An Update on COPD and New Devices

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Today's Objectives

1. Identify recently approved inhalers and devices used to treat Chronic Obstructive Pulmonary Disease (COPD).
2. Discuss the advantages and disadvantages of using specific inhalers/devices.
3. Explain how to use each specific inhaler discussed in today's presentation.
4. Recall how to develop an applicable treatment plan for a patient suffering from COPD for given patient case scenarios.

Disease Overview

Chronic Obstructive Pulmonary Disease

• GOLD Definition1
  - Common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases

Known Exposures1,2

Predisposing Factors1,2

• Genetic abnormalities
• Abnormal lung development
• Accelerated aging
Morbidity and Mortality
- 4th leading cause of death in the U.S
- 120,000 deaths annually
- ~24 million American adults have COPD
- Burden may be even greater due to underreporting

Pathophysiology
- Chronic, progressive disease causing airflow obstruction that is minimally reversed with bronchodilators

Diagnosis
- Spirometry remains the most reproducible and objective measurement of airflow limitation
  - Post-bronchodilator FEV₁/FVC <0.70 confirms the presence of persistent airflow limitation
  - Assessing the degree of reversibility of airflow limitation to inform therapeutic decisions is no longer recommended
  - Only a weak correlation exists between FEV₁ and quality of life

Spirometry Update
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The Refined ABCD Assessment Tool

Pharmacotherapy
Double checked today on Dipiro
Allison Liao, 1/30/2017
Treatment Overview

- Step therapy
- Mild cases start with short-acting beta-agonists (SABA)
- Long-acting beta-agonists (LABA) +/- Long-acting muscarinic antagonists (LAMA) are mainstay of therapy
- Inhaled corticosteroids (ICS) are controversial, but may have a place in advanced disease
- Oxygen therapy is last line
- Personalized approach

Medication Classes

- Bronchodilators
  - SABA
  - LABA
- Antimuscarinic/anticholinergics
  - LAMA
- Methylxanthines
- Inhaled Corticosteroids
- Oxygen

Device Categories

- Metered Dose Inhaler (MDI)
- Dry Powder for Inhalation (DPI)
- Soft Mist Inhaler (SMI)

Newest FDA Approved Devices

Bevespi Aerosphere®

- Active ingredients: Glycopyrrolate 9mcg/ formoterol fumarate 4.8mcg
- LABA/LAMA
- MDI
- Indication: maintenance treatment of moderate/severe COPD
- Approved: 4/7/16
- Directions: 2 inhalations twice daily
- Common ADR's (≥2% than placebo): cough, urinary tract infection
- Co-suspension technology®
2 this slide is a little redundant and could be removed
Michelle Sahr, 2/5/2017
Studies
Two 24 week randomized, double-blind, placebo-controlled, parallel-group trials:

- Greater increase in FEV\textsubscript{1} with Bevespi versus glycopyrrolate 19 mcg, formoterol fumarate 9.6 mcg and placebo at 24 weeks
- 150 ml improvement in predose FEV\textsubscript{1} at 24 weeks

Compared five doses of combination glycopyrrolate/formoterol fumarate to individual medications and tiotropium 18 mcg:

- Bevespi showed statistically significant results with similar ADRs to comparators

Bevespi Aerosphere°3

Proper Use
1. Shake the inhaler before each use (including priming)
2. Remove the cap
3. Prime the inhaler 4 times before first use
4. Exhale as much as you comfortably can
5. Close your lips around the mouthpiece and tilt your head back, keeping your tongue below the mouth piece
6. Press the canister down while deeply and slowly inhaling
7. Once you are done breathing in, remove the canister from your mouth and hold your breath for up to 10 seconds
8. Breathe out and repeat steps for second inhalation

Additional Information
- Clean the actuator once a week
- Re-prime inhaler with 2 puffs when ≥7 days without use

Utibron°7-9 Neohaler®

- Active ingredients: glycopyrrolate 15.6 mcg/indacaterol maleate 27.5 mcg
- LABA/LAMA
- DPI
- Approved: 10/29/15
- Indicated for maintenance treatment of COPD
- Dosing: Inhale contents of capsule twice daily
- Common ADR’s (≥2% of placebo): nasopharyngitis and hypertension
- Currently off-market
Studies²,⁷,⁸

Two 12-week placebo-controlled lung function trials
- UTIBRON NEOHALER 27.5 mcg/15.6 mcg, indacaterol 27.5 mcg, glycopyrrolate 15.6 mcg, or placebo.

