Portfolio of Doctorate in Health Psychology

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Submitted in fulfillment of the requirement of the degree

DOCTORATE IN HEALTH PSYCHOLOGY

(POST-CHARTERED "TOP UP" DEGREE)

City University London

School of Social Sciences

Submitted June 2012

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ACKNOWLEDGEMENTS

I have been indebted in the preparation of this portfolio of evidence to my supervisor, Dr Hayden McRobbie, who despite being on the other side of the world has always made time for me. His knowledge and expertise has been invaluable. I am also extremely grateful to Professor Peter Hajek for all his help.

My parents, Keith and Suzanne, and my sisters, Frances and Vicky, have been a constant source of support. I am very lucky to have you all.

And last but not least, my husband Neil, thank you for all your support and for making me smile every day.

DECLARATION

I grant powers of discretion to the University Librarian to allow the thesis to be copied in whole or in part without further reference to the author. This permission covers only single copies made for study purposes, subject to normal conditions of acknowledgement.

PORTFOLIO ABSTRACT

The current portfolio is presented in support of the post-chartered "Top-up" Doctorate in Psychology degree. This portfolio comprises of 3 parts; ***Part 1 -*** a ***research project*** looking at the efficacy of a combination treatment regimen for smokers (which will be referred to throughout the portfolio as the thesis), ***Part 2 -*** a ***systematic review*** looking at the effectiveness of smoking cessation interventions in acute care and ***Part 3*** - two ***case studies*** reflecting my professional practice which looks at the current clinician and patient perspective of using a combination of treatments in smoking cessation and a reflection on conducting research in an academic setting.

Part 1 describes a randomised placebo controlled trial; designed to answer the principal question of whether using a combination of varenicline and nicotine patches reduces post-quitting urges to smoke more than varenicline alone. The study found no difference in post quitting urges between the active and placebo patch groups.

Part 2 is a systematic review that was commissioned by the National Institute of Clinical Excellence (NICE) to review the available evidence concerning the efficacy of different types of smoking cessation interventions in acute care settings. Results from a meta-analysis showed that for interventions with hospital patients to be effective, an extended period of support and stop smoking medication provided for over 4 weeks after discharge is recommended.

Finally, ***part 3*** is a series of case studies looking at current clinician practice in prescribing combination nicotine replacement therapy (NRT) in UK stop smoking services (UK-SSS); a patient perspective of using combination NRT and varenicline and a reflection on my current clinical practice which gives some insight into my day-to-day role as a practicing health psychologist.

These parts are independent of one another but all reflect practice in the field of smoking cessation.

GLOSSARY OF TERMS AND ABBREVIATIONS

AD	Alzheimer's disease
AE	Adverse event
ALA	American Lung Association
BCT	Behaviour change techniques
BID (bis in die)	Twice daily
BPS	British Psychological Society
CI	Confidence interval
CO	Carbon Monoxide
COPD	Chronic Obstructive Disease
CPsychol	Chartered Health Psychologist
CQC	Care quality commission
CR	Conditioned response
CRF	Client record forms
CVD	Cardiovascular disease
CWS	Cigarette Withdrawal Scale
DNCs	De-nicotinised cigarettes
DoH	Department of Health
DPsych	Professional Doctorate in Psychology
DSM	Diagnostic and Statistical Manual
E-C	Electronic cigarette
FTND	Fagerström Test for Nicotine Dependence
GABA	Gamma aminobutyric acid
GCP	Good clinical practice
GRAND	Global research awards for nicotine dependence
GSK	Glaxo Smith Kline

HAD	Health Development Agency
HCPs	Healthcare professionals
HIS	Heaviness of Smoking Index
HTA	Health Technology Assessment
IMP	Investigational Medicinal Product
ITT	Intention to treat
JRO	Joint Research Office
KG	Kilograms
MHRA	Medicines and healthcare products regulatory agency
MNWS	Minnesota Nicotine Withdrawal Scale
MPSS	Mood and Physical Symptoms Scale
NA	Nucleus accumbens
nAChRs	Nicotinic acetylcholine receptors
NCSCT	UK National Centre for Smoking Cessation and Training
NHS	National Health Service
NHS-SSS	National Health Service Stop Smoking Services
NICE	National institute of Clinical Excellence
NIHR	National Institute for Health Research
NRES	National research ethics service
NRT	Nicotine Replacement Therapy
OR	Odds ratio
PBC	Perceived behavioural control
PCT	Primary Care Trust
PD	Parkinson's disease
PDG	Programme development group
PRIME Theory	Plans, responses, impulses, motives and evaluations

QMUL	Queen Mary University of London
R&D	Research & Development
RCT	Randomised control trial
RCT	Randomised controlled trial
REC	Research Ethics Committee
RPS	Relapse prevention service
SAE	Serious adverse event
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SS	Shiffman Scale
SUSAR	Serious unexpected serious adverse reaction
SUTS	Strength of urge to smoke
SWAP/WAP	Peer support weight action programme
SWQ	Smoking Withdrawal Questionnaire
TDRU	Tobacco Dependence Research and Treatment Unit
TMF	Trial master file
TPB	Theory of Planned Behaviour
TQD	Target quit date
TTFC	Time to first cigarette
TWS	Tobacco withdrawal syndrome
UC	Ulcerative colitis
UK	United Kingdom
USDHHS	United States Department of Health and Human Services
VBA	Very brief advice
VTA	Ventral tegmental area
WSWS	Wisconsin Smoking Withdrawal Scale

PREFACE

The preface provides an overview of the portfolio of evidence presented in support of the Professional Doctorate in Psychology (DPsych) (Post-chartered) degree. It begins by outlining my previous training as a trainee health psychologist and introduces the structure of the portfolio, which comprises of three independent parts (a research project (thesis), a systematic review and two case studies). My work experience as a health psychologist has been discussed alongside a summary of the clinical studies and the grant applications I have been involved in. Finally, an overview of how this portfolio has allowed me to use all the skills I have been developing over the last few years, which illustrates my skills as a practicing health psychologist.

Background to undertaking the Doctorate in Psychology Degree

Since completing my stage 2 training I have continued to work as a health psychologist at the Tobacco Dependence Research and Treatment Unit (TDRU); the unit is part of the Wolfson Institute of Preventive Medicine at Queen Mary University of London (QMUL) (further details of the unit can be found in Chapter 5).

Stage 2 training is a vocational degree for trainee psychologists who wish to conduct applied research and further their teaching, supervisory and consultancy skills. The training is supported by the British Psychological Society (BPS). The qualification is undertaken via two routes, university or independent. The university route is a full time lecture-based degree, which leads to the award of Doctorate in Psychology (DPsych). The independent route is the appointment of an external supervisor (a chartered health psychologist) who supervises the work of the trainee. The trainee will usually remain in their place of work (a health care setting) in order to complete the training. The award granted is chartered status as a health psychologist (CPsychol). Both routes involve the submission of a portfolio of evidence that reflects the trainees experience in 5 core areas; teaching, ethics, research (thesis project and systematic review), expert opinion and consultancy. The difference between the two routes is that the independent route trainees are not awarded the doctorate degree, as it is not undertaken with the support of a university.

In 2009 I submitted my portfolio of evidence and after a viva voce I was awarded the title of chartered health psychologist (CPsychol).

Professional Doctorate in Psychology (DPsych) ("Top-up" post-chartered degree)

The current portfolio is presented in support of the post-chartered "Top-up" post-chartered DPsych degree, which includes evidence of undertaking a research project, a systematic review and two case studies reflecting my current practice as a chartered health psychologist. The portfolio comprises of 3 parts; ***Part 1 -*** a ***research project*** looking at the efficacy of a combination treatment regimen for smokers (which will be referred to throughout the portfolio as the thesis), ***Part 2 -*** a ***systematic review*** looking at the effectiveness of smoking cessation interventions in acute care settings and ***Part 3*** - two ***case studies*** reflecting my professional practice which look at the current clinician and patient perspective of using a combination of treatments in smoking cessation and a reflection on conducting research in an academic setting. These parts are independent of one another but all reflect practice in the field of smoking cessation. A bibliography is included at the end of each part. Appendices for all parts are contained at the end of the portfolio.

Research experience

I have now been involved in eleven clinical trials which have given me the opportunity to develop my skills, not only collecting data but with data analysis and writing for publication. During my time on the DPsych course I have published twelve papers (see Table 1) and been involved in a number of projects, which are detailed below.

Table 1 – K, Myers publications (current-2009)

Author/Title	Journal	Impact factor	Citations
Myers, K., McRobbie, H. West, O. & Hajek, P. (2013) Smoking cessation interventions in acute and maternity services: Review of barriers and facilitators.	***National Institute for Health and Clinical Excellence (NICE)***	NA	NA (due to be released November 2013)
Myers, K., McRobbie, H. & Hajek, P. (2013) Smoking cessation interventions in acute and maternity services: Review of effectiveness.	***NICE***	NA	NA (due to be released November 2013)
McRobbie, H., Hajek, P. & **Myers, K.** (2013) Review of effects of nicotine in secondary care.	***NICE***	NA	NA (due to be released November 2013)
Hajek, P., McRobbie, H. & **Myers, K.** (2013) Efficacy of cytisine in helping smokers quit: systematic review and meta-analysis.	***Thorax***	6.84	NA (published Feb 2013)
Snuggs, S., McRobbie, H., **Myers, K.,** Schmocker, F., Goddard, J., Hajek, P. (2012) Using text messaging to prevent relapse to smoking: intervention development, practicability and client reactions.	***Addiction***	3.84	1
Myers, K., Hajek, P., Hinds. C. & McRobbie, H (2011) Stopping smoking shortly before surgery and postoperative complications: a systematic review and meta-analysis	***Archives of Internal Medicine***	10.64	32
Myers, K., Hajek, P., & McRobbie, H (2011) What is a reasonable threshold for worries about health risks?	***Archives of Internal Medicine***	10.64	0
Hajek, P., McRobbie, H. & **Myers, K**., Stapleton, J., & Dhanji Al-Rehan (2011) Use of varenicline for four weeks prior to quitting smoking: Effects on ad-lib smoking, post-cessation withdrawal discomfort, and short-term smoking cessation rates.	***Archives of Internal Medicine***	10.64	15
Hajek, P., McRobbie, H. & **Myers, K**., Stapleton, J., & Dhanji Al-Rehan (2011) Is Varenicline effectiveness declining in randomized trials?	***Archives of Internal Medicine***	10.64	0

McRobbie, H. & **Myers, K.** (2011) Continuing Professional Development: Understanding why people smoke and helping them to stop	***British Journal of Wellbeing***.	1.52	0
Hajek, P., **Myers, K.**, Rehan-Dhanji, A., West, O., & McRobbie H. (2011) Weight change during and after Ramadan fasting.	***Journal of Public Health***	1.88	7
Myers, K., West, O. & Hajek, P (2009). Relapse prevention for pregnant women – Review.	**NICE**	NA	NA

1. National Institute for Health and Clinical Excellence (NICE)

In September 2011, NICE announced a tender for systematic reviews in the field of smoking (six in total). The reviews were to be part of a new smoking guideline for acute and maternity services across the UK. My clinical background has been primarily working with inpatient smokers in acute care settings and I have experience of working with pregnant women, which made my expertise very relevant to the tender call and application. Applications to write three of the six reviews were submitted by Professor Hajek, Dr McRobbie and myself. We were successful in our application for all three of the reviews (one of the two papers I led on, which looks at the effectiveness of smoking cessation interventions in acute care settings is presented in ***Part 2*** of the portfolio). My role in the project was to write the proposal, conduct the literature search, systematically screen abstracts for relevant papers, extract data from included papers, data analysis and write up. Each of the three systematic reviews has been presented to the programme development group (PDG) for review who will use the reviews to inform the development of the new guidelines for acute and maternity services. The guidelines are due to be released in November 2013.

2. An open label pragmatic randomised controlled trial of nicotine preloading for smoking cessation (2012)

This randomised control trial (RCT) will examine the relative efficacy, safety and cost effectiveness of standard NHS stop-smoking treatment versus standard treatment plus the use of a nicotine patch worn for 4 weeks prior to quitting. The study has been funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme. This multisite study is being led by Birmingham University; the TDRU is one of four research sites. For this project I have been involved in the Research & Development (R&D) approval at QMUL, planning the logistics of the recruitment and will be involved in data collection. My role on this study is as the research manager, supporting two psychologists who have been recruited to co-ordinate the project. Ethical approval has been granted and recruitment started in September 2012. The outcomes of this trial will indicate whether pre-loading with a nicotine patch before stopping smoking increases abstinence rates. The findings of this trial will have important implications for guidelines and clinical practice. The project is expected to be completed in 2015.

3. Peer support weight action programme (SWAP) (2012)

The proposed study will determine whether a promising group-based weight management program (Weight Action Programme; WAP), targeting underprivileged groups has a long-term effect that is over and above the effect of a 'best practice' weight management intervention that is provided in primary care by practice nurses. The SWAP study is funded by the NIHR HTA programme. I was a co-applicant on the grant application for this project, and I have also had involvement in the protocol development and led on the application to gain ethical approval to conduct the study. I will have the role of research manager for the duration of the trial. Ethical approval has been granted and recruitment started in September 2012, with completion of data collection expected in 2015. The outcomes of this study will provide further insight into

the best methods to approach weight management in the community.

4. Comparison of the effects of the electronic cigarette and nicotine inhalator on tobacco withdrawal symptoms over 24 hours of abstinence (2012)

A randomised cross over study was recently conducted at the TDRU looking at whether the electronic cigarette (E-C) is more effective in alleviating withdrawal symptoms during 24hr abstinence than the nicotine inhalator. My role in this project is to provide guidance with regards to protocol development, ethics, medicines and healthcare products regulatory agency (MHRA) approval processes and R&D requirements for setting up this study. My role in this study will primarily be to support the lead clinician throughout the project. This study began recruitment in January 2013 and data collection is now completed. The data analysis is now being conducted. Results from this study will be important; the study has been designed to further understanding on the role E-Cs may have as a smoking cessation aid.

5. Effects of a combination of varenicline and transdermal nicotine patch on post-quitting urges to smoke (CONVICT) (2011)

CONVICT is an RCT looking at whether combining NRT and varenicline provides better withdrawal and craving relief in the first week of abstinence than varenicline alone. In 2010 an application was made for 2 investigator-initiated grants; TVIN (discussed below) and CONVICT. My role in this project has been to write and review the grant application, protocol development, ethics and MHRA approval and recruitment. I was the research manager on this trial and ran the study on a day-to-day basis. I was the lead in data entry, analysis and write up. The paper will be submitted to a high impact journal, as the results of this study will be of great interest to many in the

smoking cessation field. CONVICT will be presented as the thesis for this portfolio (***part 1***).

6. Effects of a tailored dose of varenicline on post-quitting urges to smoke (TVIN) (2011)

This RCT is investigating whether a tailored dose of varenicline provides better withdrawal and craving relief in the first week of abstinence than a standard varenicline dose. My role in this project has been to write and review the investigator-initiated grant application, protocol development, MHRA and ethics approval and the recruitment of participants. I am the research manager on this trial and oversee two psychologists who run this project on a day-to-day basis. This study is currently recruiting participants. Data collection was completed in February 2013. The results will have important implications on whether the current use of varenicline can be tailored to individual smokers.

7. Complementing current NHS Stop Smoking Service treatment for smokers with behavioural replacement: The role of de-nicotinised cigarettes (2011)

The aim of this study was to see if using a behavioural replacement for smoking (de-nicotinised cigarettes; DNCs), in addition to standard treatment during the first two weeks after the target quit date (TQD), reduces urges to smoke over the first 4-weeks of abstinence. I was a co-applicant on the grant submission and acted as the research manager on this project. The role has involved protocol development, ethics approval and supervision of two psychologists who run the project on a day-to-day basis. The study will provide useful information regarding the use of DNCs as an aid to stopping smoking.

8. Tobacco control health inequalities pilot (2011)

The aim of the project was to present the outcomes of an SMS text-based relapse prevention service enhancement provided to smokers who had successfully stopped smoking. The relapse prevention study was a health inequalities pilot sponsored by the Department of Health (DoH). My role in this project was to develop the protocol and to oversee the psychologist running the project on a day-to-day basis. The findings from the service enhancement were published in ***Addiction*** in 2012. The service enhancement proved acceptable to clients and was easily implemented. The outcomes suggest that it may be a useful, simple and easily implemented addition to the NHS-SSS. The next step will be to evaluate its efficacy in a randomised trial.

9. Stopping smoking shortly before surgery and postoperative complications (2011)

In June 2011, the systematic review I wrote for my stage 2 Health Psychology qualification was published in ***Archives of Internal Medicine*** (impact factor 10.64). The paper has been cited by 32 papers (Myers et al. 2011). The systematic review and meta-analysis examined the existing literature examining postoperative complications in people stopping smoking prior to surgery. The idea for this systematic review came about after witnessing some confusion between different health care professionals (HCPs) over the right advice to give about stopping smoking shortly before an operation. The results indicated that the concern that stopping smoking only a few weeks prior to surgery might worsen clinical outcomes is unfounded. I was the lead author on this review; my role included the development of the search terms, systematic search of the literature for relevant papers, data extraction, data analysis and write up. The conclusions have had an impact on the guidelines that are provided by NICE with regards to provision of smoking cessation advice to postoperative patients. Patients should be advised to stop smoking as early as possible, as there is no current evidence

available to suggest that health professionals should advise smokers not to quit shortly before surgery.

10. Varenicline treatment for four weeks prior to quitting smoking reduces ad-lib smoking and increases smoking cessation rates (2010)

This RCT investigated whether increasing the usual 1-week of pre-quit medication period of varenicline, to 4 weeks, would help alleviate tobacco withdrawal symptoms and facilitate quitting. The study was published in a high impact journal, ***Archives of Internal Medicine*** (impact factor 10.64) and has been cited by 15 other papers (Hajek 2011). Increasing the duration of varenicline use pre-quit, reduced the enjoyment of smoking and generated a substantial reduction on ad-lib smoking prior to quitting. Post quit withdrawal ratings were not reduced as a result of the extra pre-loading of varenicline, however, it did significantly increase 12-week abstinence rates. During this study I was involved in the submission of the grant application, development of the protocol, gaining ethical and MHRA approval, day-to-day management and running of the study including recruitment, data input, analysis and write up. The implications of these findings are that varenicline may be suitable for use in harm reduction, and longer periods of pre-loading are likely to increase the drug's efficacy. We concluded that larger studies with longer follow up periods are needed to further investigate these findings.

11. Acceptability and effects of using protein and completing hunger ratings prior to the evening meal (Protein Pre-load study) (2010)

The protein pre-load study was undertaken to explore whether eating 20g of protein, 30 minutes before eating the evening meal for two weeks would lead to weight loss, compared to not eating protein before the evening meal. My role in this project was to

develop the protocol, gain ethical approval, run the study on a day-to-day basis, data entry, analysis and write up. The results from this study are being analysed. The results will be published to inform future practice in weight management.

12. Weight change during and after Ramadan fasting (2010)

During Ramadan, observant Muslims fast from sunrise to sunset for a month. The study examined whether Ramadan fasting affects body weight. This has implications for health advice give to the Muslim community on the effects of skipping meals on body weight, and for general weight management advice. During Ramadan 2010, the study compared body weight before and after the Ramadan fast and one month later in observant Muslims attending a Mosque in East London, UK. The study was published in ***The Journal of Public Health*** (impact factor – 1.88) and has been cited by 7 other papers (Hajek et al. 2011). My role in this project was to write the protocol, gain ethical approval, the day-to-day running of the project, data collection, data entry, analysis and write up for publication. We found that observers of Ramadan lost on average about a kilogram of weight over 4 weeks, and that the lost weight is quickly regained (within the first month post-Ramadan). Current weight management treatments generally assume that skipping meals leads to weight gain and advise against it. The finding suggests that further research is needed on the justification of the 'do not skip meals' advice.

13. Pilot study on usage patterns of a novel nicotine replacement therapy – A multi-centre, open, 3-week randomized low intervention study of two different directions for use in smokers motivated to quit (2008)

In 2009 the TDRU conducted a commercially funded study looking at a new nicotine delivery system, a nicotine mouth spray, to help people to stop smoking. The study was

a pilot to see if different methods of how to administer the spray would affect its use. My role in this study was to manage and co-ordinate the day-to-day running of this trial. The results indicated that there was no benefit seen between the two directions of use. Nicotine mouth spray is now on the market and is regularly used by smokers during treatment. The study informed our practice for advising people on how to use the product.

Grant applications

As part of the process of conducting studies, I have also been involved in developing and writing protocols for grant applications. I have been a co-applicant for 10 funding applications since 2010, 9 of which were successfully funded.

1. National Institute for Health and Clinical Excellence (NICE) (2011)

As detailed in the previous section, in September 2011, NICE invited tenders for systematic reviews in the field of smoking (6 in total). I was the co-applicant on 3 grant proposals for the tender. I was the lead author on 2 of the protocols submitted; one review looking at the effectiveness of smoking interventions in acute and maternity service users and one on the barriers and facilitators for the same population. The team was successful in the application for all three of the reviews. The project was completed in 4 months and the grant awarded was £100,130.

2. Evaluation of a pilot Tier 3 multidisciplinary weight management service (2011)

I was invited to write a protocol for an evaluation of a pilot weight management programme for City and Hackney Primary Care Trust (PCT). I was the lead author on the protocol. The time frame of the project is 1 year and the project grant was £21,486.

3. A peer-support weight management programme to supplement brief advice in general practice for obese adults from deprived communities (2011)

As detailed in the previous section a grant application was submitted to the NIHR HTA programme for funding for a weight management study (SWAP). I was a co-applicant on this project. The project time frame is 3 years and the grant awarded was £886,741.

4. Tobacco control health inequalities pilot (2011)

Further details for this study are outlined in the previous section. I was a co-applicant for a health inequalities pilot sponsored by the DoH. The service enhancement was an SMS text-based relapse prevention service for smokers who had successfully stopped smoking. The project was completed in 18 months and the grant awarded was £197,850.

5. Effects of a combination of varenicline and transdermal nicotine patch on post-quitting urges to smoke (CONVICT) and 6. Effects of a tailored dose of varenicline on post-quitting urges to smoke (TVIN) (2011)

As detailed in the previous section, an investigator-initiated grant was submitted for funding for 2 trials using varenicline. I was a co-applicant for both grant applications. The CONVICT trial was completed within 1 year and the grant awarded was £148,933. The TVIN trial was completed on 18 months and the grant awarded was £196,429.

7. Complementing current pharmacological treatments for smokers with "sensory replacement": The role of low nicotine cigarettes (2011)

Further details for this study are outlined in the previous section. A grant application was submitted to the Global Research Awards for Nicotine Dependence (GRAND). The study was looking at DNCs as a behavioural replacement for smoking. I was a co-applicant on the grant proposal. The study was completed in 1 year and the grant awarded was £123,463.

Writing and submitting grant applications involves liaising with the funding bodies concerned and also the gaining approvals from my academic institution, QMUL. The processes involved include costing, peer review, protocol design and submitting a clear outline of the proposals aims and applicability (both in terms of the research setting but

also for future impact on services and research). Having the opportunity to be involved in several applications has helped to further develop my skills with regard to writing and submitting grant applications.

OVERVIEW OF PORTFOLIO OF EVIDENCE

Overview of thesis (Part 1)

Background to research project and aims

Varenicline is a popular and widely used non-nicotine treatment option for smoking cessation. Unlike NRT, which are often used and recommended in combination (e.g. using a nicotine patch alongside nicotine chewing gum), varenicline is currently not recommended in combination with any other licensed smoking cessation medications. Combining varenicline and NRT may in theory improve withdrawal relief; help to extinguish smoking rewards and lower the risk of lapses translating into relapse. The research conducted for this doctorate portfolio will look at the efficacy of using varenicline in combination with a nicotine patch and whether this combination regimen reduces urges to smoke 24 hours and 1 week post-quitting.

Methods

A randomised double blind placebo-controlled trial was conducted using a sample of 117 participants. Participants were randomised to use varenicline plus *active* nicotine 15mg/16hr transdermal patch or varenicline plus *placebo* 0mg/16hr patch.

Results

Adding nicotine patch to varenicline had no effect on post-quit urges to smoke or on other cigarette withdrawal symptoms at any time point. There was no effect on abstinence rates at any time point (79% vs 80%, 69% vs 59%, 50% vs 41% and 14% vs 12% at 24 hours, 1, 4 and 12 weeks in the nicotine and placebo patch group, respectively).

Conclusion

The efficacy of varenicline is not enhanced by the addition of nicotine patches.

Overview of systematic review (Part 2)

The guideline developed from this review will not be released until November 2013; the contents of the review remain confidential until its publication.

Background to systematic review

In 2010/11, of the 10 million National Health Service (NHS) secondary care admissions in the United Kingdom (UK), it was estimated that 460,000 were attributed to smoking tobacco (Office of National Statistics 2012). Hospitalisation provides a good opportunity to stop smoking. Such patients are often highly motivated to quit, and hospital admission brings people into direct contact with healthcare professionals who can advise on giving up smoking and offer evidence-based treatment.

Objective

This piece of work was commissioned by the National Institute of Clinical Excellence (NICE) to review the available evidence concerning the efficacy of different types of smoking cessation interventions for hospital patients and their relatives to help guide clinical recommendations for smoking cessation – acute and maternity services guidelines are due to be published in November 2013.

Methods

A systematic search for reviews and randomised controlled trials published between 1990 and December 2011 in the English language was undertaken. Electronic databases were searched including ASSIA, MEDLINE, Cochrane Central Register of Controlled Trials, CINAHL and PsychINFO. A total of 29,083 records were found of which 141

papers were identified for full text retrieval. Seventy-five trials evaluating smoking cessation interventions delivered in acute care settings were found.

Results

Hospitalised smokers – For interventions with hospital patients to be effective, an extended period of support and stop smoking medication provided for over 4 weeks after discharge is recommended. Interventions that are provided face-to-face after discharge may provide better results than support provided over the telephone.

Relatives – There is limited research for this population, however, brief stop smoking interventions with parents of hospitalised children did not show any efficacy in long term abstinence rates.

Hospital staff **–** There is evidence that providing the stop smoking medication bupropion (Zyban) with regular face-to-face support is an effective treatment for hospital staff.

Conclusion

The NHS practice currently involves interventions at bedside accompanied by medications and/or referrals to specialist stop-smoking service for treatment after discharge, which combines extended face-to-face support with smoking cessation medications. The reviewed evidence confirms that this is likely to be the optimal approach.

Overview of professional practice (Part 3)

The first case study also follows the theme of treatments for smoking cessation and provides a clinician and patient perspective on current practices.

There are two parts to the first case study. The first part of the professional practice chapter highlights the clinician view of current practices in combining smoking cessation medications; the section reviews the experience of combination NRT in current practice, which is a licensed and evidence-based combination medication option. The clinician views were taken after a presentation I gave at the "Stop Smoking Live" conference in London in December 2010. The case study is a reflection of my experience of presenting at an educational symposium. The case study also highlights the extent to which combination NRT is recommended in UK clinical practice, barriers to its use for the clinician and client and a discussion on how lessons learnt from current practice could impact on the potential combination of varenicline and NRT in the future.

For the second, patient perspective case studies for this chapter, clients at the smokers' clinic (TDRU) who were using combination treatment (varenicline and NRT) were asked to discuss why they had chosen to do this and what benefit (if any) it gave them. As previously noted, guidelines do not currently advocate the combination of varenicline and NRT due to the lack of evidence on its efficacy. However, anecdotally we know that clients will take it upon themselves to use the medications in combination and report that this is useful in helping them to stop. This piece of work gives some background into how clients attending an NHS stop smoking cessation clinic find the experience of using a combination treatment and discusses some of the potential guidelines for clinicians.

The second case study is a reflection on my current clinical practice, which discusses my day-to-day role at the TDRU. I reflect on some of the key issues when conducting research and some of the things I have learnt over last few years of my involvement in research. An example of a trial I have been involved in is also discussed.

Summary of preface

This portfolio highlights my professional growth as a psychologist and my ability to review emerging data in the field. As a practicing research health psychologist I am now able to use my training and research experience to conduct new and important pieces of research within my areas of expertise in order to help inform and try to improve smoking cessation services and treatment outcome.

As a result of undertaking the stage 2 training and completing my thesis project I have now completed a course with the BPS allowing me to supervise other trainee psychologists. The department I work in has helped me to learn on the job and develop as a psychologist and the potential to supervise and guide other trainees is a great opportunity for me. I hope to use this as part of my continued professional development over the next few years. I hope to continue to promote Health Psychology through the transferring of skills to other psychologists through supervision but also among the community of health professionals, highlighting the importance of psychology in the smoking cessation field.

After completing the DPsych training programme, I will continue in my role as a research fellow and smoking cessation clinician at the TDRU. I am in the privileged position that we are currently able to implement the results we find from our research projects straight into practice. This makes for an extremely interesting standpoint for viewing the effects of new strategies for helping smokers to quit.

In summary, undertaking the doctoral programme has allowed me to use all the skills I have been developing over the last few years allowing me to produce one concise piece of work, which I hope illustrates my skills as a health psychologist. I have had major

involvement in the conduct of eleven clinical studies at the TDRU. My level of skill and expertise is reflected in the 12 papers I have had published and the grant applications I have been awarded. Since qualifying as a Health Psychologist my confidence and ability to operate as a researcher has improved and my level of independence has increased. My continued interest in smoking cessation and behaviour change interventions has led me to continue my career in the field of Health Psychology. I hope to continue to further develop my skills in both research and clinical practice.

PART 1 – EFFECTS OF A COMBINATION OF A VARENICLINE AND TRANSDERMAL NICOTINE PATCH ON POST-QUITTING URGES TO SMOKE

Short title/Acronym: Combination of NRT and varenicline to increase cessation of tobacco (CONVICT study)

CHAPTER 1: GENERAL INTRODUCTION AND BACKGROUND

The strong link between smoking and mortality has now long been established. Almost 6 million deaths are attributed to tobacco, over 5 million of those are current and ex-smokers with around 600,000 deaths attributed to exposure to second-hand smoke (World Health Organization 2011). The importance of tackling smoking prevalence is realised as tobacco use has been highlighted as a risk factor for six of the eight leading causes of death in the world (World Health Organization 2011).

In 2011, over 450,000 hospital admissions were attributed to smoking (Office of National Statistics 2012), this accounts for 5% of all hospital admissions in adults over the age of 35. Smokers typically spend longer in hospital, and are more likely to experience complications (Health Development Agency 2004).

With such high rates of disease and hospital admissions attributed to smoking, the UK DoH continues to view the provision of smoking cessation as a top priority in public health (Department of Health 2011a).

Smoking cessation in the UK

The release of the UK government's white paper on tobacco control (Department of Health 1998); was viewed as a milestone for public health interventions in the UK. Since its release in 1998, smoking cessation and tobacco control in the UK has been a key priority for the National Health Service (NHS). The white paper outlined a

tobacco control strategy including advertising bans and smoke-free legislation. England was one of the first countries to establish a nationwide network of stop smoking services funded by the NHS shortly after the release of the white paper in 1998. The NHS-Stop smoking services (NHS-SSS) aim to provide the most effective interventions for successful smoking cessation which include both pharmaceutical, as well as intensive behavioural support provided by smoking cessation specialists. It is estimated that there are approximately 150 NHS-SSS currently providing stop smoking interventions within the UK (Brose, West, McDermott, Fidler, Croghan & McEwen 2011).

Pharmaceutical treatments in the UK

Currently there are 3 pharmaceutical treatment options available to UK smokers; NRT, bupropion (Zyban) and varenicline (Champix).

