Smoking Cessation in Patients With Chronic Obstructive Pulmonary Disease

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Introduction

As has been commented previously, respiratory disease has been identified as a medical research priority.[1] In a recent comprehensive analysis of Spanish scientific research, Camí et al[2,3] observed a notable increase in productivity in the field of respiratory medicine, not only in volume of work published but also in its impact.[4,5] The increase in research in this field has led to a corresponding increase in the importance and visibility of specialist journals dealing with respiratory medicine.[6]

There is no longer any doubt about the importance of respiratory diseases. Data on the frequency, morbidity, mortality, and social and economic repercussions of these diseases give some idea of their importance. In an epidemiological study published in 1997, 9% of people aged over 45 in Spain had chronic obstructive pulmonary disease (COPD), and this percentage reached 20% in the population over 65.[7] Analysis of the data on morbidity attributable to respiratory disease reveals a high rate of hospital admissions in 2001.[8] In recent years, there has been a steady increase in deaths attributable to respiratory diseases in both men and women, with the mortality rate rising from 80.7 per 100 000 population in 1991 to 102.2 per 100 000 in 2002. Similarly, the overall attributable mortality rate per 100 000 population for chronic diseases of the lower airways rose from 39.1 in 1991 to 41.5 in 2002.[9] According to national statistics posted on the Internet in 2004, respiratory disease as defined by the International Classification of Diseases (ICD-10, by sex and age in 2001) represented the third leading cause of death in Spain.[8]

While the appropriateness of the term COPD (and by extension its Spanish equivalent, EPOC) is still a matter of debate (for example the term COPD does not appear as a medical subject heading [MeSH] in the Index Medicus MeSH Browser[10]),[11-13] there is general agreement that the direct and indirect cost of caring for patients with the disease is rising gradually.[14,15] While spending is related primarily to hospital admissions[16,17] and in second place to the cost of medication, it is also affected by variations in clinical practice.[18] Another important aspect that needs to be analyzed is whether resources are being used in the most efficient way possible. Research has shown that the diagnostic methods and treatment protocols being used for COPD patients often diverge from the recommendations of current clinical guidelines, and such variation in practice further increases the financial burden associated with the disease.[19,20] Given the epidemiological, morphological, and genetic evidence now available, there is no longer any doubt about the etiologic relationship between COPD and smoking. Over 80% of COPD cases are caused by smoking, an indication of how that habit continues to represent a serious public health problem.

Consensus Recommendations and Guidelines for the Treatment of COPD and Smoking Addiction

A review of the latest Spanish and international guidelines for the management of COPD reveals that the weight of recommendations on smoking cessation remains small, although it must be said that the topic has received more attention in the most recent guidelines.

The guidelines published by the Global Initiative for Chronic Obstructive Lung Disease[21] in the section Component 2: Reduce Risk Factors, emphasize the importance of avoiding exposure to environmental tobacco smoke to prevent the development and progression of COPD. Moreover, they stress that smoking cessation is, in most cases, the most effective and cost-effective way of preventing the onset and progression of COPD (level A evidence). In the same section, these guidelines state that *a)* a physician's recommendation is effective and all smokers should be counseled at every visit (level A evidence), and *b)* that behavioral therapy—a combination of social support and the available pharmacologic therapies—should be used in the absence of contraindications in all smokers willing to quit (level A). These guidelines include a brief review of the components of the prevention programs and the therapeutic interventions that have been scientifically shown to be useful and effective in the treatment of tobacco dependence. They stress the importance of using such interventions in both smokers at higher risk for developing COPD and smokers already affected by the disease.

