I have the following relationships to disclose:

No current relationship, remotely held stock in Altria and British Tobacco

I will discuss the following off label use and/or investigational use in my presentation:

- E-cigarettes for tobacco cessation
- Post purchase modifications of e-cigarettes

Lancet 2015;385:857-66
Disclosures
COPD Objectives

Epidemiology
Identify patients with COPD

Management
– Outpatient/Inpatient
– Risk factor modification
– Role of inhaled medications
– Role of oral medications
  ▪ Exercise
  ▪ Oxygen
# COPD matters

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Ischemic Heart Disease</td>
<td>1</td>
<td>648K</td>
<td>1</td>
<td>563K</td>
<td>Down 14%</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>177K</td>
<td>2</td>
<td>172K</td>
<td>Down 3%</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>3</td>
<td>143K</td>
<td>3</td>
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</tr>
<tr>
<td>COPD</td>
<td>4</td>
<td>97K</td>
<td>4</td>
<td>154K</td>
<td>Up 58%</td>
</tr>
<tr>
<td>Lower Respiratory Tract Infections</td>
<td>5</td>
<td>90K</td>
<td>7</td>
<td>85K</td>
<td>Down 8%</td>
</tr>
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### COPD matters

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</table>

COPD Mortality Worldwide

Ischaemic heart disease
Cerebrovascular disease
Lower resp infection
Diarrhoeal disease
Perinatal disorders
COPD
Tuberculosis
Measles
Road Traffic Accidents
Lung Cancer

1990

3rd
6th

2020

Suicide
HIV
Stomach Cancer

COPD Epidemiology

Prevalence: 12-24 mill US, 210 mill worldwide
- <4% Washington, > 9% Kentucky
- 37% undiagnosed (NHANES III)
- ~15-20% of smokers

Morbidity:
- 2010: 715,000 hospitalizations
- 1.5 million ED visits

Mortality:
- 134,676 deaths in 2010 (3rd/4th most common and increasing)
  - 90% (3 mill) in low and middle income countries worldwide
- 1 death every 4 min (14 during this lecture)
- Only cause of death in top 10 that is rising

Cost:
- 49.9 billion

Number Deaths x 1000

Source: US Centers for Disease Control and Prevention, 2002
~72,000 women died (2009)....53%
More hospitalizations (57% of 715,000)
More severe and younger

- 71% LVRS/transplant group (<53yo, FEV1<40%) 2000
- 66% of very severe (FEV1<50%, <55yo) 2011
- ~80% of nonsmoking COPD (15%) and majority of nonsmoking NSCCA in women
Why?

Increased Smoking

- “You have come a long way baby, It’s a woman thing”
- Different brands (Slims, Eve, Satin) may have different payloads

Behavioral

- Deeper inhalation, longer breath-hold, different

Environmental exposure

Physiologic

- Airway growth, size
- Hormonal sensitivity
Risk Factors for COPD

- Cigarette smoke
- Occupational dust and chemicals
- Environmental tobacco smoke (ETS)
- Indoor and outdoor air pollution

Nutrition
Infections
Socio-economic status

Aging Populations
Definition of COPD

- **Chronic Obstructive Pulmonary Disease** is a preventable and treatable disease with some significant extrapulmonary effects.

- The pulmonary component is characterized by airflow limitation that is not fully reversible. \( \text{FEV/FVC}<0.70 \)

- The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

- Severe COPD leads to respiratory failure, hospitalization and death

Global Initiative for Chronic Obstructive Lung Disease. Goldcopd.org. NIHLBI & WHO
COPD heterogeneity

- CHRONIC BRONCHITIS
- EMPHYSEMA
- ASTHMA
- AIRFLOW OBSTRUCTION

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Heterogeneity of COPD symptoms

• Breathlessness
• Exercise intolerance
• Cough with or without purulence
• Wheezing
• Respiratory failure
• Acute exacerbations
COPD Limits Daily Activities for Patients Regardless of Age

P17. How much do you feel your respiratory condition limits what you can do in each of the following areas? n=3,265


© 2012 Virginia Mason Medical Center
COPD: WHAT IT IS!

Figure 1: Comparison of airway features in a healthy individual and in a patient with chronic obstructive pulmonary disease.

(A) Normal airway. (B) In chronic obstructive pulmonary disease airways are narrowed by infiltration of inflammatory cells, mucosal hyperplasia, and deposition of connective tissue in the peribronchiolar space.23

Pathophysiology of COPD

Airflow Limitation

Normal

Parenchymal tethering

COPD

Loss of tethering


© 2012 Virginia Mason Medical Center
Normal

Emphysema
Radiographic Changes in COPD

- Low, Flattened Diaphragm
- Increased A-P Diameter
- Hyperinflation
Decline in FEV1/TIME

MALE

FEMALE

Kohansal R, et al. Am J Respir Crit Care Med. 2009;180:3-10
Natural History of COPD

- FEV₁ (liters)
- Age (years)

Lines represent:
- Nonsmoker
- Average smoker
- Susceptible smoker

Highlights:
- Symptoms decrease with age.
- DEath occurs at a younger age for susceptible smokers compared to nonsmokers and average smokers.

© 2012 Virginia Mason Medical Center
COPD as a multisystem disease

Cardiovascular disease
Osteoporosis and low testosterone
Malnutrition and muscle wasting
Depression (23% vs 16.8% in nonCOPD)
  – Depressed COPD pts had higher mortality
  – More likely in COPD pts on oxygen

INFLAMMATION IN COPD

Small airway disease
Airway inflammation
Airway remodeling

Parenchymal destruction
Loss of alveolar attachments
Decrease of elastic recoil

AIRFLOW LIMITATION
**COPD PATHOLOGY**

**Peribronchial fibrosis**

**Loss of alveolar units**

**Cigarette smoke**

- Biomass particles
- Particulates

**Host factors**

- Amplifying mechanisms

**Pathogenesis of COPD**

- Oxidative stress
- Proteinases
- Repair mechanisms

**New Ideas**

- Cigarette smoke
- Biomass particles
- Particulates

**Amplifying mechanisms**

- Related to adenosine receptor affinity/density
- Blocked by simvastatin

**Anti-oxidants**

**Anti-proteinases**

**COPD PATHOLOGY**

- RSV in 33%
- FEV1 decline
- Latent viruses

**Genetics**

- Dust: (Al-SiO₄), kaolin
- Starvation

**Related to adenosine receptor affinity/density**

**LTB₄**

**Antibiotics**

**TGFB, IL-1B, 5mod 2,3**
Clinical predictors of COPD

- Exam or historical wheeze + smoking history (>55 pack years) strongly predicts
- Facial wrinkling + smoking predicts airflow obstruction on spirometry and emphysema on CT.