NRT

The use of NRT to help smokers trying to stop smoking has been widely available since the early 1990s (Stead, Perera, Bullen, Mant & Lancaster 2008). There are currently seven different NRT delivery systems available on the worldwide market (gum, patch, lozenge, sublingual tablet, nasal spray, inhalator, and mouth spray) and in the UK are available on prescription and over-the-counter (West & Zhou 2007). All of these products work by replacing some of the nicotine that smokers would have otherwise received from their tobacco smoke, thereby reducing tobacco withdrawal symptoms which are commonly seen when stopping smoking (e.g. irritability, depression, restlessness) (Molyneux 2004). There is an abundance of research

showing that the use of NRT increases quitting by up to 50-70%, compared with stopping without any medications (Stead et al. 2008).

Bupropion (Zyban)

Bupropion is an atypical antidepressant that is effective in aiding smoking cessation (Hughes, Stead & Lancaster 2007a). Data from 40 studies of bupropion show that this drug roughly doubles the chances of quitting smoking compared to placebo (Hughes et al. 2007a). Bupropion has over the last few years been used less since the introduction of varenicline to the market.

Varenicline (Champix)

In the last few years a new pharmacological product has been available for smokers; varenicline. Varenicline is a partial nicotinic agonist which acts on α4β2 nicotinic receptors (Cahill, Stead & Lancaster 2012). It is presumed to alleviate withdrawal discomfort, but also to diminish rewarding effects of cigarettes. Varenicline has been shown to increase the success of quitting and some evidence shows a slightly higher success rate when compared to bupropion but the results are slightly less clear for its increased efficacy compared to NRT (Cahill et al. 2012).

It is reported that up to 70% of smokers report wanting to, and many attempt to, stop smoking every year in the UK (Kava 2000). In the year April 2010- March 2011, smoking cessation interventions in England resulted in 780,000 smokers attempting to stop smoking and setting a quit date with 380,000 of those reporting successfully quitting (The NHS Information Centre 2011).

NHS-SSS use the best available evidence-based treatment, but with long-term success rates of about 15% (Ferguson, Bauld, Chesterman & Judge 2005), there remains considerable scope for improvement.

Possible solutions for improving outcomes

It has been suggested that for some smokers the standard doses of stop smoking medication offered may not be adequate to aid a successful quit attempt (Stead et al. 2008). For many illnesses, medications are tailored to the individual (e.g. diabetes, heart disease). However, this is not the standard approach when treating smokers in the UK.

The nicotine dependence centre at the Mayo Clinic, USA, is one of only a few clinics that routinely tailor smoking cessation medications to the individual smoker. The Mayo Clinic approaches patients with severe tobacco dependence on an individual basis, commonly using 3 or more smoking cessation products simultaneously (Hurt, Ebbert, Hays & McFadden 2009). Mayo Clinic patients who manage to reduce cigarettes but who do not stop smoking completely are asked to continue to take their chosen medication but at higher doses and in combination with other products until they completely stop smoking. The current approach, recommended by NICE (NICE 2008), within the UK NHS-SSS is to request the individual takes a break of at least 6 months before resuming treatment in cases where they have been unable to achieve abstinence.

The most common use of "high-dose" medications in the UK services is to use a combination of NRT products, for example, use of a nicotine patch in combination

with an oral product such as nicotine gum. The effectiveness of using combination NRT is well documented and research shows clear benefit for the smoker if they combine NRT products rather than using a single nicotine product to quit (Stead et al. 2008). NRT is currently the only medication option that is recommended in combination by current guidelines (NICE 2008). However, as NRT is freely available in most pharmacies and over-the-counter in the UK, this has enabled many smokers to try different treatment options, not all of which are within current clinical guidelines.

Unlike NRT, varenicline is currently not recommended as a product to be used in combination with other stop smoking medications (i.e. varenicline combined with a nicotine patch), as there is currently no research looking at the efficacy of using such a combination. However, despite no recommendation to use a combination of NRT and varenicline, many smokers who attend the East London Smokers' Clinic choose to use it and anecdotally report benefits from doing so.

For patients who have tried and failed to quit using combination NRT and/or varenicline, there is much discussion among smoking cessation specialists about the possibility that using a combination of varenicline alongside NRT may hold some promise. However, until data is available on the effectiveness of this treatment method then the efficacy of its use can only be speculated.

This proof of principle study is the first randomised control trial to look at whether using a combination of varenicline alongside a nicotine patch reduces withdrawal symptoms post quitting. A positive finding would ultimately lead to a larger randomised trial being conducted before any recommendations would be made to

change standard medication protocols within the NHS-SSS. A negative result would indicate that combination therapy using both varenicline and NRT does not reduce withdrawal discomfort above the use of the medications on their own.

Overview of the thesis

The thesis presented is made up of six chapters. The first theoretical part discusses the health effects of smoking and discusses the health benefits associated with stopping smoking (Chapter 2). A chapter outlining the role of nicotine in tobacco dependence follows this; which includes current definitions and measurements of dependency (Chapter 3). Chapter 4 covers the withdrawal symptoms that are associated with stopping smoking and the measures currently used to measure withdrawal will be discussed.

The current structure of the NHS stop smoking service in the UK will then be presented alongside a detailed description of the most commonly used pharmaceutical treatments that are used by smokers as part of a stop smoking quit attempt (Chapter 5).

Chapter 6 of the thesis presents a double blind randomised trial which aimed to investigate the efficacy of using a combination of NRT (15mg/16hr nicotine patch) and varenicline in a sample of smokers wanting to stop smoking who attended a stop smoking clinic in London, UK. A discussion of the results and conclusions are detailed in this chapter.

Primary Objective

The principal question this study plans to answer is whether the combination of varenicline and NRT reduce post-quitting urges to smoke more than varenicline alone.

CHAPTER 2 - HEALTH RISKS OF SMOKING AND BENEFITS OF QUITTING

This chapter provides background on the prevalence and socio-economic background of smokers in the UK. The negative health consequences associated with smoking tobacco will be discussed alongside the health benefits of smoking cessation.

Who smokes in the UK?

In the UK, smoking initially became popular among young men in the early half of the 20th Century (Wald 1991). It was not until after the Second World War that smoking among women became widespread (Wald 1991). It is now estimated that around 21% of adults in the UK smoke, which equates to around a fifth of the total population (Office of National Statistics 2012). Slightly more men smoke (22%) in the UK compared to women (21%) (Office of National Statistics 2012).

The highest prevalence of smoking is seen in 16-19 and 20-24 year olds (27%), those over 60 years have the lowest prevalence (14%) (Office of National Statistics 2012). Differences in smoking prevalence can be seen among social classes with approximately 33% of those unemployed and very low paid versus only 15% who smoke in professional and managerial occupations (West 2006a). Marital status has an effect on smoking consumption; with those divorced or separated twice as likely to be heavy smokers (20 or more cigarettes) compared with both single and married/cohabiting smokers (12% compared to 6% and 5%, respectively) and three

times more likely than those who are widowed (4%) (Office of National Statistics 2012).

In recent years the UK has made substantial progress in tackling tobacco smoking prevalence; in 2007 it was estimated that over 24% of the population was smoking, compared to just under 21% in 2011 (West & Brown 2012). Since 2008, the decline in cigarette smoking prevalence has averaged 0.5% per year (West & Brown 2012). However, despite this overall reduction in prevalence, the long-term effects of smoking remain.

The effects of smoking on health

The strong link between smoking and mortality has now long been established. Almost 6 million deaths are attributed to tobacco, over 5 million of those are current and ex-smokers with around 600,000 deaths attributed to exposure to second-hand smoke (World Health Organization 2011). The importance of tackling smoking prevalence is realised as tobacco use has been highlighted as a risk factor for six of the eight leading causes of death in the world (World Health Organization 2011).

Approximately 18% of all deaths in adults aged over 35 in the UK are estimated to be caused as a result of smoking (Office of National Statistics 2012). In 2009 over 81,000 deaths in the UK were attributed to smoking (HM Government 2011). It has been estimated that significantly more men in the UK die from smoking related diseases compared to women (23% vs. 14%) (Office of National Statistics 2012). However, this is likely as a result of the male population starting smoking over a decade earlier than the women in the UK (Peto, Darby, Deo, Silcocks, Whitley & Doll 2000). It was estimated to cost the UK NHS £2.7 billion to treat smoking related illnesses in 2006/07 (HM Government 2011).

With such high rates of disease attributed to smoking and the cost implication of treating smokers, the UK DoH views smoking cessation as a priority in public health (Department of Health 2012). The establishment and continued investment into specialist services to help smokers quit is in order to reduce the prevalence of tobacco related illnesses. Smoking cessation has adverse effects on most areas of the body but the most common smoking related diseases are cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD) and cancers of the respiratory system.

Cardiovascular disease (CVD)

Cardiovascular disease (CVD) is a global problem, as it is the leading cause of death and preventable illnesses worldwide (World Health Organisation 2007). It is estimated that 2.8 million men and women in the UK have CVD (NICE 2010a). The prevalence of CVD is estimated to cost the NHS approximately £30 billion annually (Luengo-Fernandez, Leal, Gray, Petersen & Rayner 2006).

CVD is a disease of the blood vessels. Gradual build up of fatty deposits on the walls of the blood vessels cause the artery to narrow (World Health Organisation 2011). This can lead to serious heart problems including stroke, angina and heart attacks. CVD is typically more common in people over the age of 60, and rare below the age of 30 (NICE 2010a). There are several modifiable lifestyle choices that are related to an increased risk of CVD; these include obesity, lack of physical activity and smoking.

Smokers are at an increased risk of suffering from heart disease compared to non-smokers; this is as a result of the effects of smoking which leads to damage to the arteries along with the increased blood pressure and heart needing to "work" harder as a result of smoking (World Health Organisation 2011). Most illnesses caused by smoking are often dependent on how long the smoker has smoked; however, in the case of CVD there is a significant risk of illness even with low levels of smoke exposure (Prescott 2002).

Giving up smoking significantly reduces the risks of CVD (Jha & Landsman 2013). Stopping smoking will halve the risk of CVD after 1 year of abstinence and after 15

years as a non-smoker the risk of having a stroke will be that of a non-smoker (United States Department of Health and Human Services (USDHHS) 1990). There has been some debate raised over whether the associated increase in weight post smoking cessation may negate any positive health gains associated with stopping smoking. A recent cohort study was conducted which tested the hypothesis that weight gain does not attenuate the benefits of smoking cessation in a population of over 3000 patients (Clair, Rigotti, Porneala, Fox, D'Agostino, Pencina & Meigs 2013). Their findings showed a decreased incidence of CVD in those who stopped smoking. Weight gain post cessation was not shown to negate this effect. This supports that the benefit of smoking cessation on CVD risk outweighs any negative effect of possible weight gain post cessation.

In the UK interventions to reduce the prevalence of CVD have been aimed at both the population as well as the individual level (NICE 2010a). Government implementation such as the smoke free law has been shown to reduce the number of hospital admissions for both cardiovascular as well as respiratory conditions, specifically in the UK but also globally (Bauld 2011; Gaudreau, Sanford, Cheverie & McClure 2013).

Chronic obstructive pulmonary disease (COPD)

The World Health Organization (WHO) definition of COPD is a lung disease characterised by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible (World Health Organisation 2011). COPD is estimated to kill approximately 25,000 people per year in England and Wales (National Statistics 2008). It is ranked as the 5th biggest killer in the UK (Department

of Health 2011b). As people get older they are more likely to die as a result of COPD, as the lungs get more obstructed over time (Department of Health 2011b). Diagnosis of COPD is much higher in those over 75 year olds.

COPD is common, with an estimated 3 million sufferers in the UK (Lopez, Shibuya, Rao, Mathers, Hansell, Held, Schmid & Buist 2006). It is estimated that almost 2 million people have COPD, which is yet to be diagnosed (Healthcare Commission 2006).

Smoking is the main modifiable risk factor for COPD. A great majority of the people diagnosed with COPD are either ex or current smokers and would be clinically described as being or having been highly dependent smokers (Menezes, Perez-Padilla, Jardim, Mulno, Lopez, Valdiva, Montes de Oca, Talamo, Hallal & Vicotra 2005). It is usually as a result of smoking that long-term damage to the lungs has been caused, which impairs the flow of air in and out of the lungs and causes breathlessness. Smoking is the main cause of COPD but there is also a link to other harmful fumes found in the work or home environment or exposure to airborne pollution (Menezes et al. 2005).

One of the most important pieces of advice given by health professionals when a smoker is diagnosed with COPD is to stop as soon as possible; this is regardless of the age at which they are diagnosed (NICE 2010b). It is both the most effective treatment as well as the most cost effective (Laniado-Laborin 2009). Although COPD is not fully reversible the damage can be limited and a delay in deterioration of quality of life can be seen, by stopping smoking immediately (NICE 2010). Stopping smoking

reduces respiratory symptoms such as cough, wheeze, and sputum production (Anthonisen, Connett & Kiley 1994). Lung function in those patients who continue to smoke after diagnosis have a much steeper decline than those who stop smoking immediately (Laniado-Laborin 2009).

Current NICE guidelines (NICE 2010b) specify that smoking status and an assessment of desire to quit should be done at least twice per year in those with severe COPD and at least annually with this diagnosed with mild/moderate COPD. With such strong links between COPD and smoking, there is often some stigma associated with its diagnosis. Many people view lung disease as 'self-inflicted'; this is a barrier that needs to be tackled amongst the public as well as some healthcare professionals (DoH 2011b). The current guidance on COPD management highlights this as a major challenge in the treatment of this illness.

Cancers of the respiratory system

It is estimated that 90% of cancers of the respiratory system are caused by smoking (NICE 2010b). Lung cancer is currently the leading cause of cancer death in women in the UK (NICE 2010b). A reduction in the prevalence of men who smoke in the UK has seen their rates of the disease decrease by more than a quarter (NICE 2010b). As the uptake of smoking in women was later in UK women, only now is an increase in lung cancer among women being seen (NICE 2010b).

For a smoker, the risk of developing lung cancer is approximately 15 times that in a non-smoker (Boffetta, Pershagen, Jockel, Forastiere, Gabourieau, Heinrich, Jahn, Kreuzer, Merletti, Nyberg & Rosch 1999). A recent longitudinal study followed 1.2

million UK women over an 8-year period (Pirie, Peto, Reeves, Green & Beral 2013). All participants were asked at follow up to report on their current smoking status and health. The mean age of the participants was 55 years. Results showed that two thirds of all deaths among the women in their 50s-70s were as a result of smoking, mainly from diseases such as lung cancer. Among those who stopped smoking before the age of 40, the risk associated with smoking related mortality was reduced by more than 90% compared with continued smokers.

UK treatment guidelines for lung cancer strongly recommend that the patient be told immediately the effects of continued smoking and that they should be referred for specialist treatment (NICE 2010b). Many smokers are aware of the risk of lung cancer, but are less knowledgeable about cancer of the stomach, pancreas, cervix, kidney, bladder, mouth, lips, nose and oesophagus (US Department of Health and Human Services 2004). Cancer of the bowel and ovarian cancer are now also understood to be caused primarily by smoking (US Department of Health and Human Services 2004).

Smoking to protect health

Research has suggested that there is a protective association between smoking and the onset of Parkinson's (PD) and Alzheimer's disease (AD) (Morens, Grandinetti, Reed, White & Ross 1995). Non-smokers are estimated to be two times more likely to suffer from PD or AD compared to smokers (Fratiglioni 2000). The suggestion is that cigarette smoking has a "neuroprotective" effect (Miller 2007), however the long and short-term health benefits of stopping smoking far outweigh the possibility that the individual may not suffer from PD or AD.

Smoking seems to also be beneficial for ulcerative colitis (UC) (Silverstein, Lashner & Hanauer 1994). UC is an inflammatory disease of the bowel, which is more commonly seen in never smokers and ex-smokers. Smokers who have UC who quit smoking tend to see 'flare ups' in their condition once they stop. Again, the health benefits of stopping smoking for the individual's general health far outweigh continued smoking for prevention of worsening UC symptoms.

Health benefits of stopping smoking

The health benefits of stopping smoking are seen across all age groups, ethnicities and both sexes (USDHHS 1990). Individual risk for developing smoking related illnesses often depends on duration and intensity of smoking and between those with or without pre-existing evidence of disease. The earlier in life cessation occurs the greater the health gains. Those who stop smoking before the age of 35 are expected to have the life expectancy of a non-smoker (Doll, Peto, Boreham & Sutherland 2004). Among UK women it has been shown that the risk of smoking related mortality is reduced by more than 90% if smoking cessation occurs before the age of 40 and more than 97% if stopped before the age of 30 (Pirie et al. 2013). However, stopping in later life is still associated with a reduced risk of premature death.

In a longitudinal study looking at UK smokers since 1950, which found that for men who stopped smoking at ages 60, 50, 40 and 30, the cumulative risks of lung cancer by age 75 were 10%, 6%, 3% and 2% (Peto et al. 2000). Their conclusions were that even stopping smoking into middle age resulted in a significant reduction in their risk for developing lung cancer. Stopping smoking before middle age avoided more than 90% of the risk attributable to smoking tobacco (Peto et al. 2000).

In a similar longitudinal study that started in the 1950s, British doctors who smoked were the population of interest (Doll et al. 2004). Over 34,000 doctors were followed up until 2001. The main outcome was overall mortality by individual smoking habit. The main reasons associated with mortality among the population were vascular, neoplastic and respiratory diseases. Smoking cessation at age 60, 50, 40 or 30 years resulted in an increase in life expectancy by approximately 3, 6, 9 or 10 years. Among

the men born in the early half of the 20th Century, continued cigarette smoking from an early age tripled the specific mortality rates. Smoking cessation at 50 years of age halved this risk and cessation at 30 years avoided almost all of the associated risk (Doll et al. 2004).

Smoking cessation at any age has clear benefits on overall mortality, but for smokers with smoking related illnesses the benefits of cessation are more immediate. Regarding CVD risk, the smoking associated risk of coronary heart disease is approximately halved within the first year of abstinence and the excess risk of suffering a stroke returns to that of a non-smoker after 15 years of abstinence (USDHHS 1990).

The reduction in risk of cancers is generally related to the length of abstinence; e.g. there is a 30-50% reduction in risk of developing lung cancer after 10 years of abstinence, and the risks of oral cancers are halved after five years of cessation (USDHHS 1990).

There are also many immediate effects from stopping smoking; within 20 minutes blood pressure will decrease and pulse rates slow. Carbon monoxide (CO) and oxygen levels in the blood will return to normal after 8 hours without a cigarette.

Along with these physiological benefits there are several other benefits related to health and general well being that are commonly discussed among patients; more energy, better skin complexion, and cigarette staining on fingers and teeth are reduced.

CHAPTER 3 – TOBACCO DEPENDENCE

This chapter outlines the role of nicotine in dependence and how dependence is currently defined and measured. Two theories will be described which will aim to help the reader to understand the nature of tobacco dependence and its complexities when approaching any treatment options.

Tobacco dependence

Before the 1970's smoking was viewed by most as habit and more a lifestyle choice rather than an addiction (USDHHS 1964). This was despite a 1964 surgeon general report that was released which described the harmful effects of smoking (USDHHS 1964). It was not until the late 1970's that nicotine in tobacco was widely accepted as being responsible for dependence on tobacco.

The role of nicotine in dependence

It is now agreed that the primary reason for being a regular smoker is a dependence on nicotine (Balfour 1994, Di Chiara 2000). Most people start smoking in adolescence usually due to social factors (Biglan, McConnell, Severson, Bavry & Ary 1983), such as peer pressure but it has also been suggested that parental attitude rather than behaviour to smoking is also an influence on early uptake (Newman & Ward 1989). Experimentation is common and although many young people do not progress past a few puffs, regular smoking can quickly follow (Balfour, Benowitz, Fagestrom, Kunze & Keil 2000).

Nicotine is synthesised in the roots of the tobacco plant and stored in the leaves (Haustein 2002). Nicotine remains in the tobacco leaf during the curing process and is vaporised when tobacco is burnt. Tobacco smoke is highly effective in transporting nicotine to the lungs where it is rapidly absorbed into the blood, from which it goes to several other organs including the brain (Benowitz 2001). Nicotine reaches the brain within seconds of being inhaled and it is here that it has its main effect (Rose, Behm, Westman & Coleman 1999).

The neural pathway that is involved in 'reward' or the feeling of pleasure is the mesolimbic dopamine pathway, which comprises of the ventral tegmental area (VTA), nucleus accumbens (NA) and prefrontal cortex (Balfour 1994). Nicotine acts on this pathway by binding to, and activating, nicotinic acetylcholine receptors (nAChRs) on dopamine neurons in the VTA (Balfour 1994). It is believed that there are a variety of nAChRs, which are involved in the mediation of nicotine across the brain (Picciotto, Caldarone, King & Zachariou 2000). Several neurotransmitters are released which nicotine receptors activate, these include dopamine, norepinephrine, acetylcholine and gamma aminobutyric acid (GABA) (Benowitz 2001). Direct action on the nervous system receptors are believed to be the reason for the reinforced behavioural effects that are seen in smokers (Benowitz 2001). As a result of this stimulation, behaviours become associated with nicotine delivery, e.g. drinking coffee or alcohol, socialising, dealing with stress, boredom, and these become secondary reinforcers. When people quit smoking these behaviours act as smoking cues and produce urges to smoke, this typically reflects a smokers' dependence to nicotine.

Defining nicotine dependence

Nicotine dependence is a hypothetical construct that is designed to explain and predict societally important outcomes, such as an inability to quit smoking, heavy use, and other problems associated by smoking or tobacco use (Piper, McCarthy, Bolt, Smith, Lerman, Benowitz, Fiore & Baker 2008).

There is now a wealth of research that has now been undertaken with people dependent on nicotine, primarily to characterise the symptoms associated with and define the nature of nicotine dependence (Giovino, Henningfield, Tomar, Escobedo & Siade 1995). The key attributes of a nicotine dependent person are the experience of withdrawal on cessation of smoking and the difficulty they find when attempting to quit smoking as a result of these symptoms, for those who do stop smoking there is a high rate of relapse that is reported (Ferguson et al. 2005).

Early researchers defined nicotine dependence as only a term relevant to those who were heavy daily smokers, which led to some mistaken assumptions that those who did not smoke daily or were regarded as lighter smokers were not addicted (Difranza, Wellman, Mermelstein, Pbert, Klein, Sargent, Ahluwalia, Lando, Ossip, Wilson, Balk, Hipple, Tanski, Prokhorov, Best & Winickoff 2011).

This difficulty in defining who is diagnosed as nicotine dependent can still be seen with the current and most commonly used definitions. The current American Psychiatric Association (2000) Diagnostic and Statistical Manual (DSM-IV) (Table 1) definition of substance dependence includes only 3 of a total of 7 criteria under this definition that are particularly relevant to smokers; these are (1) the occurrence of a

tobacco withdrawal syndrome; (2) a persistent desire or unsuccessful efforts to cut down or stop smoking; and (3) continued smoking despite knowledge of the health risks.

Table 1: DSM-IV-TR criteria for substance dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifest by **three (or more)** of the following, occurring at any time in the same 12-month period

1. Tolerance, as defined by either of the following:
   - A need for markedly increased amounts of the substance to achieve intoxication or desired effect
   - Markedly diminished effect with continued use of the same amount of the substance
2. Withdrawal, as manifest by either of the following:
   - The characteristic withdrawal syndrome for the substance (see later)
   - The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. The substance is often taken in larger amounts and over a longer period than was intended
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use
5. A great deal of time is spent in activities necessary to obtain the substance, use the substance or recovering from its effects
6. Important social, occupational or recreational activities are given up or reduced because of substance use
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g. current cocaine use despite recognition of cocaine induces depression)

Adapted from: American Psychiatric Association (2000)

A recent review was undertaken to look across studies to see how many smokers would be classed as nicotine dependent using the DSM-IV criteria for nicotine dependence (Hughes, Heizer & Lindberg 2006). The review found that only about half of the current smokers surveyed fulfilled the DSM-IV criteria for nicotine dependence. It is argued by the authors that the definition may be too stringent, which would explain the lower than expected numbers. It is also possible that the items included in the definition are not valid measures when applied to nicotine (Hughes et al. 2006). Another explanation may be that those smokers surveyed had not ever tried to stop and therefore had not experienced any negative withdrawal and perhaps are not then aware of their dependence.

The current usefulness and applicability of all the criteria included in DSM-IV to nicotine dependence has been highlighted in several studies. The item in the DSM-IV "important social, occupational or recreational activities are given up because of substance use" has been highlighted as an item that may not be relevant as an indicator for nicotine dependence (Lessov, Martin, Statham. Todorov, Slutske, Bucholz, Heath & Madden 2004). This item was also seen as less relevant to nicotine dependence in the review by Hughes (2006).

Currently there is no definitive definition that applies to the majority of smokers' which is accepted in the field of tobacco research, however, elements of these definitions are able to guide clinicians and researchers in highlighting and targeting intervention to the smokers who could most benefit from help.

The most striking criteria from most definitions of nicotine dependence, which is relevant to practice, is the high rate of failed stop smoking attempts. It is reported that as many as 60-70% of smokers report wanting to stop (Kava 2000), and many of these smokers attempt to quit smoking each year. However, the high number of those who want to stop smoking is not reflected in the relatively low numbers who go on to successfully quit (Ferguson et al. 2005). It is estimated that the chances of success at any given quit attempt are less than 5% (Hughes, Keely & Naud 2004a). It is these smokers that benefit the most from the structure and support that current smoking cessation behavioural and pharmaceutical treatments provide.

Methods for determining degree of dependence

Measuring dependence has been described as a construct, it is not in theory equivalent to any one criteria or measure and is more a means of testing where that individual stands on that construct (Piper et al. 2008). Establishing a smokers' dependence to tobacco is an important measure to help tailor the level of behavioural support the smoker needs. It is also a useful tool for guiding health professionals as to which type and strength of pharmaceutical treatment should be provided (West 2004a).

The more dependent the smoker is then it is assumed the harder it will be for the smoker to successfully stop, therefore, the assumption is that different treatment approaches may be more suitable for highly dependent smokers compared with less dependent smokers. There are several methods that are commonly used to establish how dependent smokers are.

Cigarette consumption

Dependence is often estimated by cigarette consumption (measured by number of cigarettes smoked per day). This measure is easy to ascertain from smokers and so is commonly used in practice. Using cigarette consumption does not always correlate well with blood nicotine levels (Benowitz 2001). Smokers can reduce their cigarette consumption but maintain their usual blood nicotine levels due to compensatory smoking (i.e. taking bigger puffs, longer duration of inhalation, smoking more of each cigarette) (Benowitz 2001).

Biological measures

Another measure of consumption is cotinine, a metabolite of nicotine, which can be quantified in blood, urine and saliva. Cotinine has a longer half-life than nicotine, which means that cotinine levels vary only slightly throughout the day (Benowitz 2001). The measure of cotinine can then be taken at any time point throughout the day and is not vastly influenced by the time of the last cigarette smoked. For the purposes of research this is a good measure of the amount of nicotine that has been consumed (Hughes 2004b).

Measuring expired carbon monoxide (CO) is commonly used to measure dependence. CO is a gas inhaled from cigarettes, which has been linked to heart disease (Glantz & Parmley 1991). CO is measured in parts per million, a CO reading of <10ppm is the recognised acceptable reading for a non-smoker (West, Hajek, Stead & Stapleton 2005).

Typically CO is eliminated from the body approximately 24-hours after smoking cessation (American Lung Association (ALA) 1990). One of the limitations of using this measure is that due to COs short half-life, the measurement is limited to being an indication of only the last few hours of smoking (Benowitz 2001). One of the other limitations of CO monitors is that they are expensive pieces of equipment, costing approximately £300 per machine, which does not include the on-going cost of the disposable tubes that are needed for each use (Bedfont Scientific Ltd 2007).

In practice, CO readings are the most common way of tracking progress by the NHS-SSS and is expected that all smoking cessation advisors will verify smoking status

four weeks after the quit day (May & McEwen 2008). CO monitors provide an instant reading and so for many smokers attempting to quit, the reading acts as a useful motivation tool.

Fagerström Test for Nicotine Dependence (FTND)

The FTND (Heatherton, Kozlowski, Frecker & Fagestrom 1991) is the most widely used measure of nicotine dependence (Colby, Tiffany, Shiffman & Niaura 2000a). The measure is based on physical constructs of dependence and is made up of six questions that are scored and summed (see Table 2). Items include; how soon after you wake up do you have your first cigarette? Do you find it difficult not to smoke in places where smoking is not allowed? Do you smoke if you were so ill you were in bed all day?

Scores of six to ten on the FTND indicate high levels of nicotine dependence; a score of 4 or more is typically seen in a typical smoking population. In a recent study the relationship between the FTND and abstinence rates was looked at across 10 RCTs (Fagerström, Russ, Yu, Yunis & Foulds 2012). The results found that those with an increasing dependence score had lower abstinence rates. This is also reflected in several other studies looking at smoking outcome (Colby, Tiffany, Shiffman & Niaura 2000b, Heatherton, Kozlowski, Frecker, Rickert & Robinson 1989, Heatherton et al. 1991, Kozlowski, Porter, Orleans, Pope & Heatherton 1994, Hughes 2007b).

The FTND is not without its limitations; they include lack of internal consistency (Heatherton et al. 1991), its relationship with outcome is not strong (Kozlowski et al. 1994) and scores do not consistently correlate with objective measures (e.g. blood

nicotine levels) or other subjective measures such as withdrawal symptoms (Hughes 2007b).

Table 2: Fagerström Test for Nicotine Dependence

How soon after you wake up do you smoke your first cigarette?	Within 5 minutes = 3 6-30 minutes = 2 31-60 minutes = 1 After 60 minutes = 0
Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes = 1 No = 0
Which cigarette would you hate most to give up?	The first one in the morning = 1 Any other = 0
How many cigarettes per day do you smoke?	Up to 10 = 0 11 – 20 = 1 21 – 30 = 2 Over 30 = 3
Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes = 1 No = 0
Do you smoke if you are so ill that you are in bed most of the day?	Yes = 1 No = 0

Source: Heatherton et al. 1991

Other scales

There are several other measures that have been developed and used to assess smokers' dependence to nicotine.

There are two items in the FTND that are the strongest predictors of outcome; time to first cigarette and cigarettes smoked per day (Colby et al. 2000a). These questions have been combined and used as a brief measure of dependence, the Heaviness of Smoking Index (HSI) (Kozlowski et al. 1994, Fagerström et al. 2012). These two items have been found to be fairly reliable over time as well as important predictors of quitting (Borland, Yong, O'Connor, Hyland & Thompson 2010).

The time to first cigarette (TTFC) item has been used as a measurement of dependence on its own (Shiffman, Gwaltney, Balabanis, Liu, Paty & Kassel 2002a). The item appears to indicate a pattern of heavy, uninterrupted, and automatic smoking and may be a good single-item measure of nicotine dependence (Baker, Piper, McCarthy, Bolt, Smith, Kim, Colby, Contil, Giovino, Hatsukami, Hyland, Krishnan-Sarin, Niaura, Perkins & Toll 2007).

A more recently developed scale to measure dependence is the Nicotine Dependence Syndrome Scale (Shiffman, Waters & Hickcox 2004). This multidimensional tool was developed from theoretical concepts and incorporates five factors; drive, priority, tolerance, continuity and stereotypy. Smokers self-complete a 23-item questionnaire, rating their answers on a 5-point scale. Validation of this tool shows that it predicts urges to smoke, abstinence effects and smoking cessation outcome (Shiffman et al. 2004). It also correlates with other markers of dependence (Shiffman et al. 2004). The

authors concluded that this scale might expand the scope of the Fagerström measures particularly as it has stronger associations with withdrawal and craving. However, it has not yet gained widespread use.

