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REVIEW

Smoking cessation in chronic obstructive pulmonary disease

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Summary
Chronic obstructive pulmonary disease (COPD) is increasing in prevalence, and is predicted to become the third leading cause of deaths worldwide by 2020. The precise prevalence of COPD is not known, as many individuals with the disease are left undiagnosed, despite the requirement of only simple spirometry testing for disease detection. The major risk factor for the development of COPD is cigarette smoking, with 90% of deaths from COPD directly attributable to smoking. Therefore smoking cessation is the most effective means of halting or slowing the progress of this disease.

This review summarizes and compares the differential characteristics of smokers with COPD vs. those without COPD in relation to their smoking behavior and quitting attempts, and discusses the various strategies that can be used to help patients quit and improve their likelihood of long-term smoking cessation. Of the various behavioral interventions available that can increase the likelihood of smoking cessation, one of the simplest and most effective strategies that physicians can use is simply to advise their patients to quit, particularly if this advice is combined with informing the patients of their ''lung age''. We also discuss the pharmacologic therapies used to enhance the likelihood of quitting, including nicotine replacement, bupropion SR and varenicline, along with novel nicotine vaccines, which are currently undergoing clinical trials.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; DALYs, disability-adjusted life years; FEV_1, forced expired volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LHS, Lung Health Study; LRI, lower respiratory illness; NHANES, National Health and Nutrition Examination Survey; NRT, nicotine replacement therapy; OR, odds ratio; SD, standard deviation; SR, sustained release.

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Introduction

Tobacco cigarette smoking is the single most preventable cause of death worldwide and accounts for approximately 438,000 deaths each year in the US.[1–3] Smoking contributes to a number of diseases and has a major impact on four of the most common causes of death in the US: (i) coronary heart disease; (ii) cancer (lung, upper aerodigestive tract, pancreas, stomach, bladder, kidney and cervix); (iii) cerebral vascular accidents;[4,5] and (iv) chronic obstructive pulmonary disease (COPD).[5]

COPD is a disease of increasing prevalence, morbidity and mortality, but suffers from under-recognition, under-diagnosis and under-treatment. It has been defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a ''preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases''.[6] Since COPD is defined mainly on the basis of its abnormal physiology, spirometry is essential for diagnosis by demonstrating fixed airflow obstruction, i.e., a ratio of forced expired volume in 1 s (FEV_1) to forced vital capacity (FVC) of $<70\%$ that does not fully reverse, i.e., does not increase to $\geq 70\%$, after a bronchodilator. GOLD staging of the severity of COPD is also based on spirometry: mild, moderate, severe and very severe diseases are defined by FEV_1 values of $\geq 80\%$, 50–79%, 30–49% and $<30\%$, respectively. The fact that spirometry is infrequently performed and that the major symptom of COPD responsible for limitation of physical activity, namely exertional dyspnea, does not appear, or is not recognized, until the airflow obstruction is advanced (or is incorrectly attributed to some other disease process) contributes to the under-diagnosis of COPD. Since prevalence surveys are generally based on self-report of physicians' diagnoses and COPD is generally under-diagnosed, prevalence figures are likely to underestimate the true prevalence of COPD. Therefore, while a US prevalence of 10 million is often cited,[7] the true prevalence is probably much higher. For example, data from the third National Health and Nutrition Examination Survey (NHANES III) indicated that 71.7% of those surveyed who had an $FEV_1/FVC < 70\%$ (and thus were likely to have COPD) were never given a diagnosis of COPD by their physicians; furthermore, 46.2% of those who might have been classified as having severe COPD by GOLD criteria ($FEV_1 < 50\%$ predicted) were never diagnosed with COPD.[8]

COPD often severely limits activities of daily living and impairs health-related quality of life.[9] It is associated with

significant morbidity and mortality and exerts a huge economic burden on our healthcare system. US estimates indicate that annually COPD has accounted for 15.4 million office visits and 721,000 hospitalizations with estimated direct and indirect costs (2007) of $42.6 billion.[10] In 1990, it was the twelfth leading cause of disability-adjusted life years (DALYs) lost worldwide and is projected to become the fifth leading cause of DALYs lost in 2020. COPD currently claims 120,000 lives annually in the US.[11] The sixth most common cause of death in the world in 1990, it is projected to become the third leading cause by the year 2020. In contrast to downward trends in the death rates due to other common diseases, such as cardiovascular disease and cancer, death rates from COPD have been rising steadily over the past few decades. The latter phenomenon is attributable to the worldwide epidemic of smoking, as well as to the decreasing mortality from other common diseases which has resulted in people in developed countries living longer and thus being at greater risk for COPD development and progression. The demographics of COPD have also changed, as smoking rates among women have increased in recent decades, leading to a faster increase in COPD prevalence and mortality among women than men, so that in the year 2000 numerically more women died of COPD than men.[7]

The major risk factor for COPD, particularly in developed countries, is cigarette smoking,[6,12] the major source of the ''noxious particles or gases'' that cause the inflammation that leads to COPD. However, other factors may be contributory in some individuals, including occupational and environmental exposures to dusts and fumes,[13] infections in early life,[14] genetic predisposition,[13,15] and asthma.[16] Nonetheless, approximately 90% of all deaths from COPD are attributable to smoking.[17] Just as smoking is the major cause of COPD, smoking cessation has been shown to be the most effective strategy for slowing or halting the progression of the disease.[18,19] Nonetheless, it is discouraging that a substantial percentage of patients with moderate to severe COPD continue to smoke, ranging from 30.4% to 43.0% in recent large-scale global clinical trials of patients with moderately severe to severe disease.[20–22] Given the fact that smoking cessation is the most effective means of favorably modifying the course of COPD and that approximately a third or more of patients with advanced COPD continue to smoke, it is obvious that a major unmet need in the management of the COPD patient who continues to smoke is the availability of more effective interventions for smoking cessation in this population of patients with a serious smoking-related disorder. This paper explores some of the differential characteristics of smokers with and without COPD relating to their smoking behavior and their attempts at quitting, and reviews the effectiveness of various interventions for smoking cessation specifically in the COPD patient.

Differential characteristics of smokers with COPD vs. those without

Level of nicotine dependence; difficulty in quitting and maintaining abstinence

In the Lung Health Study (LHS), an early intervention study in smokers with mild-to-moderate airflow limitation, it was assumed that smokers with COPD were more resistant to smoking cessation intervention than those without COPD since, despite the fact that smoking was making them sick, they continued to smoke.[23] However, this assumption could not be tested in the LHS since only smokers with airflow obstruction were included. Moreover, as indicated below, this picture is not as simple as was once assumed.

