COPD a social disease: inappropriateness and pharmaco-economics. The role of the specialist: present and future

BPCO una malattia sociale: inappropriatezze ed aspetti farmaco economici. Il ruolo dello specialista: presente e futuro

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The prevalence of chronic respiratory disorders has been increasing steadily over the past several years and currently constitutes a serious public health problem. Chronic respiratory disorders (including lung cancer) represent worldwide the second most important cause of mortality and their frequency and diffusion are probably far greater than realized, given that they are often underdiagnosed and misdiagnosed. As a matter of fact, many patients are not diagnosed until the chronic respiratory disease is severe enough to prevent normal daily activities. Underdiagnosis has not only an epidemiological relevance, but also implies clinical consequences: as little attention is paid to respiratory diseases by the individual and the community, those affected receive late and non-optimal treatment.

Furthermore, insufficient consideration is given to the general and specialist health services that should take care of chronic respiratory patients [1-2]. The future trend is for a further increase, though differentiated for the individual disorders. Chronic obstructive pulmonary disease (COPD) in particular is estimated to become the third leading cause of death worldwide by the year 2020 [3]. At present, most people are not diagnosed until they are in their late 50s when their respiratory lung function has already begun to decline in a clinically significant way [4]. The high level of underdiagnosis/undertreatment or misdiagnosis/mistreatment is evidence of the generally inadequate standards of care - a problem even in developed countries - at all levels of intervention, from prevention (that is inadequate) to long-term management (that is inappropriate) [5,6].

Given the increasing social impact of COPD, the conference on which this report is based ("COPD a social disease: inappropriateness and pharmaco-economics. The role of the specialist: present and future", held in Venice, Italy, April 21-22, 2010) was in tune with the goals and recommendations of GARD, the Global Alliance against chronic Respiratory Diseases of the World Health Organisation. GARD has formulated the following working recommendations:

1. to develop national programs of prevention and control of chronic respiratory diseases (CRDs),

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Footnote: this report is based on the conference **"COPD a social disease: inappropriateness and pharmaco-economics. The role of the specialist: present and future"** held in Venice, Italy, April 21-22, 2010, and organized by AIMAR within the 'Year of the Lung 2010' promoted worldwide by the Forum of International Respiratory Societies and within Europe by the European Respiratory Society. AIMAR is, since 2005, a partner of the Global Alliance against chronic Respiratory Diseases (GARD) of the World Health Organisation (WHO).

Multidisciplinary Respiratory Medicine 2010; 5(6): 437-449

starting with health education campaigns and a better knowledge of epidemiology, impact, and relative risk factors;
2. to provide training and continuing education on prevention and treatment of CRDs, disseminating the existing guidelines; and
3. to facilitate access to essential treatments and favour adherence to long term treatment, including drug treatment and pulmonary rehabilitation, particularly amongst disadvantaged sectors of the population.

PREVENTION

The reduction of the social and individual impact of chronic respiratory diseases is based not only on early diagnosis and treatment, but also on the modification of environmental and social factors. Today, many risk factors have been identified, such as tobacco smoke, allergens, occupational agents, and indoor and outdoor air pollution, the prevention of which will have a significant impact on morbidity and mortality.

A wide array of lifestyle modifications can help prevent COPD, including: smoking cessation, measures to avoid allergens and respiratory irritants, prevention of infections, maintaining a balanced nutrition and hydration, avoiding extreme environmental conditions, weight control, and physical exercise to increase muscle tone. Consolidated data exist only for active and secondhand cigarette smoking, occupational exposure and outdoor and indoor air pollution [7].

Smoking is the leading cause of COPD: 80 to 90% of subjects diagnosed as COPD are long-term smokers. Secondhand smoke exposure and occupational exposure may also influence the development and the progression of the disease [7,8]. The burden of non smoking-related COPD is, however, much higher than previously thought, with an estimated 25-45% of patients with COPD having never smoked.

A systematic epidemiological review by the American Thoracic Society showed that about 15% of COPD cases might be attributable to exposure to toxic gases in the workplace, grain dust in farms, and dust and fumes in factories [8].

Exposure to indoor and outdoor air pollutants is a major contributing factor to the increased morbidity, healthcare resources utilization and higher mortality among patients with COPD, but there are few studies on whether air pollution is a key factor in the development of this disease [9]. Indeed, the greatest risk factor for COPD globally might be exposure to biomass smoke, since about half the world's population (3 billion people) are exposed to smoke from biomass fuel compared with 1.01 billion who smoke tobacco. Byproducts of oxidative stress found in air pollutants (ozone, sulfur oxides, carbon monoxide, nitrogen oxides, and particulate matter) are common initiators or promoters of the damage produced in chronic diseases of the airways.

Strong evidence exists also for infections as a trigger of COPD exacerbations. Avoiding respiratory illnesses, such as influenza and pneumonia, can decrease the risk of COPD worsening [9]. Vaccinations can prevent some of the infections that cause COPD exacerbations and should be administered to all patients with COPD, although clinical trial data on this are limited. In a large cohort of COPD patients admitted to Italian hospitals for an exacerbation, the percentage of subjects who had been vaccinated against influenza and pneumococcal infections was only 58% and 13% respectively [6].

More solid data on risk factors for COPD development, progression and exacerbation are required in order to implement cost-effective prevention and management strategies.

DIAGNOSIS

The diagnosis of COPD is conventionally based on spirometry in the presence of a risk factor such as smoking or occupational exposure [11]. But the importance of adding medical history data to spirometry, stressing the importance of persistent cough and phlegm in support of an earlier diagnosis of COPD in family practice [12], must be stressed as there is still a considerable underpresentation and underdiagnosis of COPD.

