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The Epidemiology and Economics of Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease responsible for a large human and economic burden around the world. Cigarette smoking is the main risk factor for COPD in the developed world, although other important risk factors include occupational exposures, air pollution, airway hyper-responsiveness, asthma, and genetic predisposition. In most of the world, COPD prevalence and mortality continue to rise in response to increases in smoking, particularly by women and adolescents. COPD is also an important cause of disability, and is linked to comorbid diseases, such as depression and cardiovascular disease, which adds to the large economic burden associated with this disorder. Better public health and medical interventions that target both the risk factors for COPD and look toward earlier intervention may decrease the growing public health impact of COPD.

Keywords: chronic obstructive pulmonary disease; morbidity; mortality; prevalence

THE GLOBAL BURDEN OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease, responsible for a large human and economic burden around the world. It is currently the fourth leading cause of chronic morbidity and mortality in the United States, and, within the next decade, will surpass stroke to become the third leading cause of death (1).

The most important risk factor for COPD in the developed world is cigarette smoking (2, 3). Other factors, including occupational or environmental exposures to dusts, gasses, vapors or fumes (4), exposure to biomass smoke (5), malnutrition (6), early-life infections (7), genetic predisposition (8–10), increased airway responsiveness (11, 12), and asthma (12–14), are also important in some individuals. Recent research has focused on the role of gender in both the prevalence (15, 16) and progression or prognosis (17) of disease, with no clear answers so far. Similarly, the role of genetics beyond the well established α_1 -antitrypsin deficiency is a subject of extensive research (18).

This report reviews the current estimates of the burden of COPD with regard to disease prevalence, limitations, morbidity, mortality, and costs. In addition, we describe how COPD is perceived by patients, clinicians, and society, and how this perception affects disease interventions.

DEFINING COPD

The GOLD (Global Initiative for Chronic Obstructive Lung Disease) has classified COPD as “a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases” (19). This definition has, in large part, been adopted in the new American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines, with the important observation that COPD is both preventable and treatable (20).

The current GOLD and ATS/ERS definition for airflow limitation is an FEV₁:FVC ratio of less than 70%, measured with post-bronchodilator lung function (19, 20). Although this “fixed” ratio is easy to remember and simple, there is some concern that it may underestimate COPD in younger populations, overestimate it in older ones, and misclassify other patients (21, 22).

The GOLD and ATS/ERS criteria classify COPD into four stages (19, 20):

- Stage 1 (FEV₁ $\geq$ 80% predicted)
- Stage 2 (FEV₁ 30 to < 50% predicted)
- Stage 3 (FEV₁ 30 to < 50% predicted)
- Stage 4 (FEV₁ < 30% predicted)

In addition, an “at risk” stage (formerly known as GOLD stage 0) consists of patients with chronic respiratory symptoms (cough, sputum, or dyspnea) and normal lung function. Although this stage has been removed from the 2006 GOLD update because of data suggesting that this stage may not progress to GOLD stage 1 and higher COPD (19, 23), people with symptoms and normal lung function have lower quality of life and a higher risk of hospitalizations and mortality in follow-up (24, 25).

Although lung function measurement remains important for the diagnosis of COPD, other factors have emerged as being important predictors of both the quality of life and the survival of patients with COPD. Some of these factors include fat-free body mass (26, 27), functional status (28, 29), exercise capability (30), respiratory symptoms other than cough or sputum (31), and the presence of comorbid diseases, such as depression or heart failure (32, 33). Although these factors have not been formally included in the definition of COPD, they are clearly important, both clinically and epidemiologically, and need to be considered in the evaluation of patients.

COPD PREVALENCE

In national surveys in the United States, the primary means by which the prevalence of COPD has been determined is by asking adults whether they have had any 1 of 17 respiratory diseases in the past 12 months. Three of the diseases asked about in this list are chronic bronchitis, emphysema, and asthma, with the estimate of COPD prevalence made by counting the cases of chronic bronchitis and emphysema. The National Health Interview Survey is an annually conducted, nationally representative survey of about 40,000 U.S. households (34). During 2000, an estimated 10 million adults in the United States reported “physician-diagnosed COPD” (35). A major limitation of this approach

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is that a large proportion of COPD remains undiagnosed and would not be detected by asking about diagnosed disease.

