Asthma and COPD – what’s new?

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- Royal Surrey County Hospital
  Clinic Thursday pm
  Secretary - Jen Pritchard

- Nuffield Hospital, Guildford
  Clinic Thursday am

- Surrey cardiovascular clinic
  *ad hoc*
  Secretary - Sally Groves
Declarations of interest

• Travel expenses from Napp.
• Honoraria from GSK and Novartis for giving talks.

Disclaimer

• These views are my own and do not necessarily represent others’.
Overview

• Asthma
  1. Recent guidance / NRAD
  2. Assessing control
  3. Current treatment options
  4. Newer therapies
  5. Treatments in development
  6. When to refer

• COPD
  1. Recent guidance
  2. Current treatment
  3. Controversies
  4. Newer therapies
  5. Future therapies
  6. When to refer

Brief discussion of four cases
Asthma
National Review of Asthma Deaths (2014)

• 45% died without seeking medical assistance or before emergency medical care could be provided.
• 57% were not under specialist supervision during the 12 months prior to death.
• 43% had not had an asthma review in primary care in the preceding 12 months.
• 53% had never been admitted to hospital for asthma.
Prescribing and treatment

- 39% had been prescribed more than 12 SABA in the year before they died, while 4% had been prescribed more than 50 reliever inhalers!
- 80% issued with fewer than 12 preventer inhalers in the previous year

Is it other factors?

- Depression and mental health issues in 32 (16%) and substance misuse in 12 (6%)
Asthma is still a problem

- 5.4 million people are on treatment for asthma in the UK
- National variability - 5-fold difference between PCT areas in the number of emergency admissions in adults
- International variability - Premature mortality from asthma was 1.5 times as high in the UK than in the rest of Europe in 2008 (~1000/yr)
What are we aiming for with asthma control?

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controlled (All of the following)</th>
<th>Partly Controlled (Any measure presented)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None (twice or less/week)</td>
<td>More than twice/week</td>
<td>Three or more features of partly controlled asthma*†</td>
</tr>
<tr>
<td>Limitation of activities</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms/awaking</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Need for reliever/rescue inhaler</td>
<td>None (twice or less/week)</td>
<td>More than twice/week</td>
<td></td>
</tr>
<tr>
<td>Lung function (PEF or FEV₁)†</td>
<td>Normal</td>
<td>&lt; 80% predicted or personal best (if known)</td>
<td></td>
</tr>
</tbody>
</table>

The goal of management is for people to be free from symptoms and able to lead a normal, active life.
### Asthma education. Environmental control.
(If step-up treatment is being considered for poor symptom control, first check inhaler technique, check adherence, and confirm symptoms are due to asthma.)

<table>
<thead>
<tr>
<th>Controller options***</th>
<th>As needed rapid-acting $\beta_2$-agonist</th>
<th>As needed rapid-acting $\beta_2$-agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Select one</strong></td>
<td><strong>Select one</strong></td>
</tr>
<tr>
<td>Low-dose inhaled ICS*</td>
<td>Low-dose ICS plus long-acting $\beta_2$-agonist</td>
<td>Medium-or high-dose ICS plus long-acting $\beta_2$-agonist</td>
</tr>
<tr>
<td>Leukotriene modifier**</td>
<td>Medium-or high-dose ICS</td>
<td>Leukotriene modifier</td>
</tr>
<tr>
<td>Low-dose ICS plus leukotriene modifier</td>
<td>Low-dose ICS plus sustained release theophylline</td>
<td>Sustained release theophylline</td>
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<tr>
<td>Low-dose ICS plus sustained release theophylline</td>
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</tbody>
</table>
- Step-up to gain control
- Step-down...

<table>
<thead>
<tr>
<th>Level of Control</th>
<th>Treatment Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>Maintain and find lowest controlling step</td>
</tr>
<tr>
<td>Partly controlled</td>
<td>Consider stepping up to gain control</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>Step up until controlled</td>
</tr>
<tr>
<td>Exacerbation</td>
<td>Treat as exacerbation</td>
</tr>
</tbody>
</table>
Why step-down?

