Smoking cessation in routine primary care

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SMOKING CESSATION IN ROUTINE PRIMARY CARE

**Intensive practice nurse counselling versus brief general
practitioner advice**

Colophon

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SMOKING CESSATION IN ROUTINE PRIMARY CARE

**Intensive practice nurse counselling versus brief general
practitioner advice**

DISSERTATION

to obtain the degree of Doctor at the Maastricht University,
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Prof. dr. Rianne M. Letschert
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Chapter 1

General Introduction

General introduction

This thesis is about smoking cessation in routine primary care, with the emphasis on the role of the practice nurse and varenicline. Not so long ago, the practice nurse was introduced in the Netherlands as a supportive workforce in primary care. They were expected to become important game changers in smoking cessation alongside the general practitioner. Since practice nurses have more time for counselling than general practitioners, practice nurses could potentially contribute to higher smoking cessation rates in primary care in general and for smokers with COPD in particular. In addition, varenicline was the most recent pharmacotherapy on the market and has shown to be safe, well-tolerated, and more effective than other available pharmacotherapies. Nevertheless, there was no evidence to support a combination treatment of varenicline and counseling by the practice nurse or general practitioner. This first chapter describes the problem of smoking in general, the context of Dutch primary care and the available treatment options for smoking cessation, including intensive counselling from the practice nurse and varenicline. In addition, the need for pragmatic trials in primary care to obtain results that are likely to be generalisable and applicable in routine care is described. The research questions are introduced at the end of this section and answered throughout this thesis.

Impact and prevalence of smoking

Smoking increases the risk of developing cancer, cardiovascular diseases and chronic obstructive pulmonary diseases (COPD) (1, 2). This makes smoking a leading cause of illness and premature death (the probability of dying between the ages of 30 and 70) (3). Among six identified risk behaviours of premature death (smoking, alcohol use, salt intake, obesity, high blood pressure, and raised glucose), smoking is the most important risk factor in men, and the second most important risk factor in women (after high blood pressure) (3). It is estimated that smoking is responsible for 7 million deaths per year worldwide (4-6), of which exposure to second-hand smoke is responsible for nearly one million deaths (5). The chance of dying from cancer is twice as high among smokers compared to non-smokers, with heavy smokers having a four times greater risk (7). In fact, it is argued that this mortality number is still underrated (8).

In 2011, a global target was set by the United Nations General Assembly to achieve a 25% reduction of premature deaths from non-communicable diseases by 2025 ("25x25"), including an estimated 30% relative reduction in smoking prevalence (9). This implies that a substantial number of smokers would have to make a quit attempt

and that the success rate should be significantly improved (10). When the studies of this thesis started in 2010, the overall smoking rate was 32% in Europe and 29% (23.5% daily smokers and 5.5% occasional smokers) in the Netherlands (11). Meanwhile, there have been considerable changes in tobacco control policies due to the ratification of the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) (12, 13). The implementation of tobacco control strategies, such as raising the minimum age for selling cigarettes, banning smoking in public places, warning signs on tobacco products and smoking cessation programmes in primary healthcare, has led to a downward trend in smoking prevalence (14). As a result, the overall smoking rate dropped to 26% in Europe and 19% in the Netherlands in 2017 (15). A more recent Dutch national survey study also showed that the daily smoking prevalence dropped to 16% in 2019 (16).

Despite the positive decrease in smoking prevalence, the downward trend has stopped as there was no further reduction in the overall smoking rate in Europe between 2014 and 2017 (15). On the contrary, the smoking rate has increased amongst people aged 15 to 24 years (15), which is actually a worrying development. Currently, more men than women smoke (22% versus 17%) (15) and smoking is a bigger problem among people with a lower educational background (15-17), making smoking an important factor of health inequity. Considering the burden on individual health and healthcare systems and the slowdown in reduction of smoking, smoking cessation remains a priority to governments, healthcare policy makers and insurance companies.

The complexity of the tobacco addiction

When healthcare providers address smoking cessation to patients, they should understand the complexity of smoking. Smoking is a complicated, multifactorial addiction, rather than just a bad habit or a physical urge. Smoking depends on several factors, including neurobiological, genetical, environmental, psychological and behavioural factors, all of which appear to influence the smoking behaviour and/or the probability of quitting (18-25). Contrary to other addictions, smoking has so far been relatively socially accepted, but this seems to be changing. Tobacco control policies are increasingly focused on the denormalisation of smoking (12, 13, 26-28), which should encourage smokers to quit and prevent young people from taking up smoking. Evidence that unravels the full complexity of the addiction and the damage smoking causes is still accumulating, providing important input for the development of smoking cessation policies and strategies, and for the development of personalised care in the future.

Neurobiological factors

Although the toxicity of smoking mainly depends on other substances in cigarettes, nicotine is the most important neurobiological contributor to the smoking addiction. It is originally a chemical defence system of the tobacco plant against insects, causing a neurotoxic reaction (18). In humans, nicotine enters the cerebral bloodstream after taking a puff, where it binds to neuronal nicotinic acetylcholine receptors (nACh-receptors) (18, 29-31). When nicotine connects with the presynaptically located nACh-receptors, there is a release of dopamine, along with other neurotransmitters such as acetylcholine, norepinephrine, serotonin, glutamate and gamma-aminobutyric acid (29, 32). The increased levels of dopamine lead to a euphoric feeling, causing the pleasurable effects of smoking (18). Therefore, dopamine plays an important and mediating role in the reward system and influences a person's dependence on nicotine (29, 33). Individuals with a higher nicotine dependence are less likely to quit smoking (19). Even more, a smoker's brain changes in response to high levels of nicotine by a long-term upregulation of nACh-receptors (31, 34), making it even more difficult to stop. One of the most important nACh-receptors is the $\alpha_4\beta_2$ subtype, which is believed to be the dominant receptor mediating nicotine dependence (30, 35).

Genetical factors

Smoking is partly hereditary. It is understood that genetic variation plays a significant role in smoking behaviour and nicotinic, dopaminergic and glutamatergic neurotransmissions (36, 37). Research about this topic is accumulating through large genome-wide association scans (20). In the last decade, several studies have shown that common genetic variants in the nicotinic acetylcholine receptor gene cluster on chromosome 15, 15q24-25.1, were associated with the number of cigarettes per day and nicotine dependence (20, 23-25, 36). Variations in region 15q24-25.1 were also associated with a higher chance on developing smoking associated diseases, such as lung cancer (38, 39), peripheral arterial disease (38) and COPD (40). In fact, people who are genetically prone to be more nicotine dependent and to smoking more cigarettes per day, also have a higher risk of developing lung cancer, regardless of their smoking behaviour (41). Besides chromosome 15, other chromosomes are also involved in the smoking behaviour. For example, every extra copy of a certain allele on chromosome 3 (single-nucleotide polymorphism (SNP) rs1051730 in cholinergic receptor nicotine alpha 3 subunit (CHRNA3)) corresponded with smoking 1 extra cigarette per day (23).

Environmental factors

Social networks and social norms are important environmental factors in the uptake of smoking (42, 43), the chance of making a quit attempt (26, 27, 44-46) and the chance of successful quitting (44, 46, 47). Having many smokers in the social environment

increases the likelihood of being a smoker (22, 42, 44) and since smoking is often an activity done in the company of others, it can be seen as a facilitator of social relationships (48). On the other hand, when smoking is the normative behaviour, non-smokers could be excluded from certain social interactions (49, 50). Likewise, non-smoking also seems communicable. Supportive relationships are very important predictors in making a quit attempt and eventual smoking cessation. Especially having a close personal contact with someone who quitted smoking increased the chance of quitting (44). It seems that the disapproval of family and friends, the embarrassing feeling of being a smoker and having a recent quitter in the environment, can increase the chance of making a quit attempt (18, 26, 45). Having social support and anti-smoking social norms and denormalisation of smoking, seem to be particularly important for smokers in socio-economically disadvantaged situations and for ethnic minorities (45, 51).

Psychological factors

Smoking is more common among persons with mental illnesses. For example, people with mental illness are far more likely to smoke than the general population, with a percentage that is two to three times higher than in people without mental illness (52, 53). It is most likely that nicotine temporarily lessens their symptoms, such as poor concentration, low mood and stress (54). Nevertheless, prolonged smoking cessation is associated with improved mental health, such as less depression and anxiety, and enhanced mood and quality of life (55). Also factors which are part of our character can also be linked to the act of smoking and the difficulties in quitting. Higher levels of the psychologic factors neuroticism, psychoticism and psychological distress have been shown to increase the chance of relapsing within a year after quitting (19). Smokers have higher extraversion, higher neuroticism and lower conscientiousness personality scores than non-smokers. Uptake of smoking is associated with higher extraversion and lower conscientiousness, and relapse is associated with higher neuroticism (56). Furthermore, behavioural factors such as alcohol consumption have a positive association with the number of cigarettes smoked (21).

Smoking cessation treatment in primary care

Public health campaigns play a role in increasing people's knowledge about smoking and helps to denormalise smoking at population level (12, 13, 57, 58). Primary care is another key player in smoking cessation on an individual level, due to its strategic and unique position in healthcare. Healthcare providers in primary care have the skills and knowledge to support smokers to quit (59-62), especially in countries where a large percentage of smokers regularly visit their general practitioner. In the Netherlands,

primary care has complete coverage of the population and has therefore a good reach into the community. Among 80% of the smokers visit their primary healthcare centre each year (63). This is why smokers who are considered as “difficult to reach”, i.e. heavy smokers, smokers with a low socio-economic status, different ethnic background, or with mental illnesses, can be reached in primary care. Although there is no evidence supporting this statement, we feel that this group is difficult to reach through governmental health campaigns. Also smokers who are often “forgotten”, such as light smokers, can be targeted by their general practitioner (63).

Availability and use of guidelines

Ideal circumstances exist in primary care: a good reach into the population, the continuity of care and the availability of guidelines. National and international guidelines help to improve clinical practice for smoking cessation. These guidelines ensure the dissemination of the latest insights and evidence-based recommendations. Although the specific recommendations in the different guidelines vary, in general they advise healthcare professionals to identify a smoker, provide straightforward advice to quit and offer a combination treatment with behavioural counselling and pharmacotherapy when a smoker is ready to quit (10, 64-69). Nonetheless, the uptake of evidence-based treatments for smoking cessation remains low (63, 70, 71). While 80% of the smokers want to quit or feel they should quit (72), the Dutch ‘Continuous Survey of Smoking Habits’ showed that only 23% of all smokers received quitting advice and less than 5% was referred to behavioural treatment (63). In addition, smokers are reluctant to discuss difficulties regarding smoking cessation with their general practitioner (73). So while smokers could benefit from evidence-based smoking cessation treatment, such treatments are underutilised (74, 75) for a variety of reasons (76-78).

Pharmacological treatment

Recommended pharmacological options for smoking cessation include nicotine replacement therapy (NRT) (79, 80), antidepressants (81) and nicotine receptor partial agonists (82). NRT substitutes the nicotine from cigarettes and thereby attempts to reduce the cravings for nicotine from cigarettes and withdrawal symptoms. When compared to placebo or no treatment, NRT can increase quit rates by 50-60% (risk ratio (RR) 1.55, 95% confidence interval (CI) 1.49-1.61, 133 studies, 64,640 participants) (79), and a combination of two NRT treatments can even improve that effect (RR 1.25, 95%CI 1.15-1.36, 14 studies, 11,356 participants) (80). Bupropion, the most commonly used anti-depressant for smoking cessation, can increase quit rates by 52-77% (RR 1.64, 95%CI 1.52-1.77, 46 studies, 17,866 participants) compared to placebo or no treatment (81). A third type of medication, the $\alpha 4\beta 2$ nicotine receptor partial agonists,

includes varenicline. Varenicline targets the $\alpha 4\beta 2$ nicotinic acetylcholine receptors (nAChR), which are believed to have the highest specificity for nicotine (35, 83, 84). By blocking this specific receptor, it blocks the reinforcing effects of nicotine while relieving cravings and withdrawal symptoms (35, 82). Varenicline seems most effective because it doubles or triples the chances of successful long-term smoking cessation compared to placebo or no treatment (RR 2.24, 95%CI 2.06-2.43, 27 studies, 16,625 participants) (82), and compared to bupropion (odds ratio (OR) 1.75, 95%CI 1.52-2.01) and NRT (OR 1.68 95%CI 1.46-1.93) (85). Moreover, apart from NRT, varenicline is nowadays the most prescribed pharmacological aid for smoking cessation (86).

Behavioural treatment

Behavioural support can be provided, ranging from less intensive and one-off support (brief advice) to more intensive support with multiple sessions (counselling) (69, 87). The counselling can be organised in individual and/or group sessions (69, 87, 88), by different healthcare providers (59, 61, 69), and supported by a range of theoretical approaches (i.e. Motivational Interviewing or Cognitive Behavioural Therapy (89)). It has been shown that there is a strong dose-response relationship between the number of sessions, total contact time and abstinence, showing that intensive counselling increases the chance of a successful quit attempt compared to less intensive support (69). For example, Rice et al. (2013) focused on brief advice delivered by nurses and found that behavioural support with more than one follow-up contact significantly increased the quit rates when compared to no advice or usual care (RR 1.29, 95%CI 1.20-1.39, 35 studies, 17,604 participants) (61). On the other hand, also very brief advice (VBA) from the general practitioner seems to have an effect on smoking cessation compared to self-initiated strategies (59, 69, 90). Therefore, it appears that behavioural support, no matter how little, positively influences quit rates.

Combination treatment

Nowadays, smoking cessation treatment should be offered as a combination of a pharmacological and behavioural approach. While behavioural support and pharmacotherapy alone are effective treatments for smoking cessation (59, 61, 87, 91-93), the combination of behavioural support with pharmacotherapy has been shown to be the most effective approach with significantly higher quit rates compared to minimal intervention or usual care (60, 81, 87, 94). For example, Stead et al. (2016) showed that the combination of pharmacotherapy and behavioural support compared to usual care, brief advice or less intensive behavioural support increased quit rates (RR 1.83, 95%CI 1.68-1.98, 52 studies, 19,488 participants). In addition, another review from Hartmann-Boyce et al. (2019) also showed that the addition of increased behavioural support to

pharmacotherapy compared to minimal behavioural support and pharmacotherapy improved cessation rates (RR 1.08, 95%CI 1.08-1.22, 65 studies, 23,331 participants) (62). Therefore, it is nowadays advised in most guidelines that healthcare providers encourage their patients to use both counselling and pharmacotherapy when making a quit attempt (10, 64, 66-69). The vast majority of studies on combination therapies, however, investigated NRT, while there were no varenicline studies available at the time these reviews were conducted. Therefore, there was no evidence that combining varenicline with intensive behavioural counselling was effective.

Introduction of practice nurses

There is strong evidence that primary care is at the heart of a good health system (95-97). It is based on the principles of good access to care, continuity of care, comprehensiveness of care and a general practitioner who coordinates it all (98). In the Netherlands, the healthcare system is based on the pillars of a strong primary care (99, 100). While models of primary care differ internationally, general practitioners in the Netherlands play a central role as 'gatekeeper'. Every patient has a general practitioner and patients need a referral from their general practitioner in order to have access to specialists and hospital care. Around 90% of all care takes place in primary care (100) (this includes a wide variety of providers), resulting in 7% referrals to secondary care (99) while only using 4% of the total care budget (100). Advantages of having a general practitioner, is that he or she is aware of the social context and life events of the patient. In countries where having a general practitioner is not regulated as standard care, it shows that those patients with a general practitioner, are more likely to engage in healthy behaviours than those without (101, 102).

Regardless of the efficacy, primary care is nowadays faced with increasing problems such as ageing, growing prevalence of chronic diseases and multi-morbidity, and the need for preventive care alongside curative care (99). A practice nurse (in Dutch: "praktijkondersteuner") is a registered nurse working in the general practice office with the goal to support the general practitioner in patient care and helps with the provision of chronic care. After successfully completing a study program at the level of university of applied sciences, practice nurses are licensed to support the general practitioner in their daily practice (103). The deployment of the practice nurse as an additional workforce for the general practitioner may reduce the workload for the general practitioners and give room for extra responsibilities (104-106). Although training, responsibilities and tasks of nurses differ globally (107, 108), practice nurses are able to manage consultations independently and work under little supervision (104). There are indications that between 25% and 85% of the tasks can be delegated

to nurses and other non-medical healthcare providers, especially in primary care (109, 110). Patients also seem satisfied with the practice nurse (104). In total, 75% of the patients, who received care from the practice nurse, does not want to go back to the old situation without a practice nurse (111).

Since their introduction into primary care in the Netherlands, the amount of practice nurses has been growing. Nowadays, almost 90% of practices have a nurse available for their patients (112). Practice nurses are expected to cost-effectively manage chronic illnesses and perform health promotion tasks such as smoking cessation treatment (107). A recent review showed that practice nurses, along with other trained nurses, provide the same quality of care or even better care compared to general practitioners for both chronic conditions and general physical complaints (104). However, their added value in the treatment of smoking cessation has not yet been confirmed by scientific evidence (105). Because practice nurses have more time for counselling, it is believed that they are more effective in smoking cessation treatment than the general practitioner. There is also no evidence yet of the difference between a brief consultation by the general practitioner and intensive counselling by the practice nurse.

Pragmatic trials

Randomised trials give important information on what is effective and what is not. In 1967, Schwartz and Lellouch (113, 114) already warned for the essential differences in outcomes and usability of the results between explanatory and pragmatic clinical trials, regarding the transferability of results to the general population and to daily practice. Explanatory trials are designed to investigate whether interventions work under the most ideal conditions (i.e. efficacy), whereas pragmatic trials are designed to investigate the effects of an intervention in real-life conditions (i.e. effectiveness). In addition to the preliminary work of Schwartz and Lellouch, the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) tool was developed to assess whether elements of a trial could be identified as being more explanatory or more pragmatic (115).

After successful efficacy trials, there is a strong need for pragmatic trials on smoking cessation programs for the primary care population. Guidelines advise the use of a combination treatment (10, 64, 66-69), but that advice was largely based on trials that had an explanatory design. Varenicline is more effective for smoking cessation than other known single-use pharmacological aids, such as bupropion and nicotine replacement therapy (92) and together with the nicotine sublingual tablet, the most successful pharmacological aid in smokers with COPD (94). Nonetheless, at the time of

starting this thesis, there was no compelling evidence for combining varenicline with different forms of behavioural treatment. Evidence on the effectiveness of combining counselling and varenicline in primary care (116) and other settings (117, 118) was insufficient and reasons for the combination being most successful were underexplored. Therefore, a pragmatic, real-life study directly comparing intensive practice nurse counselling with brief general practitioner advice, in the context of pharmacotherapy, was needed.

Setting

All studies in this thesis were performed in one primary care setting: The Eindhoven Corporation of Primary Health Care (SGE), covering approximately 70,000 patients within 11 multidisciplinary healthcare centers in Eindhoven, the Netherlands (119). SGE and the Care and Public Health Research Institute (CAPHRI) have been working together since 2007. Working with SGE gave access to a large network of potential patients in various neighborhoods in Eindhoven, characterised by their different socio-economic composition, which may increase the generalizability of the results. Another advantage was the personal contact and engagement of healthcare providers. The organisation's close involvement in the design and implementation of the research made it very close to practice and therefore very pragmatic.

As part of the collaboration, researchers from CAPHRI had access to the electronic medical record system with data from SGE. Data from the electronic medical record system were used to improve care, registration processes and patient outcomes. These actions were largely initiated based on requirements of medical insurance companies, but also for scientific research, e.g. for the development of quality improvements in collaboration with the healthcare providers from SGE. SGE had four healthcare programmes for chronic or high burden conditions: diabetes mellitus, cardiovascular diseases, asthma and COPD, and depression. The studies in this thesis were supporting the healthcare programme for asthma and COPD and an additional goal was to develop, implement and evaluate a quality improvement programme for smoking cessation in primary care.

Outline of this thesis

To be able to develop a quality improvement programme, the first step was to evaluate underutilization of smoking cessation treatments in primary care. In *Chapter 2*, possible barriers were explored for the utilisation of smoking cessation treatments in primary

care, from the perspective of smokers, ex-smokers, practice nurses and general practitioners. Another goal was to identify solutions from practice, in order to get a better bottom-up solution for a smoking cessation innovation. These outcomes were important for understanding whether the planned randomised controlled trial was justified, how the trial could be conducted pragmatically and how the study should be conducted. The planned randomised controlled trial was the “COMbining VAREnicline with Counselling” (COVACO) trial, which was designed earlier by Daniel Kotz et al. This study was financed through an unrestricted grant from Pfizer Inc. and funding from The Eindhoven Corporation of Primary Health Care Centres. The COVACO trial fitted very well with the aims of the researchers as well as with the aims of SGE.

From the perspective of science, there was a need for evidence for the combination treatment of pharmacotherapy with intensive counselling from the practice nurse versus brief advice from the general practitioner. Moreover, from the perspective of clinical practice, there was a need for a context-specific schedule and treatment protocol that the practice nurses could use in routine care. The current guidelines and protocols did not provide sufficient direction and the current treatment time was not reimbursed by the medical insurance company. These two goals have been embodied in the COVACO study. *Chapter 3* provides a detailed description of the study protocol and a rationale for the study design in order to provide full transparency of study planning and reporting. It also describes in detail the intervention condition with the treatment protocol of the practice nurse and the control condition with the general practitioner. This should provide some insight into the potentially effective working mechanisms, which could inform future smoking cessation interventions. *Chapter 3* also offers an explanation of how pragmatic this trial was, based on the PRECIS wheel (115).

The effects of the COVACO study are described in *Chapter 4*. We hypothesised that intensive counselling from practice nurses would be more effective than usual care from the general practitioner, when given in combination with pharmacotherapy. Usual care from the general practitioner consisted of a short face-to-face-consultation with brief advice, while the practice nurse could use up to 120 minutes of counselling. *Chapter 4* provides an answer whether biochemically-validated smoking cessation rates differed between the designated groups from weeks 9 to 26 while using an intention-to-treat analysis. Another hypothesis which was tested and answered in *Chapter 4*, was that medication adherence was better with the practice nurse and resulted in increased quit rates on its own. In a previous study there was a strong relation with adherence to varenicline and abstinence from smoking (6-month abstinence rates 52% for good adherence versus 25% for bad adherence) (116).

Therefore, good adherence (>80% days taken) was measured and reasons for disrupting the intake of varenicline were evaluated. *Chapter 4* also provides information on the cost-effectiveness of practice nurses, because this information is often lacking or inadequate (120, 121). Therefore, an incremental cost-effectiveness ratio was calculated for the differences in costs per quitter between the practice nurse and general practitioner group.

The prevalence of tobacco smoking in patients with COPD is higher than in the general population. For example, a large English population-based study showed that the smoking prevalence was 22% among people without COPD, compared to 35% among people with COPD (122). Nonetheless, smoking cessation is particularly important for smokers with COPD, as this is the only treatment which can effectively decrease the accelerated decline in lung function (2, 123, 124), reduce symptoms of cough and sputum, improve health status and reduce exacerbations of COPD (125). It is assumed that smokers with COPD face more difficulties with quitting than smokers without COPD. However, smoking cessation interventions are not tailored to the needs of patients with COPD, while there are indications that they have different needs regarding smoking cessation. A cross-sectional study was undertaken to look at the differences between smokers with and without COPD (*Chapter 5*).

To sum up, the main research questions were the following:

1. What are possible barriers and solutions for the utilisation of smoking cessation treatments in primary care, from the perspective of smokers and healthcare providers? (*Chapter 2*)
2. What is an optimal and reasonable schedule in terms of treatment time and which elements of behavioural change techniques should be included in an evidence-based smoking cessation counselling protocol for the practice nurse in primary care? (*Chapter 3*)
3. What are the possibilities of performing a pragmatic trial on smoking cessation in routine primary care and which concessions have to be made in relation to daily practice? (*Chapter 3*)
4. How effective is individual counselling by a practice nurse versus brief advice by a general practitioner, both combined with open-label varenicline, on 6 months and 12-months smoking cessation? (*Chapter 4*)
5. Is there a difference in medication adherence of a 12-week open-label varenicline course of patients treated by the practice nurse with intensive counselling compared to patients treated by the general practitioner group with brief advice? (*Chapter 4*)

6. What is the short-term cost-effectiveness of a smoking cessation intervention of individual counselling by a practice nurse versus brief advice by a general practitioner? (*Chapter 4*)
7. What is the need and necessity for tailored smoking cessation interventions for smokers with COPD in primary care? (*Chapter 5*)

In *Chapter 6*, the results and strengths and limitations of this thesis are described and discussed. Finally, we will share our conclusions, consider scientific and practical implications for clinical practice and give directions for future research.

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Chapter 2

Exploration of barriers and solutions in current daily practice from the perspective of smokers and healthcare professionals

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Exploration of barriers and solutions in current daily practice from the perspective of smokers and healthcare professionals

Abstract

Background: Evidence based recommendations for smoking cessation are not followed in routine primary care. A better understanding is needed why smoking cessation treatment is still underutilized.

Objectives: To explore barriers and solutions of smoking cessation treatment, from the perspective of smokers and healthcare professionals in Dutch primary care.

Methods: Focus groups were conducted with 14 smokers (smokers and ex-smokers) and semi-structured individual interviews with nine healthcare professionals (general practitioners and practice nurses). Data was analysed using the Constant Comparative Method.

Results: Barriers that prevented successful smoking cessation treatment were the lack of awareness regarding the available smoking cessation treatments at the healthcare centre among smokers and the resistance against preventive tasks among healthcare professionals. Nonetheless, general practitioners (GPs) did not fear jeopardizing the doctor–patient relationship by discussing smoking. Quitting was regarded as the smokers' own responsibility and GPs felt that merely using medication was no guarantee for successful quitting. Even so, practice nurses and smokers preferred medication use. Proposed solutions were that GPs should advise smokers to quit, whereas someone else should deliver intensive behavioural support, preferably the practice nurse.

Conclusion: Smokers and healthcare professionals seem to wait for each other to start smoking cessation. GPs should know that they could discuss smoking cessation with every patient without jeopardizing the doctor–patient relationship, preferably followed by referral to a practice nurse for intensive behavioural support. Furthermore, more patients should know that they could receive pharmacological treatment as well as behavioural support for smoking cessation in their healthcare centre.

Introduction

Guidelines state that general practitioners (GPs) should advise every smoker to quit and discuss options for treatment (1-3). Despite these clear recommendations and the availability of evidence based behavioural and pharmacological treatments, smoking cessation activities are underutilized in primary care. In the Netherlands, only 23% of all smokers received smoking cessation advice, in 26% of the patients the GP recommended or prescribed medication, whereas in only 3% of the patients behavioural was suggested (4). The low use of evidence-based treatments for smoking cessation in primary care has been shown in other countries as well (5, 6).

The underutilization of treatments by smokers and healthcare professionals could have various reasons. For example, GPs feel they lack the skills and time to assist in smoking cessation, and they seldom receive reimbursement for such activities (7, 8). Smokers also seemed reluctant to seek treatment because of low expectations of the effects (9, 10). In 2007, the practice nurse (PN) was introduced in the Netherlands to facilitate the work of the GP by taking up behavioural treatment and monitoring of chronic diseases such as chronic obstructive pulmonary disease (COPD). The PN is also involved in smoking cessation, but the uptake of behavioural smoking cessation support still lacks (4). Nonetheless, PNs seem enthusiastic about giving smoking cessation support, and currently research is being done about their efficacy (11).

The aim of this research was to explore possible barriers and solutions to the utilization of smoking cessation treatments in Dutch primary care, both from the perspective of smokers (i.e., all ever smoking patients on the list of the GP) and healthcare professionals (GPs and PNs). Studying smokers and healthcare professionals simultaneously could give a unique and full insight into the challenges of current daily practice, and provide solutions to eliminate certain barriers.

Methods

A qualitative study was performed using focus group discussions and individual interviews with smokers and healthcare professionals of 'The Eindhoven Corporation of Primary Health Care', covering about 64 000 patients with 10 multidisciplinary healthcare centres in the city of Eindhoven, the Netherlands. A mix between a phenomenological approach and a grounded theory approach was chosen since the aim was to explore and understand the experiences from individuals. This method allowed comparison of the data between two groups, without trying to form a theory (12).

Participants

We intended to recruit a heterogeneous study population. To capture a broad spectrum of information and experiences, purposive sampling with a maximum-variation approach was used (12). All healthcare professionals were invited via an email sent by the local board of the healthcare centres. With the assistance of the responding healthcare professionals, approximately 100 smokers were selected to participate. Smokers were selected if they were current smokers or ex-smokers who quit smoking less than ten years ago, were at least 18 years old and fluent in the Dutch language. The selected smokers received information about the study and asked to participate. In total, 24 patients responded, who were then approached to schedule a focus group discussion.

Informed consent and confidentiality

Participants were asked for their written informed consent prior to the interviews and focus groups, after they received detailed information about the research. They were assured that the data from the interviews and focus groups would be dealt with confidentially. Anonymity was secured by code numbering the interviews.

Table 1. Topic list for focus group interviews with smoking patients in primary care.

-
1.	In general, can you tell me something about your smoking behaviour and the rationale behind it?
	• smoking status • advantages/disadvantages of smoking • choice or addiction
2.	In general, can you tell me something about your experience with smoking cessation and the rationale behind it?
	• advantages/disadvantages of smoking
3.	What do you think about smoking cessation treatment in primary care?
	• position/importance of the general practitioner • position/importance of the practice nurse • experiences with nicotine replacement therapy • experiences with medication (varenicline, bupropion, nortriptyline) • experiences with other resources to quit smoking (e.g. acupuncture) • what would you change about smoking cessation treatment in primary care?
4.	What are general barriers in smoking cessation treatment in primary care?
5.	Do you have any solutions to improve smoking cessation treatment in primary care?
-

Data collection

The focus group discussions and semi-structured interviews were performed in the period from November to December 2009. An interview guide was developed which

consisted of open-ended questions (Tables 1 and 2). The focus groups lasted approximately two hours and the individual interviews 30 - 40 minutes, and were recorded digitally and transcribed verbatim. The focus groups were also video recorded to ease the transcription. In addition, field notes were taken.

