Inhaled Drugs in COPD
Analysis of Available Evidence

Chronic obstructive pulmonary disease (COPD) is a chronic progressive pathology in adults that affects 4-6% of the population and is a major cause of impaired health status, hospitalisation and death.

In industrialized countries, cigarette smoke is the leading cause of COPD (more than 80% of cases, even though just 1 smoker out of 5 develops the disease): smoking cessation is fundamental in slowing down the progress of COPD.

None of the drugs used in COPD therapy, including inhaled steroids, stop or reduce the progressive loss of respiratory function that characterizes the advance of the disease.

The objective of COPD therapy is to relieve symptoms, improve exercise tolerance and reduce exacerbations.

In this information pack, the main studies on inhaled therapies in COPD management have been analysed with a view to evaluating their transferability and clinical impact, and by taking into account the stage severity of the disease and risk-benefit aspect of the therapy.

Topics

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- Asthma vs. COPD: physiopathological differences and the impact of therapies: 5
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Glossary to Facilitate Reading the Literature

**Chronic Obstructive Pulmonary Disease (COPD)**

- COPD is a disease state characterised by airflow limitation that is not fully reversible, and usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.
- The narrowing of airways can be explained by the following mechanisms:
  - Airway mucus gland hypertrophy and mucus hypersecretion
  - Destruction and remodelling of the airway walls and loss of elastic recoil of the lung tissue due to breakage of alveolar attachments
  - Airway smooth muscle contraction
- This disease usually manifests itself in patients above the age of 35 who are or have been heavy long-term smokers and suffer from frequent episodes of bronchitis.

**Spirometry**

Spirometry (Fig. 1) is fundamental for the diagnosis and classification of COPD on the basis of 2 parameters:

- **Forced vital capacity (FVC)**: volume of air exhaled from the lungs between a forced inspiration and a forced expiration
- **Forced expiratory volume in 1 second (FEV₁)**: volume of air that is exhaled in the first second of a forced expiration manoeuvre

The FEV₁/FVC ratio is an important index to help distinguish obstructive spirometric changes (if <70%) from those that are restrictive (if >70%).

The FVC and FEV₁ vary with sex, age and height, on the basis of which are calculated the theoretical values for each individual.

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**Bronchodilator Reversibility Testing**

This is a test used in clinical trials. Its use in current diagnosis is uncertain.

- Measures the change of FEV₁ 15-30 minutes after taking 2 puffs of salbutamol (equal to 400 μg)
- Identifies the percentage of reversible bronchospasm. An increase of 12-15% in basal FEV₁ or of at least 200 ml in absolute value can be indicative of asthma.

**Bronchodilators must not be used before the test** (no short-acting bronchodilators in the previous 4-6 hours and no long-acting ones in the previous 12 hours).

**The Flow-Volume Curve**

- Digital spirometers also produce a flow-volume curve (Fig. 2), which is normally present in spirometric reports
- In these reports, each flow-volume curve is associated with a table that has, for each parameter, the measured value (Meas.), the predicted normal value (Pred.) for a subject of the same age, sex, weight and height, and the ratio between the two (Meas./Pred.).

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**Figure 1. Example of a spirometric curve in a normal adult**

**Figure 2. Example of a flow-volume curve measured in a patient with severe COPD**

**Table 1. Example of some parameters of a patient with severe COPD**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measured</th>
<th>Predicted</th>
<th>Meas./Pred.</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>1.87</td>
<td>3.86</td>
<td>48.5%</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.31</td>
<td>2.98</td>
<td>43.9%</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>69.9</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
In the following pages, the main clinical trials used to develop these recommendations will be analysed.

The ATS (American Thoracic Society) and the ERS (European Respiratory Society) published a joint document, in which the standards for COPD diagnosis and therapy are outlined; the document adopts the classification of COPD by stage severity described in GOLD guidelines.

**Classification of COPD and Criteria to Assess Its Severity**

- Initial therapy for COPD, when it becomes clinically necessary, has been established on the basis of the severity of the disease.
- The assessment of severity is essentially based on the level of airflow limitation (FEV₁ and FEV₁/FVC%), but also takes into account the gravity of the symptoms and the presence of complications such as respiratory failure and right heart failure.
- Long-term therapy is regulated on the basis of the patient’s response and preferences.
- The clinical impact of the disease on an individual patient does not depend as much on the presence of airflow limitation, i.e. on the extent of reduction in FEV₁, as on the severity of the symptoms (in particular, dyspnoea and exercise limitation) and on possible complications.

