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Benefits and Risks of Pharmacological Smoking Cessation Therapies in Chronic Obstructive Pulmonary Disease

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Abstract

Smoking cessation is the most effective way to reduce the risk of developing chronic obstructive pulmonary disease (COPD) or to reduce its progression. However, little is known about the efficacy and safety of different pharmacologi-

cal smoking cessation therapies used for the treatment of patients with COPD who smoke. The aim of this review was to evaluate the benefits and risks of pharmacological smoking cessation therapies in COPD. We conducted an extensive computer-aided literature search which resulted in the identification of four papers that met the inclusion criteria and contributed to this review.

In two studies the efficacy of nicotine polacrilex (nicotine gum) was assessed. In one study, which did not have a control group, the efficacy of nicotine nasal spray was evaluated. The fourth study, a placebo-controlled trial, evaluated the efficacy of bupropion sustained release. The results of these studies indicated that nicotine gum, nicotine nasal spray and bupropion have a good safety profile and seem to increase abstinence rates in smokers with COPD. The incidence and nature of specific adverse effects occurring in patients with COPD seem to be comparable with the adverse effects reported by healthy smokers. However, the efficacy seems to depend on the follow-up period used to define success (i.e. abstinence rates decline with longer follow-up), as well as the intensity and duration of the concomitant psychosocial intervention.

This review indicates that for a continuation of the effect of pharmacological smoking cessation therapies, the combination of pharmacotherapy (to reduce craving and withdrawal) and a relapse-prevention programme, in which attention is focused on the behavioural aspects of smoking and smoking cessation, seems to increase abstinence, especially when the psychosocial intervention is prolonged for a longer period. Also, the characteristics of the smokers who are motivated to quit must be taken into account in order to increase the number of successful attempts to quit smoking and prevent relapses. We therefore recommend using a holistic approach in which the possible coexistence of multiple problems (which are known to affect the success of smoking cessation strategies) is integrated.

The link between cigarette smoking and pulmonary diseases was first recognised in the 1870s, but it was not until 1964 that the US Surgeon General's report warned of a potential relationship between smoking and emphysema.[1] It was not until 1984 that sufficient data were gathered from epidemiological and animal studies to recognise that cigarette smoking is the major cause of chronic obstructive pulmonary disease (COPD).[2] Furthermore, the Surgeon General acknowledged that the contribution of smoking cigarettes to COPD morbidity and mortality far outweighs other factors,[2] such as occupational dusts and chemicals, air pollution and infections.

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing.[3] COPD prevalence, morbidity and mortality vary across countries and across different groups within countries, but are in general directly related to the prevalence of tobacco smoking.[3] Age at onset of smoking, total pack-years smoked and current smoking status are predictive of COPD mortality.[4] Worldwide, COPD is the 12th most prevalent disease and the sixth most common cause of death.[4] It is one of the very few common causes of death that is increasing in incidence.[5] The WHO predicts that by 2020 COPD will rise to the fifth most prevalent disease worldwide, and it is expected to be the third most common cause of death in that same year.[6]

Smoking cessation is the most effective way to reduce the risk of developing COPD.[7,8] Furthermore, it positively affects outcome in patients at all stages of the disease.[7,8] Quitting smoking can prevent or delay the development of airflow limitation

or reduce its progression. Following smoking cessation, the annual decline in lung function is usually reduced, sometimes to the level of nonsmokers.[7]

Effective smoking cessation strategies are available to smokers without a chronic disease including nicotine replacement therapy, non-nicotine pharmacotherapy (bupropion or nortriptyline) and behavioural therapy or counselling.[9,10] Although smoking cessation is seen as the most important preventive measure in patients with COPD, little is known about the efficacy of different smoking cessation strategies in these patients. In other words, we do not know if the effectiveness of existing smoking cessation treatments depends on the population in which it is studied and is different in patients with COPD compared with healthy smokers (i.e. smokers without a chronic disease). The aim of this review was to evaluate the existing literature on the benefits and risks of pharmacological smoking cessation therapies in COPD. Because patients with COPD who smoke may have additional barriers for success in smoking cessation,[11] this review begins by describing what is characteristic of these patients and how these characteristics may influence an attempt to quit smoking. Furthermore, to better understand the risks and benefits of pharmacotherapy for smoking cessation, this review focuses on the addictive nature of tobacco.

1. Chronic Obstructive Pulmonary Disease (COPD)

1.1 Definition

COPD can be defined as a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[3] Although definitions differ with regard to the precise classification of airflow limitation, reversibility and severity of disease,[12] it is generally accepted that COPD encompasses chronic obstructive bronchitis, and emphysema.[5] Emphysema is defined anatomically as abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis.[13] The collapse of the airways results in airflow limitation that is independent of exertion. Clinically, the patient experiences progressive dyspnoea and variable cough.[12] Chronic bronchitis, by contrast, is defined in clinical terms by the presence of chronic or recurrent increases in bronchial secretions sufficient to cause expectoration and cough. The cough is not necessarily accompanied by airflow limitation.[5] The secretions are present on most days for a minimum of 3 months per year, for at least two successive years, and cannot be attributed to other pulmonary or cardiac causes.[14,15] Obstruction of the airways occurs as a result of varying degrees of inflammation and nonspecific bronchial hyper-reactivity associated with chronic bronchitis.[12]

1.2 Smoking Cigarettes as a Risk Factor

In the developed world, smoking accounts for at least 75% of COPD cases.[16,17] There is considerable variation among individuals regarding the susceptibility to cigarette smoke. Approximately 15–20% of smokers develop clinically symptomatic COPD. A larger number develop airflow limitation without clinically significant dyspnoea.[18,19] Moreover, symptoms of cough and sputum production can develop independently of airflow limitation.[20] Smokers have higher death rates for chronic bronchitis and emphysema; they also have a higher prevalence of lung function abnormalities. Furthermore, cigarette smokers have a greater annual rate of decline in lung function (see also section 1.3).[7,18] Differences in lung function between smokers and nonsmokers increase in direct proportion to quantity of cigarettes smoked. Also, the incidence of chronic bronchitis increases with high-tar and filterless cigarettes in most studies, but not in all (see Sethi and Rochester[1] for an overview of the literature). However, the effect of tar content and filters on the severity of the airflow limitation is uncertain.[1] This might well be explained by the fact that alterations in the nicotine or tar content of cigarettes do not typically change the total dose of either agent because smokers often adapt the way they inhale

smoke (i.e. inhaling deeper and keeping the smoke in the lungs longer) to result in the same intake of these agents.[2,19] The smoking of light and filter-tipped cigarettes is often compensated with an increased volume, frequency and duration of inhalation and a decreased inter-puff interval.[21,22] However, the Copenhagen City Heart Study showed no significant differences in lung function decline between people who smoke filter cigarettes and those who smoke cigarettes without a filter.[23]

1.3 Effects of Smoking and Smoking Cessation on Pulmonary Function

COPD has a variable natural history and not all individuals follow the same course. However, COPD is generally progressive, especially if a person continues to smoke.[3] The decline in lung function over time (expressed as the forced expiratory volume in 1 second [FEV_1]) can be used as a marker for the development of COPD. Cigarette smoking accelerates the rate of decline in pulmonary function beyond that usually seen with aging.[8,20,24-28] Fletcher et al.[20] showed that in nonsmokers the mean decline in FEV_1 due to normal aging is about 30mL per year in adults, whereas it averages more than 50mL per year in susceptible smokers, although the rate of decline also depends on the number of pack-years.[24,27] Results from an East Boston population-based study showed that in asymptomatic, non-smoking men the FEV_1 increased until the age of 23 years.[29] Following this, between the ages of 23 and 35, the FEV_1 in this non-smoking population underwent a prolonged plateau phase or continued to increase, but at a slower rate. Tager and colleagues[29] also found that the decline in lung function started after the age of 35 years. For male smokers, however, FEV_1 decline began in their early twenties and no plateau phase was observed. For women smokers and nonsmokers, similar patterns and rates of FEV_1 decline were observed as in their smoking and nonsmoking male counterparts.[29]

