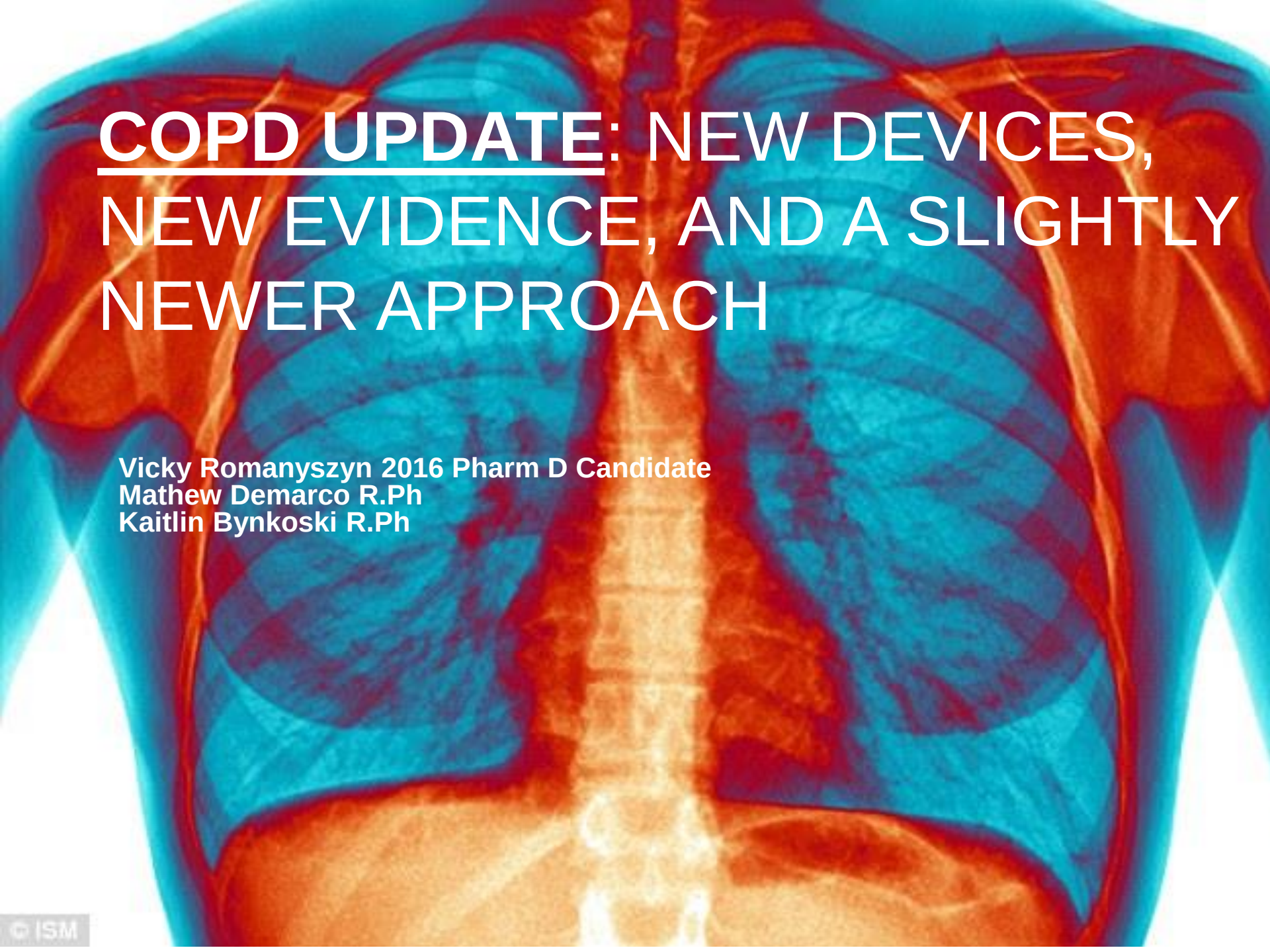

COPD UPDATE: NEW DEVICES, NEW EVIDENCE, AND A SLIGHTLY NEWER APPROACH

Vicky Romanyszyn 2016 Pharm D Candidate
Mathew Demarco R.Ph
Kaitlin Bynkoski R.Ph

Learning Objectives

- Become familiar with an evidence based approach to COPD
- Understand stepping up and down treatment with new and existing drug therapies
- Learn about comparing new devices and advantages for your patient

Presentation Outline

- Available Devices
  - Personalized therapy
- Adherence
  - Ease of use
  - Device knowledge and competence
- Available Therapeutic Agents
  - Patient's need to be aware of medication onset, mechanism of action, and goals of therapy for each agent
- Evidence Based Approach to COPD Therapy
  - Efficacy Data
  - Safety Data

Scope of Presentation: Exclusions

- Etiology & pathophysiology
- Exacerbation management
- Vaccinations, Roflumilast, theophylline
- Inhaler technique
- Smoking cessation
- Non-pharmacological therapies
  - Action plan
  - Pulmonary rehabilitation

Presentation Outline

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THERAPEUTIC PEARLS

Management of chronic airway disease

"10% medication and 90% education"

Studies have shown…

- Up to 50% of patient's are non-adherent to COPD therapy
- 50% of patients cannot demonstrate proper inhaler technique
- 28% of patients report never having demonstrated their inhaler technique to a health care provider

Compromised inhaler technique and medication non-adherence lead to poorer health outcomes and add to the economic burden of COPD

Pharmacist's Role

Optimize device competency and medication adherence by:

- Providing confident and effective verbal instruction
- Hands-on demonstration
- Repeat instructions to reinforce correct technique
- Recognize markers for inhaler underuse and incorrect use
  - Missed refills of maintenance medication
  - More frequent refills of rescue medication
  - Hospital admissions or emergency room visits for exacerbations

Expanded Scope Activities

Are we currently utilizing our full scope of practice to assist COPD patients?

- Smoking cessation counselling
- Administering substances by inhalation
- MedsCheck
  - Annual, Follow-ups, Post-Hospital Discharge
- Pharmaceutical Opinions to optimize therapy
  - Non-Compliance: refusing drug or not taking properly

Individualized Pharmacotherapy

- Diversity of choices due to recent influx of new inhalers to the market
- There is no concrete evidence to suggest one device works better than another
- Pharmacists are positioned to know the pros/cons of each device and make recommendations
- Therapy should be selected based on individual factors
  - Cognitive Function
  - Dexterity and Strength
  - Visual Impairments

What Patient's Want in a Device

- Fewer steps to operate the inhaler
- Confirmation that the dose has been taken correctly
- Easier coordination of breathing manoeuver
- Least resistance while inhaling

Inhalation Devices

- Metered Dose Inhalers
  - +/- Spacer ($)
- Soft Mist Inhalers
  - Respimat
- Dry Powder Inhalers (Breath Actuated)
  - Handihaler
  - Breezhaler
  - Turbuhaler
  - Diskus
  - Genuair
  - Ellipta

Pressurized Metered Dose Inha (pMDI)

Definition: Delivers aerosolized stream of medication over 0.2 seconds
Examples: VENTOLIN, ATROVENT, ADVAIR, ZENHALE

Advantages	Disadvantages
Suitable for all ages *spacer strongly recommended	No dose counter available (exceptions: Advair, Zenhale)
Spacer with a mask available for cognitive impairment and frail	Traveling with spacer and mask can be cumbersome
	Priming (x 4 sprays)

*The technical challenges posed by pMDIs and the inconveniences of using a spacer may contribute to patient preference for other inhaler devices.

Respimat

Definition: Using a spring to deliver a soft mist of medication over 1.5 seconds
Examples: SPIRIVA, COMBIVENT

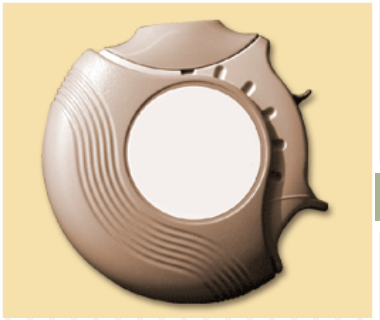
Advantages	Disadvantages
Slower actuation may improve technique vs. MDI	Requires reasonable strength to spring-load dose
Loading base locks to signal empty	Incorrect rate of inhalation results in cough
Tip: Pharmacies should pre-load the canister before dispensing	Priming (until mist is visible, then 3 more sprays) for first time use and when not used for 7 days (Spiriva) or 3 days (Combivent)

Turbuhaler

Definition: Dry powder inhaler containing a reservoir of medica
Examples: BRICANYL, OXEZE, SYMBICORT

Advantages	Disadvantages
Few steps, easy to use	Requires sharp, forceful inhalation of breath to get full dose
Dose is not lost even if base is twisted, however dose counter will no longer be accurate	Tipping device before inhalation can expel the dose
	It is difficult to tell when the product is empty (desiccant can still be heard, indicator mark hard to read)
	Humidity/moisture can clump drug in reservoir