For interpretation of the spirometry, the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Committee suggested the use of a fixed FEV_1/FVC cut-off of 0.70 instead of the more appropriate statistically defined lower limit of normal (LLN), since the fixed ratio is easy to remember and apply and not dependent on the choice of a reference equation. According to a number of recent papers, however, the fixed cut-off of 0.70 significantly *overestimates* airflow obstruction in older people, leading to misuse of resources, and individual and societal harm [13-15], while it *underestimates* airflow obstruction among young adults, leading to a missed opportunity for an early diagnosis of COPD in patients who are more likely to benefit from intervention [13]. Since diagnostic confusion between COPD and asthma is common, bronchodilation performed after spirometry may help to reduce the chance of misclassification [11].

The complexity and heterogeneity of the disorders encompassed by the term COPD with the overlap of different phenotypes has recently led to the following recommendations: i) to develop a new taxonomy in order to better define the disorders of airways obstruction and, consequently, ii) to make clinical assessment more multidimensional [16]. Besides FEV_1/FVC, lung volumes should always be included in the diagnosis of COPD as evaluation of hyperinflation is an important criterion for the phenotyping of COPD patients.

TREATMENT

Over the latest two decades, in COPD treatment a change in concept has occurred from a previously

nihilistic attitude based on smoking cessation as the only possible treatment, to the current opinion - thanks to several large trials that examined not only pharmacological agents but also pulmonary rehabilitation and lung volume reduction surgery - that COPD is not only preventable but also treatable [11,17]. Unfortunately, the value of the findings from therapeutic trials is limited as the study populations were highly selective. As a matter of fact, patients were included only if they had COPD and were free of concomitant morbidities that might impact negatively on the trial outcomes. In the real world, however, COPD patients are frequently afflicted by multiple comorbidities, such as heart disease, osteoporosis, peripheral muscle weakness and dysfunction, anemia, depression, anxiety and lung cancer, and more frequently so than the general population [18].

The pathophysiological hallmark of COPD is variable airflow obstruction resulting in pulmonary hyperinflation. Progressive decline in lung function leads COPD patients to experience in the course of time significant limitation in their daily life activities, including dyspnea, limited exercise capacity, frequent exacerbations and hospitalizations.

Over the last few years, pharmacotherapy studies have demonstrated that bronchodilators can reduce dynamic hyperinflation, increase inspiratory capacity (by reducing the functional residual capacity), decrease the work of breathing, and improve ventilatory capacity during activity and formal exercise testing. At a clinical level, bronchodilators have been shown to improve dyspnea, decrease exacerbations, ameliorate health-related quality of life (HRQoL), and decrease mortality [11,17].

Clinical studies of long-acting bronchodilators, long-acting β_2-agonists (LABA) such as formoterol, salmeterol and more recently (though to date less supported by data) indacaterol, and long-acting anti-muscarinic agents (e.g. tiotropium) showed significant improvement in trough peak FEV_1 (range, 0.1-0.3 L) and average FEV_1 (range, 0.1-0.25 L) compared to a decline in placebo-treated patients (short-acting β_2-agonists, and/or ipratropium) [19,20].

Clinical studies evaluating the use of combination of tiotropium and LABA showed that there is a synergistic effect of the combination therapy and further improvement in lung function. This combination therapy would be suitable for patients with severe disease [21].

The sustained improvement in lung function seen in these studies suggests that long acting bronchodilators may slow down the decline in lung function over time and subsequently change the clinical course of the disease.

Clinical studies using triple therapy - tiotropium and a fixed combination of LABA and inhaled corticosteroid (ICS) – have demonstrated an enhanced improvement in lung function, and reduction of exacerbations as compared with individual agents alone [22].

Several of these studies also showed improvements in morning and daytime symptoms, night-time arousal, reliever use, and HRQoL. In COPD patients with severe and very severe disease, triple therapy is highly effective.

An important issue is whether regular treatment with long-acting bronchodilators and/or the combination of LABA/ICS should be initiated at an earlier stage of the disease. Reports of a sub-analysis of the TORCH and UPLIFT studies show that patients with moderate disease would benefit from these therapies. These studies showed significant increase in trough FEV_1, peak FEV_1, dyspnea score, and HRQoL. Notably, patients also had a significant reduction in exacerbations [20].

The recent analysis of the large tiotropium database and the findings of the prospective UPLIFT study indicate a reduced risk for mortality from cardiovascular events and even overall mortality in patients receiving tiotropium. The mechanism by which tiotropium may reduce these events and improve survival could be associated with the significant reductions in exacerbations and hospitalizations observed, but conclusive evidence is lacking. In the pooled analysis of 30 trials, tiotropium treatment also resulted in significant reductions in serious cardiac adverse events [23].

In the TORCH study, the patients randomized to LABA alone had the lowest rate of cardiovascular death. A range of predictable factors increased the cardiovascular event rate, including: older age, a history of previous cardiac disease, and worse lung function. None of these factors interacted with treatment to identify a specific 'at risk' group [24].

According to recent controlled randomized trials the risk of pneumonia is higher in patients receiving inhaled fluticasone. In the TORCH study, patients receiving at least 1,000 mcg/day of fluticasone propionate equivalent, compared with non-users of inhaled corticosteroids within the past year, had a rate ratio for pneumonia hospitalization of 2.25 (95% CI 2.07– 2.44). The TORCH trial showed no difference in pneumonia mortality between patients receiving inhaled corticosteroids and those not receiving them [25]. A new class of drugs is that of the selective phospho - diesterase-4 inhibitors. The most promising agent, roflumilast, taken orally once daily targets the airways inflammation that is a hallmark of the disease. Participants in different 6- and 12-month studies who received roflumilast alone or in combination with salmeterol and/or tiotropium experienced a significant improvement in lung function, quality of life and reduction in exacerbations. The two most frequent adverse events in the roflumilast group were diarrhea and weight loss, mild in nature but disturbing in a long-term treatment [26]. This medication is on the way for approval by the regulatory agencies.