52-week long-term safety study
- 614 patients treated with indacaterol/glycopyrrolate 27.5 mcg/15.6 mcg twice-daily, indacaterol/glycopyrrolate 27.5/31.2 mcg twice-daily or indacaterol 75 mcg once-daily.
- ADRs: upper and lower respiratory tract infection, pneumonia, diarrhea, headache, gastroesophageal reflux disease, hyperglycemia, rhinitis

Additional Information⁷
- Use caution in patients allergic to milk proteins

Propriy Use⁷
1. Pull off cap
2. Open inhaler
3. Remove capsule from blister card
4. Insert capsule into capsule chamber
5. Close the inhaler until "click"
6. Pierce the capsule by pushing in both side buttons until "click" and release
7. Breathe out
8. Hold inhaler with buttons to left and right, wrap lips around mouth piece, breathe in
9. Hold breath for 5-10 seconds and breathe out
10. Repeat inhalation steps if powder still available in capsule and discard capsule

Seebri Neohaler©¹⁰,¹¹
- Active ingredients: glycopyrrolate 15.6 mcg
- LAMA
- DPI
- Approved: 10/29/15
- Indicated for maintenance treatment of COPD
- Dosing: Inhale contents of 1 capsule twice daily
- Common ADRs (≥2% more than placebo): nasopharyngitis, upper respiratory tract infections
- Currently off-market

Studies¹⁰,¹²-¹³

Four 12-week, placebo-controlled trials in 2908 subjects with COPD
- Significant improvement in lung function at Day 1 and Week 12 for Seebri®
- Improvement in dyspnea, health status and use of rescue inhaler
- 61.2% of patients had moderate COPD and 37.8% had severe COPD

One 52-week long-term safety study
- Glycopyrrolate 15.6 mcg twice-daily vs. indacaterol 75 mcg once-daily
- ADRs 2% greater than indacaterol: diarrhea, nausea, upper abdominal pain, fatigue, bronchitis, pneumonia, rhinitis, back pain, arthralgia, dyspnea, and wheezing.
- Consistent ADRs and discontinuation between both groups

Proper Use¹⁰
1. Pull off cap
2. Open inhaler
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4. Insert capsule into capsule chamber
5. Close the inhaler until "click"
6. Pierce the capsule by pushing in both side buttons until "click" and release
7. Breathe out
8. Hold inhaler with buttons to left and right, wrap lips around mouth piece, breathe in
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10. Repeat inhalation steps if powder still available in capsule and discard capsule
**Additional Information**

- Should not be used in patients with a severe allergy to milk proteins

**Stiolo® Respimat®**

- Active ingredients: tiotropium bromide 2.5 mcg and olodaterol 2.5 mcg
- LAMA/LABA
- SMI
- Approved: 5/21/15
- Indicated for maintenance treatment of COPD
- Dosing: 2 puffs once daily
- Common ADRs (>3% more than active control): nasopharyngitis, cough and back pain

**Studies**

Two 52-week trials compared Stiolo Respimat vs olodaterol 5 mcg vs tiotropium 5 mcg

- Stiolo Respimat showed significant improvement in FEV1, AUC0-3hr, and trough FEV1 after 24 weeks vs active controls
- Lung improvement was seen within 5 minutes
- Improvement lasted 52 weeks during trial

**How to:**

1. Remove clear base
2. Insert medication cartridge
3. Replace clear base
4. Turn the clear base in the directions of the red arrows
5. Open the cap
6. Press the grey button, with the inhaler pointed to the ground, until a mist is seen and then repeat steps 4-6 three more times

1. Turn the clear base towards the red arrows
2. Open the cap
3. Breathe out fully
4. Wrap your lips around the mouth piece
5. Press the grey button while slowly breathing in
6. Hold your breath for 10 seconds
7. Repeat for 2 doses
Additional Information\textsuperscript{14,15}

- The dose indicator shows approximately how many puffs are left.
- When the pointer enters the red area of the scale, there is enough medicine for 7 days or 3 days.
- Throw away the inhaler 3 months after insertion of cartridge into inhaler.
- If a Respimat has not been used for >3 days, release 1 puff towards the ground.
- If a Respimat has not been used for >21 days, repeat steps until a cloud is seen and then release 3 additional puffs (initial priming steps).

Spiriva\textsuperscript{®} Respimat\textsuperscript{®} 15

- Active ingredients: Tiotropium bromide 1.25 mcg or 2.5 mcg.
- LAMA
- SMI
- Indications:
  - Maintenance treatment of moderate/severe COPD
  - Maintenance treatment of asthma in patients 12 years of age and older.
- Approved: 9/24/14
- Directions: 2 inhalations once daily.
- Common ADR’s (≥3% than placebo): pharyngitis, cough, dry mouth, and sinusitis.

Studies\textsuperscript{15}

Five 12 and 48-week placebo-controlled lung function trials:
- Spiriva Respimat 5 mcg, 10 mcg, or placebo.
- Significant improvement in trough FEV1 compared to placebo.

Three-year long-term safety study versus Spiriva HandiHaler:
- 5711 patients treated with Spiriva Respimat or Spiriva HandiHaler.
- All-cause mortality was similar between both groups.
- Similar time to first COPD exacerbation between both groups.
- ADRs: dry mouth, pharyngitis, cough, sinusitis.

Prior to First Use\textsuperscript{15}

- Insert cartridge into inhaler.
- Prime the inhaler by actuating toward the ground until an aerosol cloud is visible.
- Repeat the process three more times.
- The unit is then considered primed and ready for use.
- If not used for more than 3 days, actuate the inhaler once.
- If not used for more than 21 days, actuate the inhaler four times.

Proper Use\textsuperscript{15}

- Turn the clear base.
- Open the cap and close your lips around the mouthpiece.
- Press the dose-release button and inhale.

