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Guidelines *versus* clinical practice in the treatment of chronic obstructive pulmonary disease

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Guidelines versus *clinical practice in the treatment of chronic obstructive pulmonary disease. N. Roche, T. Lepage, J. Bourcereau, P. Terrioux. ©ERS Journals Ltd 2001.*
ABSTRACT: The main purpose of this study was to assess whether pharmacological treatments prescribed by respiratory physicians to patients with chronic obstructive pulmonary disease (COPD) were consistent with the guidelines.

The treatments prescribed by respiratory physicians to 631 consecutive patients with COPD, compared to 879 asthmatics were prospectively recorded. All subjects underwent peak expiratory flow rate measurement, spirometry and assessment of recent evolution and dyspnoea (visual analogue and Medical Research Council scales). Patients with COPD received more treatments than asthmatics (mean±SD: 2.6±0.5 *versus* 2.2±0.4, p<0.0001). Treatments administered to patients with COPD were β_2-agonists in 78% (*versus* 94% in asthmatics), anticholinergic agents (AC) in 56% (*versus* 16% in asthma), methylxanthines in 31% (*versus* 15% in asthma) and inhaled corticosteroids in 76% (*versus* 85% in asthma). Intensity of treatment was influenced by disease severity for all treatments except AC.

In conclusion, pharmacological treatment of chronic obstructive pulmonary disease by respiratory physicians is only partially consistent with current guidelines, with a high proportion of inhaled corticosteroid prescriptions and a relative under-use of anticholinergic agents; this most likely reflects the persistent uncertainties of physicians, and emphasizes that more efforts are required to improve implementation of chronic obstructive pulmonary disease guidelines and assess the efficacy and cost-effectiveness of recommended strategies.
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Maintenance therapy of persistent asthma is well defined in international guidelines [1] on the basis of firm evidence from several adequate clinical trials [2–5]. It includes early introduction of inhaled corticosteroids (ICS), associated with long-acting bronchodilators (mostly long-acting β_2-agonists (β_2A)) when the disease is inadequately controlled by ICS alone.

Conversely, guidelines on optimal maintenance pharmacological treatment in chronic obstructive pulmonary disease (COPD) are less precise; all recommend bronchodilators in breathless patients, anticholinergic agents (AC) being at least as effective as β_2A. However, the criteria for choosing first-line therapy are often quite vague and sometimes even contradictory; the European Respiratory Society (ERS) guidelines recommend either β_2A or AC in breathless COPD patients, without clear criteria to guide the choice between these agents [6]. Conversely, American Thoracic Society (ATS) and French guidelines recommend AC as first-line treatments in patients with permanent symptoms, β_2A being more suitable in subjects with intermittent dyspnoea [7, 8]. Finally, British Thoracic Society (BTS) guidelines recommend trying "as required" β_2A first, AC being prescribed if β_2A are not effective enough or "if maintenance therapy is needed" [9]. These recommendations also underlined that the evidence regarding ICS was poor, which does not justify their wide prescription [6–9].

Thus, treatment of COPD should be quite different from that of asthma, especially in terms of the choice of bronchodilator and the rate of ICS prescription. However, studies in general practice and respiratory medicine have found that β_2A remain by far the most frequently used bronchodilators in COPD while ICS are prescribed in up to 70% of patients [10]. Observed prescriptions in respiratory medicine have been quite heterogeneous; this could be due to the main data source, *i.e.* treatment on entry into clinical trials. Recorded treatments are likely to be influenced by inclusion criteria in these trials, and selected subjects may not be representative of the "real world" population of COPD patients cared for by respiratory physicians.

To assess whether routine practice of respiratory physicians is consistent with the guidelines for COPD management, pharmacological prescriptions by respiratory physicians to patients with COPD were prospectively studied and compared to that of asthmatics. More specifically, the primary objective was to assess the frequency of ICS prescriptions and the respective prescription rates of AC and β_2A in COPD patients. The secondary objective was to assess the

patients clinical and lung function characteristics associated with these treatments.