Evidence also clearly indicates that smoking cessation is associated with reduced rates of FEV_1 decline for both men and women.[8,24,25,30,31] Burchfiel et al.[24] showed that men who quit smoking during the first 2 years of the study, and continued to stop smoking for the following 4 years, experienced a reduction in the rate of FEV_1 decline, from 32mL per year for the first 2 years to 19mL per year for the following 4 years, even among those who already had impaired lung function. The same study showed that rates of decline in past smokers were nearly identical to those of never smokers, which confirms that the accelerated decline in lung function observed among continuing smokers is reduced by smoking cessation.[24] Furthermore, although FEV_1 decline is related significantly to age,[8,24,30] smoking cessation has a beneficial effect on this decline.[24] This means that benefits of cessation exist for older, as well as for younger, middle-aged men. Although results from the Tucson Epidemiological Study of Airways Obstructive Disease showed that the beneficial effect related to smoking cessation was largest for younger individuals and decreased linearly with age, in both sexes.[30] A number of studies have suggested that quitting smoking restores the rate of decline in smokers to the rates observed in nonsmokers.[7,25,27]

Some longitudinal studies have shown that the rate of decline in lung function is dependent on the number of cigarettes smoked per day,[8,25] although others have not.[24,32] Xu and colleagues,[8] for example, found that the rate of FEV_1 decline depended linearly on the number of cigarettes smoked each day (12.6 mL/year per pack/day for a man, and 7.2 mL/year per pack/day for a woman).

Several studies have examined the time frame during which benefits of smoking cessation may be observed.[8,24,25,27] In general, results have indicated that the reduction in the rate of FEV_1 decline occurs over a relatively short period after cessation, suggesting that adverse effects of smoking on rate of FEV_1 decline can be modified for a period of time. In one study, the rate of FEV_1 decline was not associated significantly with the length of time after quitting, indicating that smoking cessation may lead to a rapid return to the usual age-related decline seen in those who have never smoked.[8,24] It is hypothesised that these patterns might represent a bronchoconstrictive or inflammatory effect of

smoking that could be reversible to some degree soon after exposure ceases.[8,24,25,27]

1.4 Characteristics of Smokers with COPD

Among physicians and nurses it is well known that only a small number of patients with COPD are able to quit smoking even with behavioural and pharmacological assistance.[33] This might be explained by the fact that patients with COPD who smoke have additional barriers for success in smoking cessation.[11] We describe what is characteristic of these patients with regard to smoking and smoking cessation and attempt to compare these characteristics with the characteristics of healthy smokers, although studies in which the characteristics of smokers with COPD are compared with those of healthy smokers are scarce.[34]

The characteristic chronic inflammation throughout the airways, parenchyma and pulmonary vasculature of a patient with COPD is mainly caused by the inhalation of noxious particles and gases from cigarette smoke. These particles and gases induce tissue destruction, impair the defence mechanisms that serve to limit the destruction and disrupt the repair mechanisms that may be able to restore tissue structure.[3] The regional deposition of smoke constituents in the lung is of direct importance to the pathogenesis of lung disease. The particles in inhaled smoke are deposited at airway branch points.[1] Total particle deposition increases with slow and deep breathing[13] and breath holding.[35] Smokers with airflow obstruction might therefore have inhalation patterns that differ from those of smokers without airflow obstruction.[33] It is hypothesised that this difference in inhalation pattern increases the chance of developing a chronic lung disease. Smokers with COPD tend to inhale more deeply and rapidly than healthy smokers,[34,36] which could cause an increase of particle deposition.

In addition to a difference in inhalation pattern, it is likely that an increase in particle disposition can also be caused by the physiological defects that are characteristic in COPD (for an overview of relevant references see Pauwels et al.[3]). Several pathological characteristics contribute to the irreversible airflow limitation that is characteristic of COPD. Remodelling of the small airways (fibrosis and narrowing of the airways) that produces fixed airways obstruction and a consequent increase in airways resistance is the primary component of airflow limitation. Although parenchymal destruction plays a smaller role in this irreversible component, it influences the increase in airways resistance by causing a loss of elastic recoil of the lung, which decreases the intra-alveolar pressure driving exhalation. With increasing severity of airflow limitation, expiration becomes flow-limited during tidal breathing. This means that emptying of the lung is incomplete during tidal breathing, and the lung volume fails to decline to its natural equilibrium point (i.e. passive functional residual capacity). This leads to hyperinflation of the lungs. Initially, this occurs only during exercise,[34] but later it is also seen at rest. Simultaneously, the functional residual capacity increases because of the combination of a decrease in the elastic properties of the lungs, premature airways closure and a variable dynamic element reflecting the breathing pattern adopted to cope with lung impairment.[3] As a result, air trapping is inevitable and causes dynamic lung hyperinflation.[3,34] Because in a sense, air trapping is comparable to slow and deep breathing and breath holding, it could be hypothesised that with increasing severity of expiratory airflow limitation, the deposition of noxious particles from cigarette smoke in the lungs increases (even though patients continue to smoke the same number of cigarettes and do not change their inhalation pattern), causing an accelerated further decline in expiratory airflow limitation.

In addition to the finding that patients with COPD who smoke might have a different pattern of inhalation compared with healthy smokers, there is some evidence that smokers with COPD are more dependent on nicotine than healthy smokers. Jimenez-Ruiz and colleagues[37] showed that almost 30% of smokers with COPD scored 7 points or more on the Fagerström test for nicotine dependence (indicating high dependency on nicotine)[38] compared with 10% of healthy smokers. With regard to smoking cessation, this finding is of utmost importance.

Findings from smoking cessation research indicate that nicotine-dependent smokers (i.e. smokers who score high on the Fagerström test for nicotine dependence) are particularly prone to relapse.[36,39,40]

The chance of a successful attempt to quit smoking can also be decreased by the presence of major depression or depressive symptoms. Depression is independently associated with failure to quit smoking and relapse,[41-45] and patients with COPD can be characterised as a population of patients with a higher prevalence of psychiatric disorders (e.g. depression) than individuals without COPD.[46,47] Although many clinicians as well as researchers remain uncertain about the exact status of psychiatric disorders in patients with a chronic disease, the physical illness itself is often considered to be reason enough for patients to be depressed and is therefore often regarded as a complication of the physical complaints.[48] However, the association between COPD and depression might also be coincidental. As a result, this group of patients might be less successful in stopping smoking than healthy smokers, especially because the complexity of nicotine addiction is often accompanied by comorbid depression or depressive symptoms (see also section 2.2).[36,39,40] This might make it even more difficult for smokers with COPD to abstain from smoking. Until now, comorbid depression or depressive symptoms complicating COPD have been overlooked in most cases when a patient has wanted to stop smoking and these disease states have been treated as separate entities.[11,48-50]

Respiratory symptoms such as dyspnoea, chronic cough and bronchial secretions, which cause expectoration, are characteristic of COPD. Next to nicotine dependence and the presence of depression, these symptoms can also determine the successfulness of an attempt to quit smoking. Smokers with respiratory complaints seem more motivated to stop smoking than smokers without these complaints, especially if they perceive their complaints to be related to smoking.[51,52] Brandt et al.[53] reported that the rates of quitting smoking were higher when the term 'smoker's lung' was used to make patients with COPD who smoke aware of their risky behaviour compared with traditional terminology. Walters and Coleman[52] have shown that if smokers attribute their respiratory symptoms to smoking, they are eight times more likely to believe that their health will improve if they stop smoking. This raises the question of why so many patients with COPD with severe respiratory complaints still smoke. It is hypothesised that these patients might not know or do not want to know that they are at risk for developing a smoking-related disease. While most smokers acknowledge that smoking is dangerous, and their chances of developing smoking-related diseases such as emphysema are elevated, they may minimise their own perceived risk of disease[54] (for an overview of the literature see Gibbons et al.[55] and Halpern[56]). Relative to nonsmokers, they might still see less risk inherent in their behaviour. As is characteristic of people who are addicted, many smokers deny or avoid information about the dangers of smoking in order to reduce cognitive dissonance.[56]