<table>
<thead>
<tr>
<th>No therapy, avoid risk factors; take influenza vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic symptoms present. Exposure to risk factors</td>
</tr>
<tr>
<td>Normal spirometry</td>
</tr>
<tr>
<td>With or without symptoms</td>
</tr>
<tr>
<td>FEV₁</td>
</tr>
<tr>
<td>&gt;80%</td>
</tr>
<tr>
<td>&lt;80% &gt;50%</td>
</tr>
<tr>
<td>&lt;50% &gt;30%</td>
</tr>
<tr>
<td>&lt;30%</td>
</tr>
<tr>
<td>FEV₁/FVC &lt;70%</td>
</tr>
<tr>
<td>0: At risk</td>
</tr>
<tr>
<td>I: Mild</td>
</tr>
<tr>
<td>II: Moderate</td>
</tr>
<tr>
<td>III: Severe</td>
</tr>
<tr>
<td>IV: Very severe</td>
</tr>
</tbody>
</table>

**Bibliography**

How the Efficacy of COPD Therapy Is Assessed in Clinical Trials

Since medical therapy does not bring about disease regression, the principal therapeutic objectives in trials are improvement in symptoms and physical performance; these events are nevertheless difficult to evaluate considering the subjectivity of the results and the complexity in interpreting symptomatic levels and functional tests which are not always valid and/or utilised.

The interpretation of COPD trial results is therefore more complicated when compared to other chronic diseases (e.g. hypertension), in which therapy affects the evolution of the pathology and the therapeutic objective is to avoid clearly defined clinical outcomes (e.g. heart attack, stroke).

Hospitalisation and mortality are two clinically relevant indicators for which available studies have not generally demonstrated differences between treatment groups: their relatively low incidence calls for carrying out bigger and more long-term trials than those conducted up to now.

Main Indicators Used

**Indicator** | Qualitative/quantitative interpretation | Clinical interpretation
--- | --- | ---
FEV₁ | ➤ Can be expressed in two ways:  
   ➤ in mL (absolute value)  
   ➤ as a % relative to the average normal reference value.  
   ➤ Can be calculated either before or after bronchodilation (reversibility testing).  
   This test excludes possible asthmatic patients (with reversibility >12-15%) and circadian variations of FEV₁ (up to 200 mL in normal adults). | ➤ It is the indicator that is used the most, however its correlation with symptoms and perceived health status is unclear.  
➤ It is not clear what clinical significance to give to relatively small variations in absolute value (e.g. 10-100 mL) that can nevertheless be statistically significant.

Number of exacerbations | ➤ Not all published studies use a clear and uniform definition of exacerbation.  
➤ Around 50% of exacerbations go unobserved by the doctor. | ➤ The role of exacerbations in the decline of lung functionality is uncertain: in fact 93% of patients regain levels of ventilatory function within 3 months of the exacerbation.

SGRQ (health status) | ➤ The SGRQ (St. George’s Respiratory Questionnaire) is a questionnaire validated for the self-assessment of health status in chronic lung diseases.  
➤ It consists of 50 questions that explore symptoms, activity, impact (social and emotional); the score can vary from 0 to 100 (0 indicates a state of excellent health). | ➤ The clinical significance of modest variations in the score that can nevertheless be statistically significant is unclear.  
➤ The clinical perceptibility threshold is represented by variations of at least 4 units. Variations of between 4 and 8 units are indicative of slight improvements.

Bibliography
8. Mahler DA. CHEST 2000;117:54s-57s
Inhaled Bronchodilators

Introduction: Asthma Vs. COPD. Differences in Physiopathology and the Impact of Therapies

A differential diagnosis is fundamental in the clinical approach to obstructive airway disease, i.e. it is essential to distinguish COPD from the three diseases that are a part of it. The three diseases are chronic bronchitis, pulmonary emphysema (both in the definition of COPD) and asthma. The therapeutic approach to the higher reversibility of airflow limitation in asthma is different from that to the lower reversibility of airflow limitation in COPD. In fact, the improvement of lung function is different from that to the lower reversibility of airflow limitation in asthma (in the definition of COPD) and asthma.

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A 2001 Cochrane systematic review pointed out that long-acting β2-agonists “produce small improvements in FEV1”. The studies analysed, however, refer almost exclusively to salmeterol and to patients with moderate to severe COPD.

More recent studies that compare long-acting β2-agonists in monotherapy to associations with steroids and placebo show a reduction in exacerbations (0.3 per year) compared to placebo and an increase of approximately 60 mL in FEV1. In this case too, the studies were conducted on patients with moderate to severe COPD. OR very severe COPD (see page 11).

Three RCTs (from 276 to 780 patients inclusive) compared long-acting β2-agonists and ipratropium in patients with moderate to severe COPD who were in continuous therapy for 3-6 months. The results of these studies were not homogeneous; an improvement of 86 mL in FEV1 in patients treated with formoterol versus those treated with ipratropium was highlighted whereas differences in FEV1 at 3 months between ipratropium and salmeterol were not highlighted.