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While the recent guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) on the diagnosis and treatment of COPD recognize that smoking cessation is the most important preventative and therapeutic measure in diagnosed patients and the best way to prevent onset of the disease, they do not include any specific information on the treatment of smoking addiction in patients with COPD.[22]

Perhaps because of growing awareness of the importance of smoking cessation interventions, the authors of the NICE guidelines[23] published in 2004 included a comprehensive review of the literature on smoking cessation and dealt specifically with the treatment of smoking dependence in patients with COPD, rejecting studies that did not deal specifically with smoking cessation or that drew conclusions on the basis of inadequate samples. It is recognized that helping patients with COPD to stop smoking is the most important preventative measure that can be taken because lung function declines more slowly in nonsmokers and this clearly benefits the patients. Smoking cessation also slows the progression of the disease and prolongs survival. The conclusion is that smoking cessation is clearly beneficial in patients with COPD since FEV_1 declines less in nonsmokers than in those who continue smoking, and it is clear that stopping smoking produces a remission in the symptoms of the disease. With respect to the smoking cessation aids available to COPD patients, we must stress the efficacy of bupropion as compared to placebo and the fact that no one device for the delivery of nicotine replacement therapy has been shown to be better than any other. Consequently, except when contraindicated, both bupropion and nicotine replacement therapy used in conjunction with an appropriate behavioral support program are recommended for the treatment of smoking addiction in patients with COPD. If a patient has made an unsuccessful quit attempt with the support of these therapies, a new attempt should not be made within 6 months except when the failure can be attributed to an external factor, in which case the patient should be encouraged to try again immediately.

The objective of the new guidelines on the management of COPD developed jointly by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) entitled "Standards for the diagnosis and treatment of patients with chronic obstructive pulmonary disease," was to update the recommendations published in 1995.[24] While acknowledging the existence of the GOLD strategy document, the ATS/ERS guidelines aim to provide additional information concerning oxygen therapy, pulmonary rehabilitation, noninvasive ventilation, surgery, air travel, and sleep, as well as new information concerning the treatment of terminal patients in developed countries. The ATS/ERS guidelines also stress the importance of smoking cessation, and include a comprehensive review of smoking cessation treatment in general based on a wide-ranging review of the literature. In the context of COPD, they indicate that smoking accelerates the rate of decline in lung function, although they do recognize that individual susceptibility varies in accordance with the interaction of a series of environmental and genetic factors. Although only 20% of smokers develop COPD, this figure underestimates the real impact of smoking because most smokers lose some lung function and reduced lung function is a risk factor associated with increased mortality. Smoking cessation slows the progressive loss of lung function and reduces the patient's symptoms irrespective of when the diagnosis is made. On the subject of passive smoking, the ATS/ERS guidelines make the point that children born of mothers who smoke weigh less at birth and have a greater risk of developing COPD in adulthood. Moreover, passive exposure to tobacco smoke compromises lung growth and leads to diminished lung function in adulthood.

The ATS/ERS guidelines[24] include a general review of all the treatments and strategies that have been shown to be effective in treating smoking addiction to date and provide some specific information concerning smokers with COPD. They indicate that intervention in COPD patients must be intensive, and that physicians must clearly explain the risks of continuing to smoke in a nonconfrontational way to patients who are not willing to make a serious quit attempt while offering to help them limit the damage.

No specific information on helping COPD patients to stop smoking is included in any of the best general recommendations on the treatment of smoking dependence published to date, although in recent years a certain amount of information of this kind has been included tentatively. The most comprehensive recommendations published to date, drawn up by Fiore et al,[25] do not deal specifically with the question of patients with COPD; even 2 later articles published by the same working group fail to include any details about the treatment of smoking dependence in COPD patients.[26,27] In a paper that exhaustively analyzed the clinical efficacy, adverse effects, and cost effectiveness of the available smoking cessation therapies, Woolacott et al[28] concluded that nicotine replacement therapy was at least as effective in COPD patients as in the general population of smokers. Moreover, based on their analysis of data on the treatment of smoking dependence with bupropion, those authors explicitly state that there is evidence that bupropion is at least as effective in COPD patients as in smokers with no specific disease, although it must be said that this assertion was based on data taken from only a single study.