It is typical to only ask about the strength and frequency of urges and cravings to smoke post quit day, however, in a recent study a measure of strength of urge to smoke (SUTS) was examined prior to quitting to see if this could predict relapse (Fidler, Shahab & West 2011). All smokers at baseline were asked 'How much of the time have you felt the urge to smoke in the past 24 hours?' And were asked to report their response on a 6 point scale from 1, 'not at all' to 6, 'all of the time' (Fidler et al. 2011). FTND, HSI and SUTS were all found to predict successful quitting, with SUTS showing the strongest association.

Theories used to explain dependence to nicotine

Conditioning Theory

The theory of conditioning is important to consider particularly when used in the field of addiction related research. Conditioning theory is typically the main model used in addiction. According to learning-based theories, cue-induced craving might partly reflect a conditioned response (CR) established by a learned association between that cue and nicotine intake (Field & Duka 2004, Niaura, Rohsenow, Binkoff, Monti, Pedraza & Abrams 1988).

Cue exposure effect (i.e. an increase in urges to use the drug in the presence of stimuli which habitually accompany its use), has been reported in numerous laboratory studies (Carter & Tiffany 1999). The effect seems to be largely due to classical conditioning (Conklin 2006).

Over the course of drug use, a range of stimuli becomes associated with drug administration (e.g. smoking paraphernalia, others smoking). After time, those stimuli become cues or conditioned stimuli, which can then elicit conditioned responses. When an individual is re-exposed to those cues in the laboratory (Conklin & Tiffany 2001) or in the real world (Shiffman et al. 2002a), he or she experiences subjective effects (e.g. craving to smoke), physiological effects (e.g. increase in heart rate) and behavioural effects (e.g. quickening of drug seeking or use). This may be one of the factors, which contribute to relapse in drug users who try to abstain.

Conditioning models are useful in helping to explain the observable features of addiction, however, they do not specify the precise role of neurobiological reinforcement mechanisms necessary in establishing reinforcement of drug seeking behaviour (Shadel, Shiffman, Niaura, Nichter & Abrams 2000). This theory also is criticised for not taking into account the role of cognition in addiction, such as thought and affect (Shadel et al. 2000), which have established roles in regulating and establishing drug behaviour (Marlatt & Gordon 1985).

PRIME theory of addiction

One of the most recent theories to emerge in the field of addiction is the PRIME theory of addiction (West 2006b), which aims to bring together many of the concepts that are in existing behaviour theories into a single simple model (e.g. intention, emotion, instincts, habituation). The theories main aim is to explain how, when and why motivation "goes wrong' in addiction. It is thought that there are 5 levels within our motivation system and that any one of these levels can function abnormally in addiction (West 2006b). The system is described in this theory by the acronym PRIME – plans, responses, impulses, motives and evaluations.

The model is seen as fluid matrix of interacting forces that can influence behaviour when all elements of the system are in place (West 2006b). The "chaotic" system can change due to any trigger whether small or large and as the result of no event or reason (West 2006b).

Ultimately the approach of the model with regards to smoking is to minimize the impulses, wants and needs to smoke of the individual and to maximise the wants and

needs to remain abstinent. In terms of PRIME Theory, the process of smoking cessation involves *forming a personal rule not to smoke followed by self-conscious implementation of that rule in the face of impulses, wants and needs to smoke* (West 2009).

The importance of the not-smoking rule is predicted by PRIME theory, in that those smokers who say they will "attempt to not smoke" rather than saying "I will not smoke" will have insufficient motivation to deal with all vulnerable situations they find themselves in and will ultimately fail in their attempt.

Medication can reduce the drive for smoking as well as the cue-induced reaction to smoking in the short term thus increasing the chances of successfully stopping. The model is recognised as a useful tool in the provision of effective cessation interventions, assessing clients motivation during a quit attempt and adjusting treatment to levels of motivation throughout any treatment programme in order to overcome addiction (West 2009).

The theory has been criticized for being too over inclusive with its varying constructs, which limits the rigorous testing that needs to be done with such a model (Redvers 2007). There are plenty of real-life applications for this model as it is soundly based on common sense, however, more research is needed to test the relevance of all PRIME constructs in its scientific applicability to treating smokers.

CHAPTER 4 - TOBACCO WITHDRAWAL SYNDROME

This chapter discusses the symptoms that are experienced by smokers on withdrawal of tobacco and the ways in which these symptoms are measured. Their time course and relationship with relapse are also discussed.

Tobacco withdrawal syndrome

When smokers attempt to abstain from cigarettes they typically experience a variety of uncomfortable reactions. These signs and symptoms have been termed the tobacco withdrawal syndrome (TWS) (Shiffman 1978). The experience of withdrawal symptoms after stopping drug use is one of the most utilised indicators of addiction and it has been proposed that the onset of these symptoms maintains smoking (Hughes, Hatsukami, Pickens, Krahn, Malin & Luknic 1984).

There are several TWS that have been observed in smokers who abstain from tobacco. These include; irritability (Hughes & Hatsukami 1986), poor concentration (Leventhal, Water, Boyd, Moolchan, Lerman & Pickworth 2007), depression (Hughes 1992), and hunger (West & Hajek 2004b) (see Table 3). One of the most common symptom after withdrawal from tobacco is an increase in craving to smoke (Shiffman 2000). The experience of increased craving for cigarettes, weight gain and post-cessation depression has been highlighted as predictors for relapse back to smoking (Hughes 1992).

A mediating factor on experience of strong craving after a period of smoking abstinence has been found to be related to those who have a high nicotine dependence (Van Den Eijnden 2003). One study showed that after a period of smoking abstinence,

craving was stronger in those with high tobacco dependence than in those with low tobacco dependence (Van Den Eijnden, Splikerman & Fekkes 2003). Experiencing strong craving when abstaining from cigarettes has been described as "potentially the most important feature of cigarette withdrawal" (West, Hajek & Belcher 1989).

For all smokers the experience of withdrawal is a daily occurrence. The craving to smoke is alleviated only by lighting and smoking the next cigarette. This cycle of smoking to alleviate discomfort of craving is one of the key mechanisms to continued use and ultimately a dependence to tobacco.

Table 3: Tobacco withdrawal – mood and physical symptoms

Symptom/Physical sign	**Average duration**
Depressed mood	<4 weeks
Sleep disturbance	<2 weeks
Irritability	<4 weeks
Difficulty concentrating	<2 weeks
Restlessness	<4 weeks
Increased appetite and increased weight	>10 weeks
Constipation	>4 weeks
Mouth ulcers	>4 weeks
Light-headedness	<2 days
Urges to smoke	>10 weeks

Sources: (West et al.1989; Hughes 1992; Hajek, Gillson & McRobbie 2003; Ussher, West, Steptoe & McEwen 2003; McRobbie, Hajek & Gillison 2004)

From a treatment perspective individual variation in withdrawal symptoms is important. The onset of withdrawal symptoms has been found to occur within 2-12 hours of the last cigarette (Shiffman et al. 2002a). Many smokers suffer with

withdrawal symptoms and some find these distressing (Hughes, Higgins & Bickel 1994). Some smokers report that withdrawal symptoms cause significant impairment in social, occupational, or other important activities of daily living (Pergadia, Heath, Martin & Madden 2006). However, tobacco withdrawal symptoms are mostly short-lived and people withdrawing from tobacco can be reassured that these should disappear within 4-6 weeks (Cummings, Giovano, Jaen & Emrich 1985). Urges to smoke usually last longer, but do decrease in frequency and people can learn to manage these (Gritz, Carr & Marcus 1991).

Most people who stop smoking will gain weight, with most of the weight gain occurring in the first 3 months after cessation (Aubin, Farley, Lycett, Lahmek & Aveyard 2012). Typically smokers gain around 5kg on average in the first year of abstinence (Aubin et al. 2012; Farley, Hayek, Lycett & Aveyard 2012). A Cochrane review (Farley et al. 2012) that examined interventions to prevent post-cessation weight gain showed clear evidence that NRT, varenicline, and bupropion (all licensed medications for cessation) all reduce weight gain by about 0.5 to 1kg during the period of use of medication.

It is common for smokers to use weight gain as a reason for not wanting to stop smoking so being able to reassure those who are concerned about their weight that the use of smoking cessation medications can help delay weight gain can be useful. It also helps the smoker to give their full attention to stopping smoking and deal with any weight concerns at a later date, after tobacco withdrawal symptoms will have subsided. Smokers can also be advised to eat a healthy high fibre diet, and where possible increase their levels of physical activity. Small bouts of exercise have also

been shown to reduce the desire to smoke and the intensity of withdrawal symptoms in abstaining smokers (Ussher, Nunziata, Cropley & West 2001).

Measuring withdrawal

There are several measures, which have been developed to measure tobacco withdrawal symptoms, which include the Wisconsin Smoking Withdrawal Scale (WSWS) (Shiffman et al. 2004), the Mood and Physical Symptoms Scale (MPSS) (West & Hajek 2004b), Shiffamn-Jarvik Smoking Withdrawal Questionnaire (SWQ) (Shiffman & Jarvik 1976), Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes & Hatsukami 1986), Shiffman Scale (SS) (Shiffman, Balabanis, Paty, Engberg, Gwaltney, Liu, Gnys, Hickox & Paton 2000) and the Cigarette Withdrawal Scale (CWS) (Etter 2005).

All scales rely on self-reported measures of withdrawal recorded on a scale, with a higher score typically indicating higher levels of withdrawal. All scales use valid withdrawal symptoms but have different labels for these symptoms. For example, the MPSS uses the term depressed only whereas the MNWS uses depressed mood/sad. This may have implications for how some people rate these items. For example, on seeing the word depressed some people may only use that term if they were clinically diagnosed rather than how they would describe a slight low mood. It is important to consider that single label items may underestimate the prevalence of the symptoms but equally using multiple labels may overestimate prevalence.

The MPSS and WSWS measures are most commonly used and after much testing are seen as the most reliable and valid measures of nicotine withdrawal. The MPSS is most commonly used in clinical practice.

The Mood and Physical Symptoms Scale (MPSS)

The MPSS is used to track the time course of tobacco withdrawal symptoms throughout the initial period of quitting smoking. There are five core withdrawal symptoms that are included in the MPSS (irritability, poor concentration, restlessness, depression, and hunger) and urges to smoke (West & Hajek 2004b). All of the withdrawal symptoms are measured with a single item, rated on five-point scales, with the exception of urges to smoke.

Urges to smoke are measured with two questions related to frequency and strength of urges on a 6-point scale. The six-point scale is used to rate 'How much of the time have you felt the urge to smoke in the past week?' (from 'not at all' to 'all of the time') and 'How strong have the urges been?' (from 'no urges' to 'extremely strong'). The five-point scale used for the other measures asks how they have been feeling during the past week with regard to depression, irritability, restlessness, hunger, poor concentration, poor sleep at night, and anxiety on a scale ranging from 1=not at all to 5=extremely.

The MPSS has been extensively tested for its reliability in assessing nicotine withdrawal symptoms. The MPSS is commonly used as a composite score, taking an average score across the five measures and comparing it pre and post quitting to establish the occurrence and severity of withdrawal symptoms. The urge question on the MPSS consists of two items; the severity of urges experienced over the previous week and the frequency of the urges. In one study that examined the internal structure and responsiveness of the MPSS measures (West & Hajek 2004b), 96 smokers were recruited who had been able to maintain 24 hours of validated abstinence. The results

of the pre and post quitting MPSS measures demonstrated a significant increase from baseline in all 5-core nicotine withdrawal measures. A high correlation was seen between the two urge questions and so these have since been combined to represent an overall urge to smoke rating (West & Hajek 2004b).

It is common practice to ask all patients to record baseline readings (before they stop smoking) on all the core withdrawal symptoms. The only exception is that the two ratings on urges to smoke are only asked post quitting. The reasoning is that when the scale was developed rating craving at baseline, whilst the person is still smoking, was not viewed as being clinically meaningful. However, in a recent study a measure of SUTS was examined prior to quitting and was seen as a strong predictor of successful quitting (Fidler et al. 2011). This research seems to indicate that the addition of the SUTS measure before a person quits may add more strength to the MPSS.

It is common for participants to question why we ask them to rate their concentration, irritability, depression, hunger, restlessness over the last week before they have stopped smoking. The reasoning behind this is to get a clean baseline score, which is not influenced by any of the mood and physical changes that occur when stopping smoking. At baseline the MPSS rating is asked to establish how depressed that person is at and to then compare the rating post-quitting. For example, if the depression score is rated as moderate at baseline and is rated again as moderate at a post quit time point then we are able to distinguish that this depression rating is not as a result of smoking whereas someone who reports no depression at baseline but post quitting reports being very depressed we can assume some influence of stopping smoking has had an effect on their mood.

When looking at withdrawal symptoms it is important to distinguish between those who have stopped smoking and those who have not as this may have major implications on the findings. Asking those who have relapsed back to smoking to gauge their frequency and intensity of urge to smoke will give distorted results as the participant may overcompensate with their marking of these symptoms to justify their relapse or continued smoking. Ultimately those who have relapsed or continued to smoke are not experiencing true withdrawal symptoms as they are still having a high intake of nicotine from cigarettes.

Treatments that help smokers' progress through the most difficult time period, for example, withdrawal oriented treatment (Hajek 1989), use knowledge of withdrawal symptom time course to help smokers understand the transition from being a smoker to an ex-smoker.

The role of environmental cues

Although the role of nicotine deprivation plays a major part in people's success when stopping smoking there are other factors which have been found to influence craving and urges to smoke which include expectations, habits and environmental cues. Higher cravings have been demonstrated in a sample of smokers who were exposed to smoking cues who were expecting to be able to smoke after the experiment when compared with a control who were instructed they could not smoke (Juliano & Brandon 1998). Smokers' perceptions of cigarette availability have been found to mediate responses to smoking cues, such as pictures of cigarettes and lighters (Dols, Willems, Van Den Hout & Bittoun 2000).

An earlier review undertaken by (Wertz & Sayette 2001) found that those addicted to substances (which included tobacco) found the urge to smoke higher when they perceived their drug of choice was available compared with when they were not. The urges to smoke were self-reported. Cue reactivity in addiction appears to depend on the availability which is signalled by other environmental cues e.g. a patient may have cigarettes on them in hospital but feel no urges to smoke as they know they cannot smoke but once the smoker leaves hospital (and therefore able to smoke) and the smoking cue (cigarettes) are still available then the urge to smoke will be increased. Anecdotally dependent smokers who have been unsuccessful at stopping smoking in the past, report that when they are hospitalised they do not think about cigarettes during their stay and feel comfortable without smoking (Myers, Rudell & Hajek 2009).

It is assumed that this is reinforced particularly after discharge by having a smoking partner or living with people who smoke as the opportunity to smoke will be increased and they are more likely to be surrounded by smoking cues e.g. others smoking, cigarettes in the house.

One study (Dar, Stronguin, Marouani, Krupsky & Frenk 2005) looked at the role smoking related habits, cues and expectations had on cravings to smoke. They used a unique group of participants to study this – Orthodox Jews. The reasoning for this was due to the fact that Orthodox Jews abstain from smoking on the Sabbath, the authors hypothesised that as they have no smoking cues or expectations of smoking during the Sabbath that craving to smoke would be lower than usual. Twenty participants were asked to rate craving scores and withdrawal ratings including irritability during three different conditions; smoke as usual during a workday, forced abstinence during a workday and during the Sabbath (no smoking). The results found that craving during the Sabbath was significantly lower than on the abstinence workday and non-abstinence workday. The conclusion of this study was that the results show that craving to smoke is determined to a large extent by smoking-related habits, cues and expectations.

Another study (Thwissen, Van Der Meijden, Havermans, Van Den Hout & Jansen 2008) also showed patients cues predicting either smoking or no smoking and the effect of this was measured in two separate rooms – one a low-smoking relevant room and the other a high-smoking relevant room. They found that a cue predicting smoking availability increased participant reports of urges to smoke than a cue predicting no availability to smoke.

Relapse

The previous sections discuss the role that dependence, the tobacco withdrawal syndrome and environmental cues have on an individual when attempting to stop smoking. Due to the complexities of overcoming tobacco dependence, many smokers who try to quit will relapse back to smoking.

For most smokers who attempt to quit without support they will relapse within the first week of abstinence, with over 60% relapsing back to smoking within the first 3 days (Hughes et al. 2004a). Approximately 60-98% of smokers who use treatment will relapse back to smoking within the first year (Garvey, Bliss, Hitchcock, Heinold & Rosner 1992), with the majority doing so within the first 6 months (Ferguson et al. 2005, Logan, Levy, Ferguson, Pomrehn & Muldoon 1992). After several months of abstinence the risk of relapse reduces, however, this does not guarantee long-term abstinence.

There is no clear definition of relapse as technically resumption of smoking anytime after the quit day can be viewed as a relapse (Hajek, Stead, West, Jarvis & Lancaster 2009). Defining what relapse is in smoking cessation is often discussed, whether it is return to daily smoking or simply having a puff of a cigarette. In clinical practice it is typical to call it a lapse if less than 5 cigarettes have been smoked with continued efforts towards remaining abstinence after the lapse. Whereas relapse is followed by a return to regular smoking.

There is a large amount of research that has focused on predictors for relapse among the smoking population. One longitudinal study looked at smokers who had

previously quit for more than a year and divided participants into 2 groups; those who were currently smoking and those who were long term abstainers (Macy, Seo, Chassin, Presson, Sherman & Macy 2007). The results from the study showed that the strongest predictor for avoiding relapse was marrying a non-smoker (OR=0.07; 95% CI =0.03-0.21). Other factors included working in a smoke-free building (OR=0.13; 95% CI=0.03-0.58). The study concluded that factors related to smoking in their social environment played the largest role in predicting long-term abstinence versus relapse.

Relapse is most commonly associated with situations that lead back to smoking; most typically associated with major life events such as bereavement, divorce, holiday and being under the influence of alcohol (Hymowitz, Sexton, Ockene & Grandits 1991).

As the health benefits of stopping smoking are only realised with long-term abstinence, relapse reduces the public health benefit of investment in smoking cessation.

The Cochrane Review (Hajek, Stead, West, Jarvis & Lancaster 2009) of relapse prevention literature identified 47 randomised trials of behavioural treatments, with no single trial or group of trials showing an effect. Most trials evaluated Marlatt and Gordon's (Marlatt & Gordon 1985) 'skills-based' approach, which includes identifying relapse situations and coping strategies. The interventions were often brief and one-off, many trials mixed smoking cessation and relapse prevention interventions, with only 36 randomising abstaining smokers, and most trials posed significant methodological problems. The Cochrane review identified the need for

good quality research in this key area as the number one priority in the field of smoking cessation.

The lack of proven relapse prevention interventions has not stopped NHS-SSS attempting to provide some relapse prevention help for their clients. A survey of current practice reported that most (58%) services were providing some kind of RPS (Coleman, Agboola, Leonardi-Bee, Taylor, McEwen & McNeill 2010). 'Common sense' approaches are usually used, such as an offer of regular drop-in sessions. Anecdotally some clients find these helpful but the sessions are usually poorly attended, and their efficacy is unknown. It has been suggested that extended use of varenicline may prevent relapse, however, research using extended use of NRT as a relapse prevention strategy are still needed (Hajek et al. 2009).

CHAPTER 5 – SMOKING CESSATION TREATMENT AND INTERVENTIONS

This chapter provides a comprehensive overview of evidence-based smoking cessation interventions. Relevant theories that have been used in the development of these interventions will be discussed. Detailed descriptions of current pharmaceutical treatments for smoking cessation are also presented.

Brief advice

Brief advice to quit smoking is one of the most important interventions a healthcare worker can deliver. The Cochrane review looking at the effectiveness of doctor advice to quit in promoting cessation (Stead, Bergson & Lancaster 2008) identified 17 studies comparing brief versus no advice. The results from 17 studies showed an increase rate of quitting in those who received brief advice from their doctor (RR 1.66; CI 95% 1.42-1.94). When looking at more intensive versus minimal advice, a small but significant effect was seen (RR 1.37; CI 95% 1.20-1.56).

Overall brief advice from a doctor in promoting cessation showed an increase in quit attempts by up to 3% (Stead et al. 2008); this is a small but important effect.

Asking patients about their smoking status should of course not be an end in itself. A recent systematic review by Aveyard, Parson & West (2011) untangled the literature on brief interventions to look at the effect of brief advice and offering assistance to quit. Advice to quit on medical grounds increased the frequency of quit attempts by 24%. However, making an offer of treatment (e.g. offering a prescription for smoking

cessation medications or referral to a stop-smoking programme), regardless of assessing readiness to quit, motivated an additional 40-60% of people.

Self-help materials

The Cochrane review, self-help interventions for smoking cessation (Lancaster 2005a) looked at the effectiveness of different forms of self-help materials compared with minimal or no treatment. When compared with no advice there was a small but significant increase in abstinence rates in those who received the self-help materials (RR 1.21; CI 95% 1.05-1.39). The significant result may be in part attributed to the additional contact or assessment required to obtain individual data. Tailoring self-help materials to individual smokers compared to no intervention showed a small benefit (RR 1.31; CI 95% 1.20-1.42). There was no evidence of added benefit using self-help materials alongside other interventions for cessation. Their conclusion was that self-help materials may increase quit rates compared to no intervention but that the effect is likely to be small. There is evidence that tailored materials are more effective than untailored materials but again the effect is likely to be small.

Group based treatment (GBT)

The structured group orientated model (Hajek, 1989) views smokers as "addicted to nicotine and that nicotine dependence is the main remediable source of difficulties smokers encounter when stopping smoking".

The model which is widely used for smoking cessation uses withdrawal-oriented therapy that focuses on helping people maintain abstinence over the first 4-weeks of a quit attempt; a period when withdrawal symptoms are most frequently experienced

and relapse is most likely. Treatment is provided over 7 weekly sessions and on-going sessions can be offered if needed.

There has been extensive research done using this model to help treat smokers, which show its effectiveness. The Cochrane review, *Group behaviour therapy programmes for smoking cessation* (Stead 2005), has looked at the evidence for the efficacy of GBTs for smoking cessation. The review includes data from 53 studies that met the inclusion criteria (that is they were randomised controlled trials investigating the efficacy of group based treatments on at least 6-month smoking cessation outcome). The meta-analysis showed the superiority of group-based interventions over self-help in achieving at least 6 months of abstinence (RR=1.98; 95% CI: 1.60-2.46).

When researchers compared the effect of GBT with individual treatment, pooling data from five studies, long-term abstinence rates were similar between the two methods (RR=1.01; 95%CI: 0.77-1.32). There was limited evidence that the addition of group therapy to other forms of treatment, such as advice from a health professional or NRT, produced extra benefit.

Data from NHS-SSS report GBT as having higher 4-week success rates than one-to–one and pharmacist led sessions (Brose et al. 2011, Judge, Bauld, Chesterman & Ferguson 2005, McEwen, West & McRobbie 2006). However, this data are not from RCTs and could be explained as a result of the differences in the clinician involved in the treatment or in the population being treated.

Individual treatment

Individual treatment follows a very similar structure to the GBT (preparation, medication options, quit day session and repeated contacts post quit day). Individual treatment is usually offered to people who are not able to commit to weekly sessions and need a more a more flexible option, do not feel the need or are inappropriate for intense group treatment. The Cochrane review on individual counselling (Lancaster 2005b), found smokers who received individual counselling compared to minimal behavioural intervention had higher cessation rates at long term follow up (RR 1.39, 95% CI; 1.24-1.57). Individual counselling was defined as a face-to-face encounter between a smoking patient and a counsellor trained in assisting smoking cessation. The intensity of the individual counselling had no effect on outcome (RR 0.96, 95% CI 0.74 to 1.25).

Other routes to quit

Telephone counselling (Quitlines)

Telephone counselling (often referred to as Quitlines) typically provides proactive behavioural support (or counselling), via the telephone, to people who want help in quitting. In the Cochrane review, *Telephone counselling for smoking cessation* (Stead & Lancaster 2006), those receiving multiple (at least 2) pro-active phone calls were significantly more likely to report abstinence at long term follow up (RR 1.37; CI 95% 1.26-1.50). There appears to be a dose-response effect, in that the more calls someone receives the greater the chances of quitting. There were 3 studies looking at providing smokers with the option for contacting a quitline. These results were not pooled; one found no effect and the other 2 showing a significant benefit of offering the option of a quitline to smokers.

In a recent UK study participants were randomised to receive NRT (6 weeks) or proactive telephone counselling in addition to standard smoking cessation support offered through a telephone quitline (Ferguson, Docherty, Bauld, Lewis, Lorgelly, Boyd, McEwen & Coleman 2012). At 6 month follow up no effect on smoking outcome was seen in either the NRT or proactive phone call condition (6.6% versus 9.4%, NRT and proactive phone call group, respectively).

Multimedia interventions

There is growing interest in using other technologies in order to provide behavioural support; such as web-based interventions and mobile phone technology. Typically multimedia is used to provide motivational messages and to provide behavioural change support throughout the course of treatment. The messages are usually tailored to the individual and are often able to provide the smoker with extra help if needed without the need to attend a clinic, which for some people can be more convenient if they have limited availability.

The Cochrane review looking at interventions delivered using mobile phones (Whittaker, McRobbie, Bullen, Borland, Rogers & Gu 2012), found 5 studies that included long term follow up of at least 6 months. Three studies looked a text messaging only, one study using an internet QuitCoach both with mobile phone intervention and without and one using video messaging delivered via mobile phones. When the text messaging interventions were pooled, mobile phone interventions showed an increase in abstinence at 6 months compared to control (RR 1.71; 95% CI; 1.47-1.99).

A recent RCT was conducted in the UK, which looked at the effectiveness of text messaging on 6-month continuous abstinence rates (Free, Knight, Robertson, Whittaker, Edwards, Zhou, Rodgers, Cairns, Kenward & Roberts 2011). They found a significantly increased validated continuous abstinence rate at 6 months in the text messaging condition compared to the control group (10.7% versus 4.9%, RR, 2.20, 95% CI 1.80-2.68, p <0.0001).

A recent service enhancement conducted at the TDRU looked at the use of text messages to help prevent relapse after quitting smoking. The service enhancement focused on documenting the development, implementation and evaluation of a text-based relapse prevention service (RPS). Clients were offered the RPS if they had successfully quit smoking for 4 weeks at routine community services (pharmacists, level 2 trained advisors) and through the NHS-SSS (Snuggs, McRobbie, Myers, Schmocker, Goddard & Hajek 2012). Text messages aimed at motivation to remain abstinent, preventing absent-minded lapses, and continuing the full course of medicine for smoking cessation were developed.

RPS was well received by both NHS-SSS clients and staff, with 70% of clients considering the intervention helpful. 85% of clients responded to at least one of the nine interactive text messages. Seventy-seven clients (38% of the total, 56% of those we managed to contact) reported abstinence at 6-months. Eighteen clients who relapsed back to smoking used RPS to re-engage with the NHS-SSS and 10 successfully re-established abstinence. A controlled trial is needed to establish whether text messaging has a significant impact on relapse.

Alternative smoking cessation treatments

There are several alternative treatment methods commonly used by people who want to stop smoking. The most commonly reported treatments reported by clients attending the NHS-SSS are ***hypnotherapy, acupuncture*** and reading the ***Allen Carr*** "easy way to stop smoking" or attending the ***Allen Carr*** smoking clinic. The efficacy of these methods are summarised below.

Hypnotherapy

There are several different ways in which hypnotherapy has been used to help treat smokers. Whether it is in order to help smokers to focus and concentrate on the task of stopping smoking or to strengthen will power and determination to quit and resist the temptation of cigarettes, smokers are attracted to hypnotherapy as a treatment option.

A Cochrane review on the effectiveness of hypnotherapy for smokers found 11 studies, which compared hypnotherapy to 18 different control interventions (Barnes, Dong, McRobbie, Walker, Mehta & Stead 2010). Control interventions ranged from no treatment, brief advice to psychological treatments including NRT. When looking at smokers six months after the intervention was delivered, those using hypnotherapy did not have higher rates of abstinence compared to other smoking cessation interventions or no treatment (RR 9.00; 95% CI; 0.55-147.95). There is a possibility that hypnotherapy may be a useful counselling approach but there is currently not enough evidence to support this and as such is not an NHS recommended treatment option for smoking cessation.

Acupuncture

Acupuncture is often used as a smoking cessation intervention in order to help reduce tobacco withdrawal symptoms. A recent Cochrane review looked at studies comparing acupuncture to no intervention, sham treatment or other interventions used for smoking cessation (White, Rampes, Liu, Stead & Campbell 2011). Two sham treatments are commonly used for research in this field; 1) using a needle in an area not recognized as a usual acupuncture 'point' or 2) using a needle in a place known to be ineffective for the condition being studied. There was a marginally significant result favouring acupuncture at short term follow up compared to sham intervention (1.18; 95% CI 1.03-1.34). However, there were high levels of bias associated with the studies included in the analysis (e.g. no validation of smoking status). There was no evidence that acupuncture reduced withdrawal symptoms at long-term follow up. Acupuncture was seen as less effective than NRT.

Allen Carr

'The easy way to quit smoking' was first published in 1985 by Allen Carr, a self titled 100 a day chain smoker. Smokers are typically seen once for a session that lasts between 4-5 hours, with shorter 'booster' sessions available if required by patients. The programme also offers a 'money back' guarantee. A review for NICE (McRobbie, Hajek, Bullen & Feigin 2007), found four cohort studies evaluating the Allen Carr method. Two small studies reported 26%, one-month, and between 4 and 20% long-term abstinence rates (Foulds 1996). Higher abstinence rates were seen in two larger studies (40-52%) using more lax outcome criteria (Csillag & Feuerstein 2005; Hutter & Moshammer 2006). Currently no adequate controlled data are available which make it difficult to ascertain the efficacy of the Allen Carr method.

Models of relevance to the treatment of smokers

Helping smokers to change their behaviour is often seen as the role of HCPs. The development of models to predict who is ready to receive health behaviour advice and to highlight who is more likely to act on that advice would in practice be a useful tool for guiding intervention and HCP advice. There are several models that are widely cited in relation to treating smokers.