Must have spirometry

COPD is not a clinical diagnosis  
Requires documentation of airflow obstruction that is not completely reversible  
Spirometry should be measured in stable, symptomatic patients
Must have spirometry

COPD is not a *clinical diagnosis*
Requires documentation of airflow obstruction that is not completely reversible

Spirometry should be measured in stable, symptomatic patients

Review of VA patients with diagnosis of COPD, 48% of VA patients did not have airflow obstruction
COPD: Diagnosis

- Always suspect in older patient with complaint of dyspnea
- Do not assume that older smoker with dyspnea necessarily has COPD
- Physical exam and chest x-ray are not reliable in establishing diagnosis
- Always confirm diagnosis with spirometry
  - Obstructive pattern - $\text{FEV}_1/\text{FVC} \leq 0.70$
  - Mild % predicted $\text{FEV}_1 > 80$
  - Moderate % predicted $\text{FEV}_1 50-80$
  - Severe % predicted $\text{FEV}_1 30-49$
  - Very severe % predicted $\text{FEV}_1 < 30$

© 2012 Virginia Mason Medical Center
All that wheezes…

- Asthma
- COPD
- CHF
- OSA
- Bronchiectasis
- Bronchiolitis
- Lung cancer
- Or…
Wheeze from a foreign body
### COPD severity

**Figure 1-2. Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV₁**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
</table>
| Stage I: Mild | FEV₁/FVC < 0.70  
FEV₁ ≥ 80% predicted                                                        |
| Stage II: Moderate | FEV₁/FVC < 0.70  
50% ≤ FEV₁ < 80% predicted                                                 |
| Stage III: Severe | FEV₁/FVC < 0.70  
30% ≤ FEV₁ < 50% predicted                                                  |
| Stage IV: Very Severe | FEV₁/FVC < 0.70  
FEV₁ < 30% predicted or FEV₁ < 50% predicted plus chronic respiratory failure |

**FEV₁:** forced expiratory volume in one second; **FVC:** forced vital capacity; **respiratory failure:** arterial partial pressure of oxygen (PaO₂) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO₂ (PaCO₂) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.
GOLD combined assessment

<table>
<thead>
<tr>
<th>GROUP A: low risk, less symptoms</th>
<th>Spirometric classification</th>
<th>Exacerbations per year</th>
<th>mMRC</th>
<th>CAT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1-2</td>
<td>≤1</td>
<td>0-1</td>
<td>&lt;10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP B: low risk, more symptoms</th>
<th>Spirometric classification</th>
<th>Exacerbations per year</th>
<th>mMRC</th>
<th>CAT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1-2</td>
<td>≤1</td>
<td>≥2</td>
<td>≥10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP C: high risk, less symptoms</th>
<th>Spirometric classification</th>
<th>Exacerbations per year</th>
<th>mMRC</th>
<th>CAT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 3-4</td>
<td>≥2</td>
<td>0-1</td>
<td>&lt;10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP D: high risk, more symptoms</th>
<th>Spirometric classification</th>
<th>Exacerbations per year</th>
<th>mMRC</th>
<th>CAT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 3-4</td>
<td>≥2</td>
<td>≥2</td>
<td>≥10</td>
<td></td>
</tr>
</tbody>
</table>
## The MRC Breathlessness Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Degree of breathlessness related to activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not troubled by breathlessness except on strenuous exercise</td>
</tr>
<tr>
<td>2</td>
<td>Short of breath when hurrying on the level or walking up a slight hill</td>
</tr>
<tr>
<td>3</td>
<td>Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace</td>
</tr>
<tr>
<td>4</td>
<td>Stops for breath after walking about 100 yds or after a few minutes on level ground</td>
</tr>
<tr>
<td>5</td>
<td>Too breathless to leave the house, or breathless when undressing</td>
</tr>
</tbody>
</table>

Stenton C Occup Med (Lond) 2008;58:226-227
Case #1

63 year old woman with dyspnea with stairs, AM cough
MRC1-2
Smoking 1 pack per day
PMH: sick sinus syndrome, osteoporosis
Case #1 Spirometry

Moderate airflow obstruction
No bronchodilator response.
What’s the first line treatment?
Smoking cessation

Only intervention that we have that makes our patients with COPD live longer
Saves the patient money
Reduces risk of heart disease, stroke, cancer.
Reduces post-operative pulmonary and wound complications
Improves quality of life.
Benefits of smoking cessation

- **25-34 years**
  - Identical mortality to nonsmokers
- **35-44 years**
  - Reduced risk of death from any cause 90%
  - Gain 9 years of life
- **45-54 years**
  - Reduced risk of death from any cause by 66%
  - Gain 6 years of life
- **55-64 years**
  - Gain 4 years of life

The Five A’s Approach

- **ASK**
- **ADVISE**
- **ASSESS**
- **ASSIST**
- **ARRANGE**

- Follow up by phone or in person 1 week after quit date
- Address failures, temptations, drug side effects
ASK

• **Do you use tobacco?**
  • 70% of smokers will visit a doctor in a year
  • Most want to quit
  • If you don’t ask, you will never advise them to quit
  • Ask every time:
    • Tobacco use documentation with the vital signs
    • Tobacco use is a chronic illness
    • 4-40% of successfully quit smokers relapse 1-5 years after quitting

AAMC Summary Report 2007

© 2012 Virginia Mason Medical Center

CS2day.com
Scope of smoking in Washington

Current Cigarette and Smokeless Tobacco Use among Adults by Demographic Characteristics

- National (median): Cigarettes 21.2, Smokeless Tobacco 1.6
- Washington: Cigarettes 17.5, Smokeless Tobacco 1.6
- White: Cigarettes 17.2, Smokeless Tobacco 1.6
- African American: Cigarettes 15.7, Smokeless Tobacco 1.2
- Hispanic: Cigarettes 13.9, Smokeless Tobacco 2.7
- Asian: Cigarettes 10.5, Smokeless Tobacco 3.1
- American Indian / Alaska Native: Cigarettes 14.8, Smokeless Tobacco 6.3
- Native Hawaiian / Pacific Islander: Cigarettes 16.2, Smokeless Tobacco 0.6
- Female: Cigarettes 16.6, Smokeless Tobacco 1.2
- Male: Cigarettes 15.8, Smokeless Tobacco 3.6
- Less than high school degree: Cigarettes 31.8, Smokeless Tobacco 3.4
- High school degree: Cigarettes 23.8, Smokeless Tobacco 3.0
- More than high school degree: Cigarettes 19.3, Smokeless Tobacco 2.7
- 18–24 years old: Cigarettes 15.8, Smokeless Tobacco 4.1
- 25–44 years old: Cigarettes 22.9, Smokeless Tobacco 4.1
- 45–64 years old: Cigarettes 17.5, Smokeless Tobacco 2.4
- 65+ years old: Cigarettes 7.5, Smokeless Tobacco 1.2