The SEPAR recommendations on the treatment of smoking dependence,[29] and the consensus document drawn up jointly by SEPAR and other Spanish scientific societies[30] explicitly state that there are no contraindications to the use of bupropion and nicotine replacement therapy in patients with COPD. The recommendations indicate that bupropion may in fact be more effective than nicotine replacement in COPD patients

and go on to stress that when nicotine replacement therapy is used, high doses should be prescribed in order to maximize the success rate.

Recent Review Articles on Smoking Cessation in COPD Patients

In recent years, a number of review articles have attempted to clarify the future direction of smoking cessation therapy in the context of COPD. The reviews published 2 to 4 years ago emphasize how important it is that patients who have been diagnosed with COPD stop smoking given that, other than oxygen therapy, smoking cessation is the only intervention that reduces mortality and the decline in lung function in these patients.[31-37] These articles only reviewed what was already known, and they stressed how important bupropion and high doses of nicotine replacement therapy would become in the future.[31] Furthermore, they stated that the available treatments yielded the same results in COPD patients as in the general population[32,33] and that COPD patients should stop smoking immediately.[34] In a review published in 2003, Donnelly et al[38] added the possibility of using an anti-nicotine vaccine in these patients. Another interesting paper was published by Sin et al,[39] who systematically reviewed the impact of all the available treatments for patients with COPD, comparing them with each other, with placebo, and with standard treatment. They did this by searching the MEDLINE and Cochrane databases to identify all relevant randomized placebo-controlled trials with a minimum follow-up of 3 months carried out between 1980 and 2002. One of the findings that emerged was that smoking cessation is the only treatment that slows the rate of decline in FEV_1. However, they observed that respiratory symptoms persist even in patients who stop smoking, so that even nonsmoking patients require additional therapy. They added that smoking cessation is the only measure that reduces overall mortality by 27%, but also acknowledged how difficult it is for smokers to quit and to remain abstinent.

In a comprehensive review of the benefits and risks of pharmacologic smoking cessation therapies in COPD, Wagena et al[40] found nicotine gum to be a useful treatment in smokers with COPD, and they further maintained that abstinence rates could be improved with a combination of nicotine replacement therapy and a behavioral program. The results tend to be better when the intervention is carried out by a doctor, although this difference is not statistically significant when a combined treatment regimen is used—individual counseling combined with group therapy—and when the behavioral therapy focuses on stress management and relapse prevention. Another interesting finding is that higher quit rates are probably obtained with 4 mg gum than with 2 mg gum. Since only 2 published studies have evaluated the nicotine nasal spray in patients with COPD, it is not known at this time whether this treatment is more effective than no intervention, placebo, or other therapies.[40] Further studies are necessary to establish its efficacy. Bupropion is an effective aid to smoking cessation in patients with mild to moderate COPD. However, this effectiveness was not sustained on follow-up after 12 months when the treatment was compared with placebo in one study.[40] Moreover, sustained abstinence on follow-up declined more in the patients who received bupropion than in the controls. In this respect, the authors pointed to the work of Tashkin et al,[41] who concluded that the success rates obtained using bupropion in patients with COPD are low. That trial will be discussed in greater detail below.

An interesting point discussed by Wagena et al[40] is the possibility that certain symptoms might be exacerbated by the smoking cessation therapy. If this were proved to be the case, it would be necessary to clearly distinguish which smoking cessation treatments should be used for each disease. García Río et al[42] advanced the hypothesis that since dopaminergic agonists are known to depress the ventilatory response to hypoxemia and hypercapnia (by way of a dopamine-mediated inhibition of the carotid body chemoreceptors), bupropion may depress peripheral chemoreceptor responsiveness to hypoxia, hypercapnia, or both, and that this could perhaps represent an additional side effect in COPD patients. However, in the opinion of Tashkin et al[43] while this effect could be important in patients with severe COPD, it would not be crucial in patients with mild to moderate disease.