Theory of planned behaviour

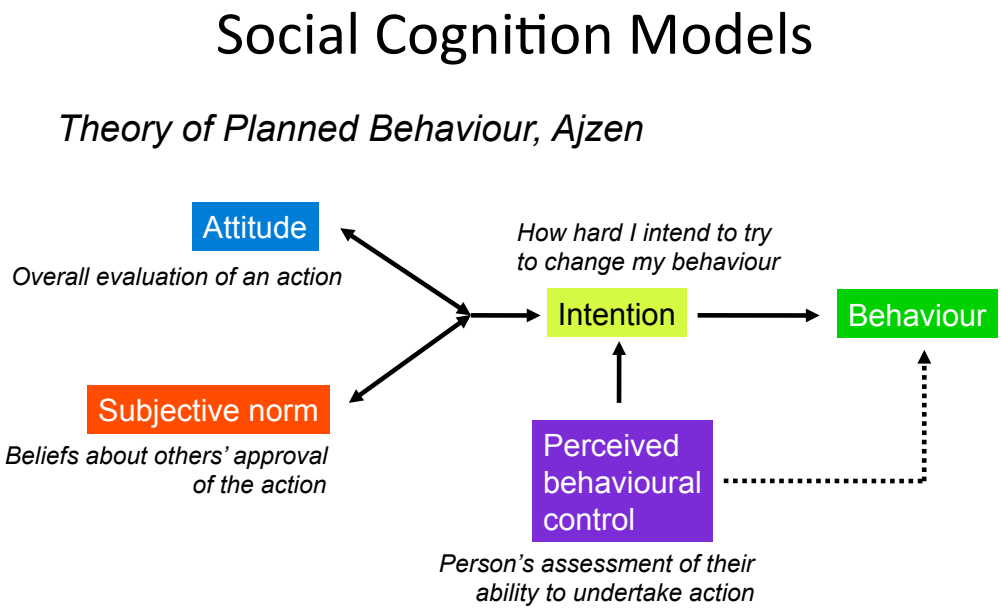
The Theory of Planned Behaviour (TPB) (Ajzen 1988) suggests that any behaviour can be placed on a continuum of the amount of control that person has over their respective actions (see Figure 1). There are 2 groups of factors that encourage or reduce behavioural control;

Internal factors – information, ability, skills of the individual alongside emotions and compulsions

External factors – opportunity to engage and change behaviour as well as the support from others that may be needed for such change

Combining both internal and external behaviours is the individuals control over a given behaviour (i.e. practicing safe sex, smoking, drinking) (Kaptein 2004). If control is high and the person intends to change their behaviour (e.g. stop smoking) then according to this model they will have a better chance of success. However, that behaviour is dependent on the individual's intention to change that behaviour.

Figure 1 – Theory of planned behaviour



Source – Ajzen 1988

The TPB has been seen to predict intent (Kaptein 2004). However, there are several criticisms of the TPB. Firstly, intention often does not lead to behaviour change, particularly in smoking cessation. A person can be intent on quitting smoking but that does not necessarily translate into making an actual quit attempt. Smoking cessation has not been found to be predicted by this model, however, measuring intention has been found to predict quit attempts (Norman, Connor & Bell 1999).

There has also been criticism over the concept of perceived behavioural control (PBC) (Armitage & Conner 1999). Increased research using the model has identified a distinction between PBC and self-efficacy whereas the model views them as

intertwining concepts (Armitage & Conner 1999). PBC has been defined as the ease or difficulty of undertaking a specific health behaviour (Armitage & Arden 2002). However, it is likely that this is ambiguous in the fact that a behaviour may be viewed as "easy" while simultaneously being "difficult" due to lack of opportunity or resources. PBC may be better viewed as an external control concept over resource and opportunity to change behaviour whereas self-efficacy is the internal control an individual has i.e. the confidence that you can change a certain behaviour (Armitage & Arden 2002). Both are believed to be crucial elements but currently the TPB lacks the distinction between these 2 concepts.

Stages of change model

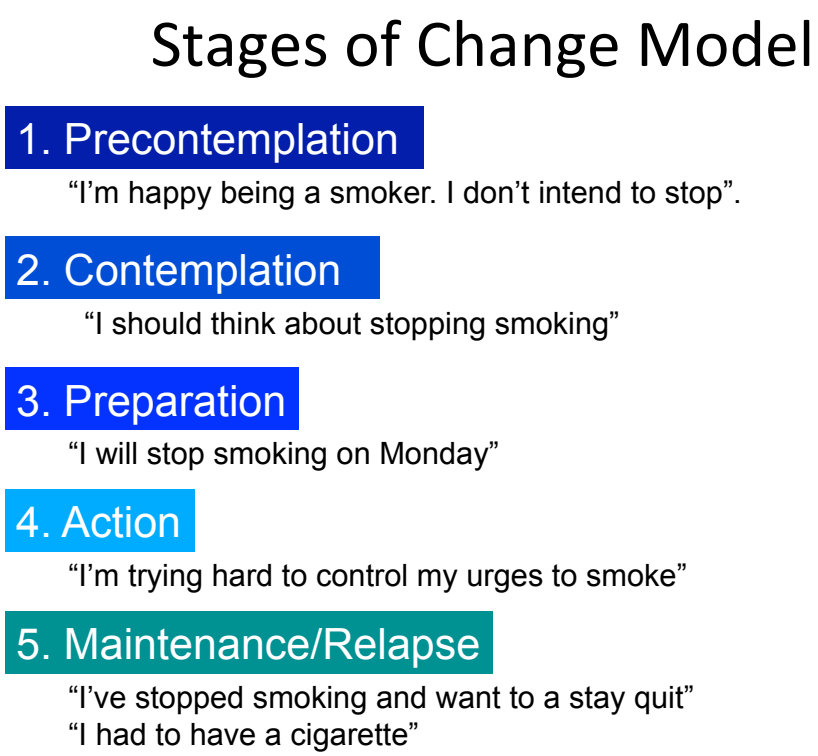
Prochaska and Diclementes's (1992) stages of change model, also known as the transtheoretical model of behaviour, is one of the most frequently cited models for guiding HCPs with regard to changing health behaviour (see Figure 2). The model sees patients go through several concrete stages with the ultimate goal of changing behaviour. The model allows movement between the stages both forwards and backwards before reaching a change in behaviour. The model is used by some NHS-SSS to assess motivation and to guide treatment.

There are five concrete stages leading ultimately to behaviour change; the first sees the person happy with their negative health behaviour (e.g. smoking), this is called the pre-contemplation stage. The second contemplation stage is when the person is thinking about stopping smoking and is ready to consider change of behaviour. The third stage is preparation where the smoker prepares to take action (contacting the NHS-SSS, reducing smoking) to stop smoking. The fourth stage is action to stop

smoking (using NHS-SSS alongside stop smoking medication). The fifth stage is relapse; this is common and expected among smokers. The model sees the smoker move through these stages gradually.

The model has time frames with regards to timing of each stage depending on which behaviour is changed. In the case of smoking cessation the 'precontemplation stage' sees the individual as not thinking about stopping smoking for at least 6 months; 'contemplation' involves an individual planning to stop between 31 days and 6 months, or less than 31 days if they have not tried to quit for 24hours in the past year; 'preparation' involves the individual having tried to stop for 24 hours in the past year and planning to stop within 30 days; 'action' involves the individual having stopped for between 0 and 6months; 'maintenance' involves the individual having stopped for more than 6 months (West 2005).

Figure 2 – Stages of change model



Source – Prochaska, Diclemente & Norcross 1992

There are several limitations with this model as it assumes that the person wants to change their behaviour and that ultimately a person will pass through each of the stages to reach the goal of behaviour change. However, applying stages of change to complex health behaviours such as smoking is beset by difficulties. Smoking is not a single behaviour, but a complex category of different specific actions, such as biochemical, environmental and the emotional aspects of smoking. The stages are arbitrary; in real life people skip several stages to reach maintenance and can be seen to be in 2 categories at once (i.e. thinking about stopping smoking and also planning to stop). They also do not necessarily do this gradually; smokers often act as soon as they think they should stop smoking and so the diving lines of the model are arbitrary.

The implication of the stage of change model is that interventions based on the model need to be directed at the stage the person is at, however, the content of this targeted information is difficult to assess. The model also assumes conscious decision making and planning and does not take into account the other aspects of addiction that need to be addressed in order to successfully change behaviour (i.e. habits, reward of smoking). As a result of these flaws most researchers in the field of smoking cessation do not believe the stages of change model is of benefit and some have argued that the model has held back the advances of health promotion (West 2005).

The interventions based on these models have not been found to be indicative of increasing abstinence rates in smokers above a common sense approach as used by most smoking cessation clinicians (West 2004a). Clinicians tend to use this approach to assess motivation in order to predict success, however, motivation appears to play a very small part in successful quitting (West 2004a).

In a recent study looking at the efficacy of an internet programme, during and after treatment, for an inpatient population; participants were asked to provide answers to several questions based on the stages of change model (Haug, Meyerr & John 2011). The answers to these questions then generated a tailored programme for each participant. No specific details are provided in the paper regarding the success of the intervention based on the tailoring of the participants. Similarly, establishing motivation by using the definitions of the stage of change was used in a randomised controlled trial looking at smoking interventions provided to hospital patients (Lacasse, Lamontagne, Martin, Simard & Arsenault 2007).

It is clear that despite the limitations of these models and the limited evidence associated with their helpfulness at targeting successful interventions with smokers, the TBM and stages of change model are still commonly used in the field of smoking cessation. However, it should be noted that some of the concepts detailed in the model are of use when providing a smoker with an intervention, such as establishing motivation to quit and perceived control over stop smoking but it should be used only to provide constructive behavioural support rather than the tailoring of interventions.

Pharmaceutical treatments for smoking cessation

Pharmaceutical treatments for nicotine dependence are commonly used in combination with the behavioural elements discussed above. Patients have access to NRT, bupropion (Zyban) and varenicline (Champix). All are proven to aid smoking cessation (Cahill et al. 2012, Hughes et al. 2007a, Stead et al. 2008).

Pharmaceutical treatments are offered to help smokers alleviate tobacco withdrawal symptoms particularly in the first few weeks of quitting when withdrawal is most acute. The medications available are not a 'magic cure'; rather they help the smoker remain abstinent through the initial stages of quitting, which most smokers find the hardest.

Nicotine Replacement Therapy (NRT)

NRT is the most widely used medicine for smoking cessation. There are extensive data showing the efficacy of NRT (Stead et al. 2008), which primarily reduces the severity of withdrawal symptoms associated with smoking cessation. The use of NRT products during a quit attempt approximately double the chances of long-term abstinence compared with placebo (Stead et al. 2008).

There are currently seven different NRT delivery systems available on the worldwide market (gum, patch, lozenge, sublingual tablet, nasal spray, inhalator, and mouth spray). In the UK these products are available on prescription as well as over-the-counter (West & Zhou 2007). All of these products work by replacing some of the nicotine that smokers would have otherwise received from their tobacco smoke and thereby reducing tobacco withdrawal symptoms (e.g. irritability, depression,

restlessness). However, although NRT replaces some of the nicotine, the amount of nicotine delivered from NRT is lower and the delivery is much slower.

Abstinence rates are improved if NRT products are combined (Stead et al. 2008). Typical combinations include a nicotine patch with a fast-acting nicotine product (e.g. gum, lozenge, nasal spray).

Directions for use

Some NRT products (patch, gum, and lozenge) come in different strengths (See Table 4). Smokers frequently start on a high-strength patch (e.g. 25mg/16 hour or 21mg/24 hour patch) (McNeil Limited 2012a). There are medium and low strength patches but these are mainly marketed for 'weaning'. A typical weaning schedule would be to use a high strength patch (e.g.25mg/16hour) for up to 6 weeks to then reduce to the 15/10/5mg patches over the remaining 6 weeks of treatment (McNeil Limited 2012a). The gum and lozenges come in high (4mg) and low (2mg) strengths. The higher dose products are usually recommended to more highly dependent smokers (e.g. people who smoke within 30 minutes of waking) (GlaxoSmithKline 2011; McNeil Limited 2010a).

Table 4 – Nicotine replacement therapy dosing, frequency of use

Formulation	Quantity	Licensed dose
16-hour Patch	7 patches per week	25mg/16 hours patch 15 mg/16 hours patch 10mg/16 hours patch 5 mg/16 hours patch
24-hour Patch	7 patches per week	21 mg/24 hours patch 14 mg/24 hours patch 7 mg/24 hours patch
Nasal spray	1 bottle per week	Use one spray in each nostril as required
Inhalator	42 cartridges per week	Use 6–12 cartridges daily
Gum	105 pieces per week	4 mg gum 2mg gum
Sublingual tablets	105 pieces	2mg
Lozenge	72 pieces per week	1mg Lozenge 2mg Lozenge 4mg Lozenge
Mini lozenge	60 pieces	1.5mg 4mg
Nicotine mouth spray	2 bottles per week	1mg

NRT should be used for at least 8 weeks. Some people may need to use NRT for considerably longer than this (Hajek 2007).

Adherence to medication

There are several issues that are frequently reported by users of NRT, which reduce adherence to medications ultimately leading to a failed quit attempt.

NRT is not a magic cure. Many smokers think that by using NRT their urges to smoke will be eliminated, so it is important to outline realistic expectations as to what benefit will be expected from using NRT (McEwen 2012).

The oral NRT products rely on the user to administer nicotine on a frequent basis; typically the compliance with a nicotine patch is higher than an oral product, for example, the nicotine nasal spray (Hajek, West, Foulds, Nilsson, Burrows & Meadow 1999). Another barrier to using NRT is the taste (Foulds, Hughes, Hyland, Le Houezec, McNeill, Melvin, Okuyemi, Shiffman, Wassum, Williams & Zeller 2009 2009). NRT can taste unpleasant but for most smokers' regular use of the product will reduce the unpleasant taste.

Smokers often worry about becoming addicted to NRT products. Helping clients to understand that the use of NRT is not giving them a new addiction but simply weaning them off their tobacco dependence is important in clinical practice (McEwen 2012).

Another common misconception is that nicotine is the dangerous substance in tobacco that causes smoking related illnesses (Bansal, Cummings, Hyland & Giovinno 2004), which again is important to address when discussing NRT in clinical practice.

Currently it is recommended that NRT is used for at least 8 weeks, however many smokers stop using NRT earlier, which has implications on relapse (McRobbie 2005).

NRT safety

There are no risks in using NRT in people who smoke as it provides only the nicotine that smokers would have otherwise received from tobacco (Stead et al. 2008). The risk of overdose is small and there is no evidence that NRT increases the risk of heart attacks (GlaxoSmithKline 2010, 2011b; McNeil Limited 2010a, 2010b, 2012a, 2012b, 2012c). There are no safety concerns with long-term use (GlaxoSmithKline 2010, 2011b; McNeil Limited 2009; McNeil Limited 2010a, 2010b, 2012a, 2012b, 2012c).

Side effects

NRT may cause adverse reactions similar to those associated with nicotine given by other means, including smoking, and these are mainly dose-dependent. (GlaxoSmithKline 2010, 2011b; McNeil Limited 2010a, 2010b, 2012a, 2012b, 2012c). At recommended doses NRT has not been found to cause any serious adverse effects (GlaxoSmithKline 2010, 2011b; McNeil Limited 2010a, 2010b, 2012a, 2012b, 2012c). The most common side effects seen when using NRT are outlined in table 5.

Table 5 – NRT side effects

Formulation	Side effects
16-hour Patch	Skin irritation
24-hour Patch	
Nasal spray	Sneezing, eyes watering, burning sensation in the nostrils
Inhalator	Hiccups, indigestion, heartburn, burning sensation in the mouth
Gum	
Sublingual tablets	
Lozenge	
Mini lozenge	
Nicotine mouth spray	

Excessive use of NRT by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches (GlaxoSmithKline 2010, 2011b; McNeil Limited 2010a, 2010b, 2012a, 2012b, 2012c).

When looking at nicotine patch users specifically, about 20% of users experience mild local skin reactions during the first weeks of treatment (McNeil Limited 2012a). In some patients the skin reactions may become more severe e.g. skin blistering or a burning sensation or may be more generalised.

Contraindications

There are no true contraindications with NRT (GlaxoSmithKline 2010, 2011b; McNeil Limited 2010a, 2010b, 2012a, 2012b, 2012c). NRT can be recommended and used in pregnant and breast-feeding women who smoke (oral products or a day-time only patch are generally seen as the products of choice) (GlaxoSmithKline 2010, 2011b; McNeil Limited 2010a, 2010b, 2012a, 2012b, 2012c).

Combination treatment

A Cochrane review looking at the effectiveness of NRT highlighted six trials that compared the use of two types of NRT with using a single type only, and one compared two types to no NRT (Stead et al. 2008). They found a significant effect of using combination NRT versus single product use (RR 1.35, 95% CI: 1.11 to 1.63). A similar result was found after removal of the no NRT control study. Only one of the trials, comparing nasal spray and patch with patch alone, showed a significantly higher rate of sustained abstinence at one year with combined NRT.

Since the release of the Cochrane review, 2 further studies have been published. Piper, Schlam, Fiore, Jorenby, Fraser & Baker (2009) conducted a study using monotherapy (single product), combination NRT (patch and lozenge) and bupropion versus placebo. The results found that all treatments showed a significant effect compared to placebo. Only patch and lozenge combination was found to be better than monotherapy (OR, 1.35, 95% CI: 1.01-1.79).

Another study used combination nicotine patch plus either active or placebo nicotine gum in alcohol dependent smokers in an outpatient setting (Cooney, Cooney, Perry, Carbone, Cohen, Steinberg, Pilkey, Sevarino, Oncken & Litt 2009). At 1 year follow up the patch plus active gum group had higher rates of validated prolonged smoking cessation rates compared to the placebo gum group (13% versus 0%).

Use of NRT in the UK

Over 60% of NHS-SSS patients used NRT in 2011 (April – December 2011) (The NHS Information Centre for Health and Social Care 2012).

Bupropion (Zyban)

Bupropion is an atypical antidepressant that is effective in aiding smoking cessation. Data from 40 studies of bupropion show that this drug roughly doubles the chances of quitting smoking compared to placebo (Hughes 2007a).

Bupropion should be started at least 1 week prior to the TQD. People take one tablet (150mg) daily for the first 6 days, and thereafter one tablet twice daily, keeping at least 8 hours between each dose. A course of treatment is 120 tablets (approximately 9 weeks).

Contraindications

There are a number of people who are unable to use bupropion, including anyone with a current seizure disorder or any history of seizures, a known central nervous system tumour, abruptly withdrawing from alcohol or sedatives, use of monoamine oxidase inhibitors within 14 days, hypersensitivity to any ingredients in bupropion or a history of bulimia or anorexia nervosa (GlaxoSmithKline 2011a). In addition the use of bupropion is not usually recommended in patients with predisposing risk factors for seizures unless there is a compelling clinical justification for which the potential medical benefit of smoking cessation outweighs the potential increased risk of seizure. Prescribers also need to be aware of possible interactions with other medicines (GlaxoSmithKline 2011a).

Side effects

The most common side effects of bupropion are dry mouth, insomnia, headache, and rash (GlaxoSmithKline 2011a). There is also a risk of seizure, although this is rare and similar to the seizure risk associated with other antidepressants (Oke, Adhiyaman, Aziz & Ross 2001).

Combination treatment

A 2007 Cochrane review identified 6 trials that used combination treatment with bupropion and NRT (Hughes 2007a). The six studies allowed analysis of 1,106 participants. Their conclusion was that there was insufficient evidence that adding bupropion to NRT increases any long-term benefit (RR 1.23; 95% CI 0.67 to 2.26).

The study by Piper et al. (2009) found a significant effect of using combination bupropion and NRT versus placebo (OR 1.74; 95% CI: 1.13-2.67).

Use of bupropion in the UK

Despite its efficacy, bupropion is rarely used by NHS-SSS. Only 1% of smokers accessing the NHS-SSS (April-December 2011) used bupropion (The NHS Information Centre for Health and Social Care 2012).

Varenicline (Champix)

The efficacy of varenicline in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 nicotinic receptors where its binding produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity) (Cahill & Lancaster 2012).

Varenicline at standard dose increases the chances of successful long-term smoking cessation between two- and threefold compared with placebo (Cahill et al. 2012).

Varenicline has been found to significantly increase long-term success rates compared to bupropion and has a marginally significant beneficial effect compared to NRT (Cahill et al. 2012). Varenicline may also have a role to play in relapse prevention interventions but further study into this is needed (Tonstad, Holme & Tonnesen 2006).

In a recent double blind randomised control study, the pre-quit period of varenicline use was extended from 1 week to 4 weeks (varenicline preloading) to determine if increasing the pre-quit medication period makes cigarettes less satisfying and facilitates quitting (Hajek, McRobbie, Myers, Stapleton & Dhanji 2011). Varenicline preloading reduced pre-quit enjoyment of smoking ($p=0.002$) and smoke intake ($p<0.001$), with 37% of participants reducing their cotinine levels and CO levels by over 50% (‘reducers’). As would be expected the 3 measures (cigarette consumption, CO and cotinine levels) were moderately correlated (range, $r=0.60$-0.65, $p<.001$).

Preloading did not affect post-quit withdrawal symptoms, but it increased 12-week abstinence rates (47% vs 21%, p=0.005). The effect was particularly strong in participants who saw an immediate effect on their smoking intake after starting to take varenicline. These "reducers" substantially reduced their smoke intake during the ad-lib smoking preloading period by over 50%.

The finding that the first 'up-titration' week on varenicline had limited impact, and that these effects needed time to emerge, is of clinical relevance. The 1-2 week period of pre-quit dosing recommended by the current drug labelling is likely to be too short to make use of this potentially important effect.

Directions for use

Varenicline should be started at least a week prior to the target quit date and is taken for a total of 12 weeks after the quit day. One tablet is taken daily for the first 3 days (0.5mg), then twice daily from days 4-7. From day seven, 2 x 1mg (BID) tablets are taken for duration of the treatment course (taken 8 hours apart) (Pfizer Limited 2011).

Contraindications

Varenicline has few contraindications. It should be avoided in people with hypersensitivity to varenicline and it is not recommended in pregnant or breastfeeding women or in people under the age of 18 (Pfizer Limited 2011). There are no known drug interactions associated with using varenicline. Varenicline does not undergo hepatic metabolisation and is generally excreted almost completely unchanged (Pfizer Limited 2011).

Having a history of mental health illness is not a contraindication for the use of varenicline, however, it should be used with caution (Pfizer Limited 2011). Mental health patients should been seen regularly for follow-up during their quit attempt. People with mental health illness are more likely to smoke and often suffer with smoking related disease (Pfizer Limited 2011). Whilst it is important to discuss the possibility of psychiatric adverse events these need to be balanced with the potential benefits of smoking cessation.

Side effects

In patients treated with the recommended dose of 1mg BID following an initial titration period the adverse event most commonly reported is nausea (28.6%) (Pfizer Limited 2011). In the majority of cases nausea occurs early in the treatment period, is mild to moderate in severity and seldom resulted in discontinuation.

Encouraging people to take varenicline with food can mitigate this (Pfizer Limited 2011). Other side effects include sleep disturbance and vivid dreams (Pfizer Limited 2011). Advice to avoid taking the drug too close to bedtime can help reduce these side effects.

There have been post-marketing reports of depression and suicidal ideation in people using varenicline (Pfizer Limited 2011). Although there is no firm evidence of causality, caution is warranted. The datasheet advises, “Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly. Varenicline should be discontinued immediately if agitation, depressed mood or

changes in behaviour or thinking that are of concern for the doctor, the patient, family or caregivers are observed, or if the patient develops suicidal ideation or suicidal behaviour" (Pfizer Limited 2011).

Combination treatment

Combination varenicline and NRT treatment has not yet been experimentally evaluated. One cohort report from an in-patient smoking cessation facility found no difference between NRT plus varenicline combination and NRT plus bupropion (Ebbert, Burke, Hays & Hurt 2009). As there was no 'NRT only' or 'varenicline only' group, the results are difficult to interpret, but the report reinforces the need to conduct a randomised 'proof-of- concept' study before launching into a large outcome trial.

Use of varenicline in the UK

In the last quarter of 2011, varenicline was used by 26% of people accessing NHS-SSS.

Helping smokers in the UK to quit

In 1998 the release of the UK government's white paper on tobacco control (Department of Health 1998), was viewed as a milestone for public health interventions in the UK. As a result England was one of the first countries to establish a nationwide network of stop smoking services. NHS-SSS aim to provide the most effective interventions for successful smoking cessation which include both pharmaceutical as well as intensive behavioural support provided by smoking cessation specialists.

Over the last 14 years, millions of pounds have been invested by the DoH to implement and maintain this specialist service. In 2009 total spending on NHS-SSS was almost £84 million, up £10 million from 2008/09 (The NHS Information Centre 2012). Tackling smoking cessation treatment is one of the most effective interventions currently available with the latest figure indicating that it costs the NHS £220 for each successful quitter (The NHS Information Centre 2012).

Smoking cessation programmes are viewed as one of the most cost-effective health behaviour change programmes available on the NHS (Coleman et al. 2010).

National Health Service – Stop Smoking Service (NHS-SSS)

When the DoH first set up smoking cessation services they approached it as a service with different levels of intensity. At the first level all healthcare professionals were encouraged to provide brief opportunistic advice to stop smoking to all people who smoke. The second level involved the provision of a structured smoking cessation treatment that could be accessed by any smoker that wanted help in stopping smoking. This was to consist of behavioural support and NRT and be provided by a group of specially trained healthcare professionals who became known as smoking cessation specialists or advisors. Further evolution gave rise to three levels of service. Level 1 was designated to be the provision of brief advice, level 2 was provision of low to moderate intensity smoking cessation treatment (behavioural support and NRT) from a trained healthcare professional (many of these were practice nurses and pharmacists and became known as Level 2 advisors) and Level 3 was a high intensity smoking cessation service delivering multi-session behavioural support combined with pharmacotherapy.

150 NHS-SSS are currently providing a range of stop smoking interventions within the UK (Brose 2011). In 2011-12 over 800,000 people set a quit date through the NHS-SSS (The NHS Information Centre for Health and Social Care 2012). Of these 400,955 (50%) were self-reported as quitting at 4 weeks and nearly 300,000 (38%) of those were confirmed by CO validation (The NHS Information Centre for Health and Social Care 2012).

Level 1 (Brief advice and referral)

Since the establishment of the NHS-SSS, the task of front line staff in the UK has been to motivate smokers to quit and refer them to a level 2 or 3 service rather than to take on the role of stop-smoking advisors.

There is no ideal way to give smoking cessation advice, but the message should be clear that stopping completely is best; be linked to a current illness if appropriate; and given to all smokers, not just those who desire to quit. Acknowledgement of the fact that stopping may be difficult and many people need to try several times before finally succeeding can be made. However, a positive message should be conveyed (i.e. there are treatments to make quitting easier and improve a smokers chances of stopping).
Currently GPs are expected as part of their duties to record smoking status. GPs are currently paid to do this therefore acting as an incentive to address smoking and cessation.

Level 2 services (Pharmacy, clinic nurse, other Health Care Professionals)

There are several level 2 routes to quit within the UK. Many pharmacists, nurses and other health care professionals (HCPs) such as midwives, social workers and physiotherapists are now trained to provide a level 2 smoking cessation service. This also includes GPs who offer advice and intervention. A level 2 trained advisor combines brief advice alongside medication. There may be follow up visits but these are less intensive and frequent than level 3 services. The level of training is also more basic. Level 3 advisors such as those at the East London specialist smokers' clinic are intensively trained and are typically more knowledgeable as smoking cessation is their primary role. Whereas many level 2 advisors provide smoking cessation advice

alongside their specialist role. Despite their lack of time and knowledge they are more likely to come in contact with people who would not want or are unable to attend level 3 services which make their role in providing smoking cessation to hard to reach groups important.

Level 3 – specialist service

Level 3 services provide intense withdrawal-oriented therapy over several weeks to patients that indicate they would like to stop smoking. In order to successfully help people to stop smoking, the aim of the sessions are to enhance motivation to quit, increasing self-efficacy, to understand the role of habits, to discuss coping skills, cue sensitivity, patterns of smoking and to ultimately endorse behaviour change. The National UK smoking cessation guidelines recommend the use of "the withdrawal oriented treatment model as a practical and proven system for specialist services" (West, McNeill & Raw 2000).

The structured group orientated model (Hajek 1989) is widely used by level 3 specialist services in the UK. There is a wealth of evidence as well as real life experience showing the effectiveness of the treatment model in many different settings and using different populations (e.g. mental health patients, pregnant women, routine and manual populations) (Stead 2005).

There are some advantages of group-based counselling over individual treatment (which is the other treatment format utilised by level 3 services). For example, groups offer smokers the opportunity to learn behavioural techniques for smoking cessation

and to provide each other with mutual support. Groups are also more time and cost efficient and they involve less clinician input.

Individual appointments and flexible drop-in clinics are also common options available to smokers seeking level 3 smoking cessation support.

An example of the group oriented model – The East London Specialist Smokers' Clinic (level 3 specialist service)

The East London specialist smokers' clinic is a level 3 service providing an NHS-SSS in the east end of London. The service provides a service to two boroughs; Tower Hamlets and City & Hackney. The unit has over the last 10 years utilised their position as an NHS-SSS level 3 service to undertake pivotal research in the field of smoking cessation.

The service provides intense withdrawal-oriented therapy over several weeks. The structure of the clinic follows GBT established at the Institute of Psychiatry by Professor Peter Hajek (Hajek 1989). The main aims of the clinic sessions are to increase motivation to quit, enhance self-efficacy, to discuss coping skills, cue sensitivity (identifying situations where they may be more vulnerable to relapse, i.e. socialising, stress at work), patterns of smoking, dealing with the habits associated with smoking with the ultimate aim of the programme being to help the patient to achieve abstinence from smoking.

Accessing the service

The most common route of accessing the service is for patients to be referred to the clinic via their GP or other HCPs. Patients are also able to self refer to the service. Clients interested in attending the clinic will be given several different locations to meet with a smoking cessation specialist, either at the Royal London Hospital site or at other venues within the local community (e.g. GP surgeries, community halls,

hospital venues). All locations are usually central and provide good accessibility for patients.

Screening clients

Patients are booked an appointment to meet with an advisor to discuss the options that are available to them. This session is to discuss the client's expectations and to assess suitability for the NHS-SSS level 3 programme. In some cases other services may be more appropriate, for example, people who chew tobacco would be referred to the local Bangladeshi stop smoking service or the client may present with other issues that are more suited to individual (one-to-one) support.

Structure of the clinic

The programme takes place over 7 weeks, with clients attending the clinic every week for a meeting with a smoking cessation advisor. The aim of the programme is to provide intensive support, both behavioural and pharmacological, to help people to remain abstinent during the first few crucial weeks of stopping, when withdrawal symptoms are at their worst. It is the advisors role in the first 3 sessions to prepare smokers to be ready to quit in the 3rd week (TQD) (full details of each session are outlined in Table 6). These sessions attempt to get clients to maximise their commitment to the quit attempt and to prepare them for stopping.

These preparatory sessions involve discussion about previous quit attempts, discussion of the different medications to use whilst quitting and how to use them, common pitfalls smokers succumb to when stopping smoking and highlighting the importance of complete abstinence from smoking.

The four post-quit day sessions monitor progress, check on medication use and adverse events and provide on-going motivational support.

A limited relapse prevention service is offered at the end of treatment where clients are free to return to, or contact, the clinic as required. The only formal contact after the end of treatment is that clients are contacted 1 year after the quit day to see how they are doing. This is also an important outcome to assess how successful the clinic is in the longer term.

Table 6 - Outline of sessions at the East London specialist stop smoking clinic

SESSION 1: Information session

- Welcome and introductions
- Explanation of treatment and 7-session programme, provision of both positive and realistic expectations
- Explanation of group support
- Provision of rationale for setting a quit date (session 3) and then maintaining complete abstinence
- Provision of information on tobacco and withdrawal
- Discussion of smoking cessation medications and how to access and use them
- Elicit commitment to group programme and quitting completely

SESSION 2: Preparation session

- Facilitate group discussion on strategies for remaining abstinent
- Ensure that each client has medication to use in the quit attempt and address and concerns or issues with medication
- Elicit commitment to group programme and quitting completely

SESSION 3: Quit day

- Facilitate group discussion on how people are feeling about quitting
- Discuss medication issues and ensure people know how to use the products correctly
- Enhance social support by 'buddy' task
- Facilitate group discussion on coping strategies

- Elicit commitment to a good start (e.g. facilitate a round of promises not to smoker a single puff in the next week)

SESSIONS 4-6: First 3 weeks after quitting

- Each member reports to the group on how the week went and reports on contact with their buddy
- Facilitate group discussion on strategies to maintain abstinence
- Provide advice and reassurance on withdrawal symptoms as required
- Check on medication use and provide advice as required
- Elicit commitment to maintaining abstinence

SESSION 7: End of treatment

- Celebrate success of group
- Each member reports to the group on how the week went and reports on buddy's progress as well
- Facilitate group discussion on strategies to maintain abstinence – basic strategies can be communicated e.g. continuing to use medications, get in touch with stop smoking service whenever needed, keep in regular contact with buddy, avoid risky situations until confident about not smoking.
- Reinforce key messages – not a single puff, will get easier over time

Role of the clinician

One of the key roles for a smoking cessation advisor is to ensure accurate information is given to clients particularly on the use of NRT. NRT is typically used only occasionally and not for not for the recommended period of time. This is often the cause for relapse back to smoking (McEwen 2012). The important message here is frequent use of medication and for use of at least 8 weeks.

