Idaho Society of Health-System Pharmacists

Chronic Obstructive Pulmonary Disease:

What's New in Therapeutic Management?

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Disclosures

- *Relevant disclosures or conflicts of interest*
  - CE Presenter, Sabrina Sherwood, PharmD
    - None
  - CE Mentors (David Young, PharmD; Zubin Bhakta, PharmD; Jennifer Wiederrich, PharmD, BCPS; Kristine Ferreira, PharmD, BCPS)
    - None
- *Off-Label Use of Medications*
  - Azithromycin for prevention of COPD exacerbations

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Learning Objectives

- Describe the importance of optimal COPD management in reducing morbidity and mortality
- Synthesize expert guidelines for COPD management
- Evaluate supportive evidence for the 2018 GOLD therapy management recommendations
- Construct a therapeutic regimen for a patient with COPD

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Abbreviations

- American Family Physician (AAFP)
- Confidence Interval (CI)
- COPD Assessment Tool (CAT)
- Chronic Obstructive Pulmonary Disease (COPD)
- Forced Expiratory Volume in 1 Second (FEV1)
- Forced Vital Capacity (FVC)
- Global Initiative for Chronic Obstructive Lung Disease (GOLD)
- Inhaled Corticosteroid (ICS)
- Long-acting β2-agonist (LABA)
- Long-acting Muscarinic Receptor Antagonist (LAMA)
- Modified Medical Research Council (mMRC)
- National Institute for Health and Care Excellence (NICE)
- Short-acting β2-agonist (SABA)
- Short-acting Muscarinic Receptor Antagonist (SAMA)
- St. George's Respiratory Questionnaire (SGRQ)
- Years old (y/o)

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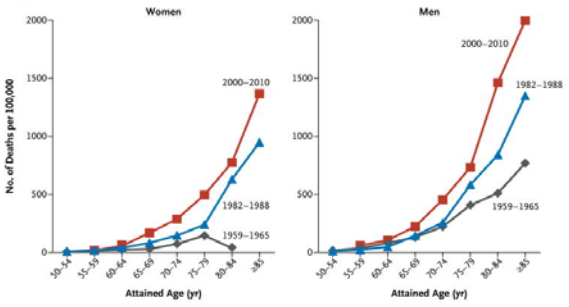
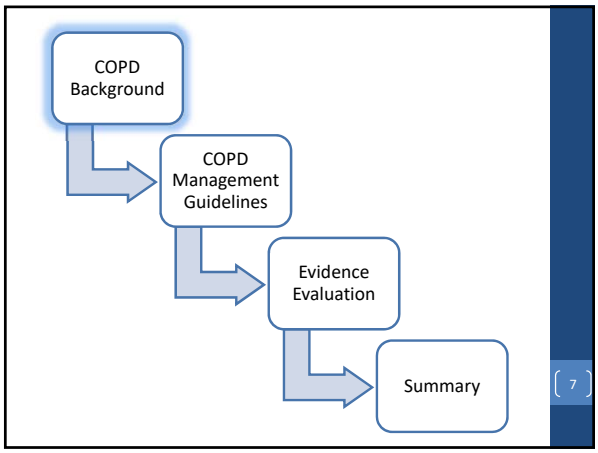
COPD Death Rates (United States)



Thun MJ, Carter BD, Feskanich D, et al. *The New England journal of medicine*. 2013;368(4):351-364.



Chronic Obstructive Pulmonary Disease (COPD)

- Common
  - Age > 40 years, Females > Males
  - Inhaled tobacco use
- Preventable
- Treatable
- Potentially disabling
  - Exacerbations can lead to hospitalization and death

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Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

Symptoms of COPD

- Shortness of breath
  - Worse with exercise
- Chronic Cough
  - Can be intermittent and unproductive
- Sputum production