Source: Behavioral Risk Factor Surveillance System, 2011

**Sample size <50**
The Five A’s Approach

• ASK

• ADVISE
  • Clear: *It is important for you to quit smoking*
  • Strong: *Quitting smoking is the most important thing that you can do for your health*
  • Personalized: *With your grandson living in the house, your smoking could impact his health.*
ASSIST-3 step process

Keys for Quitting

- PLAN AHEAD
  - Set a quit date and stick to it—not even a single puff!
  - Avoid alcohol, coffee, and other things that trigger your smoking
  - Consider past quit attempts, what worked, and what didn’t

- GET MEDICATIONS
  - Nicotine gum (OTC)
  - Nicotine inhaler (Prescription)
  - Nicotine lozenge (OTC)
  - Nicotine nasal spray (Prescription)
  - Nicotine patch (OTC and prescription)
  - Bupropion (Prescription)
  - Varenicline (Prescription)

- CALL THE QUIT LINE
  - Quit Line
    - 800.QUIT.NOW

  - Get free coaching and support that is confidential and non-judgmental

Your Quit Plan

- MY QUIT DATE IS
  - October 26, 2013

- Things to remember
  - Avoid casino
  - Tell best friend

- MY MEDICATION(S)
  - I will start taking them on

- Other Instructions
  - Time Quitline will call
    - (If participating in tax to quit)
ASSIST-3 step process

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Your Quit Plan

MY QUIT DATE IS
October 26, 2013

Things to remember
Avoid casino
Tell best friend

MY MEDICATION(S)

I will start taking them on April 26, 2013

Other Instructions

Time Quitline will call (if participating in tax to quit)

- Encourage meds
  - Only 13% of trying to quit smokers rx’d

- Choices
  - NRT/combo NRT
  - Bupropion
  - Varenicline

- 3x more effective than counseling alone in COPD

Varenicline + Bupropion SR

- RDBCT, multicenter
- Varenicline and placebo arm
- Prolonged abstinence rates at 12 and 26 weeks
- Equal at 52 weeks
- Less weight gain
- Increased anxiety
- Increased depressive symptoms

JAMA 2014; 311(2):155-63
ASSIST-3 step process

- Encourage counseling
- “Dose”-response curve to counseling

**Keys for Quitting**

1. **PLAN AHEAD**
   - Set a quit date and stick to it—not even a single puff!
   - Avoid alcohol, coffee, and other things that trigger your smoking
   - Consider past quit attempts, what worked, and what didn’t

2. **GET MEDICATIONS**
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   - Varenicline (Prescription)

3. **CALL THE QUIT LINE**
   - QuitLine 800.QUIT.NOW
   - Get free coaching and support that is confidential and non-judgmental

**Your Quit Plan**

- **MY QUIT DATE IS**
  - October 26, 2013

- **Things to remember**
  - [ ] Avoid casino
  - [ ] Tell best friend

- **MY MEDICATION(S)**
  - I will start taking them on
  - April 26, 2013

- **Other Instructions**

- **Time Quitline will call**
  (If participating in tax to quit)
• Quit line users are 4x more likely to quit
• Personalized quit plan
  ▪ 5 counseling phone calls
  ▪ Access to reduced cost meds or free meds
• Educational materials for patients and providers.

Available to all

SmartQuit App
How an electronic cigarette works:
The electronic cigarette contains a battery that activates a heating device, atomizing liquid nicotine inside a cartridge and producing a vapor that is inhaled.

Inside the e-cigarette:
1. A sensor detects when a smoker takes a drag, sending a signal to a processor that switches on a heater, known as an atomizer.
2. The atomizer heats up a nicotine solution to produce a vapor that can then be inhaled.
3. As someone draws on the e-cigarette, an LED light is also switched on by the processor, simulating a flame.
Electronic nicotine delivery systems (ENDS)

- E-cigarettes
- E-hookahs
- E-cigars
- E-pipes

- Disposable
- Refillable
- Flavors
- With or without nicotine

© 2014 Virgi
Demographics of e-cig use

- Introduced China 2003, in U.S. 2007
- Between 2010 and 2013
  - Use increased 3.3% to 8.5% surveyed
  - In former smokers, 2.5% to 9.6%
  - In current smokers, 9.8% to 36.5%
- Tend to be younger, more educated and higher income

King BA, et al.  Nicotine Tob Res. epub 2014
MORE TEENS SMOKING E-CIGS

Numbers doubled in a year, CDC says, and many move on to smoking tobacco
## 2014 MTF survey

<table>
<thead>
<tr>
<th>Grade</th>
<th>Past month ecig</th>
<th>Daily cigarette</th>
<th>Daily cig 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>8th</td>
<td>8.7%</td>
<td>1.4% (down)</td>
<td>2.7%</td>
</tr>
<tr>
<td>10th</td>
<td>16.2%</td>
<td>3.2%</td>
<td>6.3%</td>
</tr>
<tr>
<td>12th</td>
<td>17%</td>
<td>6.7%</td>
<td>11.2%</td>
</tr>
</tbody>
</table>
Acceleration of Use?

**Teen Vapers**
Percentage of U.S. students who have used electronic cigarettes in the past 30 days

- **High school**
- **Middle school**

Source: Centers for Disease Control and Prevention
The Wall Street Journal

Acceleration of Use?

Teen Vapers
Percentage of U.S. students who have used electronic cigarettes in the past 30 days

Source: Centers for Disease Control and Prevention
The Wall Street Journal

The good news: in 2013, rate of smoking down to 17% from 21% in 2005 (cdc.gov press release 11/26/14)

Daily cigarette use in teens continues to decline

Rapid adoption of ENDS may be playing a role in decrease.
Reduction in tobacco craving

• Lesser harm hypothesis
  • Role of ecigs in reduction of exposure to combustible tobacco

• RCT, n=48, Belgium
  • 4 hours of abstinence followed by ecig or cigarettes
  • Ecig-reduction in craving
  • Increased spontaneous cessation of tobacco

Reduction in # cigarettes used

- E-cigarettes have been shown to decrease total number of cigarettes smoked as well as increase time to first cigarette in AM even with a nicotine free e-cigarette.
- Some small studies have suggested this can lead to spontaneous cessation
- Concern is that medical benefits of cessation require complete cessation

Role in Tobacco Cessation

- Bullen, et al.
  - RCT, n 657, 6month abstinence rates 7.3% with ecigs, 5.8% with patches, 4.1% with placebo ecigs. No superiority

- No evidence for spontaneous cessation

- Survey of quitline users
  - E-cigarette users are less likely to quit using cigarettes than nonusers.

