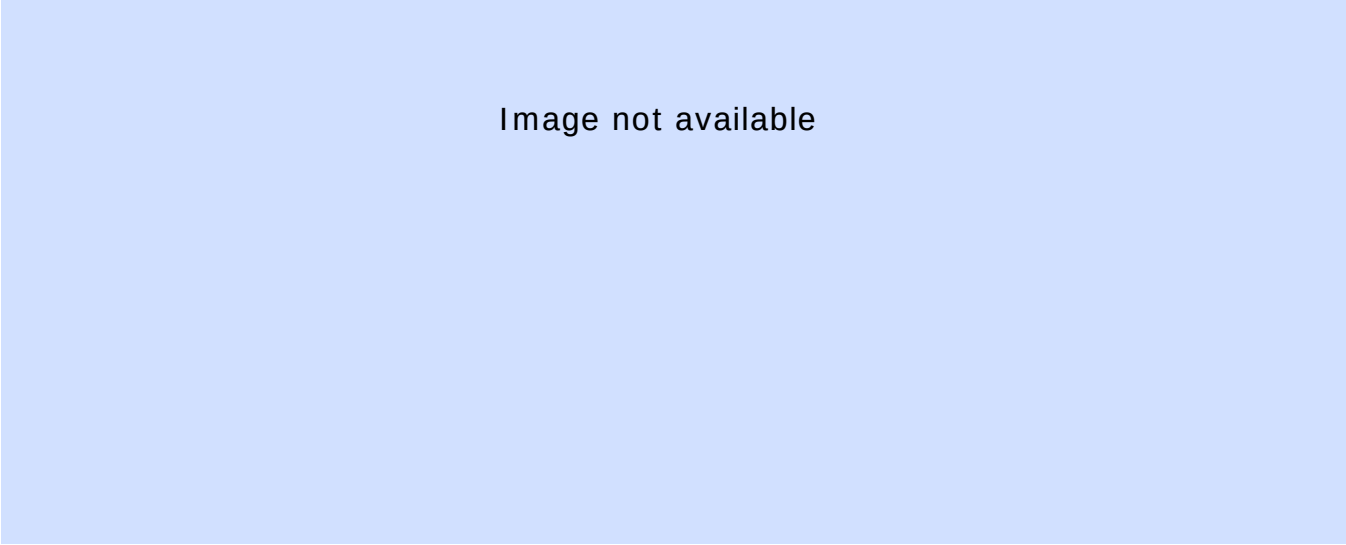
Inhaled Drugs in COPD

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	Page

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[1].
- 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[1,2].

Spirometry

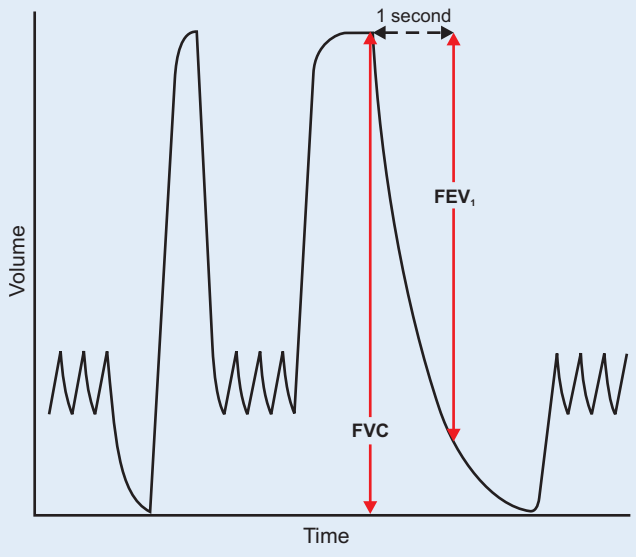
Spirometry (Fig. 1) is fundamental for the diagnosis and classification of COPD on the basis of 2 parameters:

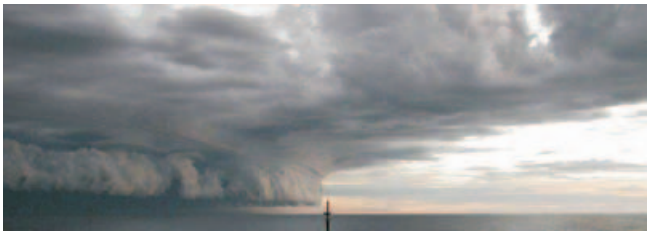
- **Forced vital capacity (FVC)**: volume of air exhaled from the lungs between a forced inspiration and a forced expiration
- **Forced expiratory volume in 1 second (FEV_1)**: volume of air that is exhaled in the first second of a forced expiration manoeuvre

The **FEV_1/FVC** ratio is an important index to help distinguish obstructive spirometric changes (if <70%) from those that are restrictive (if >70%).

