✓ Include "Pharmacist to teach" on new inhaler device prescriptions
- ✓ Advise patients to return used or unwanted inhalers to their community pharmacy for recycling

Aerosols: hand breath coordination		**Dry powder inhalers: breath actuation**					
MDI	**Respimat**	**Turbuhaler**	**Diskus**	**Ellipta**	**Genuair**	**HandiHaler**	**Breezhaler**
Steady & deep inhalation Hand strength ± Spacer Temperature sensitive	Slow & deep inhalation Dose counter Cartridge: requires insertion Audible click: cartridge loaded Locks when empty Temperature sensitive	Strong & deep inhalation Dose counter Audible click: during dose loading process Moisture sensitive	Steady & deep inhalation Dose counter Audible click: dose is ready Moisture sensitive	Long, steady & deep inhalation Dose counter [large] Audible click: dose is ready Moisture sensitive	Strong & deep inhalation Dose counter Audible click: during dose inhalation Colour control window Locks when empty Moisture sensitive	Slow & deep inhalation Capsule [opaque] Dexterity Audible vibration: during dose inhalation Moisture sensitive	Rapid, steady & deep inhalation Capsule [clear] Dexterity Small device Audible whirring: during dose inhalation Moisture sensitive

Table 4: Inhaled Medications for COPD and Asthma in Canada

Medication	Brand Name, *Inhaler Device* Dose Per Inhalation	Health Canada Indication Usual Adult Dose		Medication Cost (without markup, professional fee)	BC PharmaCare Coverage	
					Regular Benefit	Limited Coverage
SABA Short Acting Beta$_2$ Agonist[1-4]						
salbutamol	Ventolin HFA *MDI* (100 mcg) Airomir *MDI* (100 mcg) generics	COPD	1-2 inh QID (max 8 inh/day)	$6.48 /200 inh generics	✓	
			1-2 inh PRN acute symptoms			
		Asthma	1-2 inh QID (max 8 inh/day)		✓	
			1-2 inh PRN acute symptoms			
	Ventolin *Diskus* (200 mcg)	COPD	1 inh every 4-6 hours (max 4 inh/day)	$12.50 /60 inh	non benefit	
			1 inh PRN acute symptoms			
		Asthma	1 inh every 4-6 hours (max 4 inh/day)		non benefit	
			1 inh PRN acute symptoms			
terbutaline	Bricanyl *Turbuhaler* (500 mcg)	COPD	1-2 inh PRN acute symptoms (max 6 inh/day)	$8.52 /100 inh	✓	
		Asthma			✓	
SAMA Short Acting Muscarinic Antagonist[5]						
ipratropium	Atrovent HFA *MDI* (20 mcg)	COPD	2-4 inh TID-QID (max 12 inh/day)	$21.05 /200 inh	✓	
SAMA+SABA Short Acting Muscarinic Antagonist + Short Acting Beta$_2$ Agonist[6]						
ipratropium + salbutamol	Combivent *Respimat* (20 mcg/100 mcg)	COPD	1 inh QID (max 6 inh/day)	$31.00 /120 inh	✓	
LABA Long Acting Beta$_2$ Agonist[7-10]						
formoterol	Foradil *Aerolizer* (12 mcg)	COPD	1-2 inh BID (max 48 mcg/day)	$54.58 /60 inh	non benefit	
		Asthma	1-2 inh BID (max 48 mcg/day) **add on to ICS**			✓
	Oxeze *Turbuhaler* (6 mcg)	Asthma	1 inh BID (max 48 mcg/day) **add on to ICS**	$36.35 /month		✓
	Oxeze *Turbuhaler* (12 mcg)			$48.39 /month		
indacaterol	Onbrez *Breezhaler* (75 mcg)	COPD	1 inh once a day	$50.22 /month		✓
salmeterol	Serevent *Diskus* (50 mcg)	COPD	1 inh BID	$62.41 /month		✓
		Asthma	1 inh BID **add on to ICS**			✓
	Serevent *Diskhaler* (50 mcg)	COPD	1 inh BID	$61.20 /month		✓
		Asthma	1 inh BID **add on to ICS**			✓
LAMA Long Acting Muscarinic Antagonist[11-15]						
aclidinium	Tudorza *Genuair* (400 mcg)	COPD	1 inh BID	$57.35 /month		✓
glycopyrronium	Seebri *Breezhaler* (50 mcg)	COPD	1 inh once a day	$57.35 /month		✓
tiotropium	Spiriva *HandiHaler* (18 mcg)	COPD	1 inh once a day	$56.06 /month		✓
	Spiriva *Respimat* (2.5 mcg)	COPD	2 inh once a day	$56.06 /month		✓
		Asthma	2 inh once a day **add on to ICS+LABA**		non benefit	
umeclidinium	Incruse *Ellipta* (62.5 mcg)	COPD	1 inh once a day	$54.00 /month		✓
LAMA+LABA Long Acting Muscarinic Antagonist + Long Acting Beta$_2$ Agonist[16-19]						
aclidinium + formoterol	Duaklir *Genuair* (400 mcg/12 mcg)	COPD	1 inh BID	$64.80 /month		✓
glycopyrronium + indacaterol	Ultibro *Breezhaler* (50 mcg/110 mcg)	COPD	1 inh once a day	$86.84 /month		✓
tiotropium + olodaterol	Inspiolto *Respimat* (2.5 mcg/2.5 mcg)	COPD	2 inh once a day	$65.78 /month		✓
umeclidinium + vilanterol	Anoro *Ellipta* (62.5 mcg/25 mcg)	COPD	1 inh once a day	$87.48 /month		✓