Nicotine as a Gateway Drug

- **Nicotine**, not marijuana is associated with future use of cocaine
- 87.9% adults 18-34 years old who have ever used cocaine, had smoked first.
- Only 2.9% had never smoked cigarettes

Kandel ER and Kandel DB. NEJM 2014. 371:10
Nicotine as Gateway Drug

- Mouse model
  - Priming with nicotine enhanced cocaine rewards/addictiveness
  - Increased reward properties of cocaine
  - Increased FosB expression in striatum
    - Associated with increased addictiveness
    - 24 hours of nicotine insufficient, 7 days
    - No effect if nicotine given after cocaine
    - No effect if delay between nicotine/cocaine
    - Hypoacetylation of FosB (using theophylline) decreased the effect

Kandel ER and Kandel DB. NEJM 2014. 371:10
Nicotine as Gateway Drug

- Human model
  - Cocaine dependence highest amongst users who started cocaine after nicotine
  - Less dependence (6.3%) in cocaine users that started cocaine prior to nicotine
  - Less dependence (10.2%) never smokers

Kandel ER and Kandel DB. NEJM 2014. 371:10
Nicotine as a Gateway Drug

- Risk of e-cigarettes
  - Same effect on the brain
    - Acetylation of the FosB promoter
    - Pose same risk of addition to other drugs
  - New “customers”
    - Seen as safe to a younger generation
    - Unknown effect in the brain of adolescents
      - In rats, adolescents experience nicotine priming effects for cocaine not seen in adults

Kandel ER and Kandel DB. NEJM 2014. 371:10
Safety of ENDS

- *Perception* of ENDS by users
  - Safe
  - Useful in tobacco cessation
- Insufficient data to declare safe
- Insufficient data to support use in cessation
- Areas of concern
  - Overdose/poisonings
  - Polyethylene glycol and glycerin
  - Product safety: contaminants
Upstate New York boy, 1, dies after ingesting liquid nicotine

The Fort Plain boy could be the first child in the U.S. to die from liquid nicotine, the substance used in e-cigarettes, though authorities have not confirmed it was for such a device. Critics say liquid nicotine does not have childproof packaging and that the number of ‘dangerous exposures’ is on the rise.

BY LEE MORAN / NEW YORK DAILY NEWS / Monday, December 15, 2014, 8:17 AM
• Retrospective review of the American Association of Poison Control Centers ENDs related poisonings. N=1700
• June 2010-September 2013
• 42% in kids <5 years old
• 27% in age 20-39
• LD50 1mg/kg

Exposures increased 2013

Polyethylene glycol/glycerin

• Solvents for the nicotine
• Unknown effects of chronic inhalation
  • Animal data suggests safe
  • May worsen rhinitis and atopic disease, cause a dry throat, reduce lung function
• High heat may lead to break down of PEG to formaldehyde
• Acrolein released from glycerin
Contaminants

- Nicotine is not always pure
  - Products vary in other nitrosamines from the extraction process
- Unexplained metal contaminants found
- Non-nicotine vape liquids have been shown to contain nicotine
Product safety with ENDS

- China produces 90% of the world’s ENDS
  - 2007 Mattel recall of children’s toys for lead paint
  - 2007, 2013 dog food and treat recalls from China.
Continuum of Care for COPD

Clinical Presentation
- At Risk
- Symptomatic
- Exacerbations
- Respiratory Failure

Interventions
- Smoking Cessation
- Disease Management
- Pulmonary Rehabilitation
- Other Options

Disease Progression
- FEV$_1$
- Symptoms
Treatment for all with COPD

1. Smoking Cessation
   - Commit to quit
   - Nicotine replacement
   - Wellbutrin
   - Varenicline
   - QUIT LINE: 1-800-QUIT-NOW

2. Intermittent bronchodilator therapy
   - Albuterol, ipratropium, or combination

3. Influenza and pneumococcal vaccine
   - Influenza vaccine decreases serious illness and death by 50% (NIHLBI/WHO)

4. Education, exercise, diet

Global Initiative for Chronic Obstructive Lung Disease. Goldcopd.org. NIHLBI & WHO
Medical Management of COPD

Smoking cessation**
Inhaled medications
Oral medications
Pulmonary rehabilitation/exercise
Oxygen therapy*
Medical Management of COPD

Smoking cessation

Inhaled medications

Oral medications

Pulmonary rehabilitation/exercise

Oxygen therapy
Inhaler Devices

- Up to 75% errors with use
- CFC-free propellants (HFA) feel and taste different
- 10/80 rule (can reduce 10 fold with spacer)
- Actuation-inhalation coordination
- Observe, teach, practice
- Priming (3 days - 4 weeks, drop), creaming, determining when out
Outcomes in COPD treatment

Mortality
Decline in FEV1
Hospitalization
AECOPDs
Qualify of Life
  – St. George’s Respiratory Questionnaire (SGRQ)
  – Chronic Respiratory Disease Questionnaire (CRQ)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Costco</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol neb 270ml</td>
<td>$22.65</td>
</tr>
<tr>
<td>Albuterol 90mcg CFC free</td>
<td>$52.53</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>$226.65</td>
</tr>
<tr>
<td>Respimat (Albuterol/ipratropium)</td>
<td>$288.96</td>
</tr>
<tr>
<td>Tiotropium 18mcg</td>
<td>$317.33</td>
</tr>
<tr>
<td>Fluticasone/Salmeterol 250/50mcg</td>
<td>$294.41</td>
</tr>
<tr>
<td>Fluticasone/Salmeterol 500/50mcg</td>
<td>$369.11</td>
</tr>
<tr>
<td>Budesonide/formoterol 80-4.5mcg</td>
<td>$219.89</td>
</tr>
<tr>
<td>Budesonide/formoterol 160-4.5mcg</td>
<td>$251.00</td>
</tr>
<tr>
<td>Formoterol fumarate</td>
<td>$199.40</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>$208.99</td>
</tr>
<tr>
<td>Mometasone/formoterol 100/5mcg</td>
<td>$246.96</td>
</tr>
<tr>
<td>Mometasone/formoterol 200/5mcg</td>
<td>$246.96</td>
</tr>
<tr>
<td>1pack per day Marlboro’s</td>
<td>$180.00</td>
</tr>
</tbody>
</table>
Patient Specific Therapy