2. Smoking Cigarettes: Addiction or Habituation?

A central issue in understanding the risks and benefits of pharmacological smoking cessation therapies is the source of individual differences in the maintenance of cigarette smoking. Many patients with COPD continue to smoke despite knowing about or experiencing the health consequences of tobacco use.[57] Others who try to quit repeatedly fail. Most people mistakenly believe that stopping smoking requires only willpower.[57] Tobacco use, however, has complex physiological and psychological determinants.[58]

2.1 Physiological Determinants of Smoking Cigarettes

The most important physiological obstacle to quitting smoking is the addictive nature of nicotine. Therefore, cigarette smoking should be understood first and foremost as a manifestation of nicotine addiction.[59] The cigarette should be conceived not as a product, but as a package.[60] This package is an extremely efficient nicotine delivery device, deliver-

ing the optimum dose of nicotine rapidly to the brain.[59] According to the Surgeon General's Report on Nicotine Addiction, addiction is defined as the compulsive use of a drug that has psycho-activity and that may be associated with tolerance and physical dependence (i.e. may be associated with withdrawal symptoms after the cessation of drug use).[61] Nicotine dependence and withdrawal can develop with the use of all forms of tobacco (cigarettes, pipes and cigars) and with prescription medication (e.g. nicotine patch and nicotine gum).[61] The fourth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association provides diagnostic criteria for nicotine dependence and withdrawal.[62]

Symptoms of nicotine withdrawal are nonspecific, vary widely in intensity and duration, and are not correctly identified by smokers.[57] These symptoms are intensified by abrupt abstinence from nicotine, begin a few hours after the last cigarette, peak 2–3 days later, and typically last for 4 weeks.[63]

2.2 Psychological and Psychiatric Determinants of Smoking Cigarettes

While nicotine addiction is a major factor in preventing smokers from quitting successfully, psychological factors also contribute to the difficulties smokers have when trying to stay abstinent.[57,58] Tobacco use is a learned behaviour. Cigarettes become part of a smoker's daily routine, associated with particular events. The smokers in the study conducted by Bancroft et al.[64] differentiated cigarettes they smoked in response to craving or in order to avoid symptoms of nicotine withdrawal from those they smoked in order to handle negative emotions (e.g. anger or anxiety) or cope with stressful situations and boredom. These cigarettes were for the most part associated with particular contexts, including home, work and the social context.[64] These results indicated that, in addition to its reinforcing properties, nicotine also exerts effects in stressful situations.[65] It is proposed that stress can act as a stimulus for cigarette smoking; stressful situations enhance the craving to smoke (for an overview of the literature see Balfour and Ridley[65]). Although this is not specific to this agent, the potential for developing associations between stressful environmental stimuli and tobacco smoking may be particularly strong because of the repetitive nature of the habit.[65]

The prevalence of tobacco smoking is much higher in people who experience depression.[66] Several explanations for the association between psychiatric disorders and cigarette smoking have been proposed. It seems that persons with a vulnerability to depression are more likely to become regular smokers and to become dependent smokers than nondepressed individuals.[67,68] In addition, depression-prone smokers experience more severe nicotine withdrawal and have lower rates of quitting.[68] According to the notion of self-medication, smokers are using nicotine to medicate their depressed mood.[41,69] Contending explanations include a causal influence of smoking on major depression based on the possible effects of long-term nicotine exposure on neurobiological systems implicated in the aetiology of depression[70] and the effects of shared environmental or genetic factors that predispose to both smoking and major depression.[70] The observed influences from depression to subsequent daily smoking and smoking to depression support the plausibility of shared aetiologies (or at least their close interrelationship).[41]

3. Effects of Pharmacotherapy for Smoking Cessation in Patients with COPD

To evaluate the effects of pharmacological smoking cessation interventions directed at patients with COPD, both randomised and non-randomised trials, with or without a control group, were included in this systematic review. To identify relevant studies, we conducted a computer-aided search of Medline (from 1966 to October 2002), EMBASE (from 1989 to October 2002), Psyclit (from 1971 to October 2002) and the Cochrane controlled trials register (Issue 3, 2002). Bibliographies of identified studies and relevant reviews were hand checked for other relevant citations from before 1966. In addition, abstract books of relevant conferences and symposia

were screened (e.g. European Respiratory Society, annual meetings of the European and American Society for Research on Nicotine and Tobacco, American Thoracic Society). Furthermore, we searched the following online publicly accessible registers of clinical trials:[71] ClinicalTrials.gov,[72] TrialsCentral.org,[73] Controlled-Trials.com, and the National Research Register (NRR), Issue 3, 2002. The NRR is a database of ongoing and recently completed research projects funded by, or of interest to, the UK National Health Service. Unpublished studies or studies found only as abstracts were included if sufficient detail was available. The first author of identified papers was contacted and asked if he/she knew of other studies which were conducted but never published or studies that were still in progress.

Because COPD is defined on the basis of airflow limitation, we included studies in which the study population consisted of smokers with an irreversible airflow obstruction. The presence of COPD could be assessed according to guidelines for the diagnosis of COPD (e.g. American Thoracic Society,[13] British Thoracic Society,[74] European Respiratory Society,[75] Global Initiative for Chronic Obstructive Lung Disease[3]), or by a lung clinician. This also means that we included studies in which it was stated that the effectiveness of some pharmacological therapy for smoking cessation was evaluated in patients with COPD without describing spirometric characteristics of the population under study.

Although the aim of this review was to evaluate the effectiveness of pharmacotherapy for smoking cessation, the use of adjunctive nonpharmacological smoking cessation interventions was noted where appropriate (e.g. the use of a self-help guide, physician advice, behavioural therapy). Four trials were included, conducted in the US and Canada (two assessing nicotine gum,[7,76] one assessing nicotine nasal spray[77] and one assessing bupropion[78]).

3.1 Nicotine Replacement Therapy

When nicotine is inhaled during cigarette smoking, it is rapidly absorbed.[79] Once absorbed, it moves to virtually all body organs with particularly high affinity for the brain, the heart and the lungs.[79,80] The specific pharmacokinetic profile of inhaled nicotine allows for rapid behavioural reinforcement from smoking. Falling nicotine levels after smoking a cigarette allow the brain nicotinic receptors to regain sensitivity before the next cigarette is smoked.[79,81] This rapid delivery of nicotine to the brain after it is inhaled also allows the smoker to manipulate and titrate the dose of nicotine from a cigarette to achieve the desired effect.[79] As a result, tolerance to the toxic effects of nicotine (such as nausea) develops rapidly and persists, while the reinforcing effects of nicotine are renewed with each cigarette.[79]

Nicotine replacement therapy attempts to condition the brain to lower, constant levels of nicotine and slowly weaning to levels that minimise the effects of withdrawal symptoms when discontinued.[81,82] It serves primarily to break the daily addiction circle by selectively relieving withdrawal symptoms, thereby facilitating behavioural modification that is necessary for permanent smoking cessation.[81] Furthermore, nicotine replacement may also directly suppress cigarette smoking by blunting the primary reinforcing effects of nicotine, especially when higher doses are being used.[81] Lastly, nicotine replacement therapy assists smokers to stop smoking by diminishing the positive reinforcing effects of 'slip-up' cigarettes.[83] However, in contrast to smoking cigarettes, the use of nicotine medications generally provides slower, lower and less variable plasma nicotine concentrations.[63,84] This results in lower peak nicotine concentrations in arterial blood and, therefore, in the brain, as well as more time for the development of tolerance because nicotine concentrations in the brain are rising in comparison to the rapid delivery achieved with cigarette smoking.[81] Furthermore, the stimulation and euphoria from nicotine that are found pleasurable by cigarette smokers are not produced when using nicotine replacement therapy.[81]

Five formulations of nicotine are currently available for replacement therapy: nicotine polacrilex (nicotine gum), transdermal nicotine patch, nicotine nasal spray, nicotine buccal inhalator and nicotine

lozenges. For additional details and references on these formulations, the reader is referred to other reviews.[84-86]

3.1.1 Nicotine Gum

Nicotine gum is available in pieces containing 2mg and 4mg of nicotine. When patients are chewing nicotine gum, 50% of the nicotine in each piece of gum is generally absorbed through the buccal mucosa.[63,84] When 10–12 pieces of nicotine chewing gum are used per day, approximately 10 mg/day of nicotine (from the 2mg form) and 20 mg/day of nicotine (from the 4mg form) is released into the mouth. This equates to approximately one-third to one-half the usual daily intake of nicotine of a person who smokes 30 cigarettes a day.[81] In figure 1, plasma nicotine concentrations before and after smoking a cigarette and chewing nicotine gum are plotted, respectively.