Striverdi\textsuperscript{®} Respimat\textsuperscript{®} 16

- Active ingredients: Olodaterol 2.5 mcg.
- LABA
- SMI
- Indications: Maintenance treatment of moderate/severe COPD.
- Approved: 7/31/14.
- Directions: 1 inhalation once daily.
- Common ADR’s (≥2% than placebo): nasopharyngitis, upper respiratory tract infection, bronchitis, urinary tract infection, cough, dizziness, rash, diarrhea, back pain and arthralgia.
Studies

Four pairs of replicate placebo-controlled trials in 3,533 COPD patients

• Significant improvements in FEV1 AUC_0-3hr and trough FEV1 compared to placebo at week 12 and 24.
• Demonstrated a bronchodilatory treatment effect at 5 minutes after the first dose with a mean increase in FEV1 compared to placebo.
• Less rescue albuterol use compared to patients treated with placebo.

Proper Use

• Same as Stiolto Respimat & Spiriva Respimat

Incruse Ellipta®

• Active ingredients: Umeclidinium 62.5 mcg
• LAMA
• DPI
• Indications: Maintenance treatment of moderate/severe COPD
• Approved: 4/30/14
• Directions: 1 inhalation once daily
• Common ADR’s (≥2% than placebo): nasopharyngitis, upper respiratory tract infection, cough, arthralgia.

Image available from http://us.gsk.com/media/423342/incruse_frontopen.jpg

Studies

Two placebo controlled lung function trials

• Demonstrated a larger increase in mean change from baseline in trough FEV1 relative to placebo.

Four 12-week combination with an ICS/LABA efficacy trials

• (Incruse Ellipta 62.5 mcg + ICS/LABA) or (placebo + ICS/LABA)
• + Fluticasone Furoate 100 mcg/Vilanterol 25 mcg
• + Fluticasone Propionate 250 mcg/Salmeterol 25 mcg
• Larger mean change from baseline in trough FEVs relative to placebo.

Proper Use

• Open the cover of the inhaler
  • Counter will count down by 1 number
• Breathe out
• Inhale the medicine
  • Close lips firmly around mouthpiece.
  • Take a long, steady, deep breath in through the mouth.
  • Do not block the air vent with fingers

• Remove the inhaler and hold breath for about 3 to 4 seconds
• Breathe out slowly and gently
• Close the inhaler
Additional Information

• When less than 10 doses remaining in the inhaler, the left half of the counter shows red as a reminder to get a refill.

Anoro Ellipta®

• Active ingredients: Umeclidinium 62.5 mcg/Vilanterol 25 mcg
• LAMA + LABA
• DPI
• Indications: Maintenance treatment of moderate/severe COPD
• Approved: 12/18/13
• Directions: 1 inhalation once daily
• Common ADR’s (≥1% than placebo): pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain, and chest pain.

Image available from: http://www.startwithanoro.com/images/instructions-for-use-ellipta.png

Studies

Four 6 month lung function trials with 4,733 subjects
• Compared Anoro Ellipta, umeclidinium 62.5 mcg, vilanterol 25 mcg, and placebo
• Anoro Ellipta demonstrated a larger increase in mean change from baseline in trough FEVs compared to all three controls

Proper Use

• Same as Incruse Ellipta

Image available from: https://www.drugs.com/pro/images/2dbd0671-c565-40c5-bf0f-e324db26799c/anoro-ellipta-spl-graphic-23.jpg

LABA Black Boxed Warning

Long-acting beta2-adrenergic agonists (LABAs), increase the risk of asthma-related death.

A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol.

This finding of an increased risk of asthma-related death with salmeterol is considered a class effect of all LABAs.

LABA Class Wide Warnings/Precautions

• Cardiovascular risks
• Convulsive disorders or thyrotoxicosis
• Hypokalemia
• Diabetes and ketoacidosis
LAMA Class Wide Warning/Precautions

• Narrow-angle glaucoma
• Urinary retention

Clinical Pearls

• Proper inhaler training and technique is assessed frequently.
• Choice of inhaler greatly depends on availability, cost, prescribing physician, and ability of patient.
• Nebulized treatments should only be used if clear clinical benefit over cheaper, more portable options.

References

4. Glucayne/Fumarose (Buey)inhalation powder for COPD. 2015 Oct 06,151251 155-158. PmID: 25997986
Question #2
A barrier to using many of these COPD inhalers/devices is due to...
A. Cost
B. Patient's lack of accepting COPD diagnosis
C. Efficacy
D. Concomitant smoking status

Question #3
How many times does Bevespi Aerosphere® need to be primed before first use?
A. 1
B. 2
C. 4
D. 6

Question #4
Patient PM is a 42 year old on Proair® and Spiriva® who has had two COPD exacerbations in the last month. PM's doctor would like help choosing the next step of therapy that is most convenient for the patient. What is your recommendation? Assume Spiriva® will be discontinued and there are no insurance issues.
A. Spiriva® Respimat®
B. Symbicort®
C. Stiolto® Respimat®
D. Incruse Ellipta®