SMOKING CESSATION IN COPD PATIENTS

(COST-)EFFECTIVENESS OF THE SMOKESTOPTHERAPY AND VALIDATION OF ABSTINENCE

Lieke Christenhusz

The studies described in this thesis were financially supported by the Dutch Asthma Foundation (Nederlands Astma Fonds) and the Comprehensive Cancer Centre Stedendriehoek Twente. Study medication was provided by GlaxoSmithKline.

Thesis, University of Twente, 2006
ISBN 90-365-2315-X

Cover design : Kim Vreeswijk & Bas Vreeswijk
Book design : Vanille, grafisch ontwerpbureau
Printed by : FEBO-druk b.v., Enschede

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PROEFSCHRIFT

ter verkrijging van
de graad van doctor aan de Universiteit Twente,
op gezag van de rector magnificus,
prof. dr. W.H.M. Zijm,
volgens besluit van het College voor Promoties
in het openbaar te verdedigen
op vrijdag 24 maart 2006 om 13.15 uur

door

Lieke Cornelia Anna Christenhusz
geboren op 8 mei 1978
te Oldenzaal

Dit proefschrift is goedgekeurd door de promotor, **prof. dr. E.R. Seydel** en de assistent-promotoren, **dr. J.A.M. van der Palen** en **dr. M.E. Pieterse**.

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CHAPTER 1

General introduction

Lieke Christenhusz

This dissertation describes the results of the SMOKE study and the associated CAMOXI study. The SMOKE study is a randomised controlled multi-centre trial investigating the (cost-)effectiveness of the new and intensive multi-component smoking cessation programme, SmokeStopTherapy (SST), versus the Minimal Intervention Strategy for Lung patients (LMIS). This multi-centre trial took place at the outpatient departments of three hospitals in The Netherlands: Catharina hospital at Eindhoven, Medisch Spectrum Twente at Enschede and Slotervaart hospital at Amsterdam. The CAMOXI study was designed to validate three different CO monitors for determining the smoking status of patients with Chronic Obstructive Pulmonary Disease (COPD) as well as healthy volunteers.

Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is one of the major causes of death and disability worldwide.[1] The near future will show a rise in the number of COPD patients, especially among women, and it is predicted to become the fifth most common cause of disability in 2020 worldwide resulting in a major health care expenditure.[2] This stresses the huge burden of the disease and the relevance of identifying the best possible treatment strategy.

COPD also has a major effect on the health status of the patients which is strongly related to daily symptoms like chronic cough, sputum production and (exercise-induced) shortness of breath. This leads to impaired exercise performance and decreased functional capacity. Furthermore, anxiety and depression also play a major role in the poor health status of these patients.[3] Consequently, many visits to health-care workers form an inevitable aspect of a COPD patients' life.

Cause of COPD

Smoking is by far the major cause of COPD and the epidemiological data for COPD are therefore strongly linked to the demographics of smoking.[4] Only a minor part of COPD is caused by indoor pollution, inhalation of smoke from biomass fuels (particularly among women who cook in poorly ventilated homes), or a rare α_1-antitrypsin deficiency.[1] The

decline of the Forced Expiratory Volume in 1 second (FEV1) is directly related to smoking, and the lung function of COPD patients who stop smoking declines more slowly than the lung function of COPD patients who remain smokers.[5] However, only 10 to 20 percent of the smokers develop COPD which indicates a difference in the individual susceptibility to cigarette smoke, but it remains clear that inhaled cigarette smoke causes oxidative stress and smoking accounts for more than 90 percent of the COPD cases in developed countries.[6]

Treatment of COPD

Three treatment possibilities regarding COPD are identified: 1) prevention of the progression; 2) management of stable disease; 3) management of exacerbations.[1] This thesis focuses solely on the first treatment option: prevention of the progression of the disease. This mainly consists of smoking cessation interventions, because this is the only intervention known to reduce the accelerated decline of pulmonary function and improve the prognosis of the illness in terms of survival, perceived health status and overall burden of disease.[9;5;8;7]

COPD and smoking cessation

Fletcher and Peto have unequivocally shown that smoking cessation in COPD-patients prolongs life and delays invalidity, at any stage of the disease.[5] A successful smoking cessation programme can achieve the improved outcomes mentioned above, and can therefore be seen as secondary prevention. Furthermore, it has been proven that smoking cessation may confer a survival benefit even among patients with very severe COPD.[10] Halting the progression of COPD and increasing quality of life should be the main goal of smoking cessation programmes for this target group.

Given these facts, it is surprising that no proven effective (by means of a randomised controlled trial) smoking cessation intervention is available for this high-risk target group in the Netherlands. After all, COPD patients in general have a long smoking history, a long history of failed quitting attempts, a very strong nicotine addiction,[11;12] and they are

smoking despite the fact that they are suffering from a smoking related disease. Jimenez et al. investigated the difference between smokers with COPD and 'healthy' smokers. According to Jimenez, smokers with COPD have a higher nicotine dependence and tobacco consumption. Despite the fact that achieving and maintaining smoking cessation in COPD patients is a challenge, a smoking cessation programme, matched to the needs of this specific target group, for example by increasing the intensity of the counselling, might achieve a higher effect. Both the Dutch Society of general practitioners (NHG)[13] and the recent Dutch multidisciplinary medical practise guideline on tobacco addiction treatment ('Richtlijn Behandeling van Tabaksverslaving')[14] stress the urgency of smoking cessation in COPD. Unfortunately, smoking cessation programmes aimed at the high-risk COPD population are currently scarce and their effect seems limited. Until the start of the SMOKE study, the only targeted intervention for smoking lung-patients available in the Netherlands was the Minimal Intervention Strategy for Lung patients (LMIS). For COPD patients the LMIS is currently being recommended as the preferred smoking cessation treatment for lung patients in general.[13;14] The LMIS was based on a brief intervention, the MIS, originally designed for Dutch general practitioners[15] and used by 27% of the lung physicians.[16] Thus far, the effectiveness of the LMIS has not been assessed in a randomised controlled trial. Despite the lack of evidence, approximately 40% of the lung physicians use the LMIS or offer other smoking cessation interventions to their patients.[16] This underlines the urgent need for both general practitioners as well as pulmonary physicians to have adequate tools for this high-risk target population.

COPD patients have developed a very strong nicotine addiction, and most of them tried to quit smoking repeatedly without success. A medium intensive smoking cessation programme seems to be ineffective for these patients, and it should therefore be investigated whether a more intensive therapy in an outpatient setting is more effective for this high-risk target group.

What is known about smoking cessation interventions targeted at COPD patients?

Relatively little is known about smoking cessation in COPD patients. A systematic review of van der Meer et al.[17] consisted of only five randomised controlled trials investigating the effectiveness of smoking cessation interventions in COPD patients.

Based on this review it was concluded that a combination of psychosocial interventions and pharmacological interventions is superior to no treatment or psychosocial interventions alone. A behavioural smoking cessation programme, as introduced in the Lung Health Study,[7] combined with nicotine replacement therapy was found to be the most effective strategy (35%) compared with no intervention (9%) after one year. The prolonged abstinence found in this study after 5 years was 21% for the treatment group versus 5% for the control group. Compliance with smoking cessation was objectively measured by expired carbon monoxide (at each visit) and salivary cotinine (annually). Furthermore, Monninkhof et al.[18] found a cotinine validated cessation rate of 13% at nine months. In this study trained pharmacy assistants visited smoking COPD outpatients at home and applied an intensified version of the LMIS. They concluded that, given the urgency for COPD patients to quit smoking, a more intensive smoking cessation programme than the LMIS is needed for this high-risk population. Based on the quit rates in COPD patients in general, it is concluded that the currently available smoking cessation programmes are insufficient to help COPD patients to quit smoking. As a response to this conclusion we developed a new outpatient intervention for these patients.

SmokeStopTherapy (SST)

The starting point in developing this new intervention, called the SmokeStopTherapy (SST), was our belief that combining effective components and intensifying these elements would lead to a more effective smoking cessation programme. This notion is supported by a review of the U.S. Department of Health and Human Services which suggests a dose-response relationship, since increasing the intensity of the psychosocial counselling generally increases effectiveness.[19] Within the SMOKE study, intensive psychosocial counselling and pharmacological support, which consists of obligatory use of bupropion (Zyban®) and Nicotine Replacement Therapy (NRT) as a possible adjunctive treatment, are combined in the SST which is specifically targeted at COPD outpatients. Although multifaceted interventions, in which pharmacological treatment is supported by counselling, have become common, the SST introduces two innovative elements. First, we used a combination of individual and small-group counselling. Second, we introduced the concept of 'recycling' as a relapse prevention strategy. This

means that patients, who experience a lapse (a slight error or slip) during the three month intervention period, are provided with the possibility to restart the individual part of the programme instantly to prevent a total relapse (a full recurrence of the pre-treatment behaviour). The question is whether combining all these elements will increase effectiveness considerably. This has to our knowledge never been investigated before. *Chapter 2* of this thesis describes the methodology of the SMOKE study, and provides an overview of the theoretical framework of the SMOKE study as well as the detailed content of the new developed SmokeStopTherapy.

Rationale of the SMOKE study

The SMOKE study is a randomised controlled multi-centre trial. The main aim of the SMOKE study is to investigate the effectiveness of the SST compared to the LMIS expressed as cotinine-validated continuous abstinence rates after one year aimed at COPD outpatients motivated to quit smoking *(Chapter 3)*. The SMOKE study not only evaluates the innovative SST, but also provides the first clinical trial involving the widely adopted LMIS as well. This implies that besides the relative effectiveness of the SST, the outcomes of the LMIS will be of clinical importance as well.

Although smoking cessation programmes in general are quite cost-effective in terms of avoided mortality and morbidity when compared to other medical treatments,[20] we are interested to learn whether our new programme may compete on cost-effectiveness with another smoking intervention, the moderately intensive Minimal Intervention Strategy for Lung patients (LMIS) *(Chapter 4)*.

To identify predictors for successful quitting in COPD outpatients, a logistic regression analysis was carried out. The baseline characteristics of the successful quitters were compared to the patients who failed to quit. If the predictors of successful quitting are known, it is possible to register the level of these predictors before the start of the intervention for each smoking COPD patient. Such screening creates the possibility to refer a patient to a smoking cessation intervention which matches his/her individual needs

and resources. As a consequence, this approach will increase the likelihood of a successful smoking cessation attempt *(Chapter 5)*.

Rationale of the CAMOXI study

To determine smoking status, self-report and biochemical validation can be used. Depending on type of study, type of population and demand characteristics, self-report can be deceiving as a result of socially desirable responses.[21] If this is the case, biochemical validation is essential. The determination of the cotinine value is regarded as the 'gold standard'. However, measurement of carbon monoxide (CO) in expired air using CO monitors is a frequently used validation technique as well. This method has several advantages compared to other validation tools such as salivary cotinine: it is relatively inexpensive, non-invasive, easy to apply, no bodily fluids need to be obtained and stored, and it provides direct feedback.[22] The measurement of CO in expired air is generally accepted although no investigation has been done to thoroughly verify the validity of this measurement within COPD patients. One of the issues is whether exhaled CO measurements can successfully detect deceiving smokers, who failed to quit, but falsely report abstinence. The CAMOXI study was designed to investigate the validity of three different CO monitors under more critical conditions than has previously been done. Twenty-six 'healthy' smokers, 25 healthy non-smokers, 25 smoking COPD patients and 24 former smoking stable COPD patients (age 40-72 years) were included. If subjects reported to be smoking, this was sufficient to include them as smokers. If they reported to be non-smokers, self-report, COHb, and salivary cotinine were combined to verify their non-smoking status. All volunteers were measured following a 12-hour abstinence period to mimic real life practice in which smokers might try to conceal their smoking status. Sensitivity, specificity, and predictive values of a positive and negative test result were assessed for a range of cut-off points for both CO and salivary cotinine *(Chapter 6)*. Furthermore, the smoking participants (25 healthy participants and 25 COPD patients) were measured seven times with three CO-monitors: first after the 12-hour abstinence period; than one hour after smoking one cigarette and five measurements each subsequent hour. The aim of this design was to monitor the course of the CO values

over time, and to investigate whether relapsed smokers are able to conceal their smoking status by short-time abstinence, as may be expected in high-risk smokers trying to quit. Moreover, recommendations concerning possible adjustment of the prescribed cut-off points were outlined *(Chapter 7)*.

Finally, the major results of the SMOKE study and the CAMOXI study, next to recommendations and future implications regarding future research and practice implications, are discussed in *Chapter 8*.

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CHAPTER 2

The SMOKE Study: Design and baseline characteristics of a randomised controlled trial to evaluate a new developed SmokeStopTherapy for outpatients with Chronic Obstructive Pulmonary Disease

Lieke Christenhusz, Erwin Seydel, Marcel Pieterse, and Job van der Palen

Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a widespread health problem. Smoking cessation is one of the few evidence-based treatments to improve COPD prognosis. Despite this urgent need, the smoking cessation programmes currently available in the Netherlands are insufficient to help patients with smoking related diseases to quit.

This chapter describes the SMOKE study, a randomised controlled trial investigating the effectiveness of an intensive multi-component smoking cessation programme, entitled SmokeStopTherapy (SST) for COPD outpatients, compared to a brief usual care intervention, the Minimal Intervention Strategy for Lung patients (LMIS). Patients willing to quit were randomly allocated to SST or LMIS. The SST consists of small-group counselling, individual face-to-face contacts, telephone counselling, and pharmacological treatment (bupropion and Nicotine Replacement Therapy). Additionally, patients can 'recycle' in the individual counselling in case of a lapse to avoid a total relapse. The primary outcome measure was the cotinine-validated continuous abstinence rate at six, and twelve months after the start of the intervention. Furthermore, baseline characteristics of the patients and the developmental process of the SST based on theories of behavioural change, such as the Attitude-Social influence-Efficacy-model (ASE-model), the Transtheoretical Model (TTM), Marlatt's Relapse Prevention model, and Motivational Interviewing (MI) are also outlined in this chapter.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an increasingly serious health problem. The near future will show a rise in the number of COPD patients, especially among women. COPD is predicted to become the fifth most common cause of disability in 2020 worldwide resulting in a major health care expenditure.[1] Fletcher and Peto have unequivocally shown that smoking cessation in COPD patients prolongs life, and reduces the accelerated decline of pulmonary function, regardless of the timing of the smoking cessation intervention with regard to the stage of the disease.[2] Furthermore, quality of life will improve when smokers become non-smokers.[3]

Relatively little is known about smoking cessation in COPD patients. The review by Wagena et al.[4] outlines the effectiveness of different smoking cessation programmes targeted at COPD patients. They found only five usable studies from which they concluded that the combination of psychosocial and pharmacological elements in a smoking cessation programme is superior to no intervention or psychosocial intervention alone. The lowest validated quit rate achieved, based on intention to treat, was 10% (prolonged abstinence after twelve months receiving brief telephone and face-to-face counselling on stopping smoking and placebo medication)[5] and the highest validated quit rate was 35% (point prevalence abstinence at 12 months receiving advice to quit by physician, group counselling, nicotine chewing gum and ipratropium bromide inhaler).[6]

In a recent Dutch trial on self-management in COPD patients, the COPE study,[7] smoking cessation was also studied in a single-group design. All smoking COPD outpatients were offered a minimal contact smoking cessation programme, delivered by pharmacy assistants visiting patients at home. After nine months the cotinine validated cessation rate, among participants who decided to participate (N=63), was 13%. The authors concluded that, given the urgency for COPD patients to quit smoking, a more intensive smoking cessation programme for this high-risk population is needed. Another Dutch study (SMOCC) investigated the effect of a brief smoking cessation programme for COPD patients in general practice. The biochemical validated continuous abstinence rate

after 12 months was 2.5 % in the intervention group versus 1.4% in the control group and this effect was not significant.[8] The low quit rates and absence of a treatment effect in this study are probably due to the fact that the intervention was of low intensity, and patients were included regardless of their baseline motivation to quit smoking.

Based on these disappointing quit rates in the COPD population we concluded that the currently available smoking cessation programmes are insufficient to help COPD patients to quit smoking. Indeed, these patients tend to have a long smoking history, a long history of failed quitting attempts, and a very strong nicotine addiction.[5;9] Therefore, a new outpatient intervention was developed for this specific target group.

The starting point in developing this new intervention, called the SmokeStopTherapy (SST), was our assumption that an intervention for COPD smokers should provide highly intensive counselling, and should integrate all components, including bupropion, that are evidence-based at present. The importance of high-intensity counselling is supported by a recent review by Fiore et al. who suggests a dose-response relationship, since increasing the intensity of interventions generally increases effectiveness.[10] Although multifaceted interventions, in which pharmacological treatment is supported by counselling, have become common, the SST introduces two key components. First, we use a combination of individual and small-group counselling. Second, we introduce the concept of 'recycling' to prevent relapse. Patients, who lapse in the course of the 3 month intervention period, are able to restart the individual sessions instantly to avoid a total relapse.

The effectiveness of the pharmacological treatment, both Nicotine Replacement Therapy (NRT) as well as other substances, has been demonstrated repeatedly.[5;12;11] Recently, sustained-release bupropion chloride (Zyban®) was also found to be effective in smoking cessation, showing higher quit rates than placebo after one year in a healthy population. A study by Hurt et al. indicated a dose dependent quit-rate.[11] Jorenby et al. also found higher abstinence rates after one year in subjects given bupropion compared to placebo, and the combination of bupropion and NRT was even more successful.[12;13] In the SST, bupropion is provided free of charge. NRT leads to a doubling of cessation rates compared to no NRT and the combination with a nicotine inhaler for acute relief is even

more effective with quit-rates after one year of 27%.[14;15] In the SMOKE study, intensive psychosocial counselling and pharmacological support are combined in the SST.

The question is whether combining all these elements will be more effective. This has to our knowledge never been investigated before. The SST will be evaluated on both effectiveness and cost-effectiveness in a randomised controlled trial. Although smoking cessation programmes in general are quite cost-effective in terms of avoided mortality and morbidity when compared to other medical treatments,[16] we are interested to learn whether our new programme may compete with a less intensive smoking intervention, the Minimal Intervention Strategy for Lung patients (LMIS), an existing programme that is often used in pulmonary outpatient care settings in the Netherlands. Both interventions will be outlined in more detail further in this chapter.

Theoretical framework

To give a general outline of the developmental process of the SST, the theoretical framework is briefly discussed below. First, the major theoretical models of behavioural change in general, and smoking behaviour in particular, are presented. Second, some of the specific intervention techniques are described in more detail.

Theoretical foundation

Three main models underlying behavioural change and maintaining that change were used in developing both interventions. A general framework of behavioural determinants is provided by the Attitude-Social influence-Efficacy-model (ASE-model).[17] The insights of the ASE-model are integrated with notions from the Transtheoretical Model (TTM),[18] while Marlatt's theoretical model of Relapse Prevention (RP)[19] provided a further expansion. The ASE model is a comprehensive social-psychological theory, based on Fishbein and Ajzen's Theory of Planned Behaviour (TPB) and Bandura's Social Cognitive Theory.[20;21;22] These theories focus on individual motivational factors as

determinants of the performance of a specific behaviour, like smoking cessation. In the ASE model, as in Theory of Planned Behaviour, the behavioural intention is the direct antecedent of actual behaviour.[23] In turn, intention is determined by three cognitive factors; Attitude, Social influence and Self-Efficacy.[24] Attitude refers to the overall evaluation (also called the pros and cons) of the desired behaviour, in this case smoking cessation. Social influence refers to three distinctive constructs: social norms (i.e. the belief whether significant others approve or disapprove of the subject quitting smoking), perceived behaviour of others, and direct support.[17] Self-efficacy refers to the situation-specific confidence in the ability to perform the desired behaviour successfully. In the case of smoking cessation self-efficacy mainly implies confidence in being able to refrain from smoking in high-risk situations, i.e. those situations in which the quitter is tempted to relapse. This may be a stressful event evoking negative emotions, but it can also be a pleasant, often sociable, experience. In the ASE model these three factors are considered as immediate or *proximal* determinants of intention and behaviour. In addition, the model also distinguishes several *distal* variables, like personality traits or a biological predisposition, which affect behaviour indirectly through the proximal determinants.

The only known study investigating a behavioural determinant related to smoking cessation and COPD is the Lung Health Study. This study investigated the relationship of social support to smoking cessation and continued abstinence for patients with evidence of early stage COPD. Social support had an overall positive effect on smoking cessation and continued abstinence, but mainly for men.[25]

In the SMOKE study, measurements of psychosocial variables are operationalised according to the ASE model. This offers the possibility to explore the psychological mechanisms by which cause the intervention may be effective.

The Transtheoretical Model, developed by Prochaska and DiClemente,[18] describes the readiness to change and the processes employed by individuals in achieving behavioural change. Originally designed to describe addictive behaviours and based on studying self-initiated quit attempts, the model has been widely adopted for numerous health behaviours.[26] The stages of change are key constructs of the Transtheoretical Model. The model provides an algorithm that distinguishes six stages: 1) precontemplation (no

intention to quit smoking within the next six months); 2) contemplation (intending to quit smoking within the next six months); 3) preparation, which was originally called decision making (intending to quit smoking within the next thirty days and having taken some behavioural steps in this direction;[27] 4) action (being abstinent for less than six months); 5) maintenance (being continuously abstinent from smoking for more than six months), and 6) termination (no temptation to smoke again and experiencing total self-efficacy). With regard to the Transtheoretical Model, it is important to notice that in the SMOKE study all included patients are in the preparation phase at the start of the quitting process. Readiness to quit smoking is an inclusion criterion. Nevertheless, during the study patients are likely to fluctuate through the stages. To monitor these transitions, a staging algorithm will be measured at several moments during the study. The Transtheoretical Model further describes several techniques employed by smokers trying to quit. It has been suggested that people progress from for example the 'preparation-stage' to the 'action-stage' by means of 'self-liberation' (making a firm commitment to change). As such, different processes of behavioural change need to be applied at different stages of change.[18] Within the SST these suggestions were taken into account.

The Relapse Prevention model is a theory that focuses on the maintenance of habit change and describes numerous intervention strategies that can avoid relapse. Relapse is viewed as a transitional process rather than a sudden event. A distinction has been made between a temporary 'lapse', also described as a slight error or slip, and a 'relapse', a full recurrence of the pre-treatment behaviour.[19]

Intervention techniques

The social-psychological factors attitude, social influence and self-efficacy are thought to play a determinative role in achieving successful smoking cessation. Constant attention to these three factors was therefore provided in both interventions and the evolution of these constructs was also carefully monitored. Obviously, providing counselling in small groups of patients generates in-treatment social support. Likewise, achieved goals (e.g. no smoking during a wedding) and the personal efforts concerning these goals were

emphasised to maintain the feeling of being capable of becoming and remaining abstinent (self-efficacy). To maintain a positive attitude towards smoking cessation, the subjects were repeatedly involved in discussions to revive their reasons for engaging in their current smoking cessation attempt.

The Transtheoretical Model is applied in several ways in the SST. The actual quitting process is divided in three phases (preparation, action and maintenance). During these three phases stage-matched counselling (a combination of individual and group counselling), tailored to the individual needs, is pursued in order to progress in stages. Different techniques need to be applied at different stages of change.[18] For example, within the preparation phase 'stimulus control' (removing reminders or cues to engage in smoking and adding cues or reminders to engage in quitting) is activated. Participants were for example asked to sum up the advantages and disadvantages of smoking, and afterwards discussion took place. During the action phase, 'self-liberation' (making a firm commitment to change) is encouraged by complimenting the participants with every 'smoke-free' day. Finally during the maintenance phase attention is paid to 'reinforcement management' (increasing the rewards for smoking cessation and decreasing the rewards for smoking) and advice is offered concerning relapse prevention.

With regard to relapse prevention, the SMOKE study contains an innovative approach: participants experiencing a lapse can 'recycle' (patients can repeat a part of the treatment in case of a relapse). Participants experiencing a lapse are provided with the necessary tools and strategies to prevent a relapse in accordance with the Relapse Prevention approach. The three main relapse prevention strategies, i.e. skill training (e.g. teaching the participant to execute an effective coping response in a high-risk situation and to experience a perception of control), cognitive reframing (e.g. regarding a lapse as a learning experience), and lifestyle interventions (e.g. relaxation exercises), are extensively used in the SST and partly in the LMIS.

It has long been recognised that the motivation to change is essential in changing behaviour and needs to become and remain optimal. Therefore, the 'Motivational interviewing' (MI)[28] approach has been used in both interventions. There are four general principles underlying motivational interviewing: expressing empathy (accepting patients

as they are), developing discrepancy (making patients aware of the fact that the present behaviour is conflicting with important personal goals; this will motivate behavioural change), rolling with resistance (avoiding opposing the patient's resistance to change and inviting the patient to consider new perspectives or information), and supporting self-efficacy (enhancing the patients' confidence in their own ability to change). A review by Britt et al. concludes that motivational interviewing interventions are promising in promoting health behaviour change.[29] The motivational interviewing technique and the Transtheoretical Model are closely linked to each other: motivational interviewing can be seen as a guiding tool at each stage of change.

To summarise, the ASE model assesses the psychosocial determinants of changing behaviour; the Transtheoretical Model determines the motivational state the participants are in; and the Relapse Prevention model offers strategies to guide participants to prevent relapse. Finally, the motivational interviewing technique has been used throughout all the stages within the cessation process.