3.1.2 Effectiveness

Our search identified two studies in which the effectiveness of nicotine gum was evaluated in smoking patients with COPD.[7,76] The Lung Health Study was a multicentre, randomised, controlled trial designed to determine whether a programme incorporating a smoking cessation intervention and regular use of an inhaled bronchodilator in smokers at high risk of COPD, can slow down the annual decline in lung function (FEV_1).[87] It was also designed to estimate the effects on lung function decline of bronchodilator therapy over and above the effects achieved by the smoking cessation intervention. Smokers were included who were thought to be at high risk for COPD as indicated by the presence of mild airways obstruction. Airways obstruction was defined as a ratio of FEV_1 to forced vital capacity (FVC) of 70% or less. The FEV_1 was required to be 55–90% of predicted.[88]

5887 men and women, aged 35–60 years, were randomly assigned to one of three groups: a smoking cessation programme as well as inhaled bronchodilator ipratropium bromide – for the treatment of COPD (n = 1961); a smoking cessation programme as well as inhaled bronchodilator placebo (n = 1962), or usual care which provided no intervention (n = 1964).[7] The smoking cessation programme consisted of nicotine polacrilex 2mg combined with an introductory meeting with a smoking cessation specialist, a group orientation meeting, 12 group sessions spread over a 10-week period, and clinic visits every 4 months through the 5 years of follow-up. The programme also included either a maintenance programme designed to provide long-term support to participants who succeeded in quitting smoking or an extended intervention

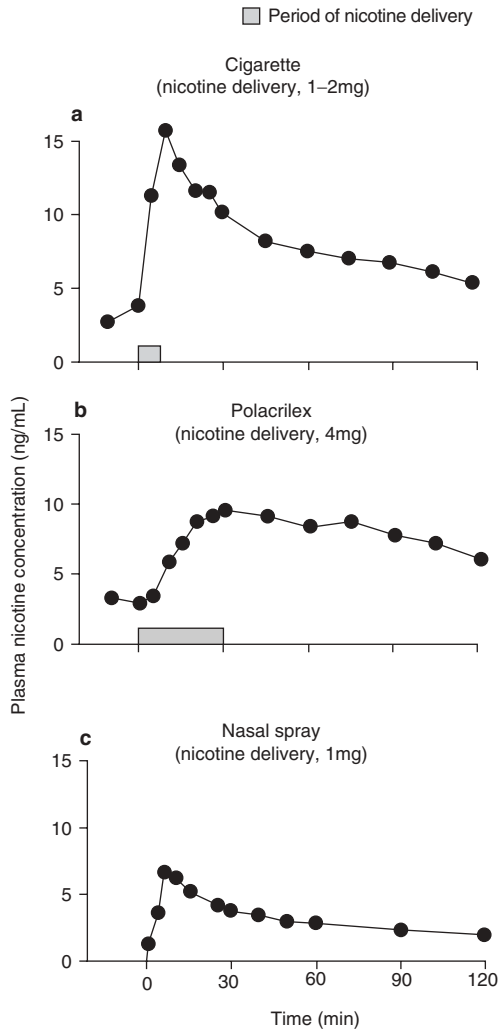

Fig. 1. Plasma nicotine concentrations before and after smoking a cigarette (**a**), after a single dose of nicotine gum (**b**) and after a single dose of nicotine nasal spray (**c**) [from Henningfield et al.,[63] with permission from the Massachusetts Medical Society. Copyright © 1995. All rights reserved].

programme, designed for smokers who did not succeed in the initial cessation programme and those who relapsed.[87,89]

Participants were strongly encouraged to use nicotine gum after quitting smoking and were instructed and monitored in its proper use.[90] Participants adopted their own preferred level of use, according to the package insert guidelines and the advice of their health educator. Of the participants who had received the intervention (i.e. smoking intervention combined with inhaled ipratropium bromide or inhaled placebo), 3094 (79%) used nicotine gum for various durations in the first year of the study. After 1 year, 1042 participants (31%) were still using nicotine gum.

The results of the Lung Health Study showed that, after 12 months, nicotine gum in combination with an intensive behavioural programme was significantly more effective in helping smokers at risk for COPD to abstain from smoking than usual care (risk difference [RD] 25.7, 95% CI 23.2–28.1;[7] table I). This difference was evident throughout the 5-year follow-up period (RD at 5-year follow-up 15.6, 95% CI 13.6–17.7). The combination of the smoking intervention with placebo bronchodilator compared with no intervention (i.e. the usual care group) yielded roughly equivalent outcomes to those of the smoking cessation programme combined with ipratropium bromide (RD at 1-year follow-up 25.3, 95% CI 22.9–27.8; RD at 5-year follow-up 16.6, 95% CI 14.5–18.6; table I). Figure 2 provides a graphical comparison of abstinence rates for the three groups in the Lung Health Study.

In the second study the authors evaluated the effectiveness of nicotine polacrilex 2 and 4mg in smokers with COPD.[76] In total, 71 patients with COPD entered this non-randomised trial: 44 patients entered the active, comprehensive treatment condition and 27 were put on a waiting list and were used as controls. The authors did not present data on demographic characteristics. Furthermore, although they stated that patients with COPD were included, no spirometric characteristics of the participants

Table I. Efficacy of nicotine replacement therapy and bupropion for smoking cessation in patients with chronic obstructive pulmonary disease who smoke

Treatment	No. of patients receiving treatment	Short-term follow-up (<12 months)		Long-term follow-up (≥12 months)	
		percentage (no.) of patients who abstained from smoking	risk difference (95% CI)	percentage (no.) of patients who abstained from smoking	risk difference (95% CI)
Nicotine replacement therapy					
Nicotine gum					
Anthonisen et al.[7]	1961	34.7 (680)[a]	25.7 (23.2–28.1)	20.8 (408)[b]	15.6 (13.6–17.7)
Sachs et al.[76]	44	43.0 (19)[c]	43.2 (28.5–57.8)	27.0 (12)[d]	27.3 (14.1–40.4)
Nicotine nasal spray					
Glover et al.[77]	32	31.3 (10)[e]	N/C	N/A	N/C
Non-nicotine therapy					
Bupropion					
Tashkin et al.[78][f]	204	18.6 (32)	6.7 (0.3–13.1)	10.3 (21)	2.9 (−3.0–8.7)

a Percentage of continuous abstinence in experimental group after 1 year of follow-up.

b Percentage of continuous abstinence in experimental group after 5 years of follow-up.

c Point prevalent abstinence rates calculated at the end of the treatment phase (between 4 and 12 months).

d Sustained abstinence at least 12 months after the end of treatment.

e Sustained abstinence after 12 weeks follow-up.

f Sustained abstinence in experimental group 26 weeks after target quit date and at 12 months. The data after 12 months are from Jarvis et al.[91]

N/A = data not available, as the study was <12 months in duration; **N/C** = data not calculated because the authors conducted a non-randomised clinical trial without a control group and thus, the risk difference could not be calculated.