Bibliography on the Following Page ➔

<table>
<thead>
<tr>
<th>Type of inflammation and cellular mechanisms</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic inflammation (sensitive to steroids)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic oxidative inflammation (less sensitive to steroids)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anatomical changes</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate and sporadic secretion of mucus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deformation of airways and destruction of lung parenchyma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucus hypersecretion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bronchodilators</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting β2-agonists</td>
<td>+ 180 ± 250 mL</td>
<td>+ 140 mL</td>
</tr>
<tr>
<td>Long-acting β2-agonists</td>
<td>+ 280 ± 370 mL</td>
<td>+ 60 ± 90 mL</td>
</tr>
<tr>
<td>Fluticasone 500-1.000 µg/day</td>
<td>+ 430 ± 530 mL</td>
<td>+ 10 ± 40 mL</td>
</tr>
<tr>
<td>Budesonide 800 µg/day</td>
<td>+ 4,7% of theoretical value</td>
<td>+ 0,8% of theoretical value</td>
</tr>
<tr>
<td>Corticosteroid + β2-agonists</td>
<td>+200 ± 275 mL</td>
<td>+ 130 mL</td>
</tr>
<tr>
<td>Short-term anticholinergic drugs</td>
<td>sporadic use</td>
<td>+ 136 mL</td>
</tr>
<tr>
<td>Long-term anticholinergic drugs</td>
<td>not indicated</td>
<td>+ 120 mL</td>
</tr>
</tbody>
</table>

Most COPD patients undergoing bronchodilator therapy show small improvements in FEV1. There also seems to be a subjective benefit, which is probably related to the reduction of hyperinsufflation due to the narrowing of airways.

Short-Acting Bronchodilators

- Short-acting bronchodilators are effective in improving ventilatory function and symptoms. This efficacy is related to the amount of reversible airflow limitation present in COPD.
- The main guidelines, therefore, recommend bronchodilator therapy as needed, starting from stage I (mild) of COPD.
- A Cochrane review points out that patients with moderate COPD (FEV1 between 60 and 70% inclusive), who are treated continuously for 1-8 weeks with short-acting β2-bronchodilators, have a post-bronchodilator FEV1 value in excess of 140 mL compared to patients treated with placebo.
- As far as anticholinergics are concerned, even ipratropium (36-40 µg 4x = one puff 4x per day) administered for 12 weeks has been shown to improve FEV1 by approximately 140 mL compared to placebo.

Long-Acting β2-Agonists

- The studies available do not permit the evaluation of efficacy of long-acting β2-agonists in the subgroup of patients with moderate COPD (FEV1 between 50 and 80% inclusive).
- A 2001 Cochrane systematic review evaluated the efficacy of these drugs compared to placebo by analysing 8 studies, which lasted a maximum of 4 months. The authors conclude that long-acting β2-agonists “produce small improvements in FEV1”. The studies analysed, however, refer almost exclusively to salmeterol and to patients with moderate to severe COPD.
- More recent studies that compare long-acting β2-agonists in monotherapy to associations with steroids and placebo show a reduction in exacerbations (0.3 per year) compared to placebo and an increase of approximately 60 mL in FEV1. In this case too, the studies were conducted on patients with moderate to severe COPD. OR very severe COPD (see page 11).
- Three RCTs (from 276 to 780 patients inclusive) compared long-acting β2-agonists and ipratropium in patients with moderate to severe COPD who were in continuous therapy for 3-6 months. The results of these studies were not homogeneous; an improvement of 86 mL in FEV1 in patients treated with formoterol versus those treated with ipratropium was highlighted whereas differences in FEV1 at 3 months between ipratropium and salmeterol were not highlighted.

Bibliography on the Following Page ➔
The characteristics of the two longer duration (1-year) trials are presented below.

Using inhaled β₂-agonists can cause dose-dependent and clinically relevant adverse reactions. Different from those produced by inhaled steroids, the importance of these adverse reactions lies in their acute toxicity which is especially favoured by repeated administrations of long-acting β₂-agonists.

In connection with this, it should be remembered that patients affected by COPD (because of old age, smoking and pre-existing heart diseases) possess a higher risk profile than asthmatics, who represent the most studied population.

The most frequent adverse effect is the onset of inflammatory episodes of the upper respiratory tract (15-24% in COPD patients treated with β₂-agonists vs. 9-12% in COPD patients treated with placebo). The pathogenetic basis of this observation is not known. The description of tremors (in 7% of patients compared to 2% of controls) and nervousness (in 7% of those treated, 3% of controls) is also frequent.