The FVC and FEV_1 vary with sex, age and height, on the basis of which are calculated the theoretical values for each individual.

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





Bronchodilator Reversibility Testing

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

- Measures the change of FEV_1 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 FEV_1 or of at least 200 ml in absolute value can be indicative of asthma[1].

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)[2].

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.**).

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

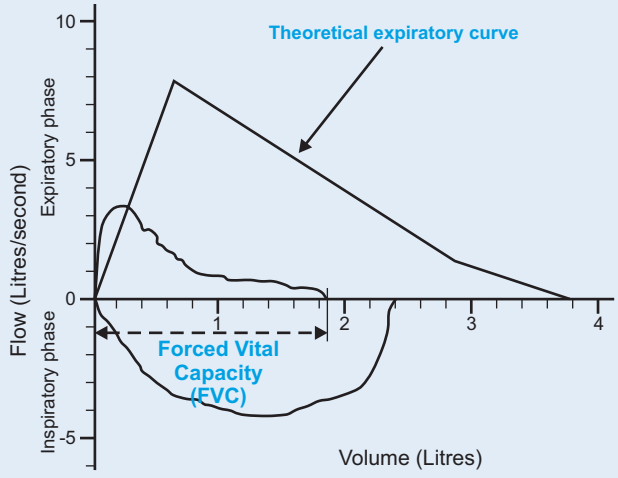


Table 1. Example of some parameters of a patient with severe COPD

Parameter	Meas.	Pred.	Meas./Pred.
FVC (L)	1,87	3,86	48,5%
FEV_1 (L)	1,31	2,98	43,9%
FEV_1/FVC (%)	69,9	–	–

Classification of COPD and Criteria to Assess Its Severity

Image not available

- 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 (FEV_1 and FEV_1/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 FEV_1, as on the severity of the symptoms (in particular, dyspnoea and exercise limitation) and on possible complications.

The ATS (American Thoracic Society) and the ERS (European Respiratory Society) published a joint document[3], 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.

Figure 3. Therapeutic recommendations taken from GOLD guidelines for treatment at each stage of COPD

				Add long-term oxygen therapy. Consider surgical treatments	THERAPY
			Add inhaled steroids in case of repeated exacerbations (>2/year)		
		Add regular treatment with one or more long-acting bronchodilators. **Add** rehabilitation			
	Start with short-acting bronchodilators when needed				
No therapy, avoid risk factors; take influenza vaccination					
Chronic symptoms present. Exposure to risk factors	With or without symptoms	With or without symptoms	Worsening of symptoms	Worsening of symptoms, chronic respiratory failure and/or right heart failure	SYMPTOMS
Normal spirometry	**FEV_1**				
	>80%	<80% >50%	<50% >30%	<30%	
	FEV_1/FVC <70%				
0: At risk	**I: Mild**	**II: Moderate**	**III: Severe**	**IV: Very severe**	

In the following pages, the main clinical trials used to develop these recommendations will be analysed.

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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
FEV_1	➤ 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)[1]. This test excludes possible asthmatic patients (with reversibility >12-15%) and circadian variations of FEV_1 (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[2]. ➤ 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[3].
Number of exacerbations	➤ Not all published studies use a clear and uniform definition of exacerbation[4]. ➤ Around 50% of exacerbations go unobserved by the doctor[5].	➤ 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[6].
SGRQ (health status)[7]	➤ 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[2]. ➤ The clinical perceptibility threshold is represented by variations of at least 4 units[8]. Variations of between 4 and 8 units are indicative of slight improvements.

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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 by taking β_2-agonists and inhaled steroids is well known in asthmatic patients, and is known to a lesser extent in COPD patients. The table on the right shows the physiopathological differences between the two clinical conditions, which in turn can explain the differences in the impact of therapies.

