The Spectrum of Obstructive Lung Disease: Asthma & COPD

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Disclosures

• No Pharma Consulting, Research, Lectures

• NHLBI - Asthma Clinical Research Network

• NHLBI - COPD Clinical Research Network

• NAEPP Coordinating Committee
The Spectrum of Obstructive Lung Disease: Asthma & COPD

Asthma:
- CFC-driven MDIs discontinued December 31, 2008
- Inhaled steroids reduce Asthma Exacerbations
- Asthma Exacerbations ----> loss of lung function
- Mild asthma may not require chronic controller Tx
- Linking ICS to β-agonist rescue seems to work
- Pneumococcus, ASA, Vitamin D
- Anti-Reflux Therapy?
- Anti-Eosinophil Therapy?
The Montreal Protocol

• International Environmental Treaty

• Banned CFCs in consumer aerosols

• US has eliminated almost all manufacture and importation of CFCs since January 1, 1996

• “Essential use Exemption” for:
  - MDIs for Asthma and COPD
  - Space Shuttle and Titan Rockets

• Single ingredient albuterol CFC MDIs banned, effective December 31, 2008.
## Short-Acting β-Adrenergic Agonists

### Table 1. Short-Acting β-Adrenergic Agonists.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Formulation</th>
<th>Dose</th>
<th>No. of Doses per MDI Canister</th>
<th>Rating in Pregnancy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>Yentolin (GlaxoSmithKline), ProAir (Teva), Proventil (Schering–Plough)</td>
<td>MDI–HFA</td>
<td>90 μg/puff</td>
<td>200</td>
<td>C</td>
<td>CFC-driven albuterol MDIs were taken off the market on December 31, 2008; generic albuterol HFA inhalers are not yet available</td>
</tr>
<tr>
<td>AccuNeb (Day), generic</td>
<td>Liquid for nebulization</td>
<td>0.63, 1.25, or 2.5 mg/vial; 5 mg/ml</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proventil Repetabs, Vospire ER (DAVA Pharmaceuticals)</td>
<td>Extended-release tablets</td>
<td>4 or 8 mg</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proventil, generic</td>
<td>Tablets</td>
<td>2 or 4 mg</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic</td>
<td>Syrup</td>
<td>2 mg/5 ml</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>Xopenex (Sepracor)</td>
<td>MDI–HFA</td>
<td>45 μg/puff</td>
<td>200</td>
<td>C</td>
<td>Single stereoisomer derived from albuterol</td>
</tr>
<tr>
<td></td>
<td>Liquid for nebulization</td>
<td>0.31, 0.63, or 1.25 mg/vial</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metaproterenol</td>
<td>Alupent (Boehringer Ingelheim), generic</td>
<td>Liquid for nebulization</td>
<td>10 or 15 mg/vial; 50 mg/ml</td>
<td>C</td>
<td>Less β₂ selectivity than albuterol, manufacture of metaproterenol MDI was discontinued in July 2008</td>
<td></td>
</tr>
<tr>
<td>Alupent, generic</td>
<td>Tablets or syrup</td>
<td>10 or 20 mg; 10 mg/5 ml</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirbuterol</td>
<td>Maxair (Graseby)</td>
<td>MDI–CFC</td>
<td>200 μg/puff</td>
<td>400</td>
<td>C</td>
<td>Breath-actuated MDI</td>
</tr>
</tbody>
</table>

* CFC denotes chlorofluorocarbons, HFA hydrofluoroalkane, and MDI metered-dose inhaler.
| A pregnancy rating of C indicates that a risk to the fetus cannot be ruled out. |

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**Fanta, CH**

*N Eng J Med 360:1002-14, 2009*
New Approach??

Short-Acting $\beta$-Adrenergic Agonist
+
Inhaled Corticosteroid
Beclomethasone vs Montelukast: Time Until First Asthma Attack

Proportion of Patients Without Asthma Attacks

Days Since Randomization

Malmstrom et al.  