Tachycardia and arrhythmia (reported in 7-18% of treated patients and in 3-11% of controls) can occur at the beginning of deterioration of heart failure. The contemporaneous use of digitalis glycosides and hypokalemia (also associated with the use of β₂-agonists) exposes patients to serious cardiac adverse effects. In case control studies, the use of short-acting inhaled β₂-agonists does not seem to be correlated to a higher risk of cardiac arrest or myocardial infarction.

Due to the individuality of the clinical response to β₂-agonists and the diversity of the risk profile of patients, it becomes important to evaluate the risk/benefit profile case by case.

### Bibliography
3. BTS guidelines for the management of COPD. Thorax 1997;52 Suppl 5:S1-S28
15. FDA specifications for salmeterol – August 2003
16. FDA specifications for formoterol – June 2003

### Tiotropium in Maintenance Therapy

Tiotropium is a long-acting anticholinergic, to be administered once a day. Three RCTs (each one constituting a combination of two small studies) conclude the efficacy and safety of tiotropium were carried out in order to obtain approval of the drug:

- **two RCTs** (one versus placebo and the other versus ipratropium) of one-year duration that provide support of the “alleviation of bronchospasm” indication;
- **one RCT** versus salmeterol and placebo of 6-month duration that provides support of the “treatment of dyspnoea associated with COPD” indication.

The characteristics of the two longer duration (1-year) trials are presented below.

<table>
<thead>
<tr>
<th>Comparison of treatments</th>
<th>Casaburi et al.</th>
<th>Vincken et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium 18 µg</td>
<td>550</td>
<td>356</td>
</tr>
<tr>
<td>Placebo</td>
<td>371</td>
<td>179</td>
</tr>
<tr>
<td>Number of patients</td>
<td>65 years</td>
<td>64 years</td>
</tr>
<tr>
<td>Average age</td>
<td>FEV₁ (average predicted normal value)</td>
<td>39%</td>
</tr>
<tr>
<td>Main exclusion criteria</td>
<td>Duration</td>
<td>one year</td>
</tr>
</tbody>
</table>

- FEV₁ >65% of predicted normal value
- therapy with long-acting β₂-agonists and disodium cromoglycate in the last 30 days
- history of asthma, allergic rhinitis, atopy, recent upper respiratory tract infection and use of oxygen

- The Food and Drug Administration (FDA) has pointed out how the comparisons of tiotropium versus ipratropium and versus salmeterol may be biased towards tiotropium, in that FEV₁ was measured in the morning with the drug dose having been taken the previous evening. In these conditions, the bronchodilatory action of tiotropium is still present (as tiotropium is long-acting) whereas that of ipratropium and salmeterol is not.

- The FDA also underlined the fact that in the trial versus salmeterol the evaluation of dyspnoea is impaired by methodological problems and by the use of a dyspnoea scale whose validity was not sufficiently demonstrated.
Efficacy of Tiotropium
Methodology and Results of the Studies

Other Notes on Methodology of the Studies
- The recommended dosage was used for tiotropium whereas the minimum dosage was used for ipratropium.
- The presence of placebo as a control group adds uncertainty to the real benefits of the treatment.
- Given that one of the objectives of the studies is the evaluation of the safety of the drug, a majority of patients were assigned to tiotropium treatment groups. Naturally, the assessment of risks and benefits is NOT affected by this imbalance because they are expressed as mean values and percentages.
- Currently there are no published studies comparing tiotropium to oxitropium (which is longer acting than ipratropium).

Population Studied
- On average, patients with severe COPD (average FEV1 approximately 40% of the predicted value) who have a long-standing clinical diagnosis of COPD (8-11 years).
- Heavy smokers or ex-smokers who smoke/ smoked an average of about 33 packs/year (in other words, one pack per day for 33 years) in the Vincken et al.2 study and as many as 62 packs/year in the Casaburi et al.1 study.
- More than half the patients were already being treated with an anticholinergic; these could come from a selected population as there are possible differences in individual sensitivity to β2-agonist bronchodilators and anticholinergics.

Benefits and Risks of Tiotropium

FEV1 – principal outcome in these studies: after a year of therapy, bronchodilation persists after a single dose (about 160 mL vs placebo). The correlation between improvement in FEV1 and health status and the practical relevance of this difference is unclear.

Exacerbations: reduction of about 0.2 events/year per person (both vs ipratropium and vs placebo); in other words, a COPD patient should be treated for 5 years in order to avoid an exacerbation.

Reduction of hospitalisations due to exacerbations: about 4% a year vs ipratropium and placebo.

Generic health status: improvement by 3.3 units vs ipratropium (relative to SGRQ scale of 0-100). However, this improvement is not clinically perceptible.

The differences compared to ipratropium could be influenced by the use of relatively low doses of this drug.