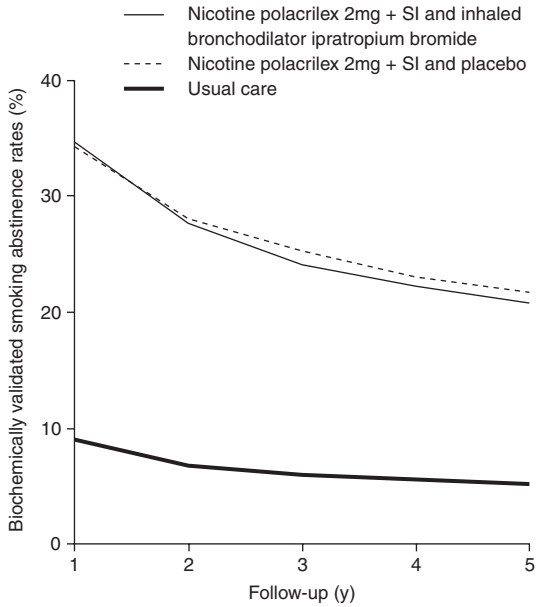

Fig. 2. Biochemically validated smoking abstinence rates as a function of years of follow-up in smokers with chronic obstructive pulmonary disease receiving nicotine gum + SI + ipratropium bromide, nicotine gum + SI + placebo or usual care. **SI** = smoking intervention programme which consisted of an introductory meeting with a smoking cessation specialist, a group orientation meeting, 12 group sessions spread over a 10-week period, and clinic visits every 4 months through the 5 years of follow-up. The programme also included either a maintenance programme designed to provide long-term support to participants who succeeded in quitting smoking or an extended intervention programme designed for smokers who did not succeed in the initial cessation programme and those who relapsed.

were presented and no definition of COPD was provided.

Patients from the active treatment group received nicotine gum ad lib and started on the 2mg dose of nicotine polacrilex with a maximum of 30 pieces of gum per day.[76] Any patient who had been unable to stop smoking completely or who reported craving for cigarettes 4–10 days after the target quit day was switched to the 4mg dose (nonblind). Patients continued to use the nicotine gum for at least 2 months. The administration of nicotine gum was combined with a visit on the target quit date, a visit 4–10 days later, and from then on monthly visits until participants were successfully tapered off nicotine gum. During the first visit, one of the researchers individualised the potential benefits that each patient would get from stopping smoking. The patients from the control group were put on a waiting list and telephoned every 6 months to determine both their smoking status and whether they were still interested in beginning treatment.

This study found a strong statistically significant effect in favour of nicotine gum.[76] At the end of the treatment phase, of the 44 patients with COPD who entered the active treatment group 19 (43%) were abstinent from smoking, compared with none of 27 in the control group. Although the timing of the follow-up assessments was different for the patients from the active treatment group, continuous abstinence was also high. Twelve (27.3%) patients with COPD who received active treatment showed continuous abstinence throughout the entire follow-up period of at least 14 months after the end of treatment. In contrast, 2 years after being placed in the control group, none of the control patients were continuously abstinent from smoking (RD 27.3, 95% CI 14.1–40.4; table I).

Patients with COPD who were continuously abstinent at the end of the study used nicotine polacrilex 2mg for an average of 7.4 months, compared with 1.8 months by those who relapsed.[76] Three of the 12 (25%) successful abstainers needed to use the 4mg dose for a mean of 2.4 months to stop smoking.

3.1.3 Safety and Tolerability

The Lung Health Study provided information on the safety and tolerability of nicotine gum from a nonblind study of 3094 users, over an extended period.[90] However, Sachs and colleagues,[76] did not present data regarding the safety and tolerability of nicotine gum. Analyses of self-reported adverse events after the first 4 months of the Lung Health Study revealed that jaw muscle ache (1.6%), nausea (1.8%), throat irritation (2.2%), hiccups (2.8%), mouth ulcers (4.0%), indigestion (5.1%) and mouth irritation (6.2%) were reported by more than 1% of the male population.[90] More than 1% of the female users reported experiencing belching (1.1%), jaw muscle ache (1.2%), throat irritation (2.8%), hiccups (3.8%), nausea (3.8%), indigestion (3.9%), mouth ulcers (5.3%) and mouth irritation (6.5%). The au-

thors did not find any gender differences in adverse event reporting rate. Some of the reported reactions seemed to depend on the number of pieces of gum used per day. The level of nicotine gum use was related to jaw muscle ache and hiccups in men and to belching in women.

Five percent of the nicotine gum users quit treatment with the medication because of the occurrence of adverse events.[90] The adverse reactions identified significantly more frequently by those discontinuing nicotine gum use included mouth irritation, mouth ulcers, indigestion, nausea, headache and 'other symptoms'.

Because a clinical trial setting is generally not suitable for studying the adverse events profile of a drug, the authors compared the number and frequency of the adverse events reported by the participants of the active treatment group with the adverse events experienced by the participants in the usual care group who obtained nicotine gum from their private physician.[90] Although these patients participated in a randomised clinical trial, the nicotine gum users in this group were not exposed to the rigid trial protocol. The authors used a list of symptoms and asked the participants if each individual event had occurred, without specific reference to nicotine gum use. Using this technique led to higher rates of reporting. This procedure was performed at the first annual visit and referred to the last 4 months of the year. The adverse events that were reported by more men receiving usual care, compared with men receiving active treatment group included dizziness (34.8% vs 11.8%), throat irritation (30.4% vs 12.1%) and headache (30.4% vs 17.1%). Only the first two differed significantly. Adverse events reported by more women in the usual care group than in the active treatment group included headache (59.3% vs 34.2%), throat irritation (40.7% vs 13.1%), belching (33.3% vs 18.9%), dizziness (37.0% vs 23.3%), insomnia (48.2% vs 31.1%) and irritability (55.6% vs 36.9%). Differences in the first two adverse events were significant. No adverse events were reported to occur significantly more frequently by participants receiving active treatment compared with those receiving usual care.[90]

In addition to the occurrence of adverse events, the use of nicotine gum bears some other risk. Nicotine gum, as all other formulations, can sustain tolerance and physical dependence.[63] The risk of dependence, however small, can develop or be maintained because nicotine concentrations in the brain are rising in comparison to the rapid delivery achieved with cigarette smoking.[81,92]

3.1.4 Nicotine Nasal Spray

Nicotine nasal spray is a prescription drug designed to deliver nicotine more rapidly than nicotine gum (although less rapidly than cigarettes[93]) and is therefore expected to serve as a better substitute for smoking cigarettes (figure 1). Each spray (0.05mL) delivers 0.5mg of nicotine, and a dose is a spray in each nostril. Therefore, one nasal spray dose delivers 1mg of nicotine, of which 20–50% is rapidly absorbed.[79] Users tend to self-administer the nasal spray to plasma nicotine concentrations that are approximately 50% of those achieved by smoking.[94] Patients are recommended to start with one to two doses per hour, which may be titrated up to the maximum dose of 5.0 mg/h or 40 mg/day for 3 months.[84,86] In figure 1, plasma nicotine concentrations before and after smoking a cigarette and the administration of a single dose of nicotine nasal spray are plotted, respectively.

Our search identified one study in which the effects of nicotine nasal spray were assessed in a group of patients with COPD. In this study by Glover et al.[77] the efficacy and safety of nicotine nasal spray as a pharmacological adjunct for smoking cessation were assessed in patients with COPD in a clinical trial without a control group. The study included a total of 32 smokers aged 30–70 years. Participants were required to have a clinical diagnosis of COPD. The authors did not elaborate on how the diagnosis of COPD was established and which criteria were used. Eight participants were diagnosed with COPD and 24 with chronic bronchitis but without a documented obstruction.[77] Therefore, it may have been the case that some of the patients did not have COPD.

