



CLINICAL YEAR IN REVIEW

Smoking cessation and COPD

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ABSTRACT: The mainstay in smoking cessation is counselling in combination with varenicline, nicotine replacement therapy (NRT) or bupropion SR. Varenicline and combination of two NRTs is equally effective, while varenicline alone is more effective than either NRT or bupropion SR. NRT is extremely safe but cardiovascular and psychiatric adverse events with varenicline have been reported. These treatments have also been shown to be effective in patients with chronic obstructive pulmonary disease (COPD).

A model study is the Lung Health Study from the USA. Findings from this study of 5,587 patients with mild COPD showed that repeated smoking cessation for a period of 5 yrs resulted in a quit rate of 37%. After 14.5 yrs the quitters had a higher lung function and a higher survival rate. A study with a new nicotine formulation, a mouth spray, showed high relative efficacy. As 5–10% of quitters use long-term NRT, we report the results of a study where varenicline compared with placebo increased the quit rate in long-term users of NRT.

Smoking cessation is the most effective intervention in stopping the progression of COPD, as well as increasing survival and reducing morbidity. This is why smoking cessation should be the top priority in the treatment of COPD.

KEYWORDS: Bupropion, chronic obstructive pulmonary disease, counselling, nicotine replacement therapy, smoking cessation, varenicline

This review is based on a presentation from the Clinical Year in Review session which was held during the 2012 European Respiratory Society Congress in Vienna, Austria. The aims of this review are to: 1) summarise smoking cessation studies with particular focus on COPD and treatment with first-line drugs, *i.e.* nicotine replacement therapy (NRT), varenicline, bupropion SR, and counselling; 2) present a model study about smoking cessation and COPD, *i.e.* the Lung Health Study; 3) review three smoking cessation studies in COPD which tested each of the three first-line drugs; 4) discuss the possible severe adverse effects of varenicline; 5) present data on a new formulation of NRT, a mouth spray; and 6) discuss the effect of varenicline in long-term NRT users. This review will be more clinically oriented and thus more subjective; therefore, not all the literature in this field has been reviewed but the most important references have been selected. After reading this review the clinician should have the necessary background information to be able to treat COPD patients who smoke, in a proper evidence-based manner.

SMOKING PREVALENCE IN COPD PATIENTS

The prevalence of smoking among COPD patients decreases over time in parallel with disease severity.

The high prevalence of smoking is striking in published studies evaluating the effects of different bronchodilators and/or inhaled corticosteroids in COPD, with smoking prevalence figures approximately 54–77% among mild COPD patients and 38–51% among severe COPD patients (table 1) [1–6]. These prevalence figures show that some COPD patients who smoke quit smoking but that a large proportion, even when suffering from severe COPD, do not quit smoking and require support in order to do so. It has been shown that in primary care in the UK in 2008 only 13% of smokers received a prescription for smoking cessation treatment and that females, patients suffering from COPD, patients suffering from depression and those aged 31–60 yrs were most likely to get a prescription for smoking cessation drugs [7].

NICOTINE ADDICTION AND SMOKING

It is important to know that when treating an addictive disorder such as smoking you cannot expect to get a 100% cure. A typical finding in most smoking cessation studies is that with adequate support and pharmacological therapy it is possible to achieve an initial quit rate of approximately 50–60% during the first 3 months in the so-called “cessation period”. From 3 months up to 12 months

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PROVENANCE

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TABLE 1 Smoking prevalence among chronic obstructive pulmonary disease patients in large randomised, placebo-controlled trials with inhaled corticosteroids and/or long-acting β_2 -agonists and/or long-acting anti-muscarinic drugs

First author [ref.]	Study	Subjects n	Age yrs	FEV ₁	Smokers %
VESTBO [1]	VESTBO	290	59	2.4 (86)	77
WATSON [2]	EUROSCOP	647	53	2.5 (80)	54
VESTBO [3]	TRISTAN	1465	63	1.4 (45)	51
CALVERLEY [4]	TORCH	5343	65	1.2 (45)	45
BURGE [5]	ISOLDE	751	64	1.4 (50)	38
WEDZICHA [6]	INSPIRE	1323	65	1.3 (39)	38

Data for forced expiratory volume in 1 s (FEV₁) is presented as L (% predicted).

almost 50% of the subjects relapse in the so-called “relapse period” ending up with a 1-yr quit rate of around 25–35%. In order to stop smoking a complex habit and addiction must be broken; in order to achieve a reasonable quit rate it is necessary to administer behavioural support, *i.e.* counselling, in combination with pharmacological drugs [8, 9].