Design

The SMOKE study is a multi-centre randomised controlled trial with one year follow-up in which two smoking cessation interventions for COPD patients (SST and LMIS) will be evaluated and compared. After signing the informed consent form and before baseline measurements took place, patients were randomly allocated to LMIS or SST. The data manager allocated the included patients based on a computerised randomisation list (stratified on hospital and within hospital randomised in blocks of four). In the following paragraphs both interventions will be described.

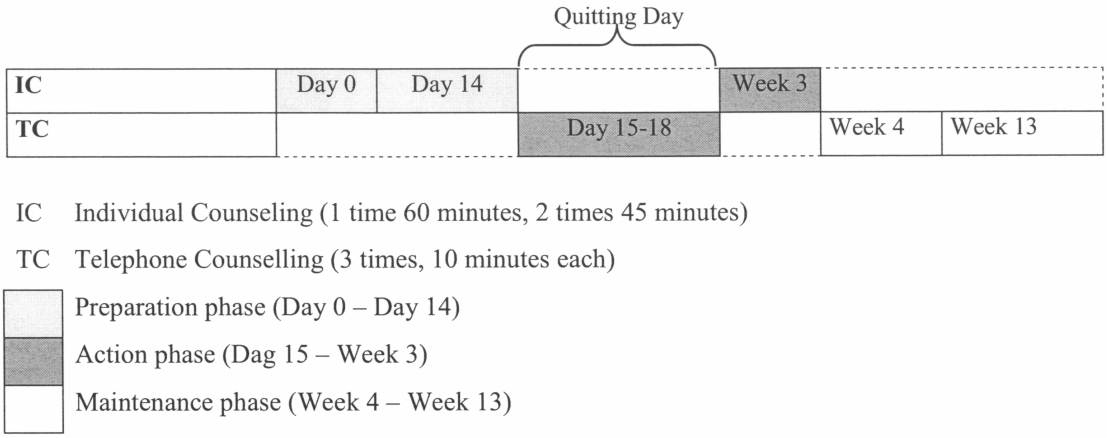
Interventions

The Minimal Intervention Strategy for Lung patients (LMIS)

The Minimal Intervention Strategy for Lung patients (LMIS) is currently being recommended as the preferred smoking cessation treatment for lung patients in the Netherlands.[30] The LMIS is adapted from a Dutch programme, the Minimal Intervention Strategy (MIS) developed for smoking cessation in General Practice[31;32] and can be considered as 'usual care' in outpatient departments of pulmonary medicine in the Netherlands.

In the LMIS the respiratory nurse counsels the patient after he/she has been advised to quit smoking by the chest physician, provided that the patient is motivated to quit smoking.[33] The LMIS contains three individual counselling sessions and three telephone contacts (See Figure 1). Pharmacological aids (e.g. Nicotine Replacement Therapy or bupropion (Zyban®) can be used by choice and at the patients' own expense. The effectiveness of the LMIS has never been investigated in lung patients before. Within the SMOKE study this intervention is primarily used as a comparator to the SST, but the study also illustrates the effectiveness of the LMIS.

Figure 1 Planning of the Minimal Intervention Strategy for Lung patients (LMIS)



SmokeStopTherapy (SST)

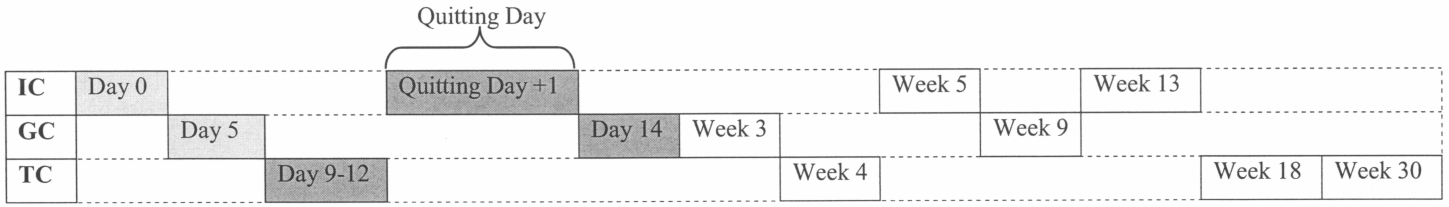
The SmokeStopTherapy (SST) is a multi-component intensive smoking cessation intervention targeted at COPD outpatients. This intervention integrates a disease-specific approach of the chronic smoking related disorder (COPD) and the chronic relapsing disorder ('nicotinism') with medical and behavioural counselling, relapse prevention, the possibility to 'recycle' in case of a lapse and within an outpatient setting (See Figure 2). The SST consists of individual, small-group and telephone counselling in which pharmacological support is strongly advised, and bupropion is provided free of charge. Patients can repeat part of the treatment in case of a lapse within the first three months. This 'recycling' principle is expected to boost the quit rates even more by avoiding a total relapse after having experienced a lapse. Only the individual sessions will be repeated in the 'recycling' period; the remaining participation in the group sessions will be unchanged. The content and structure of the counselling sessions is systematically based on the theoretical framework. More detailed information on the SST protocol is available on request.

Differences of the SST versus LMIS

The major differences between the LMIS and the SST (derived from Table 1 and Figure 1 and 2) are the following:

1) In general, the intensity of the SST is higher than the LMIS. The total number and frequency of contacts is higher (12 vs. 6). The total counselling time by the pulmonary nurse is longer (595 minutes vs. 180 minutes). Finally, the duration of the SST is 30 weeks (41 weeks if a full 'recycle' is included) compared to 13 weeks in the LMIS;
2) The SST contains group sessions unlike the LMIS;
3) Bupropion is provided for free only within in the SST;
4) Within the SST patients have the possibility to 'recycle'; this possibility is not provided within the LMIS.

Figure 2 Planning of the SmokeStopTherapy (SST)



IC Individual Counselling (1 time 60 minutes, and 3 times 45 minutes)

GC Group Counselling (4 times, 90 minutes each)

TC Telephone Counselling (4 times, 10 minutes each)

Preparation phase (Day 0 – Day 5)

Action phase (Dag 9 – Day 14)

Maintenance phase (Week 3 - Week 30)

Table 1 Psychosocial and pharmacological elements of the SST and the LMIS

SmokeStopTherapy (SST)		Minimal Intervention Strategy for Lung patients (LMIS)
Psychosocial elements	**Pharmacological elements**	**Psychosocial elements**
- Individual counselling	- Bupropion Slow Release (SR)*	- Individual counselling
- Group counselling		- Telephone contacts
- Telephone contacts		- Self-help material[2]
- Self-help material**		
- 'Recycling'		

Note. *Within the SmokeStopTherapy the Bupropion SR was provided for free
**Logbook

Preparation of the counsellors

Pulmonary nurses received eight hours of training on smoking cessation counselling for COPD patients. This training involved information about: the planning of the SMOKE study, the content of the interventions, pharmacological smoking cessation aids, and the theoretical background of the quitting process. Conversation techniques like motivational interviewing were taught through role playing and imaginary cases. In addition, the counsellors were supplied with a written manual containing the detailed protocol of the LMIS and the SST and the materials used in the interventions. During a pilot study one of the trainers also observed the meetings with the patients and provided feedback to the counselling pulmonary nurse.

Subjects

All patients were recruited through the outpatient department of pulmonary medicine of three hospitals in the Netherlands: Catharina hospital at Eindhoven, Medisch Spectrum Twente at Enschede and Slotervaart hospital at Amsterdam. Their chest physicians invited the COPD patients to participate in the study. Inclusion criteria and exclusion criteria are shown in Table 2.

Table 2 Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
-Current smoker	-Hypersensitivity for elements of Bupropion SR
-Motivated to quit smoking	-(History of) serious psychiatric co-morbidity
-40-75 years (1961-1926)	-Liver cirrhosis / alcoholism
-Clinically treated COPD. Moderate COPD (% predicted FEV1=50-69) or severe COPD (% predicted FEV1 < 50 as defined by the American Thoracic Society (ATS) criteria[34]	-Tumour in the central nervous system
	-(History of) epilepsy / fits
	-Quitting the use of alcohol and / or benzodiazepines during the course of the study
	-(History of) diabetes
	-Eating disorder(s)
	-Usage of monoamine oxidase inhibitors (MAO-inhibitors)
	-A serious other disease with a low survival rate
	-Not able to understand, read or write Dutch
	-Women who are pregnant, breastfeeding or intending to conceive during the course of the study

234 Patients have been included in the study: 117 patients received the LMIS and 117 patients received the SST. A total of nine drop outs, six from the LMIS group and three from the SST, were excluded from all analysis. Two LMIS patients quitted smoking after giving informed consent, but prior to the baseline measurement; four LMIS patients and two SST patients withdrew shortly after randomization and did not attend any intervention; one patient in SST did not meet the criteria for the diagnosis of clinical COPD

Measurements

Table 3 Measurement schedule

Variables	Measurement at month				
	Baseline	**Follow-up**			
	0	1	3	6	12
Informed consent	×				
In-/exclusion assessment	×				
Patient characteristics	×				
Smoking history	×				
Nicotine dependence (Fagerström)	×				
Blood sample (CYP2D6)			×		
Lung function tests	×			×	×
Withdrawal symptoms (WSWS)[1]		×	×		
Smoking status	×	×	×	×	×
Stage-of-change	×	×	×	×	×
Self-efficacy	×	×	×	×	×
Outcome expectancies	×	×	×	×	×
Social Influence	×	×	×	×	×
Quality of life (SGRQ)	×		×	×	×
Depression (BDI)	×	×			×
Cotinine levels[1]	×			×	×
Compliance with the intervention[2]	×	×	×	×	×
Exposure to other smoking cessation aids				×	×
Cost-effectiveness (Euroqol 5D)	×				×
Medication use[3]	×				×
Hospital days[3]	×				×
First-aid visits[3]	×				×
Outpatient visits[3]	×				×
Days lost of work[3]	×				×

Note. [1]Only measured in self-reported non-smokers; [2]Compliance is determined both by items in the questionnaires as well as by collecting participation data by the clinic personnel. For each subject a list of all essential intervention elements will be scored during the intervention phase; [3]In the previous year.

Measurements are done at baseline (prior to the intervention) and at one, three, six, and twelve months of follow-up as shown in Table 3.

Smoking history and nicotine dependence, measured by the Fagerström questionnaire,[35;36] are only assessed at baseline. Exposure to smoking cessation aids, other than the treatment, is measured at six and twelve months after the start of the intervention.[37] Lung function technicians will perform standard spirometry measuring Forced Expiratory Volume in one second (FEV1) and Forced Vital Capacity (FVC) at baseline, and after six and twelve months after the start of the intervention. During these visits 10 ml of saliva will also be obtained to determine the cotinine-validated smoking status. Withdrawal symptoms will be measured at one and three months after the start of the intervention by means of the Dutch version of the Wisconsin Smoking Withdrawal Scale (WSWS).[38] Measurements regarding self-reported smoking status, stage of change, self-efficacy, attitude, social influences, and compliance with the intervention and medication use, are carried out at every measurement moment. Quality of life will be measured by means of the St. Georges Respiratory Questionnaire (SGRQ)[39;40] which has to be completed at baseline and three, six and twelve months after the start of the intervention. The Beck's Depression Inventory (BDI)[41] has to be completed at baseline, and after one and twelve months of follow-up to measure the level of depression. The Euroqol-5D[42] has to be completed at baseline and at twelve months after the start of the intervention to measure utilities to be able to relate costs to effectiveness of both smoking cessation interventions. Furthermore, during every individual counselling session the participants will be weighed. Finally, the patients receive a logbook at the first (individual) counselling session. In the first two weeks the patients have to describe 'risky situations' with regard to the urge to smoke and their solutions to resist the temptation to smoke. After that the logbook has to be kept up to date. The aim of this logbook is to help the patient to cope with difficult situations.

The primary endpoints of the study are continuous abstinence (abstinence from any smoking from the quit date until the time measured) and point prevalent abstinence (abstinence of smoking at that point in time).[43] 40% of the patients receiving the SmokeStopTherapy are expected to quit compared to 20% of the patients receiving the

LMIS. When choosing a power of 80%, 81 patients per group would be needed. Furthermore, for future tailoring of the intervention, patient characteristics predictive for successful smoking cessation will be investigated as a secondary endpoint of the SMOKE study.

Data analysis

The main outcome parameters are the biochemically validated continuous and point prevalent abstinence at 12 months after the start of the SmokeStopTherapy. Data will be analysed on an intention-to-treat basis. Patients who drop out of the study and those with non-validated data will be assumed to be still smoking. Crude rates and corrected odds ratios for point prevalence and continuous abstinence rates of both groups will be presented. Logistic regression analysis will be used to correct for potentially confounding variables. Differences between the three hospitals will also be analysed and included as a covariate in all analyses. Within the cost-effectiveness analysis natural units will be converted to Euros (€), by using current prices and standard charges.[16] The results of the cost-effectiveness will be presented as a cost-effectiveness ratio (C/E ratio). The ratio of costs per additional quitter, hospitalisation days gained and exacerbations prevented will also be presented. A sensitivity analysis using Latin Hypercube simulations will be carried out to determine the possible variance in the C/E ratio, caused by alternative assumptions and estimates.

Conclusions

The need for an effective smoking cessation programme targeted at COPD patients has been outlined several times. Known theories of behavioural change were applied in our SMOKE study to develop a new smoking cessation programme for COPD patients, the SST. In general, the SMOKE study is characterized by a systematic application of

behavioural change theories in a treatment for smoking COPD outpatients. Whether this high-intensity and multi-component intervention will contribute to increased quit rates is the main question this trial aims to answer. Furthermore, smoking cessation aimed at patients with moderate to severe COPD has been investigated in only a few trials. The SMOKE study is, among other reasons, designed to fill this gap and contribute to the knowledge of how to shape the urgently needed (cost-) effective smoking cessation intervention for this high-risk target group.

Finally, it is important to address the applicability of this new therapy in daily clinical practice. In the SMOKE study, principles of successful innovation[44;45] were taken into account during the developmental process of the SST in several ways. For example, by involving chest physicians and lung nurses extensively in designing the SST, attempts were made to ensure the compatibility of the SST with current clinical practice. Furthermore, at the start of the study we have obtained commitment from the Dutch Association of chest physicians (NVALT), which is an important precondition as soon as nation-wide dissemination becomes reality. Likewise, the cost-effectiveness analysis should provide the necessary information to convince insurance companies.

Acknowledgements

The work presented in this chapter was supported by the Dutch Asthma Foundation (NAF grant no. 3.4.01.67) and the Comprehensive Cancer Centre Stedendriehoek Twente, The Netherlands. GlaxoSmithKline provided for the study medication. We gratefully acknowledge the department of pulmonary medicine, the lung function technicians and respiratory nurses of Slotervaart hospital, Catharina hospital, and Medisch Spectrum Twente. Furthermore, we would like to thank the data manager Betty Rinsma for her indispensable support. Finally, we would like to thank all the patients participating in our research, their dedication was vital to our study.

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CHAPTER 3

The SMOKE Study: Evaluating a high-intensity Smoking Cessation Programme for COPD Patients

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(Submitted)

Abstract

Aim: Smoking cessation is the only evidence based intervention that reduces the accelerated decline of pulmonary function and improves the prognosis of COPD. The SMOKE study compares two smoking cessation interventions for COPD patients: a high-intensity treatment including both individual and group counselling, telephone contacts, 'recycling' (a relapse prevention strategy) and bupropion for free (SmokeStopTherapy [SST]), with a medium-intensity treatment containing individual counselling and telephone contacts (Minimal Intervention Strategy for Lung patients [LMIS]).

Methods: In a randomised controlled multi-centre trial with one year follow-up 225 patients were randomly allocated to the SST or LMIS. The primary outcome measures are continuous and point prevalent abstinence from smoking after one year, validated by salivary cotinine. Analysis was by intention-to-treat.

Results: After 12 months, cotinine validated continuous abstinence rate of the SST is 19% versus 9% for the LMIS (RR= 2.22; 95% CI: 1.06-4.65; *p*=.03). The 12-month point prevalent abstinence rates are 22% for the SST versus 12% for the LMIS (RR= 1.80; 95% CI: 0.97-3.37; *p*=.06). The 'deceiving rate' was 12% in the SST and 20% in the LMIS.

Conclusion: The SST is more effective than the LMIS 12 months after the start of the intervention based on validated continuous abstinence rates.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a growing problem in particular due to the smoking trends of the last decennia.[1-3] Smoking cessation has proven to reduce the accelerated decline of pulmonary function and improve the prognosis of the illness in terms of survival, perceived health status and overall burden of disease.[4-7] Smoking cessation has been acknowledged to be the only evidence based treatment for COPD patients able to mitigate the burden of the disease.[8] Surprisingly, no effective smoking cessation programme for COPD outpatients was available at the start of the SMOKE study. The SMOKE study is a randomised controlled multi-centre trial investigating the effectiveness of a new high-intensity smoking cessation programme, SmokeStopTherapy (SST), compared to the medium-intensity Minimal Intervention Strategy for Lung patients (LMIS) currently in use as the main smoking cessation intervention by the Dutch chest physicians.

The effectiveness of different smoking cessation elements in the general population are well known compared to the knowledge of the effectiveness of these components in COPD patients. The known effective elements are outlined below.

In systematic reviews and meta-analysis an overview has been given concerning the most effective interventions in the general population. Woolacott et al.[9] found in their meta-analysis that both the use of Nicotine Replacement Therapy (NRT) and bupropion slow-release (SR) are effective interventions to support smoking cessation. The pooled Odds Ratio (OR) for any NRT compared to placebo or no treatment is 1.71 after 12 months, while the pooled OR is 2.76 for bupropion versus placebo. Wagena et al. found a 2.4-fold increased probability of abstinence when using Nortriptyline compared to placebo. Furthermore, bupropion seems to be more effective than nortriptyline but this reached no significant effect (Relative Risk (RR)=1.7).[10] In another review Coleman et al. concluded that effectiveness of smoking cessation interventions, expressed as OR, lies between 1.7 for brief advice and 2.8 for the use of Nortriptyline, compared to no advice or placebo.[11]

The abstinence rates found in general populations cannot be generalised to the COPD population, because COPD patients are in general highly addicted, have a long smoking history with often many failed quit attempts.[12;13] COPD patients are therefore likely to

encounter many difficulties in the quitting process. A different approach is therefore needed.

A recent systematic review of Wagena et al.[14] presents an overview of smoking strategies in COPD patients. An intensive behavioural smoking cessation programme combined with nicotine replacement therapy was found to be the most effective strategy and the efficacy of this intervention sustained for over 5 years.

The effectiveness of different smoking cessation interventions especially for COPD patients has not been thoroughly investigated yet. Therefore, the little information we have on successful smoking cessation elements specific for COPD patients and the elements known to be effective in other populations were combined and intensified in a new smoking cessation intervention. The content of both the LMIS and the SST is specified more in detail in the methods section. This study compares the effectiveness of the newly developed multi-component highly intensive smoking cessation intervention, SmokeStopTherapy (SST), with the medium intensive Minimal Intervention Strategy for Lung Patients (LMIS), which is the currently recommended treatment of nicotine addiction in patients with COPD in the Netherlands.[15]

Material and methods

Study subjects

The SMOKE study is a randomised controlled multi-centre trial with one year follow-up. The chest physicians asked eligible patients whether the patients was motivated to quit smoking and if the patient confirmed this he/she was invited for an informed consent meeting prior to the study. After signing a written informed consent form, blocked randomisation took place, stratified on hospital, into one of two groups: medium-intensity treatment (LMIS) or high-intensity treatment (SST). The SST was hypothesized to generate an abstinence rate of 40%, compared to 20% in the LMIS. To detect this difference with a power of 80%, 81 patients for each group were needed using 'power and sample size calculation'.[16] Due to loss of follow-up in this elderly group of patients with severe disease, a drop out of at least 20% was anticipated. Therefore, a minimum of

100 patients for each group were needed. Eventually, 225 patients were included in this study by their chest physicians.

Table 1 presents the baseline characteristics of the participants in SMOKE study. Patients receiving the LMIS were older than those receiving the LMIS. Nicotine dependence, as measured by the Fagerström questionnaire, was significantly stronger in the participants allocated to the SST compared to the LMIS (p=.02). In relation with this finding, the nicotine addiction, as indicated by the categorical outcome of the Fagerström questionnaire, was also stronger in the SST compared to the LMIS.

Table 1 Baseline characteristics of the 225 outpatients with COPD, presented as means (SD) or numbers (%)

Variables	**Minimal Intervention Strategy for Lung patients (medium-intensity) (n=111)**	**SmokeStopTherapy (high-intensity) (n=114)**
Gender, Male / Female	63 (57%) / 48 (43%)	55 (48%) / 59 (52%)
Age, yr*	59.6 (8.51)	57.0 (8.41)
FEV_1, L	1.86 (0.85)	1.93 (0.91)
FEV_1 % predicted of normal	62.8 (25.7)	65.6 (27.4)
IVC, L	4.78 (8.45)	4.71 (7.88)
Cotinine value, ng/ml	292 (144)	324 (145)
Cigarettes daily	20.5 (13.5)	24.1 (13.8)
Pack-years	41.7 (23.9)	46.4 (25.4)
Previous quit attempts (>24hr)	2.89 (5.95)	2.47 (3.38)
Smoking environment, range 0-4	0.97 (0.85)	0.96 (0.84)
Self-efficacy, range -2-2	0.09 (0.84)	0.12 (0.90)
Outcome expectancies, range -1.5-1.5	0.61 (0.54)	0.52 (0.48)
Social Influence, range 0-3	1.31 (0.87)	1.49 (0.90)

(Table continues)

Table 1 (*continued*) Baseline characteristics of the 225 outpatients with COPD, presented as means (SD) or numbers (%)

Variables	Minimal Intervention Strategy for Lung patients (medium-intensity) (n=111)	SmokeStopTherapy (high-intensity) (n=114)
Quality of life (SGRQ) three domains, range 0-100		
- Symptoms	52.2 (22.4)	51.4 (22.9)
- Activity	55.6 (22.5)	54.6 (23.4)
- Impacts	28.6 (16.8)	32.7 (19.8)
- Total	40.7 (16.7)	42.5 (19.1)
Depression (BDI), range 0-63	12.1 (8.45)	9.84 (8.37)
Nicotine dependence (Fagerström), range 0-10[†]	4.98 (2.05)	5.84 (2.14)
Nicotine addiction (Fagerström score ≥ 6), Yes / No[*]	39 (42%) / 54 (58%)	58 (59%) / 40 (41%)
Education level		
- High	20 (19%)	13 (13%)
- Middle	32 (30%)	30 (31%)
- Low	54 (51%)	54 (56%)

[*] $p < .05$. [†] $p < .01$.

Study design

The SST is an intensive smoking cessation programme combining psychological and pharmacological components. It consists of four small-group meetings (total 6 hours), four individual sessions (total 195 minutes), four telephone contacts (total 40 minutes) and the use of pharmacological aids. Bupropion was provided free of charge and was mandatory within the SST. NRT, which was used by 14% of the patients in this group next to bupropion, was optional and at the patients' own expenses. Finally, patients receiving SST could restart the individual sessions ('recycling') in case of a relapse within the first three months. The LMIS is a less intensive smoking cessation programme and contains three individual counselling sessions (total 150 minutes) and three telephone

contacts (total 30 minutes). The use of pharmacological aids, like NRT or bupropion, was allowed, but had to be paid for by the patients themselves. Ten percent of these participants used only some form of NRT, 32% used only bupropion and 8% used a combination of bupropion and NRT.

Methods

Several measurements were carried out at baseline and at six and twelve months after the start of the intervention. When patients self-reported to have quit smoking, after six and twelve months of follow-up, a 0.5-1 ml salivary sample was collected for cotinine assessment by means of a Salivette (Sarstedt AG & Co., Nümbrecht, Germany). Under supervision subjects chewed on a cotton swab for 45 seconds to stimulate the saliva flow rate. All saliva specimens were frozen until assayed and transported to the laboratory for the determination of the cotinine level from the salivary samples using a gas chromatography technique (GC-MS).[17] Saliva samples were considered to be invalid if less than 500 µl saliva was available. The accuracy and precision of this method was checked within the COPE study[18] by means of reference samples. Cotinine is a relatively long-lived metabolite of nicotine with a half-life of 15-40 hours.[19] It takes at least four days of abstinence from smoking for the cotinine level to return to that of a non-smoker.
Salivary cotinine was collected at baseline to gain insight in the distribution of the cotinine values among smoking COPD patients, and in those reporting to have quit smoking at six and twelve months after the start of the intervention. A cut-off level of 20ng /ml, which has a sensitivity of 99% and a specificity of 92%,[20] was used for the interpretation of the cotinine levels, which is commonly accepted in the literature. Validated abstinence rates are based on these results. Results were compared against self-reported quit rates to obtain an impression of the 'deceiving rate'. The primary outcome parameters are the biochemically validated continuous abstinence rate 12 months after the start of the intervention and the point prevalent abstinence rate at 12 months.

Analysis

Continuous abstinence is defined as validated point prevalent abstinence from smoking at six and twelve months after the start of the intervention. Point prevalent abstinence of

smoking is defined as abstinence at a specific point of in time. Validation was achieved by measuring salivary cotinine. Data were analysed on an intention-to-treat basis; patients that dropped out of the study, or were lost to follow-up, were assumed to be still smoking.