• Dose-response curve means benefits of increased ICS dose may be minimal
• Side-effects – dysphonia, candida, purpura, skin thinning – dose response ≥400mcg/day
• Adrenal suppression ≥800mcg/day
• Osteoporosis occurs ≥800mcg/day
• Cost...

• Combination inhaled corticosteroid and long acting bronchodilator (ICS/LABA) inhalers are now the most expensive drug class for the NHS.

Brown J. Seretide® is the most expensive drug prescribed nationally; but is it the most cost-effective combination inhaler on the market? NHS Prescriber 9, October 2010
Cost of 1m of treatment...

- Symbicort 400 ii bd £76
- Seretide 250 ii bd £59
- Flutiform 250 ii bd £46
- Seretide 500 i bd £41
- Relvar 184/22 od £38

- Symbicort 200 ii bd £38
- Seretide 125 ii bd £35
- Flutiform 125 ii bd £29
- Fostair 100 ii bd £29
- Relvar 92/22 od £28

- Symbicort 200 i bd £19
- Seretide 50 ii bd £18
- Flutiform 50 ii bd £18
Is it safe to step-down?

- RCT Scotland: 259 adult asthmatics, ≥800mcg
- Well controlled
- Step down (50%↓) vs. sham step down
- No difference in exacerbation rates

Adopting a stepdown approach to the use of high dose corticosteroids in patients with chronic stable asthma can lead to a significant reduction in the daily dose of inhaled corticosteroids without compromising asthma control

Hawkins et al. BMJ 2003;326:1115
Rate of response of different measures of asthma control over 18 months of ICS treatment. AHR is a measure of inflammation

Assessing asthma control

Clinicians frequently over-estimate asthma control and under-estimate the impact of asthma on patents’ lives

• Ask the patient
  – Unstructured – how are you?
  – Structured: RCP3, ACQ, ACT
• Measure PEF/FEV1
• FeNO
• Inhaler usage - heavy or increasing use of SABA is associated with asthma death

Prim Care Resp J 2009; 18(2): 83-88
RCP 3 questions – assess asthma control

1. Have you had difficulty **sleeping** because of asthma symptoms (including cough)?

2. Have you had your **usual asthma symptoms** during the day (cough, wheeze, chest tightness or breathlessness)?

3. Has your asthma interfered with your **usual activities** (e.g. housework, work, school, etc)?
Titrating the dose of ICS

Comparison of Physician-, Biomarker-, and Symptom-Based Strategies for Adjustment of Inhaled Corticosteroid Therapy in Adults With Asthma
The BASALT Randomized Controlled Trial
BASALT

• 342 pts with mild-moderate asthma
• Randomised to 3 groups: (9 months)
  – symptom-based adjustment (SBA) of inhaled corticosteroids
  – biomarker-based adjustment (BBA) FeNO
  – physician assessment–based adjustment (PABA) based on NHLI guidelines
• The primary outcome was time to first treatment failure, a clinically important worsening of asthma
• Neither PABA nor BBA were superior to SBA

Newer treatments for asthma

1. Using symbicort - SMART
2. Xolair (Omalizumab)
3. (Bronchial thermoplasty)
4. Fostair (MART) and Flutiform
5. Relvar Ellipta
6. Spiriva(!)
1. Symbicort SMART
(budesonide/formoterol)

• “In selected adult patients at step 3* who are poorly controlled or in selected adult patients at step 2, the use of budesonide/formoterol in a **single inhaler** as rescue medication instead of a short-acting β2 agonist, in addition to its regular use as controller therapy has been shown to be an effective treatment regime.”

* Step 3 = ICS/LABA; Step 2 = ICS
Symbicort SMART

Pro
• Convenient
• Lower ICS dosing
• Fewer exacerbations and fewer hospital admissions

Con
• May not adequately suppress airway inflammation
• Concerns about the supporting evidence
• Requires good patient understanding
• Associated with poor control in trials (17%)
2. Xolair (omalizumab)

Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201)

Issued: April 2013

1. Allergy to aeroallergen (SPT/RAST)
2. IgE 75-1000 IU/ml; pt can’t be too heavy
3. FEV1<80%
4. Optimal Rx plus >= 4 courses of OCS/y
5. Frequent symptoms
3. Bronchial thermoplasty