SMOKING CESSATION TREATMENTS

Several high-quality meta-analyses have been performed regarding smoking cessation which evaluated different interventions for smoking cessation, *i.e.* the Cochrane Library, the Agency for Healthcare Policy and Research (AHCPR) publication and the National Institute for Clinical Excellence guidelines, as well as several others [8–12]. The Cochrane Library and the AHCPR included almost the same 300 studies in their meta-analysis and published clinical guidelines (tables 2 and 3).

First-line pharmacological drugs for smoking cessation are NRTs (patches, gum, inhaler, nasal spray, lozenge/tablets and oral spray), varenicline and bupropion SR. These drugs have scientific, well-documented efficacy when used for 2–3 months [8–11].

These medications, in combination with counselling, have also shown to be effective for smokers with COPD, who often seem more reluctant to quit smoking. I will address three studies in COPD that each used one of the first-line medications.

COUNSELLING

Starting with the most minimal intervention *i.e.* self-help materials for smoking cessation, one would expect a small effect and that is the case with a 1% increase in quit rate [8, 13]. Telephone counselling is also effective and can be used as a

TABLE 2 First-line drugs for smoking cessation

	Studies	Sustained quit rates for 6–12 months
NRT versus placebo (any type of NRT)	117	1.60 (1.53–1.68)
Bupropion SR versus placebo	31	1.69 (1.53–1.85)
Varenicline versus placebo	14	2.27 (2.02–2.55)

Data are presented as n or risk ratio (95% CI). NRT: nicotine replacement therapy. Data from [8–10].

supplement to face-to-face interventions, or to substitute face-to-face contact as an adjunct to self-help interventions. Brief advice (<3 min) given by the general practitioner or nurses has shown a small but significant increase in quit rates (approximately 2.5%) [8, 14].

However, there is a dose–response effect from face-to-face counselling with regard to the time available in each session as well as with the number of sessions, *i.e.* four or more sessions seems especially effective [8]. The optimal scenario could be four sessions of 10–15 min duration during the first 3 months after the quit day (after 1–2 weeks, 3–4 weeks, 6 weeks and 10–12 weeks). There seems to be an effect of cooperation between two different types of clinician (doctor, nurse, psychologist, *etc.*) and this is often the case in daily clinics, *i.e.* the doctor will advise the smoker to quit and then the nurse will spend more time on counselling [8]. The doctor has an obligation to cooperate and assist in this area.

Group therapy also seems to be as effective as individual counselling [8, 15].

The effect of very intensive support is highlighted in a study from Sweden [16]. COPD patients that smoked were hospitalised

TABLE 3 First-line drugs for smoking cessation (1-yr quit rates) from US clinical guidelines

	OR (95% CI)	Abstinence rate %
Placebo	1.0	13.8
Monotherapies		
Varenicline	3.1 (2.5–3.8)	33.2
High-dose nicotine patch	2.3 (1.7–3.0)	26.5
Nicotine gum (>14 weeks)	2.2 (1.5–3.2)	26.1
Bupropion SR	2.0 (1.8–2.2)	24.2
Combination therapies		
Patch plus <i>ad lib</i> NRT	3.6 (2.5–5.2)	36.5
Patch plus bupropion SR	2.5 (1.9–3.4)	28.9
Patch plus inhaler	2.2 (1.3–3.6)	25.8

Meta-analysis of data from placebo, controlled trials in smoking cessation reporting 1-yr quit rates with smoking cessation drugs used for 3 months in combination with counselling. The comparator is the placebo arm without drugs but with counselling. NRT: nicotine replacement therapy. Modified from [8].