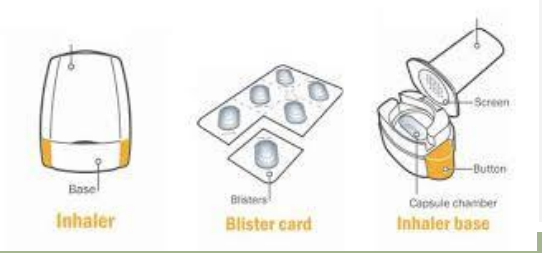
Diskus

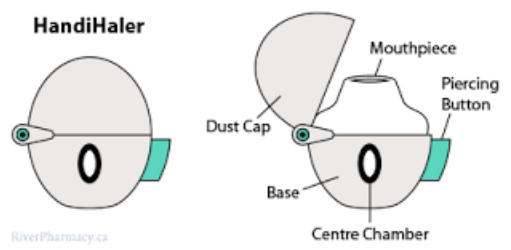


Definition: Dry Powder Inhaler containing single dose blisters of medication
Examples: ADVAIR, SEREVENT, VENTOLIN

Advantages	Disadvantages
Few steps, easy to use	Short expiry date after removal from protective packaging Advair= 1 month Serevent= 6 weeks Ventolin= 1 year
Displays exact number of remaining doses	Requires sharp, forceful inhalation of breath to get full dose

HandiHaler
Breezhaler

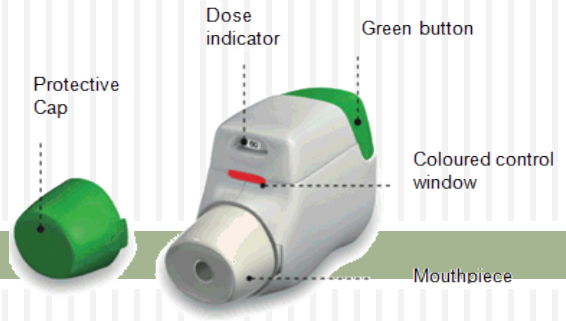




Definition: Capsules containing medication are pierced then powder is inhaled
Examples: HandiHaler-SPIRIVA; Breezhaler- SEEBRI, ULTIBRO, ONBREZ

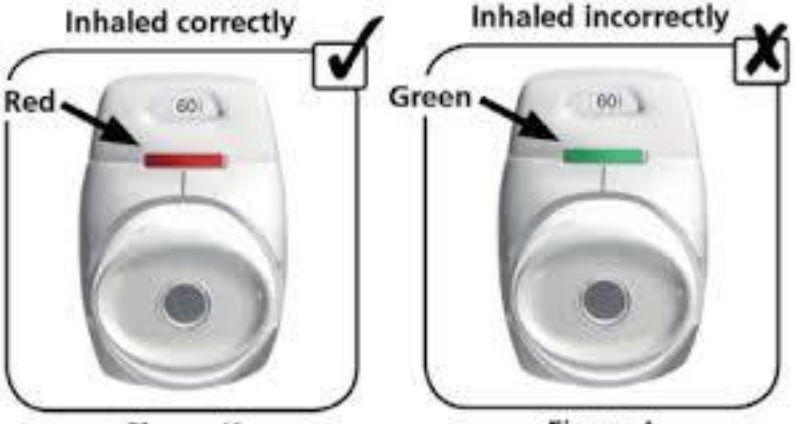
Advantages	Disadvantages
Rattling or whirring heard if capsules contents inhaled correctly	**Multi-step process**: maybe difficult for patients with poor manual dexterity or cognitive impairment
Can look to view empty capsules	Capsules are packaged in foil blisters; may be difficult to remove and are light and moisture sensitive
Low inspiratory effort needed	Pieces of capsule may be inhaled if pierced more than once
	Patients have been known to swallow capsules instead of inhaling them

Genuair



Definition: Dry Powder Inhaler containing single dose blisters of medication
Examples: TUDORZA

Advantages	Disadvantages
Simple to use and less errors during dose preparation	Requires sharp, forceful inhalation of breath to get full dose
Provides visual and audible (“click”) feedback when dose taken correctly	Some patients may experience a bitter taste
Loading button lock to signal empty	



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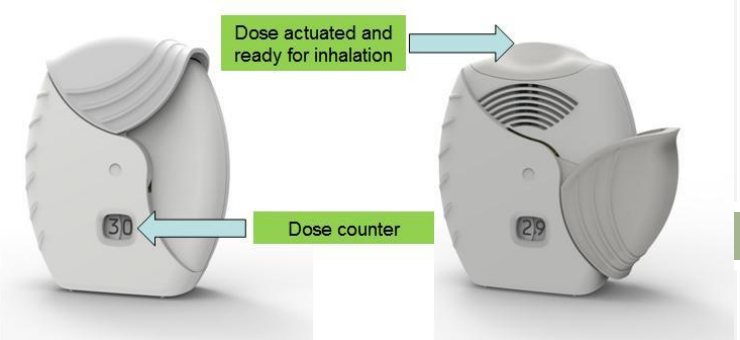
Ellipta



Definition: Dry Powder Inhaler containing single dose blisters of medication
Examples: BREO, ANORA, INCRUSE

Advantages	Disadvantages
Simple to use; one step to open and load dose	No way to determine if proper inspiratory effort is being achieved
Displays exact number of remaining doses with large numbers	Sort expiry date= 6 weeks after removal from protective packaging
	Requires sharp, forceful inhalation of breath to get full dose

Personalized Therapy

Device Type	Cognitive Impairment	Compromised Dexterity and Strength	Visual Impairment
pMDI	✓ *	✓ *	✓ *
Respimat	✓ **	✗	✗
Turbuhaler	✓	✓	✗
Diskus	✓	✓	✗
Handihaler/Breezehaler	✗	✗	✓
Genuair	✓	✓	✓
Ellipta	✓	✓	✗

** If a spacer device with mask is used*
***If Pharmacist or Care-Provider pre-load the canister and prime the device*

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AVAILABLE THERAPEUTIC AGENTS

Categorized by Class

Short-Acting Bronchodilators (SAMA & SABA)

Class	Drug	Device	Dose	MOA	Onset	Duration	Cost
SABA	Salbutamol (Ventolin)	Diskus 200mcg	1 puff QID prn	Binds to β2 pulmonary receptors, which increases cAMP, leading to relaxation of bronchial smooth muscle	<5 min	4-6h	Diskus: $38 MDI: $17* Neb: $107* (LU: 265, 266, 267, 268)
		MDI 100mcg	1-2 puffs QID prn				
		Nebules 1.25, 2.5, 5mg/mL	2.5mg QID prn				
	Terbutaline (Bricanyl)	Turbuhaler 500mcg	1 puff QID prn				$20*
SAMA	Ipratropium (Atrovent)	MDI 20mcg	2 puffs QID prn	Binds to M3 receptors, blocking acetylcholine, leading to relaxation of bronchial smooth muscle	5-15 mins	6-8h	MDI: $33* Neb: $195* (LU: 265, 266, 267, 268)
		Nebules 250, 500mcg/2mL	1 neb QID prn				

* Denotes Ontario Drug Benefit coverage

Long-Acting Muscarinic Antagonists (LAMA)

Drug	Device	Dose	MOA	Onset	Duration	Cost
Tiotropium (Spiriva)	Handihaler 18mcg	1 cap inh once daily	Slow to dissociate from pulmonary M3 receptors, leading to long acting decreased smooth muscle contraction	5mins	24h	Both $87 (*Handihaler only covered)
	Respimat 2.5mcg	2 puffs once daily				
Aclidinium (Tudorza)	Genuair: 400mcg	1 puff BID		10mins	12h	$73*
Glycopyrronium (Seebri)	Breezehaler 50mcg	1 cap inh once daily		5mins	24h	$73*
Umeclidinium (Incruse)	Ellipta 62.5mcg	1 puff once daily		5-15mins	24h	$81

* Denotes Ontario Drug Benefit coverage

Long-Acting Beta-Agonists (LABA)

Drug	Device	Dose	MOA	Onset	Duration	Cost
Formoterol (Foradil, Oxeze)	Aerolizer 12mcg	1 cap inh BID	Slow to dissociate from pulmonary B2 receptors, leading to long acting bronchodilation	<5min	12h	Aerolizer: $69** Turbuhaler: $63**
	Turbuhaler 6, 12mcg	6-12mcg inh BID				
Salmeterol (Serevent)	Diskus 50mcg	1 puff BID		2h	12h	$77*(LU: 391)
Indacaterol (Onbrez)	Breezehaler 75mcg	1 cap inh once daily		<5min	24h	$65*(LU: 443)
Olodaterol (Striverdi)	Respimat 2.5mcg	2 puffs once daily		<5min	24h	Not set