Table 2. Topic list for interviews with healthcare professionals.

1. When do you treat a patient yourself, and when do you refer him/her?
2. In what way does the discussion on smoking influence the patient–doctor relationship?
3. What do you do, to advance the motivation of a patient to quit?
4. Which therapy (behavioural and medicines) can/will you provide for smoking cessation?
5. Is there communication between the GP and the practice nurse and in what way?
6. Is there follow-up after a treatment to quit smoking? By whom?
7. What are general barriers in smoking cessation treatment in primary care?
8. Do you have any solutions to improve smoking cessation treatment in primary care?

Data analysis

A descriptive and exploratory approach was used in the analysis (12). In order to explore complementary as well as contradictory perspectives, data analysis was completed by applying the constant comparative method (CCM) (13). Comparison happened between two groups: smokers and healthcare professionals, and when opinions within groups varied too much; this was noted.

Transcripts were coded inductively and from a realistic approach (i.e., perspectives derived from the text and were represented as they are). Common elements were merged to form categories and overarching themes for the two separate groups were identified. Themes could be of a substantive nature, such as motivations or experiences, or more methodological, such as the general atmosphere of the interview or the ease or difficulty in talking about certain issues (12). The frequency of categories and themes were counted to filter the most important barriers and solutions. Subsequently, a framework of themes and categories was assembled for both groups to compare the data.

Trustworthiness

To increase the trustworthiness of the research, we used multiple methods of triangulation to overcome biases as a result of single-observer, single-methodology and/or single-source analysis (12). First, multiple authors reflected on the data to identify themes and to form meaning from the data (investigator triangulation). Second, data was obtained from semi-structured interviews or focus group discussions and field notes (methodological triangulation). Third, data from healthcare professionals and

smokers was searched for contrasting and confirming evidence to validate the data (data triangulation). We analysed the categories in the available transcripts and checked whether saturation of categories occurred (data saturation) for both groups. When necessary, additional focus groups or interviews were planned.

Results

Three focus groups were organized with a total of 14 patients (3, 4 and 7 patients, respectively). The eight men and six women were between 45 and 73 years of age, were Dutch and had various educational levels. All smokers had tried to quit smoking before, but only three were abstinent. Ten smokers smoked more than ten cigarettes per day and three of them called themselves heavy smokers. Meanwhile, we interviewed four GPs and five PNs, representing six healthcare centres. All healthcare professionals were women and aged 30–50 years. The years of employment was, on average, seven years and ranged from one to thirteen years. None of them were smokers and only one was an ex-smoker.

The data analysis revealed three important themes; (1) accountability in primary care: unawareness and resistance against smoking cessation, (2) responsibility: whose problem is it anyway, and (3) treatment: from advice to a supported quit attempt.

Accountability in primary care: unawareness and resistance against smoking cessation

Smokers and healthcare professionals both agreed that smoking cessation is a task of primary care. Both groups feel that when a person wants to stop smoking, the GP or PN should be motivated and capable of assisting a quit attempt. However, one important barrier was that not all smokers were aware that they could receive guidance for smoking cessation in their healthcare centre (Quote 1). What they did know, was that the GP can prescribe medication for smoking cessation.

That smoking cessation guidance was possible at our healthcare centre? I had no idea!? But then it is also the question if I want to talk to my doctor about this. (Quote 1, smoker.)

Smokers who were aware of the availability of smoking cessation assistance in primary care believed they would receive support when requested, but were reluctant to ask for such support. They thought it was foolish to make an appointment with the GP and take his/her time only to discuss their smoking behaviour.

Another important barrier was that ‘healthy smokers’ (smokers without smoking-related illnesses) were often not viewed eligible to receive smoking cessation treatments by the healthcare professionals. When healthcare professionals talked about ‘smokers’, they visualized the smokers with smoking-related illnesses (Quote 2). For GPs, other barriers for not discussing smoking cessation with every smoking patient were a lack of time, not having any reason to discuss smoking behaviour and ‘don’t feel like it’.

I only start about smoking cessation when patients have a chronic illness, like diabetes or high blood pressure. When people have a cold, I often do not even think about asking it. Smoking status is not asked routinely to every patient. Therefore, a group of smokers exists you do not know. (Quote 2, healthcare professional.)

Among healthcare professionals, especially among GPs, there was resistance against increasing preventive tasks, for example, smoking cessation (Quote 3). GPs accepted a small role in providing advice and referral to the PN for assistance, but they did not think that motivating every smoker to stop smoking is a task of the GP.

I know we are going towards primary prevention. In addition, I think that is good, but we have to be careful not to treat everything and think that we can control everything. And, if I am honest, I rather put my energy into someone who is very ill, than into a smoker who does not want to quit. (Quote 3, healthcare professional.)

Responsibility: whose problem is it anyway?

Both smokers and healthcare professionals recognized that when a smoker was not motivated, it was useless to provide advice (Quote 4). Such a patient would just listen, laugh politely, leave and continue to smoke.

Sometimes I [practice nurse] get people that are referred by the GP to me like ‘you are going to work with this’, and I notice that these people are often very badly motivated. They just come to visit me purely because they were referred by the GP. (Quote 4, healthcare professional.)

Healthcare professionals thought it was their responsibility to ask a patients’ smoking status and to provide advice. Some healthcare professionals found it frustrating that

smokers do not stop immediately, but they felt the burden was out of their hands after advising. More importantly, they were not afraid to jeopardize their patient–doctor relationship by talking about smoking. For smokers, it was acceptable and understandable that a GP asked about their smoking status, as long as they accepted the patients' choice and did not nag.

Smokers felt it was their responsibility to stop smoking. Some smokers believed that when they would reach a certain health problem they would stop, but when they did reach that point, they trivialized their symptoms and continued to smoke (Quote 5). About half of the smokers already experienced health problems, but they did not express a higher motivation to stop than smokers without health problems did.

They found a spot on the lungs, and the doctor called me to say that the lung pictures were no good. I was very scared. Then I only smoked five cigarettes a day and for me that is little. Eventually, it was nothing, so then I thought, yes ok, I just continue smoking like I used to. (Quote 5, smoker.)

Treatment: From advice to a supported quit attempt

It appeared that many barriers existed before smokers received treatment for their addiction in primary care. Both smokers and healthcare professionals agreed that smoking cessation support is not given properly by the GP (Quote 6). As a solution, the PN was identified as the preferred support provider for smoking cessation by both groups. Counselling by the PN was seen as a more intensive and personal form of assistance. However, smokers believed that the involvement from the GP would increase their motivation to quit. The few patients treated by the PN had positive experiences, but ironically, none of these patients stopped smoking.

Well, she [general practitioner] just tells me; listen, why don't you try stop smoking. I say yes, she tells me goodbye and the consult is over. However, she does not give me any advice or support or tells me; shall I do this or that or shall we do something together for example. No, she only gives me the advice to quit smoking, but that's it. (Quote 6, smoker.)

Some counselling styles can increase motivation and the chance of a successful quit attempt (14-16). All PNs followed a course on motivational interviewing (MI). They believed they applied MI on a certain level, but felt they had not received sufficient training and MI was not effective in every patient. PNs believed training would advance

their counselling skills. GPs were not aware of different counselling styles to approach smokers, but they often used confrontational methods (Quote 7).

I [GP] have said multiple times in a very confrontational way to patients: "listen, now you're still in a reasonable advantageous stage, when you continue to smoke, you will enter this room in one or two years with oxygen and I think you are a little too young for that. Is that what you want?" Then you see patients think "oh help". And these patients did quit. (Quote 7, healthcare professional.)

Treatment in primary care often involves medication provision, but certain barriers existed. Among smokers and healthcare professionals, positive and negative prejudices were present. Some smokers and GPs had an aversion against taking any medication for smoking cessation because they believed motivation and willpower should be enough (Quote 8). Others believed it was almost impossible without medication. PNs also recognized that motivation is most important, but were confident that medication could help. Nonetheless, PNs had difficulties with understanding the mechanism of action of the different medications. The solution would be to have a leaflet to easily explain patients the mechanisms of action, the effects and side effects of all different medications.

I create very low expectations, so that there can't be a lot of disappointment afterwards, because patients ask me "isn't there a pill that makes you stop smoking?" "no, there is not." Therefore, you have to make that clear. (Quote 8, healthcare professional.)

All smokers were familiar with nicotine replacement therapy, and most of them expressed low expectations towards it, because they used this therapy in the past but failed to quit smoking. Even though only few used bupropion or nortriptyline, most smokers had negative prejudices against these medications because they are antidepressants (Quote 9). Only one smoker was familiar with varenicline, which was a relatively new drug at that time. This smoker was more enthusiastic about the efficacy of varenicline than other medications, despite its side effects.

Well, I am not depressed, so why would I take a medicine that works against depressions. (Quote 9, smoker.)

Discussion

Main findings

Many barriers existed for smokers to receive smoking cessation advice and assistance in primary care. Among GPs, there was resistance against preventive tasks and 'healthy smokers' were often not confronted with their smoking behaviour. Smokers and healthcare professionals viewed smoking cessation as the patients' responsibility, but GPs also felt it was their duty to advise smokers to quit. GPs preferred not to use medication for quitting while PNs and smokers favoured medication. Another barrier was that smokers did not seem to be aware of the available support at their healthcare centre. Proposed solutions were that the GP should advise all smokers to quit, whereas someone else should deliver intensive behavioural support, preferably the PN.

Barriers and solutions

Proactive

On the one hand, healthcare professionals were used to waiting for the patient to ask for help. On the other hand, patients did not want to bother the GP with their smoking habit or were not aware of the availability of support in their healthcare centre. A culture change is necessary for primary care, where healthcare professionals become proactive instead of reactive. However, no solutions were given on how to decrease the threshold for smokers seeking for help to quit.

Health promotion and prevention

There was ambivalence among GPs towards health promotion in general. Despite the fact that smoking cessation was considered as an important factor in disease prevention, GPs did not want to patronize their patients, and smoking was a patient's responsibility. An underlying or secondary barrier might be that smoking was not seen as an illness; therefore, GPs did not act until a smoking-related illness was presented. It was believed that prevention is better suited as the task of the PN since nurses have already been proven their effectiveness for smoking cessation (17). However, their accessibility is limited because the Dutch healthcare system forces the GP to be a gatekeeper, and smokers need a referral from their GP to consult the PN. Solutions should be found in improving the patient's awareness of the PN as a partner in smoking cessation and easier access.

Patient-doctor relationship

Although smoking was not often discussed in the consulting room, healthcare professionals were not afraid to harm their relationship with the patients by discussing

smoking cessation. Also for smokers, it was acceptable and understandable that a GP started the discussion on smoking. Indeed, previous literature showed that two-thirds of the European smokers wanted to be supported by their GP when changing their lifestyle (18). Even among unmotivated smokers, almost 20% will make an attempt to stop when advised to stop by their GP (19).

Medication

Pharmacological support was proven to be effective in smoking cessation (20). In general, smokers were positive about taking medication for smoking cessation. However, there was resistance against nicotine replacement therapy and bupropion/nortriptyline. In correspondence with other studies, smokers' knowledge and perceived effectiveness of those pharmacological treatment was low (21-25). Additionally, GPs showed hesitation towards pharmacological treatments. They believed motivation was the key factor in a successful quit attempt and lowered patients' expectations towards medication. PNs were positive and recommended it to most patients, but the PNs had difficulties with the understanding of the different medications.

Strengths and limitations

Interviewing both smokers and healthcare professionals gave a fascinating insight into real-life practice. The data obtained has considerably improved our understanding of barriers to smoking cessation in primary care, although limitations regarding the generalizability need to be mentioned. At first, PNs are not always present or intended as supporting assistance for smoking cessation in all primary care settings in Europe. Second, data collection took place in 2009; however, we believe that perceptions of healthcare professionals about smokers and vice versa and the patient-doctor relationship have not changed during this short period. In addition, there were no major developments in smoking cessation practices, policies or opportunities in Dutch primary care in the last five years. Only the perceptions about varenicline might have changed since more patients are using varenicline nowadays. Nonetheless, personal contact with the local board, healthcare professionals and smokers of the 'The Eindhoven Corporation of Primary Health Care' through an ongoing investigation (Dutch Trial Register NTR3067) give the impression that the findings still reflect present-day practice. Third, congruent with most qualitative research, participants in smoking cessation research tend to be more motivated (to quit), more experienced (in quitting) and better aware of the available treatments. People under the age of 45, the expected group of 'healthy smokers,' were underrepresented. The healthcare professionals we interviewed seemed a representative mix of GPs and PNs, about age and level of experience. Unfortunately, we could not find male healthcare professionals

prepared to participate. Despite the low number of patients and healthcare professionals, data saturation was reached.

Implications for clinical practice, education, policy or research

Primary care can play a key role in reducing the prevalence of smoking. This research showed that a culture change is necessary for primary care for smoking cessation assistance to be successful, in which healthcare professionals become more proactive and better accept their increasing role in health promotion and prevention. GPs can easily discuss smoking cessation with every patient, and when a treatment that is more intensive is needed, the patient should be referred to the PN. The PN should receive more (practical) training in communication skills and training to improve their knowledge of pharmacological treatment. In practices without a PN, the GP can still play an important factor in motivating smokers to stop (26). More research is needed regarding the attitudes of primary healthcare professionals towards preventive tasks and the motivations of healthcare professionals to become more proactive in smoking cessation.

Conclusion

Primary healthcare professionals can and should play a key role in integrating evidence-based methods into their routine clinical practice to help more smokers try and successfully quit, by using a more proactive approach. GPs do not jeopardize the patient–doctor relationship by initiating a discussion on smoking cessation and should, therefore, discuss smoking cessation with more patients. For more extensive smoking cessation assistance, the patient should be referred to the PN. PNs require more training on how to motivate patients and more information about the different medication options for smoking cessation. Subsequently, the awareness of the PN as a partner in smoking cessation and access of smoking cessation services provided by primary care need to be improved.

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Chapter 3

Combining intensive practice nurse counselling or brief general practitioner advice with varenicline for smoking cessation in primary care: study protocol of a pragmatic randomized controlled trial

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Combining intensive practice nurse counselling or brief general practitioner advice with varenicline for smoking cessation in primary care: study protocol of a pragmatic randomized controlled trial

Abstract

Introduction: Combining behavioural support and pharmacotherapy is most effective for smoking cessation and recommended in clinical guidelines. Despite that smoking cessation assistance from the general practitioner can be effective, dissemination of clinical practice guidelines and efforts on upskilling has not lead to the routine provision of smoking cessation advice among general practitioners. Intensive counselling from the practice nurse could contribute to better smoking cessation rates in primary care. However, the effectiveness of intensive counselling from a practice nurse versus usual care from a general practitioner in combination with varenicline is still unknown.

Materials and methods: A pragmatic randomized controlled trial was conducted comparing: (a) intensive individual counselling delivered by a practice nurse and (b) brief advice delivered by a general practitioner; both groups received 12-weeks of open-label varenicline. A minimum of 272 adult daily smoking participants were recruited and treated in their routine primary care setting. The primary outcome was defined as prolonged abstinence from weeks 9 to 26, biochemically validated by exhaled carbon monoxide. Data was analysed blinded according to the intention-to-treat principle and participants with missing data on their smoking status at follow-up were counted as smokers. Secondary outcomes included: one-year prolonged abstinence, short-term incremental cost-effectiveness, medication adherence, and baseline predictors of successful smoking cessation.

Discussion: This trial is the first to provide scientific evidence on the effectiveness, cost-effectiveness, and potential mechanisms of action of intensive practice nurse counselling combined with varenicline under real-life conditions. This paper explains the methodology of the trial and discusses the pragmatic and/or explanatory design aspects.

Introduction

Tobacco use is a prominent determinant of the global burden of disease and responsible for 31% Disability Adjusted Life Years (DALY) lost (1). In the Netherlands, still one out of four people are daily smokers (2). Even though most smokers would like to quit (3), the number of quit attempts and their success rate is low (4). Increase of smoking cessation can be achieved by improving the efficacy and effectiveness of smoking cessation treatments.

Primary care is in a strategic position to play an important role in smoking cessation: it has a wide reach into the population, it is easily accessible for smokers (5), it is a familiar environment and there is access to professional and effective help (6, 7). Smokers who are considered to be difficult to reach, e.g., smokers with a low social-economic status or psychological illnesses; heavy smokers; and smokers from different ethnic backgrounds, may be more easily reached in primary care. In countries where the primary care system is well developed, such as the Netherlands, around 80% of the smokers visit their primary healthcare centre each year (2).

Smoking cessation treatments available in primary care can be categorized into behavioural support and pharmacological aids. Behavioural support can be given within a continuum of care, from less intensive and one-time support (brief advice) to more intensive behavioural support with multiple sessions (counselling). There is a strong dose– response relationship between number of sessions, total contact time, and abstinence showing that intensive counselling increases the chance of a successful quit attempt compared to less intensive support (8). Effective pharmacological aids include nicotine replacement therapy (NRT), antidepressants bupropion and nortriptyline, and the partial nicotine receptor agonists varenicline and cytisine (9-11). Varenicline had better quit rates in clinical trials compared to bupropion and NRT (12-14). Combining behavioural support and pharmacotherapy is most promising and recommended in clinical guidelines (8, 15-17).

The availability and effectiveness of multiple smoking cessation strategies from the general practitioner (GP) (6), dissemination of clinical practice guidelines, and efforts on upskilling, have not led to the routine provision of smoking cessation advice among GPs (18-20). A survey in Australia found that GPs were very pessimistic about giving cessation advice, and only half of the GPs would give such advice in an ideal situation (20). However, practice nurses (PNs), as an alternative

workforce in primary care, have recently been introduced in the Netherlands with the aim to reduce the workload of GPs. They are expected to improve the quality of care by cost-effectively managing chronic illnesses and performing health promotion tasks such as smoking cessation (21). Evidence for the effectiveness of PN smoking cessation counselling is limited, but results are positive and suggest the same effectiveness as the English Smoking Cessation Services (22). Since PNs have more time for counselling than GPs, intensive counselling by the PN can contribute to higher smoking cessation rates in primary care.

Furthermore, a recent meta-analysis showed some evidence that the combination treatment increases smoking cessation success, but most studies used NRT (23). Evidence on the effectiveness of combining counselling and varenicline is still limited and it could be that the effect of counselling is less evident when using varenicline, or that the effectiveness of varenicline is amplified by intensive counselling. Though, recent trials show promising results in favour of the combination of counselling and varenicline (24-26). For example, when varenicline was combined with an intensive 240-minute counselling program, more than half of the patients was prolonged abstinent at 6 months of follow-up, which was significantly better than the combination of placebo with the same intensive counselling program (58.1% versus 26.4%, OR 3.87, 95% CI 2.11–7.11) (24). Nonetheless, more support for the effect of combining varenicline with intensive versus less intensive counselling is needed. Moreover, reasons why the combination of intensive counselling and pharmacotherapy is most successful are still unknown. One of the underlying mechanisms to this effect might be that counselling increases adherence to medication, which finally leads to better quit rates (27). Intensive counselling is also more expensive than brief advice and therefore the cost-effectiveness should be considered. Previous clinical trials were very explanatory using very strict in- and exclusion criteria, which limits the external validity of the outcomes. Also, most evidence on the effectiveness of varenicline resulted from research in clinical settings and not in real world primary care settings.

Therefore, there is a need for evaluating the effectiveness of intensive counselling from a PN versus usual care from a GP to provide healthcare professionals, policymakers, and insurance companies with evidence on the value of counselling from the PN and on the effectiveness of the combination treatment of intensive counselling by a PN with varenicline. When the PN is equally or more effective than the GP, smoking cessation could be shifted from the GP to the PN in order to reduce the workload of the GP and approach the preferences of the patient.

Materials and methods

Objectives

The primary objective was to compare the effectiveness of individual counselling by a PN combined with open-label varenicline versus brief advice by a GP combined with open label varenicline on biochemically validated prolonged abstinence from week 9 to week 26 after treatment initiation in smokers in a Dutch primary care setting.

Secondary objectives were:

- a. to determine the prolonged abstinence rate from weeks 9 to 52;
- b. to investigate the short-term incremental cost-effectiveness from weeks 9 to 52;
- c. to investigate adherence to varenicline and whether adherence mediated the treatment effect of individual counselling by a PN on prolonged abstinence from weeks 9 to 26;
- d. to explore which participant characteristics at baseline are predictors of prolonged abstinence from weeks 9 to 26 (predictors independent of treatment assignment);
- e. to explore which participant subgroups are more likely to respond to intensive counselling by a PN (predictors dependent of treatment assignment).

Design and setting

The study was a pragmatic, parallel group, individually randomized controlled trial evaluating two behavioural support programmes combined with open-label varenicline for smoking cessation: usual care from a GP versus intensive counselling from a PN. For an overview of the study design, see Figure 1.

The trial was conducted in the Eindhoven Corporation of Primary Health Care Centres (SGE) (28), which is a network of 10 primary healthcare centres covering approximately 65,000 patients in the Netherlands. In total 42 GPs and 13 PNs from SGE were actively involved in the recruitment and treatment of the trial participants. The logistics, including baseline and follow-up measurements, were covered by the research team of Maastricht University.

Figure 1: Trial design. SGE = Eindhoven Corporation of Primary Health Care Centres, PN = practice nurse, GP = general practitioner, CO = carbon monoxide.

Study population

The aim was to recruit a study population that was a realistic reflection of smokers in primary care, since research volunteers and active treatment seekers may be unrepresentative for routine care (29, 30). Therefore, smokers who normally consulted their GP were recruited and as few exclusion criteria as possible were used. To recruit smokers who were motivated to quit smoking or at least willing to talk about smoking cessation within primary care, healthcare providers (GPs and PNs) and practice assistants were informed that smokers could be referred to the research team and leaflets entitled “Do you think about quitting?” were dispersed in the waiting rooms of the healthcare centres. The leaflet first discussed the benefits of smoking cessation, and then the trial was explained, describing it as an opportunity for smokers to quit. The costless prescription of pharmacotherapy was mentioned but not emphasized, so that this was not likely to be the main reason for participants to partake. The leaflets were printed on simple blue paper with black ink to save costs. Smokers aged 18 years or older and daily smokers at the time of randomization were included. There was no minimum limit for the number of cigarettes smoked per day. Many guidelines use a limit of 10 cigarettes per day or more for offering pharmacotherapy, mainly because pharmacological trials usually excludes smokers who smoke less (8, 15, 16). However, it has been shown that the percentage “light” smokers (i.e., smoking less than 10 cigarettes per day) has been increasing over the last few years and currently constitutes of 29% of the smokers in the Netherlands (2). Moreover, light smokers frequently use smoking cessation aids (about one in three) (31) and offering pharmacotherapy in this group of smokers is effective (32). Smokers with contra-indications for the use of varenicline were excluded from the trial, as would happen in daily practice. The individual GP decided whether or not varenicline was prescribed to the individual participant.

Intervention: intensive counselling by a practice nurse

We decided to develop a context-specific treatment protocol based on existing, evidence-based methods and a pragmatic approach because: 1) there is no international consensus about which evidence-based strategies or techniques should be used, 2) interventions are often focused on motivating the smokers to quit and not at supporting a quit attempt, 3) the intervention used in Dutch primary care is too long (180 min) (27) and gives no clear guidance what to do each consultation, 4) not all evidence about effective behaviour change strategies and techniques (33-35) has yet been translated into current counselling protocols and 5) practice based experiences of healthcare providers and patients could make a protocol more transferable to real-life conditions.

The intervention was developed through a combination of a top-down and bottom-up approach. A top-down approach means that the intervention is based on a well-formed theory or literature findings (evidence-based approach), whereas a bottom-up approach means that practical experience drives the intervention development (pragmatic approach) (36). A multidisciplinary advisory group was formed, consisting of three patients (smoker, ex-smoker, attempting ex-smoker) and three healthcare professionals from SGE (GP, PN, social psychiatric PN), three scientists and a policy maker from SGE. The goal was to develop a counselling protocol based on best practice and best evidence, which could be implemented as a small scale quality improvement in routine care. Working with the multidisciplinary team created a well-supported counselling protocol and commitment from healthcare professionals to engage in the trial.

Timing of counselling sessions

Participants from the intervention group were entitled to receive a total of 120min of counselling. The protocol consisted of three individual face-to-face sessions and seven telephone sessions with a PN (see Table 1). We believed a 120 min counselling protocol would be feasible to implement in primary care and could be reimbursed by healthcare insurance companies in the Netherlands in the future. Only a smoking cessation intervention that is effective, feasible, and cost-effective is likely to be adopted. The duration of the counselling sessions varied between 5 and 30 min. We distinguished 4 phases in the counselling protocol: preparation phase (week 1), initial quitting phase (week 2), conscious quitting phase (weeks 3–5), and the maintenance phase (weeks 6–52) (see Table 1). The timing and duration of the sessions were based on relapse curves of aided and unaided quit attempts (12, 13, 37) and efficacy of front-loaded therapy (38). While the original protocol included a first consultation with the GP for every participant, also for participants in the PN group, the healthcare providers within the multidisciplinary team decided to drop this regulation for practical reasons. Despite evidence suggests that treatment delivered by two types of clinicians (for example a GP and a PN) might be more effective than treatment delivered by only one type of clinician (39), the healthcare providers from the multidisciplinary team did not want to burden the GP with an extra consultation. Firstly, because this consultation was expected to be used solely for the prescription of varenicline. Secondly, because current practice also did not involve the GP for an extra consultation when the patient was treated by the PN. Therefore, participants in the intensive counselling group did not receive any assistance from their GP for smoking cessation.

Table 1: Content and planning of the counselling protocol

Day/week	Consult	Content of sessions	Time (minutes)
Week 1	FFC 1	- Quickly discuss smoking behaviour, motivation, barriers, reasons for quitting, previous quit attempts - Biomarker feedback (expired air carbon monoxide) - Explanation varenicline: mechanism of action, clinical efficacy, route of administration, safety profile and relation between success and adherence - Preparation and planning target quit day: - patient chooses if he/she want to quit in the morning of target quit day or after second consult - preparation on "ex-smoker-identity": abrupt and complete cessation according to the "not a puff rule" - Explanation treatment program: - treatment program of 13 weeks - first 4 weeks most important, therefore weekly contact	30
Quit day (week 2)	FFC2	- Evaluation use of varenicline - Strengthen motivation and self-efficacy - Reinforce, confirm and repeat ex-smoker-identity: <i>"since today you are an ex-smoker"</i>	15
3 days post quit day (week 2)	TC 1	- First 8 days are the toughest with a peak on the third day. <i>"If you have a difficult moment, wait with smoking until I call you, then we will discuss it first."</i> - Evaluation medication adherence - Discuss withdrawal symptoms and strategies to handle - Strengthen motivation and self-efficacy - Reinforce, confirm and repeat ex-smoker-identity	10
Week 3	TC 2	- Evaluate medication adherence - Strengthen motivation and self-efficacy - Reinforce, confirm and repeat ex-smoker-identity	10
Week 4	TC 3	- Evaluate medication adherence - Strengthen motivation and self-efficacy - Reinforce, confirm and repeat ex-smoker-identity	10
Week 5	FFC 3	- Biomarker feedback: visibility of direct health effect of smoking cessation - Discuss withdrawal symptoms and strategies to handle - Emphasis on self-efficacy and ex-smoker identity	15
Week 7	TC 4	- Discuss/stimulate medication adherence. - Emphasis on self-efficacy and ex-smoker identity	10
Week 11	TC 5	- Evaluate quit attempt - Prepare quitting varenicline - Discuss/remind motivation to quit - Discuss/remind risky moments for relapse. - Emphasis on self-efficacy and ex-smoker identity	10
Week 13	TC 6	Evaluate medication adherence	5
Week 52	TC 7	Evaluate quit attempt	5

FFC = face-to-face consultation. TC = telephone consultation

Effective elements of counselling protocol

Effects of behaviour change interventions vary with the techniques used in the intervention (34, 35). The content of the current intervention was based on six behaviour change techniques, namely: (1) front-loaded therapy (38), (2) the use of expired carbon monoxide (CO) feedback (34, 40), (3) stimulation of an ex-smoker identity (34, 41, 42), (4) stimulating adherence to varenicline (43), (5) use of a fixed target quit day (44, 45), and (6) enhancing motivation and self-efficacy (34). (1) Counselling was front-loaded which means that it started one week prior to the quit attempt and was most intensive in the first five weeks. (2) The use of CO feedback, prior to the quit attempt and 4 weeks after quitting should motivate smokers to continue quitting. With this technique, smokers were directly confronted with their lung intoxication and their risk on various diseases. After quitting, ex-smokers could see that their risk was immediately reduced. (3) Smokers were stimulated by the PN to adopt an ex-smoker identity by repeatedly using this term. This would help to remain abstinent through neurolinguistic programming. (4) Good adherence to varenicline doubles the quit rates, therefore adherence should be an important aspect during counselling (43). The PN emphasized the need for good adherence and discussed factors related to poor adherence, e.g., experiencing side-effects and the conception that varenicline was not necessary anymore (46). (5) The second session was planned on a fixed target quit date. The patient was allowed to choose prior to the appointment whether to quit smoking in the morning or after the second session. (6) The PN tried to strengthen the motivation and self-efficacy during every contact with the patient. They elaborated personal reasons to quit smoking from the patient, asked about and referred to situations where (prolonged) abstinence was difficult but successful, used verbal persuasion, and planned coping responses with the patient. An extensive description of the effective elements can be found in Table 1.