- Evidence of efficacy
- Specialist centres

Bronchial thermoplasty for severe asthma

Issued: January 2012

NICE interventional procedure guidance 419
guidance.nice.org.uk/ipg419
4. Fostair

- Beclomethasone/Formoterol
- 100mcg/6mcg
- 100mcg = 200-250mcg BDP equivalent (extrafine)
- 1-2 puffs BD, or 1-2 puffs BD and PRN (MART)
- Cheaper (£29) than Seretide (£35-£60)
- RCT evidence of non-inferiority

Fostair vs Seretide
Fostair vs Symbicort
Flutiform

- Fluticasone/Formoterol
  - 50/5 mcg (£18)
  - 125/5 mcg
  - 250/10 mcg (£46)
- 2 puffs BD
- RCT evidence of non-inferiority
Flutiform® inhaler for Asthma
The network were informed that Flutiform® is a recently launched combination inhaler and although recently launched it contains two established ingredients (Fluticasone & Formoterol). NICE guidance recommends that the least costly device that is suitable for an individual patient should be used if a combination inhaler is required. The network members concurred that Flutiform® is a cost effective alternative combination ICS/LABA. The network noted the price differential between the various combination ICS/LABA inhalers.
GP colleagues noted that if a spacer device is indicated for a patient, then the Aerochamber Plus® should be used as per the license (ie regular treatment of asthma where the use of a combination inhaled ICS/ LABA is appropriate – currently not SMART)
The network members discussed possible solutions to support implementation and requested that the author of the review discuss this with the manufacturers of Flutiform®.

Recommendations:
The Network supported the use of Flutiform® (in line with the license) as a first line alternative to Seretide Evohaler® and Symbicort Turbohaler® in adults and children over 12 years where LABA/ICS is indicated as per BTS and NHS Surrey Asthma Guidelines. (NB 250mcg strength licensed only from 18 years).
Individual practices may consider actively switching patients on Seretide Evohaler® to an appropriate dose of Flutiform® MDI or to review patients when it is clinically appropriate to step up or step down the dose of ICS/LABA.
Medicines Management of Asthma in Adults and Adolescents over 12 years

Step up Step down: Aim to achieve early control, step up treatment as necessary and down when control is good.
Review patients using one or more β2 agonist devices monthly or using β2 agonist or symptomatic three times weekly or more.

**Step 1 - Inhaled Short Acting β2 Agonist (SABA) as required**
Short term reliever therapy
1st Choice: Salbutamol MDI 2 puffs prn + spacer (Aerochamber Plus®)
Alternative device: Easyhaler Salbutamol® 100 2 puffs prn

**Step 2 - Add Inhaled Corticosteroid (ICS) 200-800mcg/day**
Start at a dose appropriate to the initial severity.
Recommended starting dose 400mcg BDP® per day
Clenil Modulite® 100 MDI 2 puffs bd
or Qvar® 50 MDI 2 puffs bd
+ spacer (eg Aerobalm Plus®)
Alternative devices: Easyhaler Beclometasone® 200 1 puff bd
Qvar Easi-Breathe® 50 2 puffs bd
BDP equivalent see overlay for dose equivalences

**Step 3 - Add Inhaled Long Acting β2 Agonist (LABA) to ICS**
Consider LABA before going above 400mcg BDP/day
Starting doses when using combination ICS/LABA:
Flutiform® 50 MDI or Seretide Evohaler® 50 2 puffs bd + spacer
(eg Aerobalm Plus®)
or Symbicort Turbohaler® 200 1 puff bd (SMART® regime in suitable patients)
or Seretide Accuhaler® 100 1 puff bd

**Step 4 - Consider Increasing ICS to 2000mcg/day**
Flutiform® 250 MDI (in adults over 18 years only)
or Seretide Evohaler® 250 2 puffs bd + spacer (Aerochamber Plus®)
or Seretide Accuhaler® 500 1 puff bd or Symbicort Turbohaler® 400 2 puffs bd
Review at 4 weekly intervals. If still stable after 12 weeks consider stepping down.
Take individual patient factors into account eg winter months or allergy season
Consider referral to a specialist if on high dose ICS for more than 6 months