Wagena et al[40] concluded that while the relapse rate in the first year is around 70% to 80% in the general population of people who try to stop smoking it is substantially higher among people with COPD. Consequently they stress that the prescription of cessation aids should be tailored more to the patient profile and should take into account certain patient factors including the presence of depression or depressive symptoms, the degree of dependence, and the type and severity of respiratory impairment. Identifying the profile of the patients who are highly motivated to stop smoking is a fundamental precondition to achieving better abstinence rates.

Some peculiarities related to the actual pathophysiology of the disease differentiate the smoker with COPD from the smoker with no known disease. Patients with airway obstruction have a different respiratory pattern; they tend to inhale more rapidly and deeply, and this may favor the deposition of external particles.[40] Furthermore, as the obstruction becomes more severe, expiration is prolonged. As a result, the lung does not empty completely when the patient is breathing normally, and this in turn alters the natural point of balance and gives rise to pulmonary hyperinflation. All of these factors favor the deposition of tobacco smoke particles in the upper airway and accelerate the progression of the airflow limitation.[40,44] There is also evidence that smokers with COPD are more nicotine dependent. In a work included in the IBERPOC study, Jiménez Ruiz et al[45] found that 30% of smokers with

COPD scored 7 points or more on the Fagerström test as compared to only 10% of the smokers who had no airflow obstruction. In an earlier work, the same authors summarized the smoking characteristics of patients with COPD.[46] They found that variables such as age, sex, educational level, and number of cigarettes smoked per day are all associated with the development of obstructive disease—more common in males with a low educational level, aged 46 or older, and smokers with a history of 30 pack-years. They found that COPD was more common among smokers who were highly nicotine dependent (as measured by the Fagerström test) and those who had higher exhaled carbon monoxide levels. Moreover, almost 50% of the COPD patients were in the precontemplation phase, and 35% of them had never made a serious attempt to stop smoking.

Other characteristics of smokers with COPD are related to the fact that the possibility of successful smoking cessation is lowered by the presence of clinical depression or, simply, by the presence of depressive symptoms. In effect, one of the characteristics of COPD patients is that they have a higher prevalence of psychiatric disorders[47,48] including depression because these comorbid disease are found in association with nicotine addiction; this makes sustained abstinence more difficult.[49-51] On the other hand, COPD patients who present chronic respiratory symptoms—mainly cough, expectoration, and dyspnea—are more motivated to stop smoking, especially if they believe their symptoms are caused by smoking. Such patients are 8 times more likely to stop smoking if they believe that their health will improve.[52]

Marlow et al[53] highlight another aspect specific to COPD in the treatment of smoking addiction. These authors point out that physicians have opportunities to encourage patients to stop smoking and they stress the importance of clinicians having a favorable attitude towards abstinence. They particularly emphasize the role of pulmonologists[54,55] because helping patients to stop smoking is part of the work of these specialists, they have the necessary knowledge, and they are usually good candidates for administering smoking cessation therapy.[56]

Treating Smoking Dependence in Patients With COPD: Research

Anthonisen et al[57] carried out a randomized clinical trial to determine whether the addition of a smoking cessation program to conventional bronchodilator treatment in patients with COPD would improve FEV_1 values. Patients were assigned to 1 of 3 groups: *a)* smoking intervention plus bronchodilator, *b)* smoking intervention plus placebo, or *c)* no intervention. The study enrolled over 5500 male and female participants with spirometric signs of early COPD aged between 35 and 60 years. The smoking intervention was intensive, with a program that included behavior modification therapy and nicotine gum; follow-up was 5 years. One of the conclusions drawn by the authors was that an aggressive smoking intervention program in middle-aged patients with early COPD significantly slows the rate of decline in FEV_1. However sustained smoking cessation was rare, with only 22% of patients abstinent after 5 years. In a complementary study, Murray et al[58] analyzed the side effects and cardiovascular consequences associated with this use of 2 mg nicotine gum. They found no evidence of serious adverse effects and concluded that the gum was a safe aid for preventing the onset of COPD. Moreover, they recommended that patients should be instructed on how to use the gum, and that the consequences of its use should be monitored in order to improve efficacy and minimize side effects. Using a pre-post-test design, Monninkhof et al[59] assessed the efficacy in COPD patients of a smoking cessation program involving minimal contact, a self-help manual, and pharmacologic therapy (nicotine replacement or bupropion). As the efficacy of this program among COPD patients was found to be comparable and similar to that observed among "healthy" smokers, the authors suggested that a more intensive intervention should be used in the case of COPD patients.