Communication style

Communication style can have a substantial impact on behaviour change (47). Research on the style and quality of counselling or the effect of counselling training on cessation is scarce but increasing (48, 49). PNs participating in this trial were previously trained in the use of Dutch smoking cessation guidelines and Motivational Interviewing (MI). MI is a counselling style whereby the knowledge and experiences from the patient; eliciting and strengthening the intrinsic motivation of the patient; and resolving ambivalence towards change, play an important role. In contrast to more paternalistic and authoritarian counselling styles, the attitude with MI is more collaborative and supportive (50). Also elements from cognitive behavioural therapy, e.g., elaborating cognitions and

emotions with smoking cessation, identifying and removing environmental cues which trigger the urge to smoke were part of the PNs counselling style in routine care (51).

The emphasis of the counselling style was on strengthening motivation, self-efficacy, and enhancing a non-smoker-identity. We assumed that the participating PNs were capable of: 1) adopting a supportive and encouraging attitude; 2) communicating in a caring and patient way; 3) encouraging participants to talk about the quitting process; 4) identifying events, internal states, or activities that increase the risk of relapse; 5) teaching problem-solving skills to cope with high-risk situations for relapse; 6) identifying and challenging irrational beliefs about smoking; 7) considering indications and contraindications of smoking cessation medication (in particular varenicline); 8) creating realistic expectations of medication effects and alleviating fears regarding side effects and dependence potential;

Implementation and adoption of the intervention

The PNs only received a short, personal explanation of the counselling protocol by the researcher of approximately 1 h, at the beginning of the trial. During the trial there was no monitoring to ensure adherence with the counselling protocol and PNs were free to deviate from the protocol when they believed this would benefit the participant. We were aware that this was insufficient to implement and control all elements of the counselling protocol perfectly. However, more instruction would have made the intervention more expensive and less pragmatic, while a real-world effectiveness trial is of substantial public health importance.

Control: brief general practitioner advice

The participants allocated to the control group received usual care from their GP. Smoking cessation interventions less than 3 min in duration have shown to be effective compared to no intervention (odds ratio (OR) 1.30, 95% CI 1.10–1.60) (8). Even among smokers who were not motivated to quit at a given time, 16% still made a quit attempt within six months after brief cessation advice (52). Furthermore, smokers who received assistance in quitting from their GP were more satisfied with their quit attempt than those who did not (53, 54). Although some variations in practice exist, the control intervention minimally consisted of general advice to quit and a prescription for varenicline. Brief advice increases the chance of a successful quit attempt compared to no advice (risk ratio (RR) 1.66, 95% confidence interval (CI) 1.42–1.94) (6). Regularly, there was no quit date

agreed and no follow-up visit arranged, but participants were free to contact their GP in case of questions or side-effects.

Choice for varenicline

The primary goal was to compare the effectiveness of two different forms of behavioural support when combined with pharmacotherapy. To eliminate one important source of confounding, the use of medication had to be standardised. Varenicline is a partial agonist and antagonist of the neuronal $\alpha 4\beta 2$ nicotinic acetylcholine receptor (nAChR), which is believed to have the highest specificity for nicotine (55-58) and was more effective than placebo for smoking cessation (RR 2.27, 95% CI 2.02–2.55) (11). Varenicline is more effective in reducing craving, withdrawal symptoms, and the reinforcing effects of smoking compared to bupropion and NRT, and generated better quit rates (12-14). Varenicline has also shown to be the only pharmacological treatment for smoking cessation with proven long-term efficacy in smokers with Chronic Obstructive Pulmonary Disease (COPD) (59). Furthermore, patients appeared to have less difficulties with taking varenicline, because this drug has been developed specifically for smoking cessation, in contrast to antidepressants as bupropion and nortriptyline (60).

Use of varenicline

Participants from both the intervention and control group received open-label varenicline to test its effectiveness under real life conditions. Varenicline was prescribed during an initial visit with the GP or PN in week 1. The use was initiated while the participant was still smoking and the target quit date was during the second week of treatment (see Table 1). The prescribed dosage was the recommended dosage of 0.5 mg once a day for days 1–3, 0.5 mg twice a day for days 4–7, and then 1 mg twice a day until the end of treatment (week 12). Nevertheless, healthcare professionals were free to deviate from this schedule when they believed this would be more appropriate for their participant. There was an interactive web-based program that is usually offered alongside the prescription of varenicline (www.liferewards.nl). Participants were allowed to visit this website.

Outcomes

Primary outcome

The primary outcome was biochemically validated prolonged abstinence from smoking from week 9 through week 26 after treatment initiation. A “grace period” was used from the target quit date in week 2 until week 9 (i.e., a period immediately after the target quit date in which continued smoking is not counted

as a failure) (61). A non-smoker was defined as a participant with a self-reported prolonged non-smoking status with a maximum of 5 cigarettes smoked after the grace period, biochemically confirmed by exhaled CO in weeks 9 and 26 with a piCO+ Smokerlyzer (Bedfont Scientific Ltd) as defined in the Russell Standard (61). A CO-level of ≤ 10 ppm was used as a biomarker of abstinence (62). Randomized participants who withdrew, were lost to follow-up, or failed to provide CO measurements for validation were classified as smokers.

Abstinence from weeks 9 to 52

The first secondary outcome was prolonged abstinence from smoking from week 9 through week 52 after treatment initiation. Successful one-year prolonged abstinence was defined as a participant with a self-reported prolonged non-smoking status, with a maximum 5 cigarettes smoked after the grace period, biochemically confirmed by exhaled CO in weeks 9, 26, and 52 with a piCO+ Smokerlyzer (Bedfont Scientific Ltd) as defined in the Russell Standard (61).

Short-term incremental cost-effectiveness

Economic evaluation studies aim to determine the costs and effects associated with an intervention in order to compare these results with other interventions or current practice (63) and to inform health policy. Calculating the costs per quitter is the primary method for economic evaluations in smoking cessation research (64). However, due to the pragmatic design of the current study, a full cost-effectiveness analysis from a societal perspective was not possible and therefore a stripped-down procedure from a payer perspective was performed, excluding offset and societal costs (65).

Since one-year follow-up is the preferred time horizon for economic evaluations of smoking cessation interventions, the secondary outcome was used as the measure of effectiveness: biochemically validated prolonged abstinence from week 9 to week 52. Costs were based on direct intervention expenses and calculated from real resource use, accounting for professional time (consultations with healthcare professionals were registered into the electronic medical system (EMS) of SGE), and costs of varenicline (based on actual prescriptions from pharmacy fill records). The costs per quitter were computed for both groups and the short-term incremental cost-effectiveness of the intervention group and the control group in comparison to each other were expressed as costs per extra quitter (65). Evaluating the incremental cost-effectiveness ratio (ICER) enables to determine which of the two treatments offers most “value for money” in terms of enabling the largest number of smokers to quit at the lowest possible costs.

Adherence to varenicline

Medication intake was measured using electronic monitoring devices (Medication Event Monitoring System (MEMS®)). Also data from pharmacy fill records and questionnaire data were gathered. The starting dose for the first two weeks of varenicline was dispensed in the original packaging of the manufacturer (11 × 0.5mg, 14 × 1 mg) by the pharmacy. From week 3, varenicline was dispensed in MEMS® vials by the pharmacy for a maximum of 4 weeks at a time. Participants had to refill their vial at the pharmacy until week 12 of treatment. The cap of these vials contained a microchip that saved the day and time of every opening (≥ 3 s) by the participant during the 10 weeks of medication provision in the MEMS® vials. It should be noted that the MEMS® vials did not prompt the participants to use their medication and participants were not stimulated by the research team to take the varenicline. The MEMS® data were read from an interface when the vial was returned to the pharmacy and transmitted into a computer using Powerview software (AARDEX Ltd.).

If patients do not use varenicline as prescribed, they do not benefit optimally from pharmacological support. Recently, it has been shown that good varenicline intake ($\geq 80\%$ of days taken) was strongly associated with smoking cessation (6-month abstinence rate 52% versus 25%) (43). Five outcome measures were used to assess adherence to varenicline in the current study: (1) daily adherence was the percentage of days on which any dose of medication was taken, (2) taking adherence was the percentage of prescribed doses taken, (3) dosing adherence was the percentage of correctly dosed days, (4) timing adherence was the percentage of inter-dose intervals not exceeding 25% of the prescribed dosing interval (12 h), and (5) persistence was the duration of medication intake in days with a maximum drug holiday of 72 hours.

Baseline predictors of quit success

Understanding the determinants of successful quitting is important to improve smoking cessation interventions. Several factors are known to predict whether a quit attempt is more or less likely to succeed, such as age, educational level, social gradient, nicotine dependence, number of cigarettes per day, age of smoking initiation, number and duration of previous quit attempts, intention to quit, confidence in success in quitting, the presence of depression and/or anxiety, and urge to smoke (66-68). The current trial included these and some unexplored, potentially interesting determinants, such as locus of control, type of smoker, and treatment preferences, which could complement the current knowledge on predictors of quit success.

Table 2: Content of measurements per questionnaire

Concepts	T0	T9	T12	T26	T52
Demographic characteristics	X				
Weight	X	X	X	X	X
Lifestyle (breakfast, coffee, alcohol)	X				
Morbidity	X				
Health	X				X
Smoking					
Heaviness of Smoking Index (HSI) (69, 70)	X				
Past and current smoking behaviour (71)	X				
Type of smoker	X				
Modified Cigarette Evaluation Questionnaire (mCEQ) (72)	X	X	X	X	
Michigan Nicotine Reinforcement Questionnaire (MNRQ) (73)	X	X	X	X	X
Modified Reasons for Smoking Scale (MRSS) (74)	X				
Quit smoking					
Previous quit attempts (71)	X				
Smoking status (61)		X	X	X	X
Health perception					
Health concerns (75)	X				
Risk perception (75)	X				
Self-exempting beliefs (75)	X				
Psychological constructs					
Reasons For Quitting scale (RFQ) (76)	X				
Smoking Specific Locus of Control (SSLC) (77)	X				
Motivation to quit or maintain quitted	X	X	X	X	X
Confidence in successful quitting	X	X	X	X	X
Self-efficacy (71)	X	X	X	X	X
Ex-smoker identity		X	X	X	X
Withdrawal and adverse effects					
Minnesota Nicotine Withdrawal Scale (MNWS) (78-80)	X	X	X	X	X
Urge to smoke (67)	X	X	X	X	X
Adverse effects during use of varenicline			X		
Adverse effects after 6 months starting varenicline				X	
Treatment					
Treatment preferences (GP versus PN)	X				
Use of varenicline		X	X		
Satisfaction with therapy		X			
Working Alliance Inventory Short-form (WAI-S) (81)		X			
Pharmacological treatment used other than varenicline		X			
Expectations regarding important success factors	X				
Expectations regarding varenicline (82, 83)	X				
Mental health					
Hospital Anxiety and Depression Scale (HADS) (84-86)	X	X	X	X	X
Life events (emotional major events in a person's life)				X	
Harm reduction (using less or alternative sources of nicotine)				X	

T0 = questionnaire sent at baseline. T9 = questionnaire sent 9 weeks after starting varenicline. T12 = questionnaire sent 12 weeks after starting varenicline. T26 = questionnaire sent 26 weeks after starting varenicline. T52 = questionnaire sent 26 weeks after starting varenicline.

Treatment response

Treatment response usually varies among individuals, and accounting for that variability in clinical study populations can be useful for translating clinical trial outcomes into recommendations for a more tailored treatment selection in routine care. In order to make responsible use of healthcare resources, identifying individual characteristics that moderate success in smoking cessation can help to match smokers with a strategy that is more likely to help them quit. For example, strategies could be tailored to personality traits (87), socio-demographic differences (88), smoking behaviour (2), or to initial response on treatment (89). Unfortunately, few studies investigate differential response to smoking cessation interventions. One recent study from Rose et al. (2013) successfully adapted pharmacological treatment according to initial response to pre-cessation nicotine patch use, which rescued smokers from an unsuccessful attempt (89). The goal was to understand which participant subgroups are more likely to respond to intensive counselling from a PN.

Questionnaires

Questionnaires were sent at baseline (T0), at 9 weeks (T9), 12 weeks (T12), 26 weeks (T26) and 52 weeks (T52) (see Figure 1). The following information was collected from each respondent: baseline demographic characteristics, self-reported health, past- and current smoking behaviour, nicotine dependence, smoking cessation treatment preferences, cigarette withdrawal symptoms, smoking-related cognitions, mental health, quality of life, life events, and therapeutic alliance. For a complete overview of the content of all questionnaires see Table 2. The questionnaires should be completed within 4 weeks after the targeted date.

Adverse events

Adverse (AEs) and serious adverse events (SAEs) reported spontaneously by the subject during telephone follow-up or observed by the researcher during CO-measurement were recorded. In questionnaire T12, participants were actively asked about the presence of adverse events. All possible adverse events of varenicline were listed with the response options “not at all”, “very minor”, “minor”, “reasonable/ moderate”, “strong”, or “very strong” (see Table 3). Questionnaire T12 (“Did you experienced any other side effects that are not mentioned in the above questions?”) and T26 (“Did you experienced side-effects after stopping varenicline or did any side-effects worsened after stopping varenicline?”) also contained open-ended questions regarding adverse events.

Table 3: Adverse events of varenicline examined in questionnaire T12

headache	nausea	cough
dizziness	vomiting	sore throat
increased fatigue	diarrhoea	post nasal drip
tensed muscles	stomach ache	eye pain
muscle twitching	constipation	tinnitus
stiffness	general discomfort	difficulties falling asleep
muscle spasms	weight gain	abnormal dreams
paralysis	increased appetite	insomnia
chest pain	weight loss	restlessness
high blood pressure	decreased appetite	anxiety
rash	increased thirst	panic reactions
acne	hoarseness	depression
sexual dysfunction	dyspnoea	suicidal thoughts
fever	infection or inflammation of the airways	

Sample size calculation

The calculation of the required sample size was based on the difference in efficacy between the intervention and control group. Because studies comparing usual care from the GP with intensive counselling from the PN in combination with varenicline were unknown at the time of study planning, the estimated quit rates derived from the results of previous varenicline trials (12, 13) and from one of our own smoking cessation trials that combined individual counselling with nortriptyline for smoking cessation (90). The estimated quit rates of the control group were based on the quit rates when using varenicline only, since we expected that the assistance of the GP would consist of solitary the prescription of varenicline and would not add up to the effect of varenicline alone. Prolonged abstinence rates from weeks 9 to 26 were expected to be 35% in the intervention group and 20% in the control group. With $\alpha = 0.05$ (two-sided), at least 136 participants needed to be included in each group to detect a clinically meaningful difference of 15% between the groups with an 80% chance. The total number of participants in the two groups should therefore be 272. We did not add participants to correct for any participants who were lost-to-follow up, because those were regarded as smokers in the primary analysis. At this moment, study recruitment has been closed earlier than expected. In total, 295 participants were eligible for data analysis.

Randomization

Eligible smokers were randomly assigned in a 1:1 ratio to either the intervention group or control group by the use of a computer determined sequence, within an interactive web-response system. After the patient was included in the trial, the

research team contacted the healthcare centre, and the computer disclosed the allocation only one time during the telephone call. The healthcare centre contacted the patient to make an appointment with the healthcare professional of the group in which the patient was allocated. The member of the research team who was mostly involved with the randomization performed no CO-measurements and was not involved in data analysis. Randomization was stratified for healthcare centre, using a 6-block randomization scheme, to ensure a similar distribution of group intervention and control group among healthcare centres. No prognostic factors were used for balancing.

When two persons from the same family or close friends wanted to participate, they were paired and randomized as one cluster to the same group. This provided protection against contamination across study groups. No more than two persons per cluster were included in the trial.

Though the healthcare centre consisted of 10 locations, an individually randomized trial was chosen instead of a cluster randomized trial. A cluster randomized trial introduces a greater complexity in design, logistics, analysis and leads to a greater required sample size to preserve statistical power (91), since the area's in which the locations assumed dependence among individuals from the same location. To prevent and check for contamination, the participants were coded in their Electronic Medical Record (EMR) as a participant in the trial so that participants from the GP group would not be treated by the PN during the 6-month follow-up for smoking cessation. This was checked in the electronic database of SGE at the end of the trial.

Blinding

Blinding of participants and healthcare professionals was impossible due to the nature of the treatments. Outcome assessment was blinded for the researchers whenever possible. Researchers never directly asked about the treatment, disclosure by the participant during telephone and face-to-face contact was avoided as much as possible. Data analysis was fully blinded to group label (i.e., the data analyst was unaware of the meaning of the group labels) and participant identification number (i.e., participants received a new, random identification number during the analyses).

Statistical analysis

All tests were conducted with $\alpha = 0.05$ (two-sided) and confidence intervals were based on a 95% confidence level. All analyses were performed with SPSS (version 21; SPSS Inc, Chicago, Illinois).

Primary analysis

The primary analysis compared prolonged abstinence rates from weeks 9 to 26 among the two groups, with successful abstinence measured by the participants' self-reported prolonged non-smoking status and confirmed by an exhaled CO measurement below 10 ppm in weeks 9 and 26. All randomized participants who received at least one dose of varenicline were included in an intention-to-treat analysis (92). Participants with missing measurements (either due to intermittent missingness, dropout, or refusal to undergo a CO testing) were coded as smokers. To get an overall impression of the effectiveness, the proportion of abstinent participants was calculated for each measurement occasion and presented as a function of time for the two groups.

A multiple logistic regression model with a fixed effect for treatment group and a categorical variable corresponding to the healthcare centres was used to examine whether the chance of prolonged abstinence from weeks 9 to 26 differed significantly between the two groups (primary outcome analysis). The centre factor was included in the model to account for any absolute differences in success rates between centres and because the randomization was stratified by this variable (93, 94). An adjusted primary analyses was performed to correct for several, a priori chosen potential confounders measured at baseline: age, gender, socio-economic status, nicotine dependence, urge to smoke, self-efficacy, duration of longest quit attempt, depression, anxiety, share of smokers in the social environment, and alcohol misuse (66-68).

Short-term incremental cost-effectiveness

Costs per quitter (CPQ) were calculated for the intervention and control group, using the following formula: $CPQ = (C \times N) / Q$, where C were the direct costs of the treatment per smoker, N was the total number of participants randomized in the group, and Q was the total number of participants that achieved prolonged abstinence from week 9 to 52 (65). Then an ICER was calculated using the cost of the intervention per quitter and intervention efficacy in means of additional life years gained, based on the direct method described by Stapleton and West (2012) (65). This method is a conservative, simple, and clear way for estimating ICERs for several age groups. Estimates of life years gained were taken from the longest

epidemiological study (95). After discounting, the additional life years gained were adjusted for lifetime cessation without the intervention and relapse after final follow-up (65).

Adherence to varenicline

The association between treatment group and adherence was investigated, as well as the association between adherence and quit success. Reasons for non-adherence were compared between the intervention and control group and predictors for good adherence were investigated. Analysis of adherence to varenicline was based on returned MEMS® vials, pharmacy fill records and questionnaire data. For participants with missing data, an appropriate strategy for handling missing data was sought (96). As compliance data are typically skewed, medication persistence and adherence were described by means, medians, and interquartile ranges.

Daily adherence, taking adherence, dosing adherence and timing adherence were compared across treatment groups by multiple linear regression analysis. In case the data showed the expected non-normal (skewed) distribution, the data was transformed. The models were adjusted for the following covariates: age, gender, educational level and heaviness of smoking index. An ancillary logistic regression analysis was performed after dichotomizing daily adherence into good adherence as $\geq 80\%$ of days taken. To understand whether high intensity, individual counselling by a PN improves smoking cessation rates through higher medication adherence, a mediation analysis (a series of regression models) was performed (97). Persistence was assessed using a Cox proportional hazard regression model to evaluate the risk of discontinuation across treatment groups, controlling for the same covariates as in the linear regression analysis. A Chi square test was used to compare the reasons for stopping varenicline given by smokers and non-smokers with treatment group as predictor variable.

Predictors of quitting success

The following potential predictors measured at baseline were analysed in a multiple logistic regression model, controlled for treatment group: age (continuous), gender (dichotomous), socio-economic status (categorical), nicotine dependence (continuous), urge to smoke (continuous), self-efficacy (continuous), duration of longest quit attempt (continuous), the presence of anxiety and/or depression (continuous), share of smokers in the social environment (continuous), reinforcing effects of smoking (measured with the Michigan Nicotine Reinforcement Questionnaire (MNRQ)) (2 domains, continuous), and alcohol misuse (categorical). Also, psychological functions of smoking (measured with the

Modified Reasons of Smoking Scale (MRSS)) (4 domains, continuous) and locus of control (2 domains, continuous) were expected to predict quitting success and were included in the model.

Treatment response

Even though multiple factors potentially relate to heterogeneity of treatment response, due to insufficient power for the interaction test, the potential treat of multiple testing, and clinical usefulness, only three dichotomous predictors were explored (98). These predictors were selected based on previous literature and clinical usefulness. Educational level (high vs. low), nicotine dependence (addicted vs. strongly addicted) and preferred treatment (yes vs. no; indicating whether the participant was assigned to the treatment s/he favoured (GP or PN)) were analysed in a logistic regression model with biochemically validated prolonged abstinence from weeks 9 to 26 as the outcome variable. Statistical significance values were presented from the change in the log-likelihood ratio on entering the interactions between the subgroup effects and the treatment effect into the model.

Time frame

Recruitment, inclusion and randomization of participants was planned to start in November 2011 and intended to continue for 18 months until April 2013. The last measurement of the primary outcome was expected in October 2013 and all secondary outcomes were expected to be collected in July 2014. The analysis of data regarding the primary research question was not initiated before the completion of follow-up and data collection in the last participants.

Logistics

An electronic, web-based Research Logistics Management System was used for data entry, review, and monitoring. The system provided a solid base for managing the personal data of the participants, as well as a randomization module for reliable distribution of the participants. The advantages of web-based data collection included the avoidance of an additional transcription step, fewer missing data, and the immediate availability of the data for cleaning and analysing. Electronic questionnaires allowed for easier tailoring of questions based on conditions and/or responses. Participants who were unable or unwilling to use the internet to fill out the questionnaires were provided with corresponding paper and pencil versions.

Ethical approval and trial registration

Ethical approval was obtained from the Medical Ethics Committee of Maastricht Academic Hospital and Maastricht University (NL30057.068.09/METC 09-03-075) and registered in the Dutch Trial Register (NTR3067).

Discussion

High quality evidence of the effectiveness of smoking cessation interventions is needed to inform health policy on smoking cessation in primary care. Primary care is in a strategic position to play an important role in smoking cessation (6, 7), and has developed guidelines which contain successful strategies for smoking cessation (8, 15-17). According to these guidelines, combining behavioural support and pharmacotherapy is most successful. However, direct evidence on the effectiveness of combining counselling and varenicline is insufficient (24-26) and reasons for the combination being most successful are still unknown. Previous clinical trials were very explanatory and a real-life study directly investigating the effectiveness of intensive counselling in combination with varenicline was needed. Our primary objective was to compare the effectiveness of individual counselling by a PN with open-label varenicline versus brief advice by a GP with open-label varenicline in smokers under real-life conditions in a primary care setting in the Netherlands. Secondary objectives included evaluating the cost-effectiveness and adherence to varenicline, and were aimed at better understanding the added value of intensive counselling.

This trial investigates the difference in effectiveness of brief advice (i.e., usual care) from a GP versus intensive counselling from a PN, and therefore not only considers a distinction between two different intensities of behavioural support, but also between two different types of healthcare providers. Research shows not only a strong relationship between intensity of support (the number of contacts and the time spent during the contacts) and success rate (39), but also that behavioural smoking cessation interventions are more effective when delivered by a GP than when delivered by a nonphysician healthcare professional, such as a PN (39). A recent study confirmed that even brief cessation advice from a GP can be powerful (52); no such evidence is available for other healthcare professionals. Conversely, literature suggests that in the Netherlands only less than a quarter of all smokers who consult their GP actually receive brief cessation advice (2). Moreover, smokers prefer assistance from the PN since the GP is very passive in smoking cessation, and a PN has more time for assistance and for offering a more tailored approach (99, 100). We expected that usual care from the GP consisted of

only a single consultation wherein varenicline was prescribed and that there was no guidance at all. Therefore, we supposed that the effect of 120 min of counselling from the PN would outweigh the effect of 10 min of counselling from the GP.

The main strength of this trial was the pragmatic design, improving the generalizability of the results. However, certain concessions to the real-life situation were made to improve the internal validity of the trial. To assess whether elements of the trial could be identified as being more pragmatic or explanatory, we used the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) tool (101). In general, pragmatic trials investigate whether the intervention works under usual conditions, whereas explanatory trials look at the effectiveness under ideal conditions (101). The PRECIS tool provides a visual representation over ten research domains and shows that the current trial is largely pragmatic (see Figure 2). Some decisions made the trial less pragmatic (see Table 4). For example: the primary outcome (domain 7), prolonged smoking cessation, was measured using a telephonic questionnaire and if the participant claimed to be a non-smoker, an appointment for a CO-measurement was made with the research team. It would have been more pragmatic if the registration of self-reported smoking status was handled by the health centres as they would normally do. However, this would have led to bias since PNs are probably more accurate in collecting smoking status than GPs and the time of registering smoking status may differ among participants. Furthermore, the smoking status needed to be biochemically validated and measured in an identical way in both research groups.

The trial had some potential limitations. The primary outcome of smoking cessation trials is preferably measured after 52 weeks of follow-up, but this would have required a much larger sample size. Nonetheless, the prolonged abstinence rate from weeks 9 to 26, as in the current trial, is a good approximation for the abstinence rate from weeks 9 to 52. Furthermore, the use of intention-to-treat (ITT) is conservative, however it needs to be mentioned that due to the pragmatic design, there is a chance of post-randomization exclusion. Potential participants were not physically seen by the research team or healthcare professionals before randomization to check their study eligibility. Therefore, it could happen that due to improper inclusion, patients were excluded post-randomization if they did not meet the eligibility criteria. Another limitation was that only patients and healthcare professionals from SGE were included in the trial. However, the participating health centres were assumed to be representative for other healthcare centres in the Netherlands regarding their size, policy, and patient characteristics. Also, GPs were not specially trained in supporting smoking

cessation and the PNs were not more trained than mandated by health insurers. Therefore, the results of the trial should be generalizable for the Dutch situation (see also domains 1, 3, and 5 in Table 4). Furthermore, no methods to check for treatment fidelity were incorporated in the protocol, which makes it difficult to judge the content of the consultations between participants and GP/PN. However, we believe that both types of healthcare providers were competent in giving smoking cessation assistance as one might expect from the training they had received. Nonetheless, we did an alternative quantitative check on the number of consultations and time spent on counselling in the trial based on the registrations in the electronic medical system (EMS) for each participant.

Figure 2. PRECIS wheel. A visual representation of the ten indicators of the PRECIS tool. Each spoke represents one of the indicators, with the inside of the spoke representing a more explanatory judgement and the outside of the spoke representing a more pragmatic judgement.

Table 4: Explanation of the different domains of the Pragmatic-Explanatory Continuum Indicator Summary for scoring.

Domain 1: Participant eligibility

Participants who smoked, regardless of their motivation to stop smoking or responsiveness to previous treatment, could have participated in the trial. As few as possible exclusion criteria were used. Participants had to be over 18 years and had no known contra-indications for the use of varenicline, which was already routinely applied in primary care. Also participants had to be sufficiently proficient in Dutch, which could lead to selection bias and exclude a group of ethnic minorities in the Netherlands. However, no figures were known about how many of those ethnic minorities are not fluent in Dutch, smoke and seek treatment in primary care. Nonetheless, ethnic minorities are often part of more deprived socioeconomic groups. Previous studies showed that lower educated patients were more likely to be smokers and smoked more cigarettes per day (102), and that deprived socioeconomic groups had the same or higher initiation ratios, were just as likely to use pharmacological aids for quitting, but had lower quitting success compared with patient in higher socioeconomic groups (88, 102).

When patients wanted to participate in the trial, they had to contact a telephone number or send an e-mail to the research team. Then, before randomization, participants were obliged to fill in the baseline questionnaire completely, which took about 30 min. This could have led to the inclusion of participants who were more motivated to participate in research, but in practice, none of the participants stepped out because of the questionnaire.

Domain 2: Intervention condition: flexibility

Though a new protocol was developed for the intensive counselling, the PNs were highly flexible on how to apply the counselling. The protocol was used as best-practice and best-evidence, but there was the possibility to give more or less sessions if needed.

Domain 3: Intervention condition: healthcare providers expertise

Similar to primary care practices elsewhere in the Netherlands, SGE employed PNs who were capable of delivering individual counselling to smokers. All nurses were trained in giving smoking cessation assistance as this is mandated by health insurers to get reimbursement. This training consisted of at least 2 days of training and included information on the behavioural and physiological reasons for smoking, the stages of change, increasing motivation, preparation and assistance on the target quit day, aftercare, possible withdrawal symptoms, pharmacological options and possible self-help materials. Most PNs also did a short Motivational Interviewing course of at least one day. Though information about training of the average Dutch PN is unknown, we believed the PNs from SGE were generalizable with PNs in the rest of the Netherlands.

The PNs were not additionally trained in the context of the trial. The PNs only received a short, personal explanation of the counselling protocol by the researcher of approximately one hour, at the beginning of the trial. During the trial there was no monitoring to check for treatment fidelity and ensure adherence with the counselling protocol and PNs were free to deviate from the content and planning of the protocol when they believed this would benefit the participant. The PNs had been trained according to the Dutch guidelines for smoking cessation and had received training 2–3 years before the start of the trial. Therefore we assumed that the PNs were capable of giving smoking cessation support at a level that can be considered representative for the average PN in the Netherlands.

Domain 4: Control condition: flexibility

GPs were asked to give care as usual and were free to organize the support as they wanted if no PN existed. GPs needed at least one face-to-face contact in order to prescribe varenicline, which was already applied in routine care. By all means, referral to the PN was not allowed.