ICS+LABA Inhaled Corticosteroid + Long Acting Beta$_2$ Agonist[20-23]						
budesonide + formoterol	Symbicort *Turbuhaler* (100 mcg/6 mcg)	Asthma	SMT: 1-2 inh once a day or BID SMART: 1-2 inh BID or 2 inh once a day plus 1 inh PRN (max 8 inh/day)	$70.96 /120 inh		✓
	Symbicort *Turbuhaler* (200 mcg/6 mcg)	COPD	2 inh BID	$92.22 /month	non benefit	
		Asthma	SMT: 1-2 inh once a day or BID SMART: 1-2 inh BID or 2 inh once a day plus 1 inh PRN (max 8 inh/day)	$92.22 /120 inh		✓
fluticasone furoate + vilanterol	Breo *Ellipta* (100 mcg/25 mcg)	COPD	1 inh once a day	$88.78 /month		✓
		Asthma				✓
	Breo *Ellipta* (200 mcg/25 mcg)	Asthma	1 inh once a day	$139.04 /month		✓
fluticasone propionate + salmeterol	Advair *Diskus* (100 mcg/50 mcg)	Asthma	1 inh BID	$87.91 /month		✓
	Advair *Diskus* (250 mcg/50 mcg)	COPD	1 inh BID	$105.23 /month		✓
		Asthma				✓
	Advair *Diskus* (500 mcg/50 mcg)	COPD	1 inh BID	$149.38 /month		✓
		Asthma				✓
	Advair *MDI* (125 mcg/25 mcg)	Asthma	2 inh BID	$105.23 /month		✓
	Advair *MDI* (250 mcg/25 mcg)			$149.38 /month		
mometasone furoate + formoterol	Zenhale *MDI* (100 mcg/5 mcg)	Asthma	2 inh BID	$87.84 /month		✓
	Zenhale *MDI* (200 mcg/5 mcg)			$108.10 /month		
ICS Inhaled Corticosteroid[24-29]						
beclomethasone dipropionate	Qvar *MDI* (50 mcg)	Asthma	100–800 mcg/day (divided BID)	$34.36 /200 inh	✓	
	Qvar *MDI* (100 mcg)			$68.52 /200 inh		
budesonide	Pulmicort *Turbuhaler* (100 mcg)	Asthma	200–2400 mcg/day (divided BID to QID) 200–400 mcg BID (usual dose)	$33.78 /200 inh	✓	
	Pulmicort *Turbuhaler* (200 mcg)			$68.97 /200 inh		
	Pulmicort *Turbuhaler* (400 mcg)			$100.44 /200 inh		
ciclesonide	Alvesco *MDI* (100 mcg)	Asthma	100–800 mcg/day (higher doses divided BID)	$49.19 /120 inh	✓	
	Alvesco *MDI* (200 mcg)			$81.31 /120 inh		
fluticasone furoate	Arnuity *Ellipta* (100 mcg)	Asthma	1 inh once a day	$41.10 /month	✓	
	Arnuity *Ellipta* (200 mcg)			$82.19 /month		
fluticasone propionate	Flovent *Diskus* (100 mcg)	Asthma	100–500 mcg BID	$25.85 /60 inh	✓	
	Flovent *Diskus* (250 mcg)			$44.59 /60 inh		
	Flovent *Diskus* (500 mcg)			$69.34 /60 inh		
	Flovent HFA *MDI* (50 mcg)	Asthma	100–500 mcg BID (taken as 2 inh per dose)	$25.85 /120 inh	✓	
	Flovent HFA *MDI* (125 mcg)			$44.59 /120 inh		
	Flovent HFA *MDI* (250 mcg)			$89.15 /120 inh		
mometasone furoate	Asmanex *Twisthaler* (100 mcg)	Asthma	100–800 mcg/day (higher doses divided BID)	$35.04 /30 inh	non benefit	
	Asmanex *Twisthaler* (200 mcg)			$35.74 /60 inh	✓	
	Asmanex *Twisthaler* (400 mcg)			$71.48 /60 inh		