Dry mouth is the main side effect of tiotropium (12-16% vs 6% with ipratropium and 3% with placebo). There are no statistically significant differences of serious adverse events (those events that cause patients to withdraw from the studies).

Population Studied
- On average, patients with severe COPD (average FEV1 approximately 40% of the predicted value) who have a long-standing clinical diagnosis of COPD (8-11 years).
- Heavy smokers or ex-smokers who smoke/ smoked an average of about 33 packs/year (in other words, one pack per day for 33 years) in the Vincken et al.2 study and as many as 62 packs/year in the Casaburi et al.1 study.
- More than half the patients were already being treated with an anticholinergic; these could come from a selected population as there are possible differences in individual sensitivity to β2-agonist bronchodilators and anticholinergics.

Benefits and Risks of Tiotropium

<table>
<thead>
<tr>
<th>Population Studied</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium</td>
<td>Placebo</td>
<td>Tiotropium</td>
<td>Ipratropium</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV1 variation after 13 weeks</td>
<td>+120 mL (+12%)</td>
<td>-20 mL (-2%)</td>
<td>not available</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV1 variation after 1 year</td>
<td>+115 mL</td>
<td>-40 mL</td>
<td>+120 mL</td>
</tr>
<tr>
<td>Mean no. of exacerbations per person (in one year)</td>
<td>0.76</td>
<td>0.95</td>
<td>0.73</td>
</tr>
<tr>
<td>Patients hospitalised per exacerbation (%)</td>
<td>5.5%</td>
<td>9.4%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Variations in SGRQ score at 1 year (scale of 0 to 100)</td>
<td>ND (only graphs)</td>
<td>ND (only graphs)</td>
<td>-3.7</td>
</tr>
<tr>
<td>Adverse events with interruption of study</td>
<td>9.6%</td>
<td>13.7%</td>
<td>10.1%</td>
</tr>
</tbody>
</table>

Statistically significant values compared to the control group are in red. * main outcome of the Casaburi et al. study. * one exacerbation was defined as a complex of respiratory events (eg. cough, wheezing, dyspnoea or sputum production) that lasted more than 3 days and that generally needed therapy with antibiotics or oral steroids. ND = not declared.

Side effects (FDA specifications)

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Tiotropium (% of 550)</th>
<th>Placebo (% of 371)</th>
<th>Tiotropium (% of 356)</th>
<th>Ipratropium (% of 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>7</td>
<td>5</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>16</td>
<td>3</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
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<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>41</td>
<td>37</td>
<td>43</td>
<td>35</td>
</tr>
</tbody>
</table>

Bibliography
Inhaled Corticosteroids in Maintenance Therapy

The ISOLDE Study

There have been many studies on the efficacy of inhaled steroids in patients with COPD in the last few years. Among the studies that have assessed these drugs in terms of frequency of exacerbations, the ISOLDE study is the one with longest follow-up and biggest sample size\(^1\). The table below describes the main characteristics of the study.

### The ISOLDE Study: Main Characteristics

**Objective**
To assess the efficacy of a long-term therapy (3 years) using fluticasone from an inhaler in patients with moderate to severe COPD

**Treatment and doses**
Inhaled fluticasone propionate, 500 μg x 2/day

**Control**
Placebo

**Patients assessed**
(N=742)
- 40-75 years (average 64)
- 38% smokers and 46% ex-smokers (average of 1 pack per day for 44 years)
- 52% with severe COPD*: mean FEV\(_1\) = 39%
- 48% with moderate COPD*: mean FEV\(_1\) = 62%
- increase in post-bronchodilator FEV\(_1\) <10% of predicted normal value (reversibility test)

**Duration**
3 years

* classification of severity according to GOLD guidelines

### Results

The following table reports the main results (at 3 years) of the ISOLDE study.

Statistically significant values are indicated in red (NS = statistically not significant)

<table>
<thead>
<tr>
<th>Clinical benefits</th>
<th>Fluticasone (N=372)</th>
<th>Placebo (N=370)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in FEV(_1) after bronchodilator (main end point)</td>
<td>-50 mL per year</td>
<td>-59 mL per year</td>
<td>NS</td>
</tr>
<tr>
<td>Exacerbations in one year per person*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– all patients</td>
<td>1,0</td>
<td>1,3</td>
<td>-0,3</td>
</tr>
<tr>
<td>– patients with severe/very severe COPD*</td>
<td>1,5</td>
<td>1,8</td>
<td>-0,3</td>
</tr>
<tr>
<td>– patients with mild/moderate COPD*</td>
<td>0,7</td>
<td>0,9</td>
<td>NS</td>
</tr>
<tr>
<td>Suspension of treatment due to respiratory events (mainly exacerbations)</td>
<td>19%</td>
<td>25%</td>
<td>-6%</td>
</tr>
<tr>
<td>SGRQ score – health status (mean variation per year)</td>
<td>2,0</td>
<td>3,2</td>
<td>-1,2</td>
</tr>
<tr>
<td>Mortality</td>
<td>32 (8,6%)</td>
<td>36 (9,7%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* defined as worsening of respiratory symptoms that required treatment with oral steroids and/or antibiotics