TABLE 4 Smoking cessation by hospitalisation for moderate chronic obstructive pulmonary disease (COPD) versus usual care

	Smoking cessation group	Usual care
COPD patients n	247	231
1-yr quit rate	52	7
3-yr quit rate	38	10
Subjects who used NRT	28	14
Subjects who used bupropion SR	5	5

Data are presented as %, unless otherwise stated. NRT: nicotine replacement therapy. Data from [16].

for 11 days with the aim of getting them to quit smoking [16]. In this randomised controlled trial, 247 COPD patients were hospitalised and 231 patients received usual care. The mean age of the patients was 52 yrs and they had a mean forced expiratory volume in 1 s (FEV₁) of 75% predicted. The third day was the target quit day and they were offered NRT and daily exercise. The counselling consisted of a 1-h daily meeting with trained smoking cessation nurses and an educational programme followed by weekly telephone calls from nurses. After 2–3 months the patients spent 2–4 days in hospital together with their spouses.

The quit rate after 1 yr was 52% for hospitalisation and 7% for usual care and the figures after 3 yrs were 38% versus 10% (table 4). These are very high abstinence rates. In my opinion this shows that there is a need for re-thinking the level of intervention for COPD patients regarding smoking cessation and to consider delivering more support than we currently do in many chest clinics.

PHARMACOTHERAPY

Nicotine replacement therapy

The best-documented and oldest drugs used for smoking cessation are NRTs in the form of gum, inhaler, nasal spray, skin patch and mouth spray [8, 9]. Lower nicotine levels are reached with NRT compared to smoking (*i.e.* the high peak plasma levels of nicotine reached during smoking are not achieved), which is the main reason why these products are not as effective as “cigarettes” regarding effects on craving and urge [17, 18]. NRT products are used for 6–12 weeks as the abstinent smoker gradually reduces their daily dose in parallel with a decrease in withdrawal symptoms. The average 1-yr success rate reported in most studies is approximately 27% or a relative increase in quit rate to a placebo of approximately 50–70% (relative risk). NRT has shown to be effective independent of the level of behavioural support [9].

Nicotine mouth spray

In a recent study we tested a nicotine mouth spray as it had shown advantages over other formulations of NRT, such as a faster uptake of nicotine and faster relief of craving [19]. It was a double blind, placebo-controlled study enrolling 318 smokers in the active arm and 161 in the placebo arm with low-intensity counselling. Active treatment yielded significantly higher

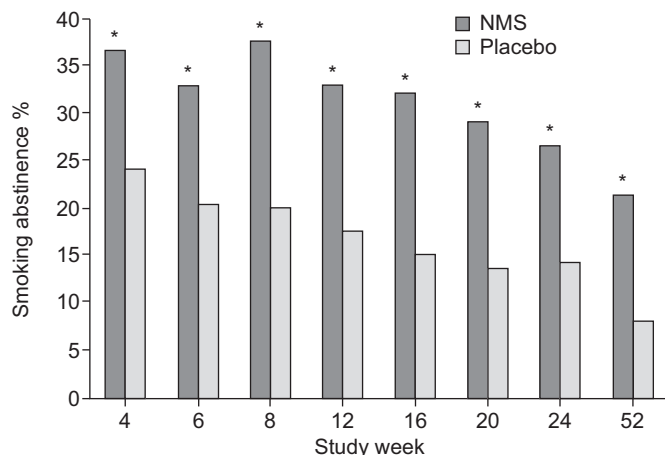


FIGURE 1. Proportion of subjects with carbon monoxide verified 7-day point prevalence of abstinence. Includes all subjects (nicotine mouth spray (NMS): n=318; placebo: n=161). *: p<0.05 between the abstinence rates in the NMS group compared with the placebo group. Reproduced from [19] with permission from the publisher.

continuous abstinence rates than placebo with a 1-yr quit rate of 13.8% versus 5.6% (relative risk 2.48) (fig. 1). Most adverse events were mild to moderate; however, approximately 50% reported transient hiccups. Overall, this formulation of NRT, due to its faster action, seems to be more effective than other NRTs. Of course, we need other confirmatory studies.