Before starting new therapy check diagnosis, compliance with current medication and inhaler technique. Eliminate trigger factors including rhinitis.
Consider adding ICS if the patient:
- has had asthma exacerbations in the last 2 years
- is using a β2 agonist or is symptomatic 3 times weekly or more
- is waking one night per week with asthma
Qvar® contains extra fine particles, adjust dose as necessary.
For information on steroids and dose equivalences see overlay.
Titrator to the lowest dose at which control is maintained

**Symbicort Maintenance And Reliever Therapy (SMART®)**
Symbicort 200/6® can be used as rescue medication instead of SABA in addition to its regular use as a preventer at Step 3, in adults over 18yr ± 12.
Check BNF for dosing.
Review if rescue dose is used more than once daily on a regular basis. Educate suitable patients who can self manage.
http://www.medicines.org.uk

**Step down when control is good.**
Dose reduction should be slow to avoid deterioration.
Consider reduction every 3 months, decreasing the dose by approximately 25-50% each time.
See overlay for more information on stepping down.
5. Relvar Ellipta

- A new once daily ICS/LABA (24-hour efficacy)
- Fluticasone *furoate* / Vilanterol
- Two strengths (92/22 and 184/22mcg)
- As efficacious as seretide
- New device (Ellipta)
- Safe
- £28/38
Experimental asthma treatments

• Inhaled
  – LAMA: Tiotropium and Glycopyrronium
  – PDE4 inhibitors (GSK256066)

• Injections
  – 4...umabs, vs. IL-5, IL-4R, IL-13(R)

• Tablets
  • Clarithromycin/azithromycin
  • Mast cell TK-inhibitor (masitinib)
When to refer

- Diagnosis unclear
- Unexpected clinical findings (ie crackles, clubbing, cyanosis, cardiac disease)
- Unexplained restrictive spirometry
- Suspected occupational asthma
- Persistent non-variable breathlessness
- Monophonic wheeze or stridor
- Prominent systemic features (myalgia, fever, weight loss)
- Chronic sputum production
- CXR shadowing
- Marked blood eosinophilia (> 1 x 10⁹/l)
- Poor response to asthma treatment
- Severe asthma exacerbation
Recommendations from NRAD

• Patients with asthma must be referred to a specialist asthma service if they have required ≥ 2 courses of OCS in the previous 12 months or require management using British Thoracic Society (BTS) stepwise treatment 4 or 5 to achieve control

• Secondary care follow-up should be arranged after every hospital admission for asthma, and for patients who have attended the ED ≥2 times with an asthma attack in the previous 12 months
Asthma Case 1

- 25-year-old woman
- Asthma with night-time waking and some limitations to exercise
- Currently on Seretide 125 2 puffs BD

Options:

a) Seretide 250, 2 puffs BD
b) Relvar 184/22, 1 puff OD
c) Flutiform 250, 2 puffs BD
d) Montelukast
e) Theophylline
f) No change
Asthma Case 2

- 25-year-old woman
- Asthma
- No symptoms
- Currently on Seretide 250 2 puffs BD

Options:

a) Seretide 125, 2 puffs BD
b) Relvar 92/22, 1 puff OD
c) Flutiform 125, 2 puffs BD
d) No change
Any questions on asthma?
### Differential Diagnosis: COPD and Asthma

**COPD**
- Onset in mid-life
- Symptoms slowly progressive
- Long smoking history

**ASTHMA**
- Onset early in life (often childhood)
- Symptoms vary from day to day
- Symptoms worse at night/early morning
- Allergy, rhinitis, and/or eczema also present
- Family history of asthma
COPD
Often treated like this:

1. SABA
2. (LABA)
3. LABA/ICS or LAMA
4. LABA/ICS and LAMA
5. + adjuncts theophylline / carbocysteine / antibiotics / OCS

Simple but likely excessive use of ICS

(NB: OCS not normally recommended)
BTS/NICE 2010

In people with stable COPD who remain breathless or have exacerbations despite use of short-acting bronchodilators as required, offer the following as maintenance therapy:

• if FEV$_1$ $\geq$ 50% predicted: either LABA or LAMA (can have ICS/LABA if remains symptomatic)

• if FEV$_1$ $<$ 50% predicted: either LABA/ICS, or LAMA
GOLD 2013 added complexity