Materials and methods

Patients

The authors prospectively studied patients with asthma or COPD, in whom pulmonary function tests (PFT) were performed (n=1,510), visiting 69 respiratory physicians over a 1-month period. The diagnosis of asthma or COPD had to be based on clinical and functional assessment according to the National Heart, Lung and Blood Institute, World Health Organization report on asthma and the ERS guidelines on COPD [1, 6].

Measurements

All patients had a detailed medical history assessment including: 1) smoking habits; 2) personal and familial history of asthma, allergy, respiratory infections, chronic or recurrent respiratory symptoms; 3) current and past respiratory treatments (including drug therapy, oxygen therapy and physical therapy); and 4) reason for the visit (*i.e.* diagnostic work-up, worsening of clinical condition including acute exacerbation, or scheduled follow-up). All pharmacological treatments prescribed at the end of the visit were recorded. Prescriptions of long-term oxygen therapy (LTOT), physiotherapy (bronchial drainage and/or exercise training) and nutritional support were also recorded.

Dyspnoea was assessed using a 10-cm visual analogue scale (VAS) and a 5-point scale derived from that of the Medical Research Council (MRC) [11, 12]. Peak expiratory flow (PEF) was measured using an Eolys peak-flow meter, the best of three consecutive measures being recorded. Patients were taught to use the peak-flow meter properly before the beginning of measurements. Spirometry was performed according to ATS and ERS guidelines [13, 14], *i.e.* with calibrated spirometers, recording the best of three reproducible (<5% variation in forced expiratory volume in one second (FEV_1)) measurements. Lung volumes were assessed using either the helium dilution method or plethysmography. Predicted values of PEF and pulmonary function variables were calculated using the ERS and European Community for Steel and Coal equations [14]. Reversibility of bronchial obstruction was tested using four puffs of a short-acting inhaled β_2A (salbutamol, pirbuterol, fenoterol or terbutaline) delivered by a metered-dose inhaler (*via* a holding chamber in patients with poor inhalation technique). FEV_1 was measured again three times after inhalation, and results were expressed as percentage increase in FEV_1 from baseline using the best of these measurements. Significant reversibility was defined as a $\geqslant$15% increase in FEV_1 from baseline. Physicians were free to decide whether blood gas tensions were measured or not. When undertaken, measurements used regularly calibrated apparatus, and oxygen (P_{a,O_2}) and carbon dioxide (P_{a,CO_2}) tensions in arterial blood were expressed in mmHg.

Statistics

Treatments of patients with COPD were compared to that of asthmatics using the Pearson Chi-squared test. Demographical characteristics, lung function (including PEF) and dyspnoea measured by the VAS were compared between asthmatics and COPD patients using analysis of variance (ANOVA). Comparisons of dyspnoea measured by the MRC scale and reason for the visit were carried out using the Pearson Chi-squared test. The influence of dyspnoea, lung function (as measured by FEV_1), reversibility of bronchial obstruction (*i.e.* percentage increase in FEV_1 after inhalation of bronchodilators) and the cause of visit on prescribed pharmacological treatments (*i.e.* final prescription and modifications of β_2A, AC, ICS, oral corticosteroids and theophyllines) was studied using multivariate logistic regression analysis in all patients (including diagnosis as an additional covariate) and separately for patients with asthma and COPD. This analysis was carried out first in patients whose cause of visit was either follow-up or worsening (*i.e.* excluding patients seen for a first diagnostic work-up or an unknown motive) to include the recent evolution of the disease in the covariates; it was then restricted to stable patients (*i.e.* those visiting the respiratory physician for follow-up only). Results are expressed as mean±SEM. A p-value <0.05 was considered to be significant.

Results

Characteristics of outpatients referred to respiratory physicians

Cause of visits in asthma and COPD patients are shown in table 1. COPD patients were older and more frequently current or exsmokers (table 2). Their dyspnoea was more severe and they had greater impairments in lung function and arterial blood gases (table 2). Although the proportion of patients exhibiting a >15% increase in FEV_1 from baseline at the time of the visit was higher in asthmatics (34% *versus* 27%, p<0.0001), the mean magnitude of FEV_1 improvement after inhalation of bronchodilators was similar in both groups (table 2).