* Denotes Ontario Drug Benefit coverage; **Denotes ODB coverage only for asthma

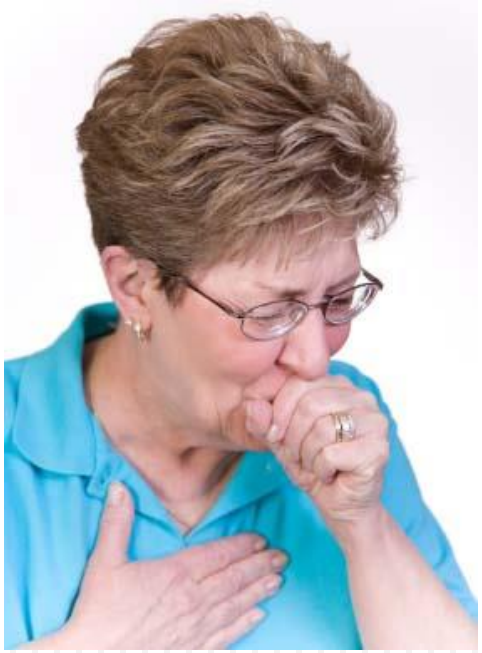
Combination Products

Class	Drug	Device	Dose	Cost
SABA+ SAMA	Salbutamol + Ipratropium (Combivent)	Nebules 2.5/0.5mg per 2.5mL	1 neb inh QID prn	$44*(LU: 256, 257, 258, 259)
		Respimat 20/100mcg	1 puff QID prn	$113
LAMA +LABA	Umeclidinium + Vilanterol (Anoro)	Ellipta 62.5/25 mcg	1 puff once daily	$107* (LU: 459)
	Glycopyrronium + Indacterol (Ultibro)	Breezhaler 50/110mcg	1 puff once daily	$105*(LU: 459)
	Tiotropium + Olodaterol (Inspiolto)	Respimat 2.5/2.5mcg	2 puffs once daily	$85
	Aclidinium + Formoterol (Duaklir)	Genuair 340/12mcg	1 puff BID	$98
LABA +ICS	Vilanterol + fluticasone (Breo)	Ellipta 25/100mcg	1 puff once daily	$153* (LU: 456)
	Salmeterol + fluticasone (Advair)	Diskus 50/100, 50/250, 50/500mcg	50/250mcg inhaled BID	$126**
	Formoterol + budesonide (Symbicort)	Turbuhaler 6/100, 6/200mcg	12/400mcg inh BID	$110**

*Denotes Ontario Drug Benefit coverage; **Denotes ODB coverage only for asthma

Goals of Therapy

- ↓ Symptoms
  - dyspnea
  - cough
  - exercise intolerance
- ↑ Activities of daily living
- ↓ Exacerbations
- ↓ Mortality rate
- ↑ Quality of life



Stages of COPD

Diagnosis of COPD: FEV1/FVC < 0.7

COPD Stage	MRC	Symptom/ Disability	FEV1
At risk	1	Breathless with strenuous exercise	>80%
Mild	2	Short of breath when hurrying on level ground or walking up a slight hill	
Moderate	3	Walk slower than people of the same age due to breathlessness or have to stop for breath on level ground	50-80%
Severe	4	Stop for breath after walking 100m or a few minutes on level ground	30-50%
Very severe	5	Too breathless to leave the house or breathless when dressing	<30%

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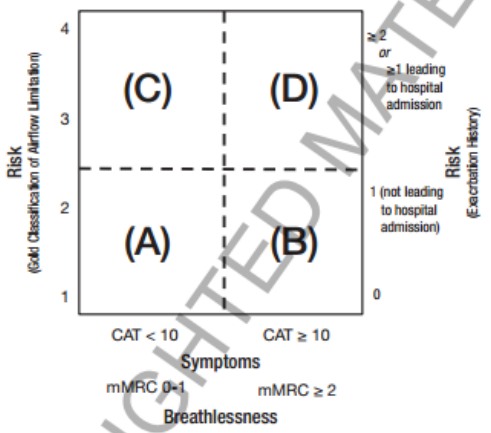
EBM Approach to COPD

Guidelines: GOLD 2015

Table 4.2. Model of Symptom/Risk of Evaluation of COPD

When assessing risk, choose the highest risk according to GOLD grade or exacerbation history. (One or more hospitalizations for COPD exacerbations should be considered high risk.)



Patient Category	Characteristics	Spirometric Classification	Exacerbations per year	CAT	mMRC
A	Low Risk, Less Symptoms	GOLD 1-2	≤1	< 10	0-1
B	Low Risk, More Symptoms	GOLD 1-2	≤1	≥ 10	≥ 2
C	High Risk, Less Symptoms	GOLD 3-4	≥ 2	< 10	0-1
D	High Risk, More Symptoms	GOLD 3-4	≥ 2	≥ 10	≥ 2

Patient Group	Recommended First Choice	Alternative Choice	Other Possible Treatments**
A	Short-acting anticholinergic prn *or* Short-acting $beta_2$-agonist prn	Long-acting anticholinergic *or* Long-acting $beta_2$-agonist *or* Short-acting $beta_2$-agonist and short-acting anticholinergic	Theophylline
B	Long-acting anticholinergic *or* Long-acting $beta_2$-agonist	Long-acting anticholinergic and long-acting $beta_2$-agonist	Short-acting $beta_2$-agonist *and/or* Short-acting anticholinergic Theophylline
C	Inhaled corticosteroid + long-acting $beta_2$-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting $beta_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor *or* Long-acting $beta_2$-agonist and phosphodiesterase-4 inhibitor	Short-acting $beta_2$-agonist *and/or* Short-acting anticholinergic Theophylline
D	Inhaled corticosteroid + long-acting $beta_2$-agonist *and/or* Long-acting anticholinergic	Inhaled corticosteroid + long-acting $beta_2$-agonist and long-acting anticholinergic *or* Inhaled corticosteroid + long-acting $beta_2$-agonist and phosphodiesterase-4 inhibitor *or* Long-acting anticholinergic and long-acting $beta_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine N-acetylcysteine Short-acting $beta_2$-agonist *and/or* Short-acting anticholinergic Theophylline

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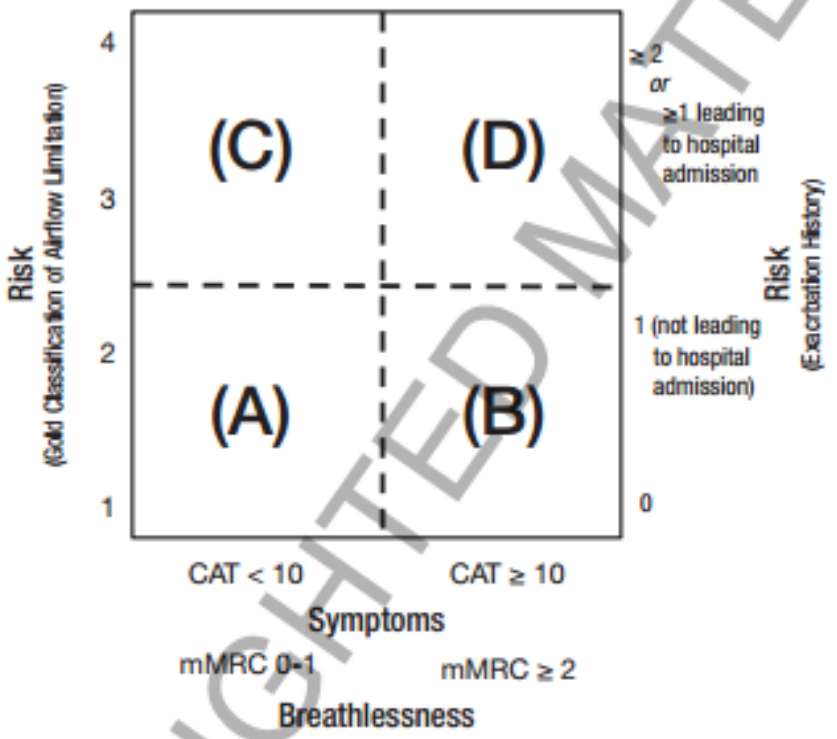

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B	Long-acting anticholinergic *or* Long-acting beta$_2$-agonist	Long-acting anticholinergic and long-acting beta$_2$-agonist	Short-acting beta$_2$-agonist *and/or* Short-acting anticholinergic Theophylline
C	Inhaled corticosteroid + long-acting beta$_2$-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting beta$_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor *or* Long-acting beta$_2$-agonist and phosphodiesterase-4 inhibitor	Short-acting beta$_2$-agonist *and/or* Short-acting anticholinergic Theophylline
D	Inhaled corticosteroid + long-acting beta$_2$-agonist *and/or* Long-acting anticholinergic	Inhaled corticosteroid + long-acting beta$_2$-agonist and long-acting anticholinergic *or* Inhaled corticosteroid + long-acting beta$_2$-agonist and phosphodiesterase-4 inhibitor *or* Long-acting anticholinergic and long-acting beta$_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine N-acetylcysteine Short-acting beta$_2$-agonist *and/or* Short-acting anticholinergic Theophylline

Hospitalized for acute exacerbation or FEV1 less than 50%

Guidelines: CHEST 2015

[Evidence-Based Medicine]