COPD with NRT

In COPD, NRT seems to be especially effective as shown in a study that evaluated the effect of sublingual nicotine and two levels of counselling in a double-blind trial in Denmark [20]. To evaluate the efficacy of nicotine sublingual tablets and two levels of support for smoking cessation in an outpatient COPD clinic, we enrolled 370 COPD patients who smoked a mean of 19.6 cigarettes per day (mean 42.7 pack-yrs; mean FEV₁ 56% pred). A 2-mg nicotine sublingual tablet or placebo for 3 months combined with either low support (four visits plus six telephone calls) or high support (seven visits plus five telephone calls) was provided by nurses (table 5).

Smoking cessation rates were statistically significantly superior with sublingual nicotine versus placebo for all measures of abstinence: 6-month point prevalence 23% versus 10%; 12-month point prevalence 17% versus 10%. There was no significant difference in effect between low versus high behavioural support. The St George’s Respiratory Questionnaire (SGRQ) score improved significantly in abstainers versus non-abstainers; the changes in mean scores were -10.9 versus -2.9 for total score and -28.6 versus -2.3 for symptom score. This is quite a surprising finding but a very positive one that should be used to motivate COPD smokers in the process of quitting smoking.

This trial demonstrated the long-term efficacy of NRT for cessation in the general population of COPD smokers, regardless of daily cigarette consumption. Cessation success rates were in the same range as in healthy smokers, and abstinence improved SGRQ scores. NRT should be used to aid

TABLE 5 Double-blind, placebo-controlled randomised smoking cessation studies in chronic obstructive pulmonary disease patients

Medication	Subjects n	FEV ₁ % pred	12-month sustained quit rates	
			Active	Placebo
Varenicline	505	70	18.6	5.6
Bupropion SR	404	72	10	8
NRT	370	56	14	5

FEV₁: forced expiratory volume in 1 s; % pred: % predicted; NRT: nicotine replacement therapy. Data from [20–22].

cessation in all smokers with COPD, regardless of disease severity and number of cigarettes smoked [20].

Long-term use of NRT

5–10% of quitters will use gum for >1 yr and might have difficulty to stop using it [23, 24]. In this double-blind, study we evaluated the effect of varenicline in combination with counselling to assist long-term NRT users to quit NRT [25]. 139 ex-smokers and long-term NRT users were allocated to varenicline or placebo and nurse counselling with visits at weeks 0, 2, 4, 6, 9, 12 and 52. At all time-points varenicline was superior compared to placebo, although the difference was only statistically significant at 12 and 36 weeks. The quit rates were 64.3% (varenicline) versus 40.6% (placebo) at 12 weeks ($p=0.006$), and 42.9% (varenicline) versus 36.2% (placebo) at 52 weeks (non-significant). Withdrawal symptoms were statistically significantly lower in the varenicline group than the placebo group.

Overall, varenicline for 3 months in combination with supportive visits was superior to placebo to help long-term NRT users to quit NRT. However, a larger study is needed to evaluate long-term efficacy (fig. 2).

A nicotine patch in combination with one of the other formulations of NRT has shown to be particularly effective

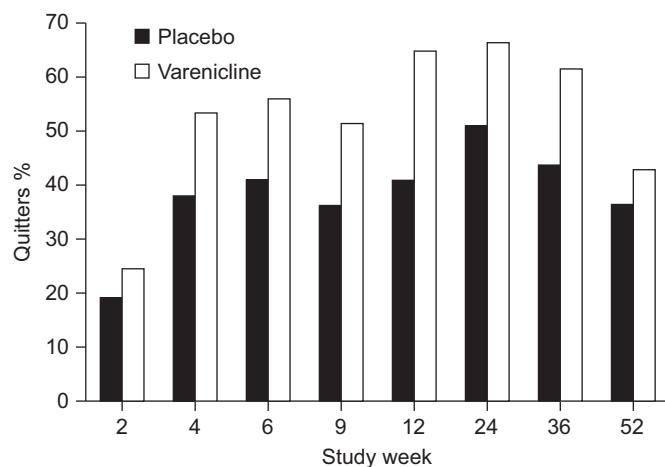


FIGURE 2. Quit rate (7-day point prevalence) for long-term nicotine replacement therapy users in the varenicline and placebo groups from weeks 2 to 52, verified by expired carbon monoxide (except week 36 which was a telephone visit). Modified from [23].

with a quit rate of approximately 36%, which is in the same range as varenicline in the meta-analysis by FIORE *et al.* [8]. In summary, NRT is a safe and effective product with only minor side-effects. These products can be used in almost every smoker who wants to quit.