Table 1. – Cause of visits in asthma and chronic obstructive pulmonary disease (COPD) patients

	Asthma	COPD
Patients n	879	631
Diagnostic work-up	23.5	29.9
Follow-up	57.8	50.5
Worsening	14.8	14.1
Other/unknown	3.6	5.0

Data are presented as percentage of patients unless otherwise stated.

Table 2. – Demographical characteristics study population

	Asthma	COPD
Patients n	879	631
Age yrs	44.2±0.7	64.3±0.5*
M/F	2.3	7.3*
BMI kg·m^{-2}	24.2±0.2	25.4±0.2*
Smokers %	33.3	100*
Tobacco smoking pack-yrs	19.5±1.1	41.0±0.8*
VAS 0–100	34.6±0.9	48.3±1.0*
PEFR		
L·min^{-1}	300.0±4.5	234.6±4.7*
%	67.7±0.8	53.6±0.9*
FEV1		
L	2.3±0.0	1.6±0.0*
%	75.7±0.8	58.2±1.0*
FEV1/VC		
Absolute value	71.9±0.5	58.4±0.7*
%	117.2±1.2	86.5±1.2*
TLC		
L	5.0±0.1	5.7±0.1*
%	92.1±0.9	93.6±1.2
Per cent increase$^{\#}$	13.9±0.8	12.5±0.9
P_{a,O_2} mmHg¶	78.1±1.1	70.9±0.7*
P_{a,CO_2} mmHg^{+}	38.8±0.6	41.1±0.4*

Data are presented as mean±SD. BMI: body mass index; VAS: visual analogue scale; PEFR: peak expiratory flow rate; FEV1: forced expiratory volume in one second; VC: vital capacity; TLC: total lung capacity; P_{a,O_2}: oxygen tension in arterial bood; P_{a,CO_2}: carbon dioxide tension in arterial blood. $^{\#}$: data are % increase in FEV1 from baseline after inhalation of bronchodilators; ¶: n=45; $^{+}$: n=112; *: p<0.0001 for the comparison between asthma and chronic obstructive pulmonary disease patients (COPD).

Initial and final treatments in chronic obstructive pulmonary disease and asthma patients

Patients with COPD were more frequently untreated when visiting the respiratory physicians (41.6% *versus* 20.0%), but those who were already receiving pharmaceutical agents were on a higher number of medications (2.35±0.06 *versus* 1.98±0.04 medications·patient^{-1}). As shown in figure 1, patients with asthma were significantly more likely to receive β_2A and ICS, while patients with COPD were more likely to receive inhaled AC and methylxanthines. Six per cent of asthmatics and 23.7% of COPD patients received both a β_2A and an AC (p<0.0001). All these differences were also present when end-of-visit (*i.e.* "final") prescriptions were considered. In both groups, 10% of patients were receiving oral corticosteroids (OCS).

Finally, COPD patients were more likely to be on LTOT (8% *versus* 0.4% in asthmatics) and to receive nutritional advice (46% *versus* 12%) and chest physiotherapy (58% *versus* 25%). In both groups, patients receiving nutritional advice had a slightly, but significantly higher body mass index than others (25.6±0.2 *versus* 24.1±0.2 kg·m^{-2}, p<0.0001).

Modifications of treatments

Treatment modifications occurred in 80% of visits for diagnostic work-up or worsening *versus* 50% of scheduled follow-up visits (p=0.02). In COPD patients, the frequency of treatment changes during follow-up visits was higher than in asthmatics (57.4% *versus* 45.2%, respectively), while there was no difference between the groups in terms of treatment modifications during visits for diagnostic work-up or worsening. At least one treatment was changed during the visit in 61% of asthmatics and 66% of COPD patients, this difference being significant (p=0.04).