Gorecka et al[60] prospectively analyzed whether spirometric diagnosis of airflow limitation in middle-aged smokers in conjunction with advice from a doctor to stop smoking would influence the smoking cessation rate after a year, and whether successful outcome could be predicted. Overall, 52 (9.3%) of the smokers screened were abstinent after a year, and a further 45 (8.1%) stopped smoking for some time. While 30 (10.1%) of the patients with airflow limitation were abstinent after a year and 26 others quit for a shorter period, in the group with normal lung function, 22 (8.4%) were nonsmokers after a year and another 19 quit temporarily; these differences were not significant. Other significant differences were, however, found between the 2 groups: the smokers with airflow limitation smoked more cigarettes per day, had been smokers for longer, and differed in lung function. The smokers most likely to quit successfully were those who were older, had started smoking later, had lower levels of tobacco exposure, or had a greater loss in lung function. Gorecka et al also found differences between men and women in cigarette consumption and lung function. The predictors of successful smoking cessation were older age, lower accumulated exposure to tobacco—fewer pack-years, lower daily consumption, or later initiation—and a greater decline in FEV_1. In a Spanish smoking cessation study, the variable "success after 3 months" was found to be a predictor of abstinence after 6 months.[61] Gorecka et al reported that patients with moderate COPD had the highest success rates and, for all the reasons cited above, concluded that the diagnosis of airflow limitation, and probably the presence of respiratory symptoms, motivates patients with moderate to severe COPD to make a serious attempt to stop smoking. In a cross-sectional descriptive study undertaken to estimate the prevalence of COPD in smokers and ex-smokers over 40 years old, Jaén Díaz et al[55] also analyzed risk factors.

They found age over 50, male sex, and accumulated exposure to be associated with the onset of COPD.

Another question that arises in this context is whether patients who have been diagnosed with a disease (in this case COPD) tend to receive more smoking cessation support and services because of their condition, and whether this leads to higher abstinence rates in such cases. In a study of a large sample of smokers, Sherman et al[62] observed that individuals diagnosed with COPD reported that they had been repeatedly advised by their doctors to stop smoking and even that they had been prescribed pharmacologic smoking cessation therapy or had been referred to a specialized clinic. In any case, abstinence rates are similar among smokers with COPD and smokers with no disease. Sherman et al make the point that the reason for this could be that the intervention is being directed towards patients who are not interested in quitting (precontemplation), and emphasize that more work needs to be done to target this group.

In a study complementing the earlier work mentioned above, Gorecka et al[63] invited the 163 patients with airflow limitation who were still smokers—that is, excluding the 30 patients who quit on the advice of their doctor—to attend a smoking cessation clinic. The 70 patients who enrolled were assigned randomly to treatment with nicotine patches or bupropion. Follow-up visits were scheduled at 2 weeks, at the end of pharmacologic treatment, and at 6 months. All participants were telephoned a year later. After 12 months, 18.5% (13/70, 8 of the patients treated with nicotine patches and 5 who received bupropion) were still abstinent. When added to those who quit in the first phase on the advice of their doctors alone, this adds 4.5% to the quit rate for the group as a whole. Clearly, the outcome was poor, and this is probably partly due to the fact that follow-up was not at all intensive, without even taking into account the small size of the final sample. This highlights even more clearly the need for intensive intervention in the case of smokers with COPD.