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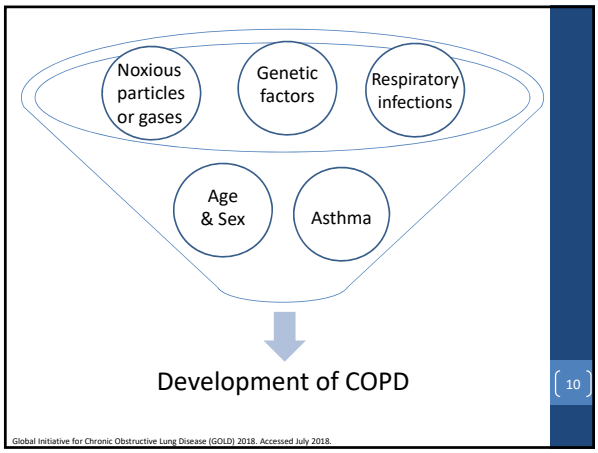
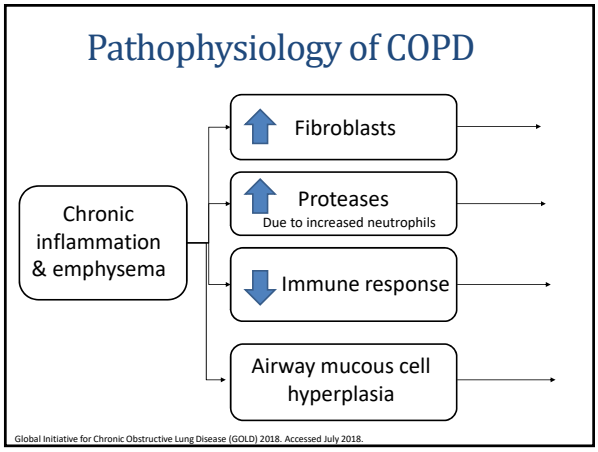
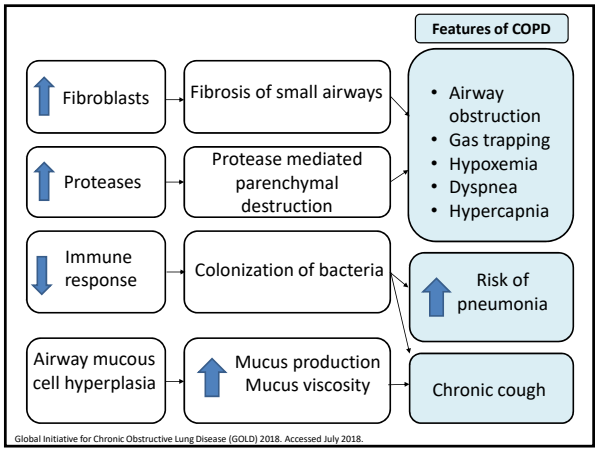

Noxious particles or gases
Genetic factors
Respiratory infections
Age & Sex
Asthma
Development of COPD
10
Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.


Pathophysiology of COPD
Chronic inflammation & emphysema
Fibroblasts
Proteases
Due to increased neutrophils
Immune response
Airway mucous cell hyperplasia
Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.


Features of COPD
Fibroblasts
Fibrosis of small airways
Proteases
Protease mediated parenchymal destruction
Immune response
Colonization of bacteria
Airway mucous cell hyperplasia
Mucus production
Mucus viscosity
• Airway obstruction
• Gas trapping
• Hypoxemia
• Dyspnea
• Hypercapnia
Risk of pneumonia
Chronic cough
Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

Spirometry for COPD Diagnosis

- Gold standard
- Calculates post-bronchodilator FEV1/FVC
  - Forced vital capacity (FVC): Maximum volume of air exhaled after a maximal inhalation
  - Forced expiratory volume in one second (FEV1): Maximum volume of air forcibly exhaled in one second

FEV1/FVC < 0.70 = Airflow Limitation

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Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

Severity of Airflow Limitation

Severity	Postbronchodilator FEV_1
GOLD 1 (Mild)	≥ 80% predicted
GOLD 2 (Moderate)	≥ 50% to < 80% predicted
GOLD 3 (Severe)	≥ 30% to < 50% predicted
GOLD 4 (Very severe)	< 30% predicted

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Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

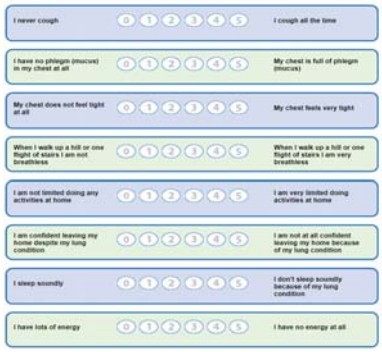
ABCD Assessment Tool

		Symptoms	
		CAT < 10 or mMRC 0-1	**CAT ≥ 10 or mMRC ≥ 2**
Exacerbation History	**≥ 2 exacerbations or ≥ 1 leading to hospital admission**	C	D
	0 or 1	A	B