CHEST

Prevention of Acute Exacerbations of COPD

American College of Chest Physicians and Canadian Thoracic Soc
Guideline

Gerard J. Criner, MD, FCCP; Jean Bourbeau, MD, FCCP; Rebecca L. Diekemper, MPH; Daniel R. Ouellette,
Donna Goodridge, RN, PhD; Paul Hernandez, MDCM; Kristen Curren, MA; Meyer S. Balter, MD, FCCP;
Mohit Bhutani, MD, FCCP; Pat G. Camp, PhD, PT; Bartolome R. Celli, MD, FCCP; Gail Dechman, PhD,
Mark T. Dransfield, MD; Stanley B. Fiel, MD, FCCP; Marilyn G. Foreman, MD, FCCP; Nicola A. Hanania,
Belinda K. Ireland, MD; Nathaniel Marchetti, DO, FCCP; Darcy D. Marciniuk, MD, FCCP;
Richard A. Mularski, MD, MSHS, MCR, FCCP; Joseph Ornelas, MS; Jeremy D. Road, MD;
and Michael K. Stickland, PhD

BACKGROUND: COPD is a major cause of morbidity and mortality in the United Sta
throughout the rest of the world. An exacerbation of COPD (periodic escalations
of cough, dyspnea, and sputum production) is a major contributor to worsening lu
impairment in quality of life, need for urgent care or hospitalization, and cost of ca
Research conducted over the past decade has contributed much to our current ur
of the pathogenesis and treatment of COPD. Additionally, an evolving literature

PICO 2: **Pharmacological inhaled therapies**

Recommended	Suggested
- **LABA** vs. placebo - **LAMA** vs. placebo LABA or SAMA - **ICS (LABA combination)** vs. placebo, LABA or ICS alone - **LABA (anticholinergic or ICS) or anticholinergic monotherapy**	- **SAMA + SABA** vs. SABA - **SAMA + LABA** vs. LABA - **SAMA** vs. SABA - **LABA** vs. SAMA - **LAMA/ICS/LABA** vs. placebo

Guidelines: Canadian Thoracic Society 2008

COPD RECOMMENDATIONS – 2008 PRIMARY CARE UPDATE

O'Donnell et al

Canadian Thoracic Society recommendation for management of chronic obstructive pulmonary disease – 2008 update – highlights for primary care

Denis E O'Donnell MD[1*†], Paul Hernandez MD[2*†], Alan Kaplan MD[3], Shawn Aaron MD[4*], Jean Bourbeau MD[5*], Darcy Marciniuk MD[6*], Meyer Balter MD[7], Gordon Ford MD[8], Andre Gervais MD[9], Yves Lacasse MD[10], Francois Maltais MD[10], Jeremy Road MD[11], Graeme Rocker MD[2], Don Sin MD[11], Tasmin Sinuff MD[12], Nha Voduc MD[4]

DE O'Donnell, P Hernandez, A Kaplan, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2008 update – highlights for primary care. Can Respir J 2008;15(Suppl A):1A-8A.

Chronic obstructive pulmonary disease (COPD) is a major respiratory illness in Canada that is preventable and treatable but unfortunately

Recommandations de la Société thoracologie pour prendre en ch pulmonaire obstructive chroniq jour 2008 : Faits saillants des s

La maladie pulmonaire obstructive chronique (

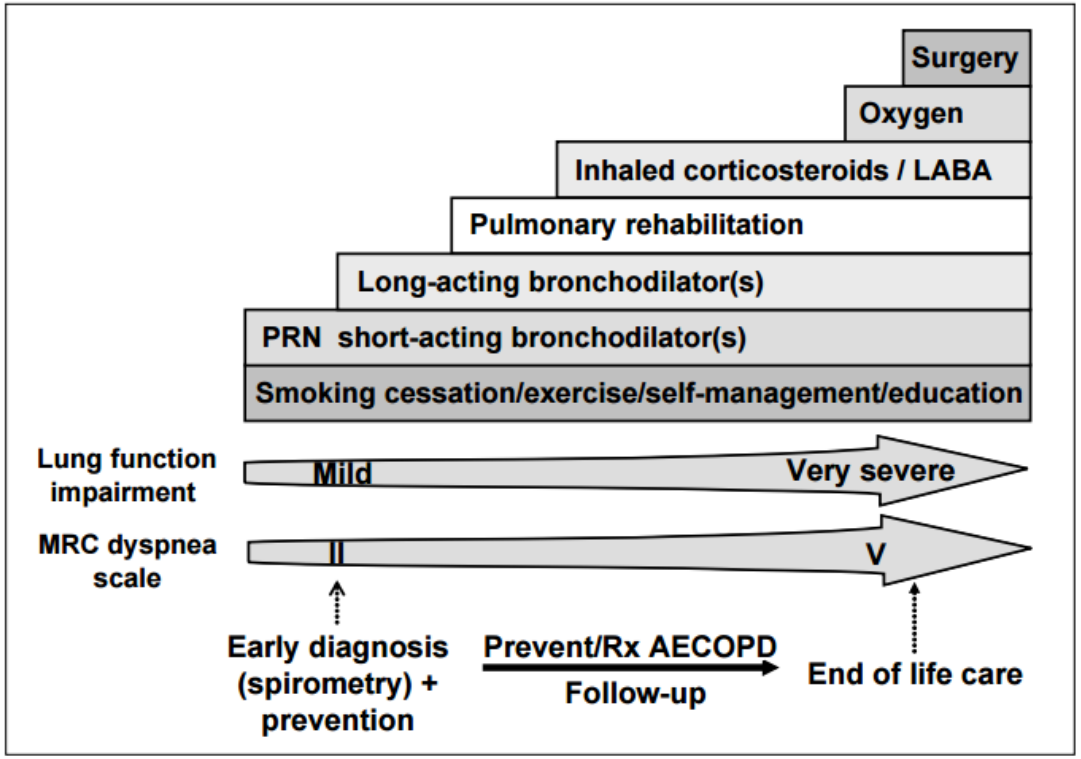


Figure 1) *A comprehensive approach to the management of chronic obstructive pulmonary disease (COPD). AECOPD Acute exacerbation of COPD; LABA Long-acting beta$_2$-agonist; MRC Medical Research Council; PRN As needed; Rx Treatment*

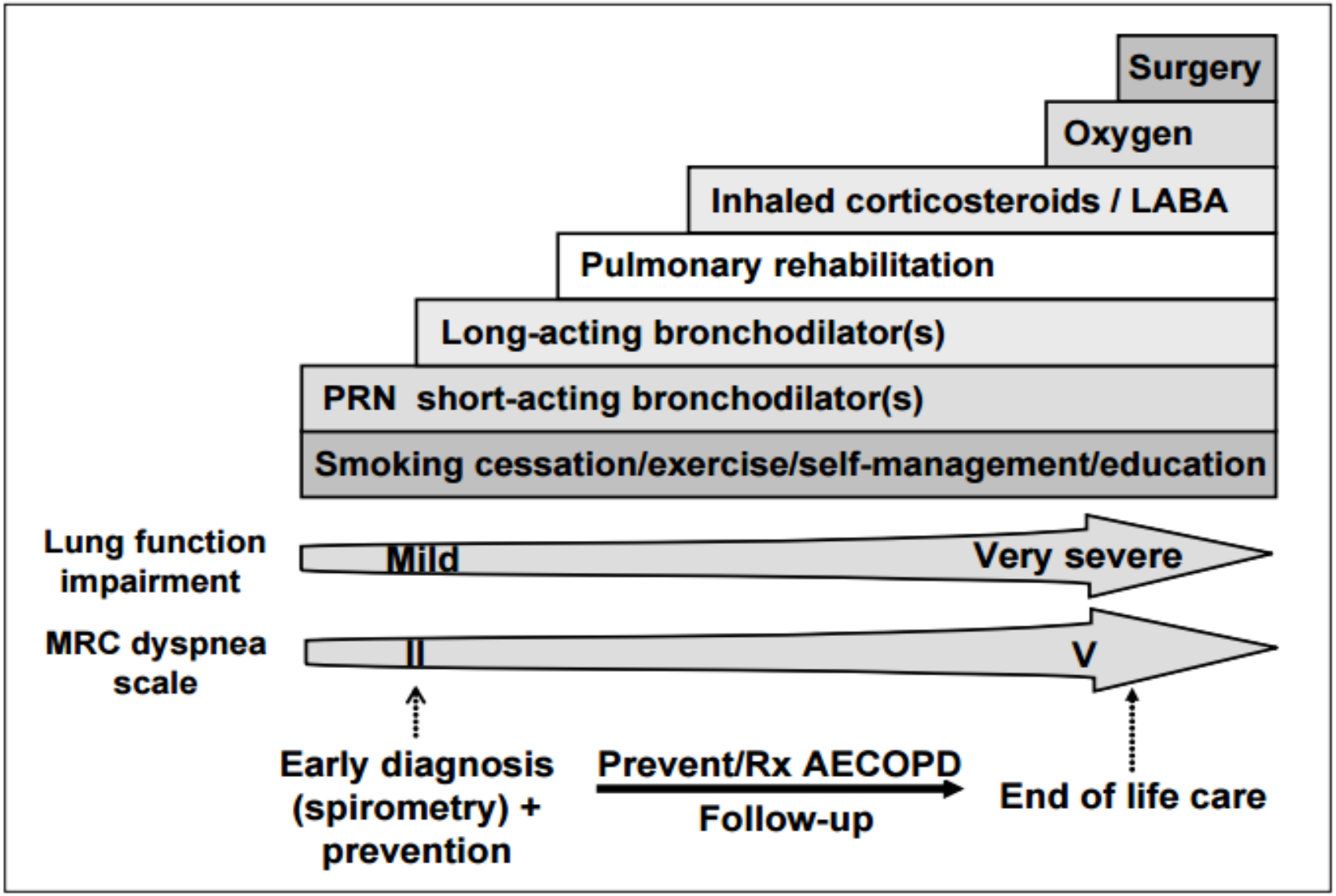


Figure 1) *A comprehensive approach to the management of chronic obstructive pulmonary disease (COPD). AECOPD Acute exacerbation of COPD; LABA Long-acting beta$_2$-agonist; MRC Medical Research Council; PRN As needed; Rx Treatment*