	Asthma	COPD
Type of inflammation and cellular mechanisms	Allergic inflammation (sensitive to steroids)	Chronic oxidative inflammation (less sensitive to steroids)
Anatomical changes	• Airway inflammation • Moderate and sporadic secretion of mucus	• Deformation of airways and destruction of lung parenchyma • Mucus hypersecretion
Bronchospasm	High and reversible	Moderate and less reversible
Long-term response to inhaled drugs *vs.* placebo (variations in FEV_1)		
Short-acting $ß_2$-agonists	+ 180 ÷ 250 mL	+ 140 mL
Long-acting $ß_2$-agonists	+ 280 ÷ 370 mL	+ 60 ÷ 90 mL
Fluticasone 500-1.000 µg/day	+ 430 ÷ 530 mL	+ 10 ÷ 40 mL
Budesonide 800 µg/day	+ 4,7% of theoretical value	+ 0,8% of theoretical value
Corticosteroid + $ß_2$-agonists	+200 ÷ 275 mL	+ 130 mL
Short-term anticholinergic drugs	sporadic use	+ 136 mL
Long-term anticholinergic drugs	not indicated	+ 120 mL

Most COPD patients undergoing brochodilator therapy show small improvements in FEV_1. There also seems to be a subjective benefit, which is probably related to the reduction of hyperinsufflation due to the narrowing of airways[1].

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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[1-4], therefore, recommend bronchodilator therapy as needed, starting from stage I (mild) of COPD.
- A Cochrane review[5] points out that patients with moderate COPD (FEV_1 between 60 and 70% inclusive), who are treated continuously for 1-8 weeks with **short-acting $ß_2$-bronchodilators**, have a post-bronchodilator FEV_1 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 FEV_1 by approximately 140 mL compared to placebo[6].

Long-Acting $ß_2$-agonists

- The studies available do not permit the evaluation of efficacy of long-acting β_2-agonists in the subgroup of patients with moderate COPD (FEV_1 between 50 and 80% inclusive).
- A 2001 Cochrane systematic review[7] 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 $ß_2$-agonists "produce small improvements in FEV_1". The studies analysed, however, refer almost exclusively to salmeterol and to patients with moderate to severe COPD.
- More recent studies that compare long-acting $ß_2$-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 FEV_1. In this case too, the studies were conducted on patients with moderate to severe[8,9] or very severe[10] COPD (see page 11).
- **Three RCTs**[11-13] (from 276 to 780 patients inclusive) **compared long-acting $ß_2$-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 FEV_1 in patients treated with formoterol *versus* those treated with ipratropium was highlighted whereas differences in FEV_1 at 3 months between ipratropium and salmeterol were not highlighted.

Bibliography on the Following Page ⇒

ß2-AGONISTS IN MAINTENANCE THERAPY

POSSIBLE SIDE EFFECTS

- Using inhaled ß2-agonists can cause dose-dependent and clinically **relevant** adverse reactions[14]. 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** ß2-agonists[14].
- 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[2].
- The most frequent adverse effect is the onset of inflammatory episodes of the upper respiratory tract (15-24% in COPD patients treated with ß2-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[14-16].
- 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 ß2-agonists) exposes patients to serious cardiac adverse effects[14-16]. 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[17] or myocardial infarction[18].
- Due to the individuality of the clinical response to ß2-agonists and the diversity of the risk profile of patients, it becomes important to evaluate the risk/benefit profile case by case.

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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) concerning 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"[1,2] indication;
- **one RCT** *versus* salmeterol and placebo of 6-month duration that provides support of the "treatment of dyspnoea associated with COPD"[3] indication.

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

	Casaburi et al.		Vincken et al.	
Comparison of treatments	tiotropium 18 µg	placebo	tiotropium 18 µg	ipratropium 40 µg 4x
Number of patients	550	371	356	179
Average age	65 years		64 years	
FEV_1 (average predicted normal value)	39%	38%	42%	39%
Main exclusion criteria	• FEV_1 >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			
Duration	one year			

METHODOLOGY OF STUDIES FOR APPROVAL OF DRUGS: A NOTE FROM THE FDA[4]

- 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 FEV_1 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 FEV_1 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 β_2-agonist bronchodilators and anticholinergics.

Benefits and Risks of Tiotropium

- **FEV_1 – 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 FEV_1 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**[5].
- 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).

	Casaburi et al.		Vincken et al.	
	Tiotropium	Placebo	Tiotropium	Ipratropium
Pre-bronchodilator FEV_1 variation after 13 weeks [4*]	**+120 mL (+12%)**	-20 mL (-2%)	not available	not available
Pre-bronchodilator FEV_1 variation after 1 year	**+115 mL**	-40 mL	+120 mL	-30 mL
			comparison not valid (see box on page 6)	
Mean no. of exacerbations per person (in one year)[#]	**0,76**	0,95	**0,73**	0,96
Patients hospitalised per exacerbation (%)	**5,5%**	9,4%	7,3%	11,7%
Variations in SGRQ score at 1 year (scale of 0 to 100)	ND (only graphs)	ND (only graphs)	**-3,7**	-0,4
Adverse events with interruption of study	9,6%	13,7%	10,1%	12,8%

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)	Tiotropium (% of 550)	Placebo (% of 371)	Tiotropium (% of 356)	Ipratropium (% of 179)
Chest pain	7	5	5	8
Constipation	4	2	1	1
Dry mouth	16	3	12	6
Dyspepsia	6	5	1	1
Vomiting	4	2	1	2
Epistaxis	4	2	1	1
Pharyngitis	9	7	7	3
Upper respiratory tract infections	41	37	43	35

Image not available

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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.