With the NHANES III (Third National Health and Nutrition Examination Survey), it was possible to determine the presence of airway obstruction, the prevalence of diagnosed COPD, and the estimated prevalence of COPD in the population. The GOLD definition of COPD (stage 1 or higher) resulted in prevalence estimates of 23.6 million adults aged 18 years and older (13.9%) with COPD. An estimated 2.4 million of these adults, or 1.4% of the population, had GOLD stage 3 or 4, with an FEV₁ of less than 50% of the predicted value. Thus, the majority of the subjects classified as having COPD by GOLD criteria have mild or moderate disease.

The overlap between reported respiratory symptoms, diagnosed disease, and impaired lung function in a population can vary. In a representative sample from the United States, less than half of the participants with evidence of GOLD stage 1 or higher COPD had ever had a diagnosis of any respiratory disease (36). The “best” means of determining the burden of COPD in the population is probably by measuring lung function, in that this measurement is least likely to be affected by any type of diagnostic or reporting bias, and lung function is a reasonable predictor of mortality and functional limitations (37, 38).

A review of international COPD prevalence estimates was published by Halbert and colleagues in 2003 and updated in 2006 (39, 40). The literature reports several different methodologies to estimate the prevalence of COPD, including those based on spirometric measurements, reporting of respiratory symptoms, reporting of diagnosed “disease,” and expert opinion. Most estimates of COPD prevalence in the adult population were in the 5 to 10% range, although these did vary by the specific criteria used (39, 40). The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study from South and Central America, published in 2005, provided a consistent methodology to assess disease prevalence with estimated prevalence of 7.8 to 19.7% of GOLD stage 1 or higher COPD (41). Finally, the BOLD (Burden of Obstructive Lung Disease) Initiative, which has been collecting data since 2004, with anticipated publication in 2007 (42), will provide international estimates of COPD determined using the same methodology and equipment from 14 different countries.

Although the measurement of lung function remains the best way to diagnose COPD, the routine use of spirometry in the periodic assessment of the adult patient remains controversial (43–45). This controversy is, in part, because no randomized clinical trial, at the time of the review by Wilt and colleagues (44), had demonstrated that earlier detection of COPD either changed the course of disease or increased the rate of smoking cessation. Recent studies, however, are starting to suggest that knowledge of COPD might increase smoking cessation (46), and that interventions other than smoking cessation may alter the natural history of COPD (47). In addition, the recent availability of inhaled therapies for nonrespiratory disease, such as diabetes (48), may result in increased use of spirometry in the general practitioner’s office.

COPD LIMITATIONS

Another manifestation of the importance of COPD is its effect on limitations and health-related quality-of-life measures associated with the presence of disease (35, 49, 50). The presence of lung function impairment is associated with lower quality of life and more limitations that, in general, are worse when lung disease is more severe (51). This relationship has been established across cultures and while using different instruments, such as the

St. George’s Respiratory Questionnaire (29), the Short Form-36 (52), and the Clinical COPD Questionnaire (53).

Limitations in the population have been established using disability-adjusted life years (DALYs) (54). Worldwide, COPD is expected to move up from the 12th leading cause of DALYs in 1990 to the fifth leading cause in 2020 (55). By 2001, COPD was the ninth leading cause of DALYs globally, accounting for 2.5% of the global burden of DALYs and 4.8% (fourth leading cause) of deaths (56).

COPD MORBIDITY AND COMORBIDITY

During 2000, COPD in the United States (35) was responsible for the following:

- 8 million physician office and hospital outpatient visits
- 1.5 million emergency department visits
- 726,000 hospitalizations
- 119,000 deaths

COPD is also associated with significant comorbid disease, such as cardiovascular disease and cancer. In a nationally representative sample of 47 million hospitalizations from 1979 to 2001, patients discharged from the hospital with a diagnosis of COPD were more likely to be hospitalized with pneumonia, hypertension, heart failure, ischemic heart disease, pulmonary vascular disease, thoracic malignancies, and ventilatory failure when compared with age-adjusted patients discharged without COPD. Furthermore, having a diagnosis of COPD was associated with higher age-adjusted in-hospital mortality for pneumonia, hypertension, heart failure, ventilatory failure, and thoracic malignancies when compared with patients who were discharged with these comorbidities but did not have a diagnosis of COPD. These results suggest that the burden of disease associated with COPD is largely underestimated, as having a diagnosis of COPD is associated with increase risk for hospitalization and in-hospital mortality from other common diagnoses (57).