In a general population study in Spain, Jiménez-Ruiz et al.[24] identified 15% of cases with COPD by spirometry among 1023 active smokers. Smokers with COPD had higher nicotine dependence scores than smokers without COPD (Fagerström test score 4.77 ± 2.45 with COPD and 3.15 ± 2.38 without COPD, $P < 0.001$).

A smoking cessation study in the Netherlands reported only 42% success at 12 months in smokers with COPD, compared to 68% success in ex-smokers without COPD. The authors enrolled 38 and 25 participants in the two groups, respectively. Results at 1-year were point-prevalence values based on urinary cotinine. Although the success rates appeared to differ between the groups with and without COPD, the authors offered no statistical demonstration that this was so.[25]

Bednarek et al.[26] recruited 4494 smokers to a study of smoking cessation. Based on spirometry, 1177 had airways obstruction and were told they had COPD and that smoking cessation would halt rapid progression of their lung disease. No pharmacologic treatment was used. After 1 year, about 70% attended a follow-up visit. The smoking cessation rate, validated by exhaled carbon monoxide, was 16.3% among those with airways obstruction and 12.0% among those with normal spirometry ($P = 0.0003$). Smoking cessation advice and spirometry had resulted in a higher cessation rate among smokers with airways obstruction than among those without obstruction. The authors concluded, however, that a large randomized clinical trial is needed to determine more conclusively whether communicating spirometry findings to smokers with airflow obstruction has a favorable impact on smoking cessation.

Stratelis et al.[27] enrolled 512 smokers in a study to demonstrate the value of brief advice and spirometry to support smoking cessation. Recruits were given spirometry, smoking cessation advice by a nurse, and a letter from a physician reinforcing the results of their spirometry, annually for 3 years. After various exclusions, of those still with the study after 3 years, 25% of smokers with COPD at baseline ($n = 119$) had been smoke-free for $\geq$1 year compared to 7% of those smokers with normal lung function who received the same level of intervention ($n = 161$, $P < 0.001$).

Use of spirometry (and ''lung age'') in quitting

Parkes et al.[28] assessed the effect on smoking quit rate of telling patients about their lung age, i.e., the age of the average healthy individual (adjusted for height and gender) with the same FEV_1 as the patient, based on the Fletcher–Peto diagram (Fig. 1) of the age-related annual rates of decline in FEV_1 in male non-smokers and smokers with varying susceptibility to the harmful effects of smoking on lung function.[29] Spirometry was performed on 561 current smokers aged >35 years recruited from the general population. Subjects were randomly divided into two groups: an intervention group that received their spirometric

results in terms of ''lung age'' and a control group that only received the raw results of their FEV_1. Both groups received advice to quit and were offered referral to local smoking cessation services. A new diagnosis of COPD was made in 16% of the participants. Verified quit rates at 12 months follow-up were 13.6% and 6.4% in the intervention and control groups, respectively ($P = 0.005$). Thus, telling smokers their ''lung age'' based on spirometry improved their likelihood of quitting. Interestingly, however, those with worse ''lung age'' (i.e., worse lung function for their age) were no more (or less) likely to quit than those with normal ''lung age'', so that the mechanism for the effectiveness of this intervention is unclear.

Age of smoking initiation, smoking amount, previous quit attempts

In the above mentioned population study in Spain, smokers with COPD were more likely to be men (odds ratio [OR] 2.18; 95% confidence interval [CI] 1.21−3.95) and were more likely to have smoked >30 pack years (OR 3.70; 95% CI 2.42−5.65; $P < 0.0001$) in an adjusted multiple logistic regression analysis.[24]

In the same study,[24] 35% of smokers with COPD and 39.4% of smokers without COPD had never tried to quit smoking; 43.6% of smokers with COPD and 42.8% of smokers without COPD reported 1−3 attempts to quit; 21.5% of smokers with COPD and 17.8% of smokers without COPD reported >3 quit attempts.[24] These differences were not significant.

Smokers who began at an earlier age are generally regarded as more likely to have difficulty in quitting. In the LHS, however, the age participants began smoking was a non-significant contributor to logistic regressions predicting 12 month smoking status among both men and women.[30] Furthermore, the lifetime number of years of smoking was a significant positive predictor of abstinence at 1 year (OR 1.12; CI 1.02−1.24).[31]

Smoking-related co-morbidities: cardiovascular, cancer, osteoporosis, endocrine disturbances

Co-morbid diseases play an important role in COPD morbidity and prognosis. Co-morbid disorders that are known to be smoking related and occur with greater frequency in COPD than non-COPD patients include lung cancer,[32] ischemic heart disease,[33] congestive heart failure[33] and osteoporosis.[34] Lung cancer, the risk of which is increased in COPD independent of the risk attributable to tobacco,[35] is clearly the driving cause of death when it occurs in the COPD patient. Co-morbid cardiovascular disease and hypertension also increase the risk of hospitalization and death in COPD, while co-morbid osteoporosis, which is associated with smoking but may also be a consequence of the systemic inflammation found in COPD, contributes to the overall morbidity of COPD.

Figure 1 Explaining lung age to participants (adapted from Parkes et al. 2008[28]).

Depression/anxiety

Wilson[36] in a review of the topic, reports that there is a high prevalence of depression in patients with COPD, with 25% of patients with severe COPD classified as depressed compared to 19.6% of patients with mild COPD and 17.5% in a control group. This depression negatively impacts compliance with smoking cessation. Patients who suffer from COPD and co-morbid depression are more likely to be smokers. Indeed, psychiatrists report that smoking appears to have an antidepressant effect.

Impact of smoking cessation (and smoking reduction) vs. continuing smoking on COPD

Progression of COPD

The LHS, a 5-year early intervention study combining behavioral therapy and nicotine gum vs. usual care in 3926 smokers with mild-to-moderate airflow limitation due to COPD, demonstrated that participants who quit smoking and remained abstinent improved their FEV_1 in the year after quitting and demonstrated a subsequent age-related decline in FEV_1 (mean ± standard deviation [SD] 31 ± 4 8 mL/year) that was half the rate among the continuing smokers (62 ± 55 mL/year).[19] This benefit of sustained smoking cessation in slowing the rate of progressive lung function loss to a level comparable to that of never smokers persisted for at least an additional 6 years among the quitters who remained abstinent (Fig. 2).[37] While intermittent quitters had a rate of lung function decline between that of the sustained quitters and the continuing smokers, the course of their lung function loss was closer to that of the continuing smokers. In a separate analysis of data from the LHS, reduction in the number of cigarettes smoked per day in the absence of complete cessation did not influence the rate of decline in lung function unless the percentage reduction was very marked (>85%), a degree of reduction that was achieved by only a small minority of the subjects (Fig. 3).[38] These findings underscore the substantial benefits of sustained and complete smoking cessation in modifying the course of COPD in contrast to the only limited benefit of partial smoking reduction. While Hughes et al.[39] found that smoking reduction did not predict future smoking abstinence in the LHS participants, the role of smoking reduction in promoting eventual smoking cessation, the best method of harm reduction, is still uncertain.[40]

