New treatment strategies in COPD

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Denmark
Early detection and smoking cessation
Correct diagnoses and patient education
Pharmacological treatment according to individual response to bronchodilators and antibiotics
Early diagnosis for early intervention
Recommendation – early detection:

Persons, that fulfill criteria

🌟 > 35 years of age
🌟 smoker/ex-smoker
🌟 daily/frequent lung symptoms

Must be offered spirometry for early diagnoses of COPD
Spirometry in 3097 persons attending primary care and no previous respiratory diagnosis:

FEV₁/FVC ratio

- FEV₁/FVC ≥ 70%: 65%
- FEV₁/FVC < 70%: 35%

Int J Obstructive Pulmonary Disease 2011:6,
Global Strategy for Diagnosis, Management and Prevention of COPD

Diagnosis and Assessment: Key Points

• A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease.

• Spirometry is required to make the diagnosis; the presence of a post-bronchchodilator \( FEV_1/FVC < 0.70 \) confirms the presence of persistent airflow limitation and thus of COPD.
Cassification of COPD according to symptoms and future risk

- **GOLD 4**
- **GOLD 3**
- **GOLD 2**
- **GOLD 1**

**Daily Symptoms**
- mMRC 0-1 (CAT < 10)
- mMRC ≥ 2 (CAT ≥ 10)

**Exacerbations per year**

1. A: mMRC 0-1 (CAT < 10)
2. B: mMRC ≥ 2 (CAT ≥ 10)
3. C: Daily Symptoms < 1
4. D: Daily Symptoms ≥ 1

Exacerbations:
- < 2
- ≥ 2
Pharmacological treatment of COPD primary choice

- **GOLD 4**
- **GOLD 3**
- **GOLD 2**
- **GOLD 1**

- **mMRC 0-1 CAT < 10**
- **mMRC ≥ 2 CAT ≥ 10**

- **A**: LAMA or LABA
- **B**: LAMA or LABA
- **C**: LAMA or ICS + LABA
- **D**: Exacerbations per year ≥ 2
Smoking and smoking cessation
The sad facts

• 1 cigarette cost 20 min of a life
• 20 cigarettes cost 7 hours of a life
• 4 years smoking of 20 cigarettes daily cost 1 year of a life

• All medical speciality has several serious diseases caused by smoking and passive smoking: cancer, COPD, heart failure, hypertension, osteoporoses etc, bronchitis and childhood asthma .......etc
## The happy facts

<table>
<thead>
<tr>
<th>Time after smoking cessation</th>
<th>Effect on health</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 min after</td>
<td>Blood pressure and pulse become normal</td>
</tr>
<tr>
<td>1 day after</td>
<td>Risk for MI and stroke are reduced</td>
</tr>
<tr>
<td>3 days</td>
<td>Oxygen uptake improves, breathing becomes easier</td>
</tr>
<tr>
<td>&gt;2 weeks</td>
<td>Vascular circulation improves, less susceptibility for infection</td>
</tr>
<tr>
<td>&gt;3 weeks</td>
<td>Improved fertility, less cough, better sleep,</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>Risk of MI halved</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>Risk of cancer halved (mouth, pancreas, cervix)</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>Risk of MI and lung cancer as in never smokers</td>
</tr>
</tbody>
</table>
Disease does not get everybody to stop smoking?

In studies testing drugs in COPD: Torch, Isolde, Euroscop

40-45 % of moderate – severe COPD patients still smoked!

Appropriate intervention: smoking cessation

Berry CE, COPD 2010;7:375-82
Relapse rates for smokers after smoking cessation

Tobacco dependence has its own code number in the WHO ICD-10 and in DSM IV

**International Classification of Diseases (ICD)**

**Diagnostic and Statistical Manual of Mental Disorders (DSM)**

Nikotine withdrawal symptoms are described by DSM IV as:

**Nicotine abstinence**

- Hunger for tobacco
- Bad temper and mood
- Sleep difficulties
- Irritability
- Frustation and anger
- Anxiety
- Difficulties of concentration
- Restlessness
- Increased appetite – weight gain
# Efficacy of smoking cessation in COPD