Varenicline

Varenicline affects the central nicotine receptors in the brain by binding to the specific nicotine receptors. In contrast to NRT varenicline can be taken as a tablet [26]. Varenicline in combination with counselling increase long-term quit rates 2- and 3-fold compared with no drug [10].

The average 1-yr success rate reported in most studies is around 33% or a relative increase in quit rate to placebo of approximately 127% (relative risk) [10, 27, 28]. In COPD patients varenicline has shown to be particularly effective.

COPD with varenicline

In a 27 centre, double-blind multinational study, 504 patients with mild-to-moderate COPD (post-bronchodilator FEV₁/forced vital capacity <70%; FEV₁ % pred normal value $\geq 50\%$) were randomised to receive varenicline ($n=250$) or placebo ($n=254$) for 3 months with a 40-week non-treatment follow-up [21]. The continuous abstinence rate for weeks 9 to 52 was significantly higher for patients treated with varenicline than placebo (18.6% versus 5.6%) (OR 4.04, 95% CI 2.13–7.67; $p<0.0001$). Nausea, abnormal dreams, upper respiratory tract infection and insomnia were the most commonly reported adverse events for patients in the varenicline group. Serious adverse events were infrequent in both treatment groups. Two patients in the varenicline group and one patient in the placebo group died during the study. Reports of psychiatric adverse events were similar for both treatment groups.

Overall, varenicline was more efficacious than placebo for smoking cessation in patients with mild-to-moderate COPD and demonstrated a safety profile consistent with that observed in previous trials.

Varenicline and serious adverse events

There have been reports about depression, suicidal behaviour and myocardial infarction, and the use of varenicline and present depression is a relative contra-indication [29]. However, there is no clear evidence that these side-effects are causally related to the drug.

TABLE 6 Meta-analysis of smoking cessation trials in chronic obstructive pulmonary disease patients

Study	Subjects n	Prolonged abstinence rate
Lung Health Study [36]	5887	12 months: 34% versus 9% (NRT)
HILBERINK [37]	392	6 months: 16% versus 9% (NRT)
TØNNESEN [20]	370	12 months: 14% versus 5% (NRT)
TASHKIN [21]	404	6 months: 16% versus 9% (BUP)
WAGENA [38]	255	6 months: 30% versus 19% (BUP)
PEDERSON [39]	64	6 months 27% versus 16%
CROWLEY [40]	49	6 months: 14% versus 14%
BRANDT [41]	56	12 months: 32% versus 16%
TASHKIN [22]	499	12 months: 19% versus 6% (VAR)

Data are presented as abstinence rates for intervention versus control groups. NRT: nicotine replacement therapy; BUP: bupropion SR; VAR: varenicline. Reproduced from [35] with permission from the publisher.

In a recent meta-analysis from the Cochrane Library it was stated that the main adverse effect of varenicline is nausea, but mostly at mild to moderate levels, that tends to subside over time. However, it cannot be ruled out that there may be links between varenicline and serious adverse events, including serious psychiatric or cardiovascular events [10].

Data from a large treatment database from general practice in primary care in the UK included 80,660 males and females aged 18–95 yrs who were prescribed a new course of a smoking cessation product between September 1, 2006 and May 31, 2008: NRT (n=63,265), varenicline (n=10,973) and bupropion (n=6,422) [30]. There was no clear evidence that varenicline was associated with an increased risk of fatal (n=2) or non-fatal (n=166) self-harm, although a 2-fold increased risk cannot be ruled out on the basis of the upper limit of the 95% confidence interval. Compared with NRT, the hazard ratio for self-harm among people prescribed varenicline was 1.12 (95% CI 0.67–1.88), and 1.17 (0.59–2.32) for people prescribed bupropion. There was no evidence that varenicline was associated with an increased risk of depression (n=2,244) (HR 0.88 (0.77–1.00)) or suicidal thoughts (n=37) (1.43 (0.53–3.85)). In conclusion, although a 2-fold increased risk of self-harm with varenicline cannot be ruled out, these findings provide some reassurance concerning varenicline's association with suicidal behaviour.