Domain 5: Control condition: healthcare providers expertise

GPs were not additionally trained in smoking cessation and gave smoking cessation assistance as usual. Although there are some variations in practice, usual care typically consisted of general advice to quit (sometimes with setting a quit date) and a prescription for varenicline.

Domain 6: Follow-up intensity

Contact for follow-up, including a quick telephone call to verify the participants' smoking status, a questionnaire and possibly a carbon monoxide measurement, took place at week 9, week 12, week 26 and week 52. Since the first five weeks seemed most important in prolonged smoking cessation, the participants did not have contact with the research team during this sensitive period. The first contact was after 9 weeks, and during all contacts, the researcher was not allowed to give any advice regarding smoking cessation or enter into a personal relationship with the participant.

Domain 7: Primary trial outcome

The primary outcome was prolonged smoking cessation, which was also a relevant outcome for participants and healthcare providers. Prolonged smoking cessation was measured by combining self-report during a telephone call and a carbon monoxide measurement using a handheld monitor when the participant claimed to be a non-smoker. These measurements were quick, convenient, quantitative, and did not require invasive procedures. However, contact with the research team was necessary to obtain those data for both groups.

Domain 8: Participant compliance with the intervention (medication and treatment)

Participants' adherence to varenicline was monitored using electronic monitoring devices (Medication Event Monitoring System (MEMS®)). Though participants did not receive any feedback on how they took their medication and were told that the information was used to associate the time of intake with adverse events, it is not unlikely that the use of such a system influenced participants' awareness to medication adherence.

Domain 9: Healthcare provider compliance with the intervention

There was no measurement of practitioner adherence to improve treatment outcomes. However, GPs and PNs were accounting for professional time by registering the consultations into the electronic database. GPs registered one single or double consultation per session PNs registered a code which represented the time spent on the consultation (5, 10, 15 and 30 min). Though the use of this code was implemented during the start of the trial, SGE needed this information for own use as well.

Domain 10: Analysis of primary outcome

We used an intention-to-treat analysis. If participants were eligible for participating, filled in the baseline questionnaire and received at least one dose of varenicline, they were accepted for analysis. The analysis included all participants in the group they were allocated, regardless of eligibility, compliance with treatment, or adherence to varenicline. In other words, the analysis attempted to see whether the treatment worked under the usual conditions, with all the noise inherent therein.

In the future, it is likely that an important portion of smoking cessation support will be delivered in primary care by GPs and PNs. Evaluation of the effectiveness and cost-effectiveness of both professions is essential to inform the discussion about how to effectively structure smoking cessation in primary care. Furthermore, empirical evidence to encourage a combination treatment of behavioural therapy and varenicline is needed. Therefore, the results of this trial will make an important contribution to the knowledge on this subject. Additionally, more research is desired in what mediates the mechanisms of change in the intervention. Not only the quantity of counselling seems important in improving quit rates, but also the quality of counselling. Questions about what is good counselling and how this influences quit success should be investigated in the future.

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Chapter 4

Effectiveness of intensive practice nurse counselling versus brief general practitioner advice, both combined with varenicline, for smoking cessation: a randomized pragmatic trial in primary care

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Effectiveness of intensive practice nurse counselling versus brief general practitioner advice, both combined with varenicline, for smoking cessation: a randomized pragmatic trial in primary care

Abstract

Aims: To study the effectiveness of intensive counselling by a practice nurse (PN) versus brief advice by a general practitioner (GP), each combined with pharmacotherapy, for 6 months tobacco abstinence (primary outcome). Secondary outcomes included 12-month abstinence, medication adherence, and incremental costs per life year gained.

Design: A multi-site (n=10), two-group, parallel, pragmatic randomized controlled trial.

Setting: A network of primary healthcare centres in the Netherlands.

Participants: A total of 295 adult daily smokers (mean age=48 years; mean cigarettes/day=19).

Intervention and comparator: Patients were randomized to receive individual counselling by a practice nurse (PN) (n=149) or brief advice by a general practitioner (GP) (146). All patients received 12 weeks of open-label varenicline.

Measurements: The primary outcome was prolonged biochemically validated abstinence from week 9 to 26 after treatment initiation. Secondary outcomes included abstinence from week 9 to 52, good dosing adherence (>80% days taken) and incremental costs per life year gained.

Findings: Abstinence rates in the PN versus GP groups were 32.2% (n=48) vs. 39.0% (n=57; odds ratio (OR)=0.71; 95% confidence interval (CI)=0.44-1.16) from weeks 9-26, and 25.5% (n=38) vs. 28.8% (n=42; OR=0.84, 95%CI=0.50-1.43) from weeks 9-52, respectively. Values of the Bayes factor indicated that the PN and GP were equally effective. Good dosing adherence was significantly lower in the PN (45.5%, n=56/123) than in the GP group (62.0%, n=75/121; OR=0.45, 95%CI=0.26-0.77), and the incremental costs per life year gained were -€416.10.

Conclusions: Among people seeking help to stop smoking from their general practice, one-off brief advice from a general practitioner appears to be as effective as several sessions of behavioural support from a practice nurse when smoking cessation medication is provided.

Introduction

Tobacco smoking remains a world-wide problem. Primary healthcare is in a strategic position to assist in smoking cessation support, especially in countries where a large percentage of smokers visit a general practitioner (GP) annually (1, 2). Guidelines recommend that every smoker visiting a GP is advised to quit and is offered treatment - preferably a combination of behavioural support with a pharmacological aid (3-5). Effective behavioural treatments include brief advice by the GP (6, 7) and the pharmacological aids varenicline (8), bupropion (9), and nicotine replacement therapy (10), of which varenicline seems most effective (11-14).

Practice nurses (PNs) are available as an additional work-force in Dutch primary care. They are trained to educate patients, guide medication use, and assist to improve their lifestyles (15). However, their added value in smoking cessation treatment has not yet been corroborated by scientific evidence (16). We hypothesized that PNs are more effective than GPs in helping smokers quit, since they have more time to support patients during their quit attempt (17). Also, Dutch PNs are trained in giving smoking cessation assistance, so they should have the necessary knowledge and skills to help patients quit. As a combination treatment is advised by clinical guidelines, it is especially valuable to investigate the PNs effectiveness when their support is combined with evidence-based pharmacotherapy. We also hypothesized that more intensive support of patients would lead to better adherence to pharmacotherapy. Medication adherence is related strongly to abstinence from smoking (18), and if patients do not receive sufficient support, they may be more inclined to stop medication.

The primary aim was to compare the effectiveness of individual counselling by a PN versus brief advice by a GP, both combined with open-label varenicline, on prolonged abstinence from weeks 9 to week 26. Secondary aims were to compare: (1) point prevalence abstinence rates at week 9; (2) prolonged abstinence rates from weeks 9 to 52; (3) adherence to varenicline; and (4) short-term cost-effectiveness at week 52.

Methods

Design

This study was a multi-site two-group parallel randomized controlled trial evaluating intensive counselling from a PN versus usual care from a GP, both combined with open-label varenicline for smoking cessation. A detailed description of the protocol has been published previously (19). Ethical approval had been obtained (NL30057.068.09/

METC 09-03-075), and the study had been registered in the Dutch Trial Register (NTR3067). Recruitment, inclusion, and randomization started in October 2011 until December 2012 (this was reported incorrectly as 2013 in the published article). Treatment and data collection continued until July 2014. During most of the inclusion period, there was no reimbursement for varenicline, while this was free for patients taking part in the trial.

Recruitment

The trial was conducted in a multi-site (n=10) primary healthcare centre in the Netherlands, covering approximately 65,000 patients (www.sge.nl). This large network was used to generate results with high external validity. Patients were recruited practice assistants, GPs, and PNs and via a brief and easily written leaflet displayed in the waiting room. Daily smokers who were 18 years or older, fluent in Dutch, and who had no contra-indications for the use of varenicline were included. 'Light' smokers (i.e. smoking fewer than 10 cigarettes per day) were also included; a growing sub-group of smokers in which pharmacotherapy can be effective (2, 20). The GP decided whether or not a patient was eligible for inclusion into the trial and thus if varenicline was prescribed to the individual patient.

Randomization

Eligible smokers were randomly assigned in a 1:1 ratio, stratified by healthcare centre, using a six-block scheme, by means of a computer-generated random number sequence. The computer disclosed the allocation once during a phone call by a member of the research team with the assistants of the healthcare centre, who then contacted the patient to schedule an appointment with the GP or PN. Family members or close friends were paired and randomized in one cluster to protect against contamination across study groups. Blinding of patients and healthcare professionals was impossible. The member of the research team who was involved in the randomization procedure was not involved in the primary outcome measurement or data analysis. Data analysts were blinded to group label and identification number.

Sample size

Abstinence rates from weeks 9 to 26 were expected to be 35% in the PN group and 20% in the GP group (19). The estimated quit rates derived from the results of previous varenicline trials when using varenicline only (11, 12), and from one of our own smoking cessation trials that combined individual counselling with nortriptyline (21). At least 136 patients needed to be included in each group to detect a 15% difference in abstinence with 80% power.

Treatments

PN group

Patients treated by the PN were offered three face-to-face and seven telephone sessions (maximum 120 minutes contact time), starting one week prior to the quit attempt until one year after the quit attempt, with most contacts scheduled during the first 13 weeks of the quit attempt. There were no consultations with the GP for smoking cessation. PNs had received training in delivering counselling for their routine clinical work according to Dutch guidelines prior to the start of the trial. The counselling protocol was developed through an intensive innovation process involving GPs, PNs, and patients (19). Counselling included the following evidence-based behaviour change techniques: planning a target quit date; advice on abrupt quitting and the 'not a puff rule'; strengthening motivation and self-efficacy; and enhancing a non-smoker-identity (22). The pragmatic nature of this trial allowed PNs to deviate from the content and planning of the protocol when they believed this would benefit their patient.

GP group

Patients treated by the GP received a minimum of one visit in which the patient received a prescription for varenicline. Dutch guidelines recommend stimulating the patient's motivation during this consultation and to have at least four follow-up visits during several months (3). However, in daily routine practice, usually only minimal advice is given, no quit date is agreed, and no follow-up visits are scheduled. Patients were free to contact their GP in case of questions or side-effects.

Varenicline (both groups)

All patients received a prescription of 12 weeks' open-label varenicline during an initial visit with the PN or GP. The usual dosage was recommended, but healthcare professionals were allowed to change the dosage when they believed this would be more appropriate for their patient (19). The starting dose of varenicline was dispensed in the original packaging, and subsequent medication was offered in Medication Event Monitoring System (MEMS®) vials from week 3 until the end of treatment.

Measurements

Primary

The primary outcome measure was prolonged abstinence from weeks 9 to 26 after treatment initiation. Prolonged abstinence was defined as self-reported prolonged abstinence with a maximum of five cigarettes after a grace period of 9 weeks, biochemically confirmed by exhaled carbon monoxide (CO<10 parts per million), as defined in the Russell Standard (23). The smoking status was measured and

biochemically validated at weeks 9, 26, and 52 after treatment initiation. Randomized patients who withdrew, were lost to follow-up, or failed to provide a CO validation, were classified as smokers. We also measured the point prevalence rate at week 9 and the prolonged abstinence rate from week 9 to 52 after treatment initiation.

Secondary

Information from the Electronic Medical System was used to analyse how many consultations and how much contact time were spent on smoking cessation during a 6-month period after treatment initiation. Information was based on independent codings, which indicated how many minutes the consultation lasted, and on consultations which were registered as encounters for "tobacco abuse". A 6-month observation period was chosen because data would have been too contaminated with subsequent quit attempts during longer periods of observation.

Medication adherence was measured with the use of MEMS® vials. Daily adherence (the number of days on which any dose of medication was taken, with a maximum drug holiday of 7 days) and persistence (the duration of medication intake in days with a maximum drug holiday of 72 hours) was calculated for each patient. Daily adherence was then dichotomized into good (>80% of the prescribed days) or poor adherence. If patients stopped pharmacological treatment within 2 weeks and did not use a MEMS® vial, their medication adherence was zero days for the remaining 10 weeks and was therefore identified as collected.

Background characteristics

Questionnaires were sent at baseline and at weeks 9, 12, 26, and 52 (see Figure 1). Information from each respondent was collected on: baseline demographic characteristics, self-reported health, past and current smoking behaviour, nicotine dependence, treatment preferences (i.e. PN treatment or GP treatment for smoking cessation), cigarette withdrawal symptoms, smoking-related cognitions, mental health, quality of life, life events, satisfaction with the treatment, and possible side effects of varenicline (week 12 follow-up). Also, adverse events reported spontaneously by the patients during telephone or personal follow-up contacts were reported. Members of the research team were not involved in the treatment of patients and in case of side effects, patients were advised to contact their GP or PN.

Statistical analyses

Statistical analyses were conducted using SPSS and R, with $\alpha=0.05$ (two-sided) and by calculating 95% confidence intervals (CI). All randomized patients were included in an intention-to-treat analysis (24). A multiple logistic regression model with a categorical

variable for healthcare centre and a dummy variable for the treatment group was used to examine whether the odds of prolonged abstinence from weeks 9 to 26 differed significantly between the two groups. To examine the results for treatment effect heterogeneity, a random effect corresponding to the treatment group dummy variable was added to the model. The corresponding variance component was tested with a likelihood ratio test.

Figure 1. Flowchart

We repeated this analysis adjusted for several covariates, a priori chosen, measured at baseline: age, gender, education, income, nicotine dependence, urge to smoke, self-efficacy, duration of longest quit attempt, depression, anxiety, share of smokers in the social environment, and alcohol misuse (we refer to this as the "adjusted" OR) (25-27). The same analyses were performed to examine the difference in abstinence at week 9 and week 9 to 52.

In a post-hoc analysis, we calculated Bayes factor to determine the strength of support for the alternative hypothesis (patients treated by a PN are more likely to quit smoking) relative to the null hypothesis (no difference) (28, 29). This is especially useful when faced with non-significant results, as Bayes factor can then be used to determine whether there is simply lack of evidence for the alternative hypothesis or whether the evidence actually supports the null hypothesis. A Bayes factor higher than 1 indicates support for the alternative hypothesis, while a Bayes factor lower than 1 indicates support for the null hypothesis. Values of Bayes factor higher than 3 or lower than 1/3 are regarded as substantial evidence for the alternative or the null hypothesis, respectively.

Daily medication adherence and medication persistence were compared across treatment groups. Median and interquartile ranges were computed because the data showed an expected non-normal (skewed) distribution. Good adherence was analysed using a logistic regression model and was adjusted for the same covariates as the primary analysis. Missing values may not have been missing at random or completely at random, because patients who were more successful in quitting and/or had more contact with the PN were probably more likely to hand in their MEMS® vial. Therefore, besides a complete case analysis, we also conducted best/worst-case sensitivity analyses for daily adherence, where all missing values in the PN group were replaced by good adherence and all missing values in the GP group were replaced by poor adherence (best case) and vice-versa (worst case) (30).

Due to the pragmatic design, a full cost-effectiveness analysis from a societal perspective was not possible. Instead, we calculated the incremental costs per life year gained. The costs refer to PN and GP consultations during 6 months after treatment initiation derived from the Electronic Medical System and based on independent codings combined with reference prices for Dutch economic healthcare evaluations (€17 per PN consultation, €33 per GP consultation) (31). Cost for varenicline was based on adherence data and the consumer price in 2012 (i.e., €50 per 2 weeks). The life years gained were estimated based on a method by Stapleton et al (32). We assumed the 3.5% discounted number of life years gained that could be attributed to our smoking

cessation intervention to be 1.9956 per patient (for the age group 45-54, i.e. the mean age of our sample). The incremental cost-effectiveness ratio (ICER) was calculated as (costs PN group – costs GP group) / (life years gained PN group – life years gained GP group).

Table 1. Baseline characteristics of participants in the practice nurse (PN) and general practitioner (GP) group

	PN group (n=149)	GP group (n=146)
Age in years	47.3±13.4	48.7 ±12.9
Men	79 (53.0)	60 (41.1)
Education (scale 1-7 = highest)	3.4±1.6	3.6±1.5
Income (scale 1-6 = highest)	3.1±1.3	3.1±1.3
Socio-economic status		
low	36 (24.4)	30 (20.5)
medium	95 (63.8)	95 (65.1)
high	18 (12.1)	21 (14.4)
Cigarettes per day	19.3±8.2	18.7±8.0
Nicotine dependence (scale 0-6 = highest level) ¹	3.2±1.3	3.0±1.4
Urge to smoke: how many times (scale 0-5)	2.7±1.1	2.6±1.2
Urge to smoke: strength of urges (scale 0-5)	2.8±0.9	2.7±0.9
Self-efficacy (scale 1-5 = highest level)	2.4±0.8	2.5±0.9
Longest duration of previous quit attempt in years	0.7±1.8	1.0±3.3
Depression (scale 0-21 = highest level) ²	4.3±3.7	4.0±3.5
Anxiety (scale 0-21 = highest level) ²	6.8±3.8	6.5±3.5
Share of smokers in social environment (scale 0-5 = highest) ³	2.3±1.1	2.2±1.0
Alcohol use (scale 0-7 = highest frequency)	3.1±1.9	2.9±2.2
Self-reported current or previous cardiovascular disease	28 (18.8)	20 (13.7)
Self-reported current or previous severe psychiatric condition	3 (2.0)	3 (2.1)

Data are presented as mean±SD or n (%). ¹Socioeconomic status was based on education and income. ²Measured with the Heaviness of Smoking Index.(33) ³Measure with the Strength of Urges to Smoke Scale (34). ⁴Measured with the Hospital Anxiety and Depression Scale (35). ⁵Composite of questions about smokers in social environment: smoking partner (counted double), smoking family members, smoking friends, and smoking co-workers.

Results

From 311 smokers who were randomized initially, 16 were found to be ineligible after randomization and were therefore excluded, resulting in a sample size of 295 (range 9-52 smokers per study site; Figure 1). Mean age was 48 (standard deviation (SD)=13.2) years, 22.4% (n=66) had a low socioeconomic status, mean cigarettes per day was 19 (SD=8.1), and 18.0% (n=53) were light smokers (<10 cigarettes per day). The PN (n=149) and GP (n=146) group were comparable at baseline, although there seemed to be slightly more men and more patients with cardiovascular disease in the former group (Table 1). Individual confirmation of the patients' smoking status during follow-up was complete in 91% (n=269) of patients at week 26 and 85% (n=251) at week 52. There were no differences in attrition rates between both treatment groups at any time point.

Table 2. Biochemically validated abstinence rates in the practice nurse (PN) and general practitioner (GP) group with associated odds ratios

Weeks	Overall (n=295)	PN group (n=149)	GP group (n=146)	OR (95%CI), Bayes factor	Adjusted OR (95%CI), Bayes factor
9	180 (61.0)	86 (57.7)	94 (64.4)	0.73 (0.45-1.19) 0.13	0.80 (0.47-1.36) 0.16
9-26	105 (35.6)	48 (32.2)	57 (39.0)	0.71 (0.44-1.16) 0.14	0.76 (0.45-1.30) 0.18
9-52	80 (27.1)	38 (25.5)	42 (28.8)	0.84 (0.50-1.43) 0.24	0.98 (0.56-1.72) 0.37

Data are presented as n (%) or odds ratio (OR) with 95% confidence interval (CI). The OR was adjusted for healthcare centre. The adjusted OR was in addition adjusted for age, gender, education, income, nicotine dependence, urge to smoke, self-efficacy, longest duration of previous quit attempt, depression, anxiety, share of smokers in the social environment, and alcohol use. For the computation of the Bayes factors, the effect sizes used to specify the standard deviation for the half-normal distributions representing the alternative hypotheses (see (29) for details) were based on the following hypotheses: abstinence rates in GP and PN group are ^a52.0% and 29.7% (OR = 2.56) in week 9, ^b35.0% and 20.0% (OR = 2.15) in weeks 9-26, ^c26.5% and 15.2% (OR = 2.00) in weeks 9-52, respectively, based on 136 participants in each group according to the sample size calculation (19). The estimated quit rates for weeks 9-26 derived from the results of previous varenicline trials when using varenicline only (11, 12) and from one of our own smoking cessation trials combining individual counselling with nortriptyline (21). The estimations for week 9 and weeks 9-52 were extrapolated from that, based on the average percentage point decrease per time point.

Abstinence

Prolonged abstinence rates in the PN and GP group were 32.2% (n=48) and 39.0% (n=57) from weeks 9 to 26 and 25.5% (n=38) and 28.8% (n=42) from weeks 9 to 52, respectively (Table 2, Figure 2). The OR of abstinence from smoking from weeks 9 to week 26 in the PN group compared with the GP group was 0.71 (95%CI=0.44-1.16), and the adjusted OR was 0.76 (95%CI=0.45-1.30). There was no indication of treatment effect heterogeneity in the unadjusted ($\chi^2=0.15$, df=1, p=0.69) and adjusted ($\chi^2=0.00$, df=1, p=1.00) models. The OR and adjusted OR of abstinence from weeks 9 to 52 were 0.84 (95%CI=0.50-1.43) and 0.98 (95%CI=0.56-1.72), respectively. Again, no statistically significant evidence of treatment effect heterogeneity was found ($\chi^2=1.44$, df=1, p=0.23 and $\chi^2=1.74$, df=1, p=0.19 in the unadjusted and adjust model, respectively). Values of the Bayes factor were under or close to 1/3 which supports the null hypothesis, indicating that the PN and GP were equally effective. We noticed considerable variation in the 6-month abstinence rates across healthcare centres, ranging from 0 to 63.2%, although the number of included patients was rather small in some centres and the corresponding abstinence rates were therefore not reliable (Table 3).

We repeated our primary analysis with a cut-off point of 8ppm for exhaled carbon monoxide to biochemically validate abstinence (36) which showed exactly the same result.

Figure 2. Carbon monoxide validated prolonged abstinence rates from smoking rates up to 52 weeks after treatment initiation in the practice nurse (PN) and general practitioner (GP) group.

Counselling

The received dose of counselling and the association with abstinence is shown in Table 4. The median number of consultations with the PN was 7 (interquartile range (IQR) = 4-9), and the median time spent was 110 minutes (IQR=75-135). In the GP group, the median number of consultations was 1 (IQR=1-2), and the median time spent was 10 minutes (IQR=10-10). In 41 patients (two from PN, 39 from the GP group), no consultation data were registered. Also 13 patients in the GP group received counselling from the PN, and 13 patients in the PN group had contact with the GP in the context of smoking cessation. A sensitivity analysis in which 59 patients with missing data or who were treated by the wrong healthcare provider were excluded, did not change the primary outcome.

Table 3. Differences in quit rates and self-reported ratings of satisfaction with treatment between healthcare centres

HCC	1	2	3	4	5	6	7	8	9	10	Total
Patients in PN group (n)	13	6	19	9	11	24	20	14	6	16	138
Abstinence PN group ³ (n, %)	3 (23.1)	0 (0.0)	12 (63.2)	5 (55.6)	5 (54.5)	7 (29.2)	8 (40.0)	2 (14.3)	2 (33.3)	3 (18.8)	48 (34.8)
Satisfaction in PN group (mean±sd)	7.2 ±2.44	6.5 ±2.73	8.5 ±2.17	9.0 ±1.12	9.3 ±0.91	8.3 ±1.44	7.0 ±2.09	8.5 ±2.21	4.0 ±3.10	8.4 ±1.31	7.9 ±2.19
Patients in GP group (n)	11	7	15	8	9	27	25	16	3	15	136
Abstinence GP group ³ (n, %)	5 (45.5)	2 (28.6)	5 (33.3)	2 (25.0)	4 (44.4)	12 (44.4)	9 (36.0)	10 (62.5)	1 (33.3)	7 (46.7)	57 (41.9)
Satisfaction in GP group (mean±sd)	6.4 ±3.35	5.6 ±3.51	8.4 ±1.60	7.1 ±2.03	6.2 ±3.31	6.2 ±3.10	5.8 ±2.89	6.6 ±2.16	5.0 ±4.00	5.9 ±3.43	6.4 ±2.91

¹HCC = healthcare centre (anonymised). ²Satisfaction with treatment was asked in a questionnaire in week 9 and ranged from 1 (lowest level of satisfaction with treatment from the healthcare provider for smoking cessation) to 10 (highest). ³Biochemically validated prolonged abstinence from week 9-26 are reported. PN = practice nurse, GP = general practitioner. The total number of patients per group deviates from the randomized patients per group, since only the patients who filled in the questionnaire at week 9 were taken into account.

Treatment preference and satisfaction

Before study enrolment, 67.5% (n=199) of the 295 patients had a preference for intensive counselling with the PN instead of brief advice from the GP. Additionally, varenicline was expected the most important form of therapy (67.5%, n=172), compared to intensive counselling by a PN (22.7%, n=58) and brief advice by a GP (9.8%, n=25). Later, at week 9 after treatment initiation, patients were more satisfied with the counselling from the PN (mean=7.91, SD=2.19) than with the brief advice from the GP (mean=6.38, SD=2.91; $p<0.001$). As with the quit rates, there were relevant differences between the healthcare centres in satisfaction with the received treatment (Table 3).

Table 4. Counselling intensity and associated abstinence rates in the practice nurse (PN) and general practitioner (GP) group

			Patients	Non-smokers
PN group (n=149)	N sessions with PN	1-4	39 (26.6)	4 (10.3)
		5-8	73 (49.0)	26 (35.6)
		>8	37 (24.8)	18 (48.6)
	N minutes with PN	15-60	30 (20.1)	4 (13.3)
		61-120	67 (45.0)	18 (26.9)
		>120	52 (34.9)	26 (50.0)
GP group (n=146)	N sessions with GP	1	117 (80.1)	47 (40.2)
		2	20 (13.7)	7 (35.0)
		>2	9 (6.2)	3 (33.3)
	N minutes with GP	0-10	114 (78.1)	45 (39.5)
		11-20	16 (11.0)	7 (43.8)
		>20	16 (11.0)	5 (31.3)

Data are presented as n(%). The presented abstinence rates show prolonged self-reported validated abstinence rates from weeks 9-26. The number and time of consultations were extracted from the Electronic Medical Record. In 39 patients from the GP group and in two patients from the PN group, there were no consultations registered. These data was imputed with 30 minutes and one consultation in the PN, and 10 minutes and one consultation in the GP, since these first consultations were mandatory to receive the medication prescription.

Daily medication adherence and medication persistence

All patients collected a starting dose of varenicline. In total, we collected medication adherence data in 244 patients (82.7%), 123 and 121 patients in the PN group and GP group, respectively. In the PN group 45.5% (n=56) had good adherence compared to 62.0% (n=75) in the GP group (OR=0.45, 95%CI=0.26-0.77; adjusted OR=0.37, 95%CI=0.20-0.67). The best/worst case sensitivity analyses yielded ORs of 1.12 (95%CI=0.70-1.81) and 0.24 (95%CI=0.14-0.39), respectively, neither of which indicated significantly higher chances for good adherence in the PN group (the adjusted ORs led to the same conclusion) (Table 5). Median daily adherence (numeric variable) was 43 days (IQR=14-73) for the PN group and 69 days (IQR=17.5-71) for the GP group. Median persistence (time variable) was 38 days (IQR=10-73) for the PN group and 68 days (IQR=17-71) for the GP group. In both groups a substantial number of patients took medication longer than the prescribed period, probably by taking only one pill instead of two pills per day: 41 patients in the PN group and 40 patients in the GP group.

Reported side effects

In total, five adverse events, all relating to psychological disorders, were reported. One patient deceased of cardiovascular disease during the trial period. However, this patient belonged to the group which was excluded after randomization because the GP did not give permission to participate (the patient did not receive any varenicline). An overview of reported side effects in the 12-week questionnaire can be found in Supporting information, Table S1.

Table 5. Complete case and sensitivity analyses for adherence

	Patients analysed	Good adherence PN group	Good adherence GP group	OR (95%CI)	Adjusted OR (95%CI)
Complete case analysis	244 (82.7)	56 (45.5)	75 (62.0)	0.45 (0.26-77)	0.37 (0.20-0.67)
Sensitivity analysis 1 (best case)	295 (100.0)	82 (55.0)	75 (51.4)	0.12 (0.70-1.81)	1.10 (0.67-1.81)
Sensitivity analysis 2 (worst case)	295 (100.0)	56 (37.6)	100 (68.5)	0.24 (0.14-0.39)	0.20 (0.11-0.35)

Data are presented as n (%) or odds ratio (OR) with 95% confidence interval (CI). The OR was adjusted for healthcare centre. The adjusted OR was in addition adjusted for age, gender, education, income, nicotine dependence, urge to smoke, self-efficacy, longest duration of previous quit attempt, depression, anxiety, share of smokers in the social environment, and alcohol use. Sensitivity analyses 1 replaced all missings for the GP groups with 'poor adherence' and all missings for the PN group with 'good adherence'. Sensitivity analyses 2 replaced all missings for the GP groups with 'good adherence' and all missings for the PN group with 'poor adherence'.

Incremental costs per life year gained

Only patients for whom medication adherence data were available were taken into account. Data were available for 123 patients in the PN group and 121 patients in the GP group. This resulted in relatively higher quit percentages for the cost analysis at weeks 9-52: 26.0% (n=32) and 33.1% (n=40) for the PN group and the GP group, respectively. The ICER was -€416.10, meaning that the PN group produced fewer life years gained at higher costs compared with the GP group (Table 6).