Meds are expensive
Don’t extend life
Goal is to improve function and symptoms and avoid accelerating decline

– For symptoms: check back after one month of therapy
– For AECOPD: keep a yearly count of events

Withdrawal noneffective therapies
Inhaled controller therapies for COPD

Anti-inflammatory

– **ICS**: inhaled corticosteroids
  - Ex: fluticasone, budesonide, mometasone

Long acting bronchodilators

– **LABA**: inhaled long acting B2 agonists
  - Ex: salmeterol, formoterol, afomoterol, indacaterol, vilanterol, olodaterol

– **LAMA**: long acting muscarinic antagonist
  - Ex: tiotropium, aclidinium (Tudorza), umeclidinium
  - glycopyrronium bromide NVA237 (Seebri)

**Combinations**: budesonide/formoterol, fluticasone/salmeterol, mometasone/formoterol, fluticasone/vilanterol, Umeq/vilant, glyco/indacaterol
<table>
<thead>
<tr>
<th></th>
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<tr>
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<td>6.75</td>
</tr>
<tr>
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<td>6.75</td>
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<tr>
<td>Pork (w/ Rice)</td>
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<tr>
<td>Roast Pork w/ Chinese Mushroom</td>
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<tr>
<td>Roast Pork w/ Mushrooms</td>
<td>4.50</td>
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<tr>
<td>Roast Pork w/ Broccoli</td>
<td>4.50</td>
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<tr>
<td>Pork w/ Black Bean Sauce</td>
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<tr>
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<tr>
<td>Pork w/ Mushroom</td>
<td>4.50</td>
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<tr>
<td>Pork w/ Snow Pea</td>
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<tr>
<td>Beef w/ Black Bean Sauce</td>
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<tr>
<td>Beef w/ Broccoli</td>
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<tr>
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<tr>
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<tr>
<td>Chicken w/ Green Pepper</td>
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<tr>
<td>Chicken w/ Unleaded Ginger</td>
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<td>Chicken w/ Fried Shrimp</td>
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<td>Chicken w/ Chinese Mushroom</td>
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<td>Chicken w/ Mushrooms</td>
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<td>Chicken w/ Snow Pea</td>
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<td>Lobster drop soup (w/ Snow Pea)</td>
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<tr>
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</tr>
<tr>
<td>Lobster drop soup (w/ Unleaded Ginger)</td>
<td>4.50</td>
</tr>
</tbody>
</table>
| Lobster drop soup (w...
LABA

Long acting bronchodilator
  – improves FEV1
  – No effect on decline of FEV1

Decreased AECOPD

Shown to improve HRQOL

Low rate of adverse events

1st line therapy choice for FEV1<60%, symptomatic COPD by guidelines
ISOLDE trial

Tragic tale in which an Irish noblewoman accidentally feeds a love potion to Tristan, only to lead to his death

Showed that ICS (fluticasone) decreased AECOPDs by 25%, mean FEV1 higher in treatment group, better rate of decline of HRQoL

No changed in rate of decline of FEV1

Burge PS, et al. BMJ. 2000; 320: 1297
Inhaled Corticosteroids

Subsequent trials show no superiority to bronchodilators

Increased side effects

WISDOM Trial *NEJM* 2014 371 pp1285-94

– 38ml decline in FEV1
– ? 19% increase in exacerbation

GLUCOLD Trial *(CHEST in press)*

– Increased rate of FEV1 decline after cessation
Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D., Paul W. Jones, M.D., Julie C. Yates, B.S., Jørgen Vestbo, M.D., for the TORCH investigators

TORCH: Towards a Revolution in COPD Health

6112 patients, 42 countries, 444 centers
3 years
FEV1 <60% mean 44%
TORCH trial

Population: N=6112, ratio<0.70, FEV1<60% without BD response

Intervention: placebo vs. LABA (salmeterol 50mcg) vs. ICS (fluticasone 500mcg) vs. LABA + ICS

Control: no other LABA or LAMA

Outcomes: primary mortality, secondary AECOPD, FEV1, HRqol

Caverley PMA, et al. NEJM. 2007; 356(8): 775-89
**TORCH-mortality results**

![Table 2. Results of the Mortality Analysis and the Efficacy Analysis for Exacerbation.](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo Group (N = 1524)</th>
<th>Salmeterol Group (N = 1521)</th>
<th>Fluticasone Group (N = 1534)</th>
<th>Combination-Therapy Group (N = 1533)</th>
<th>Comparison</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of deaths from any cause</td>
<td>231</td>
<td>205</td>
<td>246</td>
<td>193</td>
<td>Combination therapy vs. placebo (adjusted)*</td>
<td>0.825 (0.681–1.002)</td>
<td>0.052</td>
</tr>
<tr>
<td>Probability of death at 3 yr — %</td>
<td>15.2</td>
<td>13.5</td>
<td>16.0</td>
<td>12.6</td>
<td>Combination therapy vs. placebo (unadjusted)</td>
<td>0.820 (0.677–0.993)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combination therapy vs. salmeterol</td>
<td>0.932 (0.765–1.134)</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combination therapy vs. fluticasone propionate</td>
<td>0.774 (0.641–0.934)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Salmeterol vs. placebo</td>
<td>0.879 (0.729–1.061)</td>
<td>0.18</td>
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<tr>
<td>Adjusted probability of death at 3 yr — %</td>
<td>12.6</td>
<td>10.9</td>
<td>13.3</td>
<td>10.3</td>
<td>Combination therapy vs. placebo</td>
<td>0.811 (0.670–0.982)</td>
<td>0.03</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combination therapy vs. salmeterol</td>
<td>0.946 (0.777–1.151)</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combination therapy vs. fluticasone propionate</td>
<td>0.768 (0.636–0.927)</td>
<td>0.006</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Salmeterol vs. placebo</td>
<td>0.857 (0.710–1.035)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fluticasone propionate vs. placebo</td>
<td>1.056 (0.883–1.264)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Caverley PMA, et al. NEJM. 2007; 356(8): 775-89