FOLLOW UP

Exacerbations of COPD are a frequent cause at follow up of emergency visits and hospitalizations, representing the major financial burden for most

healthcare systems. An exacerbation of COPD is defined as a change in the patient's baseline dyspnea, cough, and sputum beyond day-to-day variations, that is acute in onset and may warrant a change in regular medication [11].
The management of patients with an exacerbation shows very large variability among the different settings and reveals the inadequate standards of care [6]. This applies even more so to the follow up modalities after hospitalization, which aim to optimize care and reduce the risk of a relapse (the recurrence of which is greatest within the first few weeks of the initial event) [27,28].
A number of risk factors have been identified that facilitate the occurrence of a new exacerbation, including: number of previous exacerbations, previous hospitalizations, use of long term oxygen therapy (LTOT), poor lung function, absence of a primary caregiver and choice of pharmacological therapy [6,29].
Concerning follow up, a number of points need to be better investigated, such as appropriate functional diagnosis and severity stratification (e.g. spirometry is largely underused) [6], the potential benefit of home monitoring and of noninvasive ventilation as well as the value of LTOT in borderline respiratory failure, the effectiveness of self-management programs, and of early rehabilitation (PR).
Available data suggest that an early PR intervention should be included in the follow up program. PR after an exacerbation reduces the hospitalization rate and improves exercise capacity and quality of life [30]. Therefore, efforts should be made to improve the availability of PR for COPD patients in different healthcare settings. In fact, a large multicentric Italian study demonstrated that only 14.5% of COPD patients admitted to hospital for an exacerbation were offered PR [6].

Long-term oxygen therapy (LTOT)

Oxygen therapy is an essential treatment in the care of COPD patients with chronic respiratory failure. The evidence supporting the large use of LTOT and the indications reported in international documents are based on two landmark prospective, randomized clinical trials - NOTT and MRC - published about 30 years ago [31,32]. These studies showed that survival improves in stable COPD patients who receive LTOT for more than 15 hours/day in the long term. The effectiveness of LTOT in improving survival has been documented only in COPD patients with severe chronic hypoxemia (PaO_2 < 55 mm Hg (7.3 kPa) or PaO_2 ranging from 56 to 59 mm Hg (7.4-7.8 kPa) in the presence of cor pulmonale, or hematocrit > 55%).
The LTOT indications (based on NOTT and MRC) were established in a very selected and limited number of patients that are unlikely to represent the heterogeneity of the real COPD population. These recommendations have been subsequently extended, albeit without solid evidence, to COPD patients with moderate hypoxemia (55 < PaO_2 < 65 mm Hg), and to patients with decreased oxygen saturation (SaO_2 < 90%) during exercise or sleep [11,17,33]. Comorbidities are likely to affect both prognosis and health outcomes in COPD patients but clinical practice guidelines do not provide adequate guidance for patients on LTOT with complex chronic diseases.
Disease stability before prescribing LTOT should be mandatory, but quite commonly COPD patients are prescribed oxygen at home simply because they are still hypoxemic at discharge from hospital after an exacerbation, despite an absence of data to support the short-term benefits of oxygen therapy. Actually, after an exacerbation, up to 38% of COPD patients improve peripheral blood oxygenation to PaO_2 levels above those qualifying in the selection criteria for LTOT, simply by optimizing medical therapy [34]. A reassessment of the indication for LTOT after 3 months of clinical stability could significantly reduce the number of patients eligible for LTOT soon after an episode of exacerbation [11,17].
Given the increasing numbers of patients receiving long-term supplemental oxygen, a critical review of the current indications for LTOT is needed, particularly for COPD patients with comorbidities, mild-moderate hypoxemia, exercise and sleep desaturation, so that LTOT is prescribed only for patients in whom there is a reasonable expectation of clinical benefit.

Non-pharmacological therapies

The National Emphysema Trial (NETT) represents the first case in which a surgical procedure in COPD was subjected to a randomized trail using a medical comparator, in this case optimal medical therapy and pulmonary rehabilitation. In the baseline evaluation and follow up of the patients included in NETT, a very low FEV_1 and diffusion capacity for carbon monoxide (DLCO) were associated with a very poor outcome [35]. These observations had important consequences in the clinical practice, in terms of defining which patients are most appropriate candidates for lung volume reduction procedures.
Several trials have emphasized the beneficial consequences of pulmonary rehabilitation with very little evidence regarding side effects. The only drawback related to negative outcome is that of patients who do not want to participate in rehabilitation or who do not complete the program. The percentage of patients who do not join programs is very high, around 60%, and out of those who do join close to 30% fail to complete the program. Very little has been done to better characterize those patients and evaluate the factors that led to their lack of compliance and uptake [36].

Pharmacoeconomic issues

The total cost of respiratory diseases in Europe is more than € 100 billion per year. COPD contributes to at least half of this figure, followed by asthma, pneumonia, lung cancer and tuberculosis. In general, inpatient hospital services represent 17.5% of the total cost, outpatient care 8.9%, pharmaceutical

drugs 6.6%, costs related to mortality and rehabilitation 19.6%, and lost work days 47.4% [37].

The cost of pharmacological treatment for COPD is steadily increasing across all European countries, this being due, on the one hand, to expensive, new hospital treatments with biological drugs and medications for cancer, and, on the other, to an expansion of the subpopulation of elderly people and, consequently, of the number of people with common chronic diseases including COPD. Around the end of the last century there was a growing interest in pharmacoeconomic issues corresponding to the overall need for "accountability", and the economic evaluation of working strategies progressively became the crucial point for decision makers in allocating the ever diminishing healthcare resources.