Table 6. Incremental costs (€) and life years (LY) gained in the practice nurse (PN) and general practitioner (GP) group

	Total (n)	Costs varenicline (€)	Costs PN consultation (€)	Costs GP consultation (€)	Total costs	Abstinence weeks 9-52 (n, %)	Mean LY gained/ quitter	Total LY gained	ICER ¹
PN	123	25,600	13,515	264	39,379	32 (26.0)	1.9956	616.65	-416.10
GP	121	27,450	204	5,082	32,273	40 (33.1)	1.9956	410.10	

The total number of patients differs from the randomized patients since only patients for whom adherence data was available were taken into account. The costs per life year gained were estimated based on a method by Stapleton et al (32). ¹ICER = incremental cost effectiveness ratio = (total costs PN group – total costs GP group) / (total life years gained PN group – total life years gained GP group).

Discussion

Intensive smoking cessation counselling by the PN did not increase abstinence rates compared with brief advice from the GP in patients who were treated with open-label varenicline. Overall rates of prolonged abstinence were high at 26 weeks (35.6%) and 52 weeks (27.1%) follow-up. In the GP group, adherence to varenicline was significantly better and the intervention resulted in more life years gained at lower costs. Despite the lack of added effectiveness, 70% of the patients had a preference for the PN prior to randomization, and patients treated by the PN were more satisfied with their treatment.

This study revealed high percentages of prolonged abstinence during follow-up in both treatment groups at 26 weeks (32.2%, 39.0%) and at 52 weeks (25.5%, 28.8%) for the PN and GP, respectively. It is also one of the first studies showing quit rates for varenicline with only very limited behavioural support (as in the GP group) in the same range as varenicline studies with much more behavioural support (11, 12, 37, 38). For example, the study by Swan et al. also used varenicline in real life, and showed similar cessation rates when combined with various intensities of assistance (30.7%-33.8% at 26 weeks) (37). In our power calculations, we underestimated the effectiveness of the GP in smoking cessation. A success rate of 35% in the PN group and 20% in the GP group was hypothesized, based on previously published trials (11, 12). We expected a lower quit rate for the GP because of our pragmatic design.

Though PNs were more intensively trained in giving smoking cessation assistance than the GPs in our study and had much more contact time the patients, their behavioural counselling did not seem to improve smoking cessation rates. In a randomized controlled trial with a similar design, but from a very different setting (US criminal justice system), behavioural counselling was also not more effective than brief physician advice when combined with pharmacotherapy (39). Contrary to our hypothesis, medication adherence in the GP group was significantly better than in the PN group, which might partly explain the higher quit rate (18, 40). A possible explanation for the lower adherence in the PN group, as reported before (39), might be that pharmacotherapy is seen as less important when provided with intensive behavioural counselling than when provided with only very limited behavioural support. It might also be that PNs advised patients earlier to stop the use of varenicline in case of side effects than the GP.

We found striking differences in effectiveness between healthcare centres. Variance between PNs and GPs can occur naturally, despite that the healthcare professionals in

our study had received the same training regarding smoking cessation. Also, the different social and cultural background of neighbourhoods in which the healthcare centres were located could have influenced the results. Patients with a low socio-economic background tend to have more difficulties with succeeding in quitting (41, 42). Selecting a large healthcare centre with 10 different locations increased the diversity but also the generalizability of the results.

Although the GP costs per life-year gained were much lower than the PN costs, this result should be treated with some caution. First, the cost-effectiveness analyses used a straightforward and slightly insensitive measure. Second, the costs could not be calculated for the total group of patients as medication adherence data were incomplete. This resulted in a lower relative increase in the smoking cessation rate for the PN than for the GP group (2.0% versus 14.9%), which could have influenced the outcome of cost-effectiveness in favour of the GP. Although it seems likely that treatment by the PN is more expensive, both treatments can be regarded extremely cost-effective (43). Also, since involving GPs in smoking cessation is difficult, PNs could still play a crucial role in access and reach of smoking cessation in primary care.

Strengths and limitations

The main strength of the current study is its pragmatic design, which was used specifically to increase the generalizability of our findings. Patients with real-life co-morbidities and lifestyle factors may respond differently to a combination treatment of varenicline with GP advice or PN counselling than selected patients in pre-clinical research settings (44). A more elaborated overview of the elements that made this study pragmatic can be found elsewhere (19). Though smoking is a bigger problem in patients with a low socioeconomic status, smokers with higher socioeconomic status are usually more likely to participate in research (42). In our study, however, patients with low socio-economic status were well represented which indicates good generalizability of the results. Furthermore, this is the first study assessing and comparing adherence to varenicline in patients treated by GPs and PNs electronically with MEMS®. Also, we succeeded in including a large percentage of potentially eligible patients (76.8% of 384 smokers who contacted the research team).

Nonetheless, some limitations need to be mentioned. The sample size of our trial was large enough to detect the hypothesized difference of 15% in 6-month abstinence rates between the groups, but our statistical power was too low to detect a difference of 10% or lower, which may also be regarded as clinically relevant. Blinding to treatment group was not possible and some contamination occurred in both groups. The latter could have been prevented by a cluster randomised trial design. However, our practice

network did not offer enough clusters and our sensitivity analysis, excluding patients who crossed over, did not change our primary outcome. We were also not able to monitor the quality of the behavioural support or the treatment fidelity in both groups. This makes it difficult to determine why the intensive consultations by the PN did not lead to more quitters and why there were large differences in effectiveness between healthcare centres. Nevertheless, we assume that the PNs in the study are representative for PNs in the Netherlands as a whole. Furthermore, a small number of patients who did not collect varenicline from the pharmacy was excluded. Therefore, results may not be generalizable to every single patient who would enroll in such a cessation program, but only to those motivated enough to collect medication. As the number of excluded patients was similar in both groups, however, we do not expect this to have biased our results.

Conclusion

It is generally possible to achieve high smoking cessation rates in primary care with a treatment programme that combines behavioural support with pharmacotherapy. However, intensive smoking cessation counselling by a PN does not seem to improve abstinence rates compared with brief GP advice in patients who are treated with standardized pharmacotherapy. Nonetheless, both treatments seem extremely cost-effective, and as GPs are difficult to get involved in smoking cessation routinely, PNs can still play an important role in providing accessible smoking cessation treatment in primary care. The possible mediational effect of adherence should be further investigated, and also why adherence might be better in smokers treated by their GP.

Ethical approval and trial registration

Ethical approval was obtained from the Medical Ethics Committee of Maastricht Academic Hospital and Maastricht University (NL30057.068.09/METC 09-03-075) and the trial was registered in the Dutch Trial Register (NTR3067).

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Transparency statement

All authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing statement

We are happy to share the data with researchers who are interested to analyse the data for scientific purposes. Those who are interested can contact the corresponding author.

Contributorship statement

DK was principal investigator and composed the first draft of the research protocol, applied for and received funding, and coordinated the medical and ethical approval procedure. CR was responsible for the refinement of the study protocol and ethical approval. CR, MS, OS and DK were involved in data collection and dissemination of the entire study. AL was contact person in SGE, member of the multidisciplinary advisory group and had co-responsibility for the implementation of the trial within The Eindhoven Corporation of Primary Health Care Centers. CR, MS, WV and DK were involved in the data analysis planning and execution. All authors had access to the data and contributed to the writing of subsequent versions and approved the final manuscript.

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Supporting information

Table S1 shows the self-reported overall side effects reported at 12 weeks after treatment initiation. Patients were actively asked about the presence of adverse events. All possible adverse events of varenicline were listed with the response options “not at all”, “very minor”, “minor”, “reasonable/moderate”, “strong”, or “very strong”. The total number of patients deviates from the randomized patients since only patients who filled in the questionnaire in week 12 were taken into account.

Table E1: Reported symptoms and side effects reported in week 12

Symptoms	None to very mild (%)	Mild to moderate (%)	Severe (%)
Abnormal dreaming (N=269)	55.0	27.5	17.5
Nausea (N=269)	59.9	23.0	17.1
Increased appetite (N=269)	39.4	44.2	16.4
Difficulty falling asleep (N=269)	54.6	31.6	13.8
Fatigue (N=269)	62.5	24.9	12.6
Weight gain (N=269)	43.9	43.9	12.3
Insomnia (N=269)	54.6	33.1	12.3
Restlessness (N=269)	59.5	30.9	9.7
Depressive feelings (N=269)	78.8	13.0	8.2
Dizziness (N=269)	75.5	17.5	7.1
Increased thirst (N=269)	71.0	22.7	6.3
General discomfort (N=269)	72.9	21.6	5.6
Dyspnoea (N=269)	76.6	18.6	4.8
Anxiety (N=269)	82.5	13.0	4.5
Obstipation (N=269)	82.2	13.4	4.5
Hoarseness (N=269)	84.4	11.5	4.1
Panic reactions (N=269)	85.1	10.8	4.1
Headache (N=269)	75.1	20.8	4.1
Tense muscles (N=269)	76.6	19.3	4.1
Infections of airways (N=269)	86.6	9.7	3.7
Stomach ache (N=269)	81.0	15.2	3.7
Coughing (N=269)	79.9	16.7	3.3
Sore throat (N=269)	88.5	8.2	3.3
Suicidal thoughts (N=269)	92.6	4.1	3.3
Stiffness (N=269)	82.9	13.8	3.3
Vomiting (N=269)	89.6	7.1	3.3
Rash (N=269)	90.3	6.7	3.0
Runny nose (N=269)	84.4	13.0	2.6
Muscle convulsions (N=269)	88.1	9.7	2.2
Sudden muscle spasms (N=269)	87.4	10.4	2.2
Weight loss (N=269)	94.4	4.1	1.5
Tinnitus (N=269)	93.7	4.8	1.5
Chest pain (N=269)	89.6	8.9	1.5
Increased blood pressure of heart rate (N=269)	91.1	7.8	1.1
Acne (N=269)	95.2	3.7	1.1
Sexual dysfunction (N=269)	93.7	5.2	1.1
Diarrhea (N=269)	83.3	15.6	1.1
Loss of appetite (N=269)	92.6	6.7	0.7
Eye pain (N=269)	95.5	4.1	0.4
Fever (N=269)	94.8	4.8	0.4
Paralysis (N=269)	99.3	0.7	0.0

Chapter 5

Do we need tailored smoking cessation interventions for smokers with COPD? A comparative study of smokers with and without COPD regarding factors associated with tobacco and smoking professionals

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Do we need tailored smoking cessation interventions for smokers with COPD? A comparative study of smokers with and without COPD regarding factors associated with tobacco and smoking professionals

Abstract

Background: The prevalence of tobacco smoking in patients with chronic obstructive pulmonary disease (COPD) is high. It is assumed that this group of smokers has more difficulties quitting than smokers without COPD. In order to increase the effectiveness of smoking cessation treatments in smokers with COPD it is important to identify any smoking-related factors which are specific to this group of smokers.

Objective: To compare smokers with COPD with smokers without COPD regarding factors associated with tobacco smoking and quitting.

Methods: We conducted a questionnaire survey in all smoking patients with a recorded diagnosis of COPD from a large Dutch primary healthcare network. We compared this group with twice as many age-, sex- and healthcare centre-matched smokers without COPD.

Results: Respondents were 107 smokers with COPD and 86 smokers without COPD. The number of attempts to quit was similar in both groups but more smokers with COPD had ever used pharmacological, behavioural and alternative smoking cessation treatments. Furthermore, smokers with COPD more often received triggers to quit from their environment and from their general practitioner, and they were more concerned about, and aware of, the health risks of smoking. Importantly, smokers with COPD reported higher levels of depression and cigarette dependence and a lower self-efficacy to refrain from smoking than smokers without COPD.

Conclusion: Smokers with COPD differ from smokers without COPD on several factors which are associated with tobacco smoking and quitting. Taking into account these differences may help to increase the effectiveness of smoking cessation treatments for the specific group of smokers with COPD.

Introduction

In developed countries, tobacco smoking is the most important risk factor for developing chronic obstructive pulmonary disease (COPD) (1). In the Netherlands, for example, 85% of new COPD cases are attributed to smoking (2). Furthermore, smoking has a detrimental effect on the course of this disease (3). An overview of the literature showed that the forced expiratory volume in 1 s in male smokers with mild-to-moderate COPD declined within a range of 42–82 ml/year compared with 0–49 ml/year in males with COPD who quit smoking (4). Moreover, the Lung Health Study has shown that, after 11 years, 38% of those with COPD who continued smoking had a forced expiratory volume in 1 s of less than 60% of the predicted normal value compared with 10% for those who had quit (5).

From this it becomes clear that smoking cessation is the intervention with the biggest positive impact on the course of COPD (3). The Cochrane review on smoking cessation in smokers with COPD concluded that a combination of behavioural and pharmacological interventions is superior to any other treatment separately (6). Despite the availability of these evidence-based interventions, the prevalence of smoking in patients with COPD is still high, exceeding the rate of smoking in the general population. For example, a large population-based English study showed that the prevalence of smoking currently was 35% among people with COPD compared with 22% among people without COPD (7).

The higher prevalence of smoking among COPD patients suggests that, compared with smokers from the general population, smokers with COPD find it more difficult to quit smoking. However, the results from studies that compared smokers with COPD with smokers without COPD have been ambiguous. For example, in a small longitudinal study from the Netherlands high smoking cessation rates were found in participants both with and without COPD (8), while in a different Dutch study smokers with mild-to-severe COPD were less likely to achieve abstinence than smokers without COPD (9). A study from Scandinavia including an intervention with confrontation with spirometry showed that smokers with COPD quit smoking significantly more often than smokers without COPD (10).

Research that characterizes smokers with COPD is scarce. There is little evidence that smokers with COPD are different from smokers without COPD and therefore may need tailored smoking cessation treatments. To our knowledge there are only two studies comparing characteristics of smokers with COPD with smokers without COPD (11, 12). Only one of these assessed determinants of attempts to quit

and treatment utilization and showed that motivation for quitting and frequency of receiving physician counselling and pharmacotherapy for smoking cessation were similar in both groups (12). The other study was not designed to assess determinants of attempts to quit and treatment utilization (11). In conclusion, there is not enough evidence to pinpoint the differences between smokers with and without COPD, and consequently it is still difficult to design smoking cessation interventions specifically for smokers with COPD. Therefore, we conducted a study to compare factors associated with attempts to quit and the use of evidence-based smoking cessation treatments between smokers with and without COPD.

Materials and methods

Study design

We conducted a cross-sectional study in 2013. Participants were recruited from the 'Eindhoven Corporation of Primary Health Care Centres', which is a network of ten primary healthcare centres in the city of Eindhoven, The Netherlands, covering 64,955 patients (13).

Study subjects

All patients from the Eindhoven Corporation of Primary Health Care Centres with a recorded diagnosis of COPD in their electronic medical record (EMR) and twice as many controls matched for age, sex and healthcare centre were included in the study. Matching was done in order to equalize age and sex, important risk factors for the development of COPD but not modifiable by an intervention, in smokers both with and without COPD. Cases for this study were all patients from the Eindhoven Corporation of Primary Health Care Centres with a diagnosis of COPD in their EMR (based on the international classification of primary care code R95) who were current smokers. Smokers were defined as patients who were currently daily or occasionally smoking tobacco cigarettes. The severity of COPD was categorized according to the Global Initiative for Chronic Obstructive Lung Disease guidelines (3). Controls were smokers without a recorded diagnosis of COPD. All patients were checked by their general practitioners (GP) in order to validate their disease status and to identify any contraindications for participating in this study (Figure 1).

Figure 1. Flowchart of inclusion and exclusion. Not included: not included because they were not present anymore in the latest update from the electronic medical record because of death, GP switch or other reasons. Excluded by GP: excluded by GP because of illness, language, death, GP switch, or social or other reasons.

Methods

The coordinating researcher sent the patients a package by postal mail, including an information letter about the study, a questionnaire and an informed consent form. With these, a smoking cessation information leaflet was sent, in which advice on quitting and information about smoking cessation treatments was given. Participants did not receive compensation for filling in the questionnaire. When there was no response within 2–4 weeks we sent a reminder with an enclosed reply card on which the smoking status could be specified. The study was approved by the Medical Ethics Committee at Maastricht University, The Netherlands (approval No. 11-4-145).

Measurements

We collected information on factors which, according to the literature (14-21), have been associated with smoking and smoking cessation. We collected data on date of birth, sex, occupation, and education. Socioeconomic status was computed

from occupation and education and divided into three categories – high, moderate and low (22). Furthermore, information was collected on comorbidities, mental health (hospital anxiety and depression scale) (23) and health perception (36-item short-form health survey) (24) for all patients. Additionally, there were specific questions for the COPD patients on Global Initiative for Chronic Obstructive Lung Disease status and COPD impact and symptoms (clinical COPD questionnaire) (25).

Nicotine dependence was calculated using the 'Heaviness of Smoking Index' (26), and pack-years were calculated by dividing the number of cigarettes smoked a day by 20 and multiplying it by the number of smoking years. Furthermore, reasons for smoking (27), self-exempting beliefs to justify smoking behaviour and concern and risk perception of illness through smoking were evaluated (28). Moreover, smoking and advice on quitting in the social environment was assessed.

We measured the frequency of advice from the GP on smoking cessation and motivation to quit (motivation to stop scale) (29). Furthermore, self-efficacy to refrain from smoking in different situations was measured (22). Participants who had ever undertaken an attempt to quit were additionally asked about their total number of attempts to quit and their preference for abrupt or gradual quitting.

We also included questions about the use and level of faith in different kinds of smoking cessation treatments (22). Finally, participants were asked about what they considered important when using different kinds of smoking cessation treatments (30).

Analysis

Data were analysed using SPSS 19. Data on attempts to quit, smoking cessation treatment utilization and associated factors were compared between cases and controls using χ^2 tests for categorical variables and t-tests for continuous variables.

All analyses were conducted with the total number of valid answers for every particular item in the different groups. As numbers of missing values could differ per item, different total numbers were obtained in the different analyses. If applicable, we imputed missing data corresponding to the guidelines of the specific questionnaire. When there were no guidelines available, we derived these from original guidelines of similar questionnaires.

Results

Study population

From the total population of the 64,995 registered patients, we identified 1,415 patients (2.2%) with COPD whom we matched with 2,830 patients without COPD. In total, 437 patients (31%) with COPD and 875 (31%) without COPD responded to the questionnaire. Amongst these, we identified 107 current smokers with COPD (24.5% of 437) and 86 current smokers without COPD (9.8% of 875) who entered our main analysis (Fig. 1).

We received reply cards with data on smoking status from 255 patients with COPD and 548 patients without COPD who did not respond to the questionnaire. Of these, 30.2% (n = 77) and 12.8% (n = 70) were smokers and 57.3% (n = 146) and 46.2% (n = 253) were ex-smokers, respectively. The ratio of smoking prevalence in patients with versus without COPD (30.2 vs. 12.8% = 2.4: 1) in the non-respondents was comparable with the ratio in the respondents to the questionnaire (24.5 vs. 9.8% = 2.5:1).

Table 1. Characteristics of smokers with and without chronic obstructive lung disease (COPD)

	With COPD (n=107)	Without COPD (n=86)	P-value
<i>Demographic characteristics</i>			
Age	66.6 (11.1)	66.3 (11.7)	0.85
Female sex % (n)	52.8 (56)	40.7 (35)	0.09
Socioeconomic status % (n)			0.41
Low	19.6 (21)	18.6 (16)	
Moderate	62.6 (67)	55.8 (48)	
High	17.8 (19)	25.6 (22)	
<i>Health characteristics</i>			
<i>Comorbidities % (n)</i>			
Cardiovascular	25.5 (27)	24.4 (21)	0.87
Endocrine	39.6 (42)	30.2 (26)	0.18
Musculoskeletal	4.7 (5)	9.3 (8)	0.21
Neoplasms	3.8 (4)	4.7 (4)	0.76
Psychological	23.6 (25)	9.3 (8)	0.01
Respiratory	96.2 (102)	39.5 (34)	<0.001
<i>Mental health</i>			
Anxiety ^a	6.8 (4.5)	5.6 (4.0)	0.06
Depression ^a	6.0 (4.8)	4.3 (3.7)	0.01
Perception of one's health ^b	3.7 (0.8)	3.1 (0.8)	<0.001

GOLD status (self-reported) % (n)			
Mild	27.1 (29)		
Moderate	27.1 (29)		
Severe	8.4 (9)		
Very severe	2.8 (3)		
I do not know	19.6 (21)		
COPD health status			
Respiratory symptoms ^c	2.3 (1.2)		
Mental state ^c	1.1 (1.3)		
Physical state ^c	1.6 (1.3)		
<i>Smoking characteristics</i>			
Pack-years	35.3 (21.2)	27.0 (21.3)	0.09
Level of nicotine addiction % (n)			<0.01
Low	35.0 (36)	60.0 (48)	
Medium	53.4 (55)	33.8 (27)	
High	11.7 (12)	6.3 (5)	
Reasons for smoking			
For pleasure ^d	11.8 (3.8)	11.3 (3.5)	0.40
When socializing ^e	7.2 (3.0)	6.0 (2.7)	0.01
For mental and/or physical energy boost ^d	9.2 (3.8)	7.4 (3.6)	<0.01
As habit ^e	5.9 (2.2)	4.9 (2.1)	<0.01
Justifying smoking behaviour ^b	2.7 (0.7)	2.6 (0.6)	0.26
Concern of illness through smoking ^b	3.2 (1.0)	2.9 (0.9)	0.02
Believe in illness through smoking ^b	3.3 (0.9)	3.0 (0.8)	0.01
<i>Social influence</i>			
Smoke status of partner % (n)			0.16
never smoker	10.3 (11)	18.6 (16)	
ex-smoker	17.8 (19)	20.9 (18)	
smoker	29.0 (31)	16.3 (14)	
no partner	40.2 (43)	37.2 (32)	
Partner's level of stimulation to quit ^b	3.1 (1.4)	2.8 (1.5)	0.26
Smoking status of environment % (n)			0.37
few smokers	57.9 (62)	67.5 (58)	
as many smokers as non-smokers	16.8 (18)	16.3 (14)	
more smokers	22.4 (24)	15.2 (13)	
Environments' level of stimulation to quit ^b	3.0 (1.3)	2.5 (1.1)	< 0.01

Data are presented as mean (SD) unless stated otherwise. Discrepancies between total numbers and numbers of added subcategories are due to missing values. GOLD = Global Initiative for Chronic Obstructive Lung Disease ^a0-21=highest level of anxiety/depression. ^b1-5=highest level of perceived health, justification of smoking, concerns of and beliefs in illness, and partner's stimulation to quit. ^c0-6=highest level of respiratory symptoms and mental/physical complaints. ^d4-20=highest level of agreement. ^e3-15=highest level of agreement.

Demographic and health characteristics

As a result of the matching, there were no significant differences between smokers with and without COPD regarding their age and sex (Table 1). There was also no difference in socioeconomic status. The majority of smokers with COPD (54.2%, $n = 58$) had mild-to-moderate airflow limitation. They reported more psychological comorbidities than smokers without COPD and scored higher on the depression scale. Conversely, smokers with COPD perceived their own health better.

Smoking characteristics and social influence

Smokers with COPD reported higher levels of nicotine addiction than smokers without COPD (Table 1). Both groups reported different reasons for smoking; smokers with COPD more often smoked to socialize, to get a mental and/or physical energy boost and as a habit. Moreover, they were more concerned about getting ill due to smoking and believed that smoking caused illness. With regard to social influence, smokers with COPD experienced more stimulation to quit from their environment compared with smokers without COPD.

Quit attempts

Table 2 shows data on attempts to quit and use of smoking cessation treatments. There was no significant difference in the number of previous attempts to quit and motivation to quit in the future. Smokers with COPD, however, more often received advice to quit from their GP than smokers without COPD. They also reported lower levels of self-efficacy to refrain from smoking when they were feeling stressed or angry and when they were socializing.

Smoking cessation treatments

Both smokers with and without COPD had similar levels of faith in the efficacy of different smoking cessation treatments (Table 2). About twice as many smokers with COPD, however, had ever used nicotine replacement therapy and prescription medications (bupropion, nortriptyline, varenicline), behavioural interventions and alternative treatments for smoking cessation. Furthermore, smokers with COPD found the costs of such treatments and their reimbursement by healthcare insurance more important than smokers without COPD when choosing whether or not to use such treatments (Table 2).

Table 2. Quit attempts and use of smoking cessation treatments in smokers with and without chronic obstructive pulmonary disease (COPD)

	With COPD (n=107)	Without COPD (n=86)	P- value
<i>Quit attempts</i>			
Frequency of advice to quit from GP ^a	2.6 (0.9)	1.7 (0.7)	<0.01
Motivation to quit ^b	3.1 (1.7)	2.8 (1.6)	0.30
Participants that have ever undertaken a quit attempt % (n)	70.1 (75)	69.8 (60)	0.87
Number of quit attempts ^c	4.7 (4.6)	4.0 (5.6)	0.44
Preference for abrupt quitting % (n) ^c	33.3 (25)	38.4 (33)	0.05
Self-efficacy to refrain from smoking in different situations			
When feeling stressed or angry ^d	2.4 (1.0)	2.9 (1.2)	0.01
When socializing ^d	2.8 (1.4)	3.2 (1.3)	0.04
When socializing ^d	2.8 (1.2)	3.1 (1.2)	0.11
When sorely tempted ^d			
<i>Smoking cessation treatments</i>			
Treatments ever used % (n) ^c			
NRT and prescription medication	68.0 (51)	40.0 (24)	0.001
Behavioural interventions	69.3 (52)	38.3 (23)	<
Self-help material	13.3 (10)	6.7 (4)	0.001
Alternative treatments	28.0 (21)	11.7 (7)	0.2
			0.02
Level of faith in the efficacy of different treatments			
NRT and prescription medication ^d	2.6 (1.0)	2.3 (0.9)	0.07
Behavioural interventions ^d	2.4 (0.9)	2.3 (0.8)	0.54
Self-help material ^d	1.9 (0.9)	2.1 (0.9)	0.21
Alternative treatments ^d	2.5 (1.1)	2.5 (1.0)	0.97
<i>What influences the choice for a smoking cessation treatment</i>			
Nicotine replacement therapy			
Evidence based ^d	3.1 (1.0)	2.9 (1.0)	0.20
Costs ^d	3.5 (1.2)	3.0 (1.2)	0.01
Takes little effort ^d	3.2 (1.0)	3.0 (1.0)	0.08
Easily available ^d	3.2 (1.0)	3.0 (1.1)	0.13
Reimbursed by insurance ^d	3.8 (1.2)	3.2 (1.8)	<0.01
Side effects ^d	3.8 (1.2)	3.5 (1.2)	0.17
Advised by GP ^d	3.6 (1.1)	3.3 (1.0)	0.14
Experiences of friends ^d	3.3 (1.1)	3.0 (0.9)	0.09
Antidepressants			
Evidence based ^d	3.3 (1.1)	3.1 (1.0)	0.16
Costs ^d	3.6 (1.3)	3.2 (1.1)	0.02
Takes little effort ^d	3.3 (1.1)	3.0 (1.0)	0.14
Easily available ^d	3.3 (1.2)	3.0 (1.0)	0.31
Reimbursed by insurance ^d	3.8 (1.3)	3.3 (1.2)	0.01
Side effects ^d	3.7 (1.2)	3.4 (1.2)	0.17
Advised by GP ^d	3.5 (1.1)	3.3 (1.1)	0.19
Experiences of friends ^d	3.2 (1.2)	3.0 (1.0)	0.15

Varenicline			
Evidence based ^d	3.5 (1.1)	3.2 (1.0)	0.14
Costs ^d	3.6 (1.3)	3.3 (1.1)	0.30
Takes little effort ^d	3.2 (1.1)	3.1 (1.0)	0.61
Easily available ^d	3.3 (1.2)	3.2 (1.0)	0.31
Reimbursed by insurance ^d	3.7 (1.3)	3.4 (1.2)	0.09
Side effects ^d	3.7 (1.3)	3.5 (1.2)	0.24
Advised by GP ^d	3.5 (1.2)	3.3 (1.0)	0.22
Experiences of friends ^d	3.5 (1.2)	3.0 (1.0)	0.20
Counselling			
Evidence based ^d	3.4 (1.0)	3.3 (1.0)	0.54
Costs ^d	3.6 (1.3)	3.3 (1.2)	0.12
Takes little effort ^d	3.4 (1.2)	3.2 (1.0)	0.15
Reimbursed by insurance ^d	3.8 (1.3)	3.4 (1.2)	0.08
Advised by GP ^d	3.7 (1.1)	3.3 (1.0)	0.05
Experiences of friends ^d	3.2 (1.2)	3.0 (0.9)	0.16

Data are presented as mean (SD) unless stated otherwise. GP = General practitioner. ^a1-4=highest frequency. ^b1-7=highest level of motivation to quit. ^cResponse refers to the subgroup of smokers that have ever undertaken a quit attempt (n=135). ^d1-5=highest level of self-efficacy, faith, and influence.

Discussion

We found that smokers with COPD tried to quit smoking just as often as smokers without COPD and were just as motivated to try again in the future, but they used smoking cessation treatments more often. Furthermore, smokers with COPD received triggers to quit more often, both from their environment and from their GP. In addition, they were more concerned about, and aware of, the health risks of smoking. Importantly, smokers with COPD reported higher levels of depression and cigarette dependence and a lower self-efficacy to refrain from smoking compared with smokers without COPD.

We observed the same number of attempts to quit in smokers with and without COPD. Results from intervention studies vary from fewer attempts to quit to more attempts to quit in smokers with COPD compared with smokers without COPD (8-10). In addition, there are no numbers available from population studies, and this makes the quantity of quit attempts in smokers with and without COPD still a speculative matter. Therefore, it might be more important to focus on the quality of the quit attempts and to stimulate all serious quit attempts by offering evidence-based smoking cessation interventions to all smokers.