Significant confounding was not observed for any outcome of interest (continuous abstinence and point prevalent abstinence), and no effect modification by hospital was present. Therefore, unadjusted quit rates and relative risks are presented. For all analyses $p < .05$ was considered significant. All analyses were performed with SPSS for Windows, version 12.0.1 (SPSS, Chicago, IL, USA).

Results

The validated continuous abstinence rates at the end of the one-year follow-up were 19% (20/105) for patients receiving the SST and 9% (9/105) for patients receiving the LMIS (RR= 2.22; 95% CI: 1.06-4.65; p=.03). After twelve months the point prevalent abstinence rates were 22% (23/106) in the SST and 12% (13/108) in the LMIS (RR=1.80; 95% CI: 0.97-3.37; p=.06).

In some patients the self-reported abstinence was disconfirmed by their salivary cotinine levels which exceeded 20 ng/ml at that time in these cases. This 'deceiving rate' after one year of follow up is 12% in SST and 20% in LMIS which is not significantly different between both groups. For the analysis of the 'deceiving rate' only patients with validated as well as self-reported abstinence rates were included.

The option to 'recycle' was used by 19% (22/114) of the participants in the SST group. None of the participants who chose to enter the recycling process reached abstinence from smoking at twelve months after the start of the intervention.

Discussion

This study shows that after twelve months a high-intensity intervention (SST) is twice as effective as the medium-intensity treatment (LMIS) in outpatients with COPD. One of

the innovative components of the SST, the immediate re-entering of patients experiencing a lapse ('recycling'), did not contribute to this higher success rate of the SST.

The findings in this study are compared with the results found in other randomised controlled trials investigation the efficacy of smoking cessation strategies in COPD. The highest abstinence rate in COPD patients was found in the Lung Health Study[4] for the combination of a behavioural intervention and pharmacotherapy. The point prevalence abstinence rate at 12 months was 35% for a smoking cessation intervention compared to 9% in patients receiving no intervention. These abstinence rates are higher than the point prevalence abstinence rates at 12 months in the SMOKE study. This may be due to the fact that the Lung Health Study was administered to a sample of smokers with signs of early COPD as indicated by the presence of mild airway obstruction. In contrast, within the SMOKE study patients with clinically diagnosed moderate to severe COPD were included. Furthermore, the intervention used in the Lung Health Study[21] was far more intensive than the SST: immediately after receiving a motivational message of the physician, an individual behavioural interview took place. Furthermore, at least 12 group sessions took place over a period of 12 weeks and an extended intervention (with a variable content) was provided for the relapsed participants or participants who continued to smoke. The intervention also included at least three 'maintenance' meetings annually, a weight management programme twice a year, quarterly newsletters, and telephone or clinic visits contacts on a scheduled basis. Next to the behavioural part of the intervention nicotine gum was provided for free. This intensity outweighs the intensity of the SST by far which may have contributed to the difference in quit rates. However, such an intensive and organisationally complex treatment as in the Lung Health Study makes implementation very difficult.

Although the quit rates found in the SMOKE study may seem disappointing to the professionals in the field, given the high intensity of the treatment, it is important to keep in mind the specific characteristics of the COPD population. The 19% continuous abstinence rate remains a significant finding for this specific target group with a progressive chronic disease that in most cases has resulted from a long tobacco addiction. The high-intensity SST was developed to create a more effective intervention than the medium-intensity intervention (LMIS), the currently recommended treatment in the

Netherlands. It can be concluded that a high-intensity intervention can indeed reach a significantly higher abstinence rate in COPD outpatients. First, this finding confirms the dose-response relationship between intensity and effectiveness mentioned in the guidelines of Fiori et al.[22] Second, the high-intensity treatment (SST) reaches significantly better results than the medium-intensity treatment (LMIS). Within the general population the guideline of Fiori et al. assumes that any treatment-time beyond 90 minutes does not lead to any additional effect. The findings in the SMOKE study next to the findings in the Lung Health Study[4] counter this assumption at least for a high-risk target group like COPD patients because the intensity of the interventions in these studies reach beyond 90 minutes, nevertheless they achieve substantial additional effect within COPD patients.

Another interesting outcome of this study concerns the performance of the LMIS, used in this study as the usual care treatment. Until now, the effectiveness of the LMIS, despite the fact that it has already been dispersed in the Netherlands, was not assessed in a clinical trial. A treatment that achieves 9% continuous abstinence and 12% point prevalence abstinence at twelve months may be of clinical importance as well. The point prevalence validated abstinence rate appears to be similar to the cotinine validated cessation rate of 12.7% at nine months which was found in the largely comparable population of the COPE study.[18] In this study trained pharmacy assistants visited smoking COPD outpatients at home. Although this intervention differed at some points from the LMIS protocol in our study, the intensity of the counselling seems comparable. This indicates that the effectiveness of the LMIS found within the SMOKE study is consistent with the effectiveness found in comparable studies. This also indicates that the outcome of this trial, in which the SST has shown an incremental effectiveness, is valid.

It is important to keep in mind that although providing treatment of ‘nicotinism’ should be seen as an obligation for all the medical practitioners, including (chest) physicians, Britton et al. showed that nicotine addiction has not been treated as a serious medical problem yet.[23] Nicotine addiction needs recognition and dealing with nicotine addiction, especially within subjects suffering from a smoking related disease, should be a priority instead of only a routine component of a medical consultation. Nevertheless, medical practitioners hesitate to be actively involved in smoking cessation. The SMOKE study

aims to contribute to closing the gap by developing an effective treatment, to be used by chest physicians and pulmonary nurses.

An important feature of this study was validation of abstinence with biochemical markers. Comparing the self-reported abstinence rates with salivary cotinine validated abstinence rates leads to marked differences. Despite the fact that the participants were made clearly aware of the fact that their smoking status was checked, the 'deceiving rate' was rather high. It has been shown previously that self-reported abstinence rates are not reliable, especially when the participants are suffering from smoking-related diseases, the main aim of the intervention is known to be smoking cessation,[19] and when the intervention is intensive, which all applies to this study. The SMOKE study confirms the importance of the validation of the smoking status under such circumstances.

The most rigorous definition of continuous abstinence is: abstinence from **any** smoking, starting at the quit date. An apparent limitation of this definition is that it is virtually impossible to biochemically validate this outcome parameter. At the same time, self-reported continuous abstinence is not to be trusted, given the high 'deceiving rate' found in this study and previous studies.[18] In the SMOKE study we have chosen to base the continuous abstinence measure solely on the cotinine validated abstinence at six and twelve month follow-up, assuming that subjects being abstinent at both points are likely to have sustained abstinence in between. This measure can also be labelled as *consecutive validated abstinence*. The strength of this measure is that it relies on objective measures only. A consequence of combining the six and twelve months cotinine measurements is that the first six months are disregarded, and that all subjects abstinent for *at least* six months, are counted as successful quitters. In theory, this implies a less conservative measure that may result in an overestimation of effects. On the other hand, this allows lapses, and taking delayed action, without the necessity to label such cases as permanent smokers.[24] To assess effectiveness of the high-intensity SST, this is important because it justifies the concept of 'recycling', which enables lapsers to recuperate.

Of course, this does not resolve the issue of patients that, although being validated abstinent at both endpoints, may have been smoking in between. Because patients were aware of the fact that their abstinence was validated, they could have refrained from smoking a few days to a week prior to the measurements. This would artificially inflate

our continuous abstinence rates. However, since salivary cotinine can detect smoking at least 4 days prior to the test, this would require a considerable effort of deceiving abstainers. Given the profile of this population, this seems unlikely. Additionally, such deceiving behaviour will only be a validity threat to this study if it occurs differently in the two treatment arms. There is no indication that this bias occurred in this study since the 'deceiving rates' of both groups did not differ significantly.

Future research should be focused on the cost-effectiveness of smoking cessation interventions. Elements which are not (significantly) contributing to the effectiveness of the intervention should be identified and omitted from the intervention (e.g. the 'recycling' principle within the SST). As a result, the most compact intervention can be created without abating the effectiveness. This will increase the cost-effectiveness of the intervention.

Acknowledgements

We gratefully acknowledge the data manager Betty Rinsma, the smoking cessation counsellors and the lung function technicians in all three participating hospitals. Furthermore, we thank Evelyn Monninkhof for her useful critical remarks during the progress of the study. Additionally, we thank Tonny Knuif and Jan Goolkate for their contribution in the salivary cotinine analysis.

This study was funded by the Dutch Asthma Foundation and the Comprehensive Cancer Centre Stedendriehoek Twente. GlaxoSmithKline provided Bupropion free of charge.

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CHAPTER 4

Economic evaluation to assess the cost-effectiveness of an intensive smoking cessation intervention for COPD outpatients

Lieke Christenhusz, Marcel Pieterse, Erwin Seydel, and Job van der Palen

Abstract

Objective: To support optimal treatment decisions in the context of uncertainty by means of an incremental cost-effectiveness analysis of a new smoking cessation programme for COPD outpatients (SmokeStopTherapy; SST) versus current practice (Minimal Intervention Strategy for Lung patients; LMIS) in the Netherlands.

Methods: The cost-effectiveness analysis was based on a multi-centre randomised controlled trial investigating the effectiveness of the SST compared to the LMIS with 12 months follow-up. The primary outcome measure was the cotinine validated continuous abstinence rate based on intention-to-treat. A decision-analytic model assessed the incremental cost-effectiveness of the SST as compared to the LMIS after 12 months. A health-care perspective was adopted, with outcomes assessed in terms of (incremental) additional quitters gained, exacerbations prevented and hospital days prevented. Health care resource use, associated with smoking cessation, was collected at baseline and 12 months after the start of the interventions. A Latin Hypercube simulation was performed to evaluate the robustness of the results.

Results: Over 12 months the average patient receiving SST generated €581 in health care costs, including the costs of the smoking cessation programme, versus €595 in the LMIS. Furthermore, the SST is also associated with a lower average number of exacerbations (0.38 vs. 0.60) and hospital days (0.39 vs. 1) per patient, and a higher number of quitters (20 vs. 9) at lower total costs. These findings are robust and insensitive to changes in various parameters. This leads to a dominance of the SST compared to the LMIS.

Conclusions: As a result of the analyses of the data after one year it can be concluded that SST is more cost-effective than the LMIS. This is associated with cost-savings per additional quitter, prevented exacerbations and hospital days at lower or equal costs.

Introduction

The social and economic burden of COPD is considerable; both in terms of direct medical costs as well as indirect costs (e.g. lost productivity). Due to the substantial increase in tobacco use since World War II and the changing age structure, this global burden of COPD is likely to increase. However, economic evaluations concerning COPD are scarce.[1] Investments in the treatment of COPD seem to be the key activity to mitigate the present and future burden of COPD.

Smoking cessation is the only evidence based treatment to improve the COPD prognosis.[2;3] COPD patients have a long smoking history and most have experienced numerous unsuccessful previous quit attempts.[4;5] This makes smoking cessation difficult, unless an effective smoking cessation programme can be offered to these high-risk patients.

The SMOKE study is a randomised controlled multi-centre trial with 12 months follow-up to evaluate the relative (cost-) effectiveness of a new intensive multi-component smoking cessation intervention for COPD outpatients, SmokeStopTherapy (SST), compared to the Minimal Intervention Strategy for Lung patients (LMIS). The LMIS is adapted from the Minimal Intervention Strategy (MIS) developed for smoking cessation in general practice[6;7] and can be considered as 'current practice' in outpatient pulmonary medicine in the Netherlands. The LMIS contains three individual counselling sessions (60 minutes the first meeting and 45 minutes each consecutive meeting) and three telephone contacts (10 minutes each). Pharmacological aids can be taken by choice and at the patients' own expense. The SST contains four individual counselling sessions (60 minutes the first meeting and 45 minutes each successive meeting), four telephone contacts (10 minutes each), four small-group counselling sessions (90 minutes each), and pharmacological support is strongly advised (bupropion is provided free of charge for patients in the SST group). Additionally, patients can 'recycle' (restart the individual sessions) in case of a lapse within three months. After one-year the continuous abstinence rate (salivary cotinine validated abstinence at six and twelve months) was 19% (20/105) in the SST and 9% (9/105) in the LMIS (RR= 2.22; 95% CI: 1.06-4.65; *p*=.03). The SST was concluded to be significantly more effective than the LMIS.

It is important to analyze whether the potential beneficial effects of introducing the SST outweigh the additional costs compared to the existing and currently recommended smoking cessation programme, LMIS. A probabilistic decision analysis has been performed to compare the cost-effectiveness of the SST with the LMIS, when looking at costs per additional quitter and the costs per exacerbation and hospital days prevented over the 12 month time frame.

Methods

The SMOKE study is a randomised controlled multi-centre trial with one year follow-up which evaluated the effectiveness of the SmokeStopTherapy compared with the Minimal Intervention Strategy for Lung patients (LMIS). Patients motivated to quit smoking, (checked by their own chest physician) with the age of 40-75 years at the start of the study, having no contra-indications regarding the use of bupropion and clinically diagnosed COPD as defined by the American Thoracic Society (ATS) criteria[8], were included in the study. The study was approved by the Medical Ethical Committees of all three hospitals (Medisch Spectrum Twente, Enschede, The Netherlands; Slotervaart hospital, Amsterdam, The Netherlands; Catharina hospital, Eindhoven, The Netherlands) and all patients gave informed consent.

Economic evaluation

By means of a decision tree all possible pathways a COPD patient could travel, over a time frame of 12 months, were depicted (Figures 1-5). This decision analytic model was used to determine the incremental cost-effectiveness of the SST over the LMIS. Table 1 shows the base case probabilities with the associated 95% Confidence Interval (CI) for each (upper) arm in the decision tree, based on data from the SMOKE study.

Figure 1 Decision analytic model; both interventions and abstinence distribution (part 1)

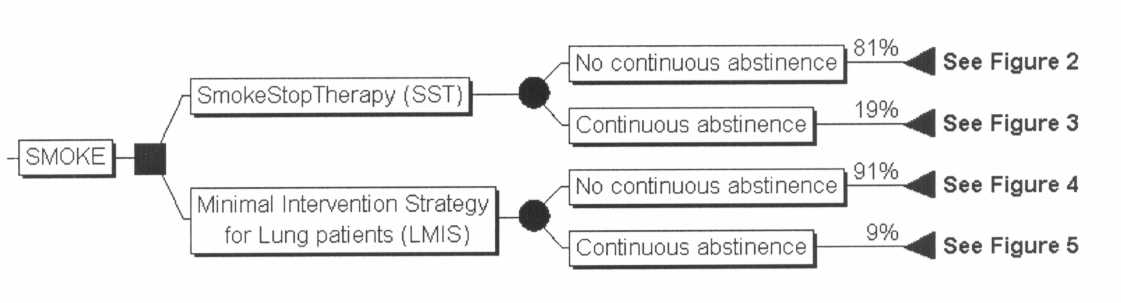


Figure 2 Decision analytic model; the not continuous abstinent arm of the SST (part 2)

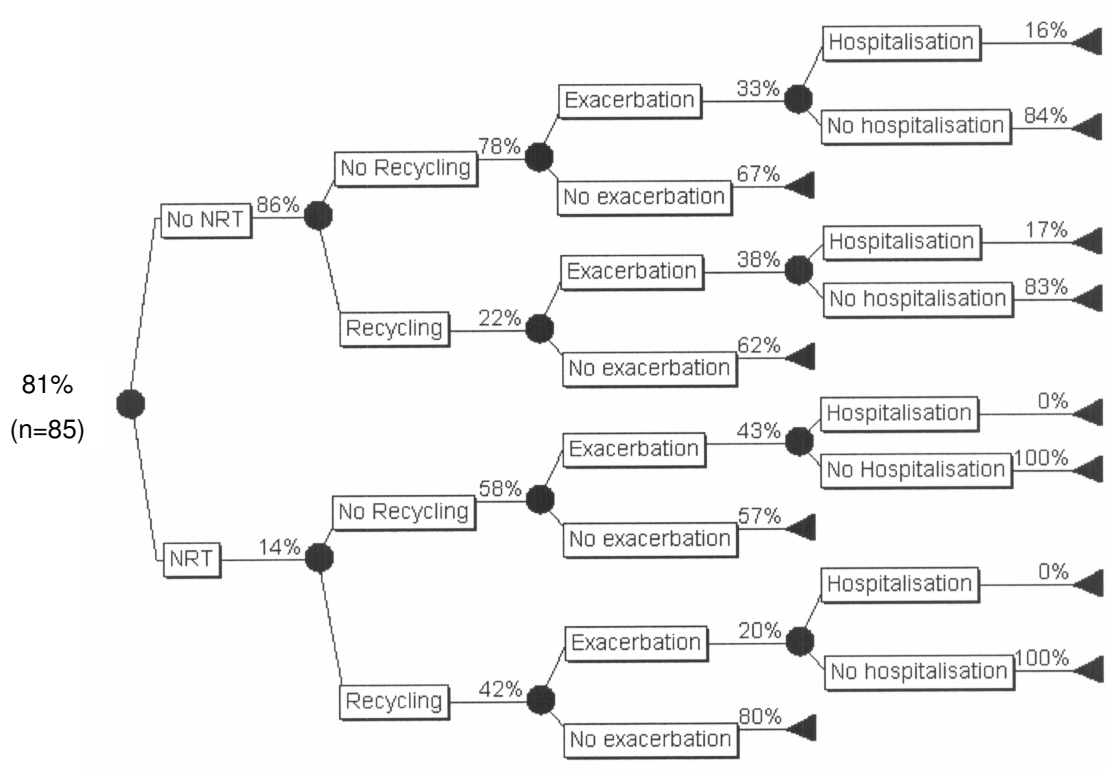


Figure 3 Decision analytic model; the continuous abstinent arm of the SST (part 3)

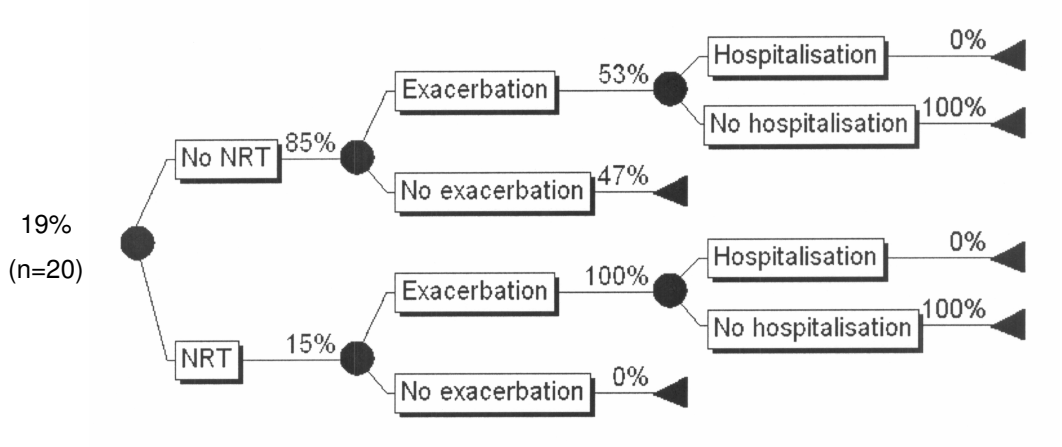


Figure 4 Decision analytic model; the not continuous abstinent arm of the LMIS (part 4)

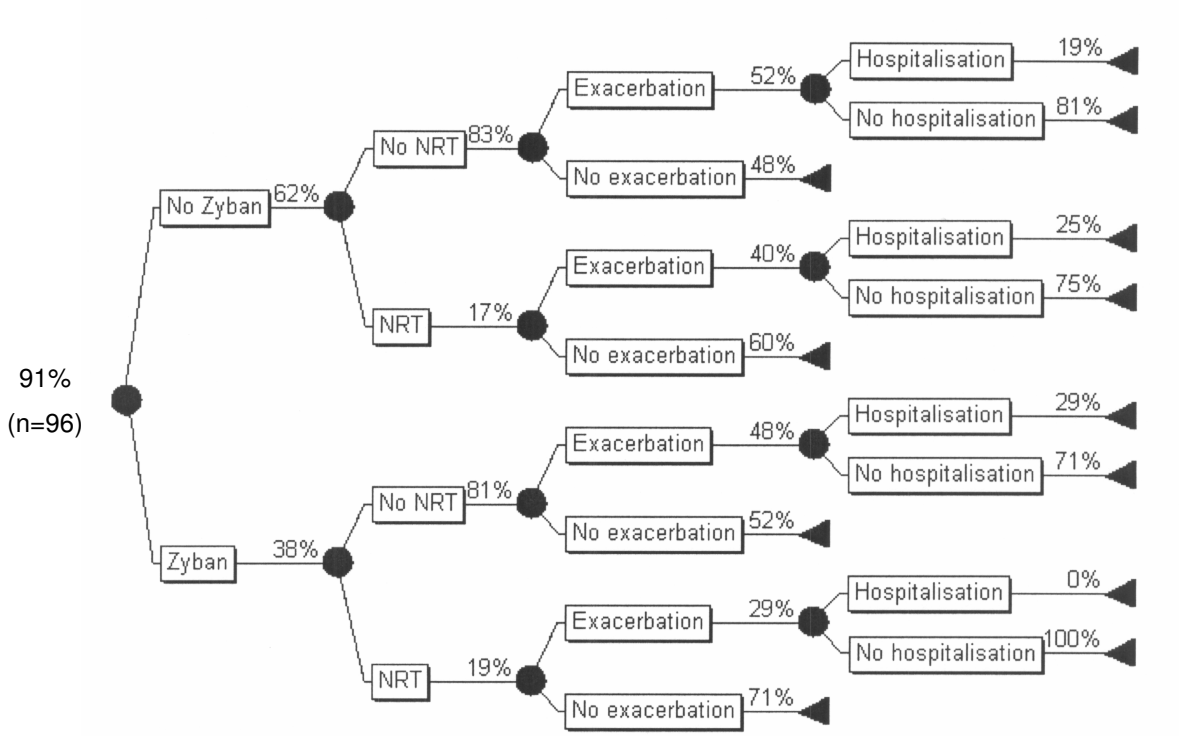
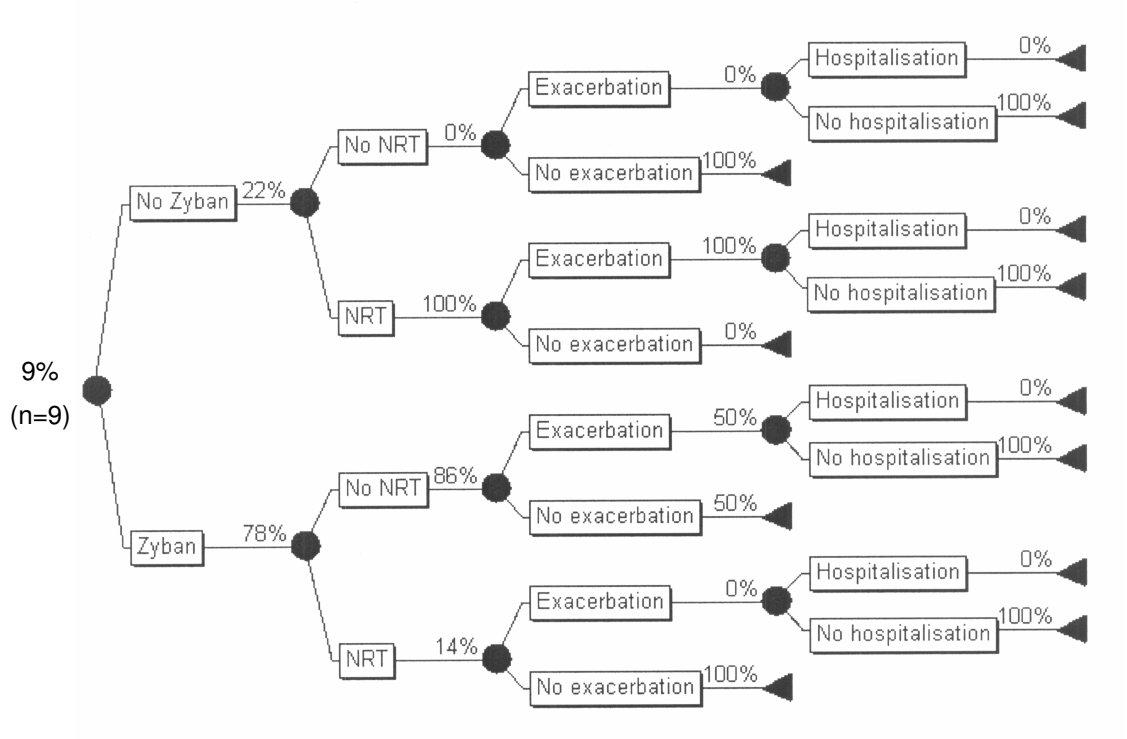


Figure 5 Decision analytic model; the continuous abstinent arm of the LMIS (part 5)



The primary outcome of the decision tree is the expected (incremental) costs of SST and LMIS per additional quitter. Because our data originated from a sample, uncertainty relating to observed data inputs existed. This uncertainty was quantified by means of a Latin Hypercube simulation with 1000 iterations to explore the variation of the total costs as well as the costs per quitter, number of exacerbations and hospital days prevented and quitters gained by varying the cost parameters and probabilities simultaneously over their ranges and the associated 95% confidence intervals. A triangular distribution was assumed for all costs and a logistic normal distribution for all probabilities.