- $p = 0.001$ beclomethasone compared with placebo
- $p = 0.006$ montelukast compared with placebo
- $p = 0.129$ montelukast compared with beclomethasone
Health Care Utilization

- Hospitalizations
  - Budesonide: 2.5
  - Nedocromil: 4.3
  - Placebo: 4.4
  - P = 0.04

- Urgent visits
  - Budesonide: 12
  - Nedocromil: 16
  - Placebo: 22
  - P < 0.001
  - P = 0.02

CAMP, NEJM 343:1054-1063, 2000
FACET Study: Formoterol and Budesonide in Moderate Asthma

Severe Exacerbations/ Patient/Year

† P = 0.01

Pauwels RA, et al.
N Engl J Med. 1997;337:1405-1411
SOCS - Treatment Failure Rate

Lazarus et al. 
Asthma Clinical Research Network 
JAMA 285:2583-2593, 2001
Kaplan-Meier Survival Curves: Withdrawal for Worsening Asthma

- **Advair 250mcg**
- **FP 250mcg**
- **SALM 50mcg**
- **Placebo**

*differs from FP 250mcg, SALM and placebo, p ≤ 0.002*

*Shapiro et al. Am J Respir Crit Care Med 2000;161:527-534*
Q1: Every patient with persistent asthma should receive:

1) Prn β-agonist
2) Regular ICS + prn β-agonist
3) Prn ICS + prn β-agonist
Should all patients with asthma be treated regularly with an inhaled corticosteroid?

The IMPACT Study

Regular Controller Therapy versus Intermittent Inhaled Corticosteroids for Mild Persistent Asthma

Homer A. Boushey, M.D., Christine A. Sorkness, Pharm.D., Tonya S. King, Ph.D., Sean D. Sullivan, Ph.D., John V. Fahy, M.D., Stephen C. Lazarus, M.D., Vernon M. Chinchilli, Ph.D., Timothy J. Craig, D.O., Emily A. Dimango, M.D., Aaron Deykin, M.D., Joanne K. Fagan, Ph.D., James E. Fish, M.D., Jean G. Ford, M.D., Monica Kraft, M.D., Robert F. Lemanske, Jr., M.D., Frank T. Leone, M.D., Richard J. Martin, M.D., Elizabeth A. Mauger, Ph.D., Gene R. Pesola, M.D., M.P.H., Stephen P. Peters, M.D., Ph.D., Nancy J. Rollings, M.Ed., Stanley J. Szeffler, M.D., Michael E. Wechsler, M.D., and Elliot Israel, M.D., for the National Heart, Lung, and Blood Institute’s Asthma Clinical Research Network
**IMPACT Protocol Design**

N = 225

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Zafirlukast</th>
<th>Placebo (therapy only as needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Budesonide</td>
</tr>
</tbody>
</table>

Week

| 4 | 6 | 8 | 21 | 34 | 47 | 56 | 60 | 62 |
|
Visit

| 3 | 5 | 6 | 7  | 8  | 11 | 12 | 13 | 14 |

All patients were taught to initiate short courses of oral or inhaled corticosteroids by a Symptom-based Action Plan*

*Coté et al., AJRCCM 1997; 155: 1509*
Change in AM Peak Flow

Baseline to End Treatment

Change in AM PEF (%)

Bud  Zaf  "PRN"

P=0.904

Boushey et al
Change in FEV$_1$
(% Change baseline to end treatment)

Pre Albuterol FEV$_1^*$

Post Albuterol FEV$_1$

*Boushey et al
Asthma Exacerbation Rates
(symptoms warranting course of oral CS)

Figure 3. Kaplan–Meier Estimates of the Time to a First Exacerbation of Asthma. There was no significant difference among the groups (P=0.39).

Boushey et al
**IMPACT: Other Outcomes**

Changes in Asthma control, Asthma-specific quality of life, and symptom-free days

<table>
<thead>
<tr>
<th></th>
<th>ACQ</th>
<th>AQLQ</th>
<th>SFD/2wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>-0.4</td>
<td>+0.5</td>
<td>+4.0</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>-0.2</td>
<td>+0.3</td>
<td>+3.1</td>
</tr>
<tr>
<td>“PRN”</td>
<td>-0.3</td>
<td>+0.3</td>
<td>+2.9</td>
</tr>
</tbody>
</table>

*P=0.001  P=0.18  P=0.03*

*Boushey et al  
N Engl J Med 352:1525-1528, 2005*
IMPACT: Summary

In adults with long-standing, mild persistent asthma, who were given medication and a symptom-based action plan, twice daily treatment with budesonide, with zafirlukast, and with placebo over one year did not differ with regard to asthma exacerbations, asthma-specific quality of life, or the rate of loss of lung function over 1 year.

Boushey et al
**IMPACT: Conclusion**

The criteria for “mild persistent asthma” may define a condition so mild that the decision as to whether to take regular daily therapy or to take only short courses of inhaled or oral corticosteroid therapy on an “as needed” basis may be left to the patient’s own assessment of the importance of the subjective improvements experienced, and of the cost, inconvenience, and perceived risks of the treatment.