β_2A, anticholinergic agents and theophylline were more frequently added in COPD patients than in asthmatics (23%, 31% and 9% in COPD *versus* 15%, 9% and 2% in asthma, respectively), while the frequency of addition of ICS or oral corticosteroids was similar in both groups (24%). After the visit, the proportion of untreated patients decreased in both groups (3.1% in asthmatics and 11.5% in COPD), but remained significantly higher in COPD (p<0.0001). In parallel, the number of medications per patient increased in both groups and remained higher in COPD (2.6±0.5 *versus* 2.2±0.4 in asthma).

Clinical and lung function factors associated with treatment prescriptions

The cause of visit, intensity of dyspnoea and FEV1 were significantly and independently associated with

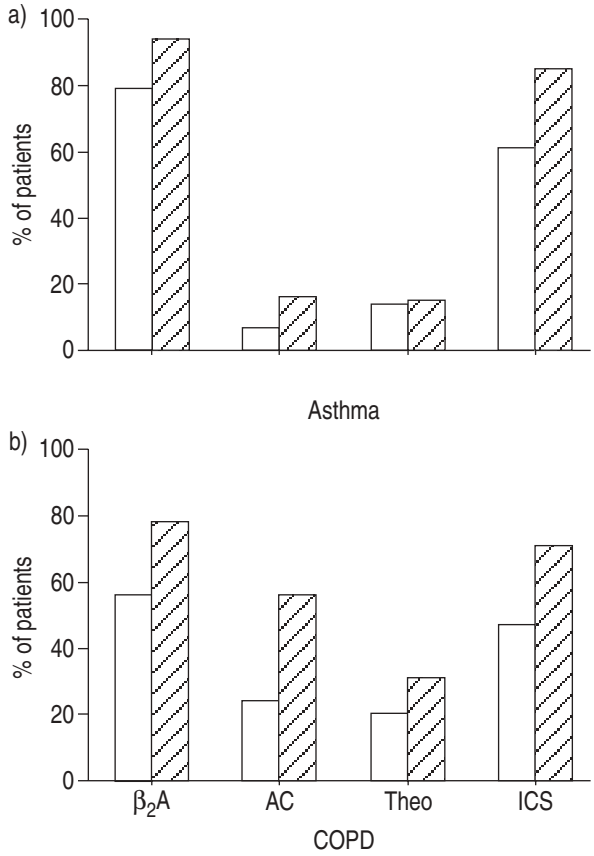

Fig. 1. – Treatments received by a) asthmatics and b) chronic obstructive pulmonary disease (COPD) patients before (□) and after (▨) a visit to the respiratory physician. β_2A: β_2-agonists; AC: anticholinergic agents; Theo: theophylline; ICS: inhaled corticosteroids.

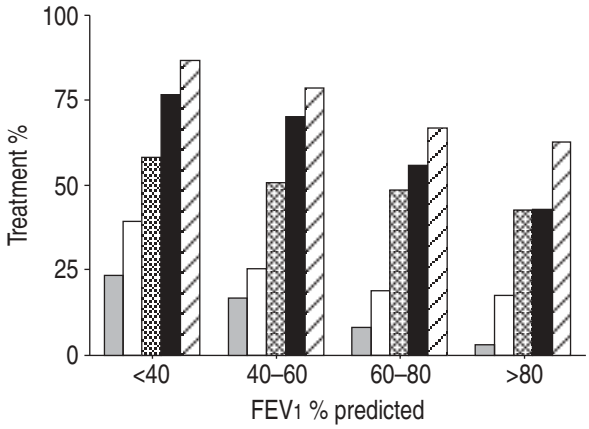

Fig. 2. – Pharmacological treatments in chronic obstructive pulmonary disease patients, stratified according to forced expiratory volume in one second (FEV1). Results are expressed as the percentage of patients in each FEV1 range who receive the considered treatment. ▨: β_2-agonists; ▩: anticholinergic agents; ■: inhaled corticosteroids; □: theophylline; ■: oral corticosteroids. $p<0.001$ for all treatments except anticholinergic agents.

most treatment modifications and final prescriptions in asthma as well as in COPD. Conversely, the diagnosis (asthma or COPD) was an independent predictor of most treatment modifications but not of final prescriptions. Figures 2 and 3 depict the frequency of ICS, β_2A, AC and theophylline final prescriptions according to lung function and intensity of dyspnoea. Prescriptions of all these treatments except AC increased with disease severity. Similar results were found for chest physiotherapy, nutritional support and LTOT (data not shown).