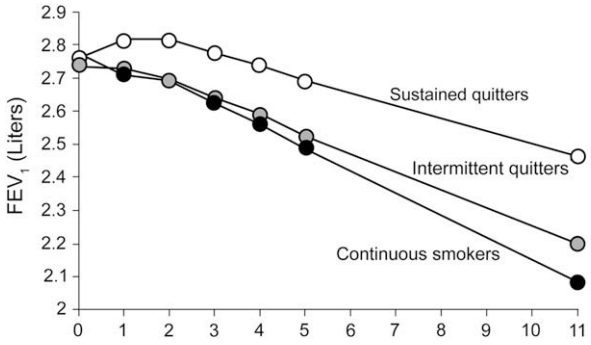

Figure 2 Loss of lung function over 11 years in Lung Health Study participants with mild-to-moderate COPD in relation to quitting status (adapted from Anthonisen et al. 2002[37]).

The Lung Health Study also examined the effect of smoking cessation followed by relapse to smoking and further attempts to quit smoking during the five years of the study. The mean annual rate of loss in FEV_1% of predicted after year 1 was the smallest for those who quit during year 1 and stayed abstinent (−0.33%/year, ±0.05%), intermediate for those who smoked intermittently during the study (−0.58%/year, ±0.05%), and greatest for those who continued to smoke throughout the study (−1.18%/year, ±0.03%). Quitting smoking for an interval followed by relapse to smoking provided a measurable and lasting benefit in comparison to continuous smoking. The relationship between dose of cigarettes and average decline in FEV_1 during the study for participants who reported smoking an average of one cigarette per day or more in any month is shown in Fig. 4. The slope of the curve decreased monotonically with increasing cigarette dose, suggesting that a given increment in cigarette dose had a more harmful effect in light smokers than it did in heavy smokers.[41]

Morbidity

Participants in the LHS were asked each year about episodes of bronchitis, pneumonia, influenza or chest colds that resulted in physician visits. These self-reported illnesses were grouped together as lower respiratory illnesses (LRI), which may be roughly equivalent to exacerbations in this population of COPD subjects. Sustained quitters had fewer LRI than continuing smokers ($P = 0.0003$).[42] Moreover, in the year that the LRI occurred, FEV_1 decreased significantly in smokers but did not change in sustained quitters ($P = 0.0001$). Over the 5-year course of the study, LRI had a significant negative effect on the rate of FEV_1 decline only in smokers. These findings provide further evidence of the benefits of sustained quitting in COPD in reducing the frequency of COPD exacerbations, in addition to prevent the deleterious effect of exacerbations on the rate of progression of lung function decline.

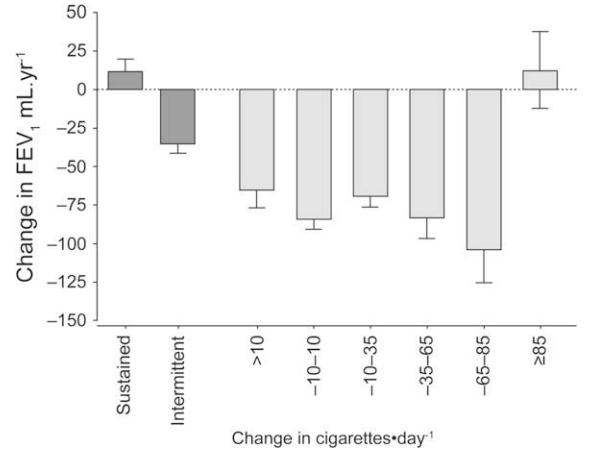

Figure 3 One year changes in FEV_1 in Lung Health Study participants, including sustained quitters, intermittent quitters and continuing smokers with varying degrees of partial smoking reduction (adapted from Simmons et al. 2005[38]).

Mortality

All-cause mortality and mortality due to cardiovascular disease, lung cancer and other respiratory disease were determined for participants in the LHS for whom vital status was followed up to 14.5 years. All-cause mortality was significantly lower ($P < 0.001$) in relation to quitting: 6.04 per 1000 patient-years in sustained quitters; 7.77 per 1000 patient-years in intermittent quitters; and 11.09 per 1000 patient-years in continuing smokers.[43] With regard to categorical causes of death, mortality rates were significantly reduced in relation to quitting smoking for coronary heart disease ($P = 0.02$), cardiovascular disease ($P < 0.001$), lung cancer ($P = 0.001$) and other causes ($P = 0.03$). Clearly, therefore, the benefits of smoking cessation are manifested by a reduction in both all-cause mortality and death due to cardiovascular disease and lung cancer in COPD patients. Since LHS participants had only mild-to-moderate COPD at study entry, the impact of smoking cessation on mortality specifically caused by COPD was probably less than it would have been in a population with more severe COPD.

Interventions for smoking cessation in the COPD patient

Physician advice

At office visits with their physician, about 3% of smoking patients who receive advice to stop (not limited to COPD

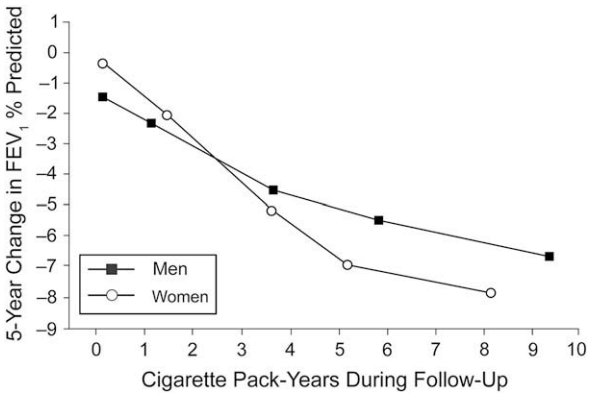

Figure 4 Five years change in FEV_1% predicted by gender as a function of cigarette dose during the study (adapted from Murray et al. 1998[41]).

patients), have been found to do so, compared with about 1% who quit on their own initiative.[44] While this may seem like a discouraging rate of success, if this small intervention is consistently followed through a year by the physician it amounts to a considerable effect at modest expense.

At enrollment in the LHS, 3923 smoking intervention participants were given an assertive and clear message by a study physician about their prognosis and its likely effect on their daily living if they continued to smoke. The study analyzed the attributes of all of the physicians at all clinical centers and the outcome of reported smoking status at the 12-month follow-up visit. Absence of physician smoking was associated with a greater likelihood that participants would not be smoking at the 12-month visit (smoking MD: 40.8%; non-smoking MD: 45.4%; $P < 0.01$), female physicians were associated with higher quit rates at 12 months (male MD: 42.6%; female MD: 47.2%; $P < 0.01$), and a younger age of the physicians in relation to the age of the participants (physician age minus participant age) was related to the percent who quit smoking at 12 months (age difference for male participants: smoking − 3.15 years, not smoking − 5.05 years; age difference for female participants: smoking − 3.36 years, not smoking − 4.67 years; $P < 0.0001$).[45] Due to some limitations in the data, these analyses were not submitted for publication and should be interpreted with caution.