### Assessment of Results

The results of the ISOLDE study and the analysis of subgroups indicate that, compared to placebo, fluticasone:

- **does not reduce the rate of decline in FEV\(_1\), used by the authors as the primary end point of the study**
- **reduces the number of exacerbations** in patients with severe COPD (FEV\(_1\) <50% of predicted normal) by 0.3 a year. In other words, it would be necessary to treat a person for more than 3 years in order to have one exacerbation less
- **improves general health status** by 1.2 units (with reference to the SGRQ scale of 0-100). This difference, although statistically significant, is nevertheless below the threshold of clinical perceptibility (4 units)
- **reduces the interruption of treatment due to respiratory events** (in particular exacerbations) by 6%
- **does not reduce mortality**
- **increases the frequency of side effects** such as throat irritation, oral candidiasis, dysphonia and bruising by 3-5%.

Letters of comment on this study have questioned the risk-benefit profile of inhaled corticosteroids (benefits are modest compared to the increase of side effects). The authors of the study have not replied to these letters\(^3\).

### Bibliography

3. The Isolde trial - letters BMJ 2000;321:1349

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Image not available
Inhaled Corticosteroids in Maintenance Therapy: possible long-term side effects

What are the risks derived from the regular RSE of inhaled steroids?

- The use of inhaled corticosteroids commonly induces local side effects in 8-10% of treated patients: the most frequent are oral candidiasis (RR 2.98, 95% CI 2.09-4.26) and dysphonia (RR 2.02, 95% CI 1.43-2.83).
- Their protracted use, most of all in high doses, can also cause clinically relevant systemic effects. There are numerous studies regarding this, but they are of relatively short duration (COPD therapy usually lasts years) and mainly involve asthmatic patients (in COPD patients the risk is aggravated by old age, smoking, hypocinesia, hypogonadism).
- There is no data available about possible side effects of inhaled corticosteroids on metabolic parameters and on arterial pressure.
- Assuming the suppression of cortisol production as an outcome of systemic effect, a dose equivalence relationship has been established, which is different with respect to the following drug formulations:

<table>
<thead>
<tr>
<th>Fluticasone spray</th>
<th>Budesonide</th>
<th>Fluticasone powder</th>
<th>Beclomethasone²</th>
</tr>
</thead>
<tbody>
<tr>
<td>111 µg</td>
<td>268 µg</td>
<td>445 µg</td>
<td>548 µg</td>
</tr>
</tbody>
</table>

Bone

- Patients affected with COPD are exposed to an increased risk of demineralisation and fractures.
- A linear relationship between cumulative dose and loss of bone-mineral density has been demonstrated: a bone-mineral density of less than 1 SD was observed in patients treated for 7 years with 2000 µg of inhaled corticosteroids/day compared to patients treated for one year with 200 µg/day. One case-control study based on 1,708 cases with nonvertebral fractures (average age 62.7 years) has shown an OR of 1.68; 95% CI 1.10-2.57 in patients treated with 700 µg beclomethasone/day (or equivalents). In a study involving more than 16,000 cases of hip fracture in elderly patients, treatment with inhaled corticosteroids was associated with a significant increase in fracture (OR 1.26; 95% CI 1.17-1.36) and there was a significant dose-response relationship.

Adrenal Gland

- Inhaled steroids induce a dose-dependent reduction of adrenal activity. These are usually situations that are not clinically noticeable, however there are some reports of acute adrenal insufficiency brought on by infectious episodes and of its occurrence in patients enjoying apparent good health. In over 90% of cases, patients were receiving 1000-1500 µg of fluticasone/day, while only few cases were associated with beclomethasone or budesonide.

Eye

- The protracted administration (over 3 months) of inhaled corticosteroids exposes mainly older patients to an increased risk of developing nuclear cataracts with a dose effect relationship (RR 1.5, 95% CI 1.2-1.9), subcapsular cataracts (RR 1.9, 95% CI 1.3-2.8) and glaucoma (RR 1.4, 95% CI 1.01-2.06).

Skin

- Therapy with inhaled steroids at high doses induces cutaneous dystrophy with thinning of the skin and an increased frequency of bruising (OR 1.62; 95% CI 1.18-2.22).

What are relative risk (RR) and odds ratio (OR)?