Table 1 Base case values of the probabilities of each possible step in the decision tree

	Base case values of the SST (95% CI)
No CA	0.81 (0.73-0.90)
No CA + No NRT + No R + Exa	0.33 (0.12-0.55)
No CA + No NRT + No R + Exa + Hosp	0.16 (0.18-0.58)
No CA + No NRT + R	0.22 (0.18-0.43)
No CA + No NRT + R + Exa	0.38 (0.18-0.77)
No CA + No NRT + R + Exa + Hosp	0.17 (0.08-0.91)
No CA + NRT	0.14 (0.16-0.79)
No CA + NRT + No R + Exa	0.43 (0.17-1.00)
No CA + NRT + No R + Exa + Hosp	0.00*
No CA + NRT + R	0.42 (0.21-0.86)
No CA + NRT + R + Exa	0.20 (0.34-1.00)
No CA + NRT + R + Exa + Hosp	0.00*
CA + No NRT + Exa	0.53 (0.13-0.86)
CA + No NRT + Exa + Hosp	0.00*
CA + NRT	0.15 (0.18-0.56)
CA + NRT + Exa	1.00**
CA + NRT + Exa + Hosp	0.00*
	Base case values of the LMIS (95% CI)
No CA	0.91 (0.85-0.97)
No CA + No Zyban + No NRT + Exa	0.52 (0.32-0.72)
No CA + No Zyban + No NRT + Exa + Hosp	0.19 (0.19-0.54)
No CA + No Zyban + NRT	0.17 (0.19-0.40)
No CA + No Zyban + NRT + Exa	0.40 (0.39-0.89)
No CA + No Zyban + NRT + Exa + Hosp	0.25 (0.22-1.00)
No CA + Zyban	0.38 (0.21-0.54)
No CA + Zyban + No NRT + Exa	0.48 (0.42-0.55)
No CA + Zyban + No NRT + Exa + Hosp	0.29 (0.18-0.74)
No CA + Zyban + NRT	0.19 (0.17-0.49)
No CA + Zyban + NRT + Exa	0.29 (0.24-0.93)
No CA + Zyban + NRT + Exa + Hosp	0.00*

(Table 1 continues)

Table 1 (continued) Base case values of the probabilities of each possible step in the decision tree

	Base case values of the LMIS (95% CI)
CA + No Zyban + No NRT + Exa	0.00*
CA + No Zyban + No NRT + Exa + Hosp	0.00*
CA + No Zyban + NRT	1.00**
CA + No Zyban + NRT + Exa	1.00**
CA + No Zyban + NRT + Exa + Hosp	0.00*
CA + Zyban	0.78 (0.46-1.00)
CA + Zyban + No NRT + Exa	0.50 (0.18-1.00)
CA + Zyban + No NRT + Exa + Hosp	0.00*
CA + Zyban + NRT	0.14 (0.56-0.29)
CA + Zyban + NRT + Exa	0.00*
CA + Zyban + NRT + Exa + Hosp	0.00*

Note. CA=Continuous Abstinence; NRT=Nicotine Replacement Therapy; R='Recycling'; 95% CI=95% Confidence Interval; Exa=Exacerbation; Hosp=Hospital admissions; Zyban= Use of bupropion (Zyban®); *The assumption was made that the point value was 0.0025 for actual point values of 0; ** The assumption was made that the point value was 0.95 for actual point values of 1

Health care resource use and costs

The health care resource use was monitored during the 12 month follow-up period in which patients were questioned with regard to hospital admissions, experienced exacerbations, and the use of medication related to their quitting attempt (bupropion, Nicotine Replacement Therapy [NRT]). Furthermore, use of medication related to an experienced exacerbation (prednisolone and antibiotics) was asked for and checked by their pharmacists reporting all drugs used in the study period. The associated costs with the drugs were calculated using standards such as the Dutch Pharmacotherapeutical Compass 2005.[9] Medication costs were based on market prices and a dispensing fee of €3 was added. Furthermore, the controllers of the hospitals were consulted regarding the prices for medical treatment and resource use, including the salaries of respiratory nurses, lung function assistants, and chest physicians at the time the treatment took place (2002). The costs associated with the use of bupropion are included in the intervention costs of

the SST and not additionally counted, but are counted separately within the LMIS. The intervention costs of the SST are €379 and the intervention costs of the LMIS are €97, including salary costs of a respiratory nurse who executed the intervention and a chest physician concerning the referral to the intervention. Finally, the costs and effects were not discounted for time preference due to the short time frame of 12 months.

Results

Base case cost-effectiveness analysis

The total costs of an average COPD patient within the SST was €581 compared with €595 in the LMIS. The costs of the SST were slightly lower and the SST achieved a larger amount of quitters compared to the LMIS. There are therefore cost-savings per additional quitter gained. The same was true for costs per additional exacerbation or hospital days. Within the SST the average number of exacerbations was 0.38 and 0.60 within the LMIS. The number of hospital days was 0.39 for patients receiving the SST compared to 1 for patients receiving the LMIS. The number of quitters is 20 in the SST versus 9 in the LMIS and the associated costs are €3101 per quitter in the SST and €6832 per quitter in the LMIS. These results are presented in Table 2.

This means that the SST has dominancy over the LMIS on each outcome parameter.

Table 2 Costs (€) and effects twelve months after the start of the SST and LMIS

	SST	**LMIS**	**Difference**
Costs per quitter	3101	6832	-3731
Number of quitters	20	9	11
Costs (per patient)			
- Total costs	581	595	-14
- Costs of an exacerbation*	3.27	8.23	-4.96
- Costs of a hospital day**	27.93	124	-96.07

(Table continues)

Table 2 (continued) Costs (€) and effects twelve months after the start of the SST and LMIS

	SST	LMIS	Difference
Effects (per patient)			
- Average number of exacerbations	0.38	0.60	-0.22
- Average number of hospital days	0.39	1.00	-0.61

*Note.**Includes salary costs of a chest physician and lung function assistant, oral steroids and antibiotics including €3 prescription costs, spirometry costs and costs of a thorax X-ray in 50% of the cases. ** Mean number of hospital days per hospital admission is assumed 10.5

Sensitivity analysis of the decision analytic model

Probabilistic sensitivity analysis using a Latin Hypercube was employed to analyse the robustness of the above mentioned findings. To obtain a representative range of costs and effects, 1000 iterations were used. After simulation, the mean difference in total costs between both interventions is €12 (95% CI: -€211; €239) in favour of the SST. The estimates of the costs and effects are presented graphically in Figures 6, 7 and 8. Figure 6 presents the results of the simulation concerning the costs per prevented exacerbation.

The majority of the simulations is equally spread around the western half of the cost-effectiveness plane which favours the SST regarding the number of exacerbations. The mean difference in the number of exacerbations per patient is -0.22 (95% CI: -0.52; 0.02). However, the costs associated with prevented exacerbations are almost similar. For 52% of the simulations, the SST is associated with a lower average number of exacerbations at lower costs, and in 45% of the simulations the SST is again associated with a lower average number of exacerbations but also at higher costs.

Figure 6 Results of a Latin Hypercube simulation on costs per exacerbation prevented. Positive costs and a negative number of exacerbations favour the SST.

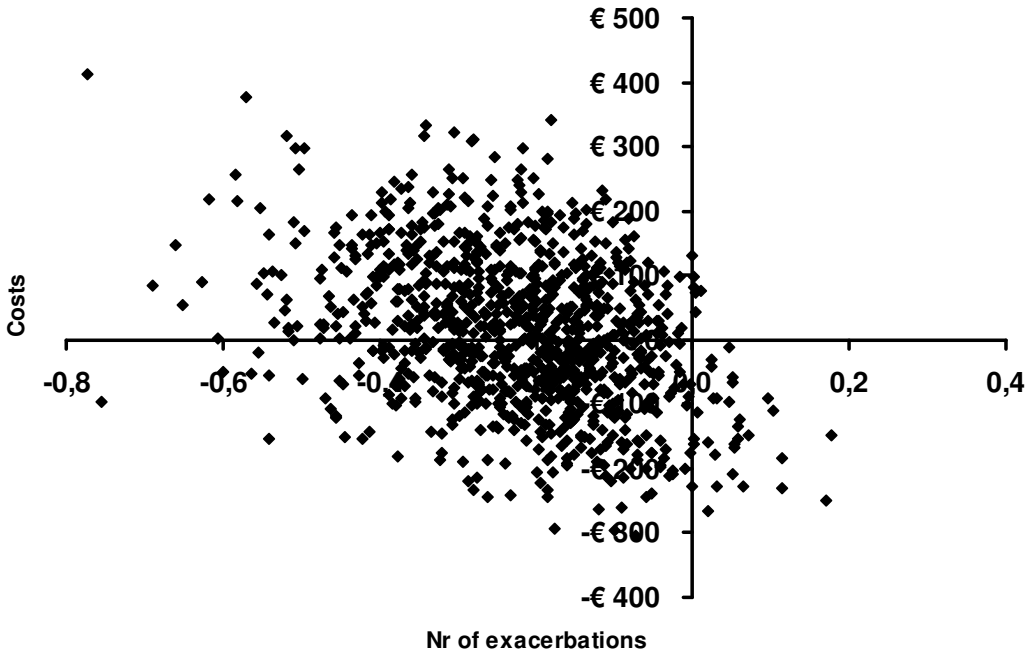
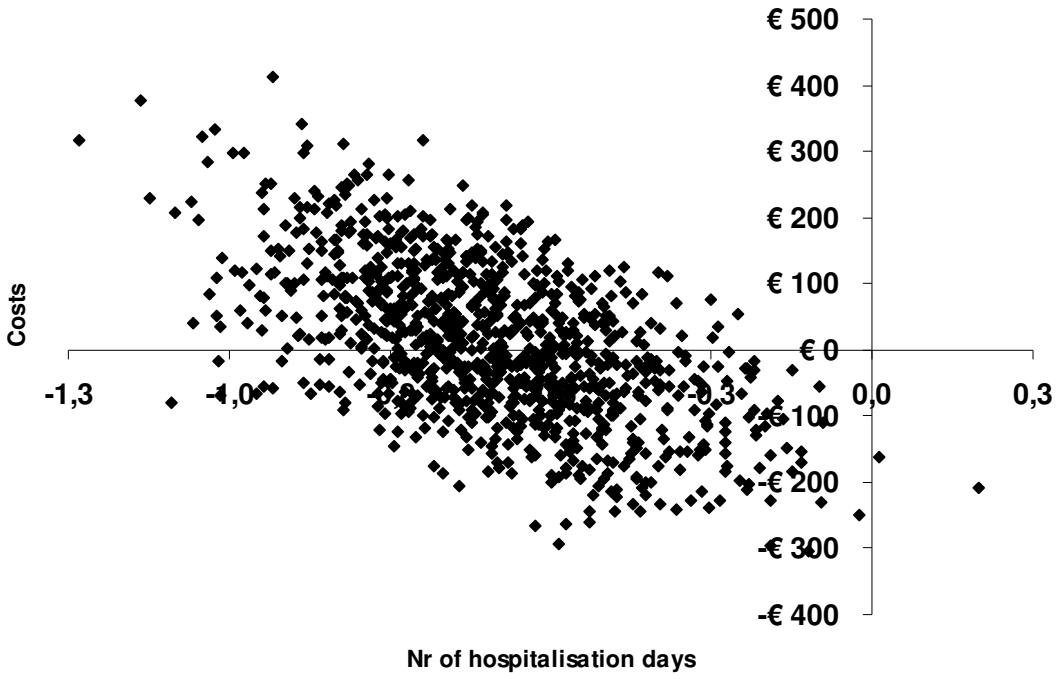


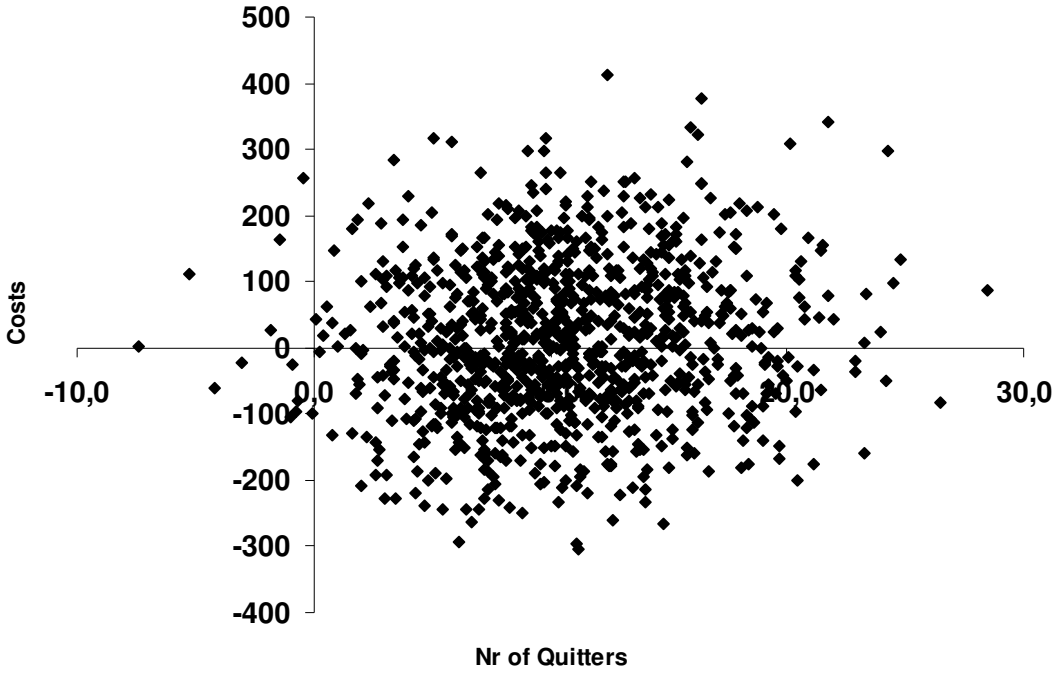
Figure 7 represents the difference in costs associated with the difference in the average number of hospital days per patient. The majority of simulations are situated in the western quadrants which favours the SST regarding the difference in the number of hospital days. However, the differences in costs associated with hospital days are almost equally spread around the north-west and south-west quadrants. The mean difference in hospital days is -0.595 (95% CI: -0.969; -0.189). The proportion of the simulations which lie in the north-west quadrant is 53%, which indicates that in 53% of the cases the SST prevents more hospital days at lower costs. Furthermore, 47% of the simulations are situated at the south-west quadrant. This indicates that the SST is again associated with a lower number of hospital days but also at higher costs.

Figure 7 Results of a Latin Hypercube simulation on costs per hospital days prevented. Positive costs and a negative difference in hospital days favour the SST.



The cost-effectiveness plane shown in Figure 8 represents the difference in costs associated with the difference in the number of quitters. In almost all simulations a higher number of quitters is associated with the SST. The costs are in 47% of the simulations lower for the SST and in 52% of the simulations associated with higher costs. The mean difference in the number of quitters is 10.5 (95% CI: 1.8; 20.5) and the mean difference in costs per quitter is €3 (95% CI: -€35; €36), which is in favour of the SST.

Figure 8 Results of a Latin Hypercube simulation on costs per additional quitter. A positive difference in costs and number of quitters favour the SST.



These results show that the findings in our sample are robust and therefore insensitive to changes in various parameters.

Conclusion and discussion

This study shows the SST to be cost-effective compared to the LMIS. The SST is not only more effective, but in approximately 50% of all simulations even less costly **and** more effective and therefore dominates the LMIS over a one year follow-up. There are no additional costs but actually savings associated with additional quitters, prevented exacerbations and prevented hospital days, as shown in the decision tree (Figures 1-5). Based on this cost-effectiveness analysis, the SST is the preferred treatment compared to the LMIS and therefore attractive for decision makers in the health care context. The sensitivity analysis showed that the findings are insensitive to changes in various

parameters which indicates that the validity of the conclusion of the economic analysis is robust.

Little is known about the effects of smoking cessation in COPD patients on mechanisms that may result in health benefits. Willemse et al.[10] concluded that respiratory symptoms, mental state and quality of life of COPD patients may improve after sustaining abstinence for one year. However, they also concluded that airway inflammation increased and that smoking cessation may have induced such inflammatory response. In contrast, the SMOKE study shows a negative association between continuous abstinence on the one hand, and exacerbations and hospital days on the other hand.

Because the smoking cessation aid bupropion (Zyban®) was an integrated part of the intervention, the total costs of the SST included the use of bupropion. Therefore, implementing the SST in the original form implies cooperation of the insurance companies with regard to reimbursement of bupropion.

The data of this study were generated from a multi-centre trial in three large general hospitals. This enhances the generalisability of the costs and the benefits found in the three hospitals.

To conclude, the results of the SMOKE study imply that the SST should always be preferred over the LMIS. However, there might be some predictors associated with an increased chance for reaching continuous abstinence with the LMIS as well. If the effectiveness of the LMIS increases by solely offering the LMIS to patients who are likely to benefit from such an intervention, the costs associated with additional quitters will drop dramatically. A higher abstinence rate is likely to result in a decrease in the number of exacerbations and hospital days. This 'matching' approach would make the LMIS a reasonable option to offer COPD patients, and this approach might lead to a different overall picture in which the LMIS might be reconsidered. More research should be done regarding the prospective determinants at baseline of smoking cessation in COPD patients.

Acknowledgements

Funding was provided by the Dutch Asthma Foundation (NAF 3.4.01.67), and the Comprehensive Cancer Centre Stedendriehoek Twente. GlaxoSmithKline provided bupropion as study medication.

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CHAPTER 5

Prospective determinants of smoking cessation in COPD patients

Lieke Christenhusz, Job van der Palen, Marcel Pieterse, and Erwin Seydel

Abstract

Background. The aim of this study was to identify characteristics of smoking COPD patients participating in a smoking cessation programme, that predict successful quitting, thus enabling health care providers to match interventions to individual needs and increase efficiency.

Methods. We compared two smoking cessation interventions in patients with COPD. One-year continuous abstinence rates were 9% for the Minimal Intervention Strategy for Lung patients (LMIS) and 19% for the SmokeStopTherapy (SST). The population consisted of 225 moderate to severe COPD patients, randomly allocated to SST or LMIS. A wide range of social-cognitive, demographic, smoking related and medical characteristics were measured at baseline. Only variables that showed a (marginally) significant ($p < .20$) univariate relationship with cotinine-validated continuous abstinence at 12 months were included in a full logistic regression model. Subsequently, variables that did not remain independent predictors of continuous abstinence were removed, one by one.

Results. Two baseline variables, attitude towards smoking and quitting and cotinine levels were independent predictors of continuous abstinence irrespective of smoking cessation intervention (SST and LMIS). The separate predictive models of SST and LMIS are also presented because the variables in the overall model did not produce the same predictive values within the LMIS or SST. For the SST subjects no independent significant predictor remained. The optimal predictive model for the LMIS group contained attitude towards smoking/quitting (OR: 11.8; 95% CI: 1.7-81.5) and cotinine level at baseline (OR: 2.1; 95% CI: 1.08-3.93).

Conclusions. This study suggests that a medium intensive intervention (LMIS) is only suitable for COPD patients with a strong positive attitude regarding smoking cessation. The more intensive SmokeStopTherapy can be seen as an alternative for patients not possessing such baseline characteristic. This stepwise approach may be useful in clinical practice and will lead to increased efficiency by matching the interventions to the patients' needs.

Introduction

The SMOKE study is a randomised controlled multi-centre trial investigating smoking cessation in COPD outpatients willing to quit smoking. A sample of 225 smoking COPD patients ranging in age from 40 to 75 with moderate to severe COPD was randomly allocated to either a moderately intensive 'usual care' intervention, the so-called Minimal Intervention Strategy for Lung patients (LMIS), or the innovative high-intensity and multi-component SmokeStopTherapy (SST). The validated continuous abstinence rate (using salivary cotinine) one year after the start of the intervention was used as the primary outcome measure. Based on this criterion the SST was found to be more effective than the LMIS (Continuous abstinence is 19% (SST) versus 9% (LMIS); RR= 2.22; 95% CI: 1.06-4.65).

The aim of this paper is to identify the baseline characteristics of COPD outpatients predictive of validated continuous abstinence. This is important for assisting health care providers in selecting patients and choosing between available smoking cessation interventions to improve the (cost-)effectiveness of these interventions offered to COPD outpatients. The theoretical framework of the Attitude-Social Support and Self-efficacy Model (ASE model)[1], readiness to quit as based on the stages- of-change algorithm,[2;3] disease characteristics, and other factors likely to influence the probability of smoking cessation in the general population, were taken into account as possible predictors of successful quitting in COPD patients.

In the general population it is known that the intensity of the intervention is associated with an enhanced likelihood of cessation[4]. Furthermore, Ferguson et al.[5] provided an overview of factors identified earlier as predictors of abstinence from smoking in adults. These factors include male gender, older age, being married, higher education, lower levels of nicotine dependence, fewer years of smoking, previous quit attempts, longer prior smoking abstinence, less time spent with other smokers, higher motivation to quit smoking, action stage of chance, higher levels of self-efficacy, social support for quitting, fewer depressive symptoms and absence of psychiatric co-morbidity. Only few studies have been done regarding smoking cessation in COPD patients. Baseline characteristics associated with abstinence among COPD patients in particular, have to our knowledge

not been thoroughly investigated yet. Sampablo et al.[6] indicated that patients with no history of previous COPD, a low FEF_{25-75} value and successful smoking cessation after one week were predictive factors in smoking cessation with combined therapy with bupropion and nicotine patches and are likely to remain non-smokers after one year follow-up. These results show that there is a void regarding baseline predictive factors in COPD patients.

The purpose of this study was to develop a model to predict continuous abstinence among COPD outpatients receiving the LMIS or the SST.

Methods

The ethical committees of all three collaborating hospitals gave their approval of the SMOKE study. Furthermore, informed consent was given prior to randomisation by all participants in this study.

Sample

A total of 234 smoking COPD patients were included in the SMOKE study. Due to drop-out 9 participants were excluded from all analyses. The COPD patients had to have clinically diagnosed moderate COPD (% predicted FEV1=50-69) or severe COPD (% predicted FEV1 < 50 as defined by the American Thoracic Society (ATS) criteria.[7] Participants were included only if they were aged between 40 to 75 years and if they had a good knowledge and understanding of the Dutch language. Willingness to participate in a smoking cessation programme was also an eligibility requirement. The only exclusion criterion was a counter indication for the use of Bupropion (Zyban®).

Eligible patients were randomly allocated to SST or LMIS. The SST is a new developed multi-component smoking cessation intervention which consists of group counselling, individual counselling and telephone contacts, supported by the obligatory use of Zyban® free of charge. The total counselling time of the SST is 595 minutes. The SST provides the possibility to repeat the individual sessions after experiencing a lapse within three months. This procedure is called ‘recycling’. The LMIS is an existing Dutch intervention that may be considered as current practise for smoking lung patients in the Netherlands,

administered in an outpatient setting. This intervention consists of individual counselling and telephone contacts. Pharmacological support is recommended during LMIS counselling, but use is voluntary and at the patients' cost. The sessions of the LMIS are less intensive and take place at a lower frequency compared to the SST. The total counselling time of the LMIS is 180 minutes.

Measurements

Measurements took place at baseline, six and twelve months. The following questionnaires were used: the smoking related questionnaire from Mudde et al.[8], the Fagerström Test for Nicotine Dependence (FTND)[9], Beck's Depression Inventory (BDI)[10] and the St. George Respiratory Questionnaire (SGRQ) .[11] Lung function was measured by spirometry and a saliva sample was collected for cotinine assessment. And finally, smoking status was determined at six and twelve months after the start of the intervention and, validated continuous abstinence was defined as abstinence confirmed by salivary cotinine level (< 20ng/ml) at both six and twelve months after the start of the intervention. Participants who reported smoking at six or twelve months or who failed to be validated as non-smokers at one of the follow-up measurements were defined as smokers.

Data Analyses

A logistic regression analysis was used to determine the attributes predicting validated continuous abstinence one year after the start of the intervention. The following baseline variables were entered in our analysis as possible predictors of smoking cessation: attitude (divided in a high positive attitude [> 0.75; scale -1.5-1.5] towards smoking cessation and a low positive attitude [≤ 0.75] towards smoking cessation), social support, self-efficacy, modelling (perceived behaviour)[12], previous quit attempts, readiness to quit, pack years, daily cigarette consumption, addiction and nicotine dependence (measured by the FTND), salivary cotinine value, inspiratory vital capacity (IVC), forced expiratory volume in second (FEV1)/IVC percentage predicted forced expiratory volume in 1 second (FEV1%predicted), hospital (3 locations), intervention (SST or LMIS), use of nicotine replacement therapy (NRT), use of bupropion (only in the LMIS), age, sex,

education level, depression (measured by the BDI) and Quality of Life (measured by the SGRQ). First, all these possible prospective determinants were univariately assessed on their relationship with continuous abstinence at twelve months, either by Students T-test (Normal distributions), Wilcoxon rank-sum tests (Non-normal distributions), or Chi-squared tests (categorical variables). Only variables that showed a significant or marginally significant ($p < .20$) univariate relationship with continuous abstinence, were included in a multivariate logistic regression model. Subsequently, variables that did not remain independent predictors of continuous abstinence were removed, one by one. Variables that were thought to correlate with each other were investigated and in case of multi-colineairity, the variable that led to the best predictive model based on the -2 log likelihood, was retained.