© 2012 Virginia Mason Medical Center
### TORCH-acute exacerbations

<table>
<thead>
<tr>
<th>Efficacy analysis for exacerbation</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Combination therapy vs. placebo</td>
</tr>
<tr>
<td>Annual rate</td>
<td>0.75 (0.69–0.81)</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>Salmeterol vs. placebo</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate vs. placebo</td>
</tr>
<tr>
<td>Requiring systemic corticosteroids</td>
<td>Combination therapy vs. placebo</td>
</tr>
<tr>
<td></td>
<td>Combination therapy vs. salmeterol</td>
</tr>
<tr>
<td></td>
<td>Combination therapy vs. fluticasone propionate</td>
</tr>
<tr>
<td>Severe (requiring hospitalization)</td>
<td>Salmeterol vs. placebo</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate vs. placebo</td>
</tr>
<tr>
<td></td>
<td>Combination therapy vs. placebo</td>
</tr>
<tr>
<td></td>
<td>Combination therapy vs. salmeterol</td>
</tr>
<tr>
<td></td>
<td>Combination therapy vs. fluticasone propionate</td>
</tr>
<tr>
<td></td>
<td>Salmeterol vs. placebo</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate vs. placebo</td>
</tr>
</tbody>
</table>

NNT=3.57
NNT=2.94
NNT=32

Caverley PMA, et al. NEJM. 2007; 356(8): 775-89
TORCH trial results

Did not meet prespecified level of significance for mortality

ICS/LABA: reduction in AECOPD
  – LABA alone also reduces AECOPDs

ICS/LABA: improvement in SGRQ (-3)
  – ICS alone also had improvement in SGRQ

Caverley PMA, et al.  NEJM. 2007; 356(8): 775-89
Adverse Events with ICS

Pneumonia
Thrush
Concern for osteoporosis, cataracts
– No evidence for increase in TORCH
Easy bruising
**Figure 2. Meta-analysis of randomized controlled trials of inhaled corticosteroid (ICS) use vs control treatment for any pneumonia. CI indicates confidence interval: LABA, long-acting β-agonist.**
How about this spiriva drug I saw on TV?
A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators*

BACKGROUND

Previous studies showing that tiotropium improves multiple end points in patients with chronic obstructive pulmonary disease (COPD) led us to examine the long-term effects of tiotropium therapy.

METHODS

In this randomized, double-blind trial, we compared 4 years of therapy with either tiotropium or placebo in patients with COPD who were permitted to use all respiratory medications as needed. The primary end point was change in forced expiratory volume in 1 second (FEV1) from baseline to week 144, with analysis by last observation carried forward.

From the David Geffen School of Medicine at the University of California, Los Angeles (D.P.T.); Caritas St. Elizabeth’s Medical Center, Boston (B.C.); Glasgow University, Glasgow, Scotland (S.S.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (D.B., S.K., S.M.); and the University of Leuven, Leuven, Belgium (M.D.). Address reprint requests to Dr.

UPLIFT: Understanding Potential Long-Term Impacts on Function with Tiotropium

5993 patients, 4 years, FEV1 <70%, mean 48%

© 2012 Virginia Mason Medical Center
UPLIFT trial

P=5993, COPD with post BD FEV1<70%, ratio <0.70
I= tiotropium 18mcg daily vs. placebo
C=placebo, allowed to use other agents other than SAMA, 60% on ICS +/- LABA
O=Primary: decline in the mean pre-post BD FEV1
  – Secondary FVC, SGRQ, AECOPD, mortality

UPLIFT outcomes

No difference in rate of decline of lung function
Improved HRqoL by SGRQ
Increased time to first exacerbation median 16.7 months compared to 12.5 months
Reduction in # of exacerbations NNT=8
Combination

- LAMA + LABA $\geq$ LAMA
- LABA + LAMA $>$ LABA + ICS
- ICS + LABA $>$ separate

- Triple inhaler therapy
  - LABA + ICS + Tio $>$ LABA + ICS
  - LABA + ICS + Tio $>$ Tio
From: Inhaled Anticholinergics and Risk of Major Adverse Cardiovascular Events in Patients With Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis


Cardiovascular outcomes composite indicates cardiovascular death, myocardial infarction, and stroke. Long-term indicates longer than 6 months to 5 years. Size of the data markers indicates weight of the study. CI indicates confidence interval.

NN to harm=174
Serious events were *less common* in the treatment group, including MI and stroke.

No increased CV events with Respimat.

Expected side effects included dry mouth, constipation, and the potential for urinary retention.

? Cautious use in pts with severe CAD.

Wise RA et al. NEJM 2013; 369:1491-1501

Patient Specific Therapy

No mortality benefit
All inhaled therapies have side effects
Withdrawal ineffective therapies
Risks

- Tremor
- Hypokalemia
- Tachycardia (vasodilation)
- Desensitization
- Glaucoma
- Urinary retention
- Other
Medical Management of COPD

Smoking cessation
Inhaled medications
**Oral medications**
Pulmonary rehabilitation/exercise
Oxygen therapy
Oral therapies

Macrolides

Phosphodiesterase inhibitors
 – Theophylline
 – Roflumilast

Oral antioxidants
**Mucous secretion**
- Decrease volume
- Improves mucociliary clearance, elasticity, and ciliary motility
- Inhibition of genes for mucoid proteins

**MACROLIDES**

**Decrease bronchial hyper-responsiveness**

**Protection from reactive O2 species**
- Increase β defensins

**Increase β defensins**
- Reduction in adhesion molecules
  (ICAM-1, sICAM-1, e-selectin, β-2 integrins, VCAM-1, LFA-3, Mac-1)
- Reduction in bacterial adhesion

**Inhibits P. aeruginosa**
- Adhesion
- Alters virulence factors
- Decreased biofilm production
- Altered quorum sensing
- Altered gene expression

**Alters PMNs**
- Reduced elastase, stabilization of degranulation

**Alters signaling pathways like VEGF and NFκB**


**Friedlander AL. et al. Chest. 2010**
COPD and role for macrolides

Mucous
Airflow obstruction
Airway neutrophilia with concomitant destruction/oxidative stress
Inflammatory
Pseudomonas colonization/infection
Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., MeiLan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porszasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciurba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network

• N=1577, >40 years of age, U.S.
• Clinical dx of COPD:
  ▪ Pack year >10
  ▪ FEV1/FVC <70, without complete reversibility
  ▪ Supplement O2 or steroids/or ER visit for AECOPD
  ▪ No AECOPD for 4 weeks prior to enrollment
  ▪ No asthma, HR>100, QTc>450, documented hearing loss
Intervention: azithromycin 250mg daily x 1y
Control: usual care (50% on LAMA/LABA/ICS)
Outcomes:
  – Primary: time to first AECOPD
  – Secondary:
    • Quality of Life
    • Nasopharyngeal colonization (NP swabs q3months)
    • Hearing at enrollment, 3mos, 12mos

Figure 2. Proportion of Participants Free from Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) for 1 Year, According to Study Group.