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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)

Clinical benefits	Fluticasone (N=372)	Placebo (N=370)	Difference
Decline in **FEV_1** after bronchodilator (main end point)	-50 mL per year	-59 mL per year	NS
Exacerbations in one year per person*			
– all patients	1,0	1,3	**-0,3**
– patients with severe/very severe COPD[2]	1,5	1,8	**-0,3**
– patients with mild/moderate COPD[2]	0,7	0,9	NS
Suspension of treatment due to respiratory events (mainly exacerbations)	19%	25%	**-6%**
SGRQ score – health status (mean variation per year)	2,0	3,2	**-1,2**
Mortality	32 (8,6%)	36 (9,7%)	NS

* 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].

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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)[1].
- 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**:

Fluticasone spray	Budesonide	Fluticasone powder	Beclomethasone[2]
111 μg	268 μg	445 μg	548 μg

Bone

- Patients affected with COPD are exposed to an increased risk of demineralisation and fractures[4].
- 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 corticosteroid/day compared to patients treated for one year with 200 μg/day[5]. One case-control study based on 1,708 cases with nonvertebral fractures (average age 62.7 years)[6] 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[7].

Adrenal Gland

- Inhaled steroids induce a dose-dependent reduction of adrenal activity[2]. 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[8-10]. 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)[11] and glaucoma (RR 1.4, 95% CI 1.01-2.06)[12].

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)[13].

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%. The practical impact would obviously be different (of 100 patients treated, the differences would be of 1.5 or 0.15 events instead of 15 events). Unfortunately, in some clinical trials, data is uniquely expressed by using relative risks and not absolute risks.
- 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).

Given that therapies with inhaled steroids are expected to last a long time – in actual fact much longer than the observation time in the available studies – it is important to carry out an accurate **risk/benefit analysis** for each patient[14,15].

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The Combination of Inhaled ß2-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[1] – 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.

Image not available

Characteristics of the Main Studies

	TRISTAN (Lancet 2003)[1]	**Calverley et al.** (Eur Resp J 2003)[2]
Objective	To assess the efficacy of a therapy lasting one year and utilising a long-acting β_2-agonist + corticosteroid combination (via inhaler), compared to single therapies and placebo, in patients with moderate to very severe COPD	
Combined therapy (drugs and doses)	➤ (500 µg fluticasone + 50 µg salmeterol) x 2/day	➤ (320 µg budesonide + 9 µg formoterol) x2/day
Comparison to other therapies	➤ fluticasone 500 µg x 2/day ➤ salmeterol 50 µg x 2/day ➤ placebo	➤ budesonide 400 µg x 2/day ➤ formoterol 9 µg x 2/day ➤ placebo
Patients included	➤ 1,465 patients (mean age 63, 72% male) ➤ 51% smokers (average of 1 pack per day for 42 years) ➤ Pre-bronchodilator FEV_1 between 25 and 70% of predicted normal value (moderate to very severe COPD, mean 44%) ➤ Increase of post-bronchodilator FEV_1 <10% of the predicted normal value	➤ 1,022 patients (mean age 64, 76% male) ➤ 35% smokers (average of 1 pack per day for 39 years) ➤ Pre-bronchodilator FEV_1 <50% of predicted normal value (severe or very severe COPD, mean 36%)
Duration	One year	One year

The Combination of Inhaled ß2-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.