The nicotine nasal spray used in this study consisted of a multidose pump dispensing nicotine and a

water-based solution with a pH of 7.[77] In this study, one dose was defined as two squirts, one squirt in each nostril, and each containing 0.5mg of nicotine. Participants used active nicotine nasal spray ad lib up to a maximum of 40 doses per day and a recommended minimum of eight doses per day for a period of 12 weeks.

In addition to using the nasal spray, participants attended seven brief, individual counselling sessions (weeks 1–6 and 12) and received written support material.[77] The counselling sessions lasted approximately 15 minutes each and were mainly used for individualised instructions regarding effective smoking cessation interventions. The content of these sessions was not explicitly stated in the paper. After 12 weeks, patients wanting to continue treatment were offered either nicotine gum or nicotine patch, free of charge. The authors did not present data on the number of participants who used these nicotine replacement therapies, how many days they used it and which doses.

The results of this study showed that after 12 weeks, ten participants (31.3%) reported that they had not smoked any cigarettes from the beginning of week 3 through week 12, validated at weeks 3 and 6–12 (weekly) by expired carbon monoxide levels of less than 10 ppm at all visits.[77]

At every visit, participants were asked about adverse events, including symptom duration, frequency and intensity.[77] The authors tabulated the following adverse events as being reported by study participants: nasal irritation, sneezing, coughing, runny nose, throat irritation and runny eyes. From the paper it is not clear if no other adverse events were reported. It seemed that shortly after the start of treatment, the frequency of reporting adverse events was highest. Only at day 2 did a number of participants report adverse events to be severe, which included nasal and throat irritation (9 patients; 28.1%), runny nose (6; 18.8%), sneezing (3; 9.4%) and coughing and runny eyes (2; 6.3%). When patients were asked how much of a problem the adverse effects from the nasal spray had been for them, ten participants (31.3%) rated the adverse events as unpleasant or unacceptable at day 2. This proportion decreased to 17% by the end of week 1 and to 4% by the end of week 6. Of the 22 patients who used the nasal spray throughout the 12 weeks, one reported the spray as unacceptable because of adverse effects.

3.2 Bupropion

Bupropion, originally marketed for the treatment of depression, was the first non-nicotine-based pharmacotherapy to become available for smoking cessation.[78,95,96] The US FDA approved bupropion sustained release (SR) as a treatment for smoking cessation in 1997.[78,95] The exact mechanism by which bupropion acts as an aid in smoking cessation is unknown, as is its exact mechanism of antidepressant activity. Bupropion is thought to produce its therapeutic antidepressant effects via inhibition of the neuronal uptake of dopamine and noradrenaline.[96,97] With regard to smoking cessation, it is hypothesised that the dopaminergic activity of bupropion affects the reward pathways involved in nicotine addiction and the noradrenergic activity is supposed to play a role in the emergence of nicotine withdrawal symptoms.[95] For additional details and references on the pharmacology of bupropion, see the review by Holm and Spencer.[96]

It is recommended that for smoking cessation oral bupropion SR is given at a dosage of 150mg twice daily.[98] Smokers should start treatment by using 150 mg/day for the first 6 days, which is increased to 300 mg/day (150mg twice daily) on the seventh day. Smokers taking bupropion SR are advised to continue to smoke until the target quit day, which should be set for within the first 2 weeks of treatment. The recommended duration of treatment with bupropion SR for smoking cessation is 7–12 weeks.[96]

In a multicentre, randomised study patients with COPD who smoked received a 12-week course of bupropion SR in combination with face-to-face counselling in promoting abstinence from smoking was compared with placebo combined with the same behavioural intervention.[78] The study population consisted of motivated-to-quit smokers who were diagnosed as having stage I or stage II COPD ac-

cording to COPD-staging guidelines from the American Thoracic Society.[13] The diagnosis was based on spirometric findings of chronic airflow obstruction (FEV_1 : FVC ratio ≤0.70) and presence of clinically defined COPD (i.e. emphysema, chronic bronchitis or smoking-related small-airways disease).[78] Tashkin and colleagues[78] defined smoking-related small airways disease as the presence of chronic airflow limitation with or without symptoms of mucus hypersecretion or emphysema, and without other specific causes of chronic airflow obstruction. Stage I COPD was defined as FEV_1 ≥50% of predicted, and stage II COPD as 35% ≤FEV_1 ≤49% of predicted.[13]

Patients received bupropion SR 150mg once daily for days 1–3, followed by 150mg twice daily for days 4–84 or matching placebo.[78] Participants selected a date on which they would stop smoking and were told not to attempt to stop before this day. Bupropion SR was started 1 week before the target quit day and continued throughout the treatment phase (days 1–84). Placebo tablets were identical in appearance to bupropion SR. The administration of bupropion SR or matched placebo was combined with individualised face-to-face counselling (performed by a trained nurse or other health professional) during the clinic visits at weeks 1–7, 10, and 12. Neither the content nor the duration of these sessions was explicitly stated.

The results of this study showed that after 26 weeks and when compared with placebo, bupropion SR seems to be an effective aid in smoking cessation for patients with mild to moderate COPD (RD 6.7, 95% CI 0.3–13.1; table I).[83] At 26 weeks, 32 (16%) smokers receiving bupropion SR were continuously abstinent compared with 18 (9%) of those receiving placebo. However, the same study showed that at 12 months this difference between the bupropion SR and placebo groups had disappeared; 21 smokers (10%) in the bupropion SR group were continuously abstinent compared with 16 (8%) of those in the placebo group (odds ratio [OR] 1.32, 95% CI 0.67–2.61).[78]

Although there has been much debate about the safety of bupropion as an aid to smoking cessation,[99] it was well tolerated in the study conducted by Tashkin and colleagues.[78] Among the patients who received bupropion SR, 90 (44%) experienced an adverse event that was possibly related to the study treatment, compared with 60 (30%) of the patients receiving placebo. The most frequently reported adverse events in the two treatment groups were insomnia (bupropion SR 49 [24%], placebo 23 [12%]), headache (12 [6%], 11 [6%]) and dry mouth (12 [6%], 10 [5%]). For 14 patients who received bupropion SR, the adverse events were reason enough to discontinue study medication. The most common adverse events leading to discontinuation of bupropion SR were anxiety (5 [2%]) and insomnia (4 [2%]). One patient from the bupropion SR group experienced a serious adverse event (lower left extremity arterial occlusion), which led to discontinuation of study medication. However, the authors reported that it was unrelated to the use of bupropion SR.[78]

Three serious adverse events were reported during or immediately after the medication phase: extreme irritability, restlessness, anger, anxiety and cravings; allergic reaction manifested by a pruritic rash, angioedema, dyspnoea and petechiae (most likely related to taking amoxicillin-clavulanic acid for the treatment of bronchitis[78]); and cardiac and pulmonary arrest 4 days after completing the treatment phase (the patient had pre-existing cardiomyopathy and hypertension).

In 2001, concerns regarding the safety of bupropion SR were raised in the UK after 35 people who used the drug died.[100] Since then 58 people from the UK have died using bupropion SR as an aid for smoking cessation.[101] Although this drug has been available since 1985, it has not previously been linked to deaths. In order to assess whether the conclusion that bupropion is responsible for these deaths is justified, Wagena and colleagues[99] used the reports of suspected adverse reactions received by the Netherlands Pharmacovigilance Foundation between December 1999 and April 2001 (the period after bupropion was registered in The Netherlands). The results showed that more than half of the cases concerned patients at risk of developing smoking-

related diseases. Furthermore, Wagena et al.[99] found that in 15 cases (7%), the simultaneous use of bupropion SR and some other antidepressant, theophylline or insulin was reported, and these combinations may lead to an increase in the risk of seizures. Also, of two patients it was reported that they were taking antiepileptics, despite the fact that use of bupropion is contraindicated in patients with seizure disorder. These results seem to illustrate that the guidelines described in the product information are not being adhered to in all cases. Provided that bupropion is used according to these guidelines, the authors concluded that it has a good safety profile.[99] The Committee for Proprietary Medicinal Products of the European Agency for the Evaluation of Medicinal Products conducted a safety review and concluded that 'the balance of risks and benefits of bupropion remains favourable for the current indication'.[101]

4. Discussion

4.1 Efficacy and Safety of Nicotine Gum

The results from two nicotine gum studies, the Lung Health Study[7] and the study conducted by Sachs and colleagues,[76] showed that the proportion of participants from the smoking intervention groups who remained abstinent were 28% after 2 years of follow-up, and a little over 27% after at least 14 months, respectively. When these abstinence rates are compared with the results of the meta-analyses conducted in healthy smokers without COPD by Silagy and colleagues[102] (18%; 95% CI 17–19%) and Fiore et al.,[103] (23.7%; 95% CI 20.6–26.7%) it seems that nicotine gum as an aid in smoking cessation is very efficacious in patients with COPD.