<table>
<thead>
<tr>
<th>Category C</th>
<th>Category D</th>
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</thead>
<tbody>
<tr>
<td>HIGH RISK, LESS SYMPTOMS</td>
<td>HIGH RISK, MORE SYMPTOMS</td>
</tr>
<tr>
<td>GOLD</td>
<td>GOLD</td>
</tr>
<tr>
<td>3 or 4</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>Exacerbations</td>
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<tr>
<td>≥2/yr</td>
<td>≥2/yr</td>
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<tr>
<td>mMRC</td>
<td>mMRC</td>
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<tr>
<td>0-1</td>
<td>≥2</td>
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<tr>
<td>CAT score</td>
<td>CAT score</td>
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<td>&lt;10</td>
<td>≥10</td>
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<table>
<thead>
<tr>
<th>Category A</th>
<th>Category B</th>
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<td>LOW RISK, LESS SYMPTOMS</td>
<td>LOW RISK, MORE SYMPTOMS</td>
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<td>≥10</td>
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</table>
In patients with FEV₁/FVC < 0.70:

<table>
<thead>
<tr>
<th>GOLD 1: Mild</th>
<th>FEV₁ ≥ 80% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 2: Moderate</td>
<td>50% ≤ FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>GOLD 3: Severe</td>
<td>30% ≤ FEV₁ &lt; 50% predicted</td>
</tr>
<tr>
<td>GOLD 4: Very Severe</td>
<td>FEV₁ &lt; 30% predicted</td>
</tr>
</tbody>
</table>

PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY)

- mMRC Grade 0. I only get breathless with strenuous exercise.
- mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.
- mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
- mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level.
- mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.
In patients with FEV₁/FVC < 0.70:

| GOLD 1: Mild | FEV₁ ≥ 80% predicted |
| GOLD 2: Moderate | 50% ≤ FEV₁ < 80% predicted |
| GOLD 3: Severe | 30% ≤ FEV₁ < 50% predicted |
| GOLD 4: Very Severe | FEV₁ < 30% predicted |

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<p>| Patient Category C | HIGH RISK, LESS SYMPTOMS |</p>
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<th>Patient Category D</th>
<th>HIGH RISK, MORE SYMPTOMS</th>
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<tr>
<td>GOLD 3 or 4</td>
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<tr>
<td>Exacerbations ≥2/yr</td>
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<td>CAT score &lt;10</td>
<td>CAT score ≥10</td>
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</table>

<p>| Patient Category A | LOW RISK, LESS SYMPTOMS |</p>
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<tr>
<th>Patient Category B</th>
<th>LOW RISK, MORE SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1 or 2</td>
<td>GOLD 1 or 2</td>
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<td>Exacerbations ≤1/yr</td>
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<td>mMRC 0-1</td>
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<td>CAT score &lt;10</td>
<td>CAT score ≥10</td>
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<td>Patient group</td>
<td>First choice</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>A Low risk, Less symptoms</td>
<td>Short-acting anticholinergic prn or Short-acting β₂-agonist prn</td>
</tr>
<tr>
<td>B Low risk, More symptoms</td>
<td>Long-acting anticholinergic or Long-acting β₂-agonist</td>
</tr>
<tr>
<td>C Higher risk, Less symptoms</td>
<td>Inhaled corticosteroid + long-acting β₂-agonist or Long-acting anticholinergic</td>
</tr>
<tr>
<td>D Higher risk, More symptoms</td>
<td>Inhaled corticosteroid + long-acting β₂-agonist or Long-acting anticholinergic</td>
</tr>
</tbody>
</table>
Important non-inhaled interventions

• Smoking cessation
• Pulmonary rehabilitation; promotion of exercise
• Vaccines
• Self-management plans; with spare ABx/Steroids for IECOPD
• Oxygen alerts / Steroid cards
• Treat cardiac co-morbidities
Current controversies

1. Tiotropium may be harmful, particularly the respimat
2. ICS are probably overused, may be associated with harm
3. Cardiac co-morbidities and their treatment
1. Spiriva/tiotropium and risk of harm

- 2008 FDA warning following MA of 29 RCTs show increased mortality.
- UPLIFT study (largest single RCT) showed no such increased risk, but excluded those at high CV risk. Improved mortality vs. placebo.
- 2011 SR/MA of all Respimat COPD studies – 50% increased CV death.
- Others corroborate these findings.
- “Level 1 scientific evidence that tiotropium Respimat increases the risk of cardiovascular and all-cause mortality”.