Another question of interest is where to situate the cutoff point between smokers and nonsmokers when measuring exhaled carbon monoxide (CO) in patients with COPD. This question was partly answered by Sato et al[64] in a study designed to identify the optimal cutoff point for use when measuring exhaled CO in smokers and nonsmokers with asthma or COPD. Among other results, they found that mean (SD) exhaled CO in former and current smokers with COPD was 7.7 (4.3) parts per million (ppm) and 13.5 (6.5) ppm, respectively. The authors concluded that 11 ppm would be the optimal cutoff level to discriminate between smokers and nonsmokers with COPD. With respect to whether or not breath CO is a reliable marker for identifying a smoker, Javors et al[65] recently demonstrated that a breath CO value of 2 ppm or 3 ppm is a good indicator of abstinence during the preceding 24 hours.

As has been discussed in the NICE guidelines,[23] the recent medical literature includes a series of studies that investigate in greater depth how to treat smoking dependence specifically in patients with COPD. Van de Meer et al[66] recently undertook a meta-analysis in order to assess the effectiveness of various types of smoking cessation interventions in patients with COPD. The specific objectives were to compare different interventions: *a)* psychosocial intervention versus no intervention, *b)* comparison of various kinds of psychosocial intervention, *c)* psychosocial intervention and pharmacologic treatment versus no intervention, and *d)* comparison of various combinations of psychosocial and pharmacologic interventions.

The authors searched the principal international databases for randomized controlled trials in which the participants had a confirmed diagnosis of COPD. The selection criteria were very strict, and only 5 out of a total of 380 relevant trials fulfilled the pre-set criteria: Pederson et al,[67] Anthonisen et al,[57] Crowley et al,[68] Brandt et al,[69] and Tashkin et al.[41] When the results were analyzed, it was found that none of these trials compared psychosocial interventions with no treatment. Two of them compared different psychosocial interventions.[67,69] One of these compared an intervention group and a control group.[69] Patients in the experimental group received individual counseling and self-help materials and their respiratory disease was always referred to as "smoker's lung" (emphysema and chronic bronchitis). The implications and the scope of this designation were explained to the patients. Patients in the control group received individual counseling and self-help materials. Quit rates at 12 months were significantly better in the intervention group (40% as compared to 20%). In the other study,[67] intensive individual counseling in the experimental group was compared with a self-help manual and very little individual follow-up in the control group. The quit rate at 6 months in the experimental group was 33% as compared to 21% in the control group. Only 1 study, which has already been discussed earlier in the present review, compared psychosocial and pharmacologic interventions with no intervention.[57] It compared 3 groups of patients: experimental group 1, in which participants received individual counseling plus group therapy in combination with nicotine gum and bronchodilator treatment; experimental group 2, in which patients followed the same program but received placebo instead of the bronchodilator medication; and a control group in which there was no intervention whatsoever. The quit rates after a year were 34.7% in group 1 and 34.4% in group 2, but only 9% in the control group. On follow-up after 5 years, the sustained abstinence rate was 21% in group 1 and 21.8% in group 2, while in the control group it had fallen to 5.2%.

Two trials were found that compared different kinds of psychosocial and pharmacologic treatments. Tashkin et al[41] compared an experimental group that received individual counseling, telephone follow-up, and bupropion treatment with a control group that received placebo instead of bupropion. From week 4 to week 26, sustained abstinence was higher in the bupropion group (15.7% as compared to 9%) leading the authors to

conclude that bupropion is useful in the treatment of patients with mild to moderate COPD, although these results were not sustained over time. Another study[68] compared different combinations of individual counseling, self-help, and pharmacologic treatment. All 3 groups received the same pharmacotherapies and self-help materials, but the individual counseling varied. The overall abstinence rate at 6 months was 13.9%.

The conclusions of that Cochrane review indicate that there is evidence that a combination of psychosocial interventions and pharmacotherapy is more effective than no intervention or psychosocial treatment alone. It was also concluded that no convincing evidence had been found that any psychosocial intervention was effective in patients with COPD. Consequently, more studies are necessary to determine the characteristics of smokers with COPD so that treatment can be tailored to these patients.