CAT: COPD Assessment Test
mMRC: Modified Medical Research Council

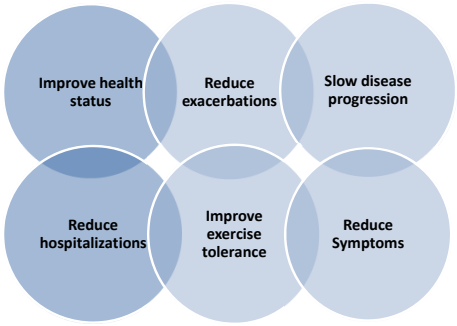
Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

COPD Assessment Test



COPD Assessment Test. GlaxoSmithKline. 2016. Available at: http://www.catestonline.org/english/indexEN.htm

Goals of Therapy



Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

Question #1

Assign a GOLD grade and severity group to the following patient:

KS is a 68 year old male

Spirometry Results	
FEV_1/FVC Ratio	0.50
FEV_1% of Predicted	40%

Clinic Assessment	
CAT Score	15
Exacerbation history	2 hospitalizations

A. GOLD grade 2, Group A
B. GOLD grade 3, Group C
C. GOLD grade 3, Group D
D. GOLD grade 4, Group C

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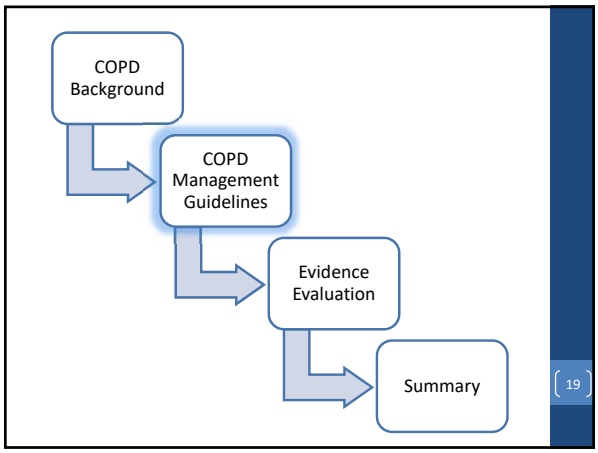

COPD Guidelines

- **Global Initiative for Chronic Obstructive Lung Disease (GOLD)**
  - Updated in 2018 (annual updates)
- American Family Physician (AAFP)
  - Updated in 2017
- National Institute for Health and Care Excellence (NICE)
  - Updated in 2010, guideline update expected in December 2018
- American Thoracic Society (ATS)
  - Updated in 2017

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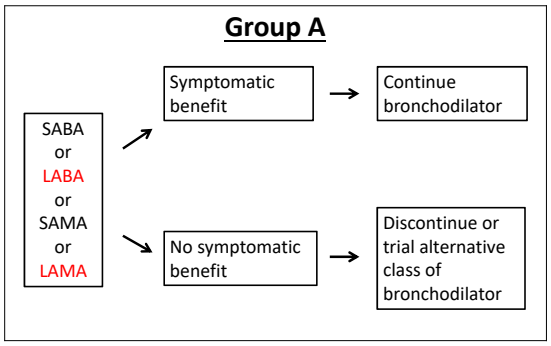
Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.
Gentry S, Gentry B. Chronic Obstructive Pulmonary Disease: Diagnosis and Management. Am Fam Physician. 2017 Apr 1;95(7):433-441.
National Clinical Guideline Centre. (2010). London: National Clinical Guideline Centre. Accessed July 2018.
Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J.

GOLD 2018: **Initial** Therapy Options

Group C	**Group D**
•LAMA +SABA PRN	• LABA + LAMA • Select patients: LABA + ICS +SABA PRN
Group A	**Group B**
One of the following: • SABA • LABA • SAMA • LAMA	One of the following: • LABA • LAMA +SABA PRN

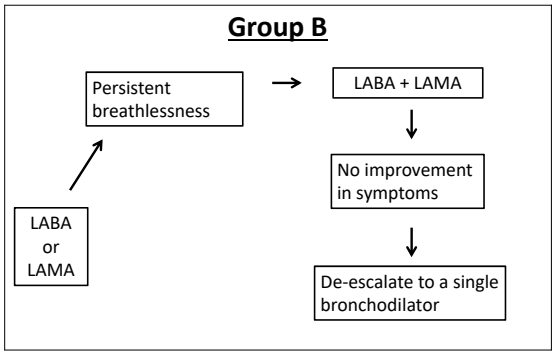
Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