What physicians tell patients with COPD about quitting

Nelson and Hamilton,[46] in an observational study of physicians' interactions with 32 COPD outpatients, found that the term ''breathing'' initiated discussion in 56% of visits, rather than a more specific reference to the nature of the disease. These discussions focused on the acute nature of the disease and only in 2% of visits the long-term frequency of symptoms was addressed. Consequently, in post-visit interviews, it was found that patients were frequently misinformed about the severity of their disease.

Telephone quitlines

Tobacco ''quitlines'' have expanded rapidly in recent years in the US and elsewhere. In a review of interventions for smokers who contact telephone quitlines, eight relevant studies of randomized or quasi-randomized controlled trials were included.[47] These compared multiple call-backs to a single contact, and found increased quitting in the intervention group (OR 1.41, 95% CI 1.27−1.57). We are not aware of any studies of telephone quitlines and smoking cessation in COPD.

Behavioral interventions

In 10 clinical centers, the LHS compared group intervention and nicotine replacement therapy (NRT; nicotine gum) ($n = 3923$; groups both with and without a short-acting anticholinergic bronchodilator) against no intervention ($n = 1964$) in smokers with early stage COPD.[18,31] Biochemically confirmed smoking abstinence was 35% after 1 year in the special intervention groups and 9% in the control group. The study continued to release results until 11 years after randomization.[48] The LHS was not designed to enable the separation between effects of group intervention and of NRT.

Crowley et al.[49] conducted a study in COPD patients among whom three groups received NRT and self-help but different levels of individual counseling. These levels ranged from high-intensity counseling from a physician to lottery tickets to reward for low carbon monoxide readings. Few patients in any of the intervention groups exhibited sustained abstinence and the groups did not differ in this regard.

Tashkin et al.[50] described two randomized groups of subjects with mild-to-moderate COPD: one with proactive telephone counseling, individual counseling and bupropion, and the other with proactive telephone counseling, individual counseling and placebo. The abstinence rate after 6 months was 9.0% in the control group, which was the effect of counseling alone in this group of COPD subjects.

A review by van der Meer et al.[51] concluded that there was insufficient evidence to infer that behavioral interventions were effective for smoking cessation in COPD. A review in the following year by the same authors came to essentially the same conclusions.[52]

A study comparing individual vs. group interventions in COPD patients was reported by Christenhusz et al.[53] They randomly allocated 225 patients to a minimal (sometimes referred to as moderate) intensity individual intervention (individual counseling and telephone contacts, overall mean duration 180 min) vs. an intensive group intervention (group counseling, individual counseling, telephone contacts and use of bupropion free of charge, overall mean duration 595 min). Twelve-month abstinence rates were 9% for the minimal intervention group and 19% for the intensive intervention group, validated by salivary cotinine. The paper leans away from emphasis on this comparison since the intensity of counseling in this paper is confounded with the use of bupropion.

Smoking cessation and weight gain

Nides et al.[54] reported that in the LHS, females who maintained abstinence until 12 months had gained 8.4% of their baseline weight (5.3 kg), whereas males gained 6.7% (5.5 kg). By 24 months, abstinent women had gained 9.8% of their baseline weight compared with 6.9% for men. The continued use of NRT contributed to a delay in part of the weight gain. The authors concluded that moderate weight gain is a consequence of smoking cessation. Although the weight gain observed in the LHS participants who succeeded in quitting smoking had a slightly negative effect on FEV_1, this was believed to be of minor significance in relation to the benefits of smoking cessation.[55]

O'Hara et al.[56] extended the findings on weight gain to abstainers at 5 years in the LHS. Over the 5 years, 33% of those maintaining abstinence had gained 10 kg in weight or more. Nineteen percent of women and 7.6% of men had gained 20% or more of their baseline weight. These changes in body weight occurred despite the fact that the LHS smoking cessation intervention had included program content on anticipating and controlling weight gain.

Social support

Natural support is support from individuals (such as spouses or significant others) linked to the participants attempting smoking cessation. Artificially created support is support from individuals (such as other group members) provided by an intervention program. In the LHS, participants were invited to bring with them to the program a significant other, either a current smoker or non-smoker, who was willing to support them in the group program. Of participants who brought a significant other who happened to be an ex-smoker, 75% of men and 72% of women achieved abstinence, verified by carbon monoxide in expired air, after 1 year. Participants supported by a smoker were less than half as likely to achieve abstinence at 1 year, 34% for men and 32% for women. Interestingly, natural social support was clearly beneficial for men in this sample, since 53.4% of men with natural support were still abstinent 1 year after quitting compared to 42.8% of men with no support. This markedly contrasts with the data for women for whom 1 year abstinence rates were 44.1 and 46.0% for those with or without support, respectively. When natural support was not available, success rates were notably less positive. The overall intervention success rate in the LHS was 35% after 1 year.[30]

Luker et al.[57] reviewed publications that addressed the role of the family in smoking cessation interventions for individuals with COPD. They identified a number of studies that specified the characteristics of families of participants, but few that described the link between family characteristics and smoking cessation success. They concluded that no inference could be drawn from the review.

Pharmacologic interventions

Nicotine replacement therapy

Studies on the effect of NRT in smoking cessation among people with COPD are rare, and are summarized in Table 1, alongside the efficacy of other pharmacotherapies. Silagy et al.[58] reviewed the effectiveness of NRT for cessation in smokers in general. They reviewed 123 randomized trials, and found the overall OR for abstinence with NRT at 6 months or more compared with control was 1.77 (95% CI 1.66–1.88). They found that all forms of NRT were effective, and the level of additional support provided to the smoker did not appear to affect the success of NRT, although it may have facilitated the likelihood of quitting.

Tønnesen et al.[59] evaluated sublingual NRT and two levels of support for smoking cessation in a double-blind, multicenter, placebo-controlled trial in 370 COPD patients. Low support consisted of four individual visits and six telephone calls; high support comprised seven individual visits and five telephone calls. NRT was significantly more effective than placebo at 12 months (carbon monoxide in expired air <10 ppm for 17% vs. 10%, respectively; OR 1.97; 95% CI 1.06–3.67), and there was no difference between low vs. high behavioral support (11% vs. 16%, respectively; OR 1.46; 95% CI 0.79–2.68).