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>Nothing/ usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counselling alone</td>
<td>1.82 (0.96-3.34), P=0.07</td>
</tr>
<tr>
<td>Counselling + antidepres.</td>
<td>3.32 (1.53-7.21), P=0.002</td>
</tr>
<tr>
<td>Counselling + NRT</td>
<td>5.08 (4.32-5.97), P&lt;0.001</td>
</tr>
<tr>
<td>Counselling + varenicline</td>
<td>4.04 (2.13-7.67) P&lt;0.001</td>
</tr>
<tr>
<td>(1 study only) (CHEST, 2009)</td>
<td></td>
</tr>
</tbody>
</table>

Eur Respir J 2009;34:634-40
Smoking cessation during hospital admission

• COPD patients: taken in hospital (N=247) vs usual treatment (N=231)
  FEV1 % predicted: 75 %          age: 52 år

• Åre Hospital in Northern Sweden

• 11 days in hospital, third day was quit day,
  Support every day: Nikotin RT; physical activity, 1 one hour counselling
  with a specially educated ”stop nurse”, educational programme
  followed up by weekly telephone calls by the nurse.

• Reinforcement after 2-3 months as a 2-4 days stay in the hospital

Sundblad, Larsson K, Nathell L, Nic Tob Res
2008;10:883-890
Smoking cessation during hospital admission

<table>
<thead>
<tr>
<th>Smoking cessation group</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year quit rate: 52 %</td>
<td>1-year quit rate: 7 %</td>
</tr>
<tr>
<td>3-year quit rate: 38 %</td>
<td>3-year quit rate: 10 %</td>
</tr>
<tr>
<td>Used NRT: 28 %</td>
<td>Used NRT: 14 %</td>
</tr>
<tr>
<td>Used BUP: 5 %</td>
<td>Used BUP: 5 %</td>
</tr>
</tbody>
</table>

A community problem – everybody need to be targeted

- Restrictions on all aspects of production sale, distribution, use, pricing, advertising,
- high cost associated with less smoking in children and young people.
- Free and intensive activities in smoking cessation by specially trained persons.
WHO FRAMEWORK CONVENTION ON TOBACCO CONTROL
Treatment developments
PDE4 inhibitor
24 hour LABA
antibiotics
Cochrane analysis – PDE4 inhibitors

- 9 trials roflumilast, 14 trials cilomilast, 15,668 patients up to one year trials
- Small improvements in quality of life (St George's Respiratory Questionnaire, MD -1.04; 95% CI -1.66 to -0.41)
- PDE(4) inhibitor associated with a reduced likelihood of COPD exacerbation (OR 0.78; 95% CI 0.72 to 0.85)

As new bronchodilators are introduced there have been more consistent improvements in outcomes for patients with COPD

<table>
<thead>
<tr>
<th></th>
<th>Duration of action (hours)</th>
<th>Lung function</th>
<th>Breathlessness</th>
<th>Exercise endurance*</th>
<th>Quality of life</th>
<th>Exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
<td>4–6</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>6–8</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>≥12</td>
<td>✓ ✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ (√†)</td>
<td>✓</td>
</tr>
<tr>
<td>Formoterol</td>
<td>≥12</td>
<td>✓ ✓</td>
<td>✓ ✓</td>
<td>✓</td>
<td>✓ (√†)</td>
<td>✓†</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>24</td>
<td>✓ ✓ ✓</td>
<td>✓ ✓ ✓</td>
<td>✓</td>
<td>✓ (√†)</td>
<td>✓ (√†)</td>
</tr>
</tbody>
</table>

- ✓ evidence of effectiveness; ✓ ✓ evidence of effectiveness over SABA or SAMA; ✓ ✓ ✓ evidence of effectiveness over LABA
- *Outcome demonstrated by all bronchodilators, lack of evidence of significant differences between them
- †Equivocal evidence depending on formulation; 5,10,11  ‡Evidence of numerical improvements over shorter acting comparator 4,8
- NA = evidence not available

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Dose Response: Indacaterol and Comparators

F12=Formoterol 12 µg BID  S50=Salmeterol 50 µg BID  T18=Tiotropium 18 µg

95% confidence interval
95% prediction interval

Renard et al. Respiratory Research 2011, 12:54
COPD Pooled Study-level Analysis: Predicted Response at Each Dose Level