*Boushey et al  
N Engl J Med 352:1525-1528, 2005*
Inhaled Steroids - not “Disease Modifying”

Inhaled Steroids - not “Disease Modifying”

Lazarus et al.  
JAMA 285:2583-93, 2001
Q2: Your patient has 3-4 exacerbations/yr. Between exacerbations she’s asymptomatic. Treat her with:

1) Regular ICS
2) Regular ICS only when symptomatic
3) Prn ICS
The START Study

N = 7,241, ages 5-66
Mild asthma; symptoms weekly; <2 years
Baseline Pre-Bronchodilator FEV1 ~86%
Baseline Post-Bronchodilator FEV1 ~97%

Intervention:
Budesonide DPI, 200 - 400 mcg 1x/day
vs Placebo
X 3 years

Outcomes:
*Budesonide reduced Exacerbations
*Budesonide reduced decline in FEV1

Romain A Pauwels, Søren Pedersen, William W Busse, Wan C Tan, Yu-Zhi Chen, Stefan V Öhlsson, Anders Ulfman, Carl Johan Lamm, Paul M O'Byrne on behalf of the START Investigators Group*

THE LANCET • Vol 361 • March 29, 2003

Pauwels et al.,
The START Study

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X 3 years

Outcomes:
*Budesonide reduced Exacerbations
*Budesonide reduced decline in FEV1

Pauwels et al.
Do Exacerbations Contribute to Decline of Lung Function Over Time in Asthma?
Asthma Exacerbations Lead to Loss of Lung Function

Change in FEV1 (%) over 3 yrs

Budesonide

Placebo

$P < 0.001$

$P = 0.57$

$P < 0.042$

O’Byrne et al. Am J Respir Crit Care Med 179:19-24, 2009
Asthma Exacerbations Lead to Loss of Lung Function

O'Byrne et al.  
Am J Respir Crit Care Med 179:19-24, 2009
FACET: Changes Associated with Exacerbations

Tattersfield et al.
Am J Respir Crit Care Med 160:594-599, 1999
FACET: Changes Associated with Exacerbations

Tattersfield et al.
Am J Respir Crit Care Med 160:594-599, 1999
Rescue Use of Beclomethasone and Albuterol in a Single Inhaler for Mild Asthma

Papi et al.
Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma

Purpose: to compare three treatments:
- Bud/FM 80/4.5 2X/d + prn Terbutaline
- Bud 320 2x/d + prn Terbutaline
- Bud/FM 80/4.5 2x/d + prn Bud/FM 80/4.5

Outcomes:
- Time to first exacerbation; number of exacerbations
- Symptoms, nocturnal awakenings, AM PEF, FEV1

Subjects: 2760 adults and children with moderately severe asthma (mean FEV1 = 73% predicted)

Time to First Exacerbation

# Inhaled Corticosteroids

Table 2. Inhaled Corticosteroids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Formulation</th>
<th>Dose per Inhalation</th>
<th>No. of Doses per Canister</th>
<th>Rating in Pregnancy</th>
<th>Patient Age</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>Qvar (Teva)</td>
<td>DPI or solution for nebulization</td>
<td>DPI: 90 or 180; solution for nebulization: 250 or 500</td>
<td>DPI: 60 or 120; solution for nebulization: prefilled single dose vials</td>
<td>B</td>
<td>DPI: 16; solution for nebulization: 1–8</td>
<td>Built-in dose counter</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>Alvesco (Sepracor)</td>
<td>MDI–HFA</td>
<td>80 or 160</td>
<td>60</td>
<td>C</td>
<td>≥12</td>
<td>Prepared as an aerosol solution, activated by airway esterases, approved for twice-daily use</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Flovent (GlaxoSmithKline)</td>
<td>MDI–HFA or DPI</td>
<td>MDI–HFA: 44, 110, or 220; DPI: 50 or 100</td>
<td>MDI–HFA: 120; DPI: 60</td>
<td>C</td>
<td>≥4</td>
<td>Built-in dose counter with both MDI and DPI</td>
</tr>
<tr>
<td>Mometasone</td>
<td>Asmanex (Schering–Plough)</td>
<td>DPI</td>
<td>110 or 220</td>
<td>30; 30, 60, 120</td>
<td>C</td>
<td>≥4</td>
<td>Approved for once-daily use; built-in dose counter</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Azmacort (Abbott)</td>
<td>MDI–CFC</td>
<td>75</td>
<td>240</td>
<td>C</td>
<td>≥6</td>
<td>Built-in small volume spacer</td>
</tr>
</tbody>
</table>