Smokers with COPD were more often advised by their GP to stop smoking than smokers without COPD but, as previously mentioned, did not undertake more

attempts to quit. In addition, their motivation to quit was similar to smokers without COPD. It was expected that smokers with COPD were more likely to receive advice from their GP, as they consulted their GP regularly for routine COPD management check-ups. A Cochrane review showed that brief advice given by the GP had a small but significant effect on cessation rates in the general smoking population (31). As we were not able to ask about the specific content of the advice in our study, we do not know whether the advice given was adapted to the needs of the smokers with COPD at that moment or not. Hilberink et al. (32) found that it would be advantageous to tailor COPD counselling to two distinct groups – motivated and unmotivated smokers. Furthermore, Tønnesen et al. (33) suggested the possibility that smokers with respiratory disease at some stage develop a ‘tolerance’, indicating that they might get tired of the quit advice which they receive repeatedly from GPs.

Another result linked to this was that smokers with COPD were more concerned about and aware of becoming ill through smoking. Probably, the frequent quit advice given by GPs and peers draws the risks of illness to their attention. Contrary to this, however, was that the smokers with COPD perceived their health significantly better than the smokers without COPD. As this result contradicts rational reasoning, this outcome might be influenced by cognitive dissonance. This means that answers from smokers with COPD are likely to be biased by optimism in order to reduce the psychological need to quit smoking (34).

In line with previous research, smokers with COPD reported higher levels of depression. Independent of smoking status, depression is more frequently seen in patients with COPD (35). Furthermore, depression is likely to adversely affect the success of an attempt to quit (36). In addition, as described in the literature, the COPD group had a higher level of nicotine dependence, which also makes it more difficult for them to quit smoking (7, 11, 21).

Smokers with COPD were more likely to smoke for social reasons, to get an energy boost and as a habit. In line with this, smokers with COPD reported a lower level of self-efficacy to refrain from smoking in emotional and habitual situations than smokers without COPD. Self-efficacy interpretations are important predictors of smoking cessation (37, 38), and frequent and intensive motivational support is likely to increase self-efficacy. As smokers with COPD have a lower level of self-efficacy, it is possible that motivational support is of even more importance to them during smoking cessation.

Finally, smokers with COPD found costs important in their decision of whether or not to use smoking cessation treatments. This might be because they had less money to spend. However, contrary to results from other research, the socioeconomic status of both groups in this study was roughly similar, which might partly be due to the matching on healthcare centre. In the Netherlands smoking rates decreased when health insurances reimbursed smoking cessation treatments and increased again when reimbursement by health insurances was stopped (39). This is in line with results from a systematic review which showed that full financial interventions directed at smokers when compared with no financial interventions increased the proportion of smokers who succeeded in quitting (40).

Strengths and limitations

This study is one of the few studies looking at differences between smokers with and without COPD with regard to smoking. Besides, it is the first study looking at a large number of factors associated with smoking, attempts to quit and the use of smoking cessation treatments.

Due to the diversity in patient characteristics in this study (Table 1), the results can be extended to make predictions about smokers with COPD in primary healthcare in other western European countries with similar healthcare systems.

The cross-sectional study design involved collecting retrospective information which may have caused recall bias. However, this only counts for some particular questions about stimulation and advice on smoking cessation, attempts to quit and the use of smoking cessation treatments. Moreover, recall bias would have been equal in smokers both with and without COPD. Furthermore, with this observational design it is not possible to identify reverse causation. This makes it uncertain whether differences between groups are fully explained by having COPD or not. However, age, sex and the number of packyears, the most important risk factors for developing COPD, were not significantly different between smokers with and without COPD.

COPD status was derived from the EMR, and the R95 code for COPD in the EMR was based on lung function test results. However, we were not able to check the lung function results again to verify the accuracy of the diagnosis. Similarly, no lung function testing was done in the group of patients without COPD in order to verify whether they had undetected airway obstruction. Therefore, we cannot exclude that some misclassification of disease status has occurred.

The number of respondents who said they were smokers was lower in both groups than one would have expected based on the prevalence numbers in the Netherlands (27%) (41). It is known that in smoking cessation research less participation is to be expected from unmotivated smokers. However, the ratio of response and nonresponse from smokers in both groups was similar.

Conclusion and implications

Smokers with and without COPD have many smoking-related characteristics in common. However, smokers with COPD also seem to differ from smokers without COPD in various aspects. In smokers with COPD, depressive symptoms, high cigarette dependence and low self-efficacy are essential aspects which should be targeted in their smoking cessation treatment. Adding these elements to the content of an intensive behavioural counselling programme for smokers with COPD and offering such counselling in combination with pharmacotherapy opportunistically and free of cost to all smokers with COPD should have an impact on reducing smoking in this patient population in the future.

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Chapter 6

General discussion

General discussion

The studies described in this thesis focused on gaining knowledge about the involvement of the practice nurse in smoking cessation treatment and the combination of practice nurse counselling and varenicline. At the start of this process, it was unclear how the practice nurse was valued in clinical practice by patients and healthcare providers for involvement in smoking cessation treatment. Then, in the main part of this thesis we presented the development and results from a randomised controlled trial on the effectiveness of intensive practice nurse counselling compared to brief general practitioner advice, when applied in combination with varenicline. Additionally, because smoking cessation is of primary importance for patients with COPD, opportunities for smoking cessation treatment were evaluated by comparing smokers with and without COPD. In this Discussion section, the main findings of all studies will be summarised, the interpretation of these findings will be described and directions for future research will be formulated.

Main findings of this thesis

Practice nurse indicated as preferred providers for smoking cessation

General practitioners find it difficult to have a substantial role in smoking cessation. They lack time, are reluctant to talk about smoking, and become frustrated when smokers do not quit immediately or relapse (*Chapter 2*). In patients without obvious smoking-related complaints, general practitioners have no leads to initiate the discussion on smoking (*Chapter 2*), which means that these smokers are less likely to be advised to quit and consequently use less evidence-based treatments (*Chapter 5*). Instead, patients and healthcare providers identified practice nurses as the preferred providers for preventive tasks and lifestyle matters, such as smoking cessation. They believed that patients received more intensive and personalised care when treated by the practice nurse (*Chapter 2*). In our trial, almost 70% of smokers preferred the practice nurse over their general practitioner and patients were more satisfied with practice nurse counselling than with brief advice from the general practitioner (*Chapter 4*).

Primary care intervention can boost smoking cessation rates

Primary care is a suitable place for smokers to get adequate help to quit in terms of accessibility and treatment success. The fast inclusion showed that smokers were easy to target in their primary healthcare centres and patients treated by practice nurses

and general practitioners showed high percentages of prolonged abstinence at 26 weeks (32.2%, 39.0%) and 52 weeks (25.5%, 28.5%). It was hypothesised that treatment success was higher among patients treated by the practice nurse. However, the trial showed that pharmacotherapy combined with intensive practice nurse counselling was not superior to pharmacotherapy combined with one-off general practitioner advice in a real-life study design, as there was no significant difference in both treatment options. In the practice nurse group 46% had good adherence compared to 62% in the general practitioner group. Adherence rates were significantly better in patients treated by the general practitioner and the general practitioner achieved more life years gained at lower costs than the practice nurse, making the general practitioner more cost-effective when using pharmacotherapy. (*Chapter 4*)

Differences exist between smokers with and without COPD

In our study, smokers with COPD reported the same motivation to quit and the same frequency of attempts to quit as smokers without COPD. Although smokers with COPD received more triggers to quit from their general practitioner and environment, this did not result in more quit attempts. Smokers with COPD reported higher levels of cigarette dependence and they perceived smoking more as a habit. They also reported higher levels of depression and lower levels of self-efficacy. Socialising and smoking for a mental or physical energy boost, were important for smoking among smokers with COPD. (*Chapter 5*)

Interpretation

Involvement of the practice nurse in smoking cessation

In the Netherlands, the number of patients living with one or more chronic conditions is increasing (1, 2) and, at the same time, there is a shift from secondary to primary care for the management of chronically ill patients (3). Practice nurses were introduced with the idea to reduce the workload of general practitioners and to increase the quality of care (4, 5). After successfully completing a study program at the level of university of applied sciences, practice nurses are licensed to support the general practitioners in their daily practice (5). Responsibilities vary among countries, healthcare systems and healthcare centres, but can include first contact care, regular care and health promotion tasks, including routine management of chronic diseases and lifestyle counselling (6). In the Netherlands, the main task of the practice nurse was protocol-based care in chronic conditions (5). In recent years there has been a growth in both the number of practice nurses and the scope of their role, including the treatment of tobacco dependence (5, 7). Therefore, practice nurses play a crucial role in the accessibility of evidence-based smoking cessation treatments in primary care.

With regard to quality of care, practice nurses were found not to be superior to general practitioners in smoking cessation treatment at 6-month and 12-month follow-up (*Chapter 4*). Nurses spent more time with their patients than general practitioners, which is in line with routine care and previous research (8-11). To our knowledge, no similar studies have been published evaluating intensive practice nurse counselling compared to brief general practitioner advice for smoking cessation (12, 13). However, a recent review on the role of nurses in primary care indicated that practice nurses were probably as effective or possibly even more effective than general practitioners in terms of improving patients' health outcomes such as mortality, health status and quality of life (6). Nevertheless, an earlier review found that higher quality randomised controlled trials reported more hospital admissions and higher mortality rates with nurse-led care, although this was only just significant or non-significant (14).

Healthcare providers can have a major impact on a smoker. They can address the health, social, financial, and emotional issues related with smoking and smoking cessation. It is important that healthcare providers understand why it is necessary to talk about smoking, as well as when and how to do so. A specific set of skills is conducive to the success of smoking cessation treatment and other lifestyle counselling treatments. In recent years there has been done extensive research to determine which behavioural change techniques are beneficial, leading to the identification of evidence-based skills for behavioural support (15-17). Practice nurses and general practitioners have previously been shown to have similar lifestyle treatment skills (8, 9, 18-21) and one reason for the potentially equal treatment success could therefore be that both providers are similarly equipped with behaviour change techniques (22).

While practice nurses can take over smoking cessation treatment, it is also assumed that if general practitioners can delegate preventive tasks to others within the primary healthcare centre, time pressure can be reduced and smoking cessation advice is more likely to be given. However, in terms of workload reduction, it is inconclusive whether practice nurses reduce the workload of the general practitioner, as evidence on this topic is scarce and results are mixed. A randomised controlled trial examining workload in the short-term, showed that the workload of general practitioners was not reduced by the introduction of the practice nurse (23). A study by the Netherlands Institute for Health Services Research (Nivel) also found that workload was only reduced to a limited extent, because general practitioners previously only partially carried out the current tasks of the practice nurse (5). Nevertheless, another study found that 77% of the out-of-hours tasks of primary care could fit within the scope of nurse practitioners, indicating nurses actually can decrease the workload, but those nurses were higher

educated than practice nurses (24). Yet, it was clear from our qualitative study that both healthcare providers and patients viewed the practice nurse as the preferred provider for preventive tasks (*Chapter 2*) and achieving an optimal skill mix with nurses working as substitutes and supplements is of utmost importance (25, 26).

A growing demand for care also increases the cost of healthcare, which is why it is important to look for ways to improve the quality of care at a lower cost. Due to the pragmatic design of our study, a full cost-effectiveness analysis was not possible, so the cost per quitter, the incremental costs per life year gained, and an incremental cost-effectiveness ratio (ICER) were calculated, using the direct method described by Stapleton and West (2012) (27). We found an ICER of -€416 in favor of the general practitioner, meaning that the costs per quitter were higher among practice nurses (€1,230 per quitter) than among general practitioners (€818 per quitter), while practice nurses were not more effective in smoking cessation treatment than general practitioners (*Chapter 4*). Nonetheless, both treatments seemed cost-effective in terms of avoided mortality, morbidity and costs of care for smoking-related diseases as the cost per quitter were far below €2,040 (28), although it should be noted that our study did not comply with the Drummond and Jefferson's economic evaluations checklist. Still, our results are in line with other reviews about the cost-effectiveness of smoking cessation treatments, indicating that the costs of these interventions are relatively lower compared to the benefits and below all benchmarks of quality-adjusted-life-years (29-33). General studies on the cost-effectiveness of practice nurses have shown mixed results (34, 35). Therefore, more robust evaluation studies on the cost-effectiveness of the practice nurse are needed in the future, before final conclusions can be drawn (35).

Effectiveness of practice nurse not superior to general practitioner

Our large randomised controlled trial found no difference in prolonged abstinence rate between practice nurses and general practitioners, when combined with pharmacotherapy. This remained the case after adjusting for covariates (age, gender, education, income, nicotine dependence, urge to smoke, self-efficacy, duration of longest quit attempt, depression, anxiety, share of smokers in the social environment, and alcohol misuse) and performing a Bayesian analysis (*Chapter 4*). A type two error seemed unlikely as the recruitment of motivated smokers was successful, more smokers were recruited than indicated by the power analysis and the follow-up rate was high. Also, there was no low uptake in the practice nurse group or over-treatment by the general practitioner (median time spent: 110 minutes with the practice nurse and 10 minutes with the general practitioner) and a lack of contrast between study groups seemed unlikely as well, as the quit percentages were relatively higher in the general practitioner group. Therefore, it seems safe to assume that practice nurses do

not generally provide a better combination treatment than general practitioners. Yet, it is possible that there are subgroups that could benefit from the intensive practice nurse counselling. For example, smokers with COPD experience more complex problems in quitting than smokers without COPD (*Chapter 5*).

It was hypothesised in advance that the effect of intensive practice nurse counselling would be significantly better than the effect of brief advice from the general practitioner on quitting success (*Chapter 3*). Previous studies have shown that general practitioners are more effective in smoking cessation treatment than non-physician healthcare providers such as practice nurses (32). However, there was also a strong relationship between success rate and intensity of support (number of contacts and time spent) and these associations seemed to be stronger than the benefit of receiving smoking cessation treatment from the general practitioner (32). In addition, practice nurses were likely to be better trained in giving patient education, lifestyle counselling and disease prevention (9, 21), to provide lifestyle advice more frequently (36), and to better adhere to guidelines (36, 37) compared to general practitioners. One reason for the lack of a significant difference between both groups (*Chapter 4*), might reflect good care in the general practitioner group. Another possible reason is that the effect of pharmacotherapy was so strong that an additional effect was not detectable or not present. However, at the time we started, no comparable studies were available that could be used to estimate the effectiveness of both treatment options with varenicline in a real-life setting. As it turned out, our study appeared to be one of the first studies showing quit rates for varenicline with only very limited behavioural support (as in the general practitioner group) in the same range as varenicline studies with much more behavioural support (38-41). Also Swan et al. (2010) who used varenicline in real life, showed similar cessation rates when combined with various intensities of assistance (30.7%-33.8% at 26 weeks)(40). It should be noted however, that adherence was higher within the general practitioner group and this could be an important factor for their success.

Patient satisfaction is an important quality indicator that provides useful insights for improving the quality and effectiveness of care. In our trial, participants were more satisfied with the practice nurse compared to the general practitioner (satisfaction score 7.9/10 versus 6.4/10, SD=2.91; $p<0.001$) (*Chapter 4*), which was in line with other research showing that patient satisfaction is equally high or sometimes even higher for nurses compared to medical doctors (6, 14, 42). Nurses spend more time with their patients and develop a strong personal relationship regarding smoking cessation because of the intensive and personal approach of counselling. It was interesting to see that even in practices with a lower success rate in the practice nurse group, satisfaction

was still high (*Chapter 4*). The same was observed in our qualitative study where patients treated by the practice nurse were highly satisfied even though none of them successfully quitted (*Chapter 2*). From previous studies, it is unclear to what extent patient satisfaction is an important factor. There are indications that higher satisfaction is associated with lower mortality rates in hospitals (43), but this was disputed in another study (44). Moreover, in a Swedish qualitative research, it was shown that patients did not see their own satisfaction as most important factor, but that they appreciated empathy from their healthcare professional (45). The absence of a strong positive correlation between patient satisfaction and better outcomes is an interesting finding in the light of current practice accreditation and quality indicators.

In addition to the effectiveness of pharmacotherapy, the chances of a successful quit attempt seems to depend on communication style (46, 47) and the content of the treatment (e.g. behavioural change techniques (15-17)), tailored to the patients' needs. Important evidence-based behavioural change techniques include strengthening an ex-smoker identity, measuring expired-air carbon monoxide concentrations and/or educating on the consequences of smoking and smoking cessation (16). Because general practitioners have limited time to apply a broad range of behavioural change techniques compared to the practice nurse and because the skill set of both healthcare providers seemed nearly identical (22), the communication style is of specific interest. One reason why the practice nurse was not more effective than the general practitioner, could be that general practitioners traditionally have more authority over patients and are therefore more effective in a shorter period of time. In an earlier study, practice nurses explained that their relationship is crucial and they believed their patients would not return on consultations when they were too stringent (48). This could lead to the practice nurse being too gentle for smokers wanting to quit, while the short and potentially more straight-forward approach of the general practitioner could lead to more clarity and responsibility on the part of the patient. Patients do feel that practice nurses are more accessible than general practitioners (49).

There were indications that general practitioners have a propensity to use a confronting style of giving advice (*Chapter 2*). However, previous research showed that more directive methods, such as confrontational counselling, do not work (50) and patients do not like to be patronised (51). In contrast, practice nurses tend to adopt a paternalistic approach and struggle with adapting to the patient's level of knowledge and patient-centeredness (48). Related to this, a recent study investigating patients' preferences for different communication styles showed that some patients preferred an autonomy-supportive communication style (offering choice and use suggestive language), while others preferred a more directive communication style (using a more

demanding language and not offering choice) (52). It was also shown that frame-tailoring the information to the desired communication style improved the perceived message relevance (52). This finding may be of specific importance for future treatments targeting smoking cessation or other lifestyle goals. Knowing the patient's preferences in terms of communication style may help to better target the patient with the most appropriate healthcare provider.

Because practice nurses may have less authority compared to general practitioners, an autonomy-supportive communication style such as motivational interviewing could be more suitable. Motivational interviewing is defined as a “directive, client-centered counselling style for eliciting behaviour change by helping clients to explore and resolve ambivalence” (53, 54). In our trial, practice nurses had been trained in motivational interviewing for their routine clinical work, but not specifically for the trial (*Chapter 3*). However, even after a training, practice nurses seem to apply motivational interviewing techniques only to some extent in chronic disease management and lifestyle counselling (36, 55-58). There is also insufficient evidence that motivational interviewing has an effect on smoking cessation rates (59). Nonetheless, nurses indicated that they could use more and better training to enhance their skills on smoking cessation treatment, as confirmed by other studies (49). While a Cochrane systematic review also found that training healthcare providers in smoking cessation had a positive effect on skills such as asking patients to set a quit date and the provision of self-help material (60), we believed that the practice nurses in our trial were already skilled on that level (*Chapter 3*). Nevertheless, it should be noted that there is room for improvement and practice nurses indicated that additional training would be desirable (*Chapter 2*). Future research has to examine how practice nurses' training on smoking cessation can be improved.

Instead of focusing on the differences in communication style between practice nurses and general practitioners, it could also be effective to use them together. Fiore et al. (2002) already recommended that the general practitioner should first give a strong message to quit, provide brief information about the health consequences, recommend and prescribe medication, and then let the practice nurses deliver additional counselling, provide education and support and offer follow-up contacts (32). This is in line with the preferences of patients, where the general practitioner was ideally viewed in more medical tasks (i.e. prescribing medication) and the practice nurse for more preventive care and follow-up (*Chapter 2*) (49).

Unfortunately, due to the pragmatic design of the study, we did not routinely monitor the consultations of practice nurses and general practitioners. Although, we had

planned to record some consultations during our trial (*Chapter 3*), only two practice nurses were willing to do so, but ultimately forgot to do it. This makes it difficult to really understand what happened during the consultations and why the intensive counselling did not lead to more quitters than the brief advice from the general practitioner (*Chapter 4*). Presumably, evaluating the content of the consultations could have made it more clear why there were large differences in effectiveness within healthcare centres, general practitioners and practice nurses. For example, we noticed considerable variation in the 6-month abstinence rates in practice nurses across healthcare centres, ranging from 0 to 63%, although the number of included patients was rather small in some centres and the corresponding abstinence rates were therefore not reliable (*Chapter 4*). In order to gain a better understanding of what is happening in a real-life smoking cessation consultation, we strongly recommend that future pragmatic studies attempt to gain more insight into which behavioural change techniques (content) and communication styles are commonly applied in routine care, by increasing the effort to have consultations monitored by healthcare providers.

A culture change is needed for prevention in primary care

It is often said that prevention is better than cure. In healthcare, it means: “Taking action or carrying out interventions with the aim to promote health and prevent or delay illnesses or health problems, and thereby achieving improvement of health” (61). Based on target group and progression of the condition, a distinction can be made between universal, selective, indicated and care-related prevention (62-64). Universal and selective (or targeted) prevention focuses on entire populations or populations at risk and is more the responsibility of the public health domain. Indicated prevention targets individuals who do not have a diagnosed disease, but who are at risk or have threshold symptoms, with the goal to prevent the onset of a disease. Care-related prevention focuses on individuals with a disease, with the aim of supporting self-management, reducing the burden of disease and preventing complications or disease progression. In the recently published ‘Toekomstvisie huisartsenzorg 2022’ in the Netherlands, both indicated and care-related prevention were seen as the responsibility of the general practitioner (63).

Another well-known saying about prevention is there is no glory in prevention, meaning that you get more credit for curing a disease than when you prevent one. Yet, prevention is effective and necessary: smoking cessation can prevent the onset and progression of COPD (65-67); lifestyle changes in patients with impaired glucose tolerance or metabolic syndrome can avoid diabetes (68-70); and timely treatment of patients with threshold symptoms of depression can prevent a clinical depression (71, 72), all in a cost-effective way (30, 73, 74). A large American study even showed that

prevention could reduce the burden of disease by half and healthcare expenditures by more than a quarter (75). In addition, a previous study within Stichting Gezondheidcentra Eindhoven (SGE) demonstrated that healthcare providers were enthusiastic about systemic screening for cardiovascular disease instead of case-finding, because of the lower workload and expected higher yield (76). Although indicated screening tools for diabetes (77, 78) and mental health (79) showed positive outcomes, implementation of such structured, large-scale prevention programmes remains suboptimal in more pragmatic circumstances (76, 78, 80). Also for smoking cessation, while care-related prevention is done during routine management of chronic diseases, case finding of smokers without obvious health complaints or threshold symptoms is generally poor. There is still a large percentage of “healthy” smokers not targeted in the treatment room, indicating there is still a world to be won.

The general practitioner has an important role in disease prevention. It is part of their competence profile (81) and ‘prevention’ is an important topic in the vision statement of general practitioner care in 2022 (63). However, implementation is still lagging behind. Our study and others (82, 83) showed that general practitioners lack time, experience an excessive workload, and are often unwilling to participate in preventive tasks such as smoking cessation (*Chapter 2*). In fact, the vast majority of healthcare providers (77%) believe that smokers are responsible for their own smoking behaviour, instead of smoking being more the result of an addiction which patients begun when they were young (84). General practitioners do not think that motivating smokers to stop is their task, they rather quickly point out that it is important to quit (*Chapter 2*). Although, if a smoking-related illness manifests itself, general practitioners do feel the responsibility to discuss smoking with their patients (*Chapter 2 and 5*). In general, however, their focus remains more on the core business of diagnostics and treatment, instead of lifestyle. A culture change seems necessary in which general practitioners become more proactive and better accept their increasing role in health promotion and prevention.

Effect of general practitioner underestimated

When designing our trial, in our sample size calculation, a big difference was expected between the general practitioner and the practice nurse (*Chapter 3*). The expected quit rates, 35% in the practice nurse group and 20% in the general practitioner group, were based on varenicline studies (38, 39) and an earlier study with nortriptyline and individual counselling (50). Also, during the interviews and meetings with the multidisciplinary advisory group, it became clear that the general practitioner does not want to partake in smoking cessation and only wanted a small role in prescribing medication (*Chapter 2 and 3*). Therefore, the potential benefit of the general

practitioner was expected to be small, as it was assumed they would simply describe pharmacotherapy and not spend any time on behavioural support. On the other hand, from previous research we know that advice to quit from a general practitioner has a small but significant effect on smoking cessation rates (85) and this can be substantially improved by combining the advice with other evidence-based treatments (13, 86-88). It was even shown that minimal counselling from the general practitioner was cost-saving compared to other cost-effective treatments (30). Our trial confirms that no matter how minimal the counselling is, the attention from a general practitioner is very powerful (*Chapter 4*).

General practitioners are the most important source of health authority in primary care. However, other reasons than their status, specific reasons on why general practitioners are so powerful are lacking and there is little evidence on what general practitioners actually do in routine care. We found some indications that general practitioners use a confrontational style (*Chapter 2*) and although this does not seem effective when used by practice nurses (50), it could be that patients accept such style from the general practitioners. Another reason is that general practitioners are in the position to build a trusting and collaborative relationship with their patients (89). It was suggested that patients feel comfortable with their general practitioner to share their struggles with behavioural change, and therefore may be more open to change instead of a specialist doctor (90). Previous research has also shown that patients were more satisfied with their general practitioner when they raised the issue of smoking cessation than those who did not, even if they were patients who were not ready to quit (91). This indicates that not raising the issue of quitting smoking might offer an excuse not to consider.

There is a necessity for empowering the role of the general practitioner in smoking cessation (92, 93). Although they “don’t feel like it” and lack time and confidence in addressing behaviour change (90), their role is substantial. During focus groups, smokers indicated that involvement of the general practitioner would increase their motivation to quit (*Chapter 2*). We know from previous research that even among unmotivated smokers, almost 20% will make an attempt to stop when advised to stop by their general practitioner (94). With very brief advice, it is possible to give general practitioners basic tools which are easy to perform, take only a little amount of time (95) and can be very effective (85, 96). In qualitative studies, general practitioners and patients were enthusiastic about very brief advice (95, 97). About 25% of the smokers were motivated to quit after receiving very brief advice, and smokers not motivated to quit knew that there was help available in primary care when needed (97). Thus, although there is resistance among smokers, when those smokers are ready to quit, they are more likely to go to primary care and get access to evidence-based treatments.

It seems important to look for ways how to integrate very brief advice from general practitioners into clinical practice. In practice, very brief advice involves the following three steps: 1) Ask -ask about the current and past smoking status; 2) Advise – provide information on consequences of smoking and smoking cessation; 3) Act – provide options for additional support and advise on medication (17, 98). This very brief advice could be offered to every patient in an opportunistic and non-confrontational way (96). Even when the patient is not motivated to quit at that time, very brief advice is expected to increase the patient's willingness to quit over time and the patient is more likely to find their way to the general practitioner to undertake a quit attempt with evidence-based strategies (97).

In the Netherlands, the number of people looking for help to stop smoking through their general practitioner has risen sharply from 13,000 in 2015 to 19,000 patients in 2018 (99). A possible reason for this is that medication is only reimbursed in the Netherlands in combination with a smoking cessation programme, such as personal guidance from a general practitioner or a practice nurse. Although change is underway, there is still little emphasis on improving communication skills of general practitioners and other medical professionals. Yet, communication is of utmost importance in the context of patient-centred care and prevention goals. Training courses are currently being developed and evaluated for general practitioners on how to give very brief advice (95, 100-102) and in the United Kingdom there is a free online training available for every general practitioner on how to give very brief advice in practice (98). It was already shown that providing training in smoking cessation treatment can improve the performance of behavioural support and abstinence rates (60, 103). Also, a recent study showed that a single training session with very brief advice can triple the percentage of advice given and cause a sevenfold increase in the supply of support (102). Thus, the scientific evidence about general practitioners being effective in smoking cessation and trainable is there, but the beliefs and attitudes has to be changed as well.

Medication adherence better when assisted by the general practitioner

What C. Everett Koop, a former US Surgeon General, said in 1985 remains true today: "Drugs don't work in patients who don't take them". In order to better understand the potential mediating effect of adherence on quit rates, medication intake was measured using electronic monitoring devices (Medication Event Monitoring System (MEMS®)), pharmacy fill records, and questionnaire data. Electronic monitoring devices are very expensive and require sophisticated data analysis skills (104). However, because it can accurately and precisely track patterns of medication intake (104-107), it is used as a

reference standard for validating other adherence measures (104, 106) and could therefore be seen as the gold standard in measuring medication adherence.

Before the start of our study, we expected that intensive guidance would lead to better medication adherence and therefore to better quit rates. This was based on the assumption that if patients were getting more support, they were more likely to continue the medication, even when experiencing adverse reactions (*Chapter 3*). Adherence has been shown to be an important factor in successful quitting (108-111). Catz et al. (2011) even showed that good medication adherence of varenicline doubled the 6-month abstinence rates (108) and Liberman et al. (2013) showed that abstinence rates nearly doubled when participants were adherent to varenicline in a real-world retrospective cohort study (109). However, both studies might be biased due to reversed causality, as adherence was not assessed prior to relapse (110). Yet, contrary to our expectations, medication adherence with the general practitioner was significantly higher than with the practice nurse (*Chapter 4*). This was despite the fact that the practice nurses were specifically instructed in the treatment protocol to ask about the use of medication (*Chapter 3*). Whether practice nurses did not adhere to the protocol, or whether stimulating medication adherence by the practice nurses did not have sufficient effect, is unknown. On the other hand, it is assumed that general practitioners did not repeatedly emphasised medication adherence, as they regularly see their patients once for a specific prescription. It may be due to the general practitioners' authority that patients take his/her advice very seriously, but also that medication is seen as a task for the general practitioners rather than the practice nurse (*Chapter 2*) (49).