Although pharmacoeconomic data are not easy to compare among the different national health systems, the following examples will reveal some points in common, in particular: i) the very high absolute and relative burden of COPD, despite its substantial underdiagnosis; ii) the progressive increase of costs with increasing disease severity, the largest share of costs being due to exacerbations and hospitalizations; iii) the high costs due to LTOT among therapies; and iv) the inadequate coverage provided to the citizen for drug expenses.

THE PHARMACOECONOMIC SITUATION IN NORTH AMERICA

Canada

According to the BOLD survey the prevalence of COPD in subjects aged 40 years or older in Canada is 11.1% (Stage I), 7.3% (Stage II) and 0.9% (Stage III-IV) or about 3.3 million, considerably higher than the official estimate of 750,000 Canadians suffering from COPD, based on reported physician diagnosis [38]. As in other countries, there is a very large undiagnosed COPD population in Canada [5]. Despite this, respiratory diseases rank fourth in Canada in terms of the proportion of healthcare costs [38].

Primary care providers (PCP) are usually the first point of care for patients with COPD and the majority of physicians (PCPs and specialists) are paid on a fee-for-service basis. Consultation by specialists is generally arranged through a PCP, because services for non-referred patients are paid at a lower rate. As for costs of delivering COPD care, the Canadian RUSIC study [39] estimated that exacerbations of COPD requiring a medication change plus a visit to an outpatient facility including an emergency department had a mean cost of $641 (CAN 2006 $), whereas the mean cost of an exacerbation requiring hospitalization was $9,557. In 2003, the Confronting COPD Survey estimated that the annual direct cost of COPD care, including laboratory tests and visits to PCPs and specialists, was almost $2000 per patient, with about half of the costs due to hospitalization [40]. The estimated economic burden of COPD through work loss was $1,198 per patient, giving an annual societal cost of $3,195 per patient. Costs increased in direct proportion to the severity of COPD as measured either by FEV_1 or MRC dyspnea score.

There is no universal drug plan in Canada, and private payments are required for many citizens for medications, with differences from province to province. Thus while the Canadian [5] and other [11] clinical practice guidelines for COPD recommend a long-acting anticholinergic bronchodilator or a LABA as first line treatment and combinations of long-acting bronchodilators with or without ICS for more advanced disease, these restrictive provincial formularies act as barriers to physicians who wish to follow guidelines.

A survey of Canadian PCP practice patterns in COPD in the provinces of Ontario and Quebec (CAGE study) observed that pharmacologic treatment that matched Canadian guidelines was present in only 34% of practices [41]. Non-prescription of long-acting bronchodilators for patients with moderate and severe COPD occurred in 27% and 21% of cases respectively and prescription of two long-acting bronchodilators for advanced COPD occurred only in 49% of subjects.

A cost effectiveness analysis of the Canadian [5] and GOLD [11] recommendations for COPD pharmacotherapy was based on the results from the Canadian OPTIMAL trial [42,43]. This study demonstrated that triple therapy with tiotropium plus fluticasone plus salmeterol was superior to tiotropium plus salmeterol, or to tiotropium alone in terms of lung function, frequency of exacerbations requiring hospitalization and quality of life.

The cost effectiveness analysis demonstrated that the incremental cost per exacerbation avoided with tiotropium plus fluticasone plus salmeterol was $6,510 (CAN) and the incremental cost per quality adjusted life year (QALY) gained was $243,180 (CAN) [42]. The authors concluded that neither tiotropium plus fluticasone plus salmeterol nor tiotropium plus salmeterol seem economically attractive alternatives compared to monotherapy with tiotropium for moderate-to-severe COPD, in the context of an acceptable societal cost per QALY gained and per exacerbation avoided [42].

Among non-pharmacologic therapies, pulmonary rehabilitation has undergone cost/benefit analysis in the Canadian context [44]. An economic analysis of a 2-month inpatient followed by 4-month outpatient program estimated a cost of $11,597 (CAN) to achieve clinically significant outcomes in dyspnea, emotional function, and mastery, with more than 90% of the costs being due to the inpatient phase of the program [44]. A more recent study demonstrated potential cost savings resulting from fewer hospitalizations for COPD patients successfully completing a pulmonary rehabilitation program [45]. It must also be emphasized the value and potential cost-effectiveness of developing smaller outpatient and home-based rehabilitation programs [46].

A recent review has suggested that the most signifi-

cant gains in COPD healthcare utilization have been realized by collaborative self-management education interventions [47]. A Canadian randomized controlled trial comparing case manager-driven self-management education versus usual care demonstrated a 40% reduction in the need for COPD patients to access healthcare resources including hospitalizations, emergency department visits and unscheduled clinic visits [48].

In many provinces a restructuring of primary care into multidisciplinary teams is in progress; these are given financial incentives to provide comprehensive care including certified respiratory educators-facilitated self-management education [49].

United States

COPD affects about 20-24 million United States citizens, being the fourth leading cause of death in the U.S. with more than 125,000 deaths annually. In 2010, the direct healthcare costs of COPD are projected to total $29.5 billion [50]. Of these costs, $13.2 billion are due to hospital care, $5.5 billion are physician costs, $5.8 billion are outpatient prescription drug costs, $1.3 billion are home healthcare costs, and $3.7 billion are nursing home care. Long-term oxygen therapy costs Medicare more than $2 billion per year for COPD and the cost is growing by 12-18% per year [51]. In addition, there are $20.4 billion in indirect costs due to lost productivity from death and disability.

The pharmacoeconomic evaluations of COPD have recently been critically reviewed with generally concordant results, despite a number of methodologic flaws [52].

Three older retrospective analyses have shown that the anticholinergic bronchodilator ipratropium in early stage COPD and a combination anticholinergic/β-agonist in more advanced COPD are associated with lower overall healthcare costs, largely because of a reduction in exacerbations requiring hospital care [53].