The LHS incorporated NRT in its intervention for smoking cessation a short 3 years after its introduction in the US as a prescription drug. It was used by 3094 participants for durations ranging from a few days to 5 years. The use of NRT was unrelated to hospitalizations for cardiovascular conditions, cardiovascular deaths or other serious side effects.[60] More recently there has been some public concern about nicotine as a carcinogenic agent. Examination of 12.5 years of LHS follow-up data has failed to find evidence of cancers related to the use of NRT.[61]

Bupropion

Bupropion sustained release (SR) was the first non-nicotine-based pharmacologic agent approved by regulatory agencies for smoking cessation. In the general smoking population, bupropion (150 mg twice daily) has been shown to double the rates of smoking cessation observed with placebo.[62,63] Two subsequent studies examined the effect of bupropion in promoting smoking abstinence specifically in subjects with COPD. The first of these studies[50] was a double-blind, randomized, controlled trial of bupropion 150 mg twice daily vs. placebo, administered along with brief individual counseling, for 12 weeks in 404 individuals with mild or moderate COPD defined according to the American Thoracic Society criteria ($FEV_1/FVC \leq 70\%$, $FEV1 \geq 50\%$ predicted [mild severity] or FEV_1 35–49% predicted [moderate severity]) who smoked $\geq$15 cigarettes/day. Continuous abstinence rates from 4 to 26 weeks were significantly higher in subjects receiving bupropion (16%) than in those taking placebo (9%) ($P < 0.05$). Symptoms of tobacco craving and withdrawal were also significantly reduced in those receiving bupropion. However, results from 4 weeks to 12 months (not presented in the original report) no longer showed a significant difference in continuous smoking abstinence between the bupropion group (10%) and the placebo group (8%).[52]

A subsequent study[64] compared the efficacy of bupropion SR (150 mg twice daily) with that of the antidepressant nortriptyline (75 mg once daily) administered with brief smoking cessation counseling for 12 weeks in a double-dummy randomized placebo-controlled trial in 255 adults either ''at risk'' for COPD (i.e., smokers without airflow limitation; $n = 111$) or with mostly mild-to-moderate COPD by GOLD criteria ($n = 144$). In patients with COPD, bupropion was significantly efficacious in achieving sustained abstinence from 4 to 26 weeks (27.3%) compared with placebo (8.3%) ($P = 0.02$). Interestingly, while similar 26-week abstinence rates were noted with bupropion therapy in the subgroup ''at risk'' for COPD (28.6%), the placebo-treated subjects in the ''at risk'' category showed substantially higher abstinence rates (22.0%) than those with COPD, so that no significant efficacy effect of bupropion could be demonstrated in the ''at risk'' subjects. While nortriptyline also showed higher long-term abstinence rates in both the COPD and ''at risk'' subjects (21.2% and 32.1%, respectively), no significant differences from placebo were noted in either the COPD patients ($P = 0.07$) or in those at risk for COPD ($P = 0.59$). Insomnia was the most commonly reported side effect of bupropion. Bupropion has also been shown to lower the threshold for seizures, so that the drug is contraindicated in patients with a seizure history or at increased risk for seizure activity.

Table 1 A summary of the efficacy of different non-pharmacologic and pharmacologic interventions in patients by COPD status.

Intervention	Reference	Follow-up	Cessation rate (%)	Control (%)	COPD Status	Counseling
Minimal advice from GP	44	None	3.0[a]	1.0[a]	General smoking population	None
Being informed of COPD status	26	1 year	16.3	12.0	General smoking population	Brief counseling
Being informed of COPD status	27	3 years	25.0	7.0	General smoking population	Brief counseling/yearly reinforcement by GP
Being informed of ''lung age''	28	1 year	13.6	6.4	General smoking population	Brief counseling/referral to smoking cessation services
NRT	18,31	1 & 5 years	35.0	9.0	Mild-moderate	Group intervention
	48	11 years	21.9	6.0	Mild-moderate	Group intervention
	59	6 months	23.0	10.0	All stages	Low vs. high support
		1 year[b]	17.0	10.0	All stages	Low vs. high support
Bupropion SR	50	6 months	16.0	9.0	Mild-moderate	Individual
		1 year	10.0	8.0	Mild-moderate	Individual
	53	1 year	19.0	9.0	Moderate-severe	Minimal vs. intensive
	64	6 months	27.3	8.3	Mild-moderate	Brief counseling
		6 months	28.6	22.0	At risk of COPD	Brief counseling
	69	1 year	16.1	8.4	General smoking population[c]	Brief counseling
	70	1 year	14.6	10.3	General smoking population[c]	Brief counseling
Varenicline	69	1 year	21.9	8.4	General smoking population[c]	Brief counseling
	70	1 year	23.0	10.3	General smoking population[c]	Brief counseling
Nortriptyline	64	6 months	21.2	8.3	Mild-moderate	Brief counseling
		6 months	32.1	22.0	At risk of COPD	Brief counseling

NRT = Nicotine Replacement Therapy; SR = Sustained Release.
[a] Proportion of patients who quit in a given year.
[b] Data from GlaxoSmithKline (not presented in published paper).
[c] Subjects with severe COPD excluded.

While the mechanism of action of bupropion is not clear, it may be related to its action in inhibiting neuronal reuptake of dopamine and norepinephrine in the nucleus accumbens and nucleus ceruleus, respectively, which may help to reduce craving and attenuate withdrawal symptoms.[65] In addition, it has been shown in rats to be a non-competitive functional inhibitor of acetylcholine receptors, a property that could hypothetically counteract nicotine dependence.[66]

Varenicline

The $\alpha4\beta2$ nicotinic acetylcholine receptor (nAChR) subtype is believed to play a role in the reinforcing effects of nicotine that are modulated by dopamine release in the nucleus accumbens.[67] This concept led to the development of varenicline, a high-affinity $\alpha4\beta2$ partial agonist, with the expectation that this compound could both stimulate dopamine release to reduce craving and withdrawal and at the same time, through its partial antagonist property, block the binding and resultant reinforcing effects of nicotine derived from smoking.[68] Randomized, double-blind controlled clinical trials have been carried out comparing the efficacy of varenicline (titrated to 1 mg twice daily) with both placebo and the active agent, bupropion (150 mg twice daily), administered for 12 weeks, along with brief smoking cessation counseling, and followed for a full year.[69,70] In one of these trials involving 1025 healthy smokers, varenicline resulted in continuous abstinence rates from 9 through 52 weeks of 21.9% vs. 8.4% for placebo ($P < 0.001$) and 16.1% for bupropion ($P = 0.057$) (Fig. 5).[69] In a similarly designed study in 1027 smokers, varenicline resulted in continuous abstinence rates from 9 through 52 weeks of 23% vs. 10.3% for placebo ($P < 0.001$) and 14.6% for bupropion ($P = 0.004$).[70] Nausea was the most common side effect of varenicline in both trials, occurring in 28.1–29.4% of the participants. Thus, varenicline appears to be more than twice as effective as placebo and 36–57% more effective than bupropion in promoting long-term (52-week) abstinence in adult smokers. Moreover, in both of these trials, varenicline reduced craving and withdrawal and, for those who smoked while receiving the drug, it also reduced smoking satisfaction, consistent with its hypothesized mechanism of action in attenuating withdrawal after smoking cessation and inhibiting the reinforcing effects of nicotine during relapse. While the FDA has received post-marketing reports of depressed mood, suicidal ideation and occasional suicidal behavior in patients taking varenicline, the role of varenicline in these cases is not clear, given the fact that smoking cessation itself may be associated with

exacerbations of underlying psychiatric illness. Nonetheless, the FDA has advised health professionals to monitor patients taking varenicline for behavior and mood changes.

