REVIEW

Smoking cessation in chronic obstructive pulmonary disease

Donald P. Tashkin a,*, Robert P. Murray b

a Department of Medicine, David Geffen School of Medicine at UCLA, 37-131 Center for Health Sciences, 10833 Le Conte Avenue, Los Angeles, CA 90095-1690, USA
b Department of Community Health Sciences, Faculty of Medicine, University of Manitoba, MS7, 820 Sherbrook Street, Winnipeg, MB R3A 1R9, Canada

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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.

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Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; DALYs, disability-adjusted life years; FEV₁, 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.

* Corresponding author. Tel.: +310 825 3163; fax: +310 206 5088.
E-mail address: dtashkin@mednet.ucla.edu (D.P. Tashkin).

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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 ≥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 ≥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. 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 leads to COPD. However, other factors may be contributory in some individuals, including occupational and environmental genetic predisposition, and asthma. Nonetheless, it is discouraging that a substantial percentage 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. 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. 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 differed between the groups with and without COPD, the authors offered no statistical demonstration that this was so.

Bednarek et al. 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. 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 ≥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 "l lung age") in quitting**

Parkes et al. 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 FEV₁ as the patient, based on the Fletcher–Peto diagram (Fig. 1) of the age-related annual rates of decline in FEV₁ in male non-smokers and smokers with varying susceptibility to the harmful effects of smoking on lung function. 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 FEV1. 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, ischemic heart disease, congestive heart failure and osteoporosis. Lung cancer, the risk of which is increased in COPD independent of the risk attributable to tobacco, 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.

Depression/anxiety

Wilson36 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 FEV1 in the year after quitting and demonstrated a subsequent age-related decline in FEV1 (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. 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
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 FEV1% 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 FEV1 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). Moreover, in the year that the LRI occurred, FEV1 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 FEV1 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.

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. 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 2](image1.png) 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).

![Figure 3](image2.png) One year changes in FEV1% 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).

![Figure 4](image3.png) Five years change in FEV1% predicted by gender as a function of cigarette dose during the study (adapted from Murray et al. 1998).
patients), have been found to do so, compared with about 1% who quit on their own initiative. 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). 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, 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. 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. 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. The LHS was not designed to enable the separation between effects of group intervention and of NRT.

Crowley et al. 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. 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. 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.

A study comparing individual vs. group interventions in COPD patients was reported by Christenhusz et al. 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. 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 (5.3 kg), whereas males gained 6.7%. 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 FEV1, this was believed to be of minor significance in relation to the benefits of smoking cessation.

O’Hara et al. 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.

Luker et al. 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. 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. 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. 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.

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. Two subsequent studies examined the effect of bupropion in promoting smoking abstinence specifically in subjects with COPD. The first of these studies 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 (FEV1/FVC ≤ 70%, FEV1 ≥ 50% predicted [mild severity] or FEV1 35–49% predicted [moderate severity]) who smoked ≥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%).

A subsequent study 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.
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.\textsuperscript{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.\textsuperscript{66}

Varenicline

The \(\alpha 4\beta 2\) 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.\textsuperscript{67} This concept led to the development of varenicline, a high-affinity \(\alpha 4\beta 2\) 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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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 \((P < 0.004)\).\textsuperscript{70} Nausea was the most common side effect of varenicline in both trials, occurring in 28.1\% to 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

| 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\(a\) | 17.0 | 10.0 | All stages | Low vs. high support |
| Bupropion SR | 50 | 6 months | 16.0 | 9.0 | Mild-moderate | Individual |
| | 53 | 1 year | 10.0 | 8.0 | Mild-moderate | Individual |
| | 64 | 6 months | 27.3 | 8.3 | Moderate-severe | Minimal vs. intensive |
| | 69 | 6 months | 28.6 | 22.0 | At risk of COPD | 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.
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. 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. 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 = ≥200), tested first-line therapies and were double-blind randomized controlled trials lasting one year or more. 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.

**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. 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.

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 buproprion in smokers with COPD. Dr. Murray reports no relevant financial conflicts of interest.

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