Results

First, an overall model of the total study population, including both SST and LMIS subjects, was explored. The baseline variables attitude towards smoking and quitting, social support, cotinine value, sex, depression, quality of life and IVC and intervention appeared to be possible predictors after univariate testing. After removing variables that did not remain independent predictors of continuous abstinence in the multivariate analysis, the optimal model (predictive model I, Table 1) included attitude and cotinine value. The intervention variable was retained in the predictive model based on the high probability of being a predictor. Subsequently, it was investigated whether or not the variables in this model produced the same Odds Ratio's for LMIS subjects and SST subjects separately. The predictive value of attitude differed markedly for SST subjects and LMIS subjects compared with the overall model which indicates that the relationship between attitude and the chance of smoking cessation differs between patients in the LMIS and patients allocated to the SST. This result was further explored by means of adding an interaction term between intervention and attitude to the overall model. Strongly different Odds Ratio's were observed for attitude (OR: 23.9; 95% CI: 1.99-286 for the LMIS subjects versus OR: 1.8; 95% CI: 0.53-6.12 for the SST subjects) and despite the fact that the interaction term did not reach significance (p=.20) it was

concluded that separate predictive models for subjects receiving LMIS and subjects receiving SST in stead of the overall model would provide more adequate information.

Table 1 Predictive values of the variables within the overall model (N=154)

	Predictive model I (SST and LMIS)		
	Sig.	**OR**	**95% CI for OR**
Attitude	0.01	3.71	1.34-10.3
Cotinine value†	0.03	1.47	1.03-2.09
Intervention	0.36	1.62	0.58-4.57

Note. Sig. =significance, OR= Odds Ratio, 95% CI = 95% Confidence Interval

† Cotinine values are divided by 100 for interpretation

The baseline variables mentioned earlier were again univariately tested for the LMIS and SST subjects separately. Sex, IVC, FEV1%predicted, depression and quality of life were found to be possible predictors in the SST. No significant independent predictors remained for the SST. In the LMIS attitude, self-efficacy, cotinine value, age and, quality of life and the use of Zyban were indicated as univariate predictors. The optimal predictive model (predictive model II, Table 2) consisted of attitude and cotinine value. If attitude towards smoking cessation was highly positive at baseline, the probability of continuous abstinence increased almost 12- fold, and each rise in the baseline cotinine value by 100 ng/ml, increased the chance of continuous abstinence 2-fold for subjects receiving the LMIS.

Table 2 Predictive values of the variable within the LMIS (n=79)

	Predictive Model II (LMIS)		
	Sig.	**OR**	**95% CI for OR**
Attitude	0.01	11.76	1.70-81.47
Cotinine value†	0.03	2.06	1.08-3.93

Note. Sig. =significance, OR= Odds Ratio, 95% CI = 95% Confidence Interval

† Cotinine values are divided by 100 for interpretation

Discussion

The best baseline predictors of continuous abstinence in COPD smokers trying to quit, irrespective of the type of smoking cessation intervention (SST and LMIS), were a strong positive attitude towards smoking cessation and higher cotinine values. However, this overall model does not seem to provide fully adequate information for subjects in SST and LMIS separately. Therefore, two separate models were defined. For patients receiving the SST no predictors for successful cessation were found. The optimal predictive model for patients receiving the LMIS contains the cotinine value and attitude. If attitude towards smoking cessation at baseline is strong, the probability of continuous abstinence is almost 12 times higher. This high predictive value is due to a large difference in attitude between relapsed participants and participants who accomplished to be continuous abstinent at twelve months. Due to the small number of quitters within the LMIS, the precise effect size of this predictor is uncertain, which can be inferred from the wide confidence interval of the Odds Ratio. Nevertheless, the importance of the baseline attitude as a predictor for abstinence in the LMIS participants remains undisputed.

Furthermore, if the cotinine value increases with 100 ng/ml, the chance for continuous abstinence in LMIS subjects increases 2.06-fold. This last finding is inconsistent with the available literature. However, the following suggestions (other than coincidence) might explain this finding. First, the counsellors may have put more effort in patients with a high baseline cotinine value because of their higher risk of relapsing. However, this explanation is unlikely because such reaction of the counsellors could also be expected within the SST in which the cotinine level was not found to be a prospective determinant for smoking cessation. Furthermore, the effort of the respiratory nurses was not measured in this study, which makes it impossible to check such effect. Second, smokers with a high cotinine level may have started the treatment with a higher internal motivation (“I smoke a lot, smoking clearly worsens my disease and I want that to stop”), while those with a lower cotinine level may have been more externally motivated (“I don’t smoke that much, but my chest physician persuaded me to stop anyway”). It can be assumed that internal motivation might be more stable than external motivation. The inclusion procedure contained an information meeting and the patients had to deliver a signed

informed consent. These elements required personal initiative and are likely to have excluded patients who were only externally motivated. Third, patients smoking more cigarettes a day might have a higher motivational level themselves which increased their chances of quitting (especially within the LMIS). Another possible explanation might be that patients who smoke less, are more likely to be more dependent on the few cigarettes they still smoke and are therefore less likely to sustain abstinent. This assumption suggests that nicotine dependence is highly correlated with the cotinine level and should therefore have been a predictor too, which is not the case. Furthermore, this still does not explain the positive relationship rather than expected negative relationship between the cotinine level and chance of continuously remaining abstinent. This finding that a high cotinine level is a prospective determinant of continuous abstinence therefore remains unexplained.

This study fails to identify a baseline variable that predicts continuous abstinence in subjects receiving the SST. This implies that the SST appears equally effective for every COPD patient willing to quit. In contrast, when participating in the LMIS, a strong positive attitude towards smoking cessation and a higher cotinine level is needed to increase the chance for continuous abstinence. This suggests that the high intensity of the SST somehow compensates for starting the intervention with a lower positive attitude.

For clinical practise this has several implications. In this case, two effective interventions for smoking cessation in COPD smokers are available, of which the LMIS is moderately intensive and the SST is highly intensive. These results suggest that the LMIS is the preferred treatment for patients who already have a highly positive attitude towards quitting. The SST is the preferred treatment for patients who, although ready to quit smoking, are less convinced about their decision. Further, for patients failing to quit within the LMIS, the SST is the indicated follow-up treatment. Luckily, the attitude towards smoking and quitting is easy to determine in COPD outpatients in clinical practice.

To conclude, when smokers are assigned to the LMIS, a highly positive baseline attitude towards smoking cessation is a strong positive predictive factor, which increases the chance to quit. On the other hand if the attitude towards smoking cessation is less positive, and the baseline cotinine value is also low, such a medium-intensity intervention

seems unsuitable and a high-intensity intervention should be offered to increase the chances of continuous abstinence. In this way the smoking cessation intervention can be matched at baseline to increase the efficiency of the smoking cessation interventions for COPD outpatients.

Acknowledgements

We gratefully acknowledge all the members of the Department of Pulmonary Medicine at Medisch Spectrum Twente, Slotervaart hospital and Catharina hospital and the Department of Communication Studies of the University of Twente. Additionally, we thank the data manager Betty Rinsma, Tonny Knuif and Jan Goolkate for their contribution in the salivary cotinine analysis.

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CHAPTER 6

Comparison of three carbon monoxide monitors for determination of smoking status in smokers and non-smokers with and without COPD

Lieke Christenhusz, Frans de Jongh; Paul van der Valk, Marcel Pieterse, Erwin Seydel, and Job van der Palen

Abstract

Objectives: The CAMOXI study validates three carbon monoxide (CO) monitors regarding their ability to distinguish smokers from non-smokers, in participants with or without COPD. Salivary cotinine measures were also validated.

Participants: 26 'healthy' smokers, 25 healthy non-smokers, 25 smoking and 24 former smoking stable COPD patients (age 40-72 years) were included (N=100). Smokers were determined by self-report and non-smokers by a combination of self-report and cotinine measurements (< 20ng/ml).

Design: All participants were measured following a 12-hour abstinence period. Sensitivity, specificity, positive predictive values and negative predictive values were calculated for a range of cut-off points for both CO and cotinine measurements.

Results: The factory-prescribed 9 ppm cut-off point of the Breath CO® generates a sensitivity of 68% and 42% for COPD patients and healthy people respectively. The factory-prescribed cut-off point of 10 ppm of the Smokerlyzer® generates 56% sensitivity for COPD patients and 23% for healthy participants. Both monitors generate 100% specificity in both groups. The cut-off point for the Micro CO meter® (5 ppm) generates 88% sensitivity and 92% specificity for COPD patients, and for healthy people 92% and 88%, respectively. Salivary cotinine has a 100% sensitivity, specificity, positive predictive value, and negative predictive value over the range of 15 ng/ml through 40 ng/ml for healthy participants and at 10 ng/ml for COPD patients using self-report as the 'gold standard' for this specific analysis of cotinine.

Conclusions: The prescribed cut-off points for all three CO monitors generate misleading results concerning the determination of the smoking status in both populations under these circumstances. The optimal cut-off points depend upon the goal of the test. Salivary cotinine measurement outperforms CO measurements and a cost-effective validation procedure combining both tools is recommended.

Introduction

Smoking cessation is the most effective treatment for Chronic Obstructive Pulmonary Disease (COPD). Developing smoking cessation programmes for COPD patients is therefore of high clinical importance. The effectiveness of a smoking cessation programme is generally expressed in terms of point prevalence abstinence rates (at 12 months) or continuous abstinence rates (during the full 12 months follow-up period). Unfortunately, self-reported quit rates in smoking cessation programmes are likely to be biased[1] and tend to overestimate programme effectiveness. Deceiving responses by participants, for example as a result of social desirability, lead to underreporting of substance use.[2]

The degree of deceiving seems to depend on three factors:[3;4] A) type of intervention (intensive smoking cessation interventions will show higher deceiving rates than self-change interventions); B) type of population (high-risk medical patients versus healthy participants); and C) demand characteristics (primary goal is smoking cessation versus no pressure concerning smoking cessation). Several biochemical validation techniques have been developed to correct for this bias. Clearly, biochemical validation of smoking cessation is imperative in intensive smoking cessation interventions for COPD patients in which the primary aim is to quit smoking.[5]

Several studies among COPD patients demonstrated high deceiving rates. For example, within the COPE study, which investigated medical and behavioural interventions in COPD, abstinence was not confirmed by salivary cotinine in 12 out of 23 self-reported quitters (deceiving rate: 52%).[6] In a trial which investigated a brief smoking cessation intervention by general practitioners, van Opstal et al. also observed a much lower validated abstinence rate (9%) compared to the self-reported abstinence rate (16%).[7]

There are two obvious explanations for discrepancies between self-report and biochemical validation: 1) Patients deny their smoking status because they tend to give a socially desirable answer or wish to report behaviour consistent with a healthy life-style or 2) biochemical validation tools (e.g. CO monitors) are not valid.[8;9]

Various biochemical validation methods are available: 1) Cotinine, typically measured in saliva, serum or urine, is the major metabolite of nicotine and has a half-life of 15 to 40

hours. Cotinine is considered to be the 'gold standard' for biochemical validation because of its superior sensitivity and specificity[3;10] and has the advantage of being almost specific to tobacco.[11] 2) Thiocyanate is a metabolic by-product of hydrogen cyanide gas and can be assessed from serum, plasma or urine. Serum Thiocyanate (SCN) has a half-life of 10-14 days but its sensitivity and specificity is low.[3;12;13] 3) Carbon Monoxide (CO) is typically measured in exhaled air, has a half-life of 4 to 5 hours and a high sensitivity and specificity[3] Carboxyhemoglobin (COHb) can be measured in blood and has a half-life of 1 to 4 hours.[12] Compared to the other techniques mentioned, exhaled CO has several advantages. The first is the possibility to provide immediate feedback to the user. Other techniques require more time-consuming chemical processing. Furthermore, exhaled CO is a non-invasive and relatively inexpensive method that is easy to apply. Unfortunately, CO in exhaled air can be confounded by many factors like variations in diet, physical exercise, exposure to atmospheric pollution, time of day, time since the last cigarette, and last but not least, environmental tobacco smoke exposure (ETS). Also, the level of CO seems to be higher in subjects with coronary heart disease and/or an inflammatory airway disease like COPD.[14] Nevertheless, despite these possible confounders, subjects can be successfully classified into broad categories of smoking activity by CO levels in exhaled air.[15]

There are only a few studies available concerning validation of exhaled CO in COPD patients. Murray et al.[4] compared CO measures, using either the MiniCO® (MSA, Pittsburgh (PA), USA) or the Smokerlyzer®, with self-report as a 'gold standard' in a large intervention study (Lung Health Study). The sample consisted of cigarette smokers with evidence of early stage chronic obstructive lung disease. They found a sensitivity of 93.7% and a specificity of 87.2% using the prescribed cut-off level of 10 ppm. Middleton et al. assessed the use of exhaled CO with the Smokerlyzer® to determine the smoking status of 41 patients attending a respiratory outpatient clinic and of 24 healthy subjects, compared to self-report.[16] They concluded that the Smokerlyzer® is a suitable instrument for assessing smoking status in a clinical setting: a breath CO level of > 6ppm gave a sensitivity of 94% and a specificity of 96%. Sato et al. assessed the optimal cut-off level of breath CO concentration, using the Smokerlyzer® to distinguish actual smokers from non-smokers among patients with asthma and COPD[17] by using serum cotinine

concentrations as the 'gold standard'. They concluded that a cut-off level of 10 ppm (85% sensitivity; 86% specificity) was optimal in patients with stable asthma, and 11 ppm (73% sensitivity; 85% specificity) in patients with stable COPD. The higher cut-off level in these patients was explained by the potential influence of underlying airway inflammation. Recently, Low et al.[18] performed a study comparing breath CO levels with self-reported smoking status in smokers with non-smokers among 195 military outpatients using the Smokerlyzer®. A cut-off level of 5 ppm (96% sensitivity; 98% specificity) was concluded to be the optimal cut-off level.

Neither in the literature nor in the manuals of the three different CO monitors has consensus been reached concerning the ideal cut-off point for exhaled CO in the general smoking population and certainly not for COPD patients. The exploration of the generated sensitivity, specificity, positive and negative predictive values may elucidate the range in which the optimal cut-off level may vary. Single optimal cut-off points, conditional upon the goal of the specific type of study or intervention and population, can be determined from the tables presented. This is essential because these three elements can influence the degree of deceiving and/or the CO value measured.

The aim of the CAMOXI (Carbon Monoxide Investigation) study is to investigate the validity of three CO monitors in smokers and current non-smokers in a healthy and COPD population. Moreover, all smoking participants were asked to remain abstinent during 12 hours prior to the tests. This mimics real life or clinical study situations in which smoking subjects know that their smoking status will be checked and may be inclined to mislead the investigator or physician by remaining abstinent immediately prior to the visit. Obviously, this procedure provides a more critical test, as it assumes that all smokers will try to conceal their smoking status. A 12-hour abstinence period prior to the CO monitor test seems reasonable as this requires only a few cigarettes not to be smoked, especially if the test is administered in the morning.

Methods

Study population

Four groups were included in the CAMOXI study: 26 'healthy' smokers, 25 healthy non-smokers, 25 current smokers and 24 ex-smokers with stable COPD, all aged between 40 and 75 years were included. Subjects reporting to be currently smoking were defined as smokers and subjects reporting a non-smoking status AND having a salivary cotinine level below 20 ng/ml were defined as non-smokers. One patient was excluded from the study because both the COHb value (3.60) as well as the cotinine value (348 ng/ml) incontestably indicated that this COPD patient was a smoker despite a self-reported non-smoking status. The healthy population was defined as a population without COPD or other clinically diagnosed illness based on self-report. The COPD patients had a clinical diagnosis of stable COPD. The COPD patients had to have clinically diagnosed moderate COPD (% predicted FEV1=50-69) or severe COPD (% predicted FEV1 < 50) as defined by the American Thoracic Society (ATS) criteria.[19]

Study design

This study compared three different CO monitors (EC50 Micro III Smokerlyzer®, Bedfont Instruments, Kent, UK; Breath CO®, Vitalograph Inc, Lenexa (KS), USA; Micro CO meter®, Micro Medical Ltd, Kent, UK[20;21]). Following a 12-hour abstinence period, end tidal expired air CO concentrations (ppm) were measured, according to standard procedures: subjects were asked to exhale completely, inhale fully and hold their breath for a minimum of 10 seconds and a maximum of 20 seconds (depending on the different manuals and the ability of the participant) and exhale slowly into the CO monitor. The sequence of the different CO monitors was randomised. The monitors were checked and calibrated daily before use. A cotton swab (Salivette®) was used to take salivary samples and specimens were frozen and subsequently assayed for cotinine (ng/ml) using a Gas Chromatography–Mass Spectrometry (GC-MS) technique.[22] The precision and accuracy of this method was checked by means of reference samples. A smoking related questionnaire[23] was administered to measure the participants' smoking characteristics and smoking status (self-reported).

All participants gave written informed consent for participation in the study. Medical ethical approval was granted by the medical ethical committee of Medisch Spectrum Twente at Enschede, the Netherlands.

Data analysis

All continuous variables were assessed for normality of their distribution. In case of normality means were compared using Analysis of Variance with Tukey's Honestly Significant Difference tests in case of pairwise post hoc comparisons. In case of non-normal distributions means were compared using Kruskall Wallis test. Wilcoxon's Rank Sum test with Holm's correction was used for pairwise post hoc comparisons. Sensitivity, specificity and the predicted outcome of a negative and positive test result of the three different CO monitors was assessed using the cut-off points for the CO value as described in the separate manuals with salivary cotinine validated smoking status as the 'gold standard'. Results are displayed in receiver operating characteristic (ROC) curves.[24]

Results

The baseline characteristics of the healthy participants and the COPD patients are presented in Table 1. The term 'Smoking environment' means the number of smokers in the direct environment. This term has been introduced to measure the amount of passive smoking. Although the two groups are clearly different, we will not elaborate on this finding because the differences are not relevant to this study.

No preference of the participants concerning the usability of the three CO monitors was indicated in this study. Table 2 shows the mean (SD) of the values of the different CO monitors in all four groups.

Table 1 Baseline characteristics of the participating COPD patients and healthy participants

	All healthy participants (n=51)	**All COPD patients (n=49)**
Male/Female, number (%)	27 (53)/24 (47)	39 (80)/10 (20)
Age in years (SD)	58 (5.6)	64 (6.0)
Smoking environment	(almost) no smokers 21 (41)	(almost) no smokers 17 (35)
	< 50% smokers 20 (39)	< 50% smokers 26 (53)
	≥ 50% smokers 9 (18)	≥ 50% smokers 7 (15)
	'Healthy' smokers (n=26)	**Smoking COPD patients (n=25)**
Number of cigarettes per day (SD)	17 (8.4)	21 (18.2)

Table 2 Mean (SD) of the CO values of the four different groups by the different CO monitors at baseline

	Non-smokers		**Smokers**	
	Healthy (n=25)	**COPD (n=24)**	**'Healthy' (n=26)**	**COPD (n=25)**
Breath CO®	2.3 (1.4)	2.6 (1.3)	9.7 (4.8)	12.8 (6.2)
Smokerlyzer®	1.7 (1.4)	2.0 (2.0)	8.0 (4.5)	11.2 (5.9)
Micro CO®	4.0 (1.2)	3.4 (1.3)	9.6 (4.1)	12.3 (5.4)

Using the independent sample T-test, no difference between healthy non-smokers and non-smoking COPD patients on all three monitors was found. On the other hand, the 'healthy' smokers show significant lower CO values on the Smokerlyzer® (p=.03; 95% CI: 0.27- 6.14) and the Micro CO® (p=.049; 95% CI: 0.14-5.40) and a borderline significant difference on the Breath CO® (p=.06; 95% CI: -0.07-6.13), compared to the smoking COPD-patients. As expected the CO values of the smokers differ significantly from the CO values of the non-smokers on all three CO monitors (all $p < .001$).

For smokers there is a correlation between exhaled CO and salivary cotinine (Correlation coefficient = 0.5; $p < .001$, for all three CO monitors). For non-smokers there is only a weak correlation between CO and cotinine. Moreover, there is no linear relationship between these two variables.

The sensitivity (% actual smokers detected as such), specificity (% actual non-smokers detected as such) and the positive predictive values (% actual smokers among the subjects classified as smokers by the CO monitor) and negative predictive values (% actual non-smokers among the subjects classified as non-smokers by the CO monitor) shown in Table 3 are generated when the cut-off points, as described in the manuals of the three monitors, are used. Values above the cut-off point are considered to be of smokers and values below and equal to the cut-off point are considered to indicate non-smokers.

The sensitivity of the Smokerlyzer® used in COPD patients and the sensitivity of the Breath CO® and the Smokerlyzer® in healthy participants differ significantly from the Micro CO®.

Table 3 Sensitivity, specificity, positive predictive value and negative predictive value of the three different CO monitors using the prescribed cut-off points for healthy participants (N=51) and COPD patients (N=49)

	Sensitivity % (95% CI)		**Specificity % (95% CI)**		**Positive PV% (95% CI)**		**Negative PV % (95% CI)**	
	COPD	**Healthy**	**COPD**	**Healthy**	**COPD**	**Healthy**	**COPD**	**Healthy**
Breath CO®	68.0	42.3	100	100	100	100	75.0	62.5
Cut-off: ***9*** *ppm*	(49.8-86.2)	(23.3-61.3)					(57.8-92.2)	(43.5-81.5)
Smokerlyzer®	56.0	23.1	100	100	100	100	68.6	55.6
Cut-off: ***10*** *ppm*	(36.6-74.5)	(6.8-39.4)					(50.0-87.2)	(36.2-75.0)
Micro CO®	88.0	92.3	91.7	88.0	91.7	88.9	88.0	91.7
Cut-off: ***5*** *ppm*	(75.3-100)	(82.1-100)	(80.7-100)	(75.3-100)	(80.9-100)	(76.7-100)	(75.7-100)	(80.9-100.)

Note. PV= Predictive Value; ppm=parts per million

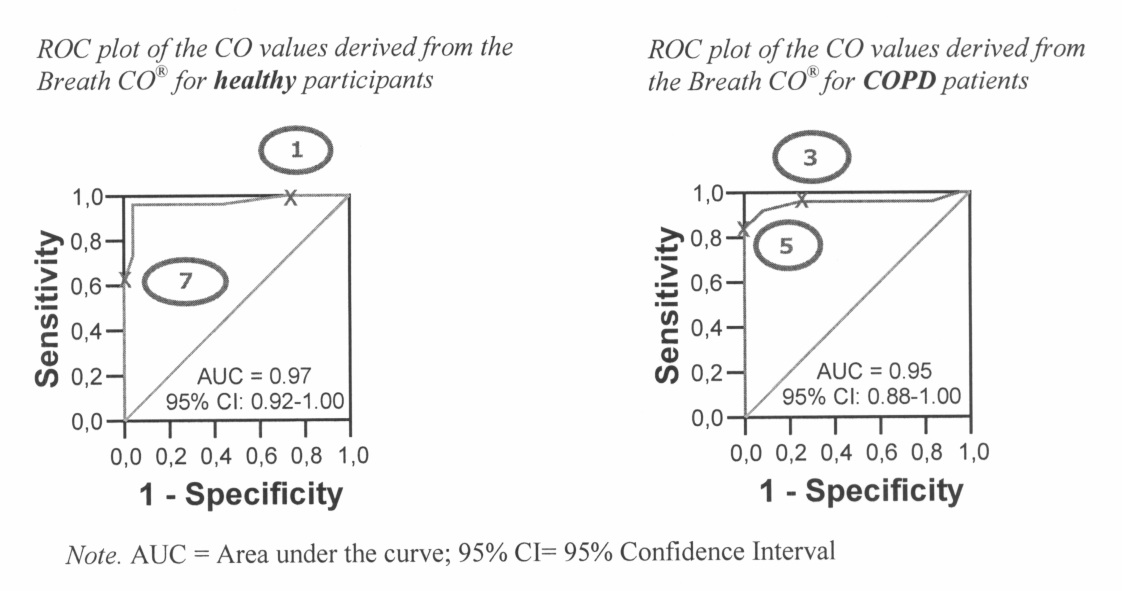
ROC curves were generated to be able to determine sensitivity, specificity, positive and negative predictive values at different cut-off levels. Because all three ROC curves look very similar, only the ROC curves of the Breath CO® are presented in this article (Figure 1) for both healthy participants and COPD patients. The optimal cut-off range is also shown in these curves. The lower boundary of the cut-off range is the cut-off point

generating 100% sensitivity and the upper boundary is presented by the cut-off point generating 100% specificity.

These ranges are presented for all monitors in tables 4 through 6. These tables are presented to enable the reader to determine the optimal cut-off point, which belongs to their specific goals. In some instances 100% sensitivity was not reached.

The optimal range, in which an acceptable cut-off point can be chosen, ranges from 1 ppm through 7 ppm for healthy participants and from 3 ppm through 5 ppm for COPD patients using the Breath CO® (Table 4). Note that a sensitivity of 100% was not reached in patients with COPD.

Figure 1 ROC plots of the CO concentrations (ppm) to the self-reported smoking status of the Breath CO® for both healthy and COPD patients



Note. AUC = Area under the curve; 95% CI= 95% Confidence Interval

For the Smokerlyzer® the optimal cut-off points range from 2 through 7 ppm for healthy participants and from 2 through 10 ppm for COPD patients, and a sensitivity of 100% was reached in neither group (table 5).