Similar findings of comorbid disease have been replicated in other populations. In a study of 38 patients with COPD and matched control subjects without COPD, the prevalence of metabolic syndrome was 47 versus 21% (58). In a large population of patients newly diagnosed with COPD compared to a control population, the incidences of myocardial infarction and angina were nearly doubled in the COPD population (59). In a clinical series of 405 patients with COPD with a COPD diagnosis, 83 (20.5%) had previously unrecognized congestive heart failure (60). Depression and anxiety were four to five times more prevalent in a study of 114 patients with COPD compared with matched control subjects, with evidence of a greater effect in women with COPD (61). Fat-free body mass is decreased in a large proportion of patients with COPD, and there is evidence of women being disproportionately affected (62).

COPD MORTALITY

During the period 1980–2000, the most substantial change in COPD mortality in the United States was the increasing rate for women—from 20.1/100,000 in 1980 to 56.7/100,000 in 2000—compared with the more modest increase in the death rate for men—from 73.0/100,000 in 1980 to 82.6/100,000 in 2000. In 2000, for the first time, the number of women dying from COPD in the United States surpassed the number of men dying from COPD (59,936 vs. 59,118) (35).

One of the limitations of the mortality database is that the deaths of many decedents with COPD were attributed to another cause (63). In 1998, only 45.4% of the 233,610 decedents with COPD mentioned on their death certificates had this ultimately

listed as the underlying cause of death. These findings have been replicated in other studies (64, 65), despite studies showing that people with COPD listed anywhere on their death certificate frequently had severe COPD (66). Progressive respiratory failure accounts for approximately one third of the COPD-related mortality; therefore, factors other than progression of lung disease must play a substantial role (67, 68).

COPD COSTS

COPD is a very costly disease in the United States, with estimated direct medical costs in 1993 of \$14.7 billion (69). The estimated indirect costs related to morbidity (loss of work time and productivity) and premature mortality is an additional \$9.2 billion, for a total of \$23.9 billion. By 2002 this cost was estimated at \$32.1 billion (70). Because COPD is frequently not listed as the underlying cause of death or the primary reason for hospitalization, these cost estimates may underestimate the true cost of COPD. For example, the "Confronting COPD" survey estimates the annual societal costs of COPD per patient in the United States as \$5,646, ranging from \$2,000 among patients with mild COPD to \$16,000 among patients with severe COPD (71, 72). Using these estimates among the 10–12 million adults in the United States with COPD yields cost estimates of \$60 billion to \$70 billion, annually. The estimate from the "Confronting COPD" survey was similar to that obtained in an analysis of the 2000 Medical Expenditure Panel Survey of \$4,932 for direct medical costs (73).

Additional estimates of the costs associated with COPD have noted a significantly higher burden of disability (22.8 vs. 7.3%) in a population aged 40–63 years, with a higher cost (\$8,559 vs. \$5,443) (74). Another important cost associated with COPD relates to end-of-life care, where one analysis showed a higher rate of intensive care unit hospitalization and higher costs during their last 6 months of life compared with patients with lung cancer (75). Finally, there is a great deal of variability in the international estimates of the annual societal cost of COPD per patient (Europe and North America), ranging from \$1,361 (The Netherlands) to \$6,475 (Spain) (71).

PERCEPTIONS OF COPD: THE PATIENT, THE PHYSICIAN, AND THE PUBLIC AT LARGE

Despite the enormous impact of COPD on the health of millions of patients around the globe, considerable evidence exists that patients, physicians and other health care providers, and the public at large do not recognize what COPD is and greatly underestimate its impact. Although terms such as "emphysema" and "bronchitis" have some public recognition, the term "COPD" has relatively little. In the Confronting COPD International Survey (50), only 23% of 3,300 United States and European subjects identified by a telephone survey reported COPD as their primary diagnosis, whereas 26% reported emphysema and 36% reported chronic bronchitis. In a 2002 public survey commissioned by GOLD, when asked "Have you ever heard of COPD?" only 15% of Americans recognized that COPD is a disease of the lungs. Unprompted responses in other countries surveyed (Germany, Brazil, and mainland China) were even lower (76). The results of the GOLD survey underscore the challenge faced by the pulmonary community in educating people worldwide about COPD. This education is especially necessary with elected public officials and individuals committed to philanthropy, because the public health impact and cost of the illness continues to grow.

It is apparent that many patients with COPD, despite considerable disability, greatly underestimate the severity of their disease. When breathlessness is measured by the Medical Research

Council (MRC) severity scale, patients with COPD demonstrate a large gap in their perception of disease severity and actual performance status (50). A total of 36% of patients who are too breathless to leave the house (MRC level 5) considered their disease mild or moderate, and 60% of patients who have to stop for breath every few minutes when walking on level ground (MRC level 4) also believed that their disease was mild or moderate. The reasons for this disconnect are undoubtedly complex. Patients are generally optimistic about the benefits of proper COPD disease management. Despite marked limitations on activities of daily living, most believe that, with proper treatment, it is possible to lead a full and active life (77). On the other hand, fear of repeated hospitalizations, nursing home placement, and dying may lead to denial and undertreatment.