Contrary to our results, a recent Cochrane systematic review found that there was moderate-certainty evidence that intensified behavioural support focusing on adherence improved medication adherence, but evidence that this would result in higher quit rates was less strong (112). Our outcomes were however in line with Cropsy et al. (2016). They found that medication adherence and quit rates were the highest among African Americans who received no counselling, compared to African Americans who received counselling and white Americans who did or did not receive counselling (113). The authors believed that African-Americans, often from disadvantaged groups or with low health literacy, were less familiar with medication use. As a result, they ignored medication use when they received counselling, whereas when they did not receive counselling, they focused on their medication with better quit rates as an effect. In our study we seemed to observe the same situation: the general practitioner group seem to perform better in healthcare centres which were located in neighbourhoods with a lower socio-economic background. However, the trial was not powered to

investigate such dynamics and the collected data was insufficient to correctly distinguish between a higher and lower socio-economic background. Nonetheless, socio-economic background in the form of educational level and income were taken into account in the our adjusted logistic regression analysis. Yet, this is an interesting finding and the impact of socio-economic background should be further evaluated in adherence studies.

In general, medication adherence in smoking cessation remains a problem because of smoker's misperceptions about effectiveness and safety (114, 115). Also for varenicline, the most important reasons for discontinuation were experiencing side effects and believing that 'medication does not work or is not necessary (108). During the start of the trial, the safety of varenicline was questioned (116-120). This could have led to practice nurses being hesitant with the use of varenicline, especially when participants showed adverse reactions. In this light, discussing side effects in an uncertain manner could have increased the attention for the side effects. Paradoxically, the intensive supervision could have led to the advice to stop varenicline, while the lack of supervision from the general practitioner made this a non-issue.

Did we reached the ceiling?

Without treatment, only 5% of the smokers trying to quit achieve long-term abstinence (121). In contrast, smoking cessation attempts in prospective real-life studies assisted by healthcare providers, pharmacological aids or a combination, showed 6-months quit rates ranging from 14% to 39% (122-126). In our study, both groups of healthcare providers showed high rates of prolonged abstinence at 6 months (32%, 39%) and 12 months (26%, 29%) (*Chapter 4*). This would indicate that nearly one out of four patients would probably remain abstinent for the rest of their lives, as a relapse is relatively rare after 12 months (121). The quit rates in both groups in our study are among the highest in prospective real-life studies (122-126), possibly indicating that there is a ceiling effect and that it is impossible or very difficult to achieve a higher level of effectiveness with the current pharmacological aids. It is unsure whether it is possible to attain a higher level of effectiveness and how much effort is needed to achieve this. Maybe, efforts should be targeted on other aspects of the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework (127). For example, increasing visibility and accessibility (reach) of smoking cessation treatments and increase the uptake of evidence-based treatments (implementation and adoption) as they are still underutilized (128-132) for various reasons (*Chapter 2*) (114, 133, 134).

Another reason for our high smoking cessation rates could be the Hawthorne effect. A Hawthorne effect is the phenomenon that people seem to change their behaviour when

being observed, such as in a trial (135, 136). For example, a study showed that subjects who were aware that they were observed, scored significantly better on pain, postoperative measures and psychological well-being compared to subjects who were not aware (136). The Hawthorne effect could be applicable to all participating subjects in the trial, meaning that practice nurses, general practitioners, and patients could have been more committed because they were aware of being part of a follow-up. Although it is unlikely that the Hawthorne effect can be eliminated, awareness of their potential impact remains important. In our case, both treatment groups had the same receptiveness to a Hawthorne effect, therefore not leading to confounding in the between-group analysis, although it could still cause an overestimation of the overall effect. Nevertheless, the Hawthorne effect in our trial is likely to be lower than in more explanatory trial with more intensive follow-up (*Chapter 3*).

Smokers with COPD better treated by the practice nurse

Smoking cessation assistance, targeted specifically on the special needs and circumstances of smokers with COPD might increase the effectiveness of a quit attempt. It seems that smokers with COPD need extra encouragement to undertake a quit attempt. They receive more triggers from their environment to quit, but still report the same number of quit attempts. Also, smokers with COPD are different in that they have higher levels of cigarette dependence and depression, but lower levels of self-efficacy. They also have more difficulties with the social aspect of smoking (*Chapter 5*). Yet, there is no COPD-specific smoking cessation intervention available, while a recent Cochrane systematic review showed that a combination of medication and behavioural support is the only effective treatment (137). We believe that practice nurses are in the best position to give such specific assistance and patient-centred care (138). Whilst support from healthcare providers is important in chronic care management of COPD with regard to their self-confidence, coping and self-care (139), it was shown that general practitioners had negative beliefs about smoking cessation in COPD (92, 140). They felt that smokers with COPD did not take their responsibility, minimised the healthcare consequences, and were dishonest about their smoking habits, which resulted in frustration towards all patients with COPD (92). This ultimately could lead to stigmatisation of patients, patients getting irritated by general practitioners' advice to quit and even to patients refusing care (141). Though the vast majority of smokers is happy about the general practitioners' advice to quit, they believed the advice should be given in an empathetic and patient-centred way (141-143). Although our trial was underpowered to see the effects in a subgroup of COPD patients, the evidence of our survey indicates that patients with COPD might be better off with the practice nurse (*Chapter 5*). Patients were more satisfied with the practice nurse (*Chapter 2 and 4*) and practice nurses

tend to give better patient-centred care (138). Therefore, it might be easier for patients with COPD to try again with the practice nurse instead of the general practitioner if they fail.

Strengths and limitations

Researching the field of smoking cessation in primary care was a challenging but encouraging task. Challenging, because of the hectic daily practice, the negative publications about serious adverse events related to varenicline at the start of the study, and the dilemmas in implementing a pragmatic study. Encouraging, because of the drive of healthcare providers to make healthcare more effective and accessible; the openness of the patients trying to quit; and the shared curiosity about the results. However, as for every scientific undertaking, the work reported has many strengths and limitations, which will be outlined in the next paragraph.

Strengths and limitations of a pragmatic design

One of the main strengths of this work was the integration in routine primary care. Our qualitative research included patients, general practitioners and practice nurses to investigate real-life barriers and solutions for smoking cessation treatment rather than basing our intervention solely on theoretical models. The trial investigated the difference in effectiveness of brief advice from a general practitioner versus intensive counselling from a practice nurse. As a consequence, not only a distinction between two different intensities of behavioural support was investigated, but also the different effects of two healthcare providers. This comparison may seem not logical, but both behavioural treatments were part of current clinical practice, making this basically a contrast between two forms of routine care. Also the survey study comparing patients with and without COPD was performed in the same cooperation of healthcare centres as the other studies, which showed to be beneficial for the response rates.

In general, a distinction between explanatory (efficacy) and pragmatic (effectiveness) studies can be made (144-146). Explanatory trials answer the question whether interventions work under ideal and controlled conditions, while pragmatic studies answer the question whether interventions work with the intended users in real-life conditions (144). A well-known example of an efficacy-effectiveness difference comes from a clinical trial on statins (used in cholesterol treatment) where the authors found that less than 5% of patients experienced adverse events in a trial setting, while this was as many as 20% in the general population (147). This discrepancy was deemed to be due to the exclusion of elderly people and non-participation of women (148).

Another example is a lifestyle intervention that was based on previous explanatory clinical trials and directly applied on a national level (149), but afterwards showed that only little benefit was obtained in real life (150). As it is known that having successful interventions does not warrant its effect into routine care, there is a growing interest in translational research on how to translate the favorable results from clinical research into routine care. Pragmatic research aims to close the gap between research and practice. In order to correctly inform evidence-based medical practice and create useful results for healthcare policy decisions, we performed a pragmatic study on smoking cessation treatment in primary care. An additional advantage of pragmatic studies is that it can lower research costs by making use of existing infrastructures and information systems (151).

Conducting a pragmatic trial was a challenging task, as there is much to take into account. To design our trial as pragmatic as possible, we followed the key features of a pragmatic design: the trial was performed in a relevant setting; a broad patient selection was used with minimal exclusion criteria; recruitment was done via the healthcare centres; a flexible intervention was used and both interventions were part of routine care; research follow-up was as minimal as possible; outcome parameters were clinically meaningful; and an intention-to-treat analysis was used (151). During the preparation we evaluated where we would be on the PRagmatic-Explanatory Continuum Indicator Summary (PRECIS) tool (144) and each of the 10 indicators was discussed in the research team and the multidisciplinary advisory group. Checking the degree of pragmatism was evaluated as proposed in a recent publication by Dal-Ré et al. (2018) (152). Nonetheless, it was difficult to balance between investigating the real-life process and having sufficient data for evaluation of the trial and we cannot rule out a Hawthorne effect for both patients and healthcare providers as discussed before (135, 136).

Bottom-up and co-creation

A bottom-up strategy gives a unique insight into the problems and possible solutions from a user perspective. It allows an individual vision from the healthcare providers and patients present in the field, contributing unique knowledge and experiences in the connection between scientific research and clinical practice. Co-creation with a bottom-up development of healthcare innovations, could decrease the knowledge transition gap or implementation gap and increase the sense of ownership, acceptance and commitment (153). To encourage this, we meaningfully involved relevant stakeholders such as patients, general practitioners, practice nurses and policy makers early on in the process of innovation and research design. We firmly believe this enhanced patient enrollment during the study. Our recruitment went faster than expected, even though

the inclusion of patients was reliant on the healthcare centres. The research team knew all the general practitioners and practice nurses by name and there was a low threshold of getting in touch with each other. The easy communication with the healthcare centres may also have led to a high response rate from the patients, even if they started smoking again, leading to a low attrition bias.

Generalisability

The goal of performing a pragmatic trial is giving relevant results for real-world populations. One of the key aspects is to enroll participants that are representative for the real-world populations as being the intended users of the intervention, resulting in a heterogeneous patient population. This, in contrast with explanatory controlled clinical trials, where the inclusion and exclusion criteria help to define a very specific patient population (154). In our trial, smokers aged 18 years or older and daily smokers at the time were included and only participants with contra-indications for varenicline at the moment of randomisation were excluded. However, because the information was in Dutch and the research team was Dutch, this could lead to a threshold for patients with a migrant background. Non-native speakers of Dutch and patients with a migrant background are often patients with a lower socio-economic status and because smoking is a greater problem in patients with a lower socio-economic status (155), this could lead to this group being under-represented. However, eligible patients could still participate with help of a relative in the consultations with the practice nurse or general practitioner. In our study, patients with low socio-economic status were well represented (*Chapter 4*), indicating a fairly good generalisability of results.

Healthcare centres as randomisation factor

Participants were recruited from 10 general practices covering populations with a range of sociodemographic characteristics in Eindhoven, the Netherlands. We choose for randomisation on an individual level, because a cluster randomised trial would lead to an unnecessary greater complexity in design, logistics, analysis and a larger sample size, as the locations may have unknown confounding effects related to the locations (156). To prevent and check for contamination, the participants were coded in their Electronic Medical Record (EMR) as a participant in the trial so that participants from the general practitioner group would not be treated by the practice nurse during the 6-month follow-up for smoking cessation, and vice versa. Also, participants from the same family were paired and randomised in the same treatment group to avoid spill-over from the different interventions.

Safety of varenicline

At the start of this thesis, varenicline was still a relatively new drug; it had been available in Europe since 2006. The results were very promising, as varenicline was more effective in clinical trials than placebo and bupropion (38, 39) and it was the only effective pharmacological option in patients with COPD after 12 months (157). However, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have added warnings about serious psychological events (116, 117) and there have been national and international publications warning healthcare providers about the possible cardiovascular and psychiatric health consequences of varenicline (118-120). Moore et al. (2011) even suggested that varenicline was unsuitable for use in primary care (118). As a result, the healthcare providers in our study started worrying about the safety of their patients, which could lead to a lower (and therefore slower) inclusion rate of participants. However, due to the friendly personal contact, the general practitioners reached out to the researchers how they should interpret the studies and this resulted in a sufficient confidence to continue the trial. At the end of our trial, we analyzed the most severe reported symptoms and side effects in our questionnaire. These were: 1) abnormal dreaming (17.5%); 2) nausea (17.1%) and; 3) increased appetite (16.4%). Only 8.2% of the participants reported severe depressive disorders, 4.5% severe anxiety, 4.1% severe panic reactions and 3.3% severe suicidal thoughts (*Chapter 4*). This was in line with previous clinical trials (38, 39).

Meanwhile, various studies have been performed about the safety of varenicline (158-162). Two studies used a large primary care database with unrestricted inclusion of patients and evaluated serious adverse events in more than 164,000 patients from the general population (159) and more than 14,000 patients with COPD (158). Both studies did not find an increased risk of cardiovascular events, depression or self-harm in the general population nor in patients with COPD of varenicline compared to NRT (158, 159). Also, the FDA is confident that varenicline is safe to use and that the risk of serious mental side effects is lower than initially expected. There is still an increased risk, especially in patients with current or previous mental illnesses such as depression, anxiety disorder or schizophrenia, but those side effects did not have serious health consequences such as hospitalisation or even death (117).

Implications

Primary care can play a key role in reducing the prevalence of smoking. The results support the important role for practice nurses and general practitioners in smoking cessation, and provide an evidence base for successful management in general practice. However, the general practitioner should have the motivation, skills and the confidence to engage in lifestyle counselling, such as smoking cessation. There are still benefits to be gained in training general practitioners in very brief advice. Ideally, general practitioners should first deliver a strong message to quit, give information about the health risks and benefits, and recommend and prescribe medication. Then the practice nurses could deliver additional counselling, provide education and support and offer follow-up contacts. Whether additional counselling is given, and how intensive this counselling is, should be tailored to the individual patient. For example patients with COPD need extra counselling and a COPD-specific smoking cessation intervention could be developed. Furthermore, evidence on frame-tailoring information to the desired communication style, could give tools to further personalised care. Although the added value of this strategy has yet to be investigated, it seems sensible that both healthcare providers can empower each other. One could use the authority of the general practitioner, and the skills of the practice nurse for practical counselling in smoking cessation.

This research showed that a culture change is necessary for primary care for smoking cessation treatment to be successful. Healthcare providers should become more proactive and accept their important role in health promotion and prevention. General practitioners should discuss smoking cessation with every smoking patient, and when a more intensive treatment is needed, the patient should be referred to the practice nurse. The practice nurse should receive more practical training in communication skills and education to improve their knowledge of pharmacological treatment. In practices without a practice nurse, the general practitioner can still play an important factor in motivating smokers to quit. Special attention is needed for patients with COPD, because they differ in some characteristics from patients without COPD. Besides that the only effective treatment for patients with COPD is a combination of pharmacological and behavioural treatment, the practice nurse is in the ideal position to learn more on the differences between patients with and without COPD and target them during the routine management of COPD.

The enactment of the practice nurse is successful but still ongoing. They are effective, cost-effective in general and provide the same quality of care as general practitioners and patients are usually very satisfied with the care given. Nurses tend to work together

with the doctors as a team, rather than alongside doctors, whether they function as supplements or substitutes. Not only in the context of smoking cessation is the effectiveness and the cost-effectiveness an interesting area of research, but also in the shifting of workload and reducing the pressure of healthcare systems in general. Overall, practice nurses function very well in the provision of smoking cessation treatment.

Although efficacy trials are highly desirable, before bringing an intervention into routine care, one should understand if and how interventions work under usual care circumstances. We found that a pragmatic design in primary care is feasible, especially when using co-creation during the preparation phase.

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Summary

Summary

Smoking is a leading cause of illness and premature death. It increases the risk of developing cancer, cardiovascular diseases and chronic obstructive pulmonary diseases (COPD). In order to reduce premature death from non-communicable diseases, a substantial number of smokers would have to make a quit attempt and the success rate of quit attempts would have to be significantly improved. Due to the efforts of implementing a comprehensive tobacco control strategy, the overall smoking rate successfully dropped to 26% in Europe and 19% in the Netherlands in 2017. However, the downward trend from the last decade seems to be slowing down.

It is important to improve smoking cessation strategies. Primary care is a key player in smoking cessation on an individual level, due to its strategic and unique position in healthcare. Primary care has a wide reach into the population, it is easily accessible for smokers, it is a familiar environment and there is access to professional and effective help. Several national and international guidelines for primary care are available in order to improve clinical practice. Most guidelines recommend that every smoker visiting a general practitioner is advised to quit and treatment is offered to those motivated to quit, preferably a combination of behavioural and pharmacological support. Nonetheless, the uptake of evidence-based treatments for smoking cessation remains low.

Behavioural support and pharmacotherapy are effective treatments for smoking cessation. There is evidence that combining both forms is most successful, and therefore this is advised in guidelines. Effective behavioural treatments include brief general practitioner advice and counselling. Recommended pharmacological options include nicotine replacement therapy, bupropion and varenicline. Varenicline is the most effective single pharmacological aid and the only documented effective pharmacological aid for long-term smoking cessation in smokers with COPD. Though, at the time of starting this thesis, there was yet no compelling evidence for the combination of varenicline with behavioural treatment.

The prevalence of tobacco smoking in patients with COPD is higher than in patients without COPD. Among people with COPD 35% smokes compared to 22% among people without COPD. Yet, smoking cessation is the only evidence-based intervention that reduces the risk of developing COPD and slows down the progression of the disease. It is assumed that this group of smokers experience more difficulties with quitting than smokers without COPD. However, smoking cessation interventions are not tailored to

the needs of patients with COPD, while there are indications that they have different needs regarding smoking cessation.

Practice nurses were introduced in the Netherlands to facilitate the work of the general practitioner. They are expected to cost-effectively manage chronic illnesses and perform health promotion tasks such as smoking cessation treatment. Evidence shows that practice nurses and other trained nurses in primary care provide the same or even higher quality of care compared to the general practitioner. Although the evidence about their effectiveness in smoking cessation treatment is lacking, they are expected to become important game changers in smoking cessation opportunities alongside the general practitioner. Their role and potential benefit should be further evaluated.

We believed that a better understanding was needed why smoking cessation treatments are underutilized in primary care. We therefore started by exploring barriers and solutions of smoking cessation treatment in Dutch primary care (*Chapter 2*). Like the other studies in this thesis, this study was carried out in The Eindhoven Corporation of Primary Health Care (SGE). We performed a qualitative study and conducted focus groups with 14 patients (smokers and ex-smokers) and semi-structured individual interviews with 9 healthcare professionals (general practitioners and practice nurses). Data analysis was completed by applying the constant comparative method (CCM). Investigating smokers and healthcare professionals simultaneously gave a unique insight into the challenges of current daily practice and provides practical solutions. The results showed that smokers and healthcare professionals seem to be waiting for each other to start the smoking cessation conversation. Barriers were the lack of awareness regarding the available smoking cessation treatments at the healthcare centre among smokers and the resistance against preventive tasks among healthcare professionals. Our study also showed that general practitioners did not fear to jeopardise their doctor-patient relationship, but quitting was regarded as the smokers' own responsibility. While practice nurses and smokers preferred pharmacological aids, general practitioners were somewhat hesitant. Proposed solutions were that general practitioners advised smokers to quit and prescribed medication, while the practice nurse delivered the intensive behavioural support.

The results of *Chapter 2* emphasised the importance of investigating the effectiveness of behavioural treatments for smoking cessation by the practice nurse, as they seem to fulfil an important role in the treatment of smoking cessation, but research on this subject is scarce. As a combination treatment is advised in guidelines and smokers preferred the support of medication, behavioural treatment from the practice nurse

should be combined with a pharmacological aid. Varenicline was the best available option, and more evidence about the combination treatment and the effectiveness in the general population is urgently needed. Especially since most studies on combination therapies investigated nicotine replacement therapy, as there were no varenicline studies available yet. Therefore, there was no evidence that combining varenicline with intensive behavioural counseling was effective.

Our goal was to develop a quality improvement within SGE and to evaluate the added-value of the practice nurse within the “COMbining VAreNicline with Counselling” (COVACO) trial. *Chapter 3* provides an extensive description of the design of the trial towards the effectiveness of the practice nurse versus general practitioners, both in combination with pharmacotherapy. It also gives a full overview of the components of the practice nurse's treatment protocol, providing insight into the potentially effective mechanisms of action. The treatment protocol was based on evidence of effective behavioural change techniques and was developed with SGE's multidisciplinary advisory team. Some effective elements of the treatment protocol were the preparation of the (future) ex-smoker identity and biomarker feedback. *Chapter 3* also shows how we have balanced ourselves between the various objectives: conducting a good randomised controlled trial, carrying out the study as pragmatically as possible and improving the quality without compromising the generalizability of the results. We used the PRagmatic-Explanatory Continuum Indicator Summary (PRECIS) wheel in order to evaluate how pragmatic the trial was. Although some decisions made the process less pragmatic, it was still pragmatic in nature and therefore more likely to produce generalizable results.

We hypothesized that practice nurses are more effective than general practitioners in helping smokers quit, since they have more time to support patients during their quit attempt. Also, Dutch practice nurses are likely to be better trained in giving smoking cessation assistance than general practitioners, so they should have the necessary knowledge and skills to help patients quit. A second hypothesis was that more intensive support of patients and more emphasis on treatment compliance would lead to better adherence of pharmacotherapy. Previous research has shown a strong association between good medication adherence and smoking abstinence, therefore adherence was expected to be a mediating factor in favor of the practice nurse. To measure medication intake, electronic monitoring devices (Medication Event Monitoring System (MEMS®)) were used, which could be seen as the gold standard in measuring medication adherence. A third hypothesis was that, although practice nurses spent more time with their patients leading to higher costs, the cost-effectiveness was better for the practice nurse when compared to the general practitioners.

The primary research question of the COVACO trial was whether individual counselling by a practice nurse increased prolonged abstinence rates compared to usual care. The trial was a multi-site, two-group, parallel, pragmatic randomized controlled trial which was performed in the ten healthcare centers from SGE. At that time, there were approximately 65,000 patients registered in SGE. After a shorter inclusion period than planned, a total of 295 adult daily smokers (mean age=48 years; mean cigarettes/day=19) were allocated to individual counselling by a practice nurse (intervention group) or brief advice by a general practitioner (control group) (*Chapter 4*). Both treatment modalities were combined with 12 weeks open-label varenicline. The primary outcome was prolonged biochemically validated abstinence from week 9 to 26 after treatment initiation. All randomized patients were included in an intention-to-treat analysis, meaning that all patients were analysed according to the group they were randomized. We used a multiple logistic regression model with a categorical variable for healthcare centre and a dummy variable for treatment group.

Of the 149 patients in the practice nurse group, 48 (32.2%) achieved prolonged abstinence, compared with 57 out of 146 patients (39.0%) in the general practitioner group. This resulted in an odds of 0.71 (95% confidence interval (CI)=0.44-1.16), indicating that there was no significant difference between abstinence rates in both groups. A secondary outcome of 12-months abstinence also indicated that the practice nurse was not more effective than the general practitioner (OR=0.84, 95%CI=0.50-1.43), and values of the Bayes factor supported this finding.

Other secondary outcomes involved good dosing adherence (>80% days taken) and incremental costs per life year gained. The odds of good dosing adherence was lower in the practice nurse group than in the general practitioner group. Of the 123 patients with complete data, 56 (45.5%) had a good dosing adherence compared with 67 out of 121 (62.0%) (OR=0.45, 95%CI=0.26-0.77). Because abstinence rates did not differ significantly, it was not possible to perform a mediation analysis to investigate whether good dosing adherence has a mediating effect on abstinence. The total costs of pharmacotherapy, consultations with the practice nurse and consultations with the general practitioner were €39,379 in the practice nurse group versus €32,273 in the general practitioner group, resulting in -€416.10 incremental costs per life year gained.

We concluded that among people seeking help to stop smoking in their general practice, there was no difference in prolonged abstinence rate between intensive practice nurses counselling and one-off brief advice from the general practitioner. We also found that medication adherence was significantly better with the general practitioner, although

reasons why are unknown. Although both treatment are cost-effective in terms of avoided mortality, morbidity and costs of care for smoking-related diseases, the general practitioner was more cost-effective than the practice nurse.

As mentioned earlier, patients with COPD are of special interest since smoking cessation is the most important preventive measure and treatment. Although smokers with COPD seem to differ in smoking characteristics than smokers without COPD, there is yet no COPD-specific smoking cessation intervention. To understand whether or not this is justifiable, we performed a cross-sectional study, comparing smokers with and without COPD on factors associated with smoking and quitting (*Chapter 5*). Different reasons were considered why smokers with COPD do not successfully quit. In order to make a good comparison, twice as many smokers without COPD were matched - based on age-, sex- and healthcare - to all smoking patients with a recorded diagnose of COPD. In total, 107 smokers with COPD responded compared to 86 smokers without COPD. Although the number of quit attempts was similar in both groups, smokers with COPD reported higher levels of depression, higher levels of cigarette dependence and lower levels of self-efficacy, maybe resulting in less successful quit attempts. They also were more concerned about the health risks of smoking as they experienced and understood the health consequences of their smoking behaviour better than smokers without COPD. Although smoking for pleasure was the main reason to smoke in both groups, there was a difference in that socializing and smoking for a mental/or physical energy boost were important reasons to smoke for smokers with COPD. They also experience smoking more as a habit than smokers without COPD, corresponding with higher levels of nicotine addiction. We concluded that smokers with COPD differed from smokers without COPD, and that smoking cessation assistance should targeted the special needs and circumstances of smokers with COPD. During behavioural treatment extra attention is needed for potential depressive symptoms, high nicotine dependence, low self-efficacy and the social environment. Practice nurses are in the position to give such assistance and patient-centred care.

In this thesis we wanted to gain knowledge about the enactment of the practice nurse for smoking cessation and understand the added value of practice nurse counselling versus brief advice from the general practitioner when using pharmacotherapy. We also wanted to contribute to the evidence on the combination of behavioural treatment and varenicline. In the general discussion (*Chapter 6*) we consider our findings and elaborate on: the contribution of the practice nurse in terms of quality, patient satisfaction, workload, and cost-effectiveness; the powerful contribution of the general practitioner for smoking cessation; the effectiveness of varenicline in combination with behavioural treatment; the added value and challenges of pragmatic trials; and the need

for tailored interventions, especially for patients with COPD. To conclude, this thesis showed that primary care plays a key role in reducing the smoking prevalence as prolonged abstinence rates were high among both groups. Nevertheless, a cultural change seems necessary as healthcare professionals should accept their role in health promotion and prevention. If smokers are ready to quit, one can use a combination treatment of pharmacotherapy such as varenicline and a behavioural treatment by the practice nurse or the general practitioner. Practice nurses can deliver more intensive and personal counselling if the patient considers it desirable, and maybe they can contribute to a COPD-specific smoking cessation intervention in the future. Although the development of the practice nurse is ongoing, it has been shown that they can be an important component in the provision of smoking cessation treatment besides the general practitioner.

Samenvatting

Samenvatting

Roken is een belangrijke oorzaak van ziekte en vroegtijdig overlijden. Het verhoogt het risico op kanker, hart- en vaatziekten en chronische obstructieve longziekten (COPD). Om de doelstelling van de Wereldgezondheidsorganisatie (WHO) te halen die is gericht op een vermindering van het aantal voortijdige sterfgevallen door zogeheten “niet-overdraagbare” aandoeningen met 25% in 2025, zou een aanzienlijk aantal rokers moeten stoppen en zou het succespercentage van die pogingen moeten verbeteren. Mede dankzij de inspanningen van de WHO en nationale regeringen om een uitgebreid tabaksontmoedigingsbeleid te voeren, zijn de totale rookcijfers in 2017 met succes gedaald tot 26% in Europa en 19% in Nederland. De neerwaartse trend van het afgelopen decennium lijkt echter te vertragen.

Het is belangrijk strategieën te ontwikkelen die rokers helpen te stoppen. De eerstelijnsgezondheidszorg vormt hierin een belangrijke schakel vanwege haar strategische en unieke positie in de gezondheidssector. De huisartsenpraktijk heeft een groot bevolkingsbereik, is laagdrempelig toegankelijk voor rokers, het is een vertrouwde omgeving voor rokers en er is professionele en doeltreffende hulp beschikbaar. Voor de eerste lijn zijn verschillende nationale en internationale richtlijnen beschikbaar die handvatten bieden om de behandeling van stoppen-met-roken te verbeteren. De meeste richtlijnen adviseren dat elke roker die een huisarts bezoekt het advies krijgt om te stoppen en dat behandeling wordt aangeboden aan degenen die gemotiveerd zijn. Een andere aanbeveling is dat de behandeling bij voorkeur een combinatie van gedragsmatige en farmacologische ondersteuning is. In de praktijk krijgen rokers echter niet vaak het advies om te stoppen met roken en wordt er onvoldoende gebruik gemaakt van wetenschappelijk-ondersteunde behandelingen.

Gedragsmatige ondersteuning en farmacotherapie zijn effectieve behandelingen om te stoppen met roken die kunnen worden ingezet in de huisartsenpraktijk. Er zijn aanwijzingen dat een combinatie van beide vormen het meest succesvol is, en dit wordt ook door richtlijnen geadviseerd. Effectieve gedragsmatige behandelingen zijn onder meer een kort stopadvies van de huisarts of intensieve gedragsmatige ondersteuning (counseling) van de praktijkondersteuner. Aanbevolen farmacologische opties zijn onder meer nicotinevervangende middelen, bupropion en varenicline. Varenicline is het meest effectieve geneesmiddel en, samen met de nicotine sublinguale tablet, het enige

geneesmiddel waarvan bewezen is dat het effectief is bij het stoppen met roken op lange termijn bij rokers met COPD. Ten tijde van het starten van dit proefschrift, was er echter nog geen overtuigend bewijs voor de combinatie van varenicline en een gedragsmatige behandeling.

De prevalentie van roken is bij patiënten met COPD hoger dan bij patiënten zonder COPD. Van de mensen met COPD rookt 35%, tegenover 22% van de mensen zonder COPD, terwijl stoppen met roken de enige bewezen effectieve interventie is die de kans op het ontwikkelen van COPD vermindert en de progressie van de ziekte vertraagt. Interventies voor stoppen-met-roken zijn echter niet afgestemd op de behoeften van patiënten met COPD, terwijl er wel aanwijzingen zijn dat zij andere kenmerken hebben. Aangenomen wordt dat deze groep rokers meer moeilijkheden ondervindt bij het stoppen met roken dan rokers zonder COPD.