Table 4 Sensitivity, specificity, and predictive values of positive and negative test results for a range of cut-off points (ppm) for the Breath CO® expressed in percentages

Ppm	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Healthy participants										
Sensitivity	**100**	96.2	96.2	96.2	88.5	73.1	61.5	50.0	42.3	34.6
Specificity	28.0	56.0	92.0	96.0	96.0	96.0	**100**	100	100	100
+ PV	59.1	69.4	92.6	96.2	95.8	95.0	100	100	100	100
- PV	100	93.3	95.8	96.0	88.9	77.4	71.4	65.8	62.5	59.5
COPD patients										
Sensitivity	96.0	96.0	**96.0**	92.0	84.0	80.0	76.0	72.0	68.0	68.0
Specificity	16.7	50.0	75.0	91.7	**100**	100	100	100	100	100
+ PV	54.5	66.7	80.0	92.0	100	100	100	100	100	100
- PV	80.0	92.3	94.7	91.7	85.7	82.8	80.0	77.4	75.0	75.0

Note. PV= Predictive Value; Ppm=parts per million

Table 5 Sensitivity, specificity, and predictive values of positive and negative test results for a range of cut-off points (ppm) for the Smokerlyzer® expressed in percentages

Ppm	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Healthy participants										
Sensitivity	96.2	**96.2**	84.6	84.6	73.1	53.8	42.3	34.6	26.9	23.1
Specificity	56.0	88.0	92.0	96.0	96.0	96.0	**100**	100	100	100
+ PV	69.4	89.3	91.7	95.7	95.0	93.3	100	100	100	100
- PV	93.3	95.7	85.2	85.7	77.4	66.7	62.5	59.5	56.8	55.6
COPD patients										
Sensitivity	96.0	**96.0**	92.0	84.0	80.0	76.0	68.0	64.0	64.0	56.0
Specificity	54.2	79.2	87.5	91.7	95.8	95.8	95.8	95.8	95.8	**100**
+ PV	68.6	82.8	88.5	91.3	95.2	95.0	94.4	94.1	94.1	100
- PV	92.9	95.0	91.3	84.6	82.1	79.3	74.2	71.9	71.9	68.6

Note. PV= Predictive Value; Ppm=parts per million

The optimal cut-off range for the Micro CO® ranges from 2 through 6 ppm for healthy participants and from 1 through 6 ppm for COPD patients (Table 6).

Table 6 Sensitivity, specificity, and predictive values of positive and negative test results for a range of cut-off points (ppm) for the Micro CO® expressed in percentages

Ppm	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Healthy participants										
Sensitivity	100	**100**	96.2	92.3	92.3	84.6	69.2	50.0	38.5	30.8
Specificity	0	16.0	28.0	68.0	88.0	**100**	100	100	100	100
+ PV	51.0	55.3	58.1	75.0	88.9	100	100	100	100	100
- PV	0	100	87.5	89.5	91.7	86.2	75.8	65.8	61.0	58.1
COPD patients										
Sensitivity	**100**	96.0	96.0	92.0	88.0	84.0	84.0	72.0	64.0	60.0
Specificity	4.2	20.8	66.7	79.2	91.7	**100**	100	100	100	100
+ PV	52.1	55.8	75.0	82.1	91.7	100	100	100	100	100
- PV	100	83.3	94.1	90.5	88.0	85.7	85.7	77.4	72.7	70.6

Note. PV= Predictive Value; Ppm=parts per million

As mentioned before, cotinine measurement is generally referred to as the 'gold standard' for validating abstinence from smoking. To verify this for both the healthy and COPD population included in this study (N=100), an additional analysis was performed, comparing salivary cotinine measurements with self-reported abstinence to determine the optimal cut-off range. The cotinine values 15 ng/ml through 40 ng/ml generate a 100% sensitivity, specificity, positive predictive value and negative predictive value for healthy participants, while in patients with COPD this is the case for a cotinine value of 10 ng/ml.

Conclusion and discussion

In general, results from smoking cessation studies, in which abstinence is based on measurement of expired CO, lack validity because they are based on unsuitable cut-off points. The CAMOXI study shows that the cut-off points as described in the manuals

lead to an underestimation of the number of smokers in both populations. If the prescribed cut-off points are adjusted properly, though, all three CO monitors are valid biochemical validation tools for the determination of the smoking status (within 12 hours after the last cigarette). The optimal cut-off point depends on the target group, type of CO monitor, and the aim of the study.

Compared to existing studies, the CAMOXI study contains four vigorous elements. First, non-smoking and smoking COPD patients were compared to non-smoking and smoking healthy participants to determine whether the cut-off point of CO in exhaled air needed to be adjusted for COPD patients. Second, the validity of three different CO monitors was investigated in this study. Third, cotinine was measured to investigate the agreement with observed CO concentrations and optimal cut-off points for cotinine in the study population. Fourth, smoking participants were asked to abstain from smoking 12 hours prior to the measurements. This abstinence period was chosen to mimic real life or clinical study situations in which smoking subjects know that their smoking status will be checked, and might try to mislead the investigator or physician by remaining abstinent immediately prior to the visit. This design enabled us to investigate whether or not 'deceivers' would be detected by CO monitors. This approach leads to an artificial increase in the amount of deceiving which might be higher than the deceiving rate found in daily clinical practice. This might have resulted in a higher amount of smokers falsely labelled as non-smokers. The sensitivity found in this study might therefore be lower than in daily clinical practice. However, it is also possible that some of the smoking participants failed to comply with the 12 hour period of abstinence, which could not be validated. As a result our design might be less conservative than originally intended. CO monitors can be used for different purposes and each requires a specific cut-off point. For example, in smoking cessation studies the main aim is validation of self-reported abstinence. Consequently, a high sensitivity (when a smoker is detected as such) is the most important outcome measure. Taking this into account, the optimal cut-off point is 1 ppm (100% sensitivity) for COPD patients and 2 ppm (100% sensitivity) for healthy people using the Micro CO® monitor. Consequently, some non-smokers will be wrongly classified as smokers (false-positives). However, if the main aim of using CO monitors is to provide positive bio-feedback to compliant subjects during counselling, the focus will

be on high specificity (when a non-smoker is detected as such). It is crucial in this case not to label a non-smoker as a smoker, and therefore to strive for a low number of false-positives. For example, with a cut-off level of 1 ppm for healthy participants using the Smokerlyzer®, 96% of all smokers will be detected. Unfortunately, only 56% of all non-smokers will be regarded as non-smokers and as a consequence the number of false positives is undesirably high.

The finding that different cut-off points need to be chosen depending on the type of CO monitor and kind of population next to the aim of the user has implications for the comparability of studies using a CO monitor as a validation tool. The outcomes of these studies cannot be compared unless the chosen cut-off is known.

All studies described in the introduction reported one specific value as the optimal cut-off point. This reduces the applicability of their findings because they are restricted to the specifics of these studies (e.g. investigated population, type of CO monitor, aim of the study).

Sato et al. concluded 11 ppm to be the optimal cut-off point for COPD patients. This exceeds the optimal range we found for the Smokerlyzer® in our study (range: 1-10 ppm for COPD patients). The trend in our results indicates that a cut-off point of 11 ppm might have generated a lower sensitivity and a higher specificity. This is probably caused by our design in which smoking participants were asked to remain abstinent 12 hours before the start of the study. The distinction between smokers and non-smokers will be less clear compared to a design without an abstinence period, which will result in a narrower optimal cut-off range with a higher sensitivity at similar cut-off points in which smokers did not refrain from smoking prior to the test. Specificity will not be influenced by the abstinence period because this only concerns the non-smokers. Murray et al. found a higher sensitivity and a lower specificity among COPD patients using the Smokerlyzer® or the Mini CO® with the prescribed cut-off point (10 ppm). This might have been due to the fact that their study was part of a larger intervention study in which self-reported abstinence, which was used as the 'gold standard', might have been unreliable. The studies of Low and Middleton with the Smokerlyzer® were performed among target groups not fully comparable with our population. However, Middleton et al. found 96% specificity and 94% sensitivity using a cut-off point of 6 ppm in patients of a respiratory

outpatient clinic. The CAMOXI study found the same specificity, but a lower sensitivity (76%) using the same monitor and cut-off value. This might be explained by the fact that Middleton et al. probably used a more heterogeneous respiratory patient group. Also, the target group included uninformed patients, unaware of the goal of the test, which decreases deceiving behaviour and will lead to a higher sensitivity and the same specificity as mentioned earlier. Low et al. tested "outpatients" among navy personnel and concluded that 5 ppm was the optimal cut-off point generating 96% sensitivity of and 98% specificity. Especially the sensitivity is higher than in our study for healthy participants using the same monitor and cut-off value. This might be caused by the forced abstinence period in our study. Unfortunately, Low et al. did not present detailed information about the study population. It is plausible that this group did not consist of COPD patients, but it remains unclear whether it is comparable with the healthy participants in our study.

Comparing the three CO monitors, the Micro CO® shows the highest sensitivity but unfortunately this is also linked to a lower specificity. Again, because the optimal cut-off point is fully conditional upon the goal of the test, in specific cases a low specificity might be problematic.

In our research setting the used devices were checked and calibrated daily before use. Remarkably, the three CO monitors needed to be calibrated daily because a deviation of ± 2 ppm (one day positive, the other day negative) was found. This occurrence is far more frequent than the occurrence described in the manuals (ranging from once a month to once per year). Although the deviation seems small, if the chosen cut-off point is low this might have important implications for daily clinical practice. Because calibration with such frequency may not be feasible, this will increase the uncertainty of the test results.

A 20 second breath hold, to allow the alveolar air (and blood) to equilibrate, is widely accepted for determining CO concentrations. This criterion seems to be mainly based on a study by Jones et al.[25] However, many COPD patients have difficulties holding their breath for so long. In our study, if COPD patients were not able to meet the 20 seconds criterion, they were asked to hold their breath for 15 seconds or at least 10 seconds before exhaling in the CO monitors. West et al. found that breath holds of 5 seconds or more

correlated almost perfect with breath holds of 20 seconds, but tend to produce lower CO levels.[26] However, Middleton et al. found representative CO concentrations even in breath holds of 3 to 4 seconds.[16] Consequently, the CO values of our COPD patients might have been slightly underestimated. However, in the healthy population the same results were observed despite the fact that this group did meet the 20 seconds criterion. Furthermore, we wanted to follow the breath hold duration as described in the manuals (ranging from 10 to 20 seconds) as closely as possible.

By using self-reported abstinence corrected by salivary cotinine measurements in self-reported non-smokers, only one COPD patient was excluded because the self-reported abstinence could not be confirmed by any biochemical validation measure. Among healthy non-smokers self-reports appeared in full agreement with cotinine measurement. This suggests that self-reported smoking status is highly valid when subjects are in no way expected to quit, even in the case of COPD patients. In this case, subjects did not participate in a cessation programme and were explicitly informed that smoking cessation was not the primary goal in this study. Belonging to a high-risk population, which is suggested as a third cause for biased self-reports of smoking abstinence[3;4], seems to play only a minor role.

For smoking cessation research we recommend using CO monitors in a two-step approach. First, all participants claiming to be abstinent from smoking should be tested by CO monitors using a cut-off point with 100% specificity, and thus a 100% positive predictive value which guarantees that identified smokers are actual smokers. Only the participants identified as non-smokers by the CO monitor should then be subjected to a subsequent salivary cotinine test. This procedure will guarantee the most accurate and cost- effective validation of self-reported abstinence.

Acknowledgements

The authors gratefully acknowledge the Department of Pulmonary Medicine for their support, and especially the technicians of the lung function laboratory; Tonny Knuif for his adequate handling of the cotinine samples and Betty Rinsma for her significant contribution in recruiting the participants and managing the data.

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CHAPTER 7

Are CO monitors still able to detect smokers 6 hours after smoking a cigarette?

Frans de Jongh, Lieke Christenhusz, Paul van der Valk, Marcel Pieterse, Erwin Seydel, and Job van der Palen

Abstract

The abstinence rate of smokers can non-invasively be validated by exhaled carbon monoxide (CO) measurements. The exhaled CO of 26 'healthy' smokers and 25 smoking COPD patients was measured by three different CO-monitors before and 1 till 6 hours after smoking a cigarette. Forty-nine non-smokers served as control group. Six hours after smoking one cigarette, Breath CO® detects 48% of the COPD patients and 15% of the 'healthy' smokers at the factory-prescribed 9 ppm cut-off point. The Smokerlyzer® (10 ppm factory-prescribed cut-off point) detects 36% and 12% respectively. The Micro CO meter® (5 ppm factory-prescribed cut-off point) detects 92% and 85%. Remarkably, the CO-values, as measured with the three monitors, are actually quite similar with minor deviations of 1 or 2 ppm. This contradiction is caused by the different factory-prescribed cut-off points. Smokers are therefore able to deceive CO monitors by short-time abstinence, unless the cut-off points are being adjusted properly.

Introduction

Smoking is the main cause of the development of COPD.[1] Agreement had been reached that smoking cessation is the only evidence based treatment for COPD.[2-5] To determine the effectiveness of a smoking cessation programme, the primary outcome measure is usually the abstinence rate. It is therefore important that this measure is valid.

The abstinence rate can be mainly measured by means of self-report or biochemical validation. Historically, abstinence rates were measured by means of self-report only. However, self-reported abstinence rates have been shown to be misleading as a result of a high deceiving rate, especially when the smoking cessation intervention has high demand characteristics (the primary aim is smoking cessation versus no pressure), the population consists of high-risk medical patients and not healthy volunteers, and/ or the smoking cessation is intensive rather than based on self-change.[6;7] It is therefore important to validate self-reported quitting, specifically in high-risk populations such as COPD patients, and this notion has become generally accepted.

A frequently used method of validating the self-reported smoking status is by measuring exhaled CO with CO monitors. The advantages of the CO monitors compared to other validation techniques are that the CO monitors are easy to use, relatively cheap and provide direct feedback. A major limitation of CO validation, though, is the rather short half-time of this measure. CO monitors are generally assumed to detect smoking up to 12 hours prior to the test. One of the consequences is that it becomes relatively easy to mislead the CO measurement, simply by refraining from smoking several hours prior to the check-up. Clearly, when COPD patients participate in a smoking cessation trial with high demand characteristics, and are fully aware that their self-reported abstinence will be validated, such deceiving behaviour is conceivable. To explore this phenomenon, we need to know how the CO value decreases during the hours after smoking a cigarette.

The CAMOXI study investigates the validity of three different CO monitors in labelling smokers and non-smokers correctly, comparing healthy volunteers with COPD patients. Furthermore, the change in the CO value was followed from one to six hours after smoking a cigarette and the sensitivity, specificity, positive predictive value and negative predictive values at each hour are reported.

Methods

100 volunteers were included in this study and they consisted of 51 smokers and 49 non-smokers. The CO of 26 'healthy' smokers and 25 smoking COPD patients was measured by three different CO-monitors before and 1 till 6 hours after smoking a cigarette. The 49 non-smokers, frequency matched on age, consisting of 25 healthy volunteers and 24 non smoking COPD patients, served as control group.

Subjects were between 40 and 75 years of age and the COPD patients had a clinical diagnosis of stable COPD defined by the American Thoracic Society (ATS) criteria.[8]

After one night of abstinence at the start, all 51 smoking participants were asked to smoke one cigarette in a separate smoking room. After this, CO measurements were taken from all participants at each subsequent hour. During the whole procedure, all participants remained in an enclosed area within the hospital. Three different CO monitors (EC50 Micro III Smokerlyzer®, Bedfont Instruments, Kent, UK; Breath CO®, Vitalograph Inc, Lenexa (KS), USA; Micro CO meter®, Micro Medical Ltd, Kent, UK) were compared and the sequence of the different CO monitors was randomised. End tidal expired air CO concentrations (ppm) were measured according to standard procedures: subjects were asked to exhale completely, inhale fully and hold their breath for a minimum of 10 seconds and a maximum of 20 seconds (depending on the different manuals and the ability of the participant) and exhale slowly into the CO monitor. The monitors were calibrated daily with a mixture of 0, 10, and 50 ppm CO in air. The EC50 MICRO III Smokerlyzer® and the Micro CO meter® display CO (ppm) which are automatically converted to COHb (%).[9;10]

The factory-prescribed cut-off point, which distinguishes a smoker from a non-smoker is 10 ppm for the Smokerlyzer, 9 ppm for the Breath CO® and 5 ppm for the Micro CO meter®. COHb (%) was also determined in venous blood and a cotton swab (Salivette®) was used to take salivary samples and specimens were frozen and subsequently assayed for cotinine (ng/ml). Nitric Oxide (NO) in exhaled air was also measured using the NIOX® (Aerocrine AB, Smidesvägen, Sweden). A smoking related questionnaire[11] was administered at baseline to measure the participants' smoking characteristics.

Written informed consent was obtained from all participants before participation in the study and the medical ethical committee of Medisch Spectrum Twente at Enschede, the Netherlands granted medical ethical approval.

Data analysis

Sensitivity, specificity and the predicted outcome of a negative and positive test result of the three different CO monitors was assessed using the cut-off points for the CO value as described in the separate manuals, comparing these with a 'gold standard'. In case of self-reported smokers, their self-report was used as 'gold standard' (assuming that smokers who self-report to be smokers are not inclined to be deceptive) and in self-reported non-smokers the salivary cotinine level below 20 ng/ml was used as the 'gold standard'. The mean CO value and accompanying standard deviations were plotted every hour.

Results

The average age of the healthy non smokers and smokers was respectively 60 and 57 years. For the COPD non smokers and smokers this was respectively 65 and 64 years. The healthy non-smoker did not differ significantly in age (p=.79; CI 95%;-3.26-5.82 or sex (p=.69) from the 'healthy' smokers. Also the COPD patients who did not smoke did not significantly differ in age (p=.80; CI 95%: -3.07-3.95) or sex (p=.44) with the COPD patients who did smoke.

As can be seen in Figure 1 all three monitors show a similar pattern over time. For 'healthy' smokers the baseline value of 8–10 ppm, depending upon the CO monitor, raised with approximately 5 ppm one hour after smoking the cigarette. This value declined each subsequent hour with about 1 ppm per hour, resulting in an end value of 7 ppm after 6 hours. The 95% CI for each data point was ± 2 ppm (smokers as well as non-smokers). For the COPD patients, as is shown in Figure 2, the curves show a comparable pattern. However, in COPD smokers the CO values at each data point are consistently 3 ppm higher than in 'healthy' smokers. The non-smoking COPD controls again have a value of around 3 ppm.

Figure 1 Mean CO values before and 1 trough 6 hours after smoking a cigarette for healthy persons. The dotted line shows the CO values of the healthy non smoking controls.

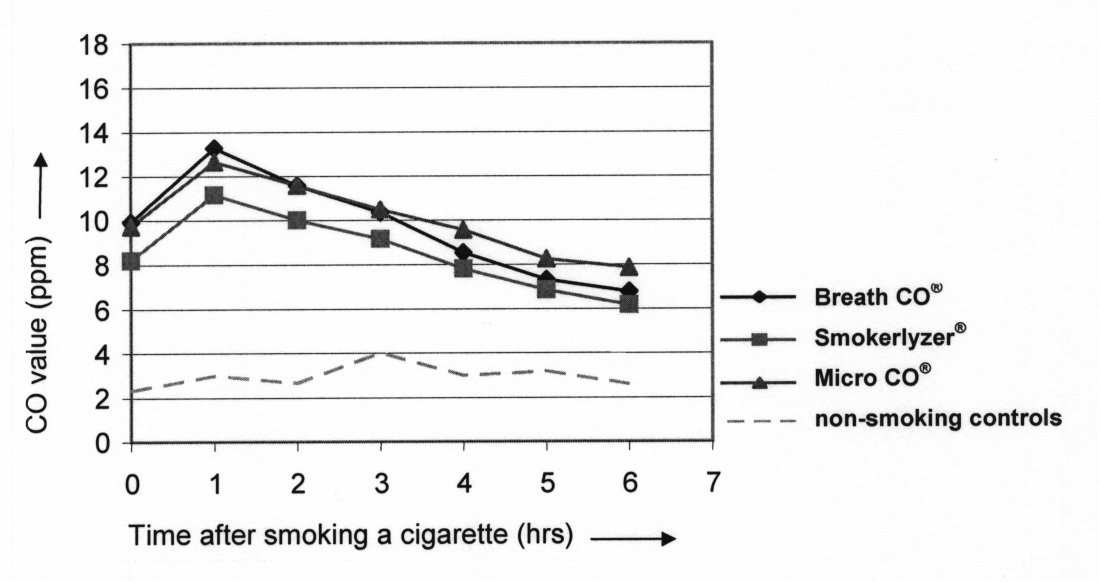
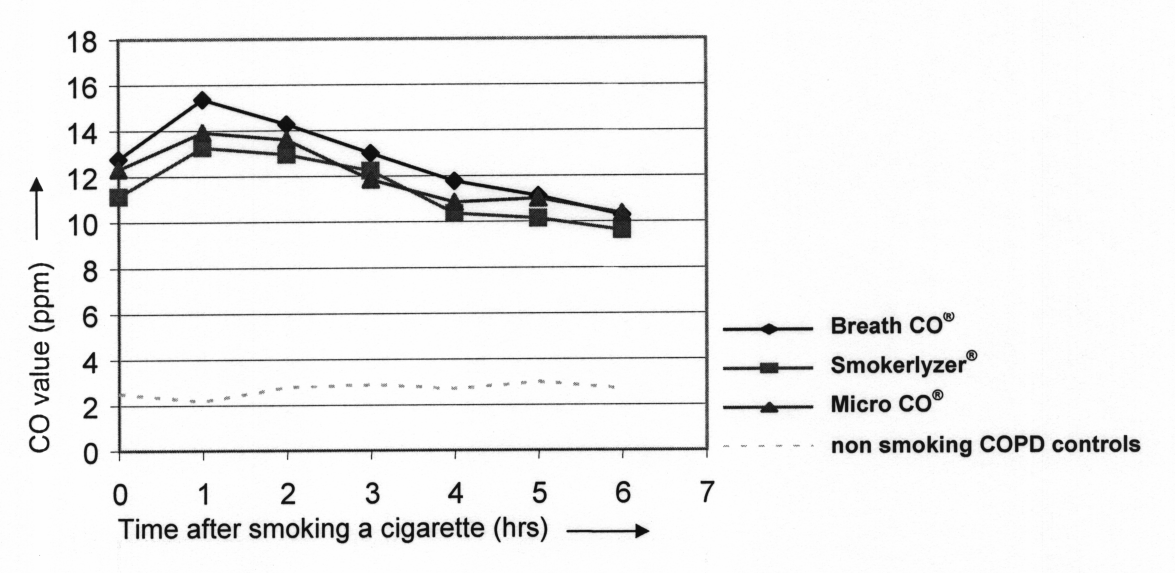


Figure 2 Mean CO values before and 1 trough 6 hours after smoking a cigarette for COPD patients. The dotted line shows the CO values for the non smoking COPD controls.



Six hours after smoking one cigarette, Breath CO® detects 48% of the smoking COPD patients and 15% of the 'healthy' smokers at the prescribed 9 ppm cut-off point. The Smokerlyzer® (10 ppm factory-prescribed cut-off point) detects 36% and 12% respectively. The Micro CO meter® (5 ppm factory-prescribed cut-off point) detects 92% and 85%.
The measured NO values were the same before and till 6 hours after smoking a cigarette.

Conclusions

An important finding of this study is the large difference in performances of the three CO monitors, as expressed in the sensitivity, specificity, and predictive values. Remarkably, the results in figure 1 and 2 show that the CO values, as measured with the three monitors, are actually quite similar, with minor deviations of 1 or 2 ppm. Apparently, this contradiction is caused by the different factory-prescribed cut-off points. It is therefore not surprising that the CO monitor with the lowest prescribed cut-off value, the Micro CO meter®, performed best in this study. After 6 hours (using the factory-prescribed cut-off points) both the Breath CO® monitor and the Smokerlyzer® fail to detect more than half of all smokers, healthy or COPD patients. Smokers are therefore able to deceive CO monitors by short-time abstinence, unless the cut-off points are being adjusted properly.

Discussion

The main difference between the three monitors is the prescribed cut-off points. Lowering the cut-off point would result in a higher detection rate of smokers. With a cut-off value of 6 ppm almost all smokers (91%) would, 1 hour after smoking a cigarette, have been detected as such, while only 4% of the non-smokers would have been misclassified.
Six hours after smoking a cigarette 80% of the COPD patients and 44% of the 'healthy' smokers would have been detected with that 6 ppm cut-off point. Especially from the 'healthy' smokers, who would be able to stop smoking for more than 6 hours, the

majority would still be misclassified, but for these highly addicted smokers to stay abstinent for such a period is difficult to accomplish.

Although patients claimed to be abstinent since the night before (so at least for 8 hrs) their initial value (as well for the 'healthy' smokers as the smoking COPD patients) was higher than the value after 6 hrs of abstinence. This could be explained if they initially had a much higher CO-value (e.g. 20-30 ppm) due to smoking several cigarettes the day before the study. After one night of abstinence, with an approximate decrease of 1 ppm per hour, they would have reached therefore a value of 10-12 ppm in the next morning. Smoking one cigarette in the morning, as the study prescribed, increases this value to 13-15 ppm after which a further decline with about 1 ppm commences during the following 6 hours of the study. Another reason might be due to nocturnal variation or the fact that some of them would have smoked a cigarette in the morning just before they entered the test.