- The relative risk (RR) expresses the ratio between risks (of a certain event to occur). For example, in a study that compares a treatment with a placebo, if the risk or frequency of candidiasis is 30% in the treatment group and 15% in the placebo group, the relative risk will be 2 (subjects treated with the drug have their risk doubled with respect to those who have received the placebo).
- The «relative» risk does not provide «absolute» indications of the impact of the treatment. In the previous example, there was the possibility of having double the risk of candidiasis even if the frequency of this event was 3% compared to 1.5%, or 0.3% compared to 0.15%.
- Odds ratio (OR), just as relative risk, expresses the efficacy or risk of a treatment compared to another. To put it simply, it can be said that odds ratio and relative risk are very similar conceptually (and often quantitatively similar too). The odds ratio is sometimes preferred because it is easier to make quantitative calculations. The odds of a treatment is the ratio between the number of patients having the event and the number of patients not having the event (in the previous example, 30/70 are the odds of the treatment and 15/85 the odds of the placebo).
- The odds ratio is the ratio between these two odds: (30/70)/(15/85).

Bibliography

1. DD Sin et al. JAMA 2003; 290: 2301-2
3. A Jones et al. The Cochrane Library, Issue 1, 2004
5. CA Wong et al. Lancet 2000; 355: 1399-403
8. JS Macdessi et al. MJ A 2003; 178: 245-216
The Combination of Inhaled \( \beta_2 \)-agonists + Corticosteroids in Maintenance Therapy

Efficacy of Combined Therapies: Available Evidence

Among the randomised studies published, three lasted a year, had a sample size of more than 800 patients and assessed the reduction of exacerbations compared to placebo and to single components.\(^1\)\(^3\).

These studies, all published in 2003, recruited patients with moderate to very severe COPD (according to the GOLD classification of severity, see page 3), with an FEV\(_1\) between 25 and 70% inclusive (mean 44%) in the TRISTAN study – published in *Lancet* – and less than 50% (mean 36%) in the two studies published in *European Respiratory Journal*\(^2\)\(^3\).

Of the 3 studies, those of TRISTAN\(^1\) and Calverley et al\(^2\) have been described below. The latter is characterised by methodology and data, which are very similar to the study that has not been presented here\(^3\) but has results that are more favourable to the use of combined therapies.

### Characteristics of the Main Studies

<table>
<thead>
<tr>
<th>TRISTAN (Lancet 2003)(^1)</th>
<th>Calverley et al. (Eur Resp J 2003)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>To assess the efficacy of a therapy lasting one year and utilising a long-acting ( \beta_2 )-agonist + corticosteroid combination (via inhaler), compared to single therapies and placebo, in patients with moderate to very severe COPD</td>
</tr>
<tr>
<td><strong>Combined therapy (drugs and doses)</strong></td>
<td>(500 ( \mu g ) fluticasone + 50 ( \mu g ) salmeterol) x 2/day</td>
</tr>
<tr>
<td></td>
<td>(320 ( \mu g ) budesonide + 9 ( \mu g ) formoterol) x2/day</td>
</tr>
<tr>
<td><strong>Comparison to other therapies</strong></td>
<td>fluticasone 500 ( \mu g ) x 2/day</td>
</tr>
<tr>
<td></td>
<td>salmeterol 50 ( \mu g ) x 2/day</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
</tr>
<tr>
<td><strong>Patients included</strong></td>
<td>1,465 patients (mean age 63, 72% male)</td>
</tr>
<tr>
<td></td>
<td>51% smokers (average of 1 pack per day for 42 years)</td>
</tr>
<tr>
<td></td>
<td>Pre-bronchodilator FEV(_1) between 25 and 70% of predicted normal value (moderate to very severe COPD, mean 44%)</td>
</tr>
<tr>
<td></td>
<td>Increase of post-bronchodilator FEV(_1) &lt;10% of the predicted normal value</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>One year</td>
</tr>
<tr>
<td></td>
<td>One year</td>
</tr>
</tbody>
</table>

Increase of post-bronchodilator FEV\(_1\) <50% of predicted normal value (severe or very severe COPD, mean 36%)
The Combination of Inhaled $\beta_2$-agonists + Corticosteroids in Maintenance Therapy

### Results of the Studies

The adjacent tables report the main results (at one year) of the two cited studies in brief. The values in red indicate statistically significant differences for combined therapy; the asterisk indicates statistically significant differences between single therapies and placebo.