GOLD 2018: Treatment **Algorithms**



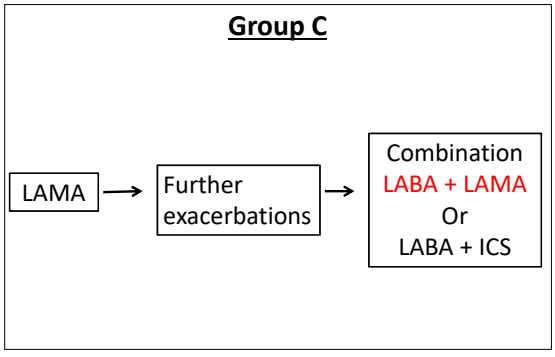
Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

GOLD 2018: Treatment **Algorithms**



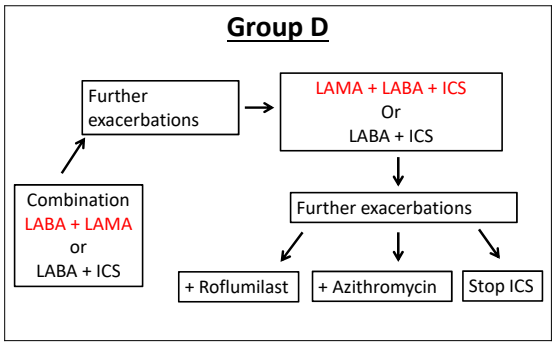
Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

GOLD 2018: Treatment **Algorithms**



Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

GOLD 2018: Treatment **Algorithms**



Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

Group D Therapy Recommendations

- Roflumilast (Daliresp)
  - Phosphodiesterase-4 (PDE-4) Inhibitor
  - Modest benefit in patients with FEV_1 < 50% predicted and chronic bronchitis
  - Therapy considerations:
    - Titrate dose for tolerability
    - Contraindicated in patients with moderate to severe hepatic impairment
    - Adverse effects: Neuropsychiatric effects, weight loss, headache, diarrhea
    - Substrate of CYP3A4 (major) and CYP1A2 (minor)

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Martinez FJ, Rabe KF, Sethi S, et al. RE(2)SPOND. Am J Respir Crit Care Med. 2016 Sep 1;194(5):559-67.
Lexi-Drugs Online. Hudson, OH: Lexi-Comp, Inc; 2018.

Group D Therapy Recommendations

- Macrolide
  - Azithromycin 250 mg/day or 500 mg three times weekly
  - Increased risk of bacterial resistance and impaired hearing tests
  - No evidence for use > 1 year
- Stop ICS after adequate trial
  - Elevated risk of adverse effects may outweigh benefits

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Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.

Question #2

KS is a 68 year old male with newly diagnosed COPD classified as GOLD grade 3, Group D. Which of the following medications is the most appropriate initial therapy choice for him?

A. **Tiotropium** (Spiriva) 18 mcg

B. **Umeclidinium** 62.5 mcg/**vilanterol** 25 mcg (Anoro Ellipta)

C. **Tiotropium** (Spiriva) 18 mcg + **budesonide** 160 mcg/**formoterol** 4.5 mcg (Symbicort)

D. **Fluticasone** 250 mcg/**salmeterol** 50 mcg (Advair)

Question #3

KS continues to have exacerbations after an adequate trial of Anoro Ellipta. His therapy is escalated to Spiriva + Symbicort, but he continues to have frequent exacerbations and is now hospitalized. Which therapeutic option would you consider for escalation of therapy?