If we go a bit deeper into the findings of Tashkin et al,[41] it is noteworthy that they found older age and a higher pack-year history to be predictors of successful sustained abstinence (weeks 4-7). However, the association between success and sex or the severity of COPD was not confirmed. They also found an association between successful outcome (abstinence) and the center where treatment was given. In effect, some healthcare facilities achieve significantly better results (higher abstinence rates) than others. Another interesting finding in this study was that the patients receiving bupropion during the treatment phase tended to gain less weight than those receiving placebo, although the differences were not significant. Moreover, patients treated with bupropion scored lower between weeks 4 and 12 on a scale used to measure withdrawal symptoms. The most common adverse events reported with bupropion were insomnia, headache, and dry mouth.

In a report of the completed Lung Health Study, Kanner et al[70] evaluated how the classic symptoms of COPD (cough, expectoration, dyspnea, and wheezing) varied over the course of the trial. They found that after 5 years the patients assigned to the smoking cessation intervention groups had fewer respiratory symptoms than those who were not. Also interesting are the following results of a trial by Scanlon et al[71] (also part of the Lung Health Study) that analyzed improvement in lung function among patients with COPD who stopped smoking: *a)* the annual rate of decline in FEV_1 over the 4 years of the study among those who stopped smoking was half that of continuing smokers (31 mL/year versus 62 mL/year); *b)* the factors that determined the improvement or stabilization of lung function were baseline FEV_1, baseline bronchodilator responsiveness, white race, methacholine reactivity, and age; *c)* there was end-point improvement in FEV_1 among those who stopped smoking after the intervention; *d)* patients with greater bronchial hyperreactivity improved more when they stopped smoking than did those whose response was less marked—in the first year both methacholine reactivity and bronchodilator responsiveness were independently predictive of change in lung function, but the latter was not predictive in subsequent years; *e)* lower initial lung function was a good predictor of later improvement, particularly during the first year; *f)* the effect of age was small, but younger people did benefit more; *g)* women improved more in the first year after quitting, but women who continued to smoke lost more lung function than did male smokers; *h)* heavy smokers benefited more from quitting, a phenomenon that appeared to be closely related to airway hyperresponsiveness; and *i)* on the other hand, baseline respiratory symptoms were not predictive of improvement in lung function.

In a further analysis of the Lung Health Study data, Wise et al[72] found that airways reactivity tended to increase over time in patients with COPD. This increase in airways reactivity occurred in all cases except when the patient stopped smoking and lung function improved. In other words, the greater the loss of lung function, the greater the increase in airways reactivity.

A recent Spanish study analyzed the efficacy of various smoking cessation therapies in patients with COPD.[73] Sixty-two patients were assigned to 3 groups receiving either nicotine replacement therapy, bupropion, or a multifaceted behavioral therapy program. The authors found higher quit rates among the patients who received pharmacologic therapy (but there were no significant differences between these therapies), and the success rate was significantly lower with behavioral therapy than with pharmacologic therapy.

There is no doubt, therefore, about the importance of smoking cessation for patients with COPD and that an intensive intervention, tailored as much as possible to the patient's profile, should be used.[74,75] Nor should we forget the work needed at an earlier stage to prevent smoking, a strategy that will obviously lead to cost savings.[17,19,76,77] As can be seen in this review, there is absolutely no doubt, as Decramer et al[78] have demonstrated, that the only treatment that reduces the rate of decline in FEV_1 is smoking cessation, and that is why active pharmacologic and psychosocial therapy is essential. Smoking cessation also improves direct and indirect airway hyperresponsiveness in patients with COPD.[79] A recent meta-analysis emphasized that smoking cessation clearly improves respiratory symptoms and bronchial hyperresponsiveness caused by chronic respiratory disease, and prevents excessive decline in lung function in asymptomatic smokers, symptomatic smokers without airway obstruction, and patients who have been diagnosed with COPD.[80] On the other hand, the data available on the effect of quitting on inflammation and remodeling are contradictory, and the authors point out that there is evidence that inflammation persists after smoking cessation in ex-smokers with COPD. A recent study found that the overall mortality rate after a number of years (follow-up of 14.5 years) was lower among patients with COPD who stopped smoking after a sustained and intensive intervention than among those who continued smoking.[81] In a study of adults with severe chronic airflow obstruction, the

authors report that the median survival of these patients was 7 years from diagnosis.[82] The length of time the patient had been a smoker and a recent history of smoking were identified as predictors of higher mortality.