As well as dealing with common misconceptions it is also important to set realistic and positive expectations for the group (Hajek 1989). Discussion of success rates and relapse rates associated with using the group-oriented treatment programme can help to encourage participants to attend the group on a weekly basis (Hajek 1989).

Medication use

Clients are advised to use medication for a minimum of 8-12 weeks. The quit day is generally set on the third visit and clients are instructed to have their last cigarette immediately before this session. The correct use of medication is discussed, strategies to boost motivation and support are provided, and the importance of complete abstinence is reinforced. All the medication (NRT or varenicline), support and guidance offered to smokers through the NHS are free of charge. The Medication is provided on NHS prescription on a weekly (for NRT) or fortnightly (for varenicline) basis. A prescription charge (£7.85) applies to each prescription, but this fee is waived in those people entitled to free prescriptions (e.g. those people on low income, under the age of 16 or over the age of 60, receiving income support) (Department of Health 2004).

Measuring success

Smoking status at 4 weeks after the TQD is used as a standard outcome measure for success for the NHS-SSS. It is estimated that approximately 60% of smokers per year successfully quit smoking through the stop smoking service (Judge et al. 2005), using the standard 4-week marker. One in seven clients who set a quit date are expected to be abstinent at 1-year follow up (Ferguson et al. 2005).

Monitoring guidance

In line with NICE best practice recommendations, service providers should aim to treat a minimum of 5% of their local population of smokers in the course of a year (NICE 2008). The DoH guidance (2011/12) specifies that NHS-SSS performance in treating smokers should reflect local smoking prevalence rates and in order to maintain standards and ensure best practice, the DoH monitors each NHS-SSS performance quarterly.

The DoH guideline outlines the good clinical practice that should be followed by the NHS-SSS. Services are responsible for delivering treatment that conforms to the current NICE recommendations. Services should be evidence-based, effective, accessible and appropriate to the needs of the local population (Department of Health 2011).

Each NHS-SSS is responsible for collecting data from service users and to ensure that the data collected is verified. Confidentiality and data protection should be inline with local protocols. Data collection for the NHS-SSS involves reporting of quit days set and validated success rate at 4 weeks (self reported abstinence rates are also reported).

Validating abstinence

For the majority of NHS-SSS objective measures of smoking status are routinely measured by CO readings. CO in expired breath can be measured as an approximation of how much someone has smoked, however, the reading that is given is dependent on time since last cigarette and also time that the reading is taken. For example, a CO reading in the morning will only reflect the first few cigarettes of the morning compared to a reading at the end of a day of smoking; the reading is likely to be significantly higher. At each session members have their CO levels measured. This acts as a motivator for abstinence (people like to see their CO reading decrease when they stop smoking) and also validates self-reported smoking status for the purposes of monitoring which are sent quarterly to the DoH.

Clinic Questionnaires

There are 2 standard questionnaires used by the East London Specialist Smokers' Clinic. Once a client books on to the clinic a questionnaire will be sent to them by post alongside an invitation letter with the time and date for their appointment at the clinic. This questionnaire collects personal information required by the clinic for contact and reporting to the PCTs in the first instance. This information will then be collated alongside the figures from the other smoking cessation services (e.g. pharmacists, GPs) within the borough and sent to the DoH. The demographics recorded include; date of birth, occupation, educational background. The questionnaire also includes questions, which are used to guide the treatment of the smoker which include smoking history, FTND, reasons for wanting to stop smoking, and questions pertaining to the state of their current health. Clients are asked to complete this at home and bring it with them to the first clinic visit. The other

questionnaire records clinic attendance, smoking status, medication use, adverse events and occurrence and severity of withdrawal symptoms over the past week.

To summarise, the aim of the East London Specialist Smokers' Clinic is to prevent relapse during the early phase of the quit attempt by providing intensive support (both behavioural and pharmacological) during the time that withdrawal symptoms are typically at their worst (i.e. in the first 2-4 weeks of abstinence). Treatment is delivered by specialist advisors, trained in providing smoking cessation treatment, in an individual or group setting over seven 1-hour sessions on a weekly basis.

CHAPTER 6 – STUDY – EFFECTS OF A COMBINATION OF VARENICLINE AND TRANSDERMAL NICOTINE PATCH ON POST-QUITTING URGES TO SMOKE

Abstract

Background to research project and aims

Most smokers in the UK want to stop smoking, but many find this a difficult task. The NHS-SSS uses the best available evidence-based treatments and achieves long-term abstinence rates of about 15% (Ferguson et al. 2005). This still leaves a large number of smokers in need of more effective help.

Nicotine replacement therapy (NRT) and varenicline are both effective in helping smokers quit (Cahill et al. 2012; Stead et al. 2008). There is growing interest in combining the two treatments to improve treatment outcomes, but no experimental data exist on whether this is efficacious. In theory a combination could improve withdrawal relief; help to extinguish smoking rewards and lower the risk of lapses translating into relapse. The research conducted for this doctorate portfolio will look at the efficacy of using varenicline in combination with a nicotine patch and whether this combination regimen reduces urges to smoke 24 hours and 1 week post-quitting.

Methods

A randomised double blind placebo-controlled trial was conducted using a sample of 117 participants. Participants were randomised to use varenicline plus ***active*** nicotine 15mg/16hr transdermal patch or varenicline plus ***placebo*** 0mg/16hr patch.

Results

Adding a nicotine patch to varenicline had no effect on post-quit urges to smoke or on other cigarette withdrawal symptoms at any time point. There was no effect on abstinence rates at any time point (79% vs 80%, 69% vs 59%, 50% vs 41% and 14% vs 12% at 24 hours, 1, 4 and 12 weeks in the nicotine and placebo patch group, respectively).

Conclusion

The efficacy of varenicline is not enhanced by the addition of nicotine patches.

Study rationale

NRT is the most widely used medicine for smoking cessation (Stead et al. 2008). There are extensive data showing the efficacy of NRT (Stead et al. 2008), however, despite its good track record people who use it still have a less than 20% chance of quitting for a year or more (Ferguson et al. 2005). It is currently recommended, and there is evidence to support that an increase in successful quitting can be seen if NRT products are used in combination when attempting to quit smoking (Stead et al. 2008).

Varenicline is a partial nicotinic agonist which acts on α4β2 nicotinic receptors. It is presumed to alleviate withdrawal discomort, but also to diminish the rewarding effects of cigarettes. In studies evaluating its efficacy, patients who lapsed and smoked after the target quit date (TQD) were asked to rate their experience. Compared to patients on placebo, bupropion and nicotine patch, those on varenicline derived less satisfaction from their cigarettes (Aubin, Bobak, Britton, Oncken, Billing, Gong, Williams & Reeves 2008; Gonzales, Rennard, Nides, Oncken, Azoulay, Billing, Watsky, Gong, Williams & Reeves 2006; Jorenby, Hays, Rigotti, Azoulay, Watsky, Williams, Billing, Gong & Reeves 2006; West, Baker, Cappelleri & Bushmakin 2008). This is presumed to be caused by the drug blocking the nAChRs, which would otherwise facilitate the reward associated with smoking.

There is currently no evidence available to show if using a combination of varenicline and NRT is effective. Anecdotal experience from the East London Specialist Smokers' Clinic indicates that it is common for people stopping smoking to use varenicline in combination with NRT and that they report it to be beneficial.

Combining varenicline and NRT may in theory improve withdrawal relief; help to extinguish smoking rewards and lower the risk of lapses translating into relapse, and/or NRT may reduce some withdrawal symptoms, which are less sensitive to varenicline and vice versa. There are smokers who report no reaction to one of the treatments who may be sensitive to the other and the combination may be of particular benefit to this group.

Based on observable effects on smokers, the two medications appear alike, although varenicline has antagonist as well as agonist effects. They both seem to achieve their effect on abstinence by alleviating the discomfort of nicotine withdrawal (Cahill et al. 2012, Stead et al. 2008). They also make cigarettes smoked while on the medications less rewarding and thus may facilitate extinction. The latter effect has been demonstrated for both varenicline (Gonzales et al. 2006; Hajek et al. 2011; Jorenby, et al. 2006; Shiffman & Ferguson 2008; West et al. 2008) and NRT (Lindson & Aveyard 2011; Shiffman & Ferguson 2008), although the evidence for the NRT seems weak (Lindson & Aveyard 2011).

In terms of neuro-physiological targets, varenicline is known to affect primarily α4β2 nAChRs where it has higher affinity than nicotine and so essentially blocks nicotine effects, as well as acting as a partial agonist (Prochaska & Hilton 2012). Nicotine from NRT acts on all nAChRs in a similar manner to nicotine from tobacco smoke, but delivery from NRT is much slower (Le Houezec 2003).

It is not clear if the central effects of the two medications are sufficiently different to allow synergy, but if they do differ, their combination could have several beneficial

effects. It could in theory improve withdrawal relief and/or assist smokers who may not react much or at all to one of them, but who may be sensitive to the effects of the other one. If their effects are due to impact on different target mechanisms, this would raise a possibility that their combination may achieve better results than using each of the medications on their own.

Another putative mechanism by which a combination could be more effective than single administration concerns the timing of the two medications. Varenicline is used for 1-2 weeks prior to quitting, concurrently with smoking. It is possible that from the TQD on, when nicotine intake from cigarettes ceases, replacing the nicotine lost from cigarettes with that from NRT could reduce post-quitting urges to smoke and withdrawal discomfort. It is of course also possible that the targets of the two medications overlap too much for their combination to provide any additional benefit, and/or that the receptor occupancy provided by varenicline blocks any additional effects of NRT.

Regarding the safety of combination use of NRT and varenicline, a single pre-marketing study showed that smokers using varenicline and a transdermal patch for 12 days reported a higher incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue than smokers who used NRT alone (Pfizer Limited 2011). However, these symptoms may have been due to varenicline use, as opposed to combined use of varenicline and NRT. Post-marketing data suggests that combined use of varenicline and NRT is well tolerated (Ebbert et al. 2009).

One cohort report from an in-patient smoking cessation facility found no difference between NRT plus varenicline combination and NRT plus bupropion (Ebbert et al. 2009). As there was no 'NRT only' or 'varenicline only' group, and the various medication combinations were not systematic, the results need to be interpreted with caution. The study, however, provides a useful reassurance that a combination of NRT and varenicline is safe and well tolerated, but the report reinforces the need to conduct a randomised 'proof-of-concept' study before launching into a large outcome trial.

This is a proposal to examine whether combining nicotine patches and varenicline in the first 4 weeks after quitting, provides better withdrawal and craving relief than varenicline alone, in a sample of 120 smokers who want to quit. Nicotine patches were used in this study due to the high level of adherance associated with the product and that they provide a standard dose of nicotine unlike oral products where daily dose is determined by how often and how well they are used.

Funding

The study was supported by an investigator-initiated grant from Pfizer, who also supplied varenicline. Nicotine and placebo patches were supplied by McNeil. The two pharmaceutical companies had no involvement in the design and conduct of the study, analysis and interpretation of the data, or preparation of the manuscript.

Conflicts of interest

The author has no conflicts of interest to declare.

Study objectives and endpoints

Primary Objective

The principal question this study plans to answer is whether the combination of varenicline and NRT reduce post-quitting urges to smoke more than varenicline alone.

Secondary Objectives

In addition to change in urges to smoke this study will determine if combined use of varenicline and NRT compared to varenicline alone:

- Affects severity of withdrawal symptoms over 4-weeks after quitting
- Affects 4-week and 12-week abstinence rates
- Is associated with an increase in adverse effects

Trial Endpoints

Primary Endpoint

Ratings of urges to smoke one week after the target quit date assessed by the Mood and Physical Symptoms Scale [MPSS] (West & Hajek 2004).

Secondary Endpoints

Ratings of urges to smoke 24 hours after target quit date, change in MPSS scores of urges to smoke and tobacco withdrawal symptoms throughout the first four weeks of abstinence; adverse events profile; abstinence rates at 4-weeks and 3-months.

Study design

A randomised double blind placebo-controlled trial was undertaken. Participants were randomised on their target quit date (TQD) to use varenicline plus nicotine 15mg/16hr transdermal patch or varenicline plus placebo 0mg/16hr patch. All participants in the study were advised to use varenicline in the standard way (commenced 1-week prior to the TQD and then continued use for upto 12 weeks). Participants were asked to smoke ad-libitum rather than try to limit their smoking up until the TQD. Participants attended standard weekly support sessions following a withdrawal-oriented treatment protocol as provided by the NHS Stop-Smoking Service. Nicotine patches were used for the first 4 weeks after TQD.

Inclusion Criteria

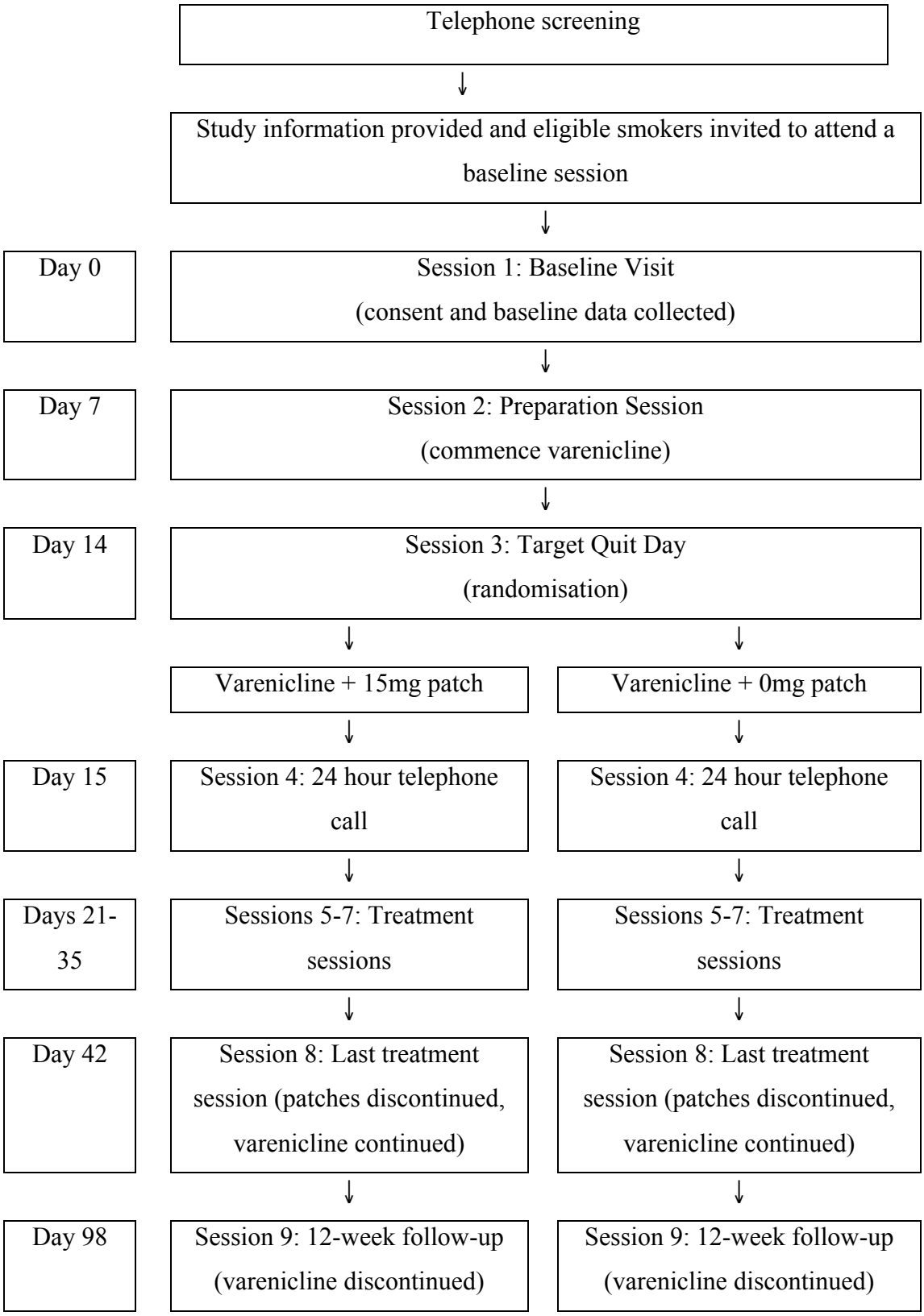
Smokers seeking treatment, aged 18 and over, consenting to take part in the trial.

Exclusion Criteria

Participants were exluded if they met any of the following criteria:

- Current psychiatric illness
- Pregnant/breastfeeding/planning to conceive during the study period
- End-stage renal disease
- Previous allergic reaction to varenicline or nicotine patches
- Unable to fill in the questionnaire in English
- Currently involved or intending to be involved in another research project

Figure 3 - Study Scheme Diagram



Study procedures

Number of Subjects and Subject Selection

The study aimed to recruit upto 120 participants who wanted to quit smoking. Participants were recruited by adverts in London newspapers including the free Evening Standard, Metro, and local papers (see Appendix 1). Those contacting the clinic who were interested were screened over the phone for initial eligibility for inclusion using a questionnaire.

Telephone screening

A questionnaire was developed to screen people who contacted the clinic interested in taking part in the study (see Appendix 2). The telephone questionnaire covered the inclusion and exclusion criteria for the study. Ineligible callers were offered standard specialist treatment for smoking cessation at the East London Clinic or if they lived out of the area were referred to their local services for treatment. If eligible, they were invited to attend a screening visit at the clinic where they were given the opportunity to speak to the study doctor before consenting to take part.

Piloting the telephone screening procedure

The questionnaire and script were developed in 'role-play' practice sessions among the researchers involved in the study. The script (Appendix 3) took approximately 5 minutes to read with a further 5 minutes to complete the screening questions. After booking an appointment slot and taking contact details for the invitation letter, the completion of the telephone sessions lasted approximately 12 minutes. No major issues arose from the role-play. Several changes were made to the wording of the questions to make them more understandable; these included examples of what fell

under the umbrella heading of psychiatric illnesses. The examples included were schizophrenia, depression and anxiety disorders.

If eligible, callers were mailed a patient information sheet (PIS) (Appendix 4) describing the study. The PIS was drafted in simple language and given to each participant, at least 24 hours before consent in order for them to have sufficient time to consider if they wish to take part. They were also sent an appointment invitation (Appendix 5) and a standard clinic questionnaire to complete before attending the baseline session (Appendix 6).

Baseline visit procedures

At the baseline session, study details were discussed and informed consent collected. Participants were screened for inclusion and exclusion criteria.

Informed Consent Procedures

The formal consent of a participant, using the approved consent form (see Appendix 7), was obtained before the participant underwent any study procedure. The consent form was signed and dated by the participant and the investigator-designated research professional (in this case the study doctor) obtaining the consent. A copy of the consent form was provided to the participant and a copy was retained for the trial master file.

Before obtaining consent, the investigator informed each participant of the objectives, benefits, risks and requirements of the study, as well as the nature of the test medication.

GP letter

All participants were asked to consent to their GP being informed of their decision to take part in the study (see Appendix 8). The letter was sent to update the GP of their patient's inclusion in the study and included a brief summary of the project. The letter was sent after the participant consented.

Randomisation Procedures

At the TQD session, participants were randomised to one of two conditions. The study treatment group received a standard dose of varenicline (Champix™), 1 mg twice daily (BID) combined with Nicorette® 15mg patch/16 hour and the standard treatment group received a standard dose of varenicline (Champix™), 1 mg bid combined with Nicorette® 0mg/16hour (placebo) patch. The placebo patch was identical to the standard patch except that it contained no nicotine.

Randomisation codes were sequentially allocated to 120 participant numbers (001-120), which were prepared by a computer in advance. The randomisation list was generated by an independent statistician not involved in the study. Once the participant was assigned a participant number, the study staff retrieved the box of patches corresponding to the relevant randomisation code. As the study was double blind both the participants and the study staff were not aware of the condition assigned to them. The allocated randomisation code and IMP label was updated on the drug accountability form for each participant.

Schedule of Treatment for each visit

Session 1: Screening and baseline Session

The majority of participants attended a weekend screening session that was held in May 2011. For those who could not make the weekend screening, weekday appointments were made available at the main offices of the East London Specialist Smokers' Clinic.

On arrival, participants were invited to ask questions about the study and were given further details by the research team about what to expect throughout the course of the study. The study doctor made the final checks for each participants eligibility to be involved in the trial before consenting.

Participants were asked at each session to complete a questionnaire asking about their smoking consumption in the previous week, MPSS ratings and a CO breath test was also taken (full details for the schedule of assessment can be viewed in Table 7). Participants were asked specifically not to cut down or to stop smoking until the TQD. Medications were not given to the participant at this session.

Session 2: Preparation session

The preparation session (session 2) was held as a group clinic following the standard NHS-SSS withrawal oriented protocol. Five groups were held in total on weekday evenings between 5-7pm. The groups only included people involved in the study. The study lead and one of the co-investigators ran all the clinics.

The preparation session was held one week prior to the participant's TQD. The aim of the session was to provide standard NHS stop smoking advice and support on how best to prepare for the TQD. Participants were given a varenicline starter pack (1st 2-week supply) to start taking the following day. Participants were told how to use the medication and provided information on how the medication worked. Participants were again asked to smoke ad-libitum untill the TQD (next session).

Session 3: TQD Session

On arrival, participants were sequentially allocated to a randomisation code and given the appropriately coded box of 28 patches. The possible side effects that may be expected from patch use were also discussed. Each participant was told how to use the patches and instructed to start using them the following morning.

Session 4: 24-hour telephone call

Participants were called 24 hours after their TQD and were asked to report on their smoking status and to rate the occurrence and severity of their urges to smoke in the last 24 hours. All participants were provided with brief behavioural support and advice. The content of the brief support covered several behaviour change techniques (BCTs) for smoking cessation (Michie, Churchill & West 2011). The protocol for this advice was based on the very brief advice (VBA) included in the UK National Centre for Smoking Cessation and Training (NCSCT) guidelines. Clinicians asked participants their smoking status (if any lapses, how many cigarettes smoked), completed the MPSS, provided information on later appointments and further advice on varenicline and the nicotine patch. Participants were then informed of the date and time of their next appointment. The call lasted approximately 10 minutes.

Sessions 5-8: Weekly treatment sessions

Participants attended the clinic weekly, for four weeks after the TQD session. Participants were asked each week about their smoking status, withdrawal symptoms and urges to smoke and were asked to report any adverse events. CO readings were taken at each face to face visit. Behavioural support and advice was provided by the clinicians running the group and participants were encouraged to discuss the weeks progress.

Varenicline continuation packs were provided at session 5 (2-week pack) and sessions 6 and 7 (4-week pack).

Session 9: 12-week follow-up

A 12 week follow-up took place to check on particpants' progress at the end of medication treatment. Smoking status since the last visit, occurrence and severity of tobacco withdrawal symptoms and adverse events were recorded. Participants who had not stopped smoking were advised and referred as appropriate.

Management of participants who did not attend sessions

For participants who did not attend the sessions when expected, every effort was made to contact them so they could either re-schedule the appointment or fill in the questionnaire on the phone. Data was only collected at + or - 2 days of the scheduled appointment date. If someone missed a session and no data was collected but they reported abstinence since their last visit and were validated as being abstinent then they were documented as self-reported abstainers for the missing session.

Participant incentives

The expected duration of participation in the study was 14 weeks (2 weeks prior to and 12 weeks after the target quit date). Participants in the study were required to attend the clinic on one extra session compared with usual practice at the NHS-SSS (8 instead of 7 sessions) and to receive an extra phone call, 24 hours after quitting. In order to cover travel expenses, participants were paid £30. Participants were paid £15 at session 4 (quit + 1 weeks) and £15 at session 7 (quit + 4 weeks). All participants were required to sign a participant expense form to declare they had received payment. All records for this were stored in the trial master file.

Procedures for unblinding

A standard operating procedure (SOP) was developed to be followed in case there was a need to unblind a participant's medication allocation. If required the chief investigator would be contacted to agree to unblinding of the medication and to determine if it was necessary. Where the chief investigator needed to remain blinded, another member of staff not involved in the study was responsible for following these procedures. Any unblinding that occurred before the official close out of the study was recorded as a protocol violation in the trial master file.

The independent study statistician held a copy of the randomisation codes. A second responsible person, who was not a member of the study team, but located at the study site held a second copy of the randomisation codes in sealed envelopes.

Investigational medicinal products (IMPs) and placebo descriptions

Varenicline (Champix™)

Commercial supplies were used as per standard labelling (0.5mg/d for the first 3 days, 1mg/d on days 4-7, followed by 2mg/d for the rest of the 12-weeks course). The varenicline used in the study was provided by Pfizer Ltd.

Formulation of varenicline

0.5mg film-coated tablets (commercial supply)

0.5 mg film-coated tablets (commercial supply): White, capsular-shaped, biconvex tablets debossed with "Pfizer" on one side and "CHX 0.5" on the other side. Each film-coated tablet contains 0.5 mg of varenicline (as tartrate).

1 mg film-coated tablets (commercial supply)

Light blue, capsular-shaped, biconvex tablets debossed with "Pfizer" on one side and "CHX 1.0" on the other side. Each film-coated tablet contains 1 mg of varenicline (as tartrate).

Nicorette® 15mg/16 hour transdermal patch

Nicotine (15mg/16 hours) and placebo patches (0mg/16 hours) were identically packaged. The patches used in the sudy (both placebo and active) were provided by McNeil Ltd.

Formulation of nicotine patch

Nicorette® 15mg/16 hour transdermal patch

Nicotine, 15mg released over 16 hours use. Each patch is 30 sq.cm, containing nicotine 0.83mg/sq.cm.

Placebo 0mg/16 hour transdermal patch

The placebo patch is identical to the standard patch except that it contained no nicotine.

Preparation and Administration of IMP

The table below shows the study treatment regimen.

Table 7 – Study treatment regimen

Day(s)	**7-13**	**14-42**	**43-98**
Session(s)	2	3 - 8	9
Varenicline dose	Days 1-3: 0.5mg o.d. Days 4-7: 0.5mg b.d.	1mg b.d	1mg b.d
Patch dose	Nil	15mg/16hr or 0mg/16hr o.d.	Nil

Varenicline was used for a total of 12 weeks. Nicotine patches were used for 4 weeks, starting from the TQD. It is usual to recommend 12 weeks use of nicotine patches but for the purpose of the study, patches were only used during the time when withdrawal symptoms are most acute (the first 4 weeks post quit).

Label design

Bilcare UK, was contracted to label and package the IMPs. The labels were designed by the study team in accordance with labelling guidance as recommended by the MHRA (see Figures 4-6). Computer generated randomisation codes were added to each label and affixed to each box. A 4-week supply of patches (active or placebo) was packaged into a single box.

Figure 4 – Nicotine/Placebo box label

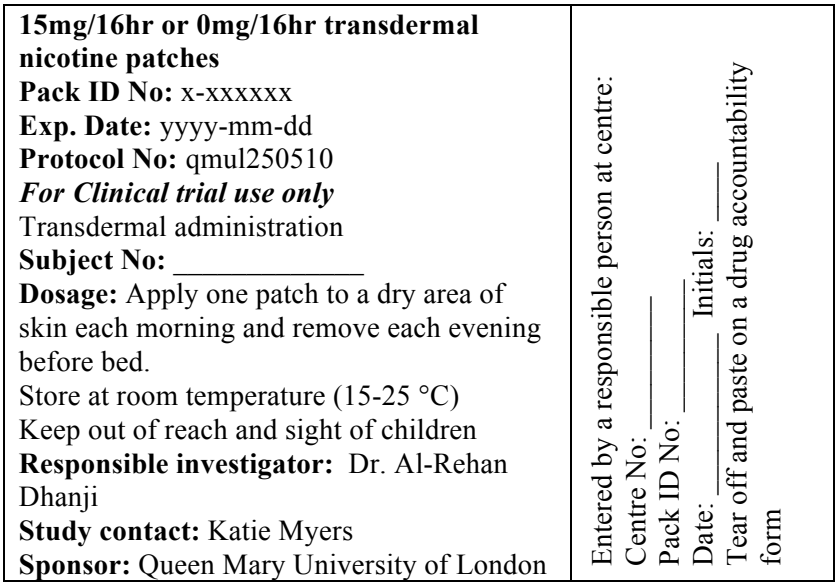


Figure 5 – Varenicline starter pack (commercial supply) label

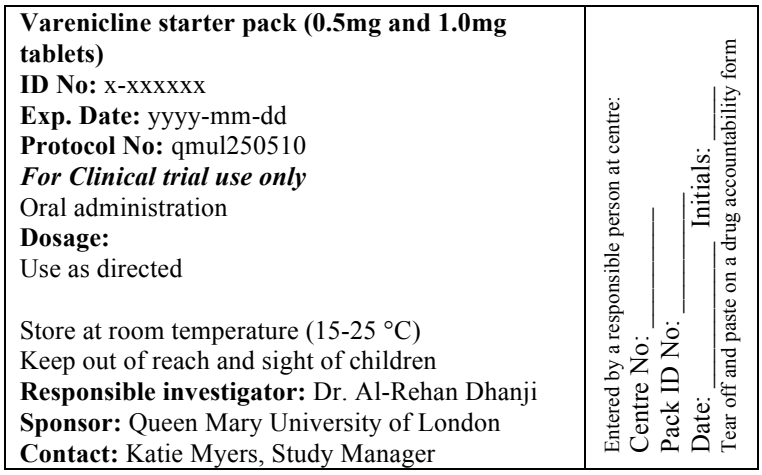
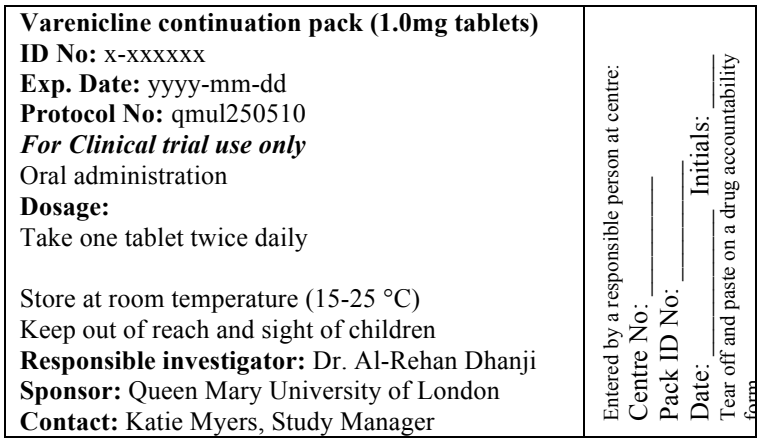


Figure 6 – Varenicline continuation pack (commercial supply) label



Handling of IMP

All packaged and labelled IMPs were shipped to the pharmacy outpatient department at The Royal London hospital where they were securely stored until required for dispensing in the study. Medications were not dispensed to participants by the pharmacy, as study visits were out of hours. After pharmacy approval was granted the study manager was responsible for collecting study medications from the pharmacy

when required and transferring to storage at the study site (TDRU). The medications were kept in a locked cabinet in a locked room.