However, the results from the Lung Health Study, in particular, cannot be completely attributed to the use of nicotine gum alone. In this study, smokers from the intervention groups not only used nicotine polacrilex 2mg, but also participated in an intensive behavioural smoking cessation intervention which was based on prevailing approaches to helping smokers deal with their addictive behaviour (see O'Hara et al.[89] and Connett et al.[87] for details on the contents of the behavioural intervention). It is very likely that the combination of nicotine replacement therapy and the additional support led to an increase in effect. First of all, there is consistent evidence that individual and group counselling increases the likelihood of quitting smoking compared with no intervention (odds ratio [OR] individual counselling 1.7, 95% CI 1.4–2.0[102]) and compared with a minimal contact intervention or self-help materials (OR individual counselling 1.6, 95% CI 1.2–2.0; OR group counselling 2.4, 95% CI 1.8–3.4[104,105]).

Furthermore, the efficacy of individual counselling seems to increase further with increasing session length (i.e. session intensity), the total number of sessions and the total amount of contact time.[103] Secondly, smoking cessation interventions delivered by a physician were likely to result in higher abstinence rates than those delivered by other clinicians (e.g. a nurse or a health educator), although the results were not statistically significant.[103] Thirdly, smoking cessation interventions that are delivered in multiple formats (e.g. individual counselling combined with group counselling) increase abstinence rates.[103] Lastly, the content of the individual and group counselling is also an important predictor of success. Based on the review conducted by Fiore et al.,[103] counselling in which attention is focused on relapse prevention and stress management increased abstinence rates compared with no counselling.

Sachs and colleagues[76] also combined the administration of nicotine gum with additional support (i.e. individual follow-up visits), which probably resulted in higher abstinence rates compared with using only nicotine gum. Furthermore, using nicotine polacrilex 4mg instead of the 2mg dose probably also increased abstinence rates. Three patients who had been unable to stop smoking completely or who reported craving for cigarettes 4–10 days after the target quit day were switched to the 4mg dose and remained continuously abstinent throughout the entire follow-up period of at least 14 months.

It is difficult to determine if the nature, timing and duration of adverse events reporting is different in patients with COPD compared with healthy individuals. This is mainly caused by the fact that randomised clinical trials are generally not suitable for studying the adverse events profile of a drug. In most trials a subset of individuals with specific characteristics is being studied. As a result, there is extensive variation in reporting the nature, timing and duration of adverse events in different studies.[102] Furthermore, in most trials in which the efficacy of pharmacotherapy for smoking cessation is being studied, smokers participate in a smoking cessation programme including intensive instruction in the use of pharmacotherapy combined with follow-up monitoring of its use.

This raises concerns regarding the external validity of the adverse events profile found in efficacy studies.[106,107] This issue has been partially addressed by Murray and colleagues,[90] who compared the number and frequency of the adverse events reported by participants in the nicotine gum treatment group with the adverse events experienced by participants in the usual care group who obtained nicotine gum from their private physician. The nicotine gum users in the usual care group did not have intensive instruction and monitoring of nicotine gum use. Although the authors did not present results regarding the occurrence of serious adverse events and the number of dropouts that could be caused by adverse effects, they found that usual care participants reported some of the recorded adverse events significantly more often than participants from the smoking intervention group.

4.2 Efficacy and Safety of Nicotine Nasal Spray

Because the study conducted by Glover and colleagues[77] was the only clinical trial in which the efficacy of nicotine nasal spray for smoking cessation was assessed in patients with COPD, we could not determine whether nicotine nasal spray is more effective than no intervention, placebo or some other intervention. Furthermore, it is difficult to compare the results of this study with those found by Silagy and colleagues.[102] In their review these authors presented the results of four randomised trials in which the efficacy of nicotine nasal spray was evaluated in patients without COPD after 12 months and concluded that the percentage of smokers who were continuously abstinent after 12 months was 24% (95% CI 20–28%). Glover et al.[77] presented the sustained rates of quitting smoking at the end of a 12-week nicotine nasal spray treatment phase and found that 10 of the 32 (31.3%) participants with COPD were continuously abstinent. The participants without COPD in the studies presented by Silagy et al.,[102] and the patients with COPD in the study conducted by Glover et al.[77] received a comparable level of additional support from counselling sessions.

Although relatively few placebo-controlled, randomised clinical trials have been conducted to compare the efficacy and safety of nicotine nasal spray with placebo,[102,103] the incidence and nature of specific adverse effects occurring in patients with COPD seem to be comparable to those of the adverse events reported by healthy smokers.[102] However, in order to obtain a valid and reliable safety profile of nicotine nasal spray (for different populations), effective postmarketing surveillance is needed.

4.3 Efficacy and Safety of Bupropion Sustained Release

Based on the medium-term results (i.e. after 26 weeks) of the study conducted by Tashkin and colleagues, it seems that bupropion SR is an effective aid in smoking cessation for patients with mild to moderate COPD.[78] However, when the results of this study are evaluated after 12 months, the efficacy of bupropion SR, compared with placebo, was not sustained.[91] Furthermore, the continuous smoking abstinence rates decline from week 26 to week 52 by 6% in the active treatment group (from 16% at 26 weeks to 10% at 52 weeks) compared with 1% in the placebo group (from 9% after week 26 to 8% after week 52).[78,91] An evaluation of the rates of continuous abstinence for weeks 4–26 show that the abstinence rates decline throughout the follow-up

period.[78] These findings underline the need to determine which follow-up period is needed before an intervention for smoking cessation can be judged as efficacious (see also Hughes[108] and Velicer et al.[109] for elaboration of this issue).

Since the approval of bupropion SR as a treatment for smoking cessation, the number of studies evaluating the efficacy of this treatment has risen considerably. The effects of bupropion SR have been studied not only in patients with COPD,[78] but also in healthy non-depressed volunteers,[110-114] in healthcare professionals who smoke,[115,116] in patients with schizophrenic disorders,[117-119] a history of major depressive disorder,[120] post-traumatic stress disorder[121] or cardiovascular disease[122] and in smokers treated previously with bupropion.[123,124] These studies generally indicated that bupropion SR in combination with behavioural therapy increases the likelihood of achieving continuous smoking abstinence through to 26 weeks,[91,125] although the abstinence rates differ considerably between studies. Furthermore, of the studies for which complete abstinence data could be obtained through to 52 weeks,[111-113,115,123] only three found a statistically significant result compared with placebo (OR 3.67, 95% CI 1.90–7.11;[112] OR 2.19, 95% CI 1.29–3.86;[114] OR 5.34, 95% CI 1.79–15.89.[123] The continuous abstinence data of participants (without COPD) from these studies who received bupropion SR (through to 52 weeks) were 9%,[123] 13.5%,[111] 21%,[114] 23%,[110] 23.4%[115] and 35.5%.[113] When compared with the abstinence rate of 10% for smokers with COPD, reported by Tashkin et al.,[78] it appears that the success of bupropion in this population is rather low.