In combination with LABA

- Budesonide with formoterol Symbicort (AstraZeneca) MDI–HFA 80 or 160 (with 4.5 µg of formoterol) 120 C ≥12 2 Puffs twice daily; built-in close counter
- Fluticasone with salmeterol Advair (GlaxoSmithKline) MDI–HFA or DPI MDI–HFA: 45, 115, or 230 (with 21 µg of salmeterol); DPI: 200, 250, or 500 (with 50 µg of salmeterol) MDI–HFA: 120; DPI: 60 C MDI–HFA: ≥12; DPI: ≥4 MDI–HFA: 2 puffs twice daily; DPI: 1 inhalation twice daily; built-in close counter

Fanta, CH
# Inhaled Long-Acting β-Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Formulation</th>
<th>Dose μg</th>
<th>Patient Age yr</th>
<th>Rating in Pregnancy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arformoterol</td>
<td>Brovana (Sepracor)</td>
<td>Liquid for aerosolization</td>
<td>15/vial</td>
<td>Adults</td>
<td>C</td>
<td>Approved for COPD but not asthma</td>
</tr>
<tr>
<td>Formoterol</td>
<td>Foradil (Schering-Plough)</td>
<td>Single-dose DPI</td>
<td>12/capsule</td>
<td>≥5</td>
<td>C</td>
<td>Rapid onset of action</td>
</tr>
<tr>
<td></td>
<td>Perforomist (Dey)</td>
<td>Liquid for aerosolization</td>
<td>20/vial</td>
<td>Adults</td>
<td>C</td>
<td>Approved for COPD but not asthma</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Serevent (GlaxoSmithKline)</td>
<td>DPI (60 doses per device)</td>
<td>50/inhalation</td>
<td>≥4</td>
<td>C</td>
<td>Multidose DPI</td>
</tr>
</tbody>
</table>

_Fanta, CH_  
_N Eng J Med 360:1002-14, 2009_
Q3: I routinely give Pneumovax to:

1) All patients with severe asthma
2) Elderly asthmatics
3) Asthmatics with co-morbid conditions
4) All asthmatics 19-64 years old
Asthma and Pneumococcal Infections

• Asthma is an independent risk factor for invasive pneumococcal disease.
  - nested case-control study
  - 2 to 49 years old

  *Talbot et al*
  N Eng J Med 352:2082-90, 2005

• Adults with asthma may be at increased risk for serious pneumococcal disease
  - (OR, 6.7; 95% CI, 1.6-27.3; P = .01)
  - retrospective case-control study
  - Rochester Minnesota (1964-1983)

  *Juhn et al*
Asthma and Pneumococcal Infections

Possible Mechanisms:

- Disrupted airway epithelial barrier
- Increased and aberrant mucus production
- Alterations in innate and adaptive immunity
- Genetic factors
- Immunosuppressive medications
- Increased pneumococcal colonization
Asthma and Pneumococcal Vaccination

October 25, 2008:

The U.S. Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) voted unanimously yesterday to recommend that adults ages 19 to 64 with asthma receive pneumococcal polysaccharide vaccine (PPSV23).
Aspirin and Asthma

- Worsens “AERD” (Triad Asthma)
- New asthma less likely among women who used aspirin frequently (Nurses’ Health Study)\(^1\)
- 22% reduction in asthma incidence in men randomized to aspirin QOD (Physicians’ Health Study)\(^2\)
- 10% reduction in asthma incidence in women randomized to aspirin QOD (Womens’ Health Study)\(^3\)

\(^1\) Barr et al: Am J Respir Crit Care Med 169:836, 2004
\(^2\) Barr et al: Am J Respir Crit Care Med 175:120, 2007
**Vitamin D and Asthma**

- Vit D has potent immunomodulatory effects
- Vit D inhibits TH1, TH2, induces IL-10, Tregs
- Maternal Vit D intake during pregnancy inversely associated with asthma symptoms in early childhood
  

- Vit D inversely associated with markers of asthma and allergy severity
  - IgE, eosinophils
  - Methacholine reactivity
  - Asthma hospitalization
  - Medication requirements

  *Brehm et al: Am J Respir Crit Care Med 179:765, 2009*
Q4: Your patient has poor asthma control, despite high-dose ICS, LABA, LTRA. Which approach is now reasonable?