<table>
<thead>
<tr>
<th>Study</th>
<th>Fluticasone + salmeterol (N)</th>
<th>Fluticasone (N)</th>
<th>Salmeterol (N)</th>
<th>Placebo (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-bronchodilator FEV₁ (at one year)</strong></td>
<td>1.396 mL</td>
<td>1.302 mL*</td>
<td>1.323 mL*</td>
<td>1.264 mL</td>
</tr>
<tr>
<td><strong>Post-bronchodilator FEV₁ (at one year)</strong></td>
<td>1.484 mL</td>
<td>1.454 mL</td>
<td>1.436 mL</td>
<td>1.408 mL</td>
</tr>
<tr>
<td>Mean no. of exacerbations a person (in one year)</td>
<td>0.97</td>
<td>1.05*</td>
<td>1.04*</td>
<td>1.30</td>
</tr>
<tr>
<td>Mean no. of exacerbations per person (in one year) that required the use of oral steroids</td>
<td>0.46</td>
<td>0.50*</td>
<td>0.54*</td>
<td>0.76</td>
</tr>
<tr>
<td>SGRQ score (scale of 0 to 100)</td>
<td>44.1</td>
<td>45.5</td>
<td>45.2</td>
<td>46.3</td>
</tr>
<tr>
<td><strong>Oropharyngeal candidosis</strong></td>
<td>8%</td>
<td>7%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

### Use of Combined Therapies: Clinical Relevance of the Results

As far as populations of patients with severe COPD are concerned, the results of the studies presented suggest the following risk/benefit profile:

**Benefits**

- **Pre-bronchodilator FEV₁**: in the TRISTAN study the differences in favour of combined therapy are approximately 130 mL compared to placebo and about 100 mL compared to single therapies.
- **Post-bronchodilator FEV₁**: the differences in favour of combined therapy are around 80 mL (TRISTAN study) and 4% (Calverley et al.) compared to placebo and approximately 30-50 mL (TRISTAN study) and 1-3% (Calverley et al.) compared to single therapies.
- **Number of exacerbations**: the differences in favour of combined therapies are less than 0.5 exacerbations per person a year compared to placebo and less than 0.3 exacerbations per person a year compared to single therapies (particularly observed in more seriously ill patients). In the TRISTAN study there are no differences between combined therapy and single therapies.
- **Hospitalisations**: in the TRISTAN study no differences have been reported in the frequency of hospitalisations between combined therapy and single therapies.
- **Health status**: it is only in one study³ that the differences in SGRQ score compared to single therapies and placebo are $>4$ units (the scale goes from 0 to 100, see page 4) and can be clinically perceived.

### Risks

- **Hospitalisations**: in the TRISTAN study no differences have been reported in the frequency of hospitalisations between combined therapy and single therapies.
- **Health status**: it is only in one study³ that the differences in SGRQ score compared to single therapies and placebo are $>4$ units (the scale goes from 0 to 100, see page 4) and can be clinically perceived.

**Bibliography**

Conclusions

- Spirometry is the fundamental diagnostic test that should be prescribed to all patients with suspected COPD.
- Smoking cessation is the only effective way of slowing down the progress of COPD.
- None of the drugs used in COPD therapy, including inhaled steroids, stop or reduce the progressive loss of respiratory function that characterizes the advance of this disease.
- Studies show that treatment with short-acting bronchodilators (β₂-agonists or anticholinergics) on an as-needed basis is useful in all stages of COPD.
- In moderate COPD long-acting β₂-agonists have the advantage of fewer daily administrations compared to short-acting bronchodilators. There is no unequivocal data so far on a different clinical efficacy in these two therapeutic approaches.
- In patients with severe COPD (FEV₁ < 50%) regular treatment with high doses of a combination of bronchodilators/inhaled steroids favours respiratory function (about a 5-10% increase of FEV₁ compared to placebo) and the reduction of exacerbations (3 years of treatment to avoid one exacerbation). At the moment there is no conclusive data on the efficacy of regular therapies in order to reduce hospitalisations and mortality.
- Available studies on the efficacy of drugs have a relatively limited duration (generally not more than 1 year) if one considers the chronicity of the disease and the fact that a progressive reduction in the efficacy of treatments has been observed in the few studies that were prolonged to over 12 months.
- Given that there is great variability within individuals, in terms of both symptoms and tolerance, the choice of therapy must take into account both the risk-to-benefit ratio of the drugs used and the preferences of the patient.
- The response to therapy is always monitored, both functionally (with serial spirometry) and clinically (by periodic checks). Pharmacological therapy is adapted to individual response.

Prescriptions Of Respiratory Drugs in Local Health Authority Modena

Figure 4 shows, for each subgroup of drugs, the number of DDD (daily definite doses) per 1,000 patients a day prescribed for patients >45 years of age in 2001-2003. These drugs are prescribed by GPs and charged to the SSN (Servizio Sanitario Nazionale/National Health Service).

In Figure 5 drug prescriptions in the year 2003 have been subdivided into classes of age.

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