Patient Outcomes

There are many outcome results in COPD RCTs

- Focus on Patient Oriented Evidence that Matters (POEMs)
  - Symptoms: SGRQ average are less than 4
  - Exacerbations (requiring prednisone or antibiotics) +/- hospitalization
  - Air flow limitation: FEV1 * Most Common*
  - Mortality

Ann Intern Med. 2007;147:639-653. Ann Intern Med 2011;155:179-191.

St George's Respiratory Questionnaire

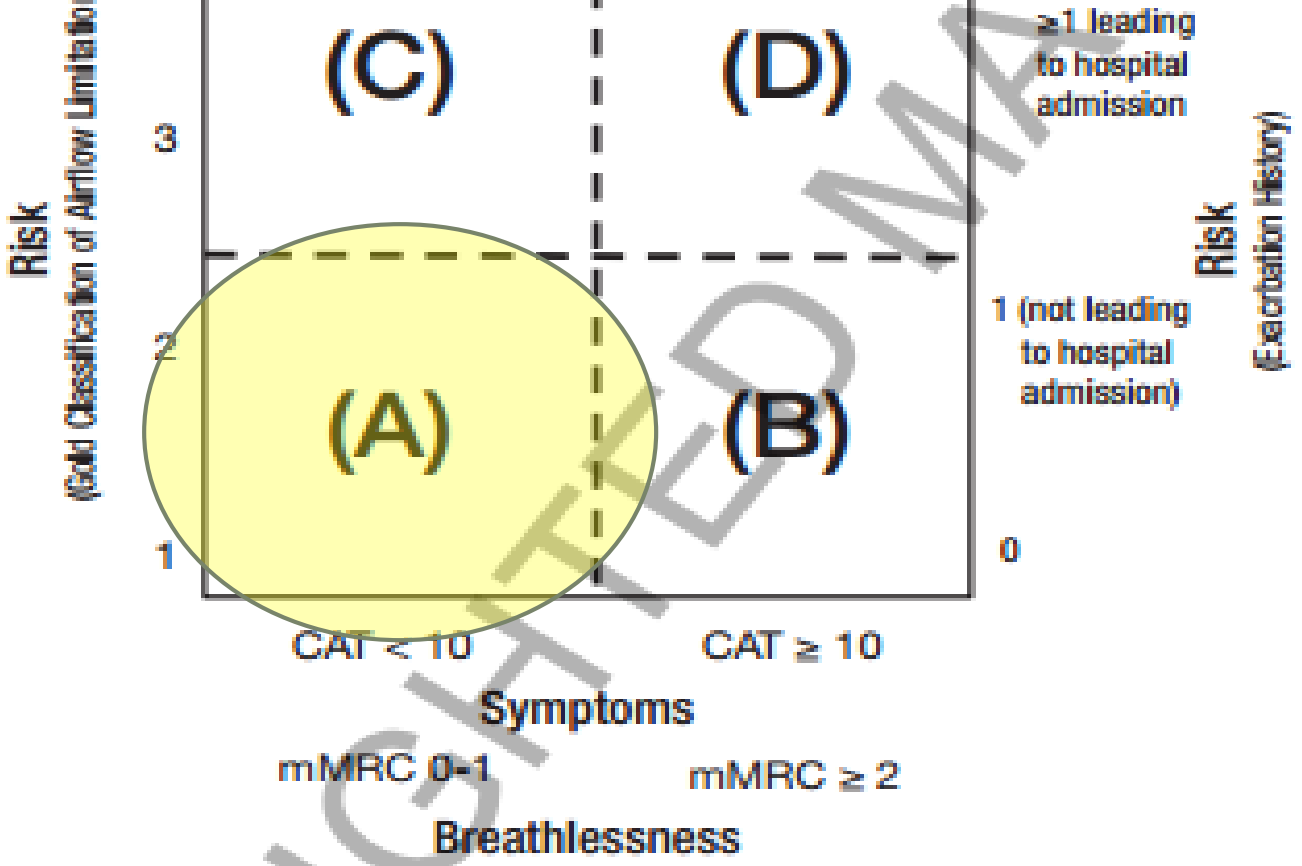
Three subscales:

- 1. Symptoms (8)
- 2. Activity (16)
- 3. Impact (26)
- Score: 50 items – Total score is given as percent of maximum: 0 (no impairment)100 (maximum impairment).
- MCID: ~4.

SGRQ Minimally important clinical difference "definition" Change of 4

- No longer takes a long time to wash or dress, can now walk up stairs without stopping and go out for entertainment.
- No longer has to stop for rest while doing housework and can now carry things upstairs.
- No longer has to walk more slowly than other people, no longer breathless on getting washed and dressed or on bending over
- In very severe COPD, 4 pts on SGRQ exists between those housebound and those not

	MEAN SGRQ vs PLACEBO
ICS	1.22
ICS/LABA	2.9
Tiotropium	3.3
LABA	1.3



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B	Long-acting anticholinergic *or* Long-acting beta$_2$-agonist	Long-acting anticholinergic and long-acting beta$_2$-agonist	Short-acting beta$_2$-agonist *and/or* Short-acting anticholinergic Theophylline
C	Inhaled corticosteroid + long-acting beta$_2$-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting beta$_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor *or* Long-acting beta$_2$-agonist and phosphodiesterase-4 inhibitor	Short-acting beta$_2$-agonist *and/or* Short-acting anticholinergic Theophylline
D	Inhaled corticosteroid + long-acting beta$_2$-agonist *and/or* Long-acting anticholinergic	Inhaled corticosteroid + long-acting beta$_2$-agonist and long-acting anticholinergic *or* Inhaled corticosteroid + long-acting beta$_2$-agonist and phosphodiesterase-4 inhibitor *or* Long-acting anticholinergic and long-acting beta$_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine N-acetylcysteine Short-acting beta$_2$-agonist *and/or* Short-acting anticholinergic Theophylline

Hospitalized for acute exacerbation or FEV1 less than 50%

GOLD A: Short Acting Bronchodilators PRN

- GOLD A patients have few symptoms and low risk of exacerbations.
  - FEV1 better than 50% predicted
  - Less than 2 exacerbation / year, none leading to hospitalization
- Symptoms:
  - Dyspnea symptoms with strenuous exertion but no interference with daily activity.
  - Short of breath when hurrying on level ground or walking up a slight hill
- First line: short acting bronchodilators
- *Alternative choice*: Combination of SAMA/SABA PRN or the introduction of a LAMA or LABA
- Specific evidence for the effectiveness of treatments in FEV1 >80 is not available.