Another retrospective analysis compared costs of COPD treatment with ipratropium versus theophylline [54]. The overall healthcare costs were 28% lower in those patients treated with ipratropium, mainly because of a reduction in exacerbations. An analysis of healthcare costs from a health maintenance organization database showed that monotherapy with ipratropium was associated with a reduction in healthcare costs compared to monotherapy with either a β-agonist, inhaled steroid, or theophylline in the first six months following COPD diagnosis. Subsequent treatment with combination therapy with ipratropium and a β-agonist was also lower in terms of healthcare costs than other therapy groups [55]. These observational studies were supported by an economic analysis of two clinical trials of ipratropium/albuterol combination compared to ipratropium or albuterol alone [56]. Both of the ipratropium arms of the study indicated lower direct healthcare costs than albuterol alone. Again, the main component of the reduced expenditures was related to fewer exacerbations and fewer hospitalizations.

Long-acting β-agonists (LABA) as monotherapy are effective in reducing COPD exacerbations compared to placebo, and this translates into a reduction in healthcare expenditures, although studies did not provide a comparison to other bronchodilator monotherapies [57]. Monotherapy with an inhaled corticosteroid, fluticasone, assessed in a placebo controlled trial was found to be associated with a reduction in both direct healthcare expenditures as well as indirect healthcare costs from days of incapacitation [58]. A clinical trial comparing the long-acting anticholinergic tiotropium to ipratropium demonstrated a 26% reduction in exacerbations and 46% reduction in hospitalizations associated with tiotropium.

The cost-effectiveness of ICS was greater in the most severely impaired individuals [59].

Three economic analyses of the TORCH trial have been published. TORCH compared salmeterol-fluticasone combinations (SFC) to the individual components and placebo.

In one study using the United States cost structure, salmeterol was the most cost-effective drug ($20,797/QALY) and SFC was second most cost-effective ($33,865/QALY). Fluticasone alone, which did not improve survival in TORCH, was not considered cost-effective [60].

A similar Markov-chain analysis of the TORCH trial, using different cost assumptions, found that SFC was the most cost-effective ($52,046/QALY), followed by salmeterol monotherapy ($56,519/QALY) and fluticasone monotherapy ($56,519) [61].

In a third analysis of TORCH, using a multinational approach to cost structure, SFC was also found to be most cost effective, compared to salmeterol monotherapy and fluticasone monotherapy. The cost-effectiveness was considerably lower for SFC in the United States ($77,100/QALY) than in Western Europe ($24,200/QALY) [62].

Analysis of a Medicare database using actual healthcare expenditures compared the costs of initial maintenance therapy for COPD using SFC, ipratropium monotherapy, ipratropium-albuterol monotherapy, and tiotropium. In this retrospective comparison, SFC was associated with slightly more cost savings than tiotropium ($110/year), and ipratropium-albuterol ($295/year), but was substantially better than ipratropium alone ($1,235/year) [63].

THE PHARMACOECONOMIC SITUATION IN EUROPE

Spain

In Spain, the prevalence of COPD was 9% in adults between 40 and 70 years of age in 1999, although only 22% were diagnosed. In another population-based study performed ten years later, the observed prevalence was 10.2% and the underdiagnosis persisted, with only 27% of individuals with COPD having a previous diagnosis of the disease [64].

Top-down estimates have been carried out on the costs generated by COPD in Spain using statistical

and epidemiological data. These studies reported figures of around €800 million annually in 1994 including both direct and indirect costs. In a micro-economic study performed in 1,510 patients with ambulatory COPD followed over one year (bottom-up), the average annual cost per patient was $1,876. From this study the approximate direct annual cost generated by COPD in Spain may be calculated from the prevalence. In the IBERPOC population-based epidemiological study, the prevalence of COPD was estimated to be 9% in the 40-69 year age group, of which only 22% were diagnosed and received treatment of some kind. Therefore, a total of 270,000 subjects would be diagnosed and treated for COPD multiplied by the annual average obtaining a total of $506.52 million annually in direct healthcare costs generated by COPD.
In a top-down calculation the hospital costs accounted for 36.3%, the expenses attributed to drugs 42.2% and the clinical consultations and diagnostic tests 22.5%. In the study using the bottom-up focus the hospital costs represented 43% of the total, drugs 40% and consultations and complementary tests 17%.
Despite the differences observed in the absolute values between the two types of studies, the distribution of the costs was very similar. If the total COPD direct cost is divided by the total Spanish population, healthcare for COPD costs each citizen $13.32 annually [65-67].

Scandinavia

The cost of COPD in Denmark amounts to 10% of all healthcare costs. The annual cost of pharmacological treatment in Scandinavia is today around €100 per inhabitant. The cost in Denmark rose from about €2 billion in 2004 to €3 billion in 2008 [68]. This huge cost is mainly covered by the public health system, some private insurance and to a minor degree by the patients themselves.
There are large differences between regions in the prescribing pattern of drugs with the same effect and side effect profiles but in some cases a 10-fold difference in cost is reported. The general guidelines for managing a disease entity are usually formulated by scientific societies, and agreement about the general use of medication by classes based on a stepwise approach according to severity is usually reached among specialists. A regulated practice has developed by law for pharmaceutical substitution in the pharmacy, i.e. the pharmacy shall deliver another and cheaper medication to the patient than the one written on the prescription form if the drugs contain the same active substance in the same amount and are used in the same way.
Each country has its own reimbursement system, that comprises a common part which applies to everybody and special rules for patients in specific circumstances. In Denmark the first €115 spent for the purchase of drugs is not reimbursed (however, in the case of age < 18 years there is a 60% reimbursement also of this cost segment provided). The % reimbursement increases gradually to 85% with purchases above €400 in all age groups. However, persons with chronic diseases pay up to a maximum of €450 out of their own pocket, and will have all additional costs covered. In special cases it is possible to apply for reimbursement of specific drug treatments, and to have additional cost cover if required by the personal economic situation, or special support for terminal care and treatments.
A special group of people are the illegal immigrants, who have no public or private insurance and have to face serious problems when falling ill. They can in principle only be treated for acute severe disease and are then transported to their homeland as soon as possible, whereas management of the cost of chronic diseases is at their own total expense.