Another new meta-analysis, which included all trials published to date, focused on events occurring during drug exposure and analysed findings using four summary estimates, and found no significant increase in cardiovascular serious adverse events associated with varenicline use [31]. For rare outcomes, summary estimates based on absolute effects are recommended and estimates based on the Peto odds ratio should be avoided [31]. A detailed analysis of adverse events of varenicline can be found on the US Food and Drug Administration website [32]. To date, surveillance reports and secondary analyses of trial data are inconclusive, but the possibility of a link between varenicline and serious psychiatric or cardiovascular events cannot be ruled out [10]. In my opinion, based on the previous data, I find no clear evidence

TABLE 7 Efficacy of smoking cessation after 6–12 months from meta-analysis of eight smoking cessation trials in chronic obstructive pulmonary disease patients

Treatment	OR (95% CI)	p-value
Nothing/usual care	1	
Counselling alone	1.82 (0.96–3.34)	0.07
Counselling + antidepressants	3.32 (1.53–7.21)	0.002
Counselling + NRT	5.08 (4.32–5.97)	<0.001
Counselling + varenicline	4.04 (2.13–7.67)	<0.001

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that varenicline is casually linked to either cardiovascular adverse events or psychiatric adverse events.

Overall, varenicline is the most effective drug for smoking cessation. In addition, varenicline tends to be more effective than bupropion and a single NRT but has a similar effectiveness as a combination of two NRT products [8]. In my opinion, taking into account that varenicline is very effective and that there is no evidence of a causal relationship between the above severe adverse events and varenicline, it is recommended as a first-line agent in smoking cessation in COPD patients. This is also the recommendation of several guidelines for smoking cessation.

Bupropion SR

Bupropion SR (tablets) is an older antidepressant drug with an effect on smoking cessation that is not related to the antidepressive effect [33]. The average 1-yr success rate reported in most studies is about 24% or a relative increase in quit rate to placebo of approximately 69% (relative risk) [11]. In COPD patients bupropion has been shown to be particularly effective.

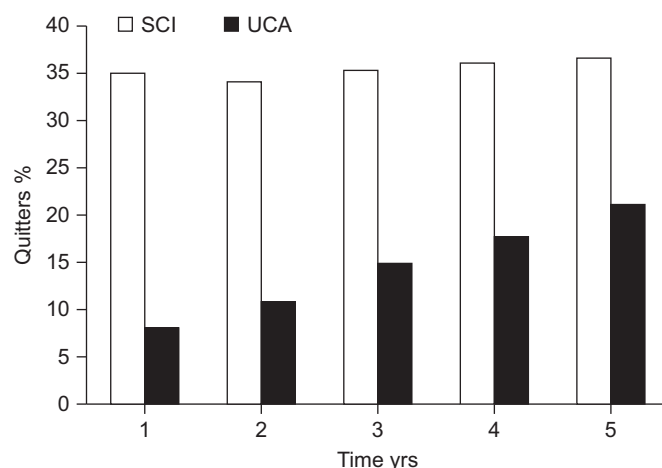


FIGURE 3. Smoking cessation rate as point prevalence quit rate from year 1 to 5 in the Lung Health Study with 5,587 chronic obstructive pulmonary disease patients. Smokers were treated with smoking cessation every 4 months in 5 yrs. SCI: smoking cessation intervention; UCA: usual care arm. Modified from [36].

The combination of bupropion SR and NRT is more effective than either treatment alone [9, 11].