A. Stop tiotropium 18 mcg

B. Add roflumilast 250 mcg once daily to the current regimen (dose to be increased in 4 weeks)

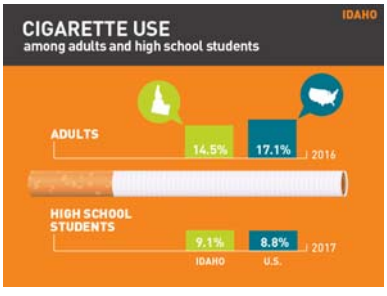
C. Add sulfamethoxazole 400 mg/trimethoprim 80 mg once daily to the current regimen

D. Switch budesonide/formoterol (Symbicort) to Fluticasone/salmeterol (Advair)

Optimal Management

- Smoking cessation:

  Only therapy with proven mortality benefit for patients with COPD

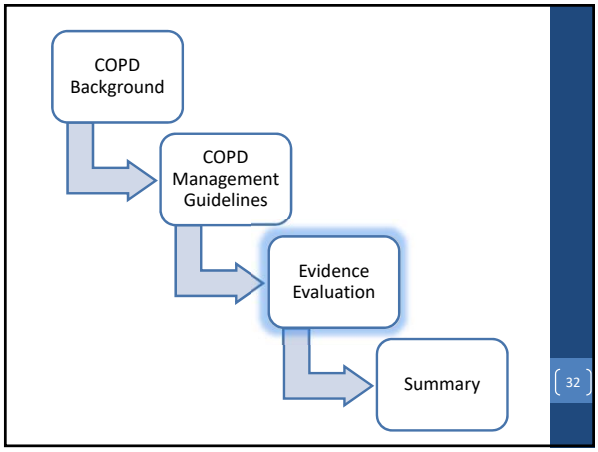


Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.
Truth initiative. 2016. Image available at: https://truthinitiative.org/tobacco-use-idaho

Optimal Management

- Transitions of Care
  - Hospital discharge:
    - Medication education, therapy selection, medication access barriers
  - Community:
    - Inhaler technique education, vaccinations, adherence
  - Clinic visit:
    - Review inhaler technique, assess control achieved with current therapy, adherence

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Accessed July 2018.
McKesson. Pneumovax 23. Image available at: https://mms.mckesson.com/product/911398/Merck-00006483703



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Supportive Evidence for GOLD 2018 Recommendations

- **FULFIL Trial**
  - Triple therapy vs dual therapy
- **RE²SPOND**
  - Role of roflumilast
- **WISDOM Trial**
  - Withdrawal of ICS
- **COLUMBUS Trial**
  - Role of macrolide antibiotics

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FULFIL Trial

Once-daily Triple Therapy (LABA/LAMA/ICS) for Patients with Chronic Obstructive Pulmonary Disease

Authors: Lipson DA, Barnacle H, Birk R, et al.
Publication Date: August 2017

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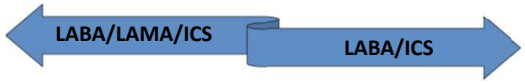
Lipson DA et al. *Am J Respir Crit Care Med* 2017; 196(4):438-446.

Methods

- Randomized, double-blind, prospective trial



Fluticasone furoate/**umelidinium/vilanterol** (100mcg/62.5mcg/25mcg)

Budesonide/formoterol Turbuhaler (400mcg/12mcg)

Co-Primary Endpoints at 24 Weeks:

- FEV_1 change from baseline (clinically meaningful change = ≥ 100 mL)
- St. George's Respiratory Questionnaire (SGRQ) change from baseline (clinically meaningful change = ≥ 4 unit decrease)

Lipson DA et al. *Am J Respir Crit Care Med* 2017; 196(4):438-446.

SGRQ

- 50-item questionnaire
- Developed to measure quality of life in patients with disease of airway obstruction
- More time intensive than the COPD Assessment Test (CAT)

Questions about other effects that your chest trouble may have on you these days.

Please tick (✔) in ***each box*** that applies to you ***these days***:

	True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

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Health Status Research. St. George's Respiratory Questionnaire. Accessed September 2018. Available at: http://www.healthstatus.sgul.ac.uk/sgrq

Results

- n = 1,810 (intention to treat cohort)
- Baseline characteristics:
  - Well balanced in the intention to treat cohort
  - Mostly male, average age 64 years
  - Almost half were current smokers (44%)
  - Average FEV_1: 45% predicted (similar between groups)