EBM: Short Acting Bronchodilators PRN

	Efficacy	Safety
Salbutamol Terbutaline (SABA)	• 1 RCT VS placebo *FEV1 ↑ and dyspnea symptoms*	• AE: Nervousness, tremor, pharyngitis URTI, palpitations, hypertension, headache
Ipratropium (SAMA) **(DPI)**	• 1 RCT VS salbutamol and placebo *FEV1 ↑ and dyspnea symptoms*	• AE: Headache, Diarrhea dizziness nausea, URTI, pharyngitis, dry mouth, nosebleed; or. muscle pain
Ipratropium + Salbutamol **(DPI)**	• 1 RCT Combo VS Salbutamol *Exacerbation reduction (NNT 19) and FEV1 ↑*	• Lowest patient withdrawal • Adverse effects not significantly significant from monotherapies

Cochrane Database Syst Rev. 2006;(2):CD001387 2) Cochrane Database Syst Rev. 2001;(2):CD002984. 3) Cochrane Database Syst Rev. 2013;9:CD009552. *Respir Med* 2010, **104:**1179-1188

Respimat Data: Short Acting Bronchodilators PRN

- Ipratropium/Salbutamol Respimat
  - FEV1 and symptoms of dyspnea equivalent to MDI Ipratropium/Salbutamol.
  - Lowest patient dropout versus Ipratropium/Salbutamol MDI and Ipratropium respimat
  - Multiple studies demonstrating increased patient satisfaction with Ipratropium/Salbutamol Respimat

1) Cochrane Database Syst Rev. 2014;7:CD009285. 2) Pulm Pharmacol Ther. 2014;;28:91-*Respir Med* 2010, **104:**1179-1188 3) Int J Chron Obstruct Pulmon Dis. 2013;8:221-30. doi: 10.2147/COPD.S31246. Epub 2013 Apr 3

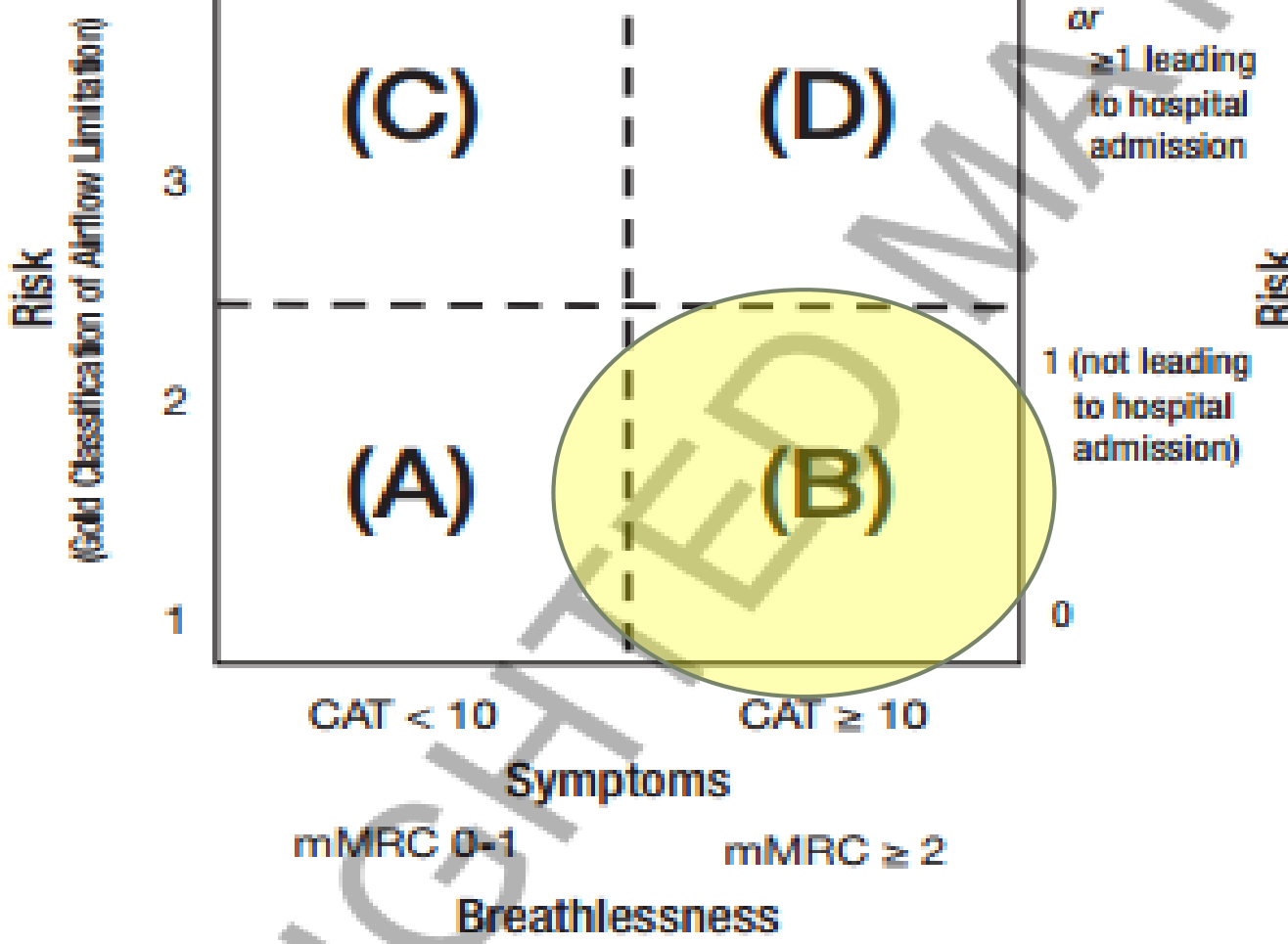
Summary: Short Acting Bronchodilators PRN

- **GOLD A place in therapy**: a short-acting bronchodilator used as needed is recommended as first choice based on its effect on lung function and breathlessness. An alternative choice is a combination of short-acting bronchodilators or the introduction of a long-acting bronchodilator

- SAMA> SABA for FEV1 improvements and symptoms

- SAMA + SABA > SABA for exacerbations and FEV1 improvements and symptoms

- Can continue to use SABA as needed for symptom management despite additional therapy



Patient Category	Characteristics	Spirometric Classification	Exacerbations per year
A	Low Risk, Less Symptoms	GOLD 1-2	≤1
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C	High Risk, Less Symptoms	GOLD 3-4	≥ 2
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Patient Group	Recommended First Choice	Alternative Choice	Other Possible Treatments**
A	Short-acting anticholinergic prn *or* Short-acting $beta_2$-agonist prn	Long-acting anticholinergic *or* Long-acting $beta_2$-agonist *or* Short-acting $beta_2$-agonist and short-acting anticholinergic	Theophylline
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C	Inhaled corticosteroid + long-acting $beta_2$-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting $beta_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor *or* Long-acting $beta_2$-agonist and phosphodiesterase-4 inhibitor	Short-acting $beta_2$-agonist *and/or* Short-acting anticholinergic Theophylline
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Hospitalized for acute exacerbation or FEV1 less than 50%

GOLD B: Long Acting Bronchodilators

- Group B patients have more significant symptoms but still low exacerbation risks.
  - FEV1 better than 50% predicted
  - Less than 2 exacerbation / year, none leading to hospitalization.

- Symptoms: **MORE!** On level ground, the patient walks slower than people of the same age because of breathlessness, or because the patient has to stop for breath when walking at their own pace.

GOLD B: Long Acting Bronchodilators

- First line: Long acting bronchodilators (LAMA or LABAs) are recommended first line because they are superior to short-acting bronchodilators and safer than ICS.
  - There is no evidence to recommend one class of long-acting bronchodilators over another for initial treatment.

- *Alternative choice*: LABA/LAMA combo for patients with persistent symptoms of dyspnea.

Monotherapy vs Placebo	Efficacy				Safety
	FEV1	SGDQ Mean	Exacerbation	Death	
Indacaterol 13 RCTs (9961 pts)	**149**	**3.6**	**NNT 30**	**ns**	•Withdrawal NNT 19 vs placebo • AE: Nasopharyngitis, tremor, cough, headache, nausea
Formoterol 10 RCTs (4564 pts)	**45**	**2.66**	**ns**	**ns**	•Withdrawal NNT 15 vs placebo • AE:Diarrhea, headache, tremor, palpitations, URTI, cough
Salmeterol 14 RCTs (8973 pts)	**101**	**1.64**	**NNT 22**	**ns**	•Withdrawal NNT 29 vs placbo •Haedache, HTN, dry mouth nasopharyngitis, cough
Aclidinium 12 RCT (9547 pts)	**90**	**2.3**	**ns**	**ns**	•Withdrawal NNT 35 vs placebo • AE: Diarrhea, dry mouth, cough, headache, vomiting
Glycopyrronium 2 RCTs (1888 pts)	**112**	**3.32**	**NNT 14**	**ns**	•Withdrawal NNT 14 vs placebo •Placebo AE>glycopyrronium • AE: Dry mouth, cough, URTI, flushing heachache, flushing
Umeclidinium 4 RCTs (2,121 pts)	**140**	**4.7-7.9**	**ns**	**ns**	•Withdrawal NS vs placebo •AE: tachycardia, blurred vision, urinary retention, dry mouth and abdo pain, cough
Tiotropium 22 RCTs (23,309)	**119**	**2.89**	**NNT 16**	**ns**	•Withdrawal NNT 19 vs placebo •AE: dry mouth, cough, constipation, urinary retention, headache
Inhaled Steroids	**70**	**1.22**	**NNT 22**	**ns**	•No withdrawal data •Oral Candidiasis (NNH 27), Voice change (NNH 34), Bruising (NNH 32), Pneumonia (NNH 30)

Head to Head Trials: Monotherapy with Long Acting Bronchodilators

Which LAMA or LABA first?