1) Empiric anti-reflux treatment (PPI)
2) 24-hr pH monitoring, to guide PPI tx
3) Careful history of GERD, to guide PPI tx
Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma

The American Lung Association Asthma Clinical Research Centers*

Treatment with a PPI does not improve asthma control in patients with poorly controlled asthma and asymptomatic GERD
Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D., Melanie Kjarsgaard, R.R.T., Mark D. Irman, M.D., Ph.D., Ann Efthimiadis, M.L.T., Emilio Pizzichini, M.D., Ph.D., Frederick E. Hargreave, M.D., and Paul M. O’Byrne, M.B.

Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma

COPD

• COPD = Inflammatory Disease

• Mortality is increasing (6th --> 1st; esp. women)

• Spirometry detects COPD without symptoms

• Smoking Cessation modifies natural history
  (lung function, mortality)

• Pharmacologic Therapy:
  (“it’s not just for symptoms anymore”)
  - exacerbations, natural history?

• Pulmonary Rehab: reduces symptoms, depression,
  health care utilization; improves Q of L, exercise
Percent Change in Age-Adjusted Death Rates (US, 1965–1998)

Proportion of 1965 Rate

- CHD: -59%
- Stroke: -64%
- Other CVD: -35%
- COPD: +163%
- All other causes: -7%
Q 5: Which of the following has been shown to slow the loss of lung function in COPD?

1) Smoking Cessation
2) Salmeterol, Fluticasone, SM/FP
3) Tiotropium
4) All of the above
Effect of Smoking Cessation on FEV₁

Post Bronchodilator FEV₁ (liters)

Screen 2 1 2 3 4 5

Follow-up in years

Sustained Quitters

Continuing Smokers

Effects of a Smoking Cessation Intervention on 14.5-year Mortality

Anthonisen et al
Effects of a Smoking Cessation Intervention on 14.5-year Mortality

Anthonisen et al

$P=0.03$
Effects of a Smoking Cessation Intervention on 14.5-year Mortality

P=0.01

Anthonisen et al
Effects of a Smoking Cessation Intervention on 14.5-year Mortality

Anthonisen et al
Continuous Abstinence with Varenicline (Chantix™)

N=3659; ≥10 cigs/day; mean = 21/day x 25 yrs
Treated x 12 weeks

% Subjects Abstinent Weeks 9-12

- **Chantix 1 BID**
  - OR - 3.85
    - (95% CI, 2.70-5.50; P<0.001)
  - OR - 1.93
    - (95% CI, 1.40-2.68; P<0.001)

- **Bupropion SR**
  - OR - 1.90
    - (95% CI, 1.38-2.62; P<0.001)

- **Placebo**
  - OR - 1.90
    - (95% CI, 1.38-2.62; P<0.001)

---

*Gonzales et al, JAMA 296: 47-55, 2006*

*Jorenby et al, JAMA 296: 56-63, 2006*
Continuous Abstinence with Varenicline (Chantix™)

N=3659; ≥10 cigs/day; mean = 21/day x 25 yrs
Treated x 12 weeks

% Subjects Abstinent
Weeks 9-52

Chantix 1 BID
Bupropion
Placebo

OR - 3.09
(95% CI, 1.95-4.91; P<0.0001)

OR - 1.46
(95% CI, 0.99-2.17; P=0.057)

Jorenby et al, JAMA 296: 56-63, 2006

OR - 2.66
(95% CI, 1.72-4.11; P<0.001)

OR - 1.77
(95% CI, 1.19-2.63; P=0.004)

Gonzales et al, JAMA 296: 47-55, 2006
Smoking Cessation

You can TAKE CHARGE

If you want to take charge, call us. We can talk about how to quit smoking or chewing tobacco.