Thorax. 2013 Jan;68(1):5-7
Autumn 2013

- RCT 17,000 pts
- Respimat 2.5mcg and 5mcg vs. handihaler
- Included CV patients
- No difference in safety or efficacy
- But no control group and study funded by BI
- Editorialist CoI

VS.

Primary Care database (Holland)
- COPD and tiotropium
- Compared mortality, correcting for known confounders
- Excess mortality (27%) with respimat vs. handihaler

Tiotropium Respimat Inhaler and the Risk of Death in COPD

Robert A. Wise, M.D., Antonio Anzueto, M.D., Daniel Cotton, M.S., Ronald Dahl, M.D., Theresa Devins, Dr. Ph., Bernd Disse, M.D., Daniel Dusser, M.D., Elizabeth Joseph, M.P.H., Sabine Kattenbeck, Ph.D., Michael Koenen-Bergmann, M.D., Gordon Pledger, Ph.D., and Peter Calverley, D.Sc., for the TIOSPIR Investigators*


Use of tiotropium Respimat Soft Mist Inhaler versus HandiHaler and mortality in patients with COPD

Katia M.C. Verhamme1,4, Ana Alfonso1,4, Silvana Romio1, Bruno C. Stricker2, Guy G.O. Brusselle2,3 and Miriam C.J.M. Sturkenboom1,2

Eur Respir J. 2013 Sep;42(3):606-15
2. Excessive use of ICS in COPD

- Guideline recommendations for the use of ICS in COPD are largely based on their preventive effect on exacerbations – although evidence is mixed.
- No evidence of improved mortality; limited evidence of slowing \( \text{FEV}_1 \) decline; insignificant improvement in HRQoL.
- Main risk – 70% increase in the rate of hospitalisation for pneumonia.
- “The indiscriminate use of ICS in COPD may expose patients to an unnecessary increase in the risk of side-effects such as pneumonia, osteoporosis, diabetes and cataracts, while wasting healthcare spending and potentially diverting attention from other more appropriate forms of management such as pulmonary rehabilitation and maximal bronchodilator use.”
3. Cardiac co-morbidities and COPD

- Commonly co-exist with COPD: IHD, AF, HT and heart failure
- Treatment including beta-blockers should be the same (β-1 selective: atenolol, bisoprolol, metoprolol, nebivolol) but often isn’t (BNF)
- CV death is the commonest cause of death in COPD and potentially treating co-morbidities will improve prognosis more than any COPD treatment!
Benefits of β-blockers

1. Treatment with βB may reduce the risk of exacerbations and improve survival in patients with COPD
   
   Arch Intern Med. 2010;170(10):880-887

2. Improved mortality in those with COPD who have an MI and are treated with β-blockers.
   
   BMJ 2013;347:f6650

3. βB may reduce mortality and AECOPD when added to established therapy, independently of overt cardiovascular disease and cardiac drugs
   
   BMJ 2011;342:d2549

4. The use of βB by inpatients with AECOPD is well tolerated and may be associated with reduced mortality
   
   Thorax 2008;63:301–305
Newer treatments for COPD

1. LABA
   - Onbrez (indacaterol), Breezhaler, Novartis
   - Striverdi (olodaterol), Respimat, BI
2. LAMAs
   - Eklira (aclidinium), Genuair, Almirall
   - Seebri (glycopyrronium), Breezhaler, Novartis
   - Incruse (umeclidinium), Ellipta, GSK
3. LABA/LAMA
   - Ultibro (IND/GLYCO), Breezhaler, Novartis
   - Anoro (VI/UM), Ellipta, GSK
   - Duaklir (FORM/IND), Genuair, Almirall
4. Once daily ICS/LABA: Relvar 92/22
5. Macrolide antibiotics
6. (roflumilast, mucolytics)
1. Newer LABAs

A) Onbrez (Indacaterol)
- Breezhaler, Novartis
- Once daily LABA
- £29
- Evidence of
  - Non-inferiority to tiotropium (different class of drug but similar use)
  - Superiority to BD salmeterol
  - Superiority to BD formoterol