Italy

The cost-of-illness for COPD in Italy was calculated in 2002 from data collected by 28 Lung Units within the framework of the National Health Service (NHS). Mean cost/patient/year ranged from €1,500 to €3,912 according to the illness severity. Direct costs, hospitalizations and emergency room (ER) admissions, in particular, represented the main cost driver [69]. Unacceptable levels for underdiagnosis and mistreatment of COPD were also underlined in that study.
In a further investigation, the mean societal cost of COPD was €1308/patient/year: as 75% of cost was due to hospitalizations, a more effective strategy for managing and controlling COPD exacerbations was further strongly recommended in order to alleviate the burden of this disease in Italy [70].
When investigating the effectiveness of different therapeutic interventions in terms of outcome optimization, it was found that both a prompt diagnosis of disease and exacerbations, together with an appropriate long-term therapeutic approach, represent the most effective strategy to optimize all outcomes related to the disease, and to substantially reduce the impact of COPD on patient, healthcare system and society [71].
In 2008, health resources consumption and costs generated by COPD were calculated on a national basis, in a real-life setting of 1-year duration, and according to a bottom-up, observational, prospective multicentric study. At the end of the survey, outcomes were compared with those of the previous year [72]. A total of 748 patients were recruited, and 561 were defined as eligible; the proportion of moderate and severe COPD was 53.7% and 16.8%, respectively. Mean total cost/p/y was €2,723.70, ranging from €913 to €5,452 according to the disease severity. At the end of the survey, the demand for health services had dropped significantly compared to baseline: GP visits by 57.4%; ER use by 12.5%; hospitalizations by 18.4%. Furthermore, even if direct costs remained the main driver of cost, the mean total cost per patient dropped by 21.7% ($p < 0.002$), mainly due to a much more appropriate interventional and therapeutic strategy. When compared to previous studies, these data identified that the mean total cost/patient/year of

COPD doubled in a 5-year period in Italy: this trend has been also registered in other countries (such as USA) over the same period. Despite this, and despite the fact that individual costs for COPD exceed by 67.7% the mean per capita expenses of the National Health System, appropriate treatment for COPD does not seem to reach more than a limited 20% of patients.

Data from a recent cross-sectional study support the evidence that also moderate COPD represents a substantial economic burden for healthcare systems, and strongly indicate both the clinical and the economic convenience of an earlier, long-term therapeutic intervention in these circumstances [73].

ROLE OF INSTITUTIONAL PLAYERS IN ITALY

The Italian NHS, National Health Service

In the 19th and first part of the 20th centuries, the prevalent diseases were infections of an epidemic nature (such as cholera, tuberculosis, poliomyelitis) and the role of the state was in the first place to guarantee drinkable water, sewage disposal and improved conditions of life and in a second phase to help protect the population through programs of mass vaccination against disorders not being controlled by the improvement in public hygiene. In the last fifty years - following progress in medicine and in the organization of the social state - Italy (as other developed countries) has seen a radical change in disease epidemiology and the main causes of death, and this change has thrown the NHS into crisis.

As a matter of fact, the chronic invalidating disorders that dominate the scene today cannot be managed with the old hospital-centred model, based on response to acute situations: the system has to be readapted to the present epidemiological situation. Today, diseases are linked to individual lifestyle rather than to global living conditions, and hence the role of the state is no longer to choose and implement the best health options on behalf of citizens but rather to help citizens themselves choose the best options, through education, health information and the provision of integrated services of primary, secondary and tertiary prevention.

The number of people affected by chronic bronchopulmonary disorders is predicted to rise substantially as the average age of the population increases. In the absence of corrective measures, health costs might more than double by 2050, becoming unsustainable for the NHS. For this reason a radical change in the organization of the NHS is deemed necessary by political authorities, also in relationship to the heavy crisis that has recently hit the world economy. The future of the NHS will thus be focused on primary prevention and early diagnosis and rehabilitation (helping citizens to reduce the invalidating consequences of diseases with the least possible impact on the community).

These changes of the NHS will take place in the context of an overall change in the whole welfare system, centered on the idea that people first try to develop their own resources to respond to their needs, and live in a free and responsible manner, actively participating in society. The new approach to welfare must orient people towards active behaviour and responsible lifestyles, preventing situations of need due to physiological events (infancy, maternity, old age) or pathological events (disease, accident, disability) or to particular economic situations (business or employment crises, unemployment, end of work). In this context, health does not mean simply 'treating the disease' but rather a priori promoting wellbeing and developing personal abilities, taking the different individual conditions into account. The citizen's active participation, a correct information and health culture, a renewed relationship of trust between family doctor and patient, are the premises for promoting healthy life in the active society.

Ministry of Health

The Ministry of Health must play a fundamental role in the implementation of policies against cigarette smoking, indoor and outdoor pollution, obesity, and communicable diseases. Presently, these actions are not well integrated, and this poor coordination is an important limitation for the NHS.

Signs of the new importance now being attributed to respiratory diseases are the fact that the Italian National Health Plan 2006-2008 placed chronic respiratory diseases among its four top health priorities, and the Ministry of Health launched in 2009 GARD-Italy, the Italian counterpart of the Global Alliance against Chronic Respiratory Diseases (GARD) of the World Health Organization (WHO), a voluntary alliance of national and international organizations, institutions and agencies that has as its goal to reduce the global burden of chronic respiratory diseases. The main objective of GARD-Italy is to promote the development of a global chronic respiratory disease program in Italy. Effective prevention implies setting up a health policy with the support of health care professionals and citizen associations at the national, regional, and district levels. What is required is a true inter-institutional synergy: prevention of respiratory diseases cannot and should not be the responsibility of physicians alone, but must involve politicians/policymakers, as well as the media, local institutions, school, and food producers. GARD may represent a significant experience and a great opportunity for Italy, and a means to implement the GARD vision of a "world where all people can breathe freely".