Smoking cessation has been identified by GOLD as the most important intervention in the prevention and treatment of COPD.[6] Unfortunately, however, continuing smokers with COPD appear to have particular difficulty in achieving sustained smoking cessation, even with the aid of pharmacologic agents for treating nicotine dependence.[50] In view of the greater success of varenicline in treating nicotine dependence in smokers in the general population compared with other currently available therapies, a clinical trial of varenicline targeted specifically at continuing smokers with COPD was deemed warranted. To this end, a randomized, double-blind, placebo-controlled multicenter study of varenicline administered for 12 weeks for a total study duration of 52 weeks was initiated in 500 subjects with spirometrically confirmed COPD. The recruitment goal for this study was recently fulfilled and the study is ongoing with expected completion by mid-2009. More information about this study (registration number NCT00285012) is available at clinicaltrials.gov.

Combination pharmacotherapy for nicotine dependence

A recently published meta-analysis of combination therapy for smoking cessation included studies that had large sample sizes ($n = \geq 200$), tested first-line therapies and were double-blind randomized controlled trials lasting one year or more.[71] A literature search covered the years 1994–2007. Five clinical trials met the inclusion criteria. These five trials combined nicotine patch and nicotine gum (2 trials), nicotine patch and nicotine nasal spray, nicotine patch and bupropion SR, and nicotine patch and nicotine inhaler. None of these studies was specific to COPD patients. The aggregated relative risk of abstinence comparing combination with single treatment groups was statistically significant at 3, 6, and 12 months. At 12 months it was 1.58 (95% CI 1.25–1.99). In a recent revision of the smoking cessation guidelines from the US Public Health Service, physicians are urged to consider medication combinations with proven effectiveness.[72]

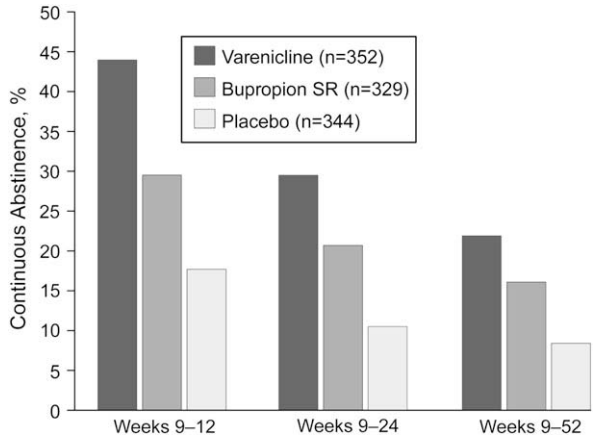

Figure 5 CO-confirmed continuous abstinence rates for varenicline vs. bupropion vs. placebo (adapted from Gonzales et al. 2006[69]).

Nicotine vaccines

Two nicotine vaccines are currently under clinical development as biologic therapeutic aids to smoking cessation. Both products NicVAX™ (Nabi Pharmaceuticals) and CYTO02-NicQb (Novartis) are conjugate vaccines that stimulate the production of antibodies that bind to smoking-derived nicotine in the circulation. The resultant nicotine-antibody complexes are too large to cross the blood–brain barrier, thus preventing nicotine from reaching nicotinic receptors in the brain. As a result, the addictive properties of nicotine would be eliminated, thereby promoting smoking cessation and preventing relapse. A theoretical advantage of nicotine vaccines is that they would result in ''enforced compliance'' since, once injected by the healthcare provider, the smokers would not be required to self-administer the medication. Both products have been evaluated in Phase II trials involving serial intramuscular injections of the vaccine at intervals of 4 weeks or more with serial measurement of antibody levels and monitoring of smoking cessation and continuing abstinence. Only preliminary data have been presented in news releases and abstract form. In a placebo-controlled trial of NicVAX™ that enrolled 301 heavy smokers, among the top 30% of antibody responders, 24.6% showed continuous abstinence between weeks 19 and 26, compared with 13.0% for the 100 patients receiving placebo ($P = 0.04$) (May 9, 2007; http://www.nabi.com). However, the quit rate for the 70% of patients who did not develop a high antibody response was not different from placebo. The challenge for further development of these vaccines is to boost the immune response so that higher and sustained levels of antibodies can be produced to ''soak up'' circulating nicotine.

Other interventions: hypnosis, acupuncture, exercise

The Cochrane collaboration review of smoking cessation in COPD found that hypnosis and acupuncture were essentially not effective as cessation aids.[51] Exercise is a more positive activity in overall quality of life, but studies demonstrating its value in smoking cessation are scarce.

Conclusions

COPD is an ever increasing burden on health budgets, often goes undiagnosed and is associated with several smoking-related co-morbidities such as lung cancer, ischemic heart disease, congestive heart failure and osteoporosis. It is therefore of the utmost importance that physicians question patients at risk about any respiratory symptoms and take appropriate action with respect to diagnosis (perform spirometry) and management.[6]

As cigarette smoking is the major risk factor for COPD, and as patients with COPD reportedly find it harder to quit, it is important that physicians offer the most efficacious means to encourage smoking cessation. We suggest a suitable strategy in Box 1 that would be useful

Box 1. Advice for the practicing physician, irrespective of whether their patients have COPD or another smoking-related illness.

Do as many of the following as are feasible:

- At every encounter, ask the patient if he/she is smoking. Chart the response.
- Advise all patients who smoke to quit. As obvious as this seems, patients do not hear what you tell them, but rather what it is they want to hear. They need a clear, assertive, non-judgmental message to stop smoking. Do not let the patient leave your office saying, ''The doctor did not tell me to quit smoking''.
- Measure your patients' carbon monoxide in expired air. A reading above 10 ppm indicates current smoking. This result will not only verify their smoking status but will indicate to them in a more graphic way what it is that they are breathing out.
- Perform office spirometry or order spirometry. Unknown diagnoses of COPD are made this way. Interpret the results for the patient. Express the spirometry result in terms of ''lung age''.
- Ask the patients if they are ready to quit and their history of quit attempts.
- Negotiate a target Quit Day in the near future. You can be sensitive to their degree of readiness, but with your status as their physician, you could effectively impose a Quit Day when quitting is a high priority.
- Have your office staff follow-up by phone on or shortly after Quit Day to remind your smoking patients to quit and assess their progress.
- Prescribe pharmacological support: NRT, bupropion SR or varenicline, as appropriate.
- Refer the patient to a behavioral support program in the community. Your staff can identify a list of such services. The Local Lung Association or Cancer Society are good places to start. Such programs are resource-intensive and not suitable to conduct from your office.
- When appropriate, a telephone quitline can be recommended.
- Schedule follow-up appointments to address your patients' smoking status.

in the treatment of all smokers, both with and without COPD.