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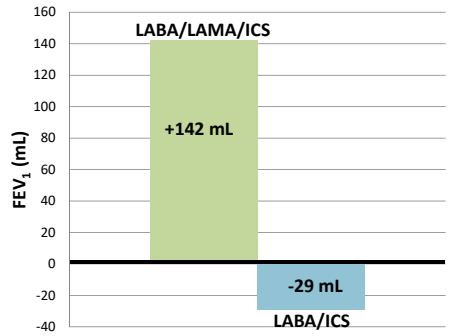
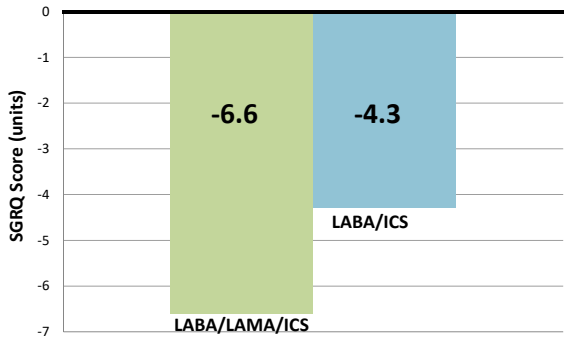
Lipson DA et al. *Am J Respir Crit Care Med* 2017; 196(4):438-446.

Change in FEV_1 from baseline



Statistically (p<0.001) and clinically significant improvement in FEV_1 in the triple therapy cohort

Change in SGRQ from baseline



Statistically (p<0.001) and clinically significant improvement in SGRQ in the triple therapy cohort

Results: Secondary Endpoints

- Moderate to severe exacerbation rates
  - Mean annual rate in the triple therapy cohort (0.22) was lower than the LABA/ICS cohort (0.34); This is a relative risk reduction of **35%** in triple therapy cohort (95% CI, 14 to 51%; p = 0.002)
- Adverse events
  - Similar between groups
  - Reflected the known profiles of the components

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Lipson DA et al. *Am J Respir Crit Care Med* 2017; 196(4):438-446.

FULFIL Conclusion

- A trial of LABA/LAMA/ICS (either as a single inhaler or as the individual components) is an appropriate option for patients with severe COPD uncontrolled with LABA/LAMA therapy

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Lipson DA et al. *Am J Respir Crit Care Med* 2017; 196(4):438-446.

RE^{2}SPOND

Effect of Roflumilast and LABA/ICS on COPD Exacerbations

Authors: Martinez FJ, Rabe KF, Sethi S, et al.
Publication Date: September 2016

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Martinez FJ et al. *Am J Respir Crit Care Med* 2016;194(5):559-67.

Methods

- Double blind, placebo-controlled, randomized trial

Primary Endpoint at 52 Weeks:
- Rate of moderate or severe COPD exacerbations

Selected Secondary Endpoints at 52 Weeks:
- Rate of moderate or severe COPD exacerbations treated with antibiotics
- Mean change from baseline FEV_1
- Mean change from baseline CAT

Martinez FJ et al. *Am J Respir Crit Care Med* 2016;194(5):559-67

Methods Continued & Results

- Inclusion criteria:
  - ≥40 years old
  - Severe or very-severe COPD
  - ≥2 exacerbations or hospitalizations in the previous year
  - Therapy with LABA/ICS +/- LAMA ≥ 3 months
- n = 2,352
- Baseline characteristics:
  - Well balanced
  - Baseline % Predicted FEV_1: Mean of 33%
  - Baseline CAT: Mean of 18 **(Group D patients)**

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Martinez FJ et al. *Am J Respir Crit Care Med* 2016;194(5):559-67

Results

- Primary Outcome:
  - Rate of moderate/severe exacerbations statically insignificant between groups
- Selected Secondary Outcomes:
  - Mean change from baseline in FEV_1 at 52 weeks in favor of roflumilast ($p<0.0001$)
  - Rate of moderate or severe exacerbations not significantly different
  - Mean change from baseline in CAT score not significantly different
  - Adverse event-related discontinuations were higher in the roflumilast cohort (11.7%) vs placebo (5.4%)

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Martinez FJ et al. *Am J Respir Crit Care Med* 2016;194(5):559-67

Post-Hoc Analysis: RE^{2}SPOND

- Roflumilast significantly reduced the rate of moderate or severe exacerbations in participants with a history of more than **3 exacerbations** and/or **1 or more hospitalizations (severe exacerbation)** in the prior year