1-800-NO-BUTTS
(1-800-662-8887)
1-800-844-CHEW
(1-800-844-2439)

California Smokers’ Helpline
## Inhaled Corticosteroids and COPD

<table>
<thead>
<tr>
<th>STUDY</th>
<th>SITES</th>
<th>COMPARISON</th>
<th>SMOKERS</th>
<th>QUITTERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Health Study</td>
<td>US + Canada</td>
<td>Smokers vs Quitters</td>
<td>62 mL</td>
<td>32 mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STUDY</th>
<th>SITES</th>
<th>COMPARISON</th>
<th>PLACEBO</th>
<th>STEROID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copenhagen City</td>
<td>Denmark</td>
<td>BUD vs PBO</td>
<td>42 mL</td>
<td>42 mL</td>
</tr>
<tr>
<td>EUROSCOP</td>
<td>Europe</td>
<td>BUD VS PBO</td>
<td>69 mL</td>
<td>57 mL</td>
</tr>
<tr>
<td>ISOLDE</td>
<td>Europe</td>
<td>FP vs PBO</td>
<td>59 mL</td>
<td>50 mL</td>
</tr>
<tr>
<td>Lung Health Study II</td>
<td>US + Canada</td>
<td>TAC vs PBO</td>
<td>47 mL</td>
<td>44 mL</td>
</tr>
</tbody>
</table>
Lung Health Study II

![Graph showing the change in FEV₁ (ml) from baseline after bronchodilator over follow-up years for Placebo and Triamcinolone (600 µg bid).]

- Change from Baseline FEV₁ (ml) (after bronchodilator)
- Follow-up (years)

- Blue triangle: Placebo
- Red circle: Triamcinolone (600 µg bid)

*NEJM 2000; 343:1902-1909*
COPD Exacerbations
(Lung Health II)

Respiratory Exacerbations (per 100 person-years)

Placebo: 28.2
Triamcinolone: 21.1

p = 0.005

NEJM 2000; 343:1902-1909
COPD Exacerbations (ISOLDE - stratified by FEV<sub>1</sub>)

Exacerbations (per year)

FEV1 (liters)

- **Placebo**
- **Fluticasone**

Effects of Inhaled Corticosteroids in COPD: Meta-Analysis

Relative Risk of Exacerbations in Patients With COPD Treated With Inhaled Corticosteroids vs Placebo

What is the Role of Inhaled Bronchodilators in COPD?
% of COPD patients with ≥15% ↑ in FEV₁ (Days 1, 29, 57 &/or 85)

<table>
<thead>
<tr>
<th>No. of Test Days With Positive Response†</th>
<th>Treatment Group, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipratropium and Albuterol (n = 292)</td>
</tr>
<tr>
<td>0 Test days</td>
<td>3</td>
</tr>
<tr>
<td>≥ 1 Test day</td>
<td>97†</td>
</tr>
<tr>
<td>≥ 2 Test days</td>
<td>90†</td>
</tr>
<tr>
<td>≥ 3 Test days</td>
<td>76†</td>
</tr>
<tr>
<td>All 4 test days</td>
<td>56†</td>
</tr>
</tbody>
</table>

*SEM < 3% for all data points.
†Pulmonary function tests performed on days 1, 29, 57, and 85.

**FEV**$_{1}$: Tiotropium vs. Placebo

![Graph showing FEV$_{1}$ values over time for Placebo (n=328) and Tiotropium (n=518).](image)

Tiotropium Reduces Exacerbations and Hospitalizations vs Ipratropium

Tiotropium reduces Exacerbations in COPD

Niewoehner et al
Annals Int Med 143:317-26, 2005
Tiotropium reduces Exacerbations in COPD

Niewoehner et al
Annals Int Med 143:317-26, 2005
Salmeterol and Fluticasone Propionate and Survival in COPD (TORCH)

N = 6112

40-80 years old; ≥10 pack-years

FEV1 < 60% predicted; FEV1/FVC ≤ 0.70

Salmeterol 50mcg BID vs Fluticasone 500mcg BID vs Salmeterol 50/Fluticasone 500 BID vs Placebo

X 3 years

Primary Outcome: Death from All Causes
B  Death from Any Cause

- Placebo
- Salmeterol
- Fluticasone
- Combination therapy

HR, 0.825  
(95% CI, 0.681–1.002)  
P = 0.052 (log-rank test)

Calverley  
NEJM 2007; 356:775-89
TORCH

Health Status (SGRQ)

Adjusted Mean Change in Total Score (units)

Weeks

Placebo
Salmeterol
Fluticasone
Combination therapy

Calverley
NEJM 2007; 356:775-89
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*

(UPLIFT)

Tashkin et al
NEJM 359:1543-54, 2008
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Tashkin et al
NEJM 359:1543-54, 2008
Survival in Hypoxic COPD Patients using Oxygen

Cumulative Survival (%) vs Time (years)

AIM 93:391, 1980
Downward Spiral In Function Associated With COPD

Dyspnea

Disease

Inactivity

Deconditioning