IMP logs

Logs were put in place to receive, store and dispense the IMPs in accordance with Good Clinical Practice Guidelines (GCP). Copies of these logs were stored in the TMF.

IMP Stability

The IMPs are stable at room temperature. Room temperature was monitored and recorded on a daily basis.

Dispensing of IMP

IMPs were dispensed by the study manager at the clinic site under supervision of the study doctor. A log was kept in the trial master file, which documented all medication dispensing activities.

Return and destruction of IMP

Participants were asked to return any unused medication each week. Quantities of returned medication were counted to assess compliance with treatment. Unused study medications were returned to the hospital pharmacy for destruction. Return of study drugs were documented in the drug accountability log.

Measures

All proposed questionnaire measures were included in the Baseline Smokers Clinic Questionnaire (Appendix 6) and Clinical Record Forms (Appendix 9). These include the following:

Standard smokers' clinic baseline questionnaire

A standard baseline questionnaire from the East London Specialist Smokers' Clinic was used. Participants were asked to complete the questionnaire prior to attending the screening session.

This questionnaire collects information on demographics including; gender, age, ethnicity, qualifications, entitlement to free prescriptions, marital status and GP details. Details of cigarette consumption, previous quit attempts and the use of stop smoking medications were recorded. All participants were asked about their current and past medical history. All medical questions were asked for the purpose of eligibility screening by the study doctor and to identify medications which may need the dose altering as a result of stopping smoking e.g. warfarin.

Client Record Forms (CRF)

A CRF was designed specifically for the study by the researcher in order to collect study measures. Items included; attendance at the clinic, smoking status, CO reading, MPSS ratings.

Table 8: Study sessions									
DAY	0	7	14	15	21	28	35	42	98
Session number	1	2	3	Phone call 1	5	6	7	8	9
Measures/ procedures	Base-line visit	Wk 1 visit	Wk 0 TQD	24h call	Wk 1 visit	Wk 2 visit	Wk 3 visit	Wk 4 visit	Wk 12 visit
Informed consent	X								
Baseline questionnaire*	X								
FTND	X								
CO	X	X	X		X	X	X	X	X
MPSS	X	X	X	X	X	X	X	X	X
Medication dispensed		X	X		X			X	
Weight	X	X	X		X	X	X	X	X
Smoking status/rate	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X

* Demographic details, health status, and smoking history

The participant completed these at each visit and at every phone contact.

Participants were also asked from session 3 onwards to report any adverse events they attributed to the medications. The CRF included a section for monitoring all adverse events that occurred during the study. Adverse events were rated by the researcher after discussion with the participants to be severe, moderate or mild. The appropriate advice was given on review of any adverse events. Details on the definition of AEs are outlined in the next section.

The CRF was anonoymised and contained no identifiable participant data other than the participant number for use by the study staff.

FTND

The FTND is a measure of dependence (Heatherton et al. 1991) that consists of six questions that are scored and summed. A score of four or above is seen in smokers in the general population, and scores of six to ten indicate high levels of dependence.

MPSS

A measure of severity of tobacco withdrawal symptoms and urges to smoke was collected using the MPSS (West & Hajek 2004). The MPSS was completed at all contacts (both face to face and by telephone). A six-point scale is used to rate 'How much of the time have you felt the urge to smoke in the past week?' (from 'not at all' to 'all of the time') and 'How strong have the urges been?' (from 'no urges' to 'extremely strong'). Clients also rated how they have been feeling during the past

week with regard to depression, irritability, restlessness, hunger, poor concentration, poor sleep at night, and anxiety on a scale ranging from 1=not at all to 5=extremely.

Smoking rate

In the sessions before stopping smoking, participants were asked to estimate the average number of cigarettes smoked per day since the last visit. Where a range was entered (e.g. 10-15), the highest number was recorded on the database for consistency.

Smoking status

At each of the sessions following the quit day, participants were asked if they had smoked at all over the past week. If participants reported smoking they were given an option of four answers (1) No, not a single puff, (2) yes, just a few puffs, (3) yes, between 1 and 5 cigarettes, and (4) yes, more than 5 cigarettes.

Carbon monoxide reading

End-expired CO readings were recorded at all face-to-face visits using a Bedfont piCO smokerlyzer monitor. Clients were instructed to hold their breath for 15 seconds before exhaling through the CO monitor. All monitors were calibrated before being used in the study. Carbon monoxide readings were entered into the CRF at each visit.

Smoking cessation outcomes

Smoking cessation outcomes were measured in the following way; *Continuous abstinence* at 4 weeks and 12 weeks after TQD was defined as a self-report of no smoking (not a puff) since TQD validated by CO readings at all time points or if the session was missed, validated by CO reading (where scheduled) at the next

attendance. Participants who self reported abstinence but were not CO validated at week 4 were considered smokers unless they were validated as abstainers at week 12. We also calculated 4 and 12 weeks sustained abstinence in accordance with the Russell Standard (West et al. 2005) as a self-report of smoking no more than 5 cigarettes since TQD validated by CO reading <10 ppm during weeks 1-4 as above. In the analyses of changes in smoking behaviour prior to quitting, only participants who provided data were included, i.e. no imputations were used. In the analysis of cessation rates, participants lost to follow-up were considered to be smoking.

Weight

Participants had their weight taken in kilograms (kg) at baseline and session 7. The same scales were used with each participant on all occasions. The scales used were Omron Body Fat Scale BF400.

Height

Height was self-reported by the participants on the baseline questionnaire. The study staff did not verify height so in cases where the participant did not know their height then this field remained blank and no BMI was calculated.

End of Study Definition

The definition of the end of the study was when the last participant completed the 3-month (post TQD) follow-up. The study was closed on 17 October 2011. The sponsor (QMUL), MHRA and ethics were informed as soon as the study data collection was complete.

Ethical considerations and patient safety

The CI alongside support from the study team was responsible for ensuring that the trial was conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of good clinical practice (GCP) and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and 2008, Trust and Research Office policies and procedures and any subsequent amendments.

Throughout the design of the study, participant's welfare and safety was the main consideration for the research team. For many people stopping smoking can be a difficult and stressful time and maintaining regular contact with smokers ensures careful monitoring of their wellbeing. Participants were made aware that at any point they could withdraw from the study if they wished without any affect to their treatment.

Other procedural considerations

Criteria for Premature Withdrawal

There were 2 main routes that participant's could withdraw before the end of the study. These were:

(1) ***The participant withdraws his/her consent to participate***

(2) ***Withdrawal events***

These are events leading to withdrawal from the trial although participants were followed up with the same schedule of clinic visits (with the participants consent). The following events were grounds for withdrawal from the study:

- Acute myocardial infarction, angina pectoris, or other serious medical condition
- A major psychiatric disorder which impedes compliance with trial protocol
- Pregnancy
- A serious adverse drug event (defined as any untoward medical occurrence that at any dose results in death, in significant or permanent disability or incapacity, is life-threatening, requires hospitalisation or prolongs hospitalisation)

Data Collection and Follow up for Withdrawn Subjects

If a participant was withdrawn from the study or withdrew consent to participate in the study part way through, attempts were made to obtain permission to record at least adverse events and other data up to the end of the last visit. This was done via phone calls to the participant and contact with the participant's general practitioner.

Confidentiality and data protection

Participants were asked to complete the standard clinic questionnaire and the additional questionnaires required for this study. Medical information about participants was not requested from their other doctors (hospital or general practitioner). All information was kept confidential, just as is normal for smokers attending the NHS-SSS. Participants GPs were informed, with the participants consent, of their participation in the study.

Only study staff had access to the study data, which were stored securely at the TDRU. CRFs were anonymised and kept separate to any personal information, baseline questionnaires and consent forms. Participants were allocated a participant number, which was used as the main identifier throughout the study. The Microsoft access, excel and SPSS (version 18) databases were also anonymised and contained no individual identifiers other than the participant and randomisation number.

Treatment setting

In cases where participants found the group setting unsuitable, individual sessions were offered.

Complaints

Participants were made aware that if they had any complaints or concerns about the study that they could contact Barts and the London Trust for advice and guidance. All relevant details for making a complaint were included in the patient information sheet.

Adverse Event (AE)

An AE is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of an Investigational Medicinal Product (IMP), whether or not considered related to the IMP.

Serious Adverse Event (SAE)

An SAE fulfils at least one of the following criteria:

- Is fatal – results in death (NOTE: death is an outcome, not an event)
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Suspected Unexpected Serious Adverse Reaction (SUSAR)

The definition of a SUSAR is any serious adverse event related to an IMP that is both suspected to be related to the IMP and unexpected. In this case the event is not outlined in the Summary of Product Characteristics (SPC) for that product.

Trained study clinicians were responsible for documenting these events including the timescale of the event and assessing the severity of the event and whether it was linked to the study medications. As per usual protocol participants experiencing medication related to adverse events were advised to reduced dose or stop medication

where appropriate. All adverse events were judged on a case-by-case basis and in full discussion with the participant. Any adverse events, which warranted contacted with the study doctor for advice, were documented in the trial master file.

Notification and Reporting of Serious Adverse Events/SUSAR

In cases where an SAE or SUSAR were reported, the following procedures were followed;

All Serious Adverse Event (SAEs) were recorded in the subjects' notes, the CRF, the sponsor SAE form and reported to the Joint Research and Development Office (JRO)/ IMP provider within 24 hours of the CI or PI or co-investigators becoming aware of the event. A nominated co-investigator was authorised to sign the SAE forms in the absence of the CI.

Any SUSARs that occur during the trial were reported to the Joint Research Office (JRO)/ main REC/IMP provider within 24 hours of the CI or co-investigator becoming aware of the event. SUSARs were to be reported to the sponsor within 24 hours as the sponsor has a legal obligation to report this to the MHRA within 7 days (for fatal or life-threatening SUSARs) or 15 days for all other SUSARs. In the case of multicentre studies, the PI or the co-investigators at the participating site must inform the CI within 24 hours of the event. The CI or co-investigators at the co-ordinating site must inform the sponsor (JRO) immediately to allow reporting to the MHRA within the allocated timelines.

The original and any subsequent follow up of SAE Forms together with the fax confirmation sheet were kept with the TMF at the study site.

Annal Safety Reporting

The Annual Safety Reports (ASR) was sent to the sponsor, the ethics committee and MHRA on 3rd January 2012.

Statistical considerations

Primary Endpoint Efficacy Analysis

The primary endpoint was MPSS ratings of urges to smoke during the first week of abstinence. The difference between groups was assessed using analysis of variance (ANOVA).

Secondary Endpoint Efficacy Analysis

Differences in validated abstinence rates over 12 weeks of abstinence were assessed using chi-square tests.

Safety Endpoints

Type and frequency of adverse events will be reported. Frequency of adverse events between groups will be assessed using chi-square tests.

Sample Size

MPSS is a rating scale sensitive to tobacco withdrawal and to both pharmacological (West 1990) and behavioural (McRobbie 2007) treatment effects. Effective treatments typically generate a difference in ratings over the first week of abstinence of at least 0.7 compared to control procedures, e.g. 1.8 (SD=1) compared to 2.5 (SD=1). As in this case the advantage of the combination over the first week of abstinence may be subtle and even a difference of 0.6 would be worth detecting, 45 participants would be needed in each group ($p<0.05$, 2-tailed test, power=0.80). Patient attrition between the TQD and Week 1 session is usually between 10% and 20%. The study aimed to randomise upto 120 participants.

Anticipated participant attrition

It is usual to expect a number of people to not complete all study procedures. Patient attrition between the Week 1 and TQD session is usually between 10% and 20% in the standard smoking cessation clinics that are run at the smokers clinic. The study aimed to randomise at least 120 participants in total to allow for a 25% rate of participant attrition (allowing 45 participants minimum in each condition).

Statistical Analysis

Differences between the study arms were assessed by analysis of variance for continuous variables and chi-square for categorical variables. The relationship between pre-quit variables and post-quit endpoints were assessed using regression modelling. Differences in urges to smoke at 24 hours and one week were compared using one way ANOVA. Changes in withdrawal symptom ratings from TQD to 24h and one week were assessed using repeated measures ANOVA. Differences were adjusted for all baseline characteristics related to outcome that differed between the two groups. As the direction of the results could not be predicted (due to this being the first study of its kind), the study statistician deemed that the use of two-tailed tests for all analysis was reported.

The results were un-blinded only after the data analysis was completed.

Estimating missing data

In cases were there were missing data, no data computation (e.g. maximum score) was undertaken. If a scale measure has one or more values missing, then SPSS will include this as a missing value if computing an overall composite score, e.g. if

someone had only rated irritability and depression then when a composite score was calculated across all 5 MPSS then this participants compsite MPSS score would be 0. There were several participants who, like in the example, had not completed all of the MPSS ratings. The decision was made to manually calcualte the composite score based on the numbers completed but only in the case were over 50% of the ratings remained.

Quality Control and Quality Assurance

Self monitoring form

A self-monitoring report was completed on 6th October 2011, which was sent to JRO to check for accuracy in recruitment, data collection and safety reporting.

Study database

In order to comply with MHRA regulations a Microsoft Access database was designed with a full audit trail and limiters, where appropriate. SOPs were developed for data entry, auditing and data export.

A non-study member of staff independently audited the database. The final database was exported first to a Microsoft Excel spreadsheet, then to SPSS (version 18) for final analysis.

Outliers

The data set was checked for inconsistencies in the data. Variables were examined to see if there were any outliers in the results that needed to be checked. As part of the data entry process, limiters had been placed on variables where there were only certain answers that could be included. For example, yes/no answers had only an option of 0 = yes, 1 = no, or the variable was left blank if there was missing data.

Record Retention and Archiving

During the study, all records were the responsibility of the CI and were kept in a secure location. Records from this study will be kept for 20 years as per standard university regulations.

Final approvals

EudraCT

All trials involving IMPs are registered with a European database of all clinical trials called EudraCT. This project was registered and assigned the EudraCT number 2010-022334-92.

Ethics

Ethical approval was given by the North London Research Ethics Committee (REC). A provisional opinion was given at first with the suggestion of changing the patient information sheet to include more detail on the differences between taking part in the study and normal clinic care and to also include an updated inclusion criteria for women; requiring them to be using contraception during the study period. All changes were included in an updated version of the protocol (version 1.1) (see Appendix 10). These documents were updated and a favourable opinion was given on 17 December 2010. The REC number was 10/H0703/85 (see Appendix 11).

Medical Health Regulatory Authority (MHRA)

After submission of an initial application, MHRA requested further details about the placebo patches and the manufacturer's authorizations certificates for Bilcare (the company labelling the study medications) and McNeil (the company providing the patches). This information was provided to them and a notice of acceptance was received on 7 January 2011 (see Appendix 12).

Sponsorship

The study was sponsored by QMUL JRO. After final approval was given by MHRA and Ethics the study was granted final research and development (R&D) approval on 2 February 2011 (Appendix 13).

Local SSI

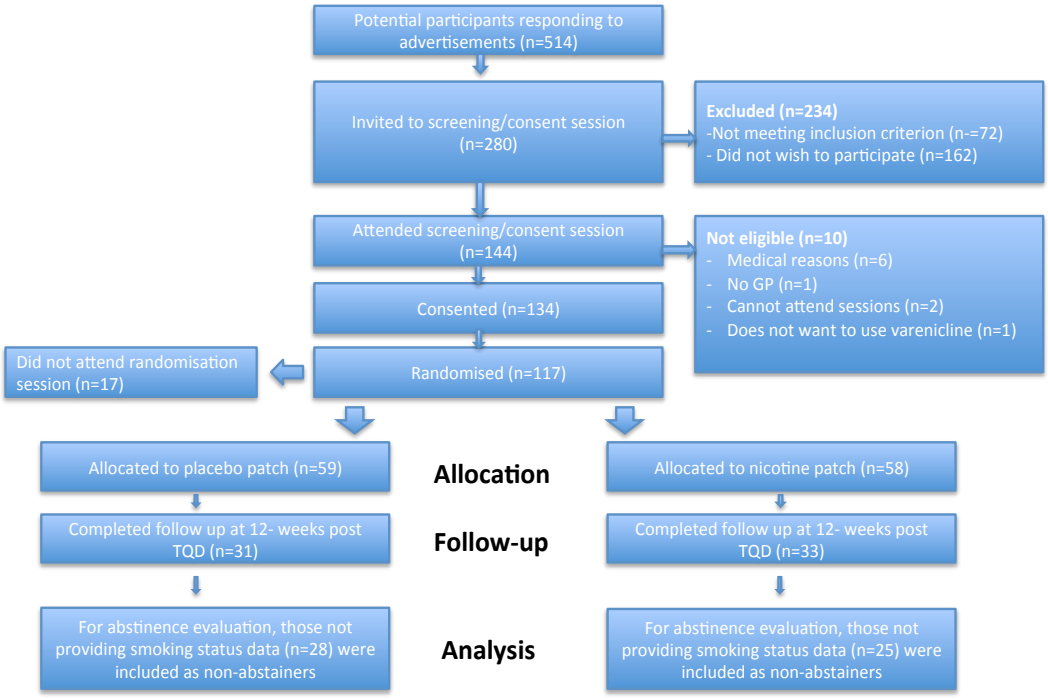
Local ethics (East London and the City Research Ethics Committee) were informed about this study and following a site-specific assessment by the local assessor the study site was approved. Official confirmation of this was received on 28 January 2011 (Appendix 14).

Results

Sample characteristics

A total of 280 people were screened as eligible over the phone and booked an appointment to attend the screening/baseline session. Of the 280 booked, 144 particpants (51%) attended, 136 (49%) were screened as eligible by the clinic doctor and consented to take part in the study. Ten (4%) were ineligible for the following reasons; unable to commit to weekly sessions, not registered with a GP and current use of medications for depression. Figure 7 shows the flow of participants through the trial.

Figure 7: Flow of participants



One hundred and seventeen participants (87%) started on varenicline at week 2. All participants returned to attend the quit day session and were randomised to receive

either nicotine or placebo patches (N=117). Table 9 shows the baseline characteristics of the participants.

Table 9: Baseline characteristics of participants

	Placebo patch (N=59)	Nicotine patch (N= 58)	Statistical significance of difference between groups
Age in years; mean (SD)	43.8 (11.0)	45.3 (10.8)	$f(115, 1) = 0.54$; $p = 0.47$
Cigarette consumption (per day); mean (SD)	18 (11)	22 (26)	$f(115, 1) = 0.83$; $p = 0.36$
Baseline CO ppm; mean (SD)	21 (10.4)	21 (8.5)	$f(115, 1) = 0.00$; $p = 0.99$
FTND; mean (SD)	5 (2.6)	5 (2.2)	$f = (115, 1)\ 0.83$; $p = 0.36$
Age when started smoking; mean (SD)	17 (6.8)	18 (5.5)	$f(115, 1) = 0.70$; $p = 0.40$
Male N (%)	40 (68)	38 (66)	$x^2 = 0.07$; $p = 0.80$
White British N (%)	36 (61)	37 (64)	$x^2 = 0.10$; $p = 0.76$
Married N (%)	16 (27)	15 (26)	$x^2 = 0.02$; $p = 0.88$
Partner smokes N (%)	15 (25)	15 (26)	$x^2 = 0.10$; $p = 1.00$
In paid employment N (%)*	49[1] (85)	41 (71)	$x^2 = 3.20$; $p = 0.08$
Body Mass Index; mean (SD)*	26[2] (4.6)	27[3] (4.8)	$f(107, 1) = 0.76$; $p = 0.39$

*N s differ due to missing data SD= standard deviation
[1]N=58; [2]N=53; [3]N=56

A total of 78 males were randomised into the study (38 in the nicotine patch group and 40 in the placebo patch group). The age range for the sample was 18-67 years, with a mean age of 45 years (45 years in the nicotine patch group and 44 years in the placebo patch group). Over 60% of the participants were white-British (n=73). Only one participant did not wish to answer the question on ethnicity.

The majority of the smokers who took part in the study were in paid employment (71% in the nicotine patch group versus 85% in the placebo patch group). Thirty one participants were married (15 versus 16 in the nicotine and placebo group, respectively). Twenty nine (25%) of the participants received free prescriptions (17 in the nicotine patch group and 12 in the placebo patch group). The average alcohol consumption per week among the participants was 11 units (SD=14).

Smoking history

Baseline average cigarette consumption was similar between the participants in the nicotine patch and the placebo groups (22 vs. 18 cigarettes per day, respectively). The groups reported a similar age of starting smoking (18 years in the active patch group versus 17 years in the placebo group) and 15 participants in each group had a partner who currently smoked.

The average CO reading that was taken at baseline was 21 ppm in both groups. Both groups had FTND scores of 5. Only 5 participants (4%) reported current use of cannabis in combination with tobacco.

Smoking cessation

Only 8 (12%) participants in the nicotine patch and 7 (14%) in the placebo patch group had never tried to stop smoking before. Regarding the longest period of time that they had managed to stop for 27 participants (23%) reported managing to stop smoking for over 3 months, with 12 (10%) managing less that 24 hours.

Twenty two (19%) of the participants had never used any form of smoking cessation medications. Only 6 (4%) participants reported using varenilcine in a previous quit attempt. The majority of participants had used a patch in previous quit attempts (n=78, 66%).

Overall the randomised groups were well matched with no significant differences seen across any of the baseline measures. The study sample profile was typical of smokers attending the East London Specialist stop smoking clinic for treatment.

Non-randomised participants

Of the 134 participants who consented to take part, 17 did not attend session 3 and were not randomised. The population who were not randomised were compared to those who were to see if there were any baseline differences between the two groups.

Table 10 - Baseline characteristics of all participants that consented			
	Randomised (N=117)	**Not randomised (N= 17)**	**Statistical significance of difference between groups**
Age in years; mean (SD)	45 (11)	48 (9)	$f(132,1) = 1.55$; p = 0.22
Cigarette consumption (per day); mean (SD)	20 (20)	19 (6)	$f(132,1) = 0.05$; p = 0.82
Baseline CO ppm; mean (SD)	21 (9.5)	20 (6.4)	$f = (131,1)$ 0.10; p = 0.80
Male N (%)	78 (67)	12 (71)	$x^2 = 0.00$; p = 1.00
Married N (%)	31 (26)	5 (29)	$x^2 = 0.01$; exact p = 1.00*
In paid employment N (%)	89 (76)	12 (71)	$x^2 = 0.10$; p = 0.32
Ethnicity – White-British N (%)	72 (62)	12 (65)	$x^2 = 0.43$; p = 0.51
FTND; mean (SD)	4.8 (2.4)	5.3 (2.0)	$f(131,1) = 0.81$; p = 0.37

*In cases where cells had an expected count of less than 5, a Fisher's exact significance test was used

There were no significant differences between those who attended the TQD session and those who did not on any baseline variable.

Effect of varenicline and nicotine patch combination on cigarette withdrawal symptoms

A total of 85 participants (43 in placebo patch and 42 nicotine patch group) of 105 (52 in the placebo and 53 in the nicotine arm) who were successfully contacted by telephone at 24 hours after their TQD reported abstinence from smoking and provided MPSS data. The two groups did not differ in urge scores (2.8 vs 2.9, F=0.18, P=0.67) or in change in withdrawal discomfort composite ratings (0.14 vs 0.07, F=0.31, p=0.58). One week after the TQD, 33 (placebo patch) and 40 (nicotine patch) participants who were abstinent at that time provided MPSS ratings. There was no

difference between the study arms in urge score (2.7 vs 3.0, F= 2.14, P=0.15) or in the change in the composite score of withdrawal discomfort (0.42 vs 0.42, F=.001, P=0.98).

At four weeks after TQD, 35 (placebo patch) and 35 (nicotine patch) of participants who achieved sustained abstinence provided MPSS data and 34 (placebo patch) and 35 (nicotine patch) provided urge ratings. There were no differences in urge score (2.1 vs 2.2, F=0.08, P=0.78) or in withdrawal discomfort (0.05 vs 0.01, F=0.08, P=0.78).

Looking at each withdrawal symptom at each time point separately, there was a significant group difference in the change in depression ratings between TQD and 24 hours post TQD in 43 participants on the placebo patch (-0.14) and 42 on nicotine patch (-0.38) (F=4.10, P=0.05). This however was due to the difference between the two groups at TQD (1.21 vs 1.43 in the placebo patch and nicotine patch group, respectively) i.e. prior to the initiation of the patch treatment. At 24 hours after TQD the ratings of the two groups were similar (1.07 vs 1.05). There were no other differences or trends emerging for any single withdrawal symptom or any time-point.

Effect of varenicline and nicotine patch combination on abstinence rates

Table 11 shows the rates of continuous abstinence (not a puff since the TQD) at 4 and 12 weeks and the Russel Standard sustained validated abstinence at 4 and 12 weeks (up to 5 cigarettes allowed). There were no differences between the two study arms at any time point.

Table 11: Effect of varenicline + NRT combination on abstinence rates			
Period after TQD	**Placebo patch**	**Nicotine patch**	**Pearson Chi-square; p value**
	N=59	***N=58***	
24 hour abstinence N (%)	47 (80)	46 (79)	x^2 =.00; p = 0.96
1 week continuous abstinence N (%)	35 (59)	40 (69)	x^2 =1.18; p = 0.28
4 weeks continuous abstinence N (%)	24 (41)	29 (50)	x^2 =1.03; p = 0.31
4 weeks sustained abstinence N (%)	35 (59)	35 (60)	x^2 =0.01; p = 0.91
12 weeks continuous abstinence N (%)	7 (12)	8 (14)	x^2 =.10; p = 0.76
12 weeks sustained abstinence N (%)	11 (19)	14 (24)	x^2 = .53; p = 0.47

The effect of nicotine patches on participants who did not have a strong reaction to varenicline during the pre-quit week was evaluated seperately. These participants were defined as those who did not reduce their CO reading by 50% or more between initiation of varenicline and the TQD session, based on the previous findings by Hajek et al. (2011). The study found that when varenicline was given to participants for upto 4 weeks before quitting their cigarette consumption, CO and cotinine levels all reduced. All 3 measures of reduction were moderately correlated. As the current study did not take cotinie measures, CO levels were taken into account to see if a similar population of participants could be seen.

There were 18 participants who were classified as varenicline reactors, as per the definition of Hajek et al. (2011). Their sustained abstinence rate at 4 weeks was 78%, compared to 57% in non-reactors (x^2 = 2.85;p=0.09). Their continuous abstinence rate at 12 weeks was 28%, compared to 10% in non-reactors (p=0.054).

Looking at the subsample of non-reactors only (49 in the placebo and 50 in the nicotine patch group), the abstinence rates at 1 and 4 weeks after TQD were 55% and 66% ($x^2 = 1.23$; $p = 0.27$) and 53% and 60% ($x^2 = 0.49$; $p = 0.49$) in the placebo patch arm and nicotine patch arm, respectively. The non-reactors in the two study arms did not differ in urges to smoke or other withdrawal symptoms at 24 hours, 1 or 4 weeks after TQD.

Adherence to study medication

Table 12 shows adherence to medication use at different time points. There was no difference between the two study arms at any time point. The adherence to medications at the crucial Session 4 (1 week post-TQD) was high, with only one participant not using the patches at all and all using varenicline.

Table 12: Adherence to medication			
	Placebo patch group	**Nicotine patch group**	**Statistical significance of difference between groups****
Not using patch at 24 h	6/52	5/53	$x^2 = 0.12$; p = 0.73
No use of patch in the past week at 1W post-TQD	0/53	1/56	$x^2 = 1.00$; exact p = 1.00**
No use of patch in the past week at 4W post-TQD	11/53	13/51	$x^2 = 0.33$; p = 0.57
Not taken varenicline at 24h	0/52	3/53	$x^2 = 3.03$; exact p = 0.24**
Not taken varenicline in the past week at 1W post-TQD	0/53	0/57	NS
Not taken varenicline in the past week at 4W post-TQD	6/53	6/53	$x^2 = 0.00$; p = 1.00
Not taken varenicline in the past week at 3M post-TQD	23/31	24/33	$x^2 = 0.18$; p = 0.89

*N varies dues to missing data
**In cases where cells had an expected count less than 5, a Fisher's exact significance test was used

Adverse events

A total of 257 AEs were reported by 104 participants in the study. Table 13 shows the summary of all adverse events which were reported by more than 5% of participants. The most frequently reported AE was nausea.

Participants were also asked weekly to rate if they had experienced nausea since the last visit. There were no differences in ratings of nausea on the MPSS scale between the two groups at any time points (1.6 vs 1.5, 1.7 vs 1.8 and 1.5 vs 1.4 at 24h, 1 week and 4 weeks after TQD in the placebo patch and nicotine patch group, respectively, all NS).

Table 13: Adverse events reported by over 5% of participants

AE reported	Number of participants experiencing the problem		Statistical significance of difference between groups**
	Placebo Patch group N=59	**Nicotine patch group N=58**	
Abnormal dreams	5	12	$x^2 = 3.51$; $p = 0.06$
Headache	4	6	$x^2 = 0.48$; exact $p = 0.53$*
Insomnia	11	11	$x^2 = 0.00$; $p = 0.97$
Nausea	26	33	$x^2 = 1.93$; $p = 0.17$
Pruritis	1	5	$x^2 = 2.90$; exact $p = 0.11$*
Somnolence	2	3	$x^2 = 0.23$; exact $p = 0.70$*

*In cases where cells had an expected count of less than 5, a Fisher's exact significance test was used

Serious adverse events

One serious adverse event (SAE) was reported during the trial. The SAE was a hospital admission for surgery owing to a crush fracture. This SAE was unrelated to the study medication.

Discussion

Adding nicotine patches to varenicline had no beneficial or detrimental effect on urges to smoke, withdrawal discomfort or abstinence rates at 24 hours and 1 week after quitting. There were no differences seen in adverse effects profile between the two groups.

Overall the randomised groups were well matched with no significant differences seen across any of the baseline measures. There were no difference seen between the participants who were randomised and those who consented but did not attend the randomisation session. Baseline demographics were similar to those seen in the population of smokers who attend the East London Specialist stop smoking clinic for treatment.

Limitations

Several issues need to be considered when interpreting these results.

The study was originally powered as a proof in principle trial to answer some key questions about the effectiveness of combining varenicline and a nicotine patch. The sample size was sufficient to detect clinically meaningful differences in withdrawal ratings and craving, but the trial was not powered to detect small differences in abstinence. We cannot rule out a possibility of a subtle effect detectable on a large sample. However, it is likely that the active ingredient of any effect would be lowering of withdrawal discomfort, which is more likely to be seen in the first few weeks of quitting. As this did not happen, we can probably rule out any robust effect on abstinence.

The study was not powered for long-term follow up and did not provide data for abstinence rates beyond 3 months. The short-term follow-up of the study would limit the generalisability of the results only if the results were positive. It is unlikely that a lack of effect during the patch use period and up to 2 months after the patch has been discontinued could change into a significant effect later on.