Trough FEV₁ – difference from placebo (mL)

Renard et al. Respiratory Research 2011, 12:54
Significant improvement in trough FEV$_1$ versus indacaterol and placebo (Day 7)

Randomized, double-blind, placebo controlled, four-period crossover study
Study A2204; data are LSM ± SE; *p<0.0001 vs placebo; #p<0.0001 vs indacaterol 300 μg and 600 μg
LSM = least squares mean; SE = standard error

Van Noord et al. Thorax 2010
QVA149 had a rapid onset of action with sustained bronchodilation over 24 hours (Day 7)

Randomized, double-blind, placebo controlled, four-period crossover study
Study 2204; data are LSM. QVA149 300/50 µg statistically superior (p<0.05) to indacaterol 300 µg, 600 µg and placebo at all post-baseline timepoints LSM = least squares mean

Van Noord et al. Thorax 2010
QVA149 safety

- Once-daily QVA149 600/100 µg, 300/100 µg and 150/100 µg produced no significant effect on 24-hour mean heart rate after 14 days of treatment.

- All QVA149 doses were well tolerated, with overall AE rates similar to placebo and indacaterol 300 µg.

- The effect of QVA149 on other cardiovascular assessments, including Fridericia’s QTc interval, appeared to be minimal with a profile similar to placebo.

- The overall incidence of abnormal vital signs was similar between treatment groups.

Van de Maele et al. COPD 2010
Non-purulent

Clear

Yellow

Green

Rust

Purulent

Courtesy of R. Wilson. Host Defence Unit. Royal Brompton Hospital London, UK
Colonisation and purulence

Mucoid= 61.4%  Purulent/mucopurulent= 38.6%

Miravitlles et al. Respir Res 2010; 11: 58
Infection and COPD

Low FEV₁

Colonisation/CBI

Frequent and severe E-COPD

Antibiotics

The “fall & rise” of bacterial AECB

Clinical efficacy – pulsed moxifloxacin. Per protocol

(A) PP EOT and ITT population

Estimate of common odds ratio (95% CI)

<table>
<thead>
<tr>
<th>AECB primary definition</th>
<th>0.57</th>
<th>0.75</th>
<th>0.99</th>
<th>p = 0.046</th>
<th>(p = 0.037)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AECB secondary definition</td>
<td>0.65</td>
<td>0.81</td>
<td>1.01</td>
<td>p = 0.059</td>
<td>(p = 0.068)</td>
</tr>
<tr>
<td></td>
<td>0.56</td>
<td>0.73</td>
<td>0.97</td>
<td>p = 0.028</td>
<td>(p = 0.020)</td>
</tr>
<tr>
<td></td>
<td>0.61</td>
<td>0.77</td>
<td>0.95</td>
<td>p = 0.017</td>
<td>(p = 0.018)</td>
</tr>
</tbody>
</table>

Sethi et al. Respir Res 2010; 11:10
Erythromycin and COPD

ERT 125 mg/tid or placebo for 6 months

P = 0.032

He et al. Respiration 2010; 80: 445-452.
Azithromycin and COPD

RCT of AZT vs placebo in 1142 patients with COPD for one year in addition to their usual care. Mean FEV1=40%. Time to 1st 266 vs 174 days. Reduction of 27% in exacerbations

Albert et al. NEJM 2011; 365: 689-98.
The beneficial effects of antibiotics are clear in prevention and treatment of COPD exacerbations.

Define the indication and patient profile more specifically.

Document short and long term side effects including resistance patterns.
Many new therapeutic options available

Bruch up our present pharmacological and non-pharmacological treatments and prophylaxis

Thank you for your attention
Azithromycin and COPD

Albert et al. NEJM 2011; 365: 689-698.
PDE4 plays an important role in inflammation