HFA hydrofluoroalkane; **MDI** metered dose inhaler; **mcg** micrograms; **inh** inhalation; **BID** twice a day; **TID** three times a day; **QID** four times a day; **PRN** when necessary
SMT Symbicort Maintenance Therapy (given with a separate fast-acting inhaled bronchodilator eg, salbutamol or terbutaline); **SMART** Symbicort Maintenance and Reliever Therapy
Cost estimated medication cost without markup and professional fee; calculated from McKesson Canada https://www.mckesson.ca/ (Accessed January 17, 2017)
British Columbia PharmaCare Special Authority Criteria http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/special-authority#Druglist

Table 5: Cost of Intensifying LABA, LAMA and ICS Therapy			
		Monthly Medication Cost	**Annual Medication Cost**
1 drug	LABA monotherapy	$50 - $109	$600 - $1308
	LAMA monotherapy	$54 - $57	$648 - $684
2 drugs	LAMA+LABA two separate devices	$104 - $166	$1248 - $1992
	LAMA+LABA combination device	$65 - $87	$780 - $1044
	ICS+LABA combination device	$89 - $149	$1068 - $1788
3 drugs	ICS+LABA combination device + LAMA device	$143 - $206	$1716 - $2472
	LAMA+LABA combination device + ICS device	$95 - $176	$1140 - $2112

Cost estimated medication cost without markup or professional fee; calculated from McKesson Canada https://www.mckesson.ca/ (Accessed January 17, 2017).

Summary

1. There is an absence of high-quality evidence regarding the effect of intensifying inhaled therapy (ie, progressing to LAMA+LABA and LAMA+LABA+ICS) on health-related quality of life and on the risk of exacerbation and death in people with COPD. The true effect cannot be firmly estimated.

2. Consider risk factors for pneumonia when weighing the suitability of inhaled corticosteroid therapy in people with COPD. These include: COPD exacerbation in the previous year, FEV_1 <50% predicted, prior history of pneumonia, lower body mass index, advancing age, and current smoker.

3. In a 2016 comparative effectiveness review of inhaled therapies for COPD, no consistent differences were identified in benefit or harm outcomes within the classes of LABA, LAMA or ICS+LABA therapies.

4. When evaluating a patient's symptomatic response to inhaled therapies using a goal-setting approach, give attention to their ability to use inhaled therapy devices.

Reference list available upon request.

Materials are designed to be used in conjunction with an academic detailing session provided by a PAD pharmacist. For more information, or to schedule an academic detailing session, please contact:

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