TRISTAN study (Lancet 2003; 361: 449-456)	Fluticasone + salmeterol (N = 358)	Fluticasone (N = 374)	Salmeterol (N = 372)	Placebo (N = 361)
Pre-bronchodilator FEV_1 (at one year)	1.396 mL	**1.302 mL***	**1.323 mL***	**1.264 mL**
Post-bronchodilator FEV_1 (at one year)	1.484 mL	**1.454 mL**	**1.436 mL**	**1.408 mL**
Mean no. of exacerbations a person (in one year)	0,97	1,05*	1,04*	**1,30**
Mean no. of exacerbations per person (in one year) that required the use of oral steroids	0,46	0,50*	0,54*	**0,76**
SGRQ score (scale of 0 to100)	44,1	**45,5**	45,2	**46,3**
Oropharyngeal candidosis	8%	7%	2%	2%
Calverley et al. study (Eur Resp J 2003; 21: 74-81)	**Budesonide + formoterol (N = 254)**	**Budesonide (N = 257)**	**Formoterol (N = 255)**	**Placebo (N = 256)**
Post-bronchodilator FEV_1 (% var. of predicted normal at one year)	-1,8%#	**-5,0%#**	**-3,2%#**	**-5,8%#**
Mean no. of exacerbations a person (in one year)	1,38	1,60	**1,85**	**1,80**
Mean no. of exacerbations per person (in one year) that required the use of oral steroids	0,63	**0,87**	**0,91**	**1,14**
Average no. of days without exacerbations	254	**178**	**154**	**96**
SGRQ score (diff. with respect to placebo – scale of 0 to 100)	**-7,5**	-3,0*	-4,1*	–
No. deceased	5 (2,0%)	6 (2,3%)	13 (5,1%)	5 (2,0%)

calculated from the graphs presented in the study

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 FEV_1**: 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 FEV_1**: 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 study[3] 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

- There were no substantial differences in **side effects** between the therapies studied (apart from – in the TRISTAN study – an increase of 6% in oropharyngeal candidosis in patients undergoing combined therapy compared to those treated with bronchodilator or placebo).
- It is necessary to emphasise that the studies lasted one year. The result of the impact of a longer-term therapy based on inhaled corticosteroids is unclear (see page 8).

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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** (β_2-agonists or anticholinergics) **on an as-needed basis** is useful in all stages of COPD.
- In **moderate COPD** long-acting β_2-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 therapeutical approaches.
- In patients with **severe COPD** (FEV_1 <50%) **regular** treatment with high doses of a combination of bronchodilators/inhaled steroids favours respiratory function (about a 5-10% increase of FEV_1 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 Autority Modena

Figure 4

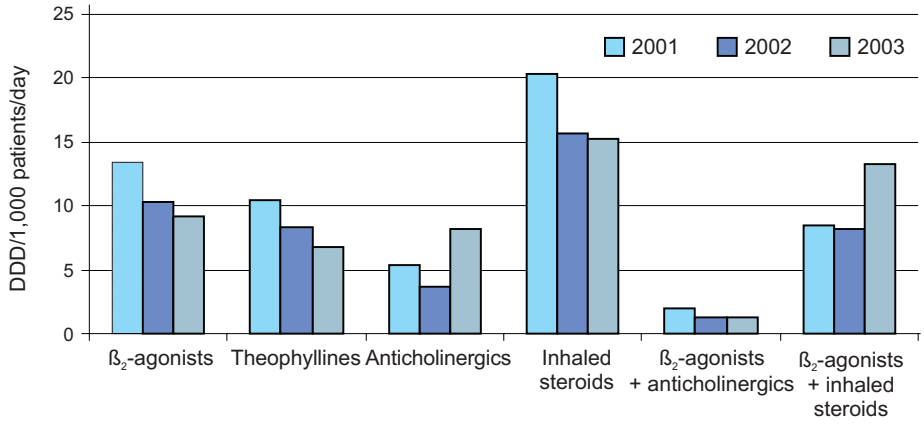

Figure 5

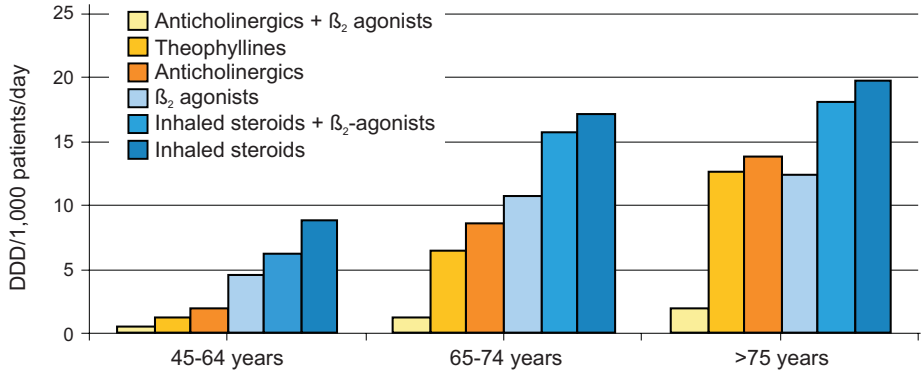

Figure 4 shows, for each subgroup of drugs, the number of DDD (daily definite doses) per 1,000 patients a day prescribed for patients >45 years of age in 2001-2003. These drugs are prescribed by GPs and charged to the SSN (Servizio Sanitario Nazionale/National Health Service).

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

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