LAMAs VS SAMA

- Tiotropium > Ipratropium: 2 RCTs, 1073 pts
  - Tiotropium had superior FEV1, Exacerbation NNT 10, however SGRQ 3.3

LAMA VS LABA

- Tiotropium > LABA: 2 RCTs, 7384 pts
  - Tiotropium reduced exacerbation NNT 19 VS placebo but no difference in mortality or quality of life.
  - Tiotropium > salmeterol, placebo. 2 RCTs
    Only tiotropium > placebo for clinically important improved quality of life NNT 11 and reduced hospitalization NNT 10

Int J Chron Obstruct Pulmon Dis. 2013;8:405-23. *BMC Pulm Med*. 2014;14:4.

Head to Head Trials: Monotherapy with Long Acting Bronchodilators

LAMA vs LAMA

- Glycopyrronium = Tiotropium 3 RCT (GLOW2, GLOW5, SHINE) for exacerbation, FEV1, SGRQ

- Review 27 RCTs and 48,140 pts. (VS placebo)
  - Umeclidinium = Aclidinium = glycopyrronium = Tiotropium (only for FEV1 and symptoms of dyspnea)
  - The new LAMAs studied had at least comparable efficacy to tiotropium, the established class standard.

Int J Chron Obstruct Pulmon Dis. 2013;8:405-23. *BMC Pulm Med*. 2014;14:4.

Respimat Data: Tiotropium

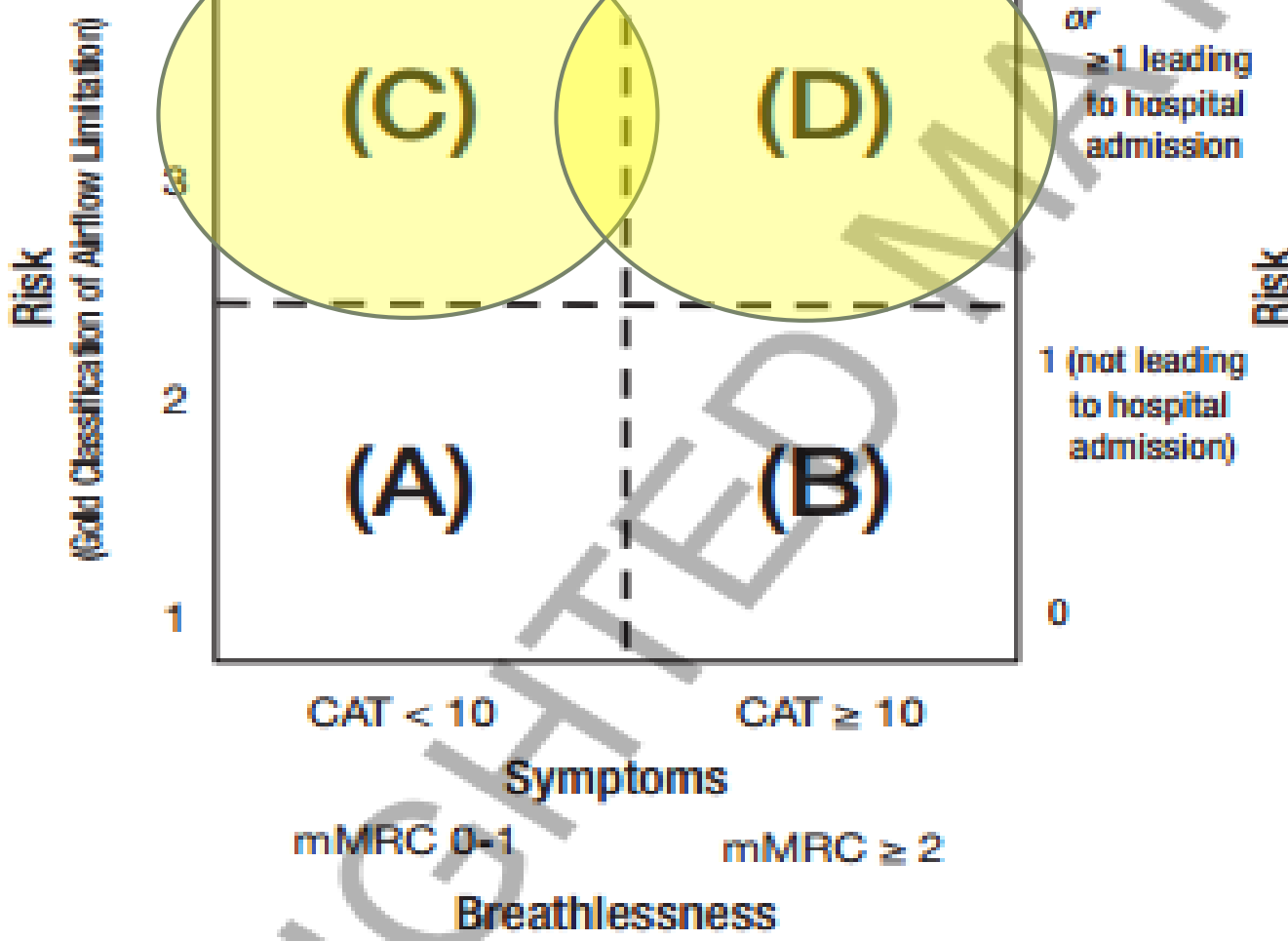
- Tiotropium Soft Myst Inhaler
  - Handihaler > Respimat. Systematic Review: 22 RCTs (23,309 pts)
    - NNH 143 for mortality for the Respimat
  - TIOSPIR (2.3 yrs, 17,135 pts): respimat mortality = handihaler; but healthy population is the criticism, FEV1 was > 60% predicted

1) Cochrane Database Syst Rev. 2014;7:CD009285. 2) Pulm Pharmacol Ther. 2014;;28:91-*Respir Med* 2010, **104:**1179-1188 3) Int J Chron Obstruct Pulmon Dis. 2013;8:221-30. doi: 10.2147/COPD.S31246. Epub 2013 Apr 3

Summary: Monotherapy with Long Acting Bronchodilators

- **GOLD B place in therapy**: LAMAs and LABAs are first line for Gold B patients and no preference of one over the other.
- However the evidence has shown Tiotropium > Salmeterol for exacerbation and FEV↑
- LAMA evidence concludes equivalence.. For now!
- Can upgrade to LAMA/LABA if LABA or LAMA is ineffective (evidence next section)

NEJM 2011; 364:1093-103. 2) Thorax 2003;58:399-404. 3) Am J Respir Crit Care Med. 2008;177:19-26. 4) Cochrane 2010;(5):CD007891. 5) Cochrane 2011;12: CD007033. 6) Ann Intern Med. 2011;155:179-191.



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Hospitalized for acute exacerbation or FEV1 less than 50%

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Hospitalized for acute exacerbation or FEV1 less than 50%

D patient difference? X3 therapy →

GOLD C: ICS/LABA or LAMA

- Group C patients have few symptoms but a high risk of exacerbation.
  - FEV1 less than 50% predicted
  - One hospitalized exacerbation in the last year or 2 or more exacerbations per year.
- Symptoms: I am too breathless to leave the house or I am breathless when dressing.

GOLD C: ICS/LABA or LAMA

- For Group C ICS/LABA or LAMA is recommended.
  - Insufficient patient outcome evidence to recommend LAMA/LABA combo over a tiotropium or LAMA alone.

- *Alternative choice*: LAMA/LABA for persistent dyspnea symptoms or intolerance to an ICS (pneumonia, hoarseness, bones, bruising, drug interactions) or LAMA with an ICS (no evidence)

GOLD C: ICS/LABA or LAMA

- ICS should not be prescribed before this stage as the risks of pneumonia and other adverse events outweighs the potential benefits.

Head to Head: ICS/LABA (blue)

	Combination Therapy Head to Head	Efficacy				Safety
		FEV1	SGDQ Mean	Exacerbation	Death	
ICS/LABA RCTs	ICS/LABA vs Plac	**90-160**	**2.9-4.1**	NNT 22	**NNT 53**	Pneumonia NNH 70
	ICS/LABA vs ICS	**50-110**	0.3-2.8	NS	**NNT 75**	-
	ICS/LABA vs LABA	70	1.58	NNT 23	NS	Pneumonia NNH 48
	ICS/LABA vs Tio	NS (40% patient drop out from study)				
	Fluticasone + Vilanterol vs Vil	10.-20	-	NS	NS	Pneumonia, hoarse throat, fractures
LAMA/LABA RCTs	Tio/LABA vs either	70	1.61	NS	NS	NS
	Umeclidinium/ Vilanterol (vs either)	**60-110**	-	NNT 42	NS	Withdrawal NNT 19
	Glycopyrronium/ Indacaterol vs Tio*	**60-100**	2.2-2.6	NNT 19-25	NS	NS

C	Inhaled corticosteroid + long-acting $beta_2$-agonist *or* Long-acting anticholinergic
D	Inhaled corticosteroid + long-acting $beta_2$-agonist *and/or* Long-acting anticholinergic

Adverse Events: ICS/LABA

Inhaled Steroids (Pneumonia)

- TORCH: Steroid groups vs placebo, 4 years:

Pneumonia: 18.9% vs 12.8% = 6.1% (NNH 17)

- Over 4 Meta-analyses found pneumonia NNH from 13-25 or 47 for Severe pneumonia (1yr)

Bottom-line: Majority of evidence suggests inhaled corticosteroids increase the risk of pneumonia.