The analyses were based on the participants who were randomly assigned to the group minus those who did not return for any follow-up assessment — 558 participants in the azithromycin group, of whom 317 (57%) had an acute exacerbation, and 559 in the placebo group, of whom 380 (68%) had an acute exacerbation.
Azithromycin results

Median time to exacerbation 266 days (8.8 months) vs. 174 days (5.8 months)
Average 1.48 AECOPD/y vs. 1.83 AECOPD/y for placebo
NNT to prevent 1 AECOPD = 2.86
Improved HrQol with SGRQ -2.8

Azithromycin side effects/concerns

• Arrhythmias—nothing notes in this cohort
  - TN cohort of 5d Rx for azithromycin showed addl 47/million CV deaths
• Hearing loss 25% vs. 20% placebo
• Resistance

Ray WA et al. NEJM 2012; 366 (20):1881-90
Phosphodiesterase inhibition

• Hydrolase of cAMP in inflammatory cells
Theophylline

When added to salmeterol in a study of about 900 patients with COPD with FEV1 < 65%  
  – Improved FEV1  
  – Improved HRqol

20% of enrolled patients were withdrawn before the start  
  – 44% of those were due to adverse events due to theophylline

Theophylline

May help overcome steroid resistance at lower doses through activation of histone deacetylators—increased steroid effect

Side effects: HA, N/V, abdominal complaints

Drug-drug interactions with macrolides and fluoroquinolones

Toxicity can lead to arrhythmias

Barnes PJ. PATS. 2005
Roflumilast

Selective PDE4 inhibitor
Shown to have anti-inflammatory effects

– Decrease leukotriene B4, decreased ROS from neutrophils, and decreased TNF-alpha release by mononuclear cells
Roflumilast

P: Moderate-severe COPD
I: roflumilast 250mcg/day vs. 500mcg/day vs. placebo
O: primary: post bronchodilator FEV1, SGRQ
   – Secondary: other spirometric values, and AECOPD

Roflumilast Results

Decrease in rate of acute exacerbations
Improvement in HRQoL
Improvement in post BD FEV1
NNT at 500mcg dose to prevent 1 AECOPD 2.6 (10 at the 250mcg dose)

Roflumilast’s Effect on HRQoL

Side effects - roflumilast

- Nasopharyngitis
- Nausea
- Headache
- 17% of patients on 500mcg dose had a side effect
  - 15% discontinued
- Weight loss, avg 2kg

- Diarrhea
Roflumilast add on to long acting bronchodilators

• Add on of roflumilast to LAMA or LABA
• Perhaps a safer anti-inflammatory than inhaled CS which carry risk of pneumonia
• Improved pre-BD FEV1
• High withdrawal rate
• High adverse event rate
• Weight loss of 2kg
REACT: Effect of Roflumilast on exacerbations in patients with severe COPD uncontrolled by combination therapy

- 1 year DB PCT, multicenter
- 1945 pts with severe airflow and > 2 exacerbations/yr on at least ICS/LABA
- 500 ug RF vs placebo
- PO: rate of exacerbations

Lancet 2015;385:857-66
REACT: results

• 13.2 % fewer exacerbations
• Improved FEV1: 56 ml
• No change in CAT
• Increased diarrhea, weight loss and nausea

Lancet 2015;385:857-66
Antioxidants

Carbocysteine and N-acetylcysteine

– Antioxidant to tip the imbalance away from oxidative stress

BRONCUS: n=523, NAC 600mg/d, no difference in AECOPD or FEV1 decline

– Subgroup analysis suggested AECOPD decrease in those not treated with ICS

PEACE: n=709, Chinese multicenter trial, carbocysteine 1500mg/d, lower AECOPD rate 1.01 vs 1.35. No difference noted between ICS tx or not

Statins

Mom
Apple pie
“Should be in the water”
Antiinflammatory
Observational studies suggested improvement in outcomes
STATCOPE (45 centers) Illinois
885 pts with moderate COPD FEV1 < .8
40-80 yo > 80% had been on steroids
No CV risk
40 mg simvastatin vs placebo for 1-3 yr
No difference in exacerbation rate
No difference in time to first exacerbation
More nausea in Simvastatin group
Vitamin D

RDBPCT in Iran
88 patients with severe COPD
100,000 IU oral vit D per month for 6 mo
Improved FEV1 and decreased exacerbations
Associated with increase IL-10
May be pertinent to those with deficiency

Global J Health Sci 2015 7(4):243-48
Not recommended

>2 weeks of prednisone for COPD
Inhaled mucolytics
<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Mortality</th>
<th>AECOPD</th>
<th>Rate of decline FEV1</th>
<th>HRQoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolde 2000</td>
<td>F vs. p</td>
<td>NS</td>
<td>Decreased 25%</td>
<td>No change</td>
<td>+2</td>
</tr>
<tr>
<td>Uplift 2008</td>
<td>T vs p</td>
<td>NS</td>
<td>Decreased time to 1&lt;sup&gt;st&lt;/sup&gt; exacerbations, NNT8</td>
<td>No change</td>
<td>-2.7</td>
</tr>
<tr>
<td>Torch 2006</td>
<td>S vs F vs FS vs p</td>
<td>NS</td>
<td>FS vs. p: reduction in AECOPD by 25%, NNT 4, S and F both showed reductions in AECOPD</td>
<td>No change</td>
<td>FS -3.0 S -1</td>
</tr>
<tr>
<td>Roflumilast 2005</td>
<td>R500 vs. R250 vs p</td>
<td>na</td>
<td>500mcg dose reduced mild AECOPD, but similar moderate and severe AECOPD</td>
<td>No change</td>
<td>-3.5</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>250 vs p</td>
<td>na</td>
<td>Increased time to 1&lt;sup&gt;st&lt;/sup&gt; exacerbation. NNT 2.86</td>
<td>na</td>
<td>-2.8</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>none</td>
<td>YES</td>
<td>reduction</td>
<td>Slows rate of decline</td>
<td>-10.9</td>
</tr>
</tbody>
</table>
Medical Management of COPD

Smoking cessation
Inhalers
Oral medications
**Pulmonary rehabilitation/exercise**
Oxygen therapy
Pulmonary rehabilitation
• Indicated for moderate to severe airflow obstruction
• Lowers dyspnea
• Improvement in HR quality of life scores
• May decrease healthcare utilization
• Persistence of effect 4 months to 1 year
• Periodization

Casaburi R. NEJM. 2009; 360:1329-35
Medical Management of COPD

Smoking cessation
Inhalers
Oral medications
Pulmonary rehabilitation/exercise

Oxygen therapy

- MRC and NOTT trials support mortality benefit to continuous (>15h/d) supplementary O2 for resting hypoxemia paO2 < 55mmHg
- No mortality or Hrqol benefits for paO2 > 60mmHg
Long-term Oxygen for COPD
Downside