Regional Health Services

The AGE.NA.S (National Agency for Regional Health Services) has, among its activities, the task of coordinating at national level the elaboration and dissemination of clinical and organizational guidelines. The strategic use of guidelines allows to evaluate the quality of the services based on scientifically valid principles, recognized by operators and decision makers alike. In fact, guidelines constitute a primary source for the identification of indicators useful for the assessment of appropriateness; they

are also a means of communication among professionals and of information to citizens.
Guidelines have been criticized for how they rate the quality of evidence and the strength of recommendations, although with the development of systems such as GRADE (Grading of Recommendations, Assessment, Development and Evaluation) this limit has been partly overcome. Concerns now remain about the need to elaborate ad-hoc initiatives for the correct implementation of guidelines at national and local (regional) levels. For several clinical conditions, including COPD, limited information is available about current practice versus standards of management as recommended by the guidelines. Significant deviations between current practice and guidelines regarding the prescription and selection of diagnosis and treatment options have been found for COPD in Italy [6].
Alongside this comes the rational use of health resources and the choice of diagnostic and therapeutic paths according to priorities which should be established on the basis of the best available evidence. Therefore, in the development of guidelines all efforts must be addressed to the evaluation and selection of interventions with a cost-effective profile.

Local health authorities and services

The actual setting in which the NHS changes described above need to be planned and carried out is the local district, i.e. it is here that the integrated responses to people's real and potential needs are put into effect, where the social and health services aimed at prevention, early diagnosis, primary care, and home care have to be developed.
This means that, in the short term, a homogeneous management of the social, health, and welfare services must be achieved at the local level, in order to create a continuum between systems of healthcare and those for social protection. Such an integrated management sees the social and health districts as the citizens' point of reference and the place where this integration may occur effectively.
At organizational level, the health care for chronic respiratory diseases, and COPD in particular, will resemble that for other chronic disorders such as diabetes. The goal is to increase the possibilities of self management for the patient, and give more responsibility to general practitioners (GPs), promoting the use of telemedicine and home care. In the specific field of pulmonology, the NHS must undertake in each local health service [74]:

1. to prevent respiratory disease developing through a substantial reduction of the number of smokers in the community and strict control of risk factors;
2. to improve and anticipate diagnosis, in particular for COPD and asthma, through a more widespread use of spirometric tests and specialist expertise;
3. to help patients to self manage their own disease, through health education and pulmonary rehabilitation;
4. to integrate the care of patients affected by respiratory diseases, by linking specialist care to primary care, and extending end of life treatment to non-oncological conditions.

Particular mention must be made of pulmonary rehabilitation: since the publication of national and international recommendations there has been significant progress in both techniques and outcome measurement, not only for COPD but also for other respiratory disorders [36]. Pulmonary rehabilitation has been largely under-prescribed up to now [6] but at present it is undergoing great development in Italy, although not homogeneously throughout the whole national territory.

Role of the pulmonary specialist

Healthcare planning

An appropriate management of chronic respiratory diseases, based on solid epidemiological data, requires today a global approach defining the best care for the patient throughout the entire course of the disease, and in a sustainable way for the community. Numerous initiatives and studies are under way everywhere. One of these is the Global Alliance against chronic Respiratory Diseases (GARD), an ensemble of national and international organizations guided and coordinated by the World Health Organization (WHO). The role of the pulmonary specialist at global and national level has been delineated within the context of GARD's strategies and corresponding actions [75].
In Italy, the Ministry of Health – which defined chronic respiratory disorders as a priority of the national Health Program 2006-2008 and hence finalized, with the National Agency for Regional Healthcare Services (AGE.NA.S), national guidelines for COPD – launched in 2009 GARD-Italy [76].
Respiratory specialists are involved in the "central" planning phase of all these initiatives, while other specialists play a role in the "peripheral" phase of implementation. Further on, these same specialists will verify the applicability in the real world and the final efficacy of what has been planned and implemented.

Implementing healthcare strategies

Patients affected by chronic pulmonary disorders are at present managed in a discontinuous and non integrated mode with inappropriate care procedures. Prevention, too, is neither systematized nor integrated. Inappropriateness costs both the individual and the community. It has been calculated that GBP £1.3 billion are spent each year in the U.K. for Emergency Care admissions (3-4 visits per patient) for a series of 18 diseases, COPD being at the top of the list and asthma in third place. Varying percentages of these visits resulted inappropriate at a retrospective analysis [77]. An optimal management of chronic diseases would simultaneously prevent the crowding of Emergency Care facilities, and improve the global healthcare costs and the quality of life of those affected.
The long-term goal must be to reduce the incidence of respiratory disorders, through a more effective

prevention, while in the shorter term the target is to reduce - in an economically sustainable way – the social and economic burden generated by those already affected, through more appropriate disease management.

The specialist has a definite role to play in primary prevention, early diagnosis and rehabilitation, as guide or coordinator or consultant depending on the type of intervention, in close cooperation with primary care physicians, other health professionals, and patient associations. In concrete terms, the specialist will build up a network in which the Operational Unit functions as the junction for the whole course of respiratory care, from primary prevention to palliative care, according to the following scheme of action:

- *in primary prevention:* implement smoking cessation, increase the opportunities for screening for COPD and associated conditions;
- *in secondary prevention:* increase accessibility to lung function assessment, experiment screening models for associated conditions, e.g. lung cancer;
- *in improvement of patient management:* further reduce hospitalization through integration with services available in the local community, e.g. home hospitalization, monitoring of patients with chronic respiratory failure, health education, telemedicine; test a model of pulmonary rehabilitation provided in the local territory; expand and rationalize semi-intensive treatment; promote the extension of palliative care to patients with severe respiratory failure.