An overwhelming number of patients with COPD believe that they brought their lung condition on themselves because of their smoking habit. This reinforces the stigma and guilt that many patients feel (78). This is similar to what is also seen in lung cancer, where patients are frequently stigmatized (79). This stigmatization extends beyond the patient and to the public health and research establishment. For example, funding for research into "tobacco-induced" cancers, such as lung cancer, was 10–15% of that for breast or prostate cancer when dollars spent per death were examined (80).

Clinical depression is a common and often profound comorbid condition that may greatly affect the illness perception of patients with COPD. It is commonly associated with other psychologic disorders. Anxiety has been found in as many as 37% of depressed patients with COPD. Depression may diminish functional ability and lower perceived quality of life. Depressed patients are less likely to follow treatment plans and more likely to be hospitalized. In addition, depressed patients with COPD are twice as likely (50% depressed vs. 23% nondepressed) to refuse cardiopulmonary resuscitative measures when questioned about end-of-life measures (81).

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* criteria for the diagnosis of a major depressive episode includes the following: (1) the subjective report of a depressed mood and/or (2) a significant loss of pleasure or interest in usual activities, and (3) at least four associated findings (including fatigue, sleep disturbance, feeling worthless, poor appetite, suicidal ideation, poor concentration, and agitation or slowing) for at least 2 weeks duration.

Considerable overlap exists between the symptoms of COPD and those of depression, and some of the overlap may result from a normal reaction to chronic illness. As a result, depression is underdiagnosed in patients with COPD. The best estimates of the prevalence of depression in COPD are between 25 and 50% (82). Web-based patient surveys (78) have shown similar results when the emotional impact of the disease is explored. A total of 45% of patients report being depressed, and 56% report a severe emotional burden due to their disease. In addition, 28% say they are embarrassed about the disease, and the same number report a feeling of being defeated. Women and younger patients with COPD are more likely to report these symptoms than men and older individuals.

Early identification and treatment of depression in the patient with COPD may benefit outcomes. Patients who are successfully treated show greater adherence to treatment plans, fewer exacerbations of COPD, and less delay in seeking medical attention when symptoms worsen. Despite these findings, depression in the patient with COPD is often undertreated. In one large cross-sectional study of patients with COPD and an anxiety and/or depressive disorder diagnosis, only 31% of patients were receiving psychiatric therapy (83). Clinical trials with antidepressants in patients with COPD have shown mixed results, and further

research in this area is needed. Patients are often reluctant to accept the diagnosis of depression, and, as a result, recruitment for such trials has been hampered. Side effects from the drugs have also been limiting. Clinical strategies have been suggested that use protocols similar to those used for subjects without COPD (84). In addition to pharmacotherapy, significant improvements in depression scores have been seen after cognitive therapy and pulmonary rehabilitation.

Little information is available regarding the attitudes, knowledge base, and perceptions of primary care physicians regarding COPD. One recent telephone interview of 400 internists and 400 family practitioners (Sidney Braman, personal communication) showed that 88% of internists and 85% of family practice physicians were very familiar with the term COPD. Nearly all felt that COPD was moderately or extremely serious. However, 69% of internists and 73% of those in family practice were unaware of professional guidelines (GOLD, ATS/ERS, etc.) for the diagnosis and management of COPD. Educational efforts for both specialists and primary care clinicians will undoubtedly improve patient care for patients with COPD in the future.

CONCLUSIONS

COPD is a preventable and treatable cause of morbidity and mortality around the world. Although there are several different means of determining the prevalence of COPD, spirometry is the most valid and offers valuable prognostic information. Determining the severity, prognosis, and optimal treatment of COPD requires additional clinical measurements.

Conflict of Interest Statement: D.M.M. serves on advisory boards for Boehringer Ingelheim, GlaxoSmithKline (GSK), and Ortho Biotech. He is on the speakers' bureau for Boehringer Ingelheim, Pfizer, GSK, and Dey, and has received research grants from GSK and Pfizer. S.B. has received industry research support from three companies (Boehringer Ingelheim, GSK, and AstraZeneca), amounting to \$200,000. In 2006, he was a consultant to GSK (\$5,800) on an advisory board. He has lectured and received support from Boehringer Ingelheim and GSK (\$12,000 in 2006).

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