The majority of the participants included in the study were assumed to be daily smokers, however, we did not ask specifically if this was the case. The current study was aimed at an increased dose of medication for use with dependent smokers. Participants who do not smoke daily would normally be advised to use oral medications in their quit attempt. This is so their medication use can be tailored around the situations they would normally smoke (e.g. use of the fast acting nicotine nasal spray when socialising). Giving these types of smokers a patch when they do not smoke every day is not usually something that is recommended. Giving non-daily smokers varenciline and a patch in combination, in the context of this study, may not be the best treatment option for them. There is no safety aspect of using NRT on days where the person would not normally smoke. However, using varenicline every day may result in nausea. Social/non-daily smokers should be screened out in any future studies looking at high dose medications.

Adding a qualitative component to this study would have been useful. Understanding how participants perceived the use of a combination and whether they felt it was of benefit might have clinical relevance. For example, smokers may find use of an oral NRT product a useful distraction whilst using varenicline rather than using the product to get added nicotine.

Despite these constraints the study findings are novel and potentially important for future practice and guidance.

The negative results found in this study cannot be attributed to low compliance with medication use, as almost all participants used both medications during the first week after TQD when any beneficial effects would be expected to be the strongest. We used 16h/15mg patch, which has extensive evidence of its efficacy (Fiore, Smith, Jorenby & Baker 1994). The 24-hour patch has been shown to have stronger effects on early urges to smoke (Shiffman & Ferguson 2008), but both types of patches have the same effect on smoking cessation outcome (Stead et al. 2008).

It could be argued that other short-acting NRT formulations, which can be used opportunistically, could be more effective (i.e. nicotine inhaler). This is possible, but any gains in better efficacy of short-acting NRT products are usually undermined by the fact that they are less user-friendly and generate much lower adherence than patches. Good sustained adherence to oral NRT products and nasal spray usually requires a period of supervised frequent and regular use (Hajek et al. 1999). Where the expectation is that the product will be used only sporadically, the adherence is likely to be low. Nevertheless, our results should be generalised to alternative NRT products with caution.

Varenicline was provided to participants as per standard dosing instructions for 12 weeks in total (Pfizer limited 2011). Nicotine patches were provided to participants on the TQD and for a total of 4 weeks. Standard practice would see use of patches for 9-12 weeks from the TQD when using the product as part of a cessation attempt

(McNeil Limited 2009). In this study the use of patches for 4 weeks was primarily to give the "extra" pharmacotherapy support during the 4-weeks when the symptoms of tobacco withdrawal are at their most acute. It may be argued that the duration of patches should be extended, however, our results on withdrawal and urges reflect that the inclusion of a nicotine patch to varenicline was not beneficial in the first few weeks of quitting which would logically be the time where any useful benefit of the combination is likely to be seen.

Adding nicotine patches to varenicline did not increase the incidence of nausea. This suggests that the nausea producing effect of varenicline may be unrelated to its effects on nicotinic receptors involved in the dopamine pathway. The finding tallies with the fact that nausea caused by varenicline is not related to the drug's effects on smoking behaviour, which has been noted by other previous studies (Hajek et al. 2011).

The one pre-marketing study conducted by Pfizer Ltd (2011) showed that smokers using varenicline and a transdermal patch for 12 days reported a higher incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue than smokers who used NRT alone. This study found no differences in the adverse events reported between the 2 groups. It is highly probable that the symptoms that were reported in this study may have been due to common medication specific reactions (i.e. varenicline (nausea) or patch use (itching)), as opposed to any combination use of varenicline and patches.

The quit rates at 4 weeks are in line with the UK standard success rate of approximately 38% (The NHS Information Centre for Health and Social Care 2012). It could be argued that you would expect a much higher quit rate just from individuals

being part of a study, acting almost as a 'placebo' effect. It is important to remember that this data was rigorous in its collection and participants had to report complete cessation over the final 2 weeks of treatment (session 6 and 7) and CO verified in order to be classed as sustained quitters. If we look at the continuous rates, a much stricter measurement with no lapses allowed throughout treatment, the results show that less than 30% at 4-weeks were abstinent. However, this is in line with previous research in this area of research (Hajek et al. 2011). Typically, high abstinence rates in practice and research are often due to a less stringent measure of abstinence, for example, using point prevalence as an outcome. Point prevalence is asking the participant whether they smoked in the last week and does not take into account any lapses before this time point.

There are two obvious interpretations of the negative finding found by this study. One is that NRT and varenicline are achieving their effects via similar target mechanisms, which overlap to a large or even full extent. Varenicline may act on a more limited range of nicotinic receptors than nicotine itself, but these seem to include those involved crucially in the rewarding effects of smoking. By blocking such receptors, varenicline may be limiting any potentially beneficial effects of NRT as well. For example, nicotine patches normally alleviate weight gain in continuous abstainers (Farley et al. 2012) but they had no such effect here.

The other explanation, which seems more likely, is that by blocking the relevant nicotinic receptors, varenicline blocks any potentially beneficial effects of NRT as well.

Patients who have a weak reaction to varenicline during an extended pre-quit period have been shown to have low success rates (Hajek et al. 2011). In theory, the addition of nicotine replacement could be of particular benefit to such patients. To test this hypothesis, we evaluated separately the effect of nicotine patches on participants who did not reduce their CO reading by 50% or more during their pre-TQD varenicline dosing. This definition was based on the work by Hajek et al. (2011), who looked at the effect of using varenicline upto 4 weeks pre-quitting. The study found that when varenicline was given to participants for upto 4 weeks before quitting their cigarette consumption per day (cpd), CO and cotinine levels all reduced, these were identified as "Reactors". Those who did not change their cpd, CO or cotinine were defined as "Non-Reactors". All 3 measures of reduction were found to be modertaly correlated. As the current study did not take cotinine measures, changes in CO level in the first week of varenicline use were taken into account to identify the number of "Reactors" in the current study.

Nicotine patches were of little additional benefit even to smokers who did not have a strong response to varenicline early on. When looking at this specific population the findings of the study are somewhat more tentative than the main result, as a trend was seen in favour of nicotine patches in this sub-analysis for abstinence rate at 4 and 12 weeks in the participants identified as "Reactors". If patch effects are blocked by varenicline in varenicline reactors and non-reactors alike, an interesting question arises as to whether varenicline non-reactors may benefit from NRT in the absence of varenicline. If this were the case, treatment efficacy could be improved by switching smokers who show no reaction to varenicline during the pre-quit period over to NRT. Future studies should evaluate this notion further.

It should be noted that the 50% cut off mark for varenicline "Reactors" and "Non-reactors" is arbitrary and was replicated, for the purposes of this study, based on the recent varenicline pre-loading study definitions outlined by Hajek et al. (2011). There is a possibility that this could be looked at differently i.e. a reduction in cpd, cotinine and CO levels of 20% may still be clinically relevant.

Apart from generating information relevant for considering the mechanisms of the two medications, the trial results have an important practical implication. Finding a positive effect would not provide a definitive proof of efficacy, but it would indicate that a large scale study with a long-term follow-up is warranted. A negative result on the other hand provides a strong indication that such a trial is unlikely to provide positive results and that combining the two treatments is not helpful. There is widespread interest in giving both medications at the same time to highly dependent smokers in the hope of providing more powerful medication. The results of this study suggest that such practice is unlikely to be productive or economical.

Next steps

This proof in principle trial has shown that a large-scale study on the use of combination varenicline and NRT is not currently warranted. However, the need for new options for the treatment of dependent smokers is needed. One study that is currently running at the TDRU is looking at the efficacy of using a tailored dose of varenicline.

The standard varenicline dosing has been formulated to avoid adverse reactions (primarily nausea) in sensitive clients. The downside of this cautious approach is that a substantial proportion of clients may be under-dosed. A blanket dose increase would inevitably increase the incidence of side effects, but it is likely that tailoring varenicline dosing to clients' needs would be safe and may further increase varenicline's efficacy.

Tailoring the dose to client need is likely to receive positive endorsement from clients who appreciate individualised care, as well as from doctors. The study will provide an indication on whether this approach is likely to increase the efficacy of varenicline and if the results are positive, the trial will also provide data essential for planning any future outcome study. The results of this study will be available in 2013.

Conclusions

The efficacy of varenicline is not enhanced by the addition of nicotine patches. The finding has theoretical implications for interpreting the effects of the two medications. It has also an important practical corollary. There is widespread interest in combining the two medications. Our results suggest that this is unlikely to be a productive or economical approach.

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PART 2: A SYSTEMATIC REVIEW OF SMOKING CESSATION INTERVENTION: A REPORT TO THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE (NICE)

Abstract

Introduction

In 2010/11, approximately 460,000 NHS secondary care admissions in the UK were estimated to be attributed to smoking tobacco (Office of National Statistics 2012). Hospitalisation provides a good opportunity to stop smoking. Such patients are often highly motivated to quit, and the hospital admission brings people into direct contact with healthcare professionals who can advise on giving up smoking and offer evidence-based treatment.

Objective

This piece of work was commissioned by the National Institute of Health and Clinical Excellence (NICE) to review the available evidence concerning the efficacy of different types of smoking cessation interventions for hospital patients and their relatives to help guide clinical recommendations for smoking cessation in acute services. The guidelines are due to be published in November 2013.

Methods

A systematic search for reviews and randomised controlled trials published between 1990 and December 2011 in the English language was undertaken. Electronic

databases were searched including ASSIA, MEDLINE, Cochrane Central Register of Controlled Trials, CINAHL and PsychINFO. A total of 29,083 records were found of which 141 papers were identified for full text retrieval. Seventy-five trials evaluating smoking cessation interventions delivered in acute care settings were found.

Results

Hospitalised smokers – For interventions with hospital patients to be effective, an extended period of support and stop smoking medication provided for over 4 weeks after discharge is recommended. Interventions that are provided face-to-face after discharge may provide better results than support provided over the telephone. ***Relatives*** – There is limited research for this population, however, brief stop smoking interventions with parents of hospitalised children did not show any efficacy in long term abstinence rates.

Hospital staff – There is evidence that providing the stop smoking medication bupropion (Zyban) with regular face-to-face support is an effective treatment for hospital staff.

Conclusion

The NHS practice for hospitalised smokers currently involves interventions at bedside accompanied by medications and/or referrals to specialist stop-smoking services for treatment after discharge, which combines extended face-to-face support with smoking cessation medications. The reviewed evidence confirms that this is likely to be the optimal approach.

Background to the systematic review

In September 2011 a tender was advertised for applications to conduct a series of systematic reviews for NICE. The reviews were to be part of a new smoking guideline for acute and maternity services across the UK, which is due for release in 2013. My clinical background has been primarily working with inpatient smokers in acute care settings, which made my expertise very relevant to the tender call and application. Applications to write 3 of the 6 reviews were submitted by Professor Hajek, Dr McRobbie and myself. We were successful in our application for all 3 of the reviews; I present one of the 2 papers I led, which looks at the effectiveness of smoking cessation interventions in acute care settings.

This guideline will not be released until 2013. The contents of the review remain confidential until its publication.

Introduction

Why help smokers during hospitalisation?

In 2010/11, of the 10 million NHS secondary care admissions in the United Kingdom (UK), it was estimated that 460,000 were attributed to smoking tobacco (Office of National Statistics 2012). Nearly 35% of admissions attributable to smoking were cancer related (Office of National Statistics 2012). With such a high number of smokers being admitted into hospital and with a high percentage of those attributed to serious illnesses, the provision of education and treatment for smokers during their hospital stay is seen as a priority for the UK DoH (Croghan 2011).

Helping smokers during hospitalisation provides a unique opportunity for people to stop smoking. Smokers who are admitted to hospital are often more receptive to information being provided about improvements to their health, are often more highly motivated to quit and the hospital setting provides a potentially supportive environment to do so (Rigotti, Munafo, Lindsay 2007). Patients report that hospitals are an appropriate and preferred place for health education (Haynes 2008).

During a hospital stay patients are often in a situation where they feel vulnerable and are more focused on the health problem they have been admitted to hospital with, and so as a result of this distraction, they may find they are able to cope with tobacco abstinence during their hospital stay better than they would under normal circumstances (Mackenzie, Pereira & Mehler 2004).

Anecdotally dependent smokers who have been unsuccessful at stopping smoking in the past, report that when they are hospitalised they do not think about cigarettes during their stay and feel comfortable without smoking (Myers & Hajek 2009).

UK hospitals have been smoke-free since 2007 (Bauld 2011), which means that smokers who are admitted undergo a period of abstinence from smoking, without being exposed to the usual environmental cues and prompts to smoke. For most hospitals smoking is forbidden in the grounds of the hospital as well as on the wards, which for many sick patients adds a further barrier to accessing an area where they can smoke.

Interestingly, previous research has noted that smokers have reported that they can "put up" with being unable to smoke and report little or no smoking withdrawal symptoms in other situations such as religious occasions, meetings and long-haul flights (Dar, Stronguin, Marouani, Krupsky & Frenk 2005). Limiting cues and prompts to smoke and restricting access to smoke appears to dampen the effects of tobacco withdrawal symptoms in these situations.

Smoking–related illness and hospitalisation are important windows of opportunity for smoking cessation interventions. Helping such smokers should be an important priority for health care staff, because in many cases stopping smoking facilitates recovery from illness and reduces the need for further demands on health service resources (Croghan 2011). The role of the inpatient smoking cessation service has been given further importance as the evidence continues to emerge, supporting the positive health impacts for those undergoing surgical procedures, even short term

abstinence can have for the individual (Kuri, Nakagawa, Tanaka, Hasuo & Kishi 2005; Lindstrom, Sadr Azodi, Wladis, Tonnesen, Linder, Nasell, Ponzer & Adami 2008). The close involvement with health care systems should make provision of such interventions relatively easy, however, in practice this is not always the case.

What is happening in the UK?

Department of Health Recommendations

Provision of stop smoking interventions in secondary care is a priority for the UK DoH and current guidelines for local stop smoking services include detailed service delivery recommendations (Croghan 2011). Recommendations include that all frontline healthcare professionals (HCPs) should be trained to provide very brief advice to all smokers admitted to hospital, assessment of dependency and to provide pharmacotherapy for patients who would like to quit smoking or to temporarily abstain during their stay in hospital.

The UK health service is much more conducive to a successful adoption of this best practice by HCPs than is the case in any other country. This is because the NHS established the stop smoking service (SSS) in 1999, and stop smoking treatment by specialists are now available throughout the UK (Croghan 2011). This makes the task of the front line NHS staff much simpler than that of their counterparts in other countries. Staff are only required to advise smokers to quit and refer those who need and want help to the NHS-SSS. The NHS-SSS is then ideally placed to support patients after discharge in the community and to continue the treatment provided in

hospital (Croghan 2011). Even in such a simplified scenario however, there are a number of practical considerations, which influence practice.

UK hospital smoking cessation in practice

In practice, the opportunity for HCPs to provide routine encouragement and advice to smokers is often missed. There are many HCPs trained to screen for tobacco use and give brief advice to quit (**nurses (**Haddock & Burrows 1997); **doctors** (Campbell, Prescott & Tjeder-Burton 1996); and **dedicated in-hospital smoking cessation advisors** (Prathiba, Tjeder, Phillips & Campbell 1998), however, they are much less likely to provide further assistance, such as referring on to the local SSS (Schofield, Hill, Johnston & Streeton 1995; Vaughn, Ward, Doebbling, Uden-Holman, Clarke & Woolson 2002; Vokes, Bailey & Rhodes 2006; Von Garnier, Kochuparackal, Miedinger, Leuppi, Tamm, Battegay & Zeller 2008, Warner 2009; Whyte, Watson & McIntosh 2006; Wilber, Sullivan, Gaeta, Walters, Camargo & Boudreaux 2011).

One study analysed audiotapes from doctor-patient interactions in an emergency department to see what advice, if any, was given to smokers (Vokes et al. 2006). Just over half were screened for smoking, with 56% of smokers given advice to quit, and 13% offered further help. Similarly in a survey of outpatients (Von Garnier et al. 2008) contacted by phone within 24 hours after their hospital appointment, 81% were asked about smoking, 28% received advice on risks, 10% received advice to quit and 9% were offered help to quit.

A consistent finding in the literature is that the more HCPs are asked to do, the less likely they are to do it (Myers, McRobbie, West & Hajek 2012). Lack of time, knowledge and skills are among the most commonly cited barriers for intervening at any level with a smoker (Thy, Boker, Gallefoss & Bakke 2007; Warner, Sarr, Offord & Dale 2004, Warner, Klesges, Dale, Offord, Schroeder, Vickers & Hathaway 2008). It is strongly recommended that in the UK, training for HCPs should focus exclusively on motivating and simply referring smokers to NHS-SSS (Myers et al. 2012). There is evidence that brief training (40 minutes) is effective in increasing referrals from UK GPs (McRobbie, Hajek, Feder & Eldridge 2008). There is no reason to expect that the same approach would not work in secondary care.

Other barriers include short hospital stays and patients leaving wards for investigations and interventions, which make on-ward stop-smoking sessions by HCPs difficult to deliver (Thompson, Caslin, Murray, Zissimos, Newhouse & Yung 2006; Vaughn et al. 2002; Goldstein 1999; Rigotti, Arnsten, McKool, Wood-Reid, Pasternak & Singer 1997). An obvious solution is to have dedicated staff providing smoking cessation treatment.

Many NHS-SSS in the UK now employ staff to provide specialist help and initiate stop-smoking interventions at the patient's bedside. There is good evidence that smoking cessation treatment that begins during a hospital stay and includes follow-up support for at least one month after discharge is effective (Rigotti et al. 2007). However, despite the evidence of the effectiveness of intensive interventions and the availability of NHS- SSS funded to provide them, such interventions are far from universal.

There are limited data describing smoking cessation support within NHS hospitals. In 2003, a survey of 260 UK Hospitals (with a 91% response rate) suggested only around 50% had a dedicated smoking cessation service on-site (Campbell, Lewis, Preston & Comm 2003). A recent e-survey in 2011 (cited in Lewis 2012) confirmed a slight overall increase in hospital provision compared with 2003 data but due to financial cuts many UK hospitals have lost their in-house smoking cessation services and there remains widespread disparity between the availability, location and content across hospitals. Another recent survey (Proctor, Myers-Smith, McRobbie & Hajek 2013) found that in a survey of hospitals employing staff to provide an inpatient smoking cessation service that most had first contact with the patient during their hospital stay. However, some services did not employ smoking cessation advisors to start treatment at bedside, but instead focused on training staff in providing interventions and/or referral to local services.

Provision of pharmacotherapy during hospitalisation

Abstaining from smoking often results in a tobacco withdrawal syndrome (TWS) that comprises of a number of changes such as mood alterations, physical symptoms and signs, as well as biochemical and physiological changes (Hughes, Stead & Lancaster 2007). Not all smokers who are hospitalised will experience TWS (Myers et al. 2009) but for those who do these symptoms can be managed. Current pharmacotherapies for smoking cessation, in particular fast acting nicotine replacement therapy (NRT) products, can be effective in alleviating tobacco withdrawal symptoms (West & Shiffman 2001) and should be offered to assist patients to abstain during their hospital stay.

A 2005 NHS Health Development Agency (HDA) survey (Health Development Agency 2004) found that although 40% of hospitals had NRT on the hospital formulary, that it was only available to the patients in 10% of hospitals. The same survey also reported that only 8% of hospitals were able to provide NRT, and pro-actively offered it to smokers.

Thirty-nine UK inpatient hospital services were surveyed in the recent report by Proctor et al. (2013). All reported being able to provide NRT, while fewer services were able to provide varenicline (57%) and buproprion (35%). After discharge, only 54% of services were able to supply patients with medication to take home. Only 23% of services provided patients with the option of hospital appointments after discharge.

May, Stocks & Barton (2008) interviewed 13 members of staff from an acute cardiac care unit in Australia where NRT was not used at all. The key barriers included the fact that NRT was not on the formulary and staff lacked relevant knowledge. Related to the latter, there were some concerns about NRT cost and its safety.

What evidence is there on hospital intervention effectiveness?

Smoking cessation counselling delivered in an acute hospital setting, combined with at least 1 month follow-up support post discharge, is associated with an increase in smoking cessation rates at both 6 and 12 months (Rigotti et al. 2007). There are also data from systematic reviews to show that intensive smoking cessation interventions delivered to people awaiting surgery can be effective in increasing long-term cessation rates (Moller & Villebro 2005; Theadom & Cropley 2006).

The aim of this piece of work was to review the available evidence concerning the efficacy of different types of smoking cessation interventions for hospital patients and their relatives and hospital staff to help guide clinical recommendations for smoking cessation in acute services. Reviewing this extensive body of literature will provide some useful pointers, which will contribute to guidelines on how best to support such smokers and to provide some direction for future implementation of such interventions.

Methods

Aim

The aim of this review was to examine the efficacy of smoking cessation delivered in acute services (including patients, partners, parents, visitors, and staff).

Research questions

This review's aim was to answer the following question posed by NICE:

Question 1: How effective are smoking cessation interventions in helping people from the populations of interest?

Populations of interest

Smoking cessation interventions delivered in acute secondary care services to:

1. Inpatients
2. Partners/parents/visitors of inpatients
3. Hospital staff

Structure of the review

The review is divided into 5 sections that address the populations of interest: (1) users of acute secondary care services and (2) staff and visitors of these services.

Section 1 covers the efficacy of interventions delivered to ***non-surgical patients***. This section concerns trials comparing interventions of different intensity with minimal support or usual care;

Section 2 covers the efficacy of interventions delivered to ***patients undergoing surgery***;

Section 3 covers the efficacy of ***pharmacotherapies*** to aid smoking cessation in acute secondary care service users. This section concerns trials where comparison groups differed in the provision of medications but not in the level of behavioural support;

Section 4 covers the efficacy of interventions delivered to ***hospital employees***;

Section 5 covers the efficacy of interventions delivered to ***parents of hospitalised children***.

Each section includes meta-analyses and an interpretative evaluation is outlined.

Types of studies considered in this review

All randomised controlled trials with the populations of interest were included.

Types of interventions considered in this review

Any intervention that was initiated during hospitalisation and that aimed to assist clients in stopping or reducing smoking or in remaining abstinent were included. Studies were also included where interventions started before and after hospitalisation, e.g. those commenced during pre-operative assessment or initiated after discharge, where such practice could be initiated by the secondary care teams. Studies of smoking interventions delivered as part of broader rehabilitation programmes were included if it was possible to extract data on the outcome of the

smoking cessation component. Interventions that were delivered to staff and visitors of acute services were also included.

Inclusion criteria

The following were included in the review:

- Systematic reviews
- Randomised controlled studies published from 1990 to the most recent available at the time of the search

Exclusion criteria

The following were excluded in the review:

- Animal studies
- Studies that do not primarily address the review questions; and
- Studies not published in English

Categorising interventions by intensity

A number of different types of behavioural interventions have been proposed to help smokers quit. They can be categorised according to their theoretical underpinning, use of treatment aids such as booklets, videos and biological feedback, background of the person delivering the intervention, etc. The Cochrane review of interventions with hospital patients (Rigotti et al. 2007) categorised the interventions according to the length of time over which support was provided. Length of support is generally related to the cost of the intervention and also to its efficacy. Such approach seems practical for informing clinical recommendations and we used it throughout this review.

The studies have been categorised by the length of time over which support was provided into the following levels of intensity:

Intensity 1: Single contact with or without take-away written and other materials, no follow-up support

Intensity 2: One or more contacts with or without take-away written and other materials up to but not beyond the TQD

Intensity 3: Any contact plus follow-up for up to but not beyond 4 weeks after TQD

Intensity 4: Any contact plus telephone/correspondence/e-mail etc. based follow-up for> 1 month

Intensity 5: Any contact plus follow-up for > 1 month including at least one face-to-face contact

We also considered whether combination with or without pharmacological treatments influenced treatment outcomes.

Issues not covered in this review

We excluded trials of interventions delivered entirely outside the secondary care and maternity care settings, and trials with psychiatric patients. This review did not consider evidence relating to the health benefits of stopping smoking.

Outcomes and data extraction

The principal outcome measure was abstinence from smoking at least six months after the start of the intervention.

Regarding data extraction, we followed the approach used in the Cochrane report (Rigotti et al. 2007) and extracted data indicating the most conservative measure of quitting at the longest follow up. Biochemically validated quit rate was preferred to self-reported abstinence, continuous or sustained abstinence was preferred to point prevalence abstinence, and abstinence at later time-points was preferred to abstinence at shorter time points. Participants lost to follow up were counted as continuing smokers.

Evaluation of trial quality

In smoking cessation studies where study arms differ in patient contact, one of the main potential sources of bias is lack of validation of self-reported abstinence. This is because participants who receive more attention and resources can feel under greater pressure to report benefit. Another factor, which has a potential to bias smoking cessation studies, is the use of short-term 7-day 'point prevalence' abstinence reported long after the intervention finished, as opposed to sustained abstinence that traces the effects of the initial intervention. Not using intention to treat (ITT) is the third major potential source of bias as patients failing in their quit attempt are more likely to drop out than those who are successful. We were able to largely remove this bias as most studies reported the original sample sizes and so we were able to re-calculate ITT results where needed. We also assessed randomization procedures and allocation concealment, but these features can be expected to have only limited impact on trials of smoking cessation interventions where there exist no strong predictors of outcome exists.

Each of the included studies was rated ++, + or - to indicate its quality. The quality of the included reviews was assessed using criteria outlined in NICE guidance (see Table 1). The quality of included trials was assessed as follows.

Table 1: Quality assessment ratings

++	Self-reported abstinence was verified biochemically, sustained or continuous abstinence reported, no other risks of bias
+	Self-reported abstinence was verified biochemically, only point prevalence abstinence reported, no major risks of bias
–	Self-reported abstinence not validated and/or other major risks of bias (e.g. incomplete randomisation, unclear N, unclear calculation of success rates)

We rated the quality of reviews as ++ for systematic reviews showing awareness of key methodological features of stop-smoking studies, + for reviews which were less systematic and/or did not take into account the key quality aspects of included studies, and – for reviews which were selective and/or posed methodological problems.

Data analysis

Where it was appropriate to pool studies, data were entered into RevMan (version 5). We pooled data using Mantel-Haenszel fixed-effect method, with 95% confidence intervals. To investigate statistical heterogeneity we used the I^2 statistic. Where there was substantial heterogeneity between studies we explored possible reasons for this using subgroup analyses. We express results as odds ratios (intervention odds/control odds) for achieving abstinence from smoking together with the 95% confidence interval for this estimate.

Applicability statements

The degree of applicability of the main conclusions to the UK setting is assessed in the narrative summary at the end of the Chapter.

Search methodology

We systematically searched reviews and trials published between 1990 and December 2011 in the English language, but we also included literature published in early 2012 while we were working on the review. The search date was restricted to studies published after 1990 with agreement from NICE, as the literature in this area does not emerge until after this date when the implementation of hospital smoking cessation services was first established. The electronic resources and websites searched are included in Appendix 1.

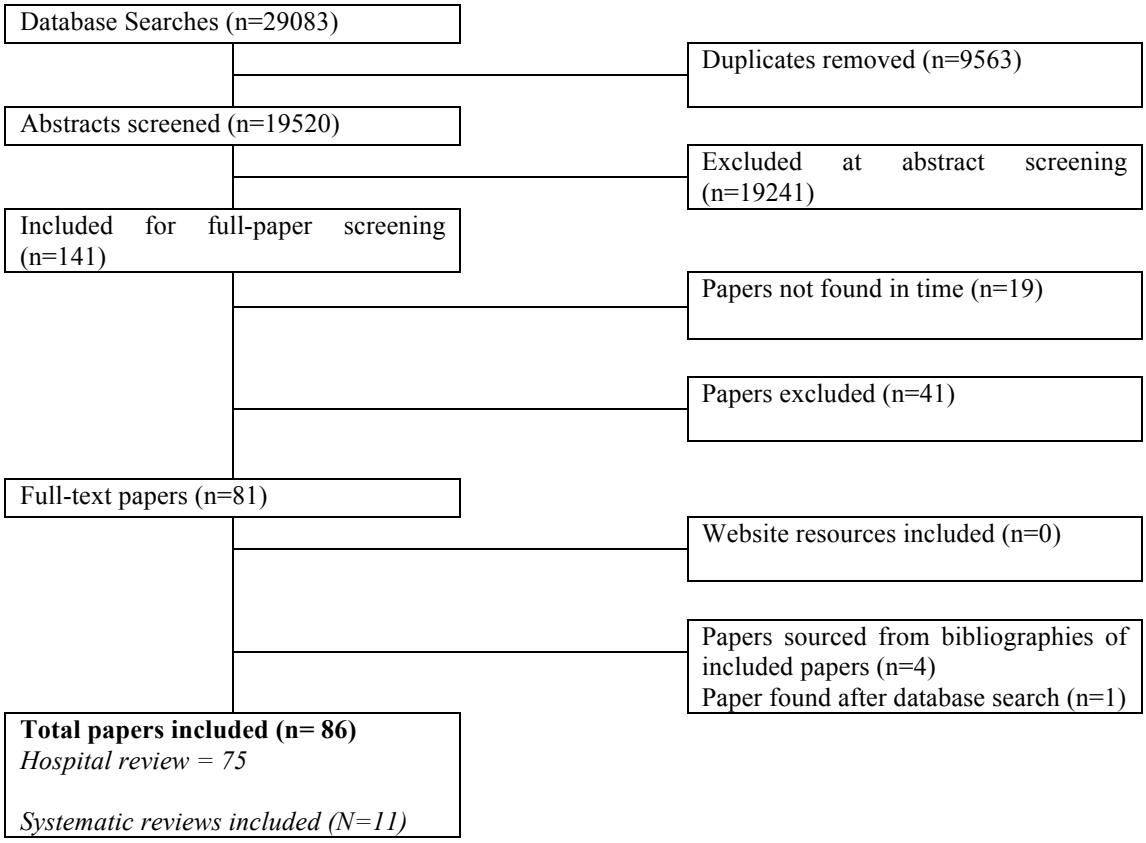
A systematic search of the grey literature was not undertaken but hand searching of bibliographies of systematic reviews that met the inclusion criteria was carried out to ensure that relevant data was included in this review. The search terms included for this review are included in Appendix 2.

Search results

Searches of the databases returned 29,083 records. After duplicates were removed a total of 19,520 titles and abstracts were screened. Full papers were also obtained where there was no abstract and the relevance could not be assessed by the title alone. One member of the project team screened all titles and abstracts and a second member of the team re-screened 30% to check accuracy, as agreed with NICE. Ideally 100% would have been double-checked but with the high number of hits returned from the search this was not feasible in the time frame available. Of the total number of

abstracts 267 (1.4%) required review from a third member of the project team as to whether they should be included in the review. These were papers where the details of the study were not clear from the abstract alone, so agreement was sought from the 3rd reviewer to check if the full paper should be reviewed. There were also 5 papers that the first 2 reviewers did not agree on so the 3rd reviewer made the final decision over its inclusion. A total of 141 papers were identified for full text retrieval. A flow diagram illustrating the screening procedure is included in figure 1 below. Studies excluded at the full-paper screening stage are listed in Appendix 3, along with a brief reason for exclusion. Papers that were unavailable for full paper retrieval are detailed in Appendix 4.

Figure 1: Flow diagram for papers



Structure of the review

We found 75 studies evaluating smoking cessation interventions with users of acute services, which had follow-up periods of at least 6 months. The studies are summarised in **Table 2**.