Discussion

The present study found a high proportion of ICS prescriptions and a marked predominance of β_2A over AC in patients with COPD, which contrasts with recently recommended treatments in these patients. It was also observed that therapeutic intensity depended on disease severity (*i.e.* intensity of dyspnoea and lung function impairment) for all treatments except AC. Finally, a high proportion of smokers (*i.e.* one-third) among asthmatics was found, which is a great cause of concern.

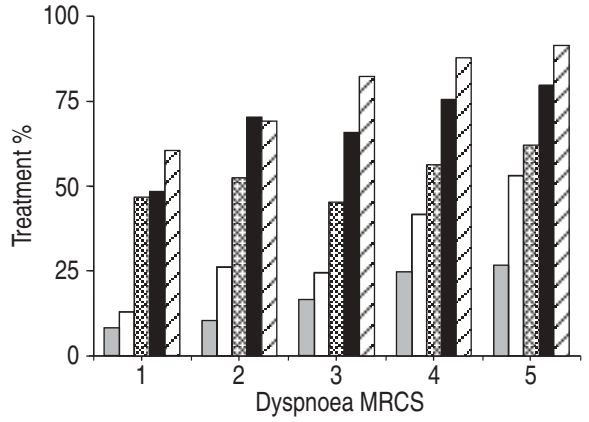

Fig. 3. – Pharmacological treatments in chronic obstructive pulmonary disease patients, stratified according to the dyspnoea Medical Research Council scale (MRCS). Results are expressed as the percentage of patients of each dyspnoea grade who receive the considered treatment. ▨: β_2-agonists; ▩: anticholinergic agents; ■: inhaled corticosteroids; □: theophylline; ■: oral corticosteroids. $p<0.001$ for all treatments except anticholinergic agents.

Several points have to be considered when interpreting the results. Firstly, results of reversibility testing in asthmatics are surprising, since significant reversibility was found in only less than half of those who had baseline airways obstruction. This suggests that, despite recommendations to investigators, not all subjects withheld bronchodilators before PFT. Despite this, almost 30% of patients diagnosed as having COPD exhibited a significant reversibility of airway obstruction. This underlines that respiratory physicians do not consider COPD as a completely irreversible disease. Secondly, asthmatics were not stratified according to disease severity, since the main purpose of this survey was to study COPD and not asthma treatments. Finally, no difference was made between short-acting and long-acting β_2A, because the purpose of the study was to assess the ratio of β_2A to AC prescriptions rather than to specifically study the frequency of long-acting β_2A prescriptions in COPD.

French guidelines on COPD management have been issued in 1997 and recommend inhaled bronchodilators as first-line therapy in all symptomatic patients, with on demand β_2A in case of intermittent symptoms, regular AC when permanent exertional dyspnoea is present, or both [8]. Insufficient efficacy of first-line treatment should lead to use of a different bronchodilator, combination therapy or addition of aminophylline if inhaled combination therapy was already administered. These guidelines also state that the use of ICS should be restricted to patients with either bronchial hyperresponsiveness, an objective response to systemic glucocorticoids or severe airway obstruction (FEV1 <35% predicted) [8]. Thus, according to these recommendations AC should be prescribed to most symptomatic patients while ICS should be administered in only a minority.