Although, as can be seen from all the information reviewed up to this point, it is crucially important for patients with COPD to stop smoking, very little research has focused on COPD-specific interventions. In a recent study that analyzed the efficacy of systematic smoking cessation interventions (behavioral therapy, pharmacotherapy, and combinations of both) in patients with COPD, Wagena et al[83] suggested that the highest prolonged abstinence rates are achieved in these patients with a combination of nicotine replacement therapy and an intensive relapse prevention program. In another study, Jonsdottir et al[84] assessed the effect of a multicomponent smoking cessation program in patients with chronic lung disease after a year. This intensive program, which was started when the patients were hospitalized, achieved higher abstinence rates than have been reported in other studies—a finding that further underscores the importance of intensive intervention. In a study published in 2005 that analyzed the effect of a smoking cessation program among the relatives of patients with COPD and lung cancer, it was found that having a relative with these diseases did not appear to motivate smokers to quit.[85]

We have already mentioned how difficult it is for patients with COPD to stop smoking. For this reason, another alternative worth considering in the context of smoking cessation might be to achieve a reduction in the number of cigarettes smoked per day. Although very few studies have dealt with this approach, it has been found that a controlled reduction in daily consumption coupled with adequate monitoring reduces symptoms and improves lung function in patients with COPD.[86-90]

Since COPD tends to be underdiagnosed, suspected diagnosis and examination of these patients should start in primary care, with referral to specialized care when this becomes necessary.[19,54,91-93] Clinical follow-up is required to ensure an adequate quality of life for the patients by way of a comprehensive treatment regimen.[94,95] Another problem affecting specialized care is whether respiratory specialists are familiar with and follow the guidelines for treating COPD. A recent study demonstrated the efficacy of the SEPAR guidelines in helping patients to quit smoking.[96] However, the question remains, are we using these guidelines? Others' experience suggests that we might not be. In a recent Belgian study, Decramer et al[97] analyzed how closely the treatment of COPD prescribed by a group of pulmonologists followed the GOLD guidelines and compared their practice to that of a group of Belgian general practitioners. With respect to the treatment of smoking dependence in COPD patients, 34% of the pulmonologists had implemented a program to help their patients to stop smoking, and only 45% of these physicians used pharmacotherapies to help their patients quit. This confirms the underutilization of available smoking cessation aids. Similar results were found by Rutschmann et al[98] with respect to knowledge of COPD guidelines among primary care physicians. However, it is recognized that pulmonologists routinely advise their COPD patients to stop smoking[56,99] and use methods involving considerable social support to help these patients to quit. However, they need to be convinced that these strategies will increase the number of nonsmoking patients and believe in their own ability to achieve the desired result. It is, therefore, essential to include courses on the subject of smoking not only in the undergraduate curriculum but also in postgraduate training.[100,101] Students should be obliged to attend these courses and learn the material taught.

The most important conclusion of this review is that more prospective randomized double-blind trials studying large numbers of patients are undoubtedly needed to ascertain which of the available treatments would be the best smoking cessation therapy for use in patients with COPD, and in what circumstances. In the meantime, it is clear that the treatment of smoking dependence in patients diagnosed with COPD should comprise both pharmacotherapies and psychobehavioral treatment (with the focus on stress management and relapse prevention). Interventions should be intensive, individualized, and sustained over time. When patients with COPD do not want to stop smoking, it is imperative to make them understand the risks of continuing and they should be apprised of the reduction in lung damage that would be achieved by a reduction in the number of cigarettes they consume while they continue to work towards future total abstinence.

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