The data show that there were smokers who had a start value of 3 ppm, so comparable with the value of the controls, but others started wit a value of 11 ppm, which makes it plausible that they had smoked more cigarettes before they entered the period of abstinence the day before the test.

The daily calibration of the CO monitors showed that adjustments were mostly limited from 1 till 2 ppm in which there was no trend found. This random variations were therefore almost within the accuracy of the device, which is ± 1 ppm. However, for the non-smokers with an average value of 3 ppm this is in absolute sense around 30% of the measured value. The reasoning behind the calibration was that a pilot-study showed that there was a (small) day-to-day variation and we wanted to prevent that after 1 month measured data might have considerably drifted.

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CHAPTER 8

General discussion

Lieke Christenhusz

The main objective of this thesis was to evaluate the effectiveness of a new developed intensive multi-component smoking cessation intervention, the SmokeStopTherapy (SST), specifically aimed at smoking patients with moderate to severe COPD (Chronic Obstructive Pulmonary Disease) and motivated to quit smoking. Within the SMOKE study, a randomised controlled trial, the SST was compared with the Minimal Intervention Strategy for Lung patients (LMIS). The secondary objectives were: 1) to investigate the prospective determinants of smoking cessation in COPD patients; 2) to analyze whether the potential beneficial effects of introducing the SST outweigh the additional costs compared to the existing smoking cessation programme LMIS.

The CAMOXI study was designed to validate the use of three different Carbon Monoxide (CO) monitors within smoking and non-smoking COPD patients compared with smoking and non-smoking healthy volunteers under more critical conditions than has previously been done.

This chapter will discuss theoretical as well as methodological issues of both the SMOKE study and the CAMOXI study. The SST will be evaluated in the light of our findings and future implications and research will be outlined.

Theoretical framework

ASE model

Within the ASE-Model, Attitude, Social influence and (Self-) Efficacy are the key-components of intention which can be seen as a direct antecedent of the actual behaviour. Social influence consists of 1) social support (encourage or discourage smoking); 2) social norm (the perceived opinion of the environment concerning smoking); 3) Environment (the number of smokers in the environment). The social norm has not been measured as part of the Smoking Related Questionnaire used in the SMOKE study. Fortunately, Godin and Kok[1] concluded that subjective (social) norm (e.g. personal perception of the social expectations regarding smoking cessation), is a weak prospective determinant with regard to health behaviour relative to attitude or perceived behavioural control.

Relapse Prevention

Strategies based on relapse prevention are intended to foster the maintenance of behavioural change by preventing relapses or at least reducing the severity of the experienced lapse. A self-control programme concerning the anticipation of and coping with high-risk situations is likely to be effective with regard to relapse prevention[2]. A review of Carroll[3] found mixed results regarding the evidence of relapse prevention in both illicit (e.g. cocaine use) as well as licit (e.g. smoking) substance abuse. For smoking there is good evidence for relapse prevention approaches compared with no treatment, but the evidence is less consistent if compared with other relapse prevention strategies. Including relapse prevention strategies in a smoking cessation intervention can contribute to a longer durability of the effect of the intervention and a reduction of the severity of an experienced lapse. Carroll et al. also suggested that if the relapse prevention strategy is also matched to the individual patient, even stronger effects are expected although further research should provide more information concerning this specific issue.

Within the SMOKE study the traditional cognitive-behavioural approach as recommended by Marlatt et al.[2] was introduced. This approach was adopted in both the LMIS and the SST and includes for example the identification of high-risk situations for relapse, strategies for coping with those situations, self-monitoring and behavioural analysis of smoking habits, and problem-solving strategies. Recycling has been introduced in the SST as an extra relapse prevention strategy. The participants were offered the possibility to 'recycle' (restart the individual sessions) once after a lapse, defined as a slight error or slip, occurred within three months after the start of the intervention. However, this strategy focuses on the early detection and toning down of the possible Abstinence Violation Effect (AVE)[4] which can occur immediately after experiencing a lapse. The AVE occurs when the person attributes the cause of the lapse to internal, stable and global factors within him-of herself (e.g. lack of persistence to maintain abstinent). The aim of the relapse prevention strategy is to direct attention of the quitter to the more controllable external or situational factors that might have triggered the lapse (e.g. a high-risk situation) and help the participant to recover the weakened self-efficacy. Furthermore the quitter was provided with tools to cope with such factors to avoid future lapse when confronted with the same sort of situation in stead of losing

control resulting in a total relapse. Within the 'recycling' period the focus of the intervention was aimed at these relapse prevention strategies.

Several studies focus on the relationship between the AVE and the chance of relapsing and relapse prevention strategies are also based on the prevention of the AVE. Marlatt and Gordon[2] hypothesized that the AVE is characterized by cognitive dissonance (conflict and guilt) and a personal attribution effect (blaming the self after a lapse). Research by Shiffmann et al.[5] did support the relevance of the intensity of AVE for progression towards relapse, but did not support the structure or determinants of the AVE as suggested by Marlatt and Gordon. Within the SMOKE study 19% (22/114) of the participant used the option to 'recycle' but these participants failed to remain abstinent. Our hypothesis is that participants who experienced the AVE are unlikely to engage in the 'recycling' option and are therefore at least indirectly more likely to experience a relapse. This is supported by the findings of Shiffmann et al.[5] which proved that negative reactions derived from the AVE theory predict failure to undertake another quitting attempt. Furthermore, Curry et al.[6] concluded earlier that so-called booster interventions are most effective directly following a lapse. To conclude, the content of our relapse prevention strategy might have to be adjusted and the timing of the 'recycling' should preferably be offered immediately (< 24 hours) after experiencing a lapse. With these adjustments, 'recycling' is likely to be more effective in avoiding a total relapse. Within the SMOKE study, the individual counselling was planned as soon as possible after a participant notified the pulmonary nurse that he/she experienced a lapse. A more immediate execution of the 'recycling' principle seemed to be impracticable. Furthermore, combating a possible lapse resulting in a relapse should begin earlier in the quitting process; the focus on AVE by means of relapse prevention strategies was therefore already inserted in the 'regular' part of the intervention. However, this study did not show any positive effect as a result of the 'recycling' principle. Developing other and more effective relapse prevention strategies should therefore be given priority.

Methodological issues

This section discusses the methodological questions which may rise reading this thesis. These issues concern the design of the study (e.g why the LMIS was used as comparison in this trial) and an explanation of the chosen definitions for outcome measures used in this study which might be arbitrary.

The Minimal Intervention Strategy for Lung patients as comparison in this trial

Internationally, the level of contact in smoking cessation programmes can be divided in: no contact, minimal counselling (< 3 minutes), low intensity counselling (3-10 minutes) and high intensity counselling (> 10 minutes).[7] Furthermore, the available evidence suggests that intensive interventions are more effective than less intensive interventions and should be used whenever possible, although there is no evidence that more than 90 minutes of contact time increases abstinence rates further[7]. The guideline of Rigotti[8] also mention the dose-response relationship between effectiveness and intensiveness and recommends the use of drugs accompanied by counselling, which also indicates a high-intensity treatment. In this perspective, the label 'LMIS' can lead to confusion because it is not considered minimal in an international perspective.

What does this imply for the SMOKE study? To conclude that the intensive SST has been compared with a medium-intensity (rather than a minimal/brief) intervention, renders the SMOKE study even more ambitious. It is obvious that a comparison between an intensive intervention and a mere opportunistic cessation advice is more likely to show significant differences than in a comparison with a competing comprehensive treatment. Moreover, the conclusion that the SST is more effective than the LMIS is of additional clinical importance in the Netherlands, where the LMIS can be seen as 'usual care'. Because of the urgency to quit in this group of patients, and the fact that the LMIS, as shown in this trial, leads to a modest cessation rate of 9%, it seems clinically irrelevant to compare the SST with a 'truly' minimal intervention. Finally, the decision to incorporate the LMIS in the SMOKE study design provides the first test of the LMIS in a rigorous study. Since the LMIS is already disseminated among Dutch hospitals and is being used in many lung departments, reliable information regarding its effectiveness is important.

Although we still cannot say whether the LMIS is more effective than a truly minimal intervention, at least it is effective to some degree, all be it less than a very intensive intervention.

Effective elements within the SmokeStopTherapy.

The SST is an intensive multi-component intervention and this multimodal treatment approach is evaluated in the SMOKE study. Due to the design of the study it is impossible to evaluate the effectiveness of the separate elements of the SST. Because the effectiveness of former interventions was not satisfactory for COPD patients, the first step was to find out whether a 'maximal' intervention could create a satisfactory effectiveness within this high-risk patient group. Based on this study, the SST has proven to be effective, and more effective than the LMIS. Future research should focus on the identification of the effective elements of the SST in order to determine the most cost-effective intervention to promote implementation of the SST, preferably in a more compact form. This is also important with regard to patient adherence, because the more techniques and approaches applied in a multimodal treatment, like the SST, the more difficult it becomes for a patient to comply[9].

Bupropion (Zyban®)

Bupropion (Zyban®) was obligatory and provided for free within the SST. As a result, all participants receiving the SST used bupropion. The use of bupropion should therefore be seen as a regular ingredient of the SST instead of additional support. This has been analysed likewise within the cost-effectiveness analysis presented in chapter 5. Fourteen percent of the participants used some form of Nicotine Replacement Therapy (NRT) next to bupropion.

Since the recommendation to use (additional) pharmacological smoking cessation aids is also part of the LMIS protocol, many participants in the LMIS group also used pharmacological treatment. Ten percent of these participants used only some form of NRT and 32% used only bupropion and 8% used both bupropion and NRT.

This also implies that, as mentioned earlier, it is impossible in this trial to determine whether or not bupropion attributed to the effectiveness of the intervention, because this element was not limited to one of both study arms.

Validated continuous abstinence as the primary outcome measure

The most rigorous definition of continuous abstinence is: refraining from **any** smoking, starting at the quit date. An apparent limitation of this definition is that in practice it is virtually impossible to biochemically validate this outcome measure. In case of cotinine measurements, which detect smoking to maximum of the seven days in the past, this would require weekly measurements during 12 months. To overcome this problem, researchers combine the biochemically validated abstinence measures, with a self-reported measure of abstinence during the intervals, in an estimate of continuous abstinence. However, as is shown in both the SMOKE study and in previous research[10], self-reported measures in trials among these populations are highly deceptive. Therefore, in the SMOKE study the continuous abstinence rate was solely based on cotinine validated abstinence measures, assuming that the participants were likely to have sustained abstinence in between the measurement points. The strength of this concept, obviously, is that it relies on objective measures only. At the same time, it ignores the possibility of relapse during the intervals between measurements. This outcome measure can also be labelled as *consecutive validated abstinence*.

Further, in the SMOKE study the continuous abstinence measure was limited to the six and twelve month follow-up. This was necessary since the maximum duration of the SST, in case of full recycling, is six months, during which patients may be using NRT which interferes with the cotinine measurement. As a consequence of combining the six and twelve month's cotinine measurements, the first six months are disregarded and abstinence for *at least* the last six months was therefore defined as a successful quit attempt. In theory, this implies that we did not use the most conservative measure, which may have resulted in an overestimation of the absolute continuous abstinence rate. But because this is true for both interventions, the relative outcome will not be influenced by this phenomenon.

The definition of 'deceiving'?

The term 'deceiving' is precarious because it implies deliberate or intentional lying. In this context, deceiving relates to the situation in which the patient self-reported to be abstinent from smoking, which was disconfirmed by their salivary cotinine levels which exceeded 20 ng/ml. In the SMOKE study the COPD patients were aware of the fact that 1) smoking cessation was the primary aim of both interventions; 2) smoking is the main cause of their illness and smoking cessation is the only possible treatment to improve the prognosis. As mentioned in chapter 3, under such circumstances participants tend to respond in a socially desirable manner. This may explain the high deceiving rate (12% in the SST and 20% in the LMIS) found in the SMOKE study. An alternative explanation may be a difference in the definition of total abstinence between the patient and the investigators. Perhaps some patients have their own definition of successful quitting, in which for instance an occasional slip is allowed. However, in the SMOKE study a patient was determined a self-reported quitter if he/she gave a positive answer to all of the following, rather unambiguous, questions: "Did you smoke since your quit-day, even if it was just one cigarette or shag? If yes, how long ago?", "Did you smoke one or more cigarettes within the last seven days?" and, "Did you smoke one or more cigarettes within the last 24 hours?". It seems unlikely that these questions leave much room for less stringent definitions of abstinence. Therefore, the urge to give a socially desirable answer to conform to the injunctive norm is more likely to be the explanation for this finding.

Patient characteristics

Were the participating COPD patients really motivated to quit?

The SMOKE study was aimed at COPD patients motivated to quit smoking. The lung physician asked the patients if they were willing to quit smoking within the next month, following the stages-of-change algorithm. If the patients confirmed this, they were considered motivated to quit and were asked to participate in the study. It is questionable whether or not the participants of the SMOKE study are motivated or not because this procedure is likely to be influenced by the fact that participants may be inclined to give their own lung physician a social desirable answer which results in an overestimation of

their patients' self-reported motivation level. This presumption is supported by the fairly high deceiving rate found in the SMOKE study, a phenomenon that has been shown previously to occur when participants are suffering from smoking-related diseases[11], as in the SMOKE study.

Nevertheless, this procedure mimics daily clinical practice in pulmonary medicine, where patients are often urged to engage in smoking cessation interventions. Furthermore, this concerns both interventions and the validity of the study is therefore not jeopardised, although the absolute effect of the interventions, which are originally aimed at patients motivated to quit smoking, may be underestimated.

Nicotine dependence

Nicotine dependence was measured by means of the Fagerström Test of Nicotine Dependence (FTND). One of the items in the FTND concerns the time between waking up and smoking the first cigarette (within 5 minutes after waking up – more than 60 minutes after waking up). The sooner the first cigarette is being smoked the higher the score on nicotine dependence. However, most COPD patients suffer the most from their disease in the morning. As a consequence, many COPD patients simply need more time to get out of bed and will not be able to smoke their first cigarette within 5 minutes after waking up. Using the Fagerström questionnaire, which includes this 5 minutes criterion, can therefore lead to an underestimation of nicotine dependence in COPD patients. Although this implies that the true nicotine dependence of the COPD population within the SMOKE study will probably be higher than the FTND-scores suggest, it does not bias the results of the SMOKE study as this will have affected both study arms similarly.

SmokeStopTherapy in a wider perspective

The effectiveness of the SmokeStopTherapy in comparison with other studies

The SmokeStopTherapy is developed based on the knowledge that increasing the intensiveness leads to an increased effectiveness.[7;8;12] The effectiveness of the SmokeStopTherapy based on the validated 12 months point prevalence abstinence rate is 22% for the SST versus 12% for the LMIS. Only few studies are known investigating

smoking cessation in COPD patients. The highest point prevalence quit rate (35%) ever achieved in COPD patients using a combination of behavioural therapy and pharmacological support, was found in the Lung Health Study (LHS).[13] Several differences between the LHS and SMOKE might explain the lower quit rate of the SST. First, the target population in LHS consisted of smokers with signs of early COPD as indicated by mild airway obstruction, whereas in the SMOKE patients with clinically diagnosed moderate to severe COPD were enrolled. Second, the intensity of the intervention used in the LHS exceeded the SST considerably. In other studies, the target group and the design of these studies differ markedly from the SMOKE study. This impedes a thorough comparison.

Cost-effectiveness

Over 12 months the average patient receiving SST generates €581 versus €595 within the LMIS. Furthermore, The SST is, compared with the LMIS, associated with a lower number of exacerbations (0.38 vs. 0.60) and hospitalisation (0.39 vs. 1), and a higher number of quitters (20 vs. 9) at lower total costs. Furthermore, these findings are robust and insensitive to changes in various parameters. This leads to an indisputable dominance of the SST compared to the LMIS within a 12 months time frame. A cost-effectiveness analysis is usually performed to support optimal treatment decisions in the context of uncertainty. The analysis performed in the SMOKE study indicates that the SST should be preferred over the LMIS. However, the SMOKE study also investigated prospective determinants associated with a higher chance of reaching continuous abstinence (Chapter 4). If the chances of quitting are increased by offering the LMIS to patients with a high positive baseline attitude towards smoking cessation, the costs associated with additional quitters in the LMIS might drop dramatically. This ‘matching’ approach keeps the LMIS a reasonable option to offer to COPD patients, and this approach might lead to a different treatment policy.

Predictors

Two effective smoking cessation interventions aimed at smokers with COPD are available: the LMIS and the new developed SST. The LMIS is moderately intensive and

less invasive than the high-intensity SST. Within the LMIS a predictive factor for successful quitting is a high positive baseline attitude towards smoking cessation. On the other hand if the baseline attitude towards smoking cessation is less positive, and the baseline cotinine value is also low, the LMIS does not seem to be suitable and the SST should be offered to increase the chances of continuous abstinence. This is based on the outcome that no predictive factor for successful quitting within the SST could be identified, concluding that the SST is equally effective for each COPD patient. This way the smoking cessation intervention can be matched at baseline to increase the efficiency of the smoking cessation interventions for COPD outpatients. Further, for patients failing to quit within the MIS, the SST is the indicated follow-up treatment. Luckily, the attitude towards smoking and quitting is easy to determine in COPD outpatients in clinical practice, which may facilitate the implementation of such a stepped-care approach.

Implementation of the SST

From several perspectives, implementation of the SmokeStopTherapy can be recommended, based on the outcome of the SMOKE study. First, the SST is found to be more effective than the LMIS and is therefore a promising smoking cessation intervention to add to the already available LMIS. Second, the cost-effectiveness of the SST compared to the LMIS has also been proven in which the SST generated lower costs and a higher effectiveness. Third, the baseline attitude is an important predictor of successful abstinence within the LMIS, whereas the SST seems to be successful regardless of any of the baseline characteristics of the COPD patients. The determination of the attitude towards smoking cessation is therefore sufficient to match the patients to either LMIS or the SST. Patients who are less convinced of smoking cessation should immediately be offered the SST, while patients with a highly positive attitude towards smoking cessation can be offered the LMIS initially. This clear strategy is easy to apply is also likely to increase the effectiveness of the interventions. These factors contribute to the likelihood of the implementation of the SST as a complementary intervention next to the LMIS and other available smoking cessation interventions.

Combining the results of the SMOKE study and the CAMOXI study

An important feature of the SMOKE study was biochemical validation of abstinence. To verify the smoking status of the participants in the SMOKE study, salivary cotinine was used. Unfortunately, salivary cotinine is expensive, immediate feedback can not be provided due to the insurmountable interference of the laboratory, and the administration of saliva is rather invasive. All these factors can be avoided by using exhaled carbon monoxide (CO) as biochemical validation, provided that the factory-prescribed cut-off point is adjusted to the CO monitor used, the tested population and the goal of the test. CO monitors are likely to generate misleading results concerning the determination of the smoking status in the general population as well as the COPD patients if the factory-prescribed cut-off points are used. This may occur in particular under conditions that might be expected in a smoking cessation trial, where relapsed participants may be inclined to deceive the counsellor or investigator. To achieve this, a 12 hour period of abstinence may be sufficient. In reality, this implies that a patient, in anticipation of a hospital visit the next morning, simple needs to postpone the first cigarette that day till after the CO measurement. Furthermore, the sensitivity of the CO monitors was shown to decrease within six hours in both populations. This can be avoided by lowering the cut-off points of the CO monitors. It should be kept in mind that, even with these adjusted cut-off points, salivary cotinine measurements still outperform CO measurements. A cost-effective validation procedure combining both tools is therefore recommended, especially in studies evaluating the effectiveness of smoking cessation interventions. All participants claiming to be abstinent from smoking should be tested by CO monitors using a cut-off point with 100% specificity, and thus a 100% positive predictive value which guarantees that identified smokers are actual smokers. Only the participants identified as non-smokers by the CO monitor should then be subjected to a subsequent salivary cotinine test. This procedure will guarantee the most accurate and cost-effective validation of self-reported abstinence.

Future Research

(Further) improvement of the cost-effectiveness of the SST

To make the SST even more cost-effective, separate elements of the SST which are not (significantly) contributing to the effectiveness of the intervention should be identified and either improved or omitted from the intervention (e.g. the 'recycling' principle within the SST). As a result, the most compact intervention can be created without abating the effectiveness. This will increase the cost-effectiveness of the intervention.

Applicability to heterogeneous high-risk groups

The main aim of this study was to create a (cost-) effective intervention for COPD patients, because the urgency to quit smoking is high in this population. However, this urgency also applies to other high-risk populations (e.g. patients with a cardiovascular disease, pregnant women etc.). If both interventions can be applied to a heterogeneous group which consists of different high-risk subgroups, the implementation of the interventions becomes more cost-effective and therefore more feasible. This possibility should be investigated in the near future.

Smoking reduction

A specific subgroup of COPD patients are beyond the reach of the SST and other smoking cessation interventions because these interventions focus on total abstinence as the primary outcome. Possible alternative strategies for this specific target group, aimed at 'harm reduction', should be investigated. Reasons for not being interested in a smoking cessation intervention for these patients may be that they are comfortable with their smoking status and do not intend to quit. However, it is also possible that a large part of this subgroup evaluates itself as being incapable of getting abstinent from smoking. An intervention, which does not aim at *total* abstinence at the beginning, may be able to attract this specific target group. It should be stressed that this should only be seen as an alternative in case smoking cessation is failing because the health benefits of smoking reduction for COPD patients are still uncertain.[14] The reduction of smoking can be a worthwhile goal in smokers unable or simply unwilling to quit smoking completely. And

it should be considered a valuable first step toward cessation at the longer term because sustained reduction has shown to be feasible in smoking COPD patients[15] and seems to predict total abstinence.[16] A recent randomised controlled trial of Bolliger et al.[17] showed a successful reduction (smoking less than 50% compared to baseline) in 9.5% of the participants, using comprised nicotine replacement through an inhalation device, versus 3% in the placebo group ($p < .05$) after two years. Although this was a reduction trial among healthy volunteers in stead of COPD patients, and nicotine inhalers are not available in the Netherlands, it is a reasonable first step towards smoking cessation in people not able or willing to adopt total smoking cessation.

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CHAPTER 9

Summary

The SMOKE study

Background

Chronic Obstructive Pulmonary Disease (COPD) is a widespread and growing health problem merely due to the smoking trends of the last decades, smoking is the only avoidable cause of the disease. Approximately 15% of the cases develop COPD and only 5% of the COPD patients never smoked. Smoking cessation is the only evidence based intervention that reduces the accelerated decline of pulmonary function and improves the prognosis of COPD. The urgency of developing an effective smoking cessation programme is therefore high. Previous research also indicates that the quality of life will increase if a smoker becomes an ex-smoker.

COPD patients generally have a long smoking history and are heavily addicted to smoking. COPD patients have a strong nicotine dependency which is illustrated by the fact that they maintain their smoking behaviour despite the fact that they experience smoking related complaints. In addition, most COPD patients have undertaken several quit attempts. The LMIS is currently recommended in the Netherlands as the preferred smoking cessation programme in COPD patients. Unfortunately, this intervention seemed to be unsatisfying for this specific target group. A more intensive smoking cessation programme might be more effective for these outpatients.

The SMOKE study is a randomised controlled multi-centre trial. This trial compares the effectiveness of a new developed high-intensity smoking cessation programme targeted at COPD outpatients, the SmokeStopTherapy (SST), with the Minimal Intervention Strategy for Lung patients (LMIS). Both interventions are based on theories of behavioural change: the Attitude-Social influence-Efficacy-model (ASE-model), the Transtheoretical Model (TTM), and Marlatt's Relapse Prevention model. Motivational Interviewing (MI) was used as a counselling tool throughout the whole intervention.

Effectiveness of the new developed intervention

Outpatients with moderate to severe COPD, willing to quit smoking, were randomly assigned to the SST or LMIS. 234 patients were randomised but due to 9 drop outs before the baseline measurements, 225 patients were eventually followed up. The SST consists of both individual and group counselling, telephone contacts and bupropion free of charge. Additionally, patients can re-enter the individual sessions after they experienced a lapse within three months after the start of the intervention ('recycling') to prevent a total relapse. The LMIS consists of individual counselling and telephone contacts which could be combined with pharmacological support at the patients' own expenses.

The primary outcome measures are continuous and point prevalent abstinence from smoking after one year, validated by salivary cotinine. Analysis was by intention-to-treat. The cotinine validated continuous abstinence rates after 12 months are 19% for SST and 9% for the LMIS (RR= 2.22; 95% CI: 1.06-4.65; p=0.03). The 12-month point prevalent abstinence rates are 22% for patients receiving SST versus 12% for patients receiving LMIS (RR= 1.80; 95% CI: 0.97-3.37; p=0.06). Discrepancy between the self-reported and validated smoking status was found in 12% in the SST group and in 20% in the LMIS group. The SST is therefore concluded to be more effective than the LMIS after one year follow-up based on validated continuous abstinence rates.

Baseline characteristics predicting continuous abstinence

Another aim of this study was to identify characteristics of smoking COPD patients participating in a smoking cessation programme that predict successful quitting.

A wide range of social-cognitive, demographic, smoking related and medical characteristics were measured at baseline. Only variables that showed a (marginally) significant ($p < .20$) univariate relationship with cotinine-validated continuous abstinence at 12 months were included in a full logistic regression model. Subsequently, variables that did not remain independent predictors of continuous abstinence were removed, one by one.