1) N Engl J Med. 2007;356:775-89 2) JAMA. 2008;300:2407-16 3) Arch Intern Med. 2009;169: 219- 29. 4) Cochrane 2007;4:CD003794. 5) Cochrane 2014;3: CD010115. 6) Lancet 2009; 374: 712–19

Adverse Events: ICS/LABA

Inhaled Steroids (Bones)

- Case-control studies: Mixed results1,2
  - One RCT showed decreased bone density.
  - Fracture risk **NNH 83** over 3 years.

Bottom-line: Likely Harm

1) Am J Respir Crit Care Med. 2004 Apr 1;169(7):855-9. 2) Chest. 2005;127:89-97. 3) NEJM 2000;343:1902-9. 4) Thorax 2011;66(8):699-708

Head to Head: LAMA/LABA (pink)

	Combination Therapy Head to Head	Efficacy				Safety
		FEV1	SGDQ Mean	Exacerbation	Death	
ICS/LABA RCTs	ICS/LABA vs Plac	**90-160**	**2.9-4.1**	NNT 22	**NNT 53**	Pneumonia NNH 70
	ICS/LABA vs ICS	**50-110**	0.3-2.8	NS	**NNT 75**	-
	ICS/LABA vs LABA	70	1.58	NNT 23	NS	Pneumonia NNH 48
	ICS/LABA vs Tio	NS (40% patient drop out from study)				
	Fluticasone + Vilanterol vs Vil	10.-20	-	NS	NS	Pneumonia, hoarse throat, fractures
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	Umeclidinium/ Vilanterol (vs either)	**60-110**	-	NNT 42	NS	Withdrawal NNT 19
	Glycopyrronium/ Indacaterol vs Tio*	**60-100**	2.2-2.6	NNT 19-25	NS	NS

Head to Head: LAMA/LABA

Table 2: Summary of selected outcome evidence for efficacy from individual RCTs *(See full evidence review for more detail)*

	Mortality	Exacerbations	SGRQ health status	Dyspnoea	Lung Function (FEV_1)
Ultibro Breezhaler		*(Exacerbation rate)*			
vs. placebo[4,7]	-	-	-	↑	↑
vs. glycopyrronium[5]	-	↑↑	↑↑	-	↑↑
vs. indacaterol[7]	-	-	-	-	↑↑
vs. tiotropium[b 5,4,7]	-	↔ ↑↑[c]	↑↑	↑↑	↑↑
vs. Seretide[6]	-	-	↔	↑↑	↑↑
Anoro Ellipta		*(Time to first exacerbation)*			
vs. placebo[10]	-	↑	↑	↑	↑
vs. umeclidinium[10]	-	-	↔	↔	↔[9] ↑↑[10]
vs. tiotropium[8,9]	-	↔[9] ↑↑[8]	↔ ↑↑[8]	↔	↑↑
Duaklir Genuair					
vs. placebo[11-13]	-	↑[d]	↑↔	↑	↑
vs. aclidinium[11-13]	-	-	↔	↑↑[d]	↑↑
vs. formoterol[11-13]	-	-	↔	↑↑[d]	↑↑

Key: ↑ significantly better than placebo; ↑↑ significantly better than active comparator; ↔ no significant difference vs. placebo; ↔ No significant difference vs. active comparator; – No data available in trials reviewed .[b]Tiotropium: open-label in two trials and masked in a second; [c]no significant difference in rate for severe exacerbations and those leading to hospitalisation, significant difference in rate of all exacerbations; [d]from pooled data analyses in EPAR, no significant difference in individual trials

- Chest 2015

23. For patients with stable COPD, we recommend inhaled long-acting anticholinergic/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD.

  - LAMA/LABA combos are just as effective as tiotropium and other LAMAs alone at reducing exacerbation

- Gold 2015

(**Evidence B**). Combinations of a long-acting beta$_2$-agonist and a long-acting anticholinergic have shown a significant increase in lung function whereas the impact on patient reported outcomes is still limited[560, 589]. There is still too little evidence to determine if a combination of long-acting bronchodilators is more effective than a long-acting anticholinergic alone for preventing exacerbations[561].

  - Insufficient patient outcome evidence to recommend LAMA/LABA combo over a tiotropium or LAMA alone

Guideline update again in 2016?

- The data showed that a dose of 110/50 mcg of (indacaterol/glycopyrronium) once per day met its primary non-inferiority outcome and also demonstrated clinical superiority to 50/500 mcg of Seretide (salmeterol/fluticasone) twice per day in decreasing the rate of mild/moderate/severe COPD exacerbations over a course of one year of treatment.

GOLD D: 3X Therapy

- Adding Fluticasone/Salmeterol to Tiotropium

  Review, 6 RCTs, 1268 patients

  - FEV1 improved 55 mL
  - Exacerbation NNT 18
  - SGRQ: 4.63
  - Any adverse events: NNH 20

  Bottom-Line: Adding dual therapy to Tiotropium will have what is likely a clinical insignificant change in FEV1 but improve COPD quality of life to small, meaningful level. It also reduces exacerbation for one in 18 people over ¾ of a year.

  European J Internal Med 2014; 25: 491–495

Withdrawal

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

Helgo Magnussen, M.D., Bernd Disse, M.D., Ph.D., Roberto Rodriguez-Roisin, M.D., Anne Kirsten, M.D., Henrik Watz, M.D., Kay Tetzlaff, M.D., Lesley Towse, B.Sc., Helen Finnigan, M.Sc., Ronald Dahl, M.D., Marc Decramer, M.D., Ph.D., Pascal Chanez, M.D., Ph.D., Emiel F.M. Wouters, M.D., Ph.D., and Peter M.A. Calverley, M.D. for the WISDOM Investigators

N Engl J Med 2014; 371:1285-1294 | October 2, 2014 | DOI: 10.1056/NEJMoa1407154

Comments open through October 8, 2014

BACKGROUND

Treatment with inhaled glucocorticoids in combination with long-acting bronchodilators is recommended in patients with frequent exacerbations of severe chronic obstructive pulmonary disease (COPD). However, the benefit of inhaled glucocorticoids in addition to

MEDIA IN THIS ARTICLE

FIGURE 1

Summary: ICS/LABA or LAMA

- **GOLD C place in therapy**: For Group C ICS/LABA or LAMA is recommended**. Evidence is needed to support LAMA/LABA efficacy vs LAMA.**

- However evidence exist supporting LAMA/LABA efficacy non-inferior and even superior, in some case to LAMAs including tiotropium relative to FEV1, SGRQ, and exacerbations.

- Steroid usage for GOLD C/D does have exacerbation and **mortality** evidence to support combo therapy, however pneumonias and adverse effect is NNH 17

NEJM 2011; 364:1093-103. 2) Thorax 2003;58:399-404. 3) Am J Respir Crit Care Med. 2008;177:19-26. 4) Cochrane 2010;(5):CD007891. 5) Cochrane 2011;12: CD007033. 6) Ann Intern Med. 2011;155:179-191.

Thank You All For a Great First Year of Education!!

Extra Bonus Slides

Adverse Events: Long Acting Bronchodilators

Adverse Events: LABA Serious Adverse Events

- One meta-analysis of COPD suggested a mix of Beta-agonists (vs placebo) increased respiratory death (NNH= 131)
- Subsequent studies of LABA (RCT and Meta-analysis) refute this.
- **Bottom-line:** No clear support of increased serious respiratory adverse events with LABA in COPD

N Engl J Med. 2009; 360: 1592-95. 2) J Gen Intern Med. 2006;21:1011-9. & ACP journal club 2007; 146: 19

Head to Head: ICS/LABA or LAMA

- LABA vs Steroid, Review 7 RCTs, 5997 pts
  - No difference in exacerbation or quality of life
  - Steroids increased pneumonia and approached statistically significant increased mortality

GOLD C: ICS/LABA or LAMA

- LABA/Steroid = Placebo

2 RCTs, 3 year, 6112 pts, 4 arms:
Fluticasone vs salmeterol vs combo vs placebo

- LABA vs placebo Hospitalization NNT 32
- ICS/LABA vs placebo Mortality NNT 56
- ICS/LABA vs ICS NNT 44
- Most of the effect seems to come from the LABA

GOLD C: ICS/LABA or LAMA

- LABA/Steroid = Tiotropium (3 RCTs 1323 pts) salmeterol/ fluticasone 50/500ug BID vs tiotropium.
  - No difference in exacerbations or quality of life.
  - Drop-out high (39%) and no outcome on drop-outs.

Presentation Outline

- Available Devices
  - Personalized therapy
- Adherence
  - Ease of use
  - Device knowledge and competence
- Available Therapeutic Agents
  - Patient's need to be aware of medication onset, mechanism of action, and goals of therapy for each agent
- Evidence Based Approach to COPD Therapy
  - Efficacy Data
  - Safety Data