Compared with studies in which healthy smokers constitute the study population,[110-114] it is striking that both the number and incidence of adverse events reported by patients with COPD is lower. However, from the paper by Tashkin et al.,[78] it could not be inferred what procedure they used for adverse event reporting. Tashkin et al.,[78] reported adverse events that were possibly related to the study treatment. In other studies,[110-114] adverse events were reports of symptoms that began after or were exacerbated by treatment. Only adverse reactions that were reported at least once by more than 10% of the participants during or immediately after the treatment phase were listed. These results highlight the need for postmarketing surveillance in different patient populations. Furthermore, clinical trials cannot define uncommon adverse events of medicines.[126] For further discussion of this topic see Eypasch and colleagues[127] and Cox and Anton.[126]

As hypothesised by García-Río and colleagues,[128] bupropion might have an effect on the respiration regulatory system. Dopamine agonists depress ventilatory responses to hypoxaemia and hypercapnia by dopamine-mediated inhibition of carotid-body chemoreception.[129] If bupropion, in the therapeutic doses administered to aid smoking cessation, might indeed depress peripheral chemosensitivity to hypoxia, hypercapnia, or both, it could have a potentially harmful effect in patients with these disorders and COPD.[129] However, as Tashkin and colleagues[129] propose, it is not expected to play a crucial role in patients with mild to moderate COPD, because an alteration in the regulation of respiration is more likely to be present in patients with severe COPD.

4.4 Smoking Cessation in Patients with COPD: Using a Physiological or Psychological Approach?

Nicotine addiction has complex physiological and psychological determinants. The most important physiological obstacle to quitting is the addictive nature of nicotine. Nicotine affects mood and performance and can produce pleasure, stimulation and relaxation, as well as relief of anxiety or depression.[81] The effects of nicotine on the brain include increased expression of brain nicotine receptors, changes in regional brain glucose metabolism, electroencephalographic changes and the release of catecholamines.[63] These effects result in neuroadaptation, which is manifested as the development of tolerance and physiological dependence.[81] The brain systems that are changed include those normally involved in the process of incentive

motivation and reward.[130] The critical neuroadaptations for nicotine addiction render these brain reward systems hypersensitive or sensitised to nicotine and smoking-related stimuli.[130] This means that tobacco use is also a learned behaviour. Through associative learning the enhanced incentive value becomes focused specifically on drug-related stimuli, leading to more and more compulsive patterns of cigarette smoking,[130] by producing positive reinforcement (with the administration of nicotine) and withdrawal symptoms (with abstinence).[57,63] Robinson and Berridge[130] postulate that it is this psychological process that is responsible for instrumental cigarette smoking.

The presented view of addiction has a number of implications for the treatment of nicotine-addicted smokers. In accordance with Robinson and Berridge,[130] we suggest that pharmacotherapeutic approaches which fail to address the neuroadaptive processes that lead to addiction in the first place will probably provide only relief of associated symptoms, and in the long term will probably be of limited efficacy. The existing literature on the efficacy of nicotine replacement therapy is in line with this assumption.[102,131-133] Approximately 70–80% of motivated, non-chronically ill smokers who use nicotine replacement therapy as an aid for smoking cessation relapse within the first year.[101,102] Nicotine replacement therapy is used to condition the brain to lower, constant levels of nicotine, slowly weaning to levels that minimise the effects of withdrawal symptoms when discontinued.[81,82] It is intended primarily to break the daily addiction circle by selectively relieving withdrawal symptoms and thereby facilitating behavioural modification that is necessary for permanent smoking cessation.[81] The results from the Lung Health Study underline this role for nicotine replacement therapy.[7] This study showed that although the number of sustained nonsmokers declined during the 5 years of the study, the relative efficacy compared with usual care could be sustained during these 5 years of follow-up. We want to emphasise that for nicotine-addicted people the prolonged cessation of cigarette smoking, during which time withdrawal symptoms decay, is by no means a guarantee of a cure. Relapse to compulsive use of cigarettes, even long after withdrawal effects have diminished, remains a major problem. This means that combining nicotine replacement therapy with individual or group counselling for an extensive period of time can increase the success of an attempt to quit smoking.

Although the postulated mechanism of action of bupropion differs from that of nicotine replacement therapy, the results show that the use of bupropion SR also does not result in high long-term (i.e. 12 months or longer) continuous abstinence rates.[110-114] The available literature seems to indicate that bupropion may help some people refrain from smoking because it produces an effect that serves as a suitable substitute for nicotine in individuals who are motivated to quit smoking.[134] On the basis of the proposed mechanisms of action of bupropion SR,[134-137] it is not surprising that also with this aid, approximately 70–80% of smokers who are motivated to quit smoking relapse within the first year. Although bupropion and nicotine replacement therapy are effective aids in helping smokers to quit, they most likely fail to address the neuroadaptive processes. They probably provide only symptomatic relief (i.e. reduce craving and withdrawal).

As mentioned above, tobacco use is also a learned behaviour. Sensitisation of brain reward systems is not an inevitable consequence of repeated exposure to nicotine. Instead, the ability of drugs to induce or express sensitisation is powerfully modulated by learning and the circumstances surrounding the administration of nicotine.[130] We already know that smokers not only smoke cigarettes in response to craving or in order to avoid symptoms of nicotine withdrawal; they also smoke to handle negative emotions (e.g. anger or anxiety) or cope with stressful situations and boredom.[64] Through associative learning, the incentive value of smoking cigarettes becomes focused specifically on drug-related stimuli.[130] This means that, for a continuation of the effect of smoking cessation therapies, the combination of pharmacotherapy (to reduce craving and withdrawal) and a relapse prevention programme in

which attention is focused on the behavioural aspects of smoking and smoking cessation might increase (prolonged) abstinence. In other words, we recommend the combination of a physiological approach (i.e. using pharmacotherapy) as well as a psychological approach (i.e. behavioural therapy). Two studies[7,113] corroborate this and indicate that an intensive smoking cessation strategy results in (relatively) high sustained quit rates.

5. Conclusion

The Global Initiative for Chronic Obstructive Lung Disease and other guidelines on the diagnosis and management of patients with COPD acknowledge the importance of smoking cessation for these patients: 'Above all, a patient with COPD who still smokes must be encouraged and supported in an effort to quit.'[3] It seems that although smoking cessation is considered to be the most important treatment for patients with COPD, guidelines for the management of COPD have been based on efficacy trials in which the research population have consisted of healthy smokers. In this review we have argued, however, that smokers with COPD cannot be compared with healthy smokers with regard to the efficacy of smoking cessation interventions.

The available smoking cessation literature shows that approximately 70–80% of the motivated non-chronically ill smokers relapse within the first year.[10,95,125,138] The success rates in smokers with COPD seem to be even lower.[91] These results stress the need to individualise the management of smoking cessation therapies. The characteristics of the smokers who are motivated to quit must be considered in order to increase the number of successful quit attempts and prevent relapse.

In conclusion, for a continuation of the effect of smoking cessation strategies in patients with COPD and, as a result, to increase the number of successful quitters, we recommend using a holistic approach in which the possible coexistence of multiple problems (which are known to affect the success of smoking cessation strategies) is being integrated. This means that smoking cessation therapies should be tailored with regard to the presence of comorbid depression or depressive symptoms, the level of dependence on nicotine and the type and intensity of respiratory complaints. Furthermore, we advise health professionals to confront patients with COPD who smoke with the effects of smoking on their health in addition to providing information about the risks of smoking in general and promoting healthy behaviour.

We suggest that while most smokers acknowledge that smoking is dangerous, and their chances of developing smoking-related diseases such as emphysema are elevated, patients with COPD might minimise their own perceived risk of disease. As is characteristic of people who are addicted, they might deny or avoid information about the dangers of smoking in order to reduce cognitive dissonance. As a result, health professionals need to interact with every individual smoker in a confronting and directive manner, to make smokers aware of the tricks they cognitively perform to justify their own smoking. For example, they could use the results of spirometry to make smokers aware of the dangers of smoking, so they can no longer reduce the dissonance that is created by the paradox between smoking cigarettes and knowing that they are at increased risk for developing a smoking-related disease.

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