Thorax 2010;65:473e479
AJRCCM 2010; 182:155–162
ERJ 2011; 37: 273–279
B) **Striverdi** (olodaterol)
- Respimat, BI
- Once daily LABA
- £26
2. New LAMAs

Spiriva (tiotropium) was the only LAMA, now there are options

• They may be more effective
• They may be safer
• They are cheaper
a) Eklira (Aclidinium)

- Twice daily LAMA 400mcg
- £28
- Good things:
  - Good device
  - Best improvement in SGRQ (vs. Placebo)
  - Few side-effects and possibly no CV s/e
- Bad things:
  - No adequate trials vs. competitors
b) Seebri (Glycopyrronium)

- Once daily LAMA
- £28 (compared with spiriva £33)
- Evidence of non-inferiority to tiotropium

Eur Respir J 2012; 40: 1106–1114
C) Incruse (Umeclidinium)

- Once daily LAMA
- Umeclidinium
- £27.50 (compared with spiriva £33)
- Ellipta device

“Triple therapy”

<table>
<thead>
<tr>
<th>LAMA &amp; ICS/LABA</th>
<th>30-DAY COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incruse Ellipta 55 mcg &amp; Relvar Ellipta® (vilanterol/fluticasone furoate) 92/22 mcg</td>
<td>£55.30</td>
</tr>
<tr>
<td>Spiriva® Handihaler® 18mcg &amp; Seretide® Accuhaler® 500/50 mcg</td>
<td>£74.42</td>
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</table>
# Prescribing Clinical Network

<table>
<thead>
<tr>
<th>Policy Statement</th>
<th>Long acting muscarinic antagonists (LAMAs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy No:</td>
<td>PCN 61-2013 (replaces 53-2013)</td>
</tr>
<tr>
<td>Date of Issue</td>
<td>29th May 2013</td>
</tr>
<tr>
<td>Review Date:</td>
<td>May 2016</td>
</tr>
</tbody>
</table>

(Unless new published evidence becomes available before this date OR there is new published national guidance e.g. NICE)

**Recommendations:**

- Glycopyrronium (Seebri Breezhaler®) to be the first line LAMA of choice on the basis of evidence and cost effectiveness.
- Aclidinium (Eklira Genuair®) can be considered as an alternative device for patients who are unable to use the Seebri Breezhaler® / Spiriva Handihaler® devices
- Tiotropium Respimat® should no longer be recommended due to increasing reports of cardiovascular side effects and will be given a BLACK status on the prescribing advisory database.
3. LABA/LAMAs

Patients with preserved lung function and without recurrent exacerbations but symptomatic

A) **Ultibro**
   - Novartis
   - indacaterol /glycopyrronium bromide
   - Once daily
   - Advantages of both onbrez and seebri in one package
   - £44
   - Compared to individual constituents, spiriva or seretide, or placebo – all showed advantages of Ultibro
B) Anoro Ellipta
- GSK
- Umeclidinium / Vilanterol
- Once daily
- Available, £32/m

Data on superiority to TIO or individual constituents

C) Duaklir
- Almirall
- Aclidinium/Formoterol
- Twice daily
- Not yet available
4. Relvar Ellipta

- A new once daily ICS/LABA (24-hour efficacy)
- Fluticasone *furoate* / Vilanterol
- Two strengths (92/22 for COPD)
- As efficaceous as seretide
- Safe, without increased risk of pneumonia*
- New device (Ellipta)
Experimental COPD treatments

• Inhaler
  – Combination ICS/LABA/LAMA

• Injection
  – Mepolizumab (anti-IL5)

• Antibiotics
• NAC
• Phosphodiesterase inhibitors

http://www.ukmi.nhs.uk/applications/NDO/
When to refer COPD patients?