The PDE4 enzyme in inflammatory cells related

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Action of roflumilast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage</td>
<td>TNF-α and LTC4 expression reduced</td>
</tr>
<tr>
<td>CD8+ T lymphocyte</td>
<td>Cytokine production and lymphocyte proliferation reduced</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>IL-8 and LTB4 expression, phagocytosis and chemotaxis reduced</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>Degranulation, arachidonic acid, LTC4 and ROS reduced</td>
</tr>
<tr>
<td>Airway smooth muscle</td>
<td>Eotaxin expression reduced</td>
</tr>
<tr>
<td>Epithelial cell</td>
<td>IL-6 and TNF-α production reduced</td>
</tr>
<tr>
<td>Endothelial cell</td>
<td>Vascular permeability and adhesion molecule expression reduced</td>
</tr>
<tr>
<td>Sensory nerve</td>
<td>Neuropeptide secretion reduced</td>
</tr>
<tr>
<td>Fibroblast</td>
<td>Eotaxin and ICAM-1 expression reduced</td>
</tr>
</tbody>
</table>

Field SK: Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine 2011:5 57–70
Roflumilast significantly reduced the rate of Moderate/Severe Exacerbations

### Adverse effects

- Adverse effects occurred mainly within the first weeks of therapy and mostly resolved on continued treatment.

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Roflumilast*</th>
<th>Placebo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>1271 (22)</td>
<td>587 (10.7)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>585 (10.1)</td>
<td>143 (2.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>297 (5.2)</td>
<td>79 (1.4)</td>
</tr>
<tr>
<td>Investigations</td>
<td>811 (14.1)</td>
<td>584 (10.6)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>394 (6.8)</td>
<td>101 (1.8)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>615 (10.7)</td>
<td>304 (5.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>266 (4.6)</td>
<td>110 (2.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>139 (2.4)</td>
<td>65 (1.2)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>344 (6.0)</td>
<td>164 (3.0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>148 (2.6)</td>
<td>50 (0.9)</td>
</tr>
</tbody>
</table>

- Changes in weight, and neuropsychiatric events should be monitored.

*Expressed as number and percent of total study population.

Rabe KF. Brit Jour Pharmacol (2011) **163**
53–67
Weight decrease associated with roflumilast during the first 6 months

Weight related to BMI

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy SECOND CHOICE

- **GOLD 4**
  - C: LAMA and LABA

- **GOLD 3**
  - D: ICS and LAMA or ICS + LABA and LAMA or ICS + LABA and PDE4-inh or LAMA and LABA or LAMA and PDE4-inh.

- **GOLD 2**
  - B: Exacerbations per year ≥ 2

- **GOLD 1**
  - A: LAMA or LABA or SABA and SAMA
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy ALTERNATIVE CHOICES

- **GOLD 4**
  - **GOLD 3**
  - **GOLD 2**
  - **GOLD 1**

<table>
<thead>
<tr>
<th>Quadrant</th>
<th>mMRC 0-1</th>
<th>mMRC ≥ 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Theophylline</td>
<td>SABA and/or SAMA, Theophylline</td>
</tr>
<tr>
<td>B</td>
<td>SABA and/or SAMA, Theophylline</td>
<td>Carbocysteine, SABA and/or SAMA, Theophylline</td>
</tr>
<tr>
<td>C</td>
<td>PDE4-inh. SABA and/or SAMA, Theophylline</td>
<td>Carbocysteine, SABA and/or SAMA, Theophylline</td>
</tr>
<tr>
<td>D</td>
<td>Carbocysteine, SABA and/or SAMA, Theophylline</td>
<td>SABA and/or SAMA, Theophylline</td>
</tr>
</tbody>
</table>

Exacerbations per year:

- 0
- 1
- ≥ 2
Manage Stable COPD: Goals of Therapy

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

Reduce symptoms

Reduce risk
Randomized, double-blind, placebo-controlled, parallel-group, 14-day study; n=257
Study A2203; *None of the CIs crossed the pre-specified equivalence margin of +5 and –5 bpm.
Data are LSM and the corresponding 95% CIs; safety population
CI = confidence interval; LSM = least squares mean
Van de Maele et al. COPD 2010
Smoking Cessation: Effects on Mortality

CHD=coronary heart disease; CVD=cardiovascular disease.

Lack of Tachyphylaxis over 52 Weeks

Study B2335S/SE

All p<0.001 vs placebo
Dotted line shows prespecified 120 mL level of clinically important difference
Trough FEV₁ = mean of measurements at 23 h 10 min and 23 h 45 min post-dose