Although physician advice and communicating clinical facts to patients, such as their spirometry results and lung age, have some efficacy in encouraging patients to quit smoking, a growing number of studies indicate that the benefits of behavioral therapies in promoting smoking cessation can be enhanced by the use of pharmacologic therapies such as nicotine replacement, bupropion SR and varenicline, including medication combinations with proven effectiveness. While these therapies have also been found to increase long-term abstinence rates, it is imperative that the physician continues to encourage cessation and maintenance of abstinence in order to slow the rate of progressive lung function loss in those with COPD.

Conflict of interest statement

Dr. Tashkin is a consultant to Pfizer and has received grant support to study varenicline in smokers with COPD. He has also received grants from Nabi Pharmaceuticals to study NicVAX™ and, previously, from GlaxoSmithKline to study bupropion in smokers with COPD. Dr. Murray reports no relevant financial conflicts of interest.

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References

1. Centers for Disease Control and Prevention. National Center for Health Statistics, Health United States, 2003, With Chartbook on Trends in the Health of Americans. Accessed Dec 5 2006; http://cdc.gov/nchs/data/hus/tables/2003/03hus031.pdf.
2. Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and economic costs — United States, 1995—1999. *MMWR Morb Mortal Wkly Rep* 2002;**51**:300—3.
3. U.S. Department of Health and Human Services. The health consequences of smoking: a report of the surgeon general. *Office Smoking Health*; 2004.
4. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American heart Association. American Heart Association Task Force on Risk Reduction. *Circulation* 1997;**96**:3243—7.
5. U.S. Department of Health and Human Services. Tobacco use among U.S. racial/ethnic minority groups — African Americans, American Indians and Alaska natives, Asian Americans and Pacific Islanders, and Hispanics: a report of the surgeon general. Atlanta, GA: USKHHS, CDC, 1998. Accessed Dec 5 2005; http://www.cdc.gov/tobacco/data_statistics/sgr_1998/index.htm.
6. Global Initiative for chronic obstructive lung disease (GOLD). Guidelines: global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated December 2007. Accessed Sept 2008; http://www.goldcopd.org.
7. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance — United States, 1971—2000. *MMWR Surveill Summ* 2002;**51**:1—16.
8. Petty TL. Scope of the COPD problem in North America: early studies of prevalence and NHANES III data: basis for early identification and intervention. *Chest* 2000;**117**:326S—31S.
9. Rennard S, Decramer M, Calverley PM, et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of confronting COPD international survey. *Eur Respir J* 2002;**20**:799—805.
10. National Heart Blood and Lung Institute. Morbidity & Mortality. 2007 Chartbook on Cardiovascular, Lung, and Blood Diseases. Accessed Mar 17 2008; http://www.nhlbi.nih.gov/resources/docs/07a-chtbk.pdf.

11. Arias E, Smith BL. Deaths: preliminary data for 2001. *Natl Vital Stat Rep* 2003;**51**:1—44.
12. Mannino DM. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. *Chest* 2002;**121**:121S—6S.
13. Mayer AS, Newman LS. Genetic and environmental modulation of chronic obstructive pulmonary disease. *Respir Physiol* 2001; **128**:3—11.
14. Shaheen SO, Barker DJ, Holgate ST. Do lower respiratory tract infections in early childhood cause chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 1995;**151**: 1649—51 (discussion 1651—2).
15. Lomas DA, Silverman EK. The genetics of chronic obstructive pulmonary disease. *Respir Res* 2001;**2**:20—6.
16. Sparrow D, O'Connor G, Weiss ST. The relation of airways responsiveness and atopy to the development of chronic obstructive lung disease. *Epidemiol Rev* 1988;**10**:29—47.
17. Chen JC, Mannino DM. Worldwide epidemiology of chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 1999;**5**: 93—9.
18. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The lung health study. *JAMA* 1994;**272**:1497—505.
19. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The lung health study. *Am J Respir Crit Care Med* 2000;**161**:381—90.
20. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;**356**:775—89.
21. Tashkin DP, Celli B, Decramer M, et al. Regional patterns in the characteristics of patients recruited into a long-term global clinical trial in COPD (UPLIFT). *Am J Respir Crit Care Med* 2005; **2**:A412 [Abstract].
22. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008;**177**: 19—26.
23. Pride NB. Smoking cessation: effects on symptoms, spirometry and future trends in COPD. *Thorax* 2001;**56**(2):ii7—10.
24. Jiménez-Ruiz CA, Masa F, Miravitlles M, et al. Smoking characteristics: differences in attitudes and dependence between healthy smokers and smokers with COPD. *Chest* 2001;**119**: 1365—70.
25. Willemse B, Lesman-Leegte I, Timens W, Postma D, ten Hacken N. High cessation rates of cigarette smoking in subjects with and without COPD. *Chest* 2005;**128**:3685—7.
26. Bednarek M, Gorecka D, Wielgomas J, et al. Smokers with airway obstruction are more likely to quit smoking. *Thorax* 2006;**61**:869—73.
27. Stratelis G, Mölstad S, Jakobsson P, Zetterström O. The impact of repeated spirometry and smoking cessation advice on smokers with mild COPD. *Scand J Prim Health Care* 2006;**24**: 133—9.
28. Parkes G, Greenhalgh T, Griffin M, Dent R. Effect on smoking quit rate of telling patients their lung age: the Step2quit randomised controlled trial. *BMJ* 2008;**336**:598—600.
29. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977;**1**:1645—8.
30. Murray RP, Johnston JJ, Dolce JJ, Lee WW, O'Hara P. Social support for smoking cessation and abstinence: the Lung Health Study. Lung health study research group. *Addict Behav* 1995; **20**:159—70.
31. Murray RP, Gerald LB, Lindgren PG, Connett JE, Rand CS, Anthonisen NR. Characteristics of participants who stop smoking and sustain abstinence for 1 and 5 years in the lung health study. *Prev Med* 2000;**30**:392—400.
32. Mannino DM, Doherty D, Buist AS, Holguin F. Global initiative on obstructive lung diseases (GOLD) classification of COPD and incident lung cancer: findings from a cohort study. *Chest* 2004; **126**:853S (Abstract).
33. Holguin F, Folch E, Redd SC, Mannino DM. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest* 2005;**128**:2005—11.
34. Sin DD, Man JP, Man SF. The risk of osteoporosis in Caucasian men and women with obstructive airways disease. *Am J Med* 2003;**114**:10—4.
35. Wasswa-Kintu S, Gan WQ, Man SF, Pare PD, Sin DD. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. *Thorax* 2005;**60**:570—5.
36. Wilson I. Depression in the patient with COPD. *Int J Chron Obstruct Pulmon Dis* 2006;**1**:61—4.
37. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of lung health study participants after 11 years. *Am J Respir Crit Care Med* 2002;**166**:675—9.
38. Simmons MS, Connett JE, Nides MA, et al. Smoking reduction and the rate of decline in FEV(1): results from the lung health study. *Eur Respir J* 2005;**25**:1011—7.
39. Hughes J, Lindgren P, Connett J, Nides M. Smoking reduction in the lung health study. *Nicotine Tob Res* 2004;**6**:275—80.
40. Hughes JR, Carpenter MJ. Does smoking reduction increase future cessation and decrease disease risk? A qualitative review. *Nicotine Tob Res* 2006;**8**:739—49.
41. Murray RP, Anthonisen NR, Connett JE, et al. Effects of multiple attempts to quit smoking and relapses to smoking on pulmonary function. *J Clin Epidemiol* 1998;**51**:1317—26.
42. Kanner RE, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV(1) decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the lung health study. *Am J Respir Crit Care Med* 2001;**164**:358—64.
43. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005;**142**:233—9.
44. Morgan MD, Britton JR. Chronic obstructive pulmonary disease 8: non-pharmacological management of COPD. *Thorax* 2003; **58**:453—7.
45. Murray RP. The effect of the physician message on smoking cessation in the Lung Health Study. In: Annual Meeting of the American Thoracic Society; 20—24 May 1990; Boston, MA.
46. Nelson M, Hamilton HE. Improving in-office discussion of chronic obstructive pulmonary disease: results and recommendations from an in-office linguistic study in chronic obstructive pulmonary disease. *Am J Med* 2007;**120**:S28—32.
47. Stead LF, Perera R, Lancaster T. A systematic review of interventions for smokers who contact quitlines. *Tob Control* 2007; **16**:i3—8.
48. Murray RP, Connett JE, Rand CS, Pan W, Anthonisen NR. Persistence of the effect of the lung health study (LHS) smoking intervention over eleven years. *Prev Med* 2002;**35**: 314—9.
49. Crowley TJ, Macdonald MJ, Walter MI. Behavioral anti-smoking trial in chronic obstructive pulmonary disease patients. *Psychopharmacology (Berl)* 1995;**119**:193—204.
50. Tashkin D, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001;**357**: 1571—5.
51. van der Meer RM, Wagena EJ, Ostelo RWJG, Jacobs JE, van Schayck CP. Smoking cessation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2003;**2**:CD002999. doi:10.1002/14651858.CD002999.