1. Diagnostic uncertainty
2. Suspected severe COPD
3. The patient requests a second opinion
4. Onset of cor pulmonale
5. Assessment for oxygen therapy, long-term nebuliser therapy or oral corticosteroid therapy
6. Bullous lung disease
7. A rapid decline in FEV$_1$
8. Assessment for pulmonary rehabilitation, lung volume reduction surgery or lung transplantation
9. Dysfunctional breathing
10. Onset of symptoms under 40 years or a family history of alpha-1 antitrypsin deficiency

NICE 2010
COPD Case 1

- 65-year-old woman
- COPD, ex-smoker
- 1 exacerbation in past year
- FEV\(_1\) 60% predicted
- Complaining of excessive breathlessness
- Currently on ‘blue and brown’

Options:
- a) Relvar
- b) Anoro
- c) LAMA
- d) LABA
COPD Case 2

- 65-year-old woman
- COPD, ex-smoker
- No exacerbations in past year
- SOB on walking up hills
- FEV₁ 65% predicted
- Currently on Seretide 250 2puffs BD

Options:

a) Add LAMA
b) Change to LABA or LAMA
c) Relvar
d) No change

Unnecessary ICS
Summary

1. Increasing options for inhaled therapies for asthma and COPD
2. Reflected in increasing complexity of guidelines
3. Developments likely to offer real advantages
4. Allows more appropriate and effective treatment
Or...

**ASTHMA**
- The right amount of ICS
- Maybe no LABA
- Never LABA alone
- Rarely LT OCS

**COPD**
- Maximal LABA/LAMA
- Maybe no ICS
- Never ICS alone
- Hopefully never on LT OCS
Many thanks for listening

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SUMMARY
Inhaled therapies for COPD
July 2014

LABA
FORMOTEROL SALMETEROL

ICS
FLUTICASONE P. BUDESONIDE BECLOMETHASONE

(\text{None as monotherapy})

LAMA

SYMBICORT SERETIDE

TIOTROPIUM (SPIRIVA)

BOLD=ONCE DAILY
\text{* No COPD LICENSE}
SUMMARY
Inhaled therapies for COPD
July 2014

LABA

FORMOTEROL
SALMETEROL

INDACATEROL (ONBREZ)
OLODATEROL (STRIVERDI)

SYMBICORT
SERETIDE
FLUTIFORM*
FOSTAIR
RELVAR

FLUTICASONE P.
BUDESONIDE
BECLOMETHASONE

ANORO
ULTIBRO
DUAKLIR

TIOTROPIUM (SPIRIVA)
GLYCOPYRRONIUM (SEEIBRI)
UMECLIDINIUM (INCRUSE)

ACLIDINIUM (EKLIRA)

ICS
(No as monotherapy)

LAMA

BOLD=ONCE DAILY
* No COPD LICENSE
Relvar

**Pro**
- Once daily
- Not inferior
- Device
- Cheap

**Con**
- Confusing name?
- Confusing colour?
- Lose capacity to increase or decrease with symptoms.
- In asthma, too much steroid? (94mcg FF is approx. equivalent to FP 500mcg = BDP 1000mcg daily = more than step 2)
ICS/LABA and licenses for COPD

• Initially FEV1 <40%, then <50% and now <70% for Relvar.

• The only licensed formulation of seretide for COPD is seretide accuhaler 500, one BD.

• By contrast, the lower dose of ICS/LABA in Relvar has the COPD license
Pulmonary rehabilitation at RSCH

• “All COPD patients benefit from exercise training programs with improvements in exercise tolerance and symptoms of dyspnea and fatigue.” GOLD 2014

• PR service at RSCH delivered by large team of experienced respiratory physiotherapists

• PR runs at RSCH, Cranleigh and Haslemere sites

With thanks to Helen Best – Lead PR Physiotherapist
What’s on offer?

• Individualised exercise and education
• **Twice a week for 6 weeks**
• Meet QOF targets (Spirometry, MRC and oximetry)
• Liaison with respiratory nursing team and Drs, SS/community matron/MHS, Smoking cessation, breathe-easy groups as required.
• Screen for LTOT and ambulatory oxygen requirements
• Content and delivery in accordance with BTS guidelines

**Strong emphasis on self management and supporting long term life style changes**

With thanks to Helen Best – Lead PR Physiotherapist
How to access

• 01483 464 153
• Direct referrals from GPs are welcome
• Not just for COPD (most other respiratory diagnoses)
• All appropriate AECOPD in-patients enrolled after discharge

With thanks to Helen Best – Lead PR Physiotherapist