A positive attitude with regard to smoking cessation (OR 11.8; 95% CI: 1.7-81.5) and the cotinine level at baseline (OR 2.1; 95% CI: 1.08-3.93) were independent predictors of continuous abstinence for the LMIS. For the SST subjects no independent significant

predictor for continuous abstinence remained. It can be concluded that the LMIS is only suitable for COPD patients with a strong positive attitude regarding smoking cessation at baseline. The SST can be seen as an alternative for patients not possessing such baseline characteristic. This stepwise approach may be useful in clinical practice and will lead to increased efficiency by matching the interventions to the patients' needs.

CAMOXI study

Biochemically validated smoking status should be the primary outcome measure when investigating the effectiveness of smoking cessation programmes because of the high 'deceiving-rate' in such circumstances. Because Carbon Monoxide (CO) measurements have several advantages over the measurement of cotinine (e.g. non-invasive, direct feedback, less costly) the use of CO measurements might be very useful. CO monitors are also widely used in research concerning the effectiveness of smoking cessation interventions. These factors contribute to the relevance of validating CO monitors for their use in smoking cessation research.

The CAMOXI study validates three carbon monoxide (CO) monitors regarding their ability to distinguish smokers from non-smokers, in participants with and without COPD. Salivary cotinine measures were also validated. 26 'healthy' smokers, 25 healthy non-smokers, 25 smoking and 24 former smoking stable COPD patients (age 40-72 years) were included (N=100). Smokers were determined by self-report and non-smokers by a combination of self-report and cotinine measurements (< 20ng/ml) and COHb in blood. The exhaled CO level of the 51 smokers was measured before, and 1 through 6 hours after smoking one cigarette. Because the 49 non-smokers naturally did not smoke a cigarette after one hour, they solely served as control group for the measurements beyond one hour. All smoking participants were measured following a 12-hour abstinence period. Sensitivity, specificity, positive predictive values and negative predictive values were calculated for range of cut-off points for both CO and cotinine measurements.

The Breath CO® generates a sensitivity of 68% for COPD patients and 42% for the healthy participants, using the factory-prescribed cut-off point of 9 ppm. The 10 ppm factory-prescribed cut-off point of the Smokerlyzer® generates 56% sensitivity for COPD

patients and 23% for healthy participants. Both monitors generate 100% specificity in both groups. The factory-prescribed cut-off point for the Micro CO meter® (5 ppm) generates 88% sensitivity and 92% specificity for COPD patients, and for healthy people 92% sensitivity and 88% specificity. Salivary cotinine has a 100% sensitivity, specificity, positive predictive value, and negative predictive value over the range of 15 ng/ml through 40 ng/ml for healthy participants and at 10 ng/ml for COPD patients. For this specific analysis, self-reported smoking status was used as the 'gold standard'.

The validation of the CO monitors over time was also investigated. Six hours after smoking one cigarette, Breath CO® detects 48% of the COPD patients and 15% of the 'healthy' smokers at the prescribed 9 ppm cut-off point. The Smokerlyzer® (10 ppm factory-prescribed cut-off point) detects 36% and 12% respectively. The Micro CO meter® (5 ppm factory-prescribed cut-off point) detects 92% and 85%. Remarkably, the CO-values, as measured with the three monitors, are actually quite similar with minor deviations of 1 or 2 ppm. This contradiction is caused by the different factory-prescribed cut-off points.

The prescribed cut-off points for all three CO monitors generate misleading results concerning the determination of the smoking status in both populations after a 12-hour period of abstinence. For the measurement of CO over time, it can be concluded that smokers are able to deceive CO monitors by short-time abstinence, unless the cut-off points are being adjusted properly. The optimal cut-off points depend upon the goal of the study but salivary cotinine measurements outperforms the CO measurements and can therefore be considered the 'gold standard'. Cotinine measurements are relatively costly; a cost-effective validation procedure combining both tools is therefore recommended.

Samenvatting (Dutch summary)

De SMOKE studie

Achtergrond

Chronisch obstructief longlijden, ook wel 'Chronic Obstructive Pulmonary Disease' (COPD) genoemd, word gezien als een wereldwijd gezondheidsprobleem. Ten gevolge van onder andere de rooktrends van de afgelopen decennia is COPD een groeiend probleem. Roken is namelijk de belangrijkste te vermijden oorzaak voor het ontstaan van deze longziekte. Ongeveer 15% van de rokers ontwikkelt COPD en slechts 5% van de COPD patiënten heeft nooit gerookt. Stoppen-met-roken is dan ook de enige behandeling die effectief is gebleken en heeft daarom een hoge urgentie binnen deze doelgroep. Fletcher en Peto hebben aangetoond dat stoppen met roken, ongeacht het stadium van de ziekte, leidt tot een verlengde levensverwachting en uitstel van invaliditeit. Ook blijkt uit de literatuur dat de kwaliteit van leven toeneemt wanneer een roker een niet-roker wordt.

COPD patiënten kenmerken zich door hun lange rookgeschiedenis en een zware rookverslaving. Een COPD patiënt vertoont een sterke afhankelijkheid van het roken, die zich onder meer uit in het blijven roken ondanks het ervaren van aan roken gerelateerde klachten. Ook hebben de meeste COPD patiënten al meerdere stoppogingen achter de rug. Op het moment dat de SMOKE studie van start ging was de Minimale Interventie Strategie voor Long patiënten (LMIS) het aanbevolen stoppen-met-roken programma voor COPD patiënten in de (poli)klinische praktijk in Nederland. Deze interventie leek echter onvoldoende voor deze moeilijke doelgroep en een intensievere stoppen met roken interventie specifiek gericht op poliklinische COPD patiënten zou de effectiviteit kunnen verhogen.

De SMOKE studie is een gerandomiseerd en gecontroleerd onderzoek wat heeft plaatsgevonden in drie ziekenhuizen. Binnen dit onderzoek wordt de effectiviteit van deze nieuw ontwikkelde en intensieve stoppen-met-roken interventie voor COPD patiënten, de RookStopTherapie (RST), vergeleken met de LMIS. Beide programma's zijn gebaseerd op theorieën van gedragsverandering: het ASE-model waarin de Attitude,

Sociale invloed en Eigen effectiviteit centraal staan, het transtheoretische model (TTM), en Marlatt's model van terugvalpreventie. Binnen de gehele interventie werd het principe van de motiverende gesprekstechniek ('Motivational Interviewing') toegepast.

Effectiviteit van de RookStopTherapie

COPD patiënten met matig tot ernstig COPD die bereid waren om te stoppen-met-roken werden 'at random' toegewezen aan de RST of de LMIS. 234 patiënten werden gerandomiseerd, maar 9 mensen vielen uit alvorens de basismeting kon worden uitgevoerd. Hierdoor bleven er uiteindelijk 225 patiënten over die gedurende de gehele periode van 1 jaar zijn gevolgd. De RST bestaat uit individuele- en groepsbijeenkomsten, telefonische contacten en het kosteloos gebruiken van bupropion. Tevens kunnen de deelnemers aan de RST de individuele sessies opnieuw volgen, meteen nadat zij een terugval ('lapse') hebben ervaren binnen drie maanden nadat ze zijn ingestroomd in het programma ('recycling'). Dit ter voorkoming van een volledige terugval ('relapse'). De LMIS is opgebouwd uit individuele en telefonische contacten die kunnen worden gecombineerd met farmacologische ondersteuning, maar dit laatste wel op kosten van de deelnemer.

De zelfgerapporteerde stoppercentages worden gecontroleerd door middel van het cotininegehalte in het speeksel. De primaire uitkomstmaten zijn de gevalideerde continue abstinentie en punt prevalente abstinentie na 12 maanden. De analyse die hierop werd toegepast was op basis van 'intention-to-treat'. Deelnemers die gedurende de studie niet meer op kwamen dagen werden verondersteld niet te zijn gestopt met roken.
Na 1 jaar is de gevalideerde continue abstinentie 19% binnen de RST en 9% binnen de LMIS (RR= 2.22; 95% CI: 1.06-4.65; p=0.03). De stoppercentages gebaseerd op punt prevalentie na één jaar zijn 22% binnen de RST groep versus 12% binnen de LMIS groep (RR= 1.80; 95% CI: 0.97-3.37; p=0.06). Er bestaat een discrepantie tussen de zelfgerapporteerde en gevalideerde rookstatus. Binnen de RST kon bij 12% van de deelnemers de zelfgerapporteerde abstinentie niet worden bevestigd met het cotininegehalte van het speeksel. Dit percentage was 20% binnen de LMIS groep.

Gebaseerd op de strenge continue abstinentie maat, is de RST effectiever dan de LMIS na één jaar.

Welke basiskarakteristieken voorspellen continue abstinentie?

Binnen de SMOKE studie werden tevens voorspellers voor succesvol stoppen gezocht. Een fors aantal sociaal-cognitieve, demografische, aan roken gerelateerde en medische karakteristieken werden in de basismeting meegenomen. Alleen de factoren die ten minste een marginaal significante univariate relatie ($p < .20$) lieten zien met de continue abstinentie na 12 maanden, werden meegenomen in het complete logistische regressie model. Vervolgens werden alle variabelen die geen onafhankelijke voorspellers voor continue abstinentie bleken te zijn stuk voor stuk verwijderd.

Een sterk positieve attitude wat betreft stoppen met roken (OR 11.8; 95% CI: 1.7-81.5) en een hoog cotinine niveau (OR 2.1; 95% CI: 1.08-3.93) tijdens de basismeting bleken onafhankelijke voorspellers te zijn voor continue abstinentie na 1 jaar voor de LMIS. Er waren geen onafhankelijke en significante voorspellers voor continue abstinentie binnen de RST. In het algemeen kan worden geconcludeerd dat de LMIS de meest geschikte behandeling is voor COPD patiënten met een sterke positieve attitude ten opzichte van stopppen-met-roken. De RST kan vervolgens worden gezien als een alternatief voor patiënten die een minder sterke positieve attitude ten opzichte van stoppen-met-roken hebben bij de basismeting. Deze getrapte benadering kan erg bruikbaar zijn in de klinische praktijk. Het zal leiden toe een toegenomen efficiëntie doordat het stoppen-met-roken programma wordt aangeboden aan patiënten waar een dergelijk programma het beste bij past.

De CAMOXI studie

Doordat er vaak een discrepantie tussen zelfgerapporteerde rookstatus en gevalideerde rookstatus wordt gevonden binnen wetenschappelijk onderzoek naar de effectiviteit van stoppen-met-roken programma's, is een biochemische validatie van de rookstatus noodzakelijk. Koolmonoxide (CO) metingen hebben in vergelijking met cotinine gevalideerde metingen meerdere voordelen. CO metingen zijn bijvoorbeeld niet invasief

en verschaffen direct feedback. Deze CO metingen zijn daarom erg bruikbaar binnen onderzoek naar de effectiviteit van stoppen-met-roken interventies en worden hier ook veelvuldig voor ingezet. Deze factoren dragen bij aan de relevantie van onderzoek naar de validiteit van dit meetinstrument binnen stoppen-met-roken onderzoek, ook omdat dit voor zover bekend niet eerder zo uitgebreid is onderzocht.

Binnen de CAMOXI studie worden drie verschillende CO monitoren gevalideerd voor wat betreft het vermogen om rokers van niet-rokers te onderscheiden binnen mensen met en zonder COPD. De cotinine metingen uit speeksel werden eveneens gevalideerd. 26 'gezonde' rokers, 25 gezonde niet-rokers, 25 rokers en 24 ex-rokers met stabiel COPD tussen de 40 en 72 jaar werden geïncludeerd in de studie (N=100). De rokers werden door middel van zelfrapportage bepaald en niet-rokers werden bepaald door middel van zelfrapportage in combinatie met een meting van het cotinine niveau in het speeksel (< 20 ng/ml) en het COHb in het bloed. Het gehalte van uitgeademd CO werd bij de 51 rokers gemeten vóór het roken van één sigaret en 1 tot 6 uur ná het roken van deze sigaret. Uiteraard bleven de 49 niet-rokers gedurende het onderzoek rookvrij, zij dienden zuiver als controlegroep voor de metingen na 1 uur. De rokers werd verzocht tot 12 uur vóór de basismeting niet meer te roken. De sensitiviteit, specificiteit, positief voorspellende waarde en negatief voorspellende waarde voor zowel de cotinine metingen als de CO metingen werden berekend voor een reeks van afkappunten.

Bij het voorgeschreven afkappunt van 9 ppm genereerde de Breath CO® een sensitiviteit van 68% voor COPD patiënten en 42% voor gezonde deelnemers. De Smokerlyzer® heeft een voorgeschreven afkappunt van 10 ppm; hierbij werd een sensitiviteit van 56% gevonden voor COPD patiënten en 23% voor gezonde deelnemers. Beide monitoren laten bij deze afkappunten een specificiteit van 100% zien voor zowel COPD patiënten als gezonde deelnemers. De Micro CO meter® heeft een sensitiviteit van 88% en een specificiteit van 92% voor COPD patiënten. Voor gezonde deelnemers is dit respectievelijk 92% en 88%, bij het voorgeschreven afkappunt van 5 ppm. De cotininebepalingen uit speeksel laten een 100% sensitiviteit, specificiteit, positief voorspellende waarde en negatief voorspellende waarde zien wanneer er een afkappunt wordt gekozen van 15 ng/ml tot en met 40 ng/ml voor gezonde deelnemers en bij een

afkappunt van 10 ng/ml voor COPD patiënten. Bij deze laatste analyses werd de zelfgerapporteerde rookstatus als 'gouden standaard' gebruikt.

Daarnaast werd ook het beloop van de validiteit van de CO monitoren over de tijd onderzocht. Wanneer het voorgeschreven afkappunt van 9 ppm wordt aangehouden dan vindt de Breath CO® monitor zes uur na het roken van een sigaret 48% van de rokers met COPD en 15% van de 'gezonde' rokers. Wanneer het voorgeschreven afkappunt van 10 ppm wordt gebruikt, vindt de Smokerlyzer® zes uur na het roken van een sigaret 36% van de rokers met COPD en 12% van de 'gezonde' rokers. De Micro CO meter®, die een voorgeschreven afkappunt van 5 ppm hanteert, spoort 92% van de rokende COPD patiënten op en 85% van de 'gezonde' rokers. Het is opmerkelijk dat de gevonden CO waarden in de drie verschillende CO monitoren gelijkenis vertonen met slechts kleine afwijkingen van 1 tot 2 ppm. Aan de ene kant zijn de gevonden CO waarden bij de verschillende CO monitoren dus gelijk, maar verschillen de uitkomstmaten, zoals onder andere sensitiviteit, aanzienlijk. Deze tegenstelling wordt veroorzaakt door de verschillende afkappunten die worden voorgeschreven voor de verschillende CO monitoren.

Er kan geconcludeerd worden dat de voorgeschreven afkappunten voor alle drie de CO monitoren misleidende resultaten voortbrengen wanneer de monitoren ingezet worden bij het bepalen van de rookstatus in beide populaties en na een periode van 12 uur abstinentie. Daarnaast is gebleken dat rokers de metingen van uitgeademd CO kunnen misleiden door een korte tijd voor de metingen te stoppen-met-roken. Naar aanleiding van het onderzoek naar het verloop van de CO waarden in uitgeademde lucht over de tijd blijkt dat ook naar aanleiding van deze bevindingen geconcludeerd kan worden dat de voorgeschreven afkappunten aangepast moeten worden om validiteit van het meetinstrument te vergroten binnen stoppen-met-roken onderzoek bij COPD patiënten alsook bij gezonde deelnemers. De optimale afkappunten zijn afhankelijk van het doel van het gebruik van de monitoren, maar het bepalen van het cotininegehalte van speeksel blijkt het meest valide en daarmee de 'gouden standaard'. Omdat cotininebepalingen relatief kostbaar zijn, lijkt een combinatie van beide meetmethoden de meest kosteneffectieve validatie procedure binnen stoppen-met-roken onderzoek.

Dankwoord (Acknowledgements in Dutch)

Terugkijkend op het gehele promotie traject kan ik met recht zeggen dat het een leerzame en erg boeiende periode was, welke een mooie afronding heeft gekregen met dit proefschrift. Graag wil ik alle mensen die me geholpen hebben gedurende het gehele traject bedanken voor hun steun. Het is bijna onvermijdelijk mensen te vergeten bij het opnoemen van mensen 'in het bijzonder'. Toch wil ik u dat niet onthouden.

Ten eerste wil ik mijn promotor *Erwin Seydel* bedanken voor zijn toegankelijkheid en het overzichtelijk maken van al mijn schrijfsels. Je stond altijd vierkant achter me. Ook wil ik mijn 'dagelijks begeleiders'/assistent-promotoren, *Job van der Palen* en *Marcel Pieterse*, bedanken voor hun steun en toeverlaat. Job, begeleiden is voor jou een uitermate breed begrip. Van jou heb ik op allerlei vlakken 'tips en trucs' gekregen waar ik ontzettend veel aan heb gehad. Marcel, discussies met jou waren altijd verrassend en verfrissend. Dit heeft vaak geleid tot nieuwe ideeën en het helder krijgen van oude ideeën. Met jullie als begeleiders had ik het zeldzame geluk onderdeel te kunnen zijn van een echt team.

Natuurlijk wil ik ook alle patiënten en andere vrijwilligers bedanken die deel hebben genomen aan zowel de SMOKE studie als de CAMOXI studie. U bent werkelijk onmisbaar!

Ook wil ik de afdeling Communicatiewetenschap van de Universiteit Twente bedanken voor het bieden van deze uitgelezen kans om kennis te maken met het wetenschappelijk onderzoek. De vele collega's, en in het bijzonder de promovendi met wie ik veel tijd heb doorgebracht, wil ik bedanken voor de prettige werksfeer. Daarnaast wil ik het secretariaat, *Ria Stegehuis*, *Edith Nijhuis* en *Jeanine Lodeweges*, danken voor het verlichten van mijn 'administratieve rompslomp'. Verder wil ik *Joost Baneke* bedanken. Jij hebt ervoor gezorgd dat ik de psychologie in de praktijk niet uit het oog verloor. Mede dankzij jou kan ik mijn wens vervullen om de praktijk met de theorie ook in de toekomst te kunnen blijven combineren.

Binnen de afdeling Longgeneeskunde (longartsen, longfunctie, secretariaat en longverpleegkundigen) van Medisch Spectrum Twente heb ik voor het eerst kennis gemaakt met het klinisch onderzoek. De dinsdagen waren voor mij evenzeer een verademing als een uitdaging. De afdeling heeft als een team gewerkt voor zowel de SMOKE, als de CAMOXI studie en zonder jullie medewerking was het niet gelukt, dank daarvoor. In het bijzonder wil ik het 'Onderzoeksbureau Longgeneeskunde' bedanken voor de ondersteuning. Door al jullie ervaring ben ik een stuk wijzer geworden. De promovendi binnen Medisch Spectrum Twente, *Evelyn Monninkhof* (inmiddels doctor), *Yvette Bulthuis*, *Marjolein Keizer* en *Tanja Effing*, wil ik bedanken voor zowel hun morele als wetenschappelijke ondersteuning. Als 'broeders in dezelfde strijd' heb ik heel erg veel aan jullie gehad. *Paul van der Valk*, als vliegende dokter en doctor heb je me vertrouwd gemaakt met de afdeling Longgeneeskunde en het doen van pulmonair onderzoek. De COPE studie die je samen met Evelyn Monninkhof hebt volbracht was werkelijk een opmaat voor dit proefschrift. *Frans de Jongh,* in een razend tempo hebben we samen met anderen de CAMOXI studie opgezet en uitgevoerd, zo konden we mooie ideeën omzetten in een uniek klinisch onderzoek. *Heleen Mulder*, *Christa ten Bolscher*, *Anneke Bosch*, *Ansje Uunk* en *Henriëtte Kosters*, jullie hebben binnen Medische Spectrum Twente als longverpleegkundigen goed werk afgeleverd, ik kon me geen betere uitvoerders wensen. De Stoppen-met-roken poli kan mijns inziens dan ook worden gezien als een bekroning op dit harde werken!

De afdelingen Longgeneeskunde (longartsen, longfunctie, secretariaat en longverpleegkundigen) van het Slotervaart ziekenhuis te Amsterdam (*Paul van Spiegel*, *Roos Blom*, *Tineke Kerstens*, *Suzanne Craig* en *Suzan van Kempen*) en het Catharina ziekenhuis te Eindhoven (*Frank Smeenk*, *Walter van Litsenburg* en *Annet Jager*), wil ik hartelijk danken voor de samenwerking. Multi-centre onderzoek schijnt nogal wat energie te kosten, maar dankzij jullie inzet is dit hard meegevallen, dank daarvoor.

Dan mijn kamergenoten. Aan de start van mijn aanstelling was *Maaike van der Haak* mijn kamergenote. Samen hebben we veel meegemaakt. Zo hebben we met helmen op door de puinhopen van de brand gestruind om onze verwoeste werkplek te bezichtigen.

Dat was wel een heel bruut einde van ons 'kamergenootschap'. Maaike, dank voor je interesse, het delen van lief en leed en natuurlijk de Engelse puntjes op de i! Op de Institutenweg werd *Martine Veehof* mijn kamergenote en al snel kwam *Mark van Vuuren* daarbij toen we terugkeerden naar het (inmiddels) Cubicus gebouw. Martine, samen konden we bakkeleien over het doen van onderzoek in de medische setting: ik denk dat we moeten concluderen dat we helden zijn, alleen al door het aanvaarden van een dergelijke uitdaging (knipoog). Mark, dank je voor de letterlijk wonderlijke gesprekken die we zo regelmatig gevoerd hebben. We zijn heel verschillend, maar in dit geval is dat een krachtig gegeven.

Omdat al het werk achter de schermen niet minder belangrijk is, wil ik een aantal mensen bedanken die ervoor hebben gezorgd dat ik aan de verschillende randvoorwaarden voor wetenschappelijk onderzoek kon voldoen: *Cees Neef*, *Tonny Knuif* en *Jan Goolkate*, dank voor al die cotininebepalingen en het enthousiasme waarmee jullie dit voor mij hebben gedaan, 'Goodgoan'. *Marjolein Wobben*, *Pieter Schaefer*, *Wim Subelack* en *Wim Ranselaar,* dank voor het beheren van het budget en het verzorgen van allerlei personeelszaken. *Thijs Rinsma*, dank je voor het nauwgezet controleren van al mijn vragenlijsten. *Epidemiologen Twente*, een 'kijkje in de keuken van de epidemiologie' is wat mij betreft de beste omschrijving voor onze leerzame refereerbijeenkomsten.

Mijn paranimfen, *Bart Christenhusz* en *Betty Rinsma.* Bart, voor jou lijkt een promotie als een harnas van ceremoniële regels en verplichtingen. Maar omdat je weet dat dit alles voor mij erg belangrijk is, ben je bereid mij daarin als paranimf te ondersteunen, dikke prima! Betty, als data manager heb je goed werk verricht, het heeft een zeer waardevolle database opgeleverd. Dat je ook deze 'laatste taak' voor mij wilt doen geeft me vertrouwen. Jullie zijn voor mij een fantastisch duo!

Henny Christenhusz en *Tine Christenhusz*, mijn ouders. Jullie zijn voor mij als een rots in de branding met jullie onverbeterlijke Twentse nuchterheid. Door regelmatig te informeren naar 'het project' en omdat ik weet dat jullie trots op me zijn, heb ik me altijd erg gesteund gevoeld.

Tom Tijink, 'last but not least', op momenten dat ik op mijn werk mijn twijfels en onzekerheden verborg achter een schild van schijnbare onbewogenheid en temperament (zo heb ik me laten vertellen), kon ik mijn gevoelige kanten thuis aan jou tonen, dank daarvoor. Jij brengt de rust die ik soms zo hard nodig heb.

Curriculum Vitae (About the author)

Lieke Christenhusz werd geboren op 8 mei 1978 te Oldenzaal. In 1996 haalde ze haar Atheneum diploma aan het Thijcollege te Oldenzaal. Vervolgens is ze in 1996 gestart met de opleiding psychologie aan de Katholieke Universiteit Nijmegen, met als afstudeerrichting Neuro- en Revalidatie psychologie. Op 23 november 2000 heeft ze daarvoor haar doctoraal diploma ontvangen. Hierop volgde een periode waarbij ze werkzaam was als (neuro-)psychologisch testassistente bij de afdeling Medische Psychologie verbonden aan het St. Anna ziekenhuis te Geldrop. Vanaf april 2001 werd het in dit proefschrift beschreven onderzoek naar 'stoppen-met-roken bij COPD patiënten' uitgevoerd binnen het samenwerkingsverband tussen de Universiteit Twente en Medisch Spectrum Twente. In de periode waarin ze was aangesteld als assistent in opleiding, werd ze 5 maanden gedetacheerd als beleidsmedewerker van de Concernstaf Medisch Spectrum Twente, Taakgroep 'Zorg en Innovatie'(ZIN), afdeling 'Research & Development'(R&D). Ook heeft ze bijgedragen aan het coördineren en opzetten van de Stoppen-met-roken poli binnen Medisch Spectrum Twente. Sinds september 2005 is Lieke zowel werkzaam bij de Universiteit Twente, als ook bij Mediant; Geestelijke Gezondheidszorg in Oost en Midden Twente. Hierbij houdt ze zich bezig met het uitvoeren van psychologische onderzoeken, wetenschappelijk onderzoek en doceren waarbij een 'brugfunctie' tussen Mediant en de Universiteit Twente wordt vervuld.