- Restricted mobility
- Sense of invalidism
- Nasal drying, irritation, bleeding
- Cost
  - Estimated 800,000 patients in USA
  - Estimated annual cost $1.8 billion in USA
## Therapy at Each Stage of COPD

<table>
<thead>
<tr>
<th>I: Mild</th>
<th>II: Moderate</th>
<th>III: Severe</th>
<th>IV: Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>• $\text{FEV}_1/\text{FVC} &lt; 70%$</td>
<td>• $\text{FEV}_1/\text{FVC} &lt; 70%$</td>
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<td>• $\text{FEV}_1/\text{FVC} &lt; 70%$</td>
</tr>
<tr>
<td>• $\text{FEV}_1 \geq 80%$ predicted</td>
<td>• $50% \leq \text{FEV}_1 &lt; 80%$ predicted</td>
<td>• $30% \leq \text{FEV}_1 &lt; 50%$ predicted</td>
<td>• $\text{FEV}_1 &lt; 30%$ predicted or $\text{FEV}_1 &lt; 50%$ predicted plus chronic respiratory failure</td>
</tr>
</tbody>
</table>

- **Active reduction of risk factor(s); influenza vaccination**
  - Add regular treatment with one or more long-acting bronchodilators (when needed); Add rehabilitation
  - Add inhaled glucocorticosteroids if repeated exacerbations
- Add long term oxygen if chronic respiratory failure. Consider surgical treatments
ATS/ERS Algorithm for Pharmacologic Treatment in COPD

Confirm Dx of COPD

Intermittent Sx (cough, wheeze, dyspnea)

SA-BD p.r.n.

Persistent Sx (dyspnea, pm awakenings)

LA-BD/SA-BD q.i.d. with rescue

Limited Benefit?

Yes

Alternative class/combination (LA-BD/ICS)

Limited Benefit? AE?

Yes

Add/substitute oral theophylline

ICS: inhaled corticosteroid
LA-BD: long-acting bronchodilator
SA-BD: short-acting bronchodilator

Measure spirometry to diagnose airflow obstruction in *symptomatic, stable* patients, not in patients with symptoms

FEV1<60% give LAMA or LABA

AE: ICS/LABA or combination

FEV1<50% with symptoms refer to pulmonary rehab...or sooner

Resting hypoxemia PaO2<55, or spO2</=88%, continuous oxygen

Airflow Obstruction ratio < 0.70 without bronchodilator reversibility

Smoking cessation

Vaccinations

Resting oxygen assessment

No symptoms

Symptoms, no AECOPD

Symptoms, freq AECOPD

LAMA

LABA

ICS/LABA

LAMA

Combination therapy LABA/ICS, or LABA/LAMA, or LABA/LAMA/ICS

Combination therapy LABA/ICS, or LABA/LAMA, or LABA/LAMA/ICS, macrolide or roflumilast

Ongoing symptoms

Symptoms, freq AECOPD

Pulmonary Rehabilitation/Exercise
BUT....

COPD is a heterogeneous disease
So who knows what the right combination or step up therapy is best
Case #2

- 65 yo man with severe COPD (FEV1/FVC=0.54, FEV1 31%)
- Recent ER visit for increased cough, sputum, albuterol use and wheeze.
- Yearly AECOPDs
- Sob, cough with sputum production
COPD exacerabtions defined:

“An event in the natural course of the disease characterized by a change in the patient’s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.”
AECOPD

Risk factor for deterioration
Marker of increased mortality
25% COPD patients
AECOPD Risk Factors

Severity of disease
Prior exacerbations
Duration of disease
Age
Comorbidities
GERD
Pulmonary Htn
Biomarkers

61,650 pts, 6,574 with COPD
Followed for 5 years
Those with 3 elevated markers had a significantly higher risk (~4x) of exacerbation than those without any
Those with 1 or 2 had an intermediate risk
WBC >9, fibrinogen >14, CRP >4

JAMA 2013; 309:2353-61
Triggers

Infection
Air pollution
Idiopathic
PE, MI.....
Spiral CT and US

– 211 pts with AECOPD
  • Not requiring mechanical ventilation
  • No acute bronchitis
  • Disparity between CXR and ABG’s
– 49/197 (25%) positive for PE
  • 43 by CT (19 pos US)
  • 6 by US
– Associations:
  • Prior PE, malignancy, drop of 5 mmHg CO₂

Antibiotics in Exacerbations

• Moderate to severe: 2/3 (dyspnea, sputum volume or purulence), or hospitalization
• No benefit of sputum culture
• Generally generic: doxy, tmp/smz, not amox
• Broader for sicker or at ≥ risk
• Duration: 3-7 days
• No overall benefit to prophylactic use?
Bronchodilators

Albuterol is mainstay
  – 2.5 mg
  – Watch potassium
Ipratropium may be added
Typically nebulized q4 or more
No benefit to continuous nebs
Oral preparations just increase toxicity
AECOPD--Steroids

Beneficial
Decrease length of stay
Accelerate return of FEV1
SCOPE (2 vs 8 week) similar
Cochrane review: no difference between <7 days and > 7 days
Short-term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease
The REDUCE Randomized Clinical Trial

- 314 pts presented to 1/5 Swiss ER’s
- RDBCT of 40 mg prednisolone for 5 vs 14 days
- Noninferiority trial
- PO: time to exacerbation <180 days

JAMA 2013; 309:2223-31
REDUCE Trial
Results

• Exacerbation rates were similar (36% vs 37%)
• Time to exacerbation 43 days vs 29 days
• No difference in # of patients requiring mechanical ventilation, or time to death
• Lung function at 4 different time points after discharge no different (improvement in 1/3)

No difference in steroid-related adverse events
Oral vs IV steroids

Cohort study
79,985 pts admitted with AECOPD
92% IV, 8% oral
P: mortality, mechanical ventilation after 2\textsuperscript{nd} day, readmission rate within 30 days, hospital length of stay and cost
Results

Similar low mortality: 1.4 vs 1%

In propensity matched analysis treatment failure was lower among orally treated patients

Lower los and costs

Lindenauer JAMA 2010; 303 pp2359-2367
When to refer to pulmonary

COPD at age < 40 years old
AECOPD > 2x year
Rapid loss of function or weight
Severe COPD
Severe, life-limiting dyspnea
Consideration of surgical or bronchoscopic therapies.
Summary of Management of COPD

Smoking cessation is life saving
Clinical benefits seen in mod-severe COPD with pharmacotherapies, but no mortality benefit
Encourage exercise and pulmonary rehab
Resting hypoxemia should be treated
End of life discussions (DPOA, POLST)
THANK YOU