Healthcare planning for respiratory diseases must reappraise its whole "mission" and reorganize the specialist network based on a redefinition of the role of the specialist. Having as a main target the need to promote health rather than treat a disease and to shift in-hospital to out-hospital care in a patient-centered vision, the goal in practical terms is to achieve greater possibilities of self-management for the patient, greater involvement of primary caregivers, through use of telemedicine, optimal exacerbation management, and more options for dedicated and planned home care.

The model for the hospital pulmonary unit is analogous to that of modern cardiology (i.e. intensive management of the acute episodes in the hospital) while the model for the local community is similar to the one existing for the services of diabetology (i.e. specialist consultation and guidance) with particular focus on self-management and pulmonary rehabilitation for patients with respiratory failure. The hospital specialist, who needs to be integrated in a Specialist Unit in order to have full knowledge of all the aspects, maintains the direct management of emergencies. For this the Pulmonology Unit must be an integral part of Intensive care and not part of the medical ward, and its role in activities of non invasive respiratory intensive care needs to be recognized and promoted.

There is evidence that information and communication technologies (ICT) can play an enabling role over the whole range of services, from life-style and self-management of health to improving health related quality of life of patients as well as managing chronic disease conditions [78]. Properly designed innovative health services supported by ICT could have a positive impact on chronic disease modulation and prognosis, shifting resources from traditional acute care to integrated long-term home care, focusing on early diagnosis and prevention of exacerbations.

Despite the many advances and acknowledged potential of technology, ICT adoption in healthcare has lagged behind the scene. The barriers to ICT originate at different levels and are associated to a series of technological, cultural, legal, and market related factors. Adoption of ICT in healthcare is currently a major priority in Europe as shown by the major e-health deployment initiatives (e.g. epSOS) launched through the Competitiveness and Information Framework Program [79].

Role of the general practitioner (GP)

In a reformed NHS, one will need to go beyond the concept of "integration" between hospital and local territory in favour of a new interdisciplinary and inter-professional approach placing the person at the centre of the management process (which must flow without discontinuity). In this vision, the hospital will return to its "historical" role as a provider of emergency and acute care while the general practitioner, no longer operating "in isolation" but in a collaborative network in association with other professionals, will be the patient's first reference point for any health problem and the real case-manager throughout the whole course of a disease requiring complex interventions. The use of a personal electronic dossier containing all relevant information about the patient is now adopted by many GPs in Italy and is an extremely useful tool, but it should become a general standard nationwide, shared by all professionals involved.

Due to its increasing prevalence, COPD is considered a social disease which necessitates special attention at primary care level.

GPs have a central role in disease prevention, detection, treatment, and management. Smoking cessation intervention is the cornerstone for preventing COPD: the offer of brief advice by the GP to every smoker who visits the GP's office is becoming a rule, as well as GPs' growing awareness of belonging to the wider network of anti-smoking services. The manifold contacts on a yearly basis with their patients who smoke allow GPs to carry out early detection by means of spirometry, and to collaborate with pulmonologists if needed. COPD treatment should be based on regular therapy with inhaled drugs (long-acting bronchodilators and steroids) to ensure a good quality of life.

Prevention and treatment of exacerbations is of the utmost importance: avoiding airborne pollutants (environmental tobacco smoke and urban pollution) is mandatory, while early recognition of an

exacerbation, and starting oral steroids and antibiotics courses, are the cornerstone of good practice by GPs. Finally, COPD management must be based on planning regular clinical and functional follow up.

Role of patients' associations

The right to health, as defined in the Italian Republic's Constitution, is one of the fundamental rights of an individual. The search for a different, new balance in which it is the individual, and not the disease, at the centre of the system, requires a greater responsibility on the part of all the players involved - including the patient - with the aim of preventing or delaying the development of complications.

Interventions must be coordinated among scientific societies, professional associations, volunteer organisations, and public and private institutions.

It is then necessary to develop profiles for care based on a multidisciplinary approach and ensure continuity among actions for prevention, cure and rehabilitation, with inter-sectorial interventions, both medical and social, involving the family and the volunteer organisations.

In the approach to chronic diseases in general, and to COPD in particular, we must work to empower the people, i.e. enable subjects to participate actively in the therapeutic choices and in the decisional process aimed at improving quality of life and preventing complications.

Patients must be helped to acquire "ability" through a better knowledge of the disease and treatments available. Indeed, knowledge is essential to obtain a good level of healthcare with the patient placed at its centre. On the other hand, it is also necessary that the healthcare system and social services become aware of people's needs, and are able to work together to trigger a process of improvement, in respect of the individual's rights and freedom.

To conclude, we are all confident that new studies on the pathogenesis, pathophysiology, and pharmacology of COPD will give us new insight into how best to classify and treat at clinical level what likely is a set of different disorders with the same label. At the same time, it is not out of place to reiterate that the real challenge for achieving an appropriate approach to COPD - from both the individual's and society's point of view - is to effectuate a conceptual revolution in the context of long-term healthcare, in the sense that a patient-tailored attitude must prevail over the old concept of a rigid health system offering a very limited range of solutions to different problems. Such a change has started, but we are still far from reaching a satisfactory set of minimal recommended standards [80]. There is wide opportunity for quality improvement and the scientific societies of pulmonary specialists can play a pivotal role in implementing recommendations and developing research for reliable performance measures that are necessary in the search for efficacy, efficiency and equity in the management of COPD as of all other chronic disorders.

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