COPD with bupropion SR

In this study 404 COPD patients (≥ 15 cigarettes per day) from 11 US centres were allocated to bupropion SR for 3 months or placebo in a design with moderate intensive support (*i.e.* 10 visits) with weekly individual sessions during the first 7 weeks [22]. Most patients were mild COPD in stage I (FEV₁ >50%) and 15% in stage II (FEV₁ 35–49%) with a cigarette consumption of 28 cigarettes per day and 52 pack-yrs and a Fagerstrom score of 7 (maximal score 11). Abstinence rate was significantly higher up to 6 months in the bupropion group *versus* placebo (16% *versus* 9%).

The most common adverse events from bupropion are insomnia and dry mouth. The most serious adverse event is major motor seizures, which have been reported in 0.1% of patients treated with bupropion, and allergic reactions (1–2%), with 0.1% of serious cases of hypersensitivity. There are also many contraindications for the use of bupropion [8, 11, 34].

In summary, bupropion SR is of similar efficacy as NRT. Compared with NRT and varenicline, bupropion has more serious side-effects and more contraindications.

Overall, NRT, varenicline and bupropion SR have shown higher relative efficacy in COPD patients. These studies have also reported a very low quit rate among COPD patients using placebo, probably because these smokers are more nicotine dependent and not able to quit without the support of smoking cessation drugs (tables 6 and 7) [35].

RE-TREATMENT IN COPD PATIENTS

The Lung Health Study I (LHS) is an exemplary model of a smoking cessation study [36]. The LHS was a multicentre, randomised study of smoking intervention *versus* usual care that also tested an inhaled anticholinergic bronchodilator. A total of 5,887 subjects with mild COPD, *i.e.* a mean FEV₁ of 75% pred (mean \pm SD 2.7 \pm 0.6 L), were enrolled in the study. They had a mean age of 48 yrs with a smoking history of 40 pack-yrs. During the first 3 months an intensive 12-session smoking cessation programme took place with the use of nicotine chewing gum plus adjunctive behavioural modification with a relapse prevention programme every 4 months over 5 yrs. At entry, strong physician advice to quit was given, and a target quit day was set. 2 mg nicotine gum was used aggressively.

The sustained quit rate was high in the intervention group and declined as predicted over the study period from 35% after 1 yr to 22% after 5 yrs compared with 10% after 1 yr and 5% after 5 yr in the usual care group. The cross-sectional quit rate increased slightly during the 5 yrs to 39% in the intervention group and 22% in the usual care group (fig. 3).

The other important finding was that smoking cessation significantly reduced the age-related decline in FEV₁ (-72 mL per 5 yrs for sustained quitters and -301 mL per 5 yrs for continuing smokers). Follow-up after 11 yrs showed that 22% (OR 4.45) of the subjects assigned to the intervention group maintained abstinence *versus* only 6% in the usual care group [42].

After 14.5 yrs, 731 subjects had died: 33% from lung cancer, 22% from cardiovascular disease and 8% from respiratory

disorders. All-cause mortality was lower in the intervention group compared with the usual care group, *i.e.* 8.83 per 1,000 person-yrs *versus* 10.38, with greater mortality benefit for those who actually quit smoking [43]. Thus, smoking cessation programmes substantially reduce mortality even when only a minority of participants stops smoking (22%).

Overall, this large well-conducted study showed that aggressive and intensive smoking cessation programmes can produce high long-term quit rates in smokers with mild airway obstruction. Also, the finding of the decline of FEV₁ supports the view that smoking cessation is the first and most important intervention in smokers with mild “sub-clinical” COPD.

CONCLUSION

An optimal approach to smoking cessation today should contain an adequate support programme, either individual or in groups, in combination with a first-line pharmacological smoking cessation agent, *i.e.* NRT (two formulations), varenicline or bupropion SR for 3 months. When relapse occurs, re-treatment should be offered. COPD patients need more support than smokers without comorbidities and smoking intervention should have top priority as it is very cost-effective, reduces the decline in lung function and reduces morbidity and mortality [44].

STATEMENT OF INTEREST

P. Tønnesen has received fees for speaking about smoking cessation from Johnson & Johnson and McNeil, he has received fees for participating in advisory boards from Pfizer and GSK, and he has participated in smoking cessation studies sponsored by Pfizer and McNeil.

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