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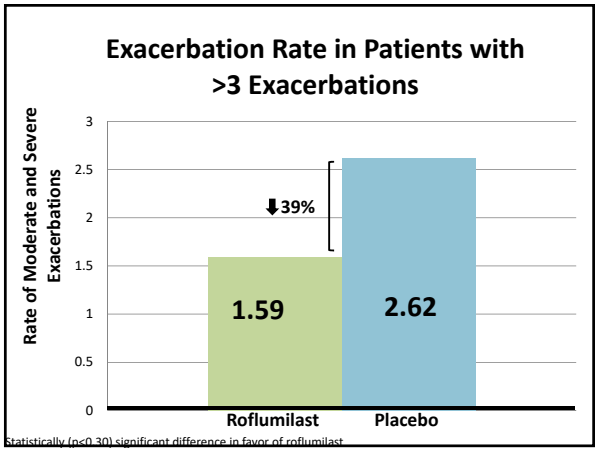
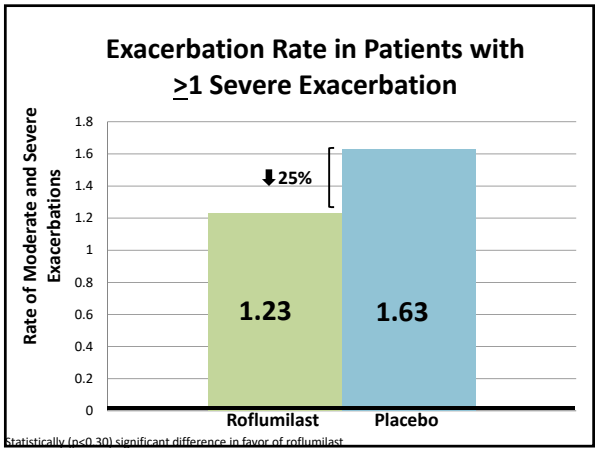
Martinez FJ et al. *Am J Respir Crit Care Med* 2016;194(5):559-67.



Statistically (p<0.30) significant difference in favor of roflumilast



Statistically (p<0.30) significant difference in favor of roflumilast

RE²SPOND Conclusion

- A trial of roflumilast may be considered in GOLD **Group D** patients with **>3 exacerbations** and/or ≥**1 hospitalizations** in the prior year

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Martinez FJ et al. *Am J Respir Crit Care Med* 2016;194(5):559-67.

WISDOM

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

Authors: Magnussen H, Disse B, Rodriguez-Roisin R, et al
Publication Date: October 2014

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Magnussen H et al. *N Engl J Med* 2014;371(14):1285-94.

Methods

- Double-blind, parallel-group study

- Primary endpoint at week 52
  - Time to first moderate or severe COPD exacerbation
- Inclusion:
  - ≥40 years old
  - Former or current smoker
  - FEV_1<50%
  - ≥1 exacerbation in the previous year

Magnussen H et al. *N Engl J Med* 2014;371(14):1285-94.

Results

- n = 2485 subjects
- Baseline characteristics:
  - Well balanced
  - Mean age: 63.8 years old
  - Mean % Predicted FEV1: 32.8%
  - Mean mMRC Score: 1.8

Magnussen H et al. *N Engl J Med* 2014;371(14):1285-94.

Results

- Primary endpoint:
  - Time to first moderate or severe exacerbation
    - **Non-inferiority** when ICS discontinued (HR 1.06)
- Selected secondary endpoint:
  - Mean reduction from baseline of FEV1 was 38mL greater in the withdrawal group than the continuation group ($p<0.001$) at week 18

Magnussen H et al. *N Engl J Med* 2014;371(14):1285-94.

WISDOM Conclusion

The withdrawal of an ICS from a regimen containing LAMA/LABA/ICS may be considered in GOLD **Group D** patients

Magnussen H et al. *N Engl J Med* 2014;371(14):1285-94.

COLUMBUS

Azithromycin Maintenance Treatment in Patients with Frequent Exacerbations of COPD

Authors: Uzun S, Djamin R, Kluytmans J, et al
Publication Date: April 2014

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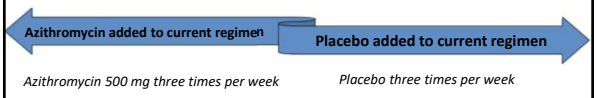
Uzun S et al. *Lancet Respir Med* 2014; 2(5):361-8.

Methods

- Randomized, double-blind, placebo-controlled trial



Azithromycin 500 mg three times per week

Placebo three times per week

- Primary endpoint at week 52
  - Rate of COPD exacerbation (any severity)
- Inclusion:
  - ≥18 years of age
  - ≥3 exacerbations in the previous year treated with steroids or antibiotics

Uzun S et al. *Lancet Respir Med* 2014; 2(5):361-8.