In the present survey, the ratio of β_2A to AC in COPD was ~1.3, AC being prescribed in 56% of patients (*versus* 16% of asthmatics). Such data are broadly consistent with that of clinical trials and prescription surveys in Europe [10]. However, all these studies found quite wide variations in the β_2A to AC ratio, which is probably not only due to differences in disease severity, but also to a lack of consensus between physicians [10]. Indeed, in the present study AC prescriptions did not vary significantly according to FEV1 or dyspnoea, suggesting that some physicians prescribe AC in COPD systematically while others do not, irrespective of disease severity. Conversely, a remarkably high rate of ICS prescriptions in COPD (76%) was found, greater than levels observed in patients recruited by respiratory physicians into clinical trials [10] but similar to results of a UK survey in general practice [10]. Over-prescription of ICS could be a significant source of unnecessary expenses, and it has recently been estimated that the "gap" between

recommendations and prescriptions of ICS in COPD represents up to £42 million annually in the UK [10]. Such a figure is based on the assumption that ICS are indicated in only ~10–30% of patients [6, 9].

It is of utmost importance to understand the reasons for such discrepancies between guidelines and "real world" practice, in order to design clinical trials addressing unanswered questions and increase the impact of new recommendations [15, 16]. In the present study, a lack of confidence in the differential diagnosis between COPD and asthma is unlikely because included subjects were only those in whom there was a "firm" diagnosis of asthma or COPD by respiratory physicians. Thus, other explanations have to be considered.

The most obvious reason for lack of adherence to guidelines is the physicians' lack of awareness [15]. Such an explanation is rather unlikely in the present case since guidelines on COPD were largely disseminated through press conferences, symposia at national meetings of respiratory medicine, articles in French respiratory medicine and general practice journals and widely distributed summaries. However, it is well known that simple dissemination of guidelines through printed material and formal lectures is markedly insufficient to obtain an impact [17–19]. Therefore, other methods need to be used in combination, including encouraging local adaptation and implementation, interactive continuous medical education sessions, reminders, office-based peer-review and audit [20]. The use of financial incentives or coercive measures has also been advocated [15]. None of these methods were employed after the publication of the guidelines, which could participate towards explaining their modest impact.

Another reason for not adhering to guidelines could be an insufficient involvement of concerned healthcare providers in the guidelines development process [15]. This is again unlikely since a representative working party including almost 10% of all French respiratory physicians participated in this process. Lack of confidence in the level of evidence supporting the guidelines, disagreement with recommended strategies and awareness of more recent data are other causes of nonadherence [16]. Indeed, levels of evidence were not indicated in the expert report, but would have been useful since there is some controversy surrounding the choice of first-line bronchodilators and indications of ICS. An effect of recently published trials [21–23] on the prescription rate of ICS is doubtful: these trials suggest an efficacy of the agents on symptoms, exacerbation rate and quality of life in COPD patients with a mean FEV_1 of ~50% [21–23], but the present data show that ICS were largely prescribed in patients with FEV_1 >50% of predicted (62.1%), and even in those with FEV_1 >70% (54.4%). It has also been shown that guidelines which require marked changes in clinical practice, generate high costs, or may induce hostile reactions from patients, are less likely to be followed [16]; here, all these factors are unlikely to be involved.

Conversely, the belief that following the guidelines would only have limited effects on patient outcomes may play a role. Several practitioners still consider COPD to be an irreversible disease which cannot be altered by pharmacological agents, as reflected by the higher proportion of untreated COPD patients. In addition to the data mentioned earlier on ICS, several trials showing beneficial effects of AC on symptoms, exacerbation rate and quality of life have been published after the guidelines [24–26] and may increase the confidence of physicians in the utility of these pharmacological treatments in COPD. Finally, unclear, vague or complex and inapplicable statements are a source of nonadherence [15]. The applicability of the guidelines was not tested before their publication, which would have been useful to improve the way they were justified, written and explained.

To conclude, this survey found discrepancies between guidelines and prescription rates of inhaled corticosteroids and anticholinergic agents in chronic obstructive pulmonary disease, which underlines persistent uncertainties of physicians; these findings support the need for providing updated guidelines stating more clearly the level of scientific evidence supporting each recommendation. Such guidelines should be tested before their release and efforts directed at improving their implementation should be increased. Finally, the impact of recommended strategies on clinical practice and their efficacy and cost-effectiveness should be assessed more systematically.

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