Table 2 - Summary of studies included

	Summary
Bolman et al 2002 Netherlands	*Participants:* 789 inpatients recruited from cardiac wards across 11 hospitals *Intervention:* Advice from a cardiologist and 15-30 min nurse counselling on ward. Advice again in the outpatient clinic at 4-6 weeks post discharge. (Intensity 5) *Control procedure:* Usual care *Outcomes:* 12 months sustained abstinence *Validation:* None *Quality:* - *Notes:* Data from 25 deaths, 38 refusals, and 64 people with missing baseline data were excluded from analysis.
Borglykke et al 2008 Denmark	*Participants:* 223 patients hospitalised with COPD *Interventions:* Standard information offered in hospital and group counselling over 5 weeks, NRT offered (Intensity 5) *Control procedure:* Standard information only *Outcomes:* 7 day PP at 12m *Validation:* Blood COHb *Quality:* + *Notes:* Blood samples assessed in 84% of patients
Brandt 1997, Denmark	*Participants:* 56 hospitalised COPD patients *Interventions:* Smokers informed they have an illness called 'smokers lung' (Intensity 1) *Control procedure:* Smokers informed they have an illness called chronic bronchitis *Outcomes:* 12 months (not clear if PP or cont) *Validation:* CO *Quality:* +
British Thoracic Society A	*Participants:* 1462 chest outpatients *Interventions:* advice + TQD discussed, 5 letters and 2 HV contacts (Intensity 5)

1990, UK	*Control procedure:* Advice only *Outcomes:* 9 months continuous abstinence *Validation:* Blood COHb *Quality: ++*
British Thoracic Society B 1990, UK	*Participants:* 1392 chest outpatients *Interventions:* (1) advice only; (2) advice + agreement to quit; (3) advice + 6 letters; and (4) advice + agreement + letters *Outcomes:* 6 months continuous abstinence *Validation:* Blood COHb *Quality: ++* Notes: We merged 1+2 (one-off intervention, Control) and 3+4 (extended contact; Intensity 4) for analysis
Campbell et al 1991, UK	*Participants:* 212 in-patients with smoking-related diseases *Intervention:* Physician advice plus a single session of inpatient counselling and nicotine gum for 3 months. Followed up at 2, 3, 5 weeks, 3 months, and 6 months by counsellor (Intensity 4) *Control procedure:* Same as intervention but with placebo gum *Outcomes:* 12 month sustained abstinence *Validation:* CO *Quality: ++*
Campbell et al 1996, UK	*Participants:* 62 Inpatients with respiratory or cardiovascular disease *Intervention:* Physician advice plus a single session of inpatient counselling and nicotine patch for 3 months. Outpatient follow-up by counsellor at 2, 4, 8, and 12 weeks (Intensity 4) *Control procedure:* Same as intervention but with placebo patch *Outcomes:* 12 months sustained abstinence *Validation:* CO *Quality: ++*
Carlsson 1997, Sweden	*Participants:* 168 MI patients, intervention after discharge *Interventions:* CVD prevention programme with exercise, diet and stop-smoking advice (Intensity 5) *Control procedure:* Usual care via GP *Outcomes:* Abstinence from smoking at 1 year (not clear if PP or cont)

	Validation: none *Quality:* -
Caruthers 2005, USA	*Participants:* 80 smokers after discharge from hospital *Interventions:* 8 phone calls, some used medications (Intensity 4) *Control procedure:* Usual care *Outcomes:* 7 day PP at 6 months *Validation:* CO validated *Quality:* + *Notes:* Unpublished PhD thesis. Controls for baseline differences not clear.
Chan et al 2005, Hong Kong	*Participants:* 80 smoking parents of sick children brought to hospital *Interventions:* Motivational interviewing and telephone reminders 1 week after intervention (Intensity 3) *Control procedure:* Healthy diet counselling *Outcomes:* 7 day PP at 1 months *Validation:* None *Quality:* - Note: Intervention with parents of patients
Chouinard et al 2005, Canada	*Participants:* 168 inpatients with CVD or PVD *Interventions:* (1) Single session of inpatient nurse counselling plus pharmacotherapy (nicotine patches, gum and bupropion). (Intensity 2); (2) Same as intervention (1), but with 6 follow-up telephone calls over 2 months post discharge (Intensity 4) *Control procedure:* Cessation advice *Outcomes:* 6 months sustained abstinence *Validation:* Urine cotinine or CO *Quality:* ++ *Notes:* 23% used pharmacotherapy.
Croghan et al 2005, USA	*Participants:* 30 smokers undergoing surgical resection of lung or oesophageal cancers *Intervention:* Advice from surgeons and study nurses and a single session of inpatient counselling (Intensity 2) *Control procedure:* Physician advice only

	Outcomes: 6 months 7-day PP *Validation:* CO or saliva tobacco alkaloid *Quality:* +
Dalsgaro et al 2004, Denmark	*Participants:* 336 hospital employees *Interventions:* 5 counselling sessions, 2 phone calls over 6 months, and 7 weeks Bupropion. (Intensity 5) *Control procedure:* Identical support + 7 weeks placebo *Outcomes:* 6 months continuous abstinence *Validation:* CO validated *Quality:* ++ Notes: Hospital employees, not patients
De Busk et al 1994, USA	*Participants:* 252 inpatients with acute MI *Intervention:* Physician advice plus single session of counselling and NRT. Self help materials and relaxation tapes were also provided. Follow-up at 48hrs, 1 weeks and then monthly for 6-months via telephone (Intensity 4) *Control procedure:* Advice only *Outcomes:* 12 months continuous abstinence *Validation:* CO and plasma cotinine. *Quality:* ++ *Notes:* NRT was provided to only the 'highly-addicted' patients. Intervention post-discharge.
Dornelas et al 2000, USA	*Participants:* 100 smokers. Inpatients with acute MI. *Intervention:* Single inpatient counselling session followed by telephone calls at weeks 1, 4, 8, 12, 16, 20, and 26 (Intensity 4) *Control procedure:* Advice only *Outcomes:* 7 day PP at 12 months *Validation:* Significant other *Quality:* - Note: Validation available for only 70% of cases
Feeney et al 2001, Australia,	*Participants:* 198 inpatients with acute MI *Intervention:* Physician advice to quit plus single session of nurse counselling. Outpatient telephone follow up at 1,2,3,4 weeks and

	2,3,6,12 months (Intensity 4) *Control procedure:* Same as above but no proactive follow-up contact *Outcomes:* 12 months continuous abstinence *Validation:* Urinary cotinine *Quality: ++*
Froelicher et al 2004 USA	*Participants:* 277 inpatients with CVD or PVD from across 10 hospitals *Intervention:* Physician advice plus single session of nurse counselling. Then outpatient telephone follow-up at 2,7,21,28,90 days (Intensity 4) *Control procedure:* Physician advice + booklet *Outcomes:* 7-day PP at 12 months *Validation:* Saliva cotinine OR verification by significant other *Quality: +*
Hajek et al 2002, UK	*Participants:* 540 inpatients with acute MI. *Intervention:* Nurse advice and single session of inpatient counselling with self-help materials (Intensity 2) *Control procedure:* Brief advice and booklet *Outcomes:* 12 months continuous abstinence *Validation:* CO and salivary cotinine. *Quality: ++*
Hand et al 2002, *UK*	*Participants:* 245 hospital in-patients and outpatients with smoking related diseases *Interventions:* Advice and support + 3 weeks use of nicotine patch and nicotine inhalator (Intensity 5) *Control procedure:* Advice and support only *Outcomes:* 1 year continuous abstinence *Validation:* CO validated *Quality: ++*
Hanssen et al 2009, *Norway*	*Participants:* 288 MI patients *Interventions:* pro-active telephone follow-up included smoking cessation advice (8 calls in 6 months + access to reactive line) (Intensity 4) *Control procedure:* No intervention

	Outcomes: 18 months (not clear if PP or cont) *Validation:* None *Quality:* - *Notes:* 7 died in each group. Intervention was provided post-discharge
Hasuo et al 2004, Japan	*Participants:* 120 inpatients with any diagnosis *Intervention:* 3 sessions of inpatient nurse counselling and then telephone follow up at 7, 21, 42 days (Intensity 4) *Control procedure:* Same as above, but no follow-up calls *Outcomes:* 12 months (not clear if PP or cont) *Validation:* urinary cotinine (not clear if results are self-report or cotinine validated) *Quality:* -
Haug et al 2011, Germany	*Participants:* 477 patients in a rehabilitation centre (following acute medical illnesses) *Interventions:* Internet based smoking cessation intervention + 6 post discharge email invites to log on (Intensity 4) *Control procedure:* Baseline smoking assessment only *Outcomes:* 7 day PP at 6 months *Validation:* None *Quality:* -
Hennrikus et al 2005, USA	*Participants:* 2095 inpatients (all diagnoses) from across 4 hospitals *Interventions:* (1) Physician advice and smoking cessation booklet with an additional booklet mailed after discharge (Intensity 1); (2) Physician advice plus single session of inpatient nurse counselling followed by 3-6 telephone calls over 6 months (Intensity 4) *Control procedure:* Smoking cessation booklet in hospital *Outcomes:* 7-day PP at 12 months *Validation:* Saliva cotinine *Quality:* + *Notes:* 43% of counselling sessions in intervention 2 were conducted after discharge by telephone rather than at bedside
Hennrikus et al 2010,	*Participants:* 124 outpatients with peripheral arterial disease *Interventions:* minimum of 6 counselling sessions over 5 months +

USA	pharmacotherapy (a choice of NRT, bupropion or varenicline) (Intensity 5) *Control procedure:* Brief advice and information about smoking cessation services *Outcomes:* 7 day PP at 6 months *Validation:* CO validated or salivary cotinine *Quality:* +
Hilleman et al 2004, USA	*Participants:* 39 smokers who had recently undergone CABG *Interventions:* referred immediately to smoking cessation service for 8 week course + NRT (Intensity 5) *Control procedure:* Called monthly and if reported smoking then referred onto 8 week course *Outcomes:* 12 months continuous abstinence *Validation:* CO validated *Quality:* ++
Horn et al 2008, USA	*Participants:* 75 teenage smokers *Interventions:* In-hospital counselling, audio workbook, personalised postcard sent after discharge and 3 FU calls (1, 3 and 6 months) (Intensity 4) *Control procedure:* Basic advice *Outcomes:* 6 months – asked, "did you smoke in the last month?" *Validation:* None *Quality:* -
Kim 2005, South Korea	*Participants:* 401 general outpatients *Interventions:* Nurse advice, stage matching, setting TQD, booklets, mailed reminders, phone calls at 1 week and 1 month (Intensity 3) *Control procedure:* Usual care *Outcomes:* Abstinence from smoking at 5 months ('since the last quit attempt') *Validation:* CO *Quality:* +
Lacasse et al 2008,	*Participants:* 196 patients on cardio-pulmonary wards *Interventions:* Psychological support and NRT + up to 4 phone calls

Canada	within 6 weeks post discharge (Intensity 4) *Control procedure:* Usual care *Outcomes:* 7 day PP at 1 year *Validation:* Urine cotinine, but not taken into account *Quality:* -
Lewis 2009, UK	*Participants:* 450 hospitalised smoker *Interventions:* (1) counselling + 4 weekly out-patients appointments and information about stop smoking services (Intensity 4); (2) as above but given an appointment at the stop smoking service (Intensity 5). Patients were recommended to use NRT or bupropion. *Control procedure:* brief intervention *Outcomes:* 7 day PP at 1 year *Validation:* CO validated *Quality:* +
Lewis et al 1998, USA	*Participants:* 185 inpatients with any diagnosis except certain cardiac conditions *Interventions:* (1) Physician advice, a single session of counselling, nicotine patch for 6 weeks and self-help materials. Follow-up telephone calls at 1,3,6 weeks and 6 months. [Intensity 4]; (2) As above but with placebo patch (Intensity 4) *Control procedure:* Advice only *Outcomes*: 7 day PP at 6 months *Validation:* CO *Quality:* +
Li et al 2008 USA	*Participants:* 277 female smokers hospitalized with CVD *Interventions:* Inpatient counselling + 5 follow up phone calls over 3 months (Intensity 4) *Control procedure:* Usual care *Outcomes:* 7 day PP at 30 months *Validation:* None *Quality:* -
Lindström et al 2008,	*Participants:* 117 smokers undergoing elective surgery *Interventions:* Weekly sessions, face-to-face or by telephone and NRT,

Sweden	4 week pre and post surgery (Intensity 5) *Control procedure:* Usual care *Outcomes:* Abstinence from 3 weeks pre to 4 weeks post surgery *Validation:* CO validation *Quality:* ++
Mahabee-Gittens et al 2008, USA	*Participants:* 365 smoking parents of paediatric patients admitted to the emergency department. *Interventions:* Brief advice + fax referral to a quitline (Intensity 1) *Control procedure:* Usual care *Outcomes:* 7 day PP at 3 months *Validation:* None *Quality:* - *Notes:* Parents of patients
Martucci et al 2010 Italy	*Participants:* 233 smokers undergoing bronchoscopy *Interventions:* 15 minutes advice before and after surgery. Pharmacotherapy suggested but only prescribed on demand (Intensity 2) *Control procedure:* Usual care *Outcomes:* 7 day PP at 12 months *Validation:* CO validation *Quality:* +
Metz et al 2007, Germany	*Participants:* 307 smokers at a rehabilitation centre for acute and chronic disorders *Interventions:* CBT or Motivational Treatment in hospital + 5 telephone booster sessions (Intensity 4) *Control procedure:* CBT or Motivational Treatment in hospital + usual care *Outcomes:* 7 day PP at 12 months *Validation:* None *Quality:* -
Miller et al 1997, USA	*Participants:* 1942 general hospital inpatients *Interventions:* (1) Physician advice, single inpatient counselling session and self help materials. Telephone follow-up at 48 hours, 1, 3,

	and 12 weeks (Intensity 4); (2) As above by only one follow-up call (at 48 hours) (Intensity 3). *Control procedure:* Advice only *Outcomes:* 12 months continuous abstinence *Validation:* Plasma cotinine or family member corroboration *Quality:* +
Mohiuddin et al 2007, USA	*Participants:* 209 in-patients with acute coronary syndrome or decompensated CHF *Intervention:* Single session of inpatient counselling, self-help booklet, and NRT and/or bupropion. Outpatient follow-up consisted of weekly group meetings for up to 3m. (Intensity 5) *Control procedure:* Same as intervention but without any follow up (Intensity 2) *Outcomes:* 12 months continuous abstinence *Validation:* CO *Quality:* ++ *Notes:* NRT or bupropion offered on individualized basis to both groups
Moller et al 2002, Denmark	*Participants:* 120 smokers undergoing surgery *Intervention:* Weekly counselling initiated 6-8 week pre-operatively with NRT (type not specified). Abstinence or reduction option. (Intensity 5) *Control procedure:* Usual care *Outcomes:* 12 months continuous abstinence *Validation:* CO validation *Quality:* ++
Molyneux et al 2003, UK	*Participants:* 274 medical and surgical inpatients *Interventions:* (1) brief counselling plus a self-help booklet, no NRT and no follow up (Intensity 2), (2) brief counselling plus a self-help booklet and an offer of 6-week supply of NRT. No follow up (Intensity 2) *Control procedure:* Usual care *Outcomes:* 12 months sustained abstinence

	Validation: CO *Quality:* ++ *Notes:* NRT offered= gum, patch, inhalator, lozenge, nasal spray; 96% used NRT
Mosca et al 2010, USA	*Participants:* 304 admitted to hospital with CHD *Interventions:* Counselling during hospital + 3 FU calls (2, 4, 12 weeks) and a final visit/call at 6 weeks post discharge (Intensity 4) *Control procedure:* Usual care *Outcomes:* 6 months (not clear if PP or cont) *Validation:* CO validated *Quality:* +
Nagle et al 2005, Australia	*Participants:* 1422 inpatients (all diagnoses, but those in ICU were excluded) *Intervention:* Two sessions of inpatient nurse counselling plus a booklet and offer of NRT in hospital and for 5 days post-discharge. There was no follow-up (Intensity 2) *Control procedure:* Physician advice and booklet *Outcomes:* 7-day PP at 12 months *Validation:* Saliva cotinine *Quality:* +
Neuner et al 2009, Germany	*Participants:* 1044 smokers at an emergency department *Interventions:* in-hospital counselling + telephone booster sessions (nicotine gum given to those who set a TQD) (Intensity 3) *Control procedure:* Usual care *Outcomes:* 7 day PP at 12 months *Validation:* None *Quality:* -
Ortigosa *et al* 2000, Spain	*Participants:* 90 Inpatients with acute MI *Intervention:* Physician advice with telephone follow up at 2,3 and 4 weeks (Intensity 3) *Control procedure:* Usual care *Outcomes:* 7 day PP at 12 months *Validation:* CO

	Quality: +
Papadakis et al 2011, Canada	*Participants:* 28 patients at stroke prevention clinic *Interventions:* 4 weeks supply of free smoking cessation medication (a choice of NRT, bupropion or varenicline) + a prescription for further supply (Intensity 1) *Control procedure:* Prescription only *Outcomes:* 7 day PP at 6 months *Validation:* CO validated *Quality:* +
Pedersen *et al* 2005, Denmark	*Participants:* 105 inpatients with CHD *Intervention:* Advice to quit plus information about NRT (NRT was available). Patients attended 5 outpatient visits post discharge (Intensity 5) *Control procedure:* As above, but without follow-up *Outcomes:* 7 day PP at 12 months *Validation:* None *Quality:* -
Pederson *et al* 1991, USA	*Participants:* 74 inpatients with COPD. *Intervention:* Physician advice (prior to admission), followed by 3-9 sessions of inpatient counselling and self help materials, but no outpatient follow-up (Intensity 2) *Control procedure:* Advice only *Outcomes:* 7 day PP at 6 months *Validation:* Serum COHb *Quality:* + *Notes:* Only a subset validated
Pelletier *et al* 1998, Canada	*Participants:* 504 inpatients with acute MI. *Intervention:* Physician advice and self-help materials (Intensity 2) *Control procedure:* Usual care *Outcomes:* 7 day PP at 12 months *Validation:* None *Quality:* - *Note:* Not fully randomised

Quist-Paulsen *et al* 2003, Norway	*Participants:* 240 inpatients admitted to a cardiac ward *Intervention:* 1-2 sessions of inpatient nurse counselling and advice on using NRT. Telephone follow up at 2,7 and 21 days and 3 and 5 months, with a clinic visit with a cardiac nurse at 6 weeks (Intensity 4) *Control procedure:* Advice to quit and self-help booklet *Outcomes:* 7 day PP at 12 months *Validation:* Urine cotinine *Quality:* + *Notes:* Nicotine gum or patch encouraged for patients with strong urges to smoke in hospital
Ralston *et al* 2008, USA	*Participants:* 42 smoking caregivers of children admitted to hospital for respiratory illness *Interventions:* Counselling >30 minutes and offered NRT (Intensity 2) *Control procedure:* Brief counselling *Outcomes:* 6 months (not clear if PP or cont) *Validation:* None *Quality:* -
Ratner et al 2004, Canada	*Participants:* 237 patients awaiting surgery *Interventions:* Face-to-face counselling 1-3 weeks pre surgery and written materials, nicotine gum and smoking cessation hotline number. Post surgery counselling in hospital and via telephone (Intensity 4) *Control procedure:* Usual care *Outcomes:* Abstinence at 12 months (not clear if PP or cont) *Validation:* CO validation or urine cotinine *Quality:* +
Reid et al 2003 Canada	*Participants:* 254 inpatients admitted with CVD *Intervention:* A single session of brief nurse counselling followed by telephone call at 4 weeks. If patients were smoking at this time they were offered 3 counselling sessions (weeks 4, 8 and 12) and nicotine patch for 8 weeks (Intensity 4) *Control procedure:* Same as above, but without outpatient follow-up. *Outcomes:* 7-day PP at 12 months *Validation:* CO validation in a random sample of 25 self-reported

	abstainers *Quality:* +
Reid et al 2007 Canada	*Participants:* 99 hospitalised smokers with CAD *Interventions:* Counselling in hospital and offer of NRT + interactive voice response follow up (contact patients at 3,14 and 30 days post discharge) (Intensity 4) *Control procedure:* Counselling in hospital and offer of NRT + usual care *Outcomes:* 7 day PP at 12 months *Validation:* None *Quality:* -
Rigotti *et al* 1997 USA	*Participants:* 615 inpatients in medical or surgical services. *Intervention:* Physician advice and a single session of inpatient counselling plus self-help materials. Telephone follow-up was provided weekly for 3 weeks post discharge (Intensity 3) *Control procedure:* Usual care *Outcomes:* 7 day PP at 6 months *Validation:* Salivary cotinine. *Quality:* +
Rigotti *et al* 1994 USA	*Participants:* 87 inpatients scheduled for CABG surgery *Intervention:* 3 inpatient counselling sessions, plus self-help material, followed by one telephone call 1 week post discharge (Intensity 3) *Control procedure:* Advice only *Outcomes:* 12 months continuous abstinence *Validation:* Salivary cotinine. *Quality:* ++
Rigotti *et al* 2006 USA	*Participants:* 254 inpatients with CVD or PVD from across 5 hospitals *Intervention:* Bupropion 150 mg b.d. for 12 weeks plus a single session of nurse counselling in hospital. Patients were also given a self-help booklet and received 5 follow up phone calls at 2,7,21 days, and 2 and 3 months (Intensity 4) *Control procedure:* Same as above but with placebo *Outcomes:* 12 months continuous abstinence

	Validation: Saliva cotinine *Quality:* ++
Rodriguez et al 2007 *USA*	*Participants:* 111 smokers undergoing deep sedation (for incision and drainage of abscess, or orthopaedic reduction or relocation) *Interventions:* 30 minutes of music played during sedation + scripted smoking-cessation message (Intensity NA) *Control procedure:* Music only *Outcomes:* 2 week sustained abstinence *Validation:* Self report *Quality:* - *Notes:* Study was stopped due to lack of effect
Rosal et al 1992, USA	*Participants:* 267 inpatients (smokers or recent quitters) with coronary artery stenosis. *Intervention:* 2 sessions of inpatient counselling, plus self help materials and relaxation tapes. Telephone follow up at 1, 3 weeks and 3 months if quit, or 2 and 4 months if did not quit (Intensity 4) *Control procedure:* Advice only *Outcomes:* 12 months continuous abstinence *Validation:* CO *Quality:* ++
Schiebel et al 2007 *USA*	*Participants:* 39 smokers at an emergency department *Interventions:* Advice to quit + proactive quitline intervention (baseline session + 4 FU calls around TQD) (Intensity 3) *Control procedure:* Advice to quit + self help manual *Outcomes:* 7 day PP at 6 months *Validation:* None *Quality:* -
Schofield et al 1999, *Australia*	*Participants:* 4158 hospitalised smokers *Interventions:* Personalised letter urging them to quit from physician, sent 1-2 weeks post discharge (Intensity 1) *Control procedure:* Usual care *Outcomes:* 7 day PP at 12 months *Validation:* Urine cotinine or CO validated

	Quality: +
Simon *et al* 2003, USA	*Participants:* 223 inpatients (all diagnoses) *Intervention:* A single session of nurse or health educator counselling and booklet, plus nicotine patch treatment for 8 weeks. Telephone follow-up conducted at 1 and 3 weeks and 1, 2, and 3 months (Intensity 4) *Control procedure:* A single session of nurse or health educator counselling and booklet, plus nicotine patch treatment for 8 weeks but no telephone contact *Outcomes:* 7-day PP at 12 months *Validation:* Saliva cotinine OR report by spouse *Quality:* +
Simon et al 2009, USA	*Participants:* 85 smokers admitted to hospital for at least 24 hours *Interventions:* counselling and 5 FU calls +7 weeks Bupropion (Intensity 4) *Control procedure:* counselling and 5 FU calls + 7 weeks placebo *Outcomes:* 7 day PP at 6 months *Validation:* Salivary cotinine *Quality:* +
Simon et al 1997, USA	*Participants:* 229 smokers undergoing non-cardiac surgery *Intervention:* Inpatient counselling (30-60 mins), self-help materials, video and nicotine gum (3mg) if no contraindications. Telephone FU 5 times in 1-3 weeks post discharge, 2m and 3m (Intensity 4) C*ontrol procedure:* Advice only *Outcomes:* 7 day PP at 12 months *Validation:* CO or corroboration by significant other *Quality:* -
Sivarajan et al 2004, USA	*Participants:* 277 women hospitalized with CVD *Interventions:* Counselling at bedside, tapes and booklets + 5 FU calls (Intensity 4) *Control procedure:* Usual care *Outcomes:* 7 day PP at 30 months *Validation:* None

	Quality: -
Smith et al 2009, Canada	*Participants:* 276 patients admitted with MI or for a CABG *Interventions:* Counselling, take home materials + 7 FU calls over 2 months post discharge (Intensity 4) *Control procedure:* Advice from doctor/nurse + 2 pamphlets *Outcomes:* 7 day PP at 12 months *Validation:* None *Quality:* -
Smith et al 2011, Canada	*Participants:* 643 inpatients *Interventions:* In-hospital education + multiple FU calls (up to 60 days post discharge) (Intensity 4) *Control procedure:* Brief in-hospital advice + pamphlets *Outcomes:* 7 day PP at 12 months *Validation:* Salivary cotinine *Quality:* +
Steinberg et al 2011, USA	*Participants:* 79 hospitalised smokers *Interventions:* Brief behavioural support (5-10 mins) + varenicline. Data collection visits at 4, 12 and 24 weeks (Intensity 5) *Control procedure:* Support + placebo *Outcomes:* 7 day PP at all time points (4, 12 and 24 weeks) *Validation:* CO validated *Quality:* +
Stevens *et al* 1993, USA	*Participants:* 1119 general hospital inpatients admitted for >36 hours *Intervention:* Single session of inpatient counselling supplemented by self-help materials. 1-2 telephone contacts were provided in the first 3 weeks of discharge (Intensity 3) *Control procedure:* Usual care *Outcomes:* 12 month sustained abstinence *Validation:* None *Quality:* -
Stevens *et al* 2000, USA	*Participants:* 1173 general hospital inpatients admitted for >36 hours *Intervention:* Single session of counselling supplemented by self-help materials, video. Follow up consisted of 1 telephone call at 1-week

	post discharge (Intensity 3) *Control procedure:* Usual care *Outcomes:* 12 months sustained abstinence *Validation:* None *Quality:* -
Taylor *et al* 1990, USA	*Participants:* 173 inpatients with acute MI. *Intervention:* A single session of inpatient counselling supplemented by self-help materials and relaxation tapes. Nicotine gum was available. 6-7 telephone follow-up calls were undertaken over 4 months post discharge (Intensity 4) *Control procedure:* Usual care *Outcomes:* 12 months sustained abstinence *Validation:* Serum thiocyanate and CO *Quality:* +
Taylor et al 1996, USA	*Participants:* 328 hospitalised smokers *Interventions:* 1 hour in-hospital counselling session + 4 FU calls after discharge (Intensity 4) *Control procedure:* Brief advice *Outcomes:* 7 day PP at 1 year *Validation:* plasma cotinine or family confirmation *Quality:* +
Thomsen et al 2010a, Denmark	*Participants:* 130 female smokers undergoing breast cancer surgery *Interventions:* Single smoking cessation counselling session and NRT, 3-7 days pre surgery (Intensity 3) *Control procedure:* Usual care *Outcomes:* 12 month continuous abstinence *Validation:* None *Quality:* +
Tonnesen et al 2000, Denmark	*Participants:* 446 smokers referred to a lung clinic *Interventions:* 1) 15mg patch 2) nicotine inhaler 3) 15mg patch + inhaler for 3 months (Intensity 4) *Control procedure:* 5mg patch "placebo" for 3 months *Outcomes:* 12 month continuous abstinence

	Validation: Salivary cotinine *Quality:* ++
Tonnesen et al 2006, Denmark	*Participants:* 370 COPD patients *Interventions:* 12 week course of nicotine sublingual tablets with low (4 visits + 6 phone calls) or high (7 visits + 5 phone calls) intensity support (Intensity 5 for both) *Control procedure:* 12 week course of placebo sublingual tablets with low (4 visits + 6 phone calls) or high (7 visits + 5 phone calls) intensity support *Outcomes:* 1 year continuous abstinence *Validation:* CO validated *Quality:* ++
Vial *et al* 2002, Australia	*Participants:* 102 inpatients from medical and surgical wards *Interventions:* (1) Pharmacist consultation about NRT use, supplemented by a booklet and up to 16 weeks of subsidized nicotine patches that could be obtained at weekly visits to the hospital pharmacist; (2) As above, but patches were obtained from a community pharmacists (Intensity 5) *Control procedure:* advice to quit plus a booklet *Outcomes:* 12 months continuous abstinence *Validation:* CO test 'whenever possible' *Quality:* -
Wakefield et al 2004, Australia	*Participants:* 137 cancer patients *Interventions:* Motivational intervention and a FU call (Intensity 4) *Control procedure:* Usual care *Outcomes:* 6 months continuous abstinence *Validation:* Urine cotinine or CO validated *Quality:* ++
Wiggers et al 2006, Netherlands	*Participants:* 385 smokers at outpatient departments (vascular surgery, cardiology and vascular medicine) *Interventions:* counselling, 8 weeks nicotine patches + a FU call (Intensity 3) *Control procedure:* Usual care

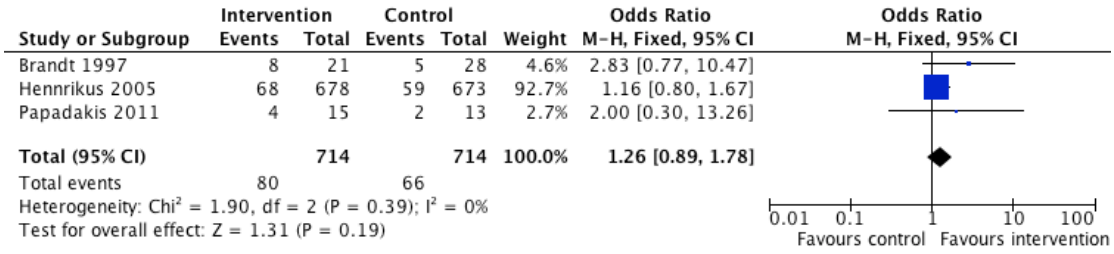
	Outcomes: 7 day PP at 12 months *Validation:* Urine or Salivary cotinine; *Quality:* +

1) Efficacy of interventions delivered to non-surgical patients

Intervention intensity

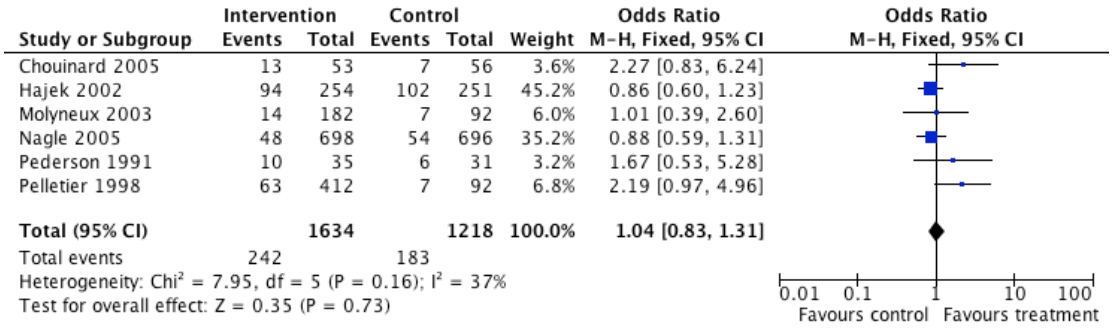
Below we analyse all studies where more intensive support was compared with less intensive or no support. Drug trials where both study arms received the same intensity of behavioural support are analysed in **Section 3**.

Figure 2 – Efficacy of intervention to non-surgical patients - Intensity 1 (Single contact in hospital lasting up to 15 minutes, no follow-up support)