In Nederland werden praktijkondersteuners geïntroduceerd, met als doel het ontlasten van de huisarts en het verbeteren van de patiëntenzorg. Er werd verwacht dat zij op kosteneffectieve wijze patiënten met chronische aandoeningen konden begeleiden en gezondheidsbevorderende taken konden uitvoeren, zoals de behandeling van stoppen-met-roken. Hoewel het bewijs over hun effectiviteit bij de behandeling van stoppen met roken ontbreekt, wordt verwacht dat zij een belangrijke rol kunnen vervullen in de mogelijkheden om te stoppen met roken. Er zijn aanwijzingen dat praktijkondersteuners en andere opgeleide verpleegkundigen in de eerstelijnszorg bij bepaalde taken dezelfde of zelfs een hogere kwaliteit van zorg leveren in vergelijking met de huisarts. Hun rol en potentiële voordeel bij de behandeling van rookverslaving moeten echter verder worden geëvalueerd.

Wij waren van mening dat het belangrijk was om onderzoek te doen naar de redenen waarom er onvoldoende gebruik wordt gemaakt van de mogelijkheden voor stoppen-met-roken in de huisartsenpraktijk. Daarom werd begonnen met een onderzoek naar de belemmeringen en potentiële oplossingen van de stoppen-met-roken-zorg in de dagelijkse praktijk en de rol van de praktijkondersteuner (*Hoofdstuk 2*). Net als de andere studies in dit proefschrift, werd dit onderzoek uitgevoerd binnen Stichting Gezondheidscentra Eindhoven (SGE). We deden een kwalitatieve studie waarin gebruikt werd gemaakt van focusgroepen met 14 patiënten (rokers en ex-rokers) en semigestructureerde individuele interviews met 9 zorgprofessionals (huisartsen en praktijkondersteuners). De data werd geanalyseerd met de Constant Comparative Methode (CCM). Het gelijktijdig onderzoeken van patiënten en zorgprofessionals gaf een uniek inzicht in de uitdagingen van de huidige dagelijkse praktijk en bood

praktische oplossingen voor dit probleem. De resultaten toonden aan dat patiënten en zorgprofessionals op elkaar lijken te wachten om het gesprek over stoppen-met-roken aan te gaan. Andere belemmeringen waren het gebrek aan bewustzijn over beschikbare interventies voor stoppen-met-roken in de huisartsenpraktijk en de weerstand tegen preventieve taken onder zorgverleners. Tevens toonde het onderzoek aan dat huisartsen niet bang zijn om hun arts-patiëntrelatie op het spel te zetten en dat stoppen-met-roken wordt gezien als de eigen verantwoordelijkheid van de patiënt. Terwijl praktijkondersteuners en patiënten de voorkeur gaven aan farmacologische hulpmiddelen, waren huisartsen hier enigszins terughoudend in. De ideale situatie was volgens patiënten en zorgverleners dat huisartsen rokers adviseerden om te stoppen met roken en medicatie voorschreven, terwijl de praktijkondersteuner intensievere gedragsmatige ondersteuning leverde.

De resultaten van *hoofdstuk 2* benadrukten het belang van onderzoek naar de effectiviteit van gedragsmatige behandelingen voor stoppen-met-roken door de praktijkondersteuner. De praktijkondersteuner werd geacht een belangrijke rol te vervullen, echter was onderzoek hiernaar schaars. Ook omdat in richtlijnen een combinatiebehandeling wordt geadviseerd en rokers de voorkeur geven aan medicatie, zou gedragsbehandeling door de praktijkondersteuner gecombineerd moeten worden met een farmacologisch hulpmiddel. Varenicline was de best beschikbare optie, en meer wetenschappelijk bewijs over de combinatiebehandeling en de effectiviteit in de algemene bevolking was dringend nodig. Vooral omdat in de meeste studies naar een combinatie van behandelingen gebruikt werd gemaakt nicotinevervangende middelen en er nog geen studies beschikbaar waren over varenicline.

Naast onderzoek was het de doelstelling om een zorginnovatie binnen SGE te ontwikkelen en de toegevoegde waarde van de praktijkondersteuner te evalueren in het kader van de "COmbining VArenicline with Counselling" (COVACO) studie. *Hoofdstuk 3* geeft een uitgebreide beschrijving van de opzet van de studie, waarin de effectiviteit van de praktijkverpleegkundige wordt vergeleken met de huisarts, wanneer de inzet van beide zorgprofessionals wordt gecombineerd met farmacotherapie. Ook wordt een volledig overzicht gegeven van de onderdelen van het behandelprotocol van de praktijkondersteuner, wat inzicht geeft in de mogelijk werkzame onderdelen van de behandeling. Het behandelingsprotocol was gebaseerd op wetenschappelijk-ondersteunde gedragsveranderingstechnieken en ontwikkeld met het multidisciplinaire adviesteam van SGE. Enkele effectieve elementen van het behandelprotocol waren de voorbereiding van de (toekomstige) ex-roker identiteit en biomarker-feedback. *Hoofdstuk 3* laat ook zien hoe we moesten balanceren tussen verschillende doelstellingen: het uitvoeren van een goede gerandomiseerde

gecontroleerde studie, het zo pragmatisch mogelijk uitvoeren van de studie en het uitvoeren van een zorginnovatie zonder afbreuk te doen aan de generaliseerbaarheid van de studieresultaten. Wij hebben gebruikt gemaakt van de PRagmatic-Explanatory Continuum Indicator Summary (PRECIS) methode, om te kunnen evalueren hoe pragmatisch het onderzoek was. Hoewel sommige beslissingen het proces minder pragmatisch maakten, was het nog steeds pragmatisch van aard en daardoor meer waarschijnlijk om generaliseerbare resultaten te produceren.

Onze hypothese was dat praktijkondersteuners effectiever zouden zijn dan huisartsen in stoppen-met-roken, omdat zij meer tijd hebben om patiënten te ondersteunen tijdens hun stoppoging. Ook zijn praktijkondersteuners beter opgeleid in het geven van hulp bij het stoppen met roken dan huisartsen, waardoor zij de nodige kennis en vaardigheden hebben om patiënten te helpen met stoppen. Een tweede hypothese was dat intensievere ondersteuning van patiënten en meer nadruk op therapietrouw zou leiden tot betere therapietrouw van medicatie en een hogere langdurige abstinentie. Eerder onderzoek heeft een sterke associatie aangetoond tussen goede medicatietrouw en stoppen-met-roken, daarom werd verwacht dat therapietrouw een mediërende factor zou zijn in het voordeel van de praktijkondersteuner. Om therapietrouw van medicatie te kunnen evalueren, werd gebruik gemaakt van elektronische monitoring (Medication Event Monitoring System (MEMS®)). Deze kan worden gezien als de gouden standaard voor het vaststellen van medicatie-therapietrouw. Een derde hypothese was dat de kosteneffectiviteit van praktijkondersteuners beter was in vergelijking met huisartsen, ondanks de hogere kosten bij de praktijkondersteuners doordat ze meer tijd aan hun patiënten zouden besteedden.

De primaire onderzoeksvraag van de COVACO studie was of individuele begeleiding door een praktijkondersteuner leidde tot een hogere langdurige abstinentie in vergelijking met gebruikelijke zorg. De studie betrof een pragmatische gerandomiseerde gecontroleerde studie die werd uitgevoerd in de tien gezondheidscentra van SGE. Op dat moment waren er ongeveer 65.000 patiënten geregistreerd bij SGE. Na een kortere inclusieperiode dan gepland, werden in totaal 295 volwassen, dagelijkse rokers (gemiddelde leeftijd=48 jaar; gemiddelde sigaretten/dag=19) toegewezen aan individuele counseling door een praktijkondersteuner (interventiegroep) of kort advies door een huisarts (controlegroep) (*Hoofdstuk 4*). Beide behandelmogelijkheden werden gecombineerd met 12 weken open-label varenicline. De primaire uitkomstmaat was langdurige biochemisch gevalideerde abstinentie van week 9 tot 26 na aanvang van de behandeling. Alle gerandomiseerde patiënten werden opgenomen in een intention-to-treat analyse. Alle patiënten die niet beschikbaar waren voor follow-up, werden

geclassificeerd als rokers. We gebruikten een meervoudig logistisch regressiemodel met een categorische variabele voor gezondheidscentrum en een dummy variabele voor behandelgroep.

Van de 149 patiënten in de groep van de praktijkondersteuner waren er 48 (32,2%) na 6 maanden langdurig gestopt, in vergelijking met 57 van de 146 patiënten (39,0%) in de groep van de huisarts. Dit resulteerde in een odds ratio (OR) van 0,71 en een 95% betrouwbaarheidsinterval (BI) van 0,44-1,16, wat aangeeft dat er geen significant verschil was tussen de abstinentiepercentages in beide groepen. Een secundaire uitkomst van 12-maanden abstinentie gaf ook aan dat de praktijkondersteuner niet effectiever was dan de huisarts (OR=0,84, 95%BI=0,50-1,43). Waarden van de Bayes-factor waren onder of dichtbij 1/3, wat deze bevinding ondersteunde.

Secundaire uitkomsten betroffen medicatie-therapietrouw en bijkomende kosten per gewonnen levensjaar. De kans op een goede medicatie-therapietrouw (>80% ingenomen dagen) was lager bij de praktijkondersteuner dan bij de huisarts. Van de 123 patiënten met volledige gegevens hadden 56 (45,5%) een goede medicatie-therapietrouw bij de praktijkondersteuner, in vergelijking met 67 van de 121 patiënten (62,0%) (OR=0,45, 95%BI=0,26-0,77) bij de huisarts. Omdat de stoppercentages niet significant verschillend waren, was het niet mogelijk om te kijken of een goede therapietrouw een mediërende factor was voor abstinentie. De totale kosten van farmacotherapie, consulten met de praktijkondersteuners en consulten met de huisarts bedroegen €39.379 in de groep van de praktijkondersteuner en €32.273 in de groep van de huisarts, wat resulteerde in een verschil van -€416,10 bijkomende kosten per gewonnen levensjaar in het voordeel van de huisarts ten opzichte van de praktijkondersteuner.

Wij concludeerden dat voor mensen die hulp zochten bij het stoppen met roken in de huisartsenpraktijk, er geen verschil was in het percentage langdurige abstinentie tussen intensieve begeleiding door praktijkondersteuners en eenmalig kort advies van de huisarts. We constateerden ook dat de medicatie-therapietrouw significant beter was bij de huisarts. Ondanks het feit dat beide behandelingen kosteneffectief waren in termen van het verminderen van mortaliteit, morbiditeit en zorgkosten voor aan roken gerelateerde ziekten, was de huisarts kosteneffectiever dan de praktijkondersteuner.

Zoals eerder vermeld, is het voor patiënten met COPD belangrijk om te stoppen met roken omdat dit de belangrijkste preventieve maatregel en behandeling is. Hoewel rokers met COPD andere roken-gerelateerde kenmerken lijken te hebben dan rokers zonder COPD, bestaat er nog geen COPD-specifieke stoppen-met-roken-interventie. Om

de verschillen in kaart te brengen, is een cross-sectionele studie uitgevoerd, waarin rokers met en zonder COPD werden vergeleken op kenmerken die gerelateerd waren aan stoppen-met-roken (*Hoofdstuk 5*). Er werd gekeken naar verschillende redenen die mogelijk konden verklaren waarom rokers met COPD moeilijker kunnen stoppen. Om een goede vergelijking te kunnen maken, werden twee keer zoveel rokers zonder COPD gekoppeld - op basis van leeftijd, geslacht en gezondheidszorg - met alle rokende patiënten met een geregistreerde diagnose COPD. In totaal reageerden 107 rokers met COPD en 86 rokers zonder COPD. Hoewel het aantal stoppogingen in beide groepen vergelijkbaar was, rapporteerden rokers met COPD hogere niveaus van depressie en nicotineafhankelijkheid en lagere niveaus van eigen-effectiviteit. Dit zou kunnen resulteren in minder succesvolle stoppogingen. Rokers met COPD waren ook meer bezorgd over de gezondheidsrisico's van roken omdat zij de gevolgen van hun rookgedrag voor de gezondheid beter begrepen dan rokers zonder COPD. Hoewel roken voor het plezier de belangrijkste reden was om te roken in beide groepen, was er een verschil in die zin dat het sociale aspect van roken en roken voor een mentale en/of fysieke energieboost belangrijke redenen waren om te roken voor rokers met COPD. Zij ervaarden roken ook meer als een gewoonte dan rokers zonder COPD, wat overeenkomt met hogere niveaus van nicotineverslaving. Wij concludeerden dat rokers met COPD verschillen van rokers zonder COPD, en dat hulp bij het stoppen met roken gericht moet zijn op de speciale behoeften en omstandigheden van rokers met COPD. Tijdens een gedragsmatige behandeling is extra aandacht nodig voor mogelijke depressieve symptomen, een grotere nicotineafhankelijkheid, een lage eigen-effectiviteit en de invloed van de sociale omgeving. Wij geloven dat praktijkondersteuners geschikt zijn om deze begeleiding te geven.

In dit proefschrift wilden we kennis opdoen over de inzet van de praktijkondersteuner bij stoppen met roken in de huisartspraktijk en inzicht krijgen in de meerwaarde van intensieve gedragsmatige counseling van de praktijkondersteuner in vergelijking met kort advies van de huisarts. Ook wilden we bijdragen aan de evidentie over de combinatiebehandeling van gedragsbehandeling en varenicline. In de algemene discussie (*Hoofdstuk 6*) staan we stil bij onze bevindingen en gaan we in op: de bijdrage van de praktijkondersteuner in termen van kwaliteit, patiënttevredenheid, werkdruk en kosteneffectiviteit; de sterkte invloed van de huisarts bij stoppen-met-roken; de effectiviteit van varenicline in combinatie met gedragsbehandeling; de meerwaarde en uitdagingen van pragmatische trials; en de noodzaak van interventies op maat, vooral voor patiënten met COPD. Uit het onderzoek in dit proefschrift, blijkt dat de huisartsenpraktijk een sleutelrol speelt bij het terugdringen van de prevalentie van roken omdat de langdurige stoppercentages bij beide groepen hoog waren. Desalniettemin lijkt een cultuuromslag noodzakelijk, omdat zorgprofessionals hun rol

in gezondheidsbevordering en preventie zouden moeten accepteren. Als rokers klaar zijn om te stoppen, kan men bij voorkeur een combinatiebehandeling aanbieden van farmacotherapie, zoals varenicline, en een gedragsbehandeling door de praktijkondersteuner of de huisarts. Praktijkondersteuners kunnen intensievere en persoonlijkere begeleiding geven als de patiënt dat wenselijk vindt, en wellicht kunnen zij in de toekomst bijdragen aan een COPD-specifieke stoppen-met-roken-interventie. Hoewel de ontwikkeling van de praktijkondersteuner nog in volle gang is, is wel aangetoond dat zij, naast de huisarts, een belangrijke rol spelen in het aanbieden van behandelingen op het gebied van stoppen met roken.

Valorisation

Valorisation

Valorisation has been formulated as the third core task of universities, alongside education and research. It is the translation of scientific knowledge into practice, making it accessible to society. With the pragmatic design used in this thesis and the intensive cooperation with The Eindhoven Corporation of Primary Health Care (SGE), we endorse the importance of making scientific knowledge accessible and more directly applicable in healthcare. The knowledge gathered in this thesis will be discussed throughout this valorisation addendum in four sections: societal and economic relevance, target groups, products and the innovative value.

Societal and economic relevance

The burden of smoking-related diseases on society is enormous. Smoking increases the risk of developing cancer, cardiovascular and pulmonary diseases (1, 2) and is the leading cause of illness and premature death worldwide (3). For example, the vast majority of cases of lung cancer and chronic obstructive pulmonary diseases (COPD) are caused by smoking (4, 5). In fact, tobacco is a legal product that kills almost half of its users if used as intended (6). Of the total burden of disease in the Netherlands (expressed in Disability-Adjusted Life years Lost), 9.4% can be attributed to smoking (7). This makes smoking one of the most important preventable risk factors for serious health consequences. In 2019, 584,600 people in the Netherlands had COPD and it was the fourth greatest contributor to the national burden of disease (8). Smoking also represents an enormous economic burden for society. In the Netherlands alone, the costs of smoking-related care amounted to €2.4 billion in 2015 and COPD care to about €912 million in 2017 (8).

Besides having a huge impact on health, smoking is also a major contributor to inequality of health and mortality. Tobacco use accounts for about a third of the difference in life expectancy between those with lower and higher education (9). For example, the risk of dying from lung cancer was about three times higher for people with a lower education than for people with a higher education (10) and people with a lower socio-economic status are also more likely to develop COPD and even to die from it (11). Positively influencing health for all people is a shared responsibility of society and therefore an important topic when it comes to smoking.

Giving up smoking is the most effective way to prevent premature disability and death and the only effective way to slow down the worsening of COPD (5, 12, 13). Yet, one out of five adults in the Netherlands still smoke (6) and the number of smokers is even higher among patients with COPD (14). Although 80% of the smokers want to quit or feel they should (15), the Dutch 'Continuous Survey of Smoking Habits' showed that only 23% of all smokers received quitting advice and less than 5% was referred to behavioural treatment (16). Besides the fact that the number of quit attempts should be improved, also the use of evidence-based treatments should increase to further decrease the number of smokers. Therefore, it is of utmost importance for societal, economical and health inequity reasons that smokers and especially smokers with COPD are supported in their attempts to quit smoking. We will discuss what primary care can do to successfully reduce smoking.

Target groups

Primary care

As explained and shown in this thesis, primary healthcare is an important key player in smoking cessation at the individual level, due to its strategic and unique position in the health sector. Healthcare providers in primary care have the skills and knowledge to support smokers to quit (17-20), especially in countries where a large percentage of smokers regularly visit their general practitioner. In the Netherlands, primary care has complete coverage of the population and has therefore a good reach into the community. Among 80% of the smokers visit their primary healthcare centre each year (16).

General practitioners and practice nurses

All primary care healthcare professionals, such as physiotherapist, dentists and home nurses have an important role in smoking cessation. However, this thesis focusses on the role of the general practitioner and practice nurse in primary care. Both healthcare providers are important target groups for the dissemination of our research results. The first study we conducted was exploratory in nature, in order to get an idea of current routine care. It revealed that smoking cessation is a difficult topic to discuss in the consulting room and that especially general practitioners have a certain aversion to this type of primary prevention. Yet, the results of our trial showed that general practitioners and practice nurses are both very effective in offering smoking cessation, when their counseling is combined with pharmacotherapy (*Chapter 4*). This information should be a stimulus for healthcare providers to increase the use of combined smoking cessation treatment.

We found that patients and caregivers have a strong preference for smoking cessation assistance from the practice nurse (*Chapters 2 and 4*) as they would have more time to spent, would be better educated in giving smoking cessation treatment and could provide more personalised care. It appeared however, that practice nurses were not more effective than general practitioners in providing smoking cessation support (*Chapter 4*). This was an interesting finding, since both the health professionals and we had expected that the practice nurse would be more effective. This makes the dissemination of research results even more important, because currently the practice nurse is often considered to be more effective. Nevertheless, it is important to acknowledge that the practice nurses achieved high effectiveness rates (32% at 26 weeks and 26% at 52 weeks). This thesis provides a scientific basis for their involvement in smoking cessation assistance and an encouragement to engage the nurse practitioner for smoking cessation support.

The strongest aspect of our research is that we evaluated interventions in a routine care setting, which makes the results very applicable to other primary care settings. Routine care means that general practitioners can give brief advice to quit smoking as they would normally do, and provide pharmacotherapy. The practice nurse can offer more intensive counselling with a least one session for preparing a quit date and providing pharmacotherapy. The total number of counselling sessions that a practice nurse can provide can fluctuate based on the needs of the patient and insights of the practice nurse, with a maximum of 120 minutes (*Chapter 3 and 4*). Because both treatment modalities were part of routine care and are already described in the practice guidelines (21, 22), we believe that no extra training or adjustment is needed to implement these results in other primary care settings in the Netherlands. Another benefit of our research is that our results may increase general practitioners' and practice nurses' confidence in their own abilities. Actively helping smokers to quit in primary care could help to increase the number of successful quit attempts.

As explained before, health inequality between those with a lower and higher socioeconomic status is to a large extent caused by smoking. Smoking inequalities emerge mainly in early adolescence under the influence of friendship networks (23), while later in life, these existing inequalities are worsened by differences in quit rates (24). Although this thesis does not address this issue in detail, we would like to mention the importance of developing targeted smoking cessation treatments that meet the specific needs of patients with a lower socioeconomic background. General practitioners and nurse practitioners can also contribute to closing the health inequality gap by discussing smoking or other lifestyle factors in the consultation room, especially for those with a disadvantaged background. People of higher socioeconomic status are

often more able to ask for help themselves, while those with lower socio-economic status have lower self-efficacy (25). Because a large percentage of smokers visit their primary healthcare centre annually, we believe that they have the potential to reach this particular group.

Guideline developers

Our research can inform Dutch and international stop-smoking guidelines general practitioner and the practice nurse. At the start of this thesis, there was no evidence about the effectiveness of the practice nurse in smoking cessation treatment. Our results provides a strong foundation for their involvement in smoking cessation. Also, our outcomes support the use of a combination therapy of counselling with varenicline. Varenicline was fairly new and not yet evaluated in routine care. The results of our trial were also published in a Cochrane Systematic Review evaluating additional behavioural support as adjunct to pharmacotherapy (20).

Chapter 5 provides an overview of differences between smokers with and without COPD. This indicates that smokers with and without COPD should be treated differently, which is currently not mentioned in the guidelines, which state that both types of smokers should be advised to quit, during their regular visits and smokers with COPD also during their routine COPD management check-ups. However, the type of help that is needed is not specified. A recent Cochrane review found that a combination of behavioural treatment and pharmacotherapy is the only effective treatment for smokers with COPD (26). Although there was no convincing evidence for a particular form of behavioural treatment (26), we firmly believe that the practice nurse could give better smoking cessation assistance which is targeted specifically on the special needs and circumstance of smokers with COPD. Yet, this has to be developed and investigated further.

One of the main barriers of implementing smoking cessation assistance in primary care, seems the resistance of general practitioners to talk about smoking cessation and the unawareness of smokers that smoking cessation assistance is available in their primary care centre. Despite the availability of the smoking cessation guideline from the Dutch College of General Practitioners (21), many general practitioners do not seem to comply with the recommendations in this guideline (16). More attention could be paid to the effectiveness of very brief advice in guidelines. Our results show the power of the general practitioner, even when their time is limited. Nonetheless, despite evidence of their effectiveness, effort is needed to overcome the obstacles of implementing evidence-based medicine in daily practice.

Services

In the Netherlands, smoking cessation assistance is fragmented and there are no widely implemented services for treating nicotine addiction. Therefore, smokers depend mainly on the services provided by their primary care centre. Yet, as explained in *Chapter 2*, patients are often not aware that smoking cessation assistance is available in their primary healthcare centre. Also from a healthcare providers perspective, there are certain barriers to start the discussion on smoking cessation, such as a lack of time and experience. Practice nurses are a way to address this gap, as they prove to be good substitutes for general practitioners (27).

Another possibility is to look at the Stop Smoking Services in the United Kingdom, which are able to provide practical support and pharmaceutical treatments on prescription, often free of charge. This service was established in 1999 to target disadvantaged smokers (28). The advantage is that the treatment of smoking cessation is offered by trained professionals, which could be a solution for the lack of time. Although we showed that general practitioners and practice nurses can offer good care as well, we do see promise in such comprehensive service, since implementation of practice guidelines is open to improvement.

Complete reimbursement of stop smoking aids could improve accessibility of professional and evidence-based help to quit, especially for those with a lower socioeconomic background. For example, pharmacotherapy in our trial was freely available for patients included in our study, and the proportion of patients with lower socioeconomic background was fairly high.

Trainers and curriculum

Although the recently published 'Toekomstvisie huisartsenzorg 2022' pays attention to indicated and care-related prevention (29), we found that general practitioners were not confident in providing smoking cessation assistance and also trained practice nurses said they would like more training (*Chapter 2*), despite their already high effectiveness rate. A short course is currently available on the website of the National Health Service United Kingdom (NHS UK), and courses are developed in the Netherlands and Germany (30, 31), but those are specially developed for general practitioners. Nonetheless, in our view, curricula of medical training should focus more on the preventive task of the general practitioner and should teach medical students how to give brief advice on smoking, but also on topics like weight gain or other lifestyle matters. It seems especially important to train healthcare professionals how to address the subject in a non-compulsory way.

Products

It was found that smokers with COPD differed from smokers without COPD, in that they reported higher levels of depression, higher levels of cigarette dependence and lower levels of self-efficacy. They also experienced smoking more as a habit and viewed smoking more as a social engagement than smokers without COPD. Therefore, we believe that smokers with COPD have special needs regarding smoking cessation. Smoking cessation assistance, targeted specifically to the needs and circumstances of smokers with COPD might increase the effectiveness of a quit attempt. Because general practitioners have negative beliefs about smoking cessation for patients with COPD, we believe that practice nurses are in the best position to give such specific assistance and patient-centred care. Also, a special counselling programme for smokers with COPD could be developed, since there is no COPD-specific smoking cessation intervention available. More research is needed to define the content of this special intervention for smokers with COPD and a separate guideline.

Innovative value

Pragmatic study design

The aim was to conduct a pragmatic study in which the research results were relevant to the real world situation. There are several examples of interventions that worked well in a very controlled setting, but did not maintain their effectiveness in the real world. Also for healthcare providers, it is important to have the trust that the evidence they build upon is transferable to routine care. In order to design our trial, we followed the main characteristics of a pragmatic trial (32, 33). It was shown in this thesis that conducting a pragmatic trial within a primary care centre is feasible and produces valuable results. However, a good description of the trial is of utmost importance and the Pragmatic-Explanatory-continuum Indicator Summary (PRECIS) showed to be a good method for this (*Chapter 3*). As far as we know, we were one of the first authors to use the PRECIS tool to justify our decisions and to check whether the trial was as pragmatic as we thought it would be. Although conducting a pragmatic trial is challenging, we would like to recommend researchers to consider a pragmatic design and to test the pragmatism with the PRECIS tool.

Open dialog between science and practice

Researchers are often blamed for being stuck in their ivory tower and for developing ideas and theories that do not work in daily practice. Although the rationale behind those ideas and theories are often very good, it is important to check whether the ideas

are feasible in real-life. While science is viewed as a top-down approach, the opposite is a bottom-up approach in which the ideas are derived from practice. We prefer to view the development of our trial as an open dialog between science and practice, rather than bottom-up or top-down. Yet, using a bottom-up approach at the start of this thesis, showed us a unique insight into the barriers and possible solutions from a user's perspective. It allowed for a unique view from healthcare professionals and patients, contributing valuable knowledge and experience. Also, co-creation with a bottom-up development of healthcare innovations, or the conduct of research increased the sense of ownership, acceptance and commitment. We firmly belief that the bottom-up and co-creation approach enhanced the patient enrolment and decreased the attrition rate. Therefore, we would recommend other researchers to use a pragmatic design and keep patients and caregivers involved.

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The background of the page is a dark-to-light gradient, transitioning from a deep charcoal grey on the left to a bright, almost white light on the right. Scattered throughout this gradient are numerous small, white, petal-like shapes, some of which are slightly blurred, giving the impression of petals falling or floating through the air. The overall effect is soft and ethereal.

Dankwoord

Dankwoord

Een thesis schrijven doe je niet alleen. Vele mensen rondom mij hebben bewust of onbewust een kleine of grote bijdrage geleverd aan de uitvoering van deze thesis. Ik wil daarom graag van de gelegenheid gebruik maken om hen te bedanken voor hun steun, inzet en/of inspiratie. Voor mij persoonlijk is dit een langdurig proces geweest van inmiddels meer dan 10 jaar. Het was een tijd met mijlpalen en successen, maar ook met vertwijfeling en een constante strijd om de balans te vinden tussen andere banen, promotie en zeker ook privé. Heel veel dank dus aan de mensen die een onverminderd vertrouwen hebben gehad in een goede afloop.

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gelukt. Alle onderzoeken die in dit proefschrift geschreven zijn, zijn gebaseerd op data die verzameld werden in SGE. Daarnaast was onze samenwerking intensief vanwege de jaarlijks terugkerende rapportages met zorgindicatoren. In het bijzonder wil ik nog Annelies, Robert en Katinka bedanken, met wie ik altijd een zeer prettig en intensief contact heb gehad

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Curriculum Vitae and Publications

Curriculum Vitae

Carolien van Rossem was born on July 30, 1984, in Dirksland, The Netherlands. She was a daughter of Erik and Chris van Rossem-Dierckx, and sister of Sarah and Hilde.

On completion of her secondary education at the Pleincollege Eckart in Eindhoven, she started Physiotherapy at Fontys Hogescholen in Eindhoven in 2002. She qualified as physiotherapist and started working for several years in two practices in Schijndel. Then, after enjoying travelling through Australia with Sebastiaan, Carolien starts the Master of Sports and Physical Activity Interventions at Maastricht University. Carolien completed her master thesis at the Department of General Practice under supervision of Mark Spigt and André Knotnerrus. In 2010, this resulted in a position as a PhD candidate in smoking cessation research in general practice. In 2015, the official appointment at Maastricht University was coming to an end and she started working in various research positions.

Carolien is happily together with Sebastiaan van der Tas. They have four children Pieter (2014), Florian (2015), Eveline (2017) and Jasmijn (2018) and live a beautiful life on their farm in Best with many, but never enough, animals.

Publications

Van Rossem C, Spigt MG, Kleijisen JRC, Hendricx M, van Schayck CP, Kotz D. Exploration of barriers and solutions in current daily practice from the perspective of smokers and healthcare professionals. *Eur J Gen Pract* 2015; 21(2): 111-117

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