Results

- n = 92 subjects
- Baseline characteristics:
  - Well balanced
  - Mean age: 64
  - Mean % Predicted FEV_1: 44.6%
  - Mean SGRQ total score: 57.5

Uzun S et al. *Lancet Respir Med* 2014; 2(5):361-8.

Results

- Primary endpoint:
  - **Significant reduction in exacerbation rate in the azithromycin cohort vs placebo (Adjusted rate ratio of 0.58, 0.42-0.79; p=0.001)**
- Selected secondary endpoints:
  - Azithromycin group experienced more diarrhea (19%) than placebo (2%)
  - No significant difference in FEV1
  - Macrolide-resistant bacteria noted in three (6%) of patients in the azithromycin group compared with 11 (24%) in the placebo group (p=0.036)

Uzun S et al. *Lancet Respir Med* 2014; 2(5):361-8.

COLUMBUS Conclusion

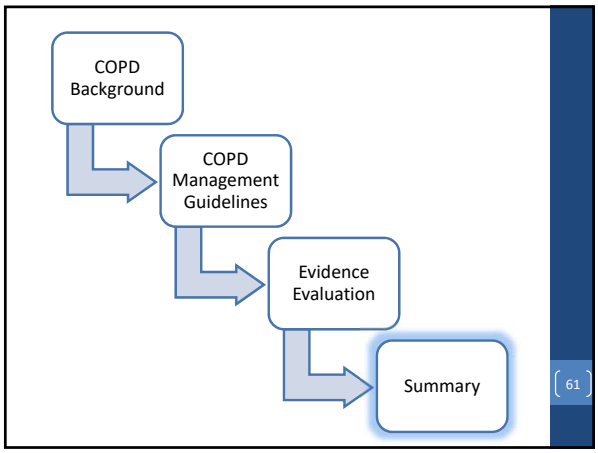
The addition of azithromycin as maintenance treatment may be considered in GOLD **Group D** patients to reduce exacerbation rate

Magnussen H et al. *N Engl J Med* 2014;371(14):1285-94.

Think, Pair, Share

From the studies listed below, write down which study you believe will have the greatest impact on COPD management. List 2-3 reasons why you chose that study.

1. FULFIL
2. RE^{2}SPOND
3. WISDOM
4. COLUMBUS



Key Takeaways

1. COPD related mortality continues to rise
2. Long acting bronchodilators (LAMA and LABA inhalers) are being increasingly recognized as cornerstones to chronic therapy
3. Regimens including LAMA inhalers are becoming preferential based on a growing evidence base
4. The FULFIL, RE^{2}SPOND, WISDOM, and COLUMBUS trials are well recognized studies that support newer GOLD guideline recommendations
5. The role of the pharmacist in COPD management is apparent at every stage of a patient's care

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Assessment Question #1

Which of the following therapy options has been shown to decrease mortality in patients with COPD?

A. Tiotropium (Spiriva)
B. Fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta)
C. Budesonide (Pulmicort)
D. Smoking Cessation

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Assessment Question #2

Which therapeutic class is recommended as a potential initial treatment option in every COPD disease group (A,B,C,D)?

A. LAMA
B. LABA
C. ICS
D. LABA/LAMA combination

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Assessment Question #3

Which trial found non-inferiority in time to first moderate/severe exacerbation when fluticasone propionate was withdrawn from a treatment regimen with tiotropium and salmeterol in patients with frequent COPD exacerbations?

A. COLUMBUS
B. FULFIL
C. WISDOM
D. RE^{2}SPOND

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Assessment Question #4

CR is a 54 year old female with newly diagnosed COPD classified as GOLD grade 2, Group B. She does not complain of severe breathlessness. Which of the following medications is the most appropriate initial therapy choice for her?

A. **Tiotropium** (Spiriva) 18 mcg
B. **Umeclidinium** 62.5 mcg/**vilanterol** 25 mcg (Anoro Ellipta)
C. **Tiotropium** (Spiriva) 18 mcg + **budesonide** 160 mcg/**formoterol** 4.5 mcg (Symbicort)
D. **Fluticasone** 250 mcg/**salmeterol** 50 mcg (Advair)

Questions?

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