52. Wagena EJ, van der Meer RM, Ostelo RJ, Jacobs JE, van Schayck CP. The efficacy of smoking cessation strategies in people with chronic obstructive pulmonary disease: results from a systematic review. *Respir Med* 2004;**98**:805—15.
53. Christenhusz L, Pieterse M, Seydel E, van der Palen J. Prospective determinants of smoking cessation in COPD patients within a high intensity or a brief counseling intervention. *Patient Educ Counsel* 2007;**66**:162—6.
54. Nides M, Rand C, Dolce J, et al. Weight gain as a function of smoking cessation and 2-mg nicotine gum use among middle-aged smokers with mild lung impairment in the first 2 years of the lung health study. *Health Psychol* 1994;**13**:354—61.
55. Wise RA, Enright PL, Connett JE, et al. Effect of weight gain on pulmonary function after smoking cessation in the lung health study. *Am J Respir Crit Care Med* 1998;**157**:866—72.
56. O'Hara P, Connett JE, Lee WW, Nides M, Murray R, Wise R. Early and late weight gain following smoking cessation in the lung health study. *Am J Epidemiol* 1998;**148**:821—30.
57. Luker KA, Chalmers KI, Caress AL, Salmon MP. Smoking cessation interventions in chronic obstructive pulmonary disease and the role of the family: a systematic literature review. *J Adv Nurs* 2007;**59**:559—68.
58. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2004:CD000146.
59. Tønnesen P, Mikkelsen K, Bremann L. Nurse-conducted smoking cessation in patients with COPD using nicotine sublingual tablets and behavioral support. *Chest* 2006;**130**:334—42.
60. Murray RP, Bailey WC, Daniels K, et al. Safety of nicotine polacrilex gum used by 3,094 participants in the lung health study. Lung health study research group. *Chest* 1996;**109**: 438—45.
61. Murray RP, Connett JE, Zapawa LM. Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study, submitted for publication.
62. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;**340**:685—91.
63. Schapira RM, Reinke LF. The outpatient diagnosis and management of chronic obstructive pulmonary disease: pharmacotherapy, administration of supplemental oxygen, and smoking cessation techniques. *J Gen Intern Med* 1995;**10**:40—55.
64. Wagena EJ, Knipschild PG, Huibers MJ, Wouters EF, van Schayck CP. Efficacy of bupropion and nortriptyline for smoking cessation among people at risk for or with chronic obstructive pulmonary disease. *Arch Intern Med* 2005;**165**:2286—92.
65. Lerman C, Shields PG, Wileyto EP, et al. Effects of dopamine transporter and receptor polymorphisms on smoking cessation in a bupropion clinical trial. *Health Psychol* 2003;**22**: 541—8.
66. Cryan JF, Bruijnzeel AW, Skjei KL, Markou A. Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat. *Psychopharmacology (Berl)* 2003;**168**:347—58.
67. Maskos U, Molles BE, Pons S, et al. Nicotine reinforcement and cognition restored by targeted expression of nicotinic receptors. *Nature* 2005;**436**:103—7.
68. Coe JW, Brooks PR, Wirtz MC, et al. 3,5-Bicyclic aryl piperidines: a novel class of alpha4beta2 neuronal nicotinic receptor partial agonists for smoking cessation. *Bioorg Med Chem Lett* 2005;**15**:4889—97.
69. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;**296**: 47—55.
70. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;**296**: 56—63.
71. Shah SD, Wilken LA, Winkler SR, Lin S-J. Systematic review and meta-analysis of combination therapy for smoking cessation. *J Am Pharm Assoc* 2008;**48**:659—95.
72. Kuehn BM. Updated US smoking cessation guideline advises counseling, combining therapies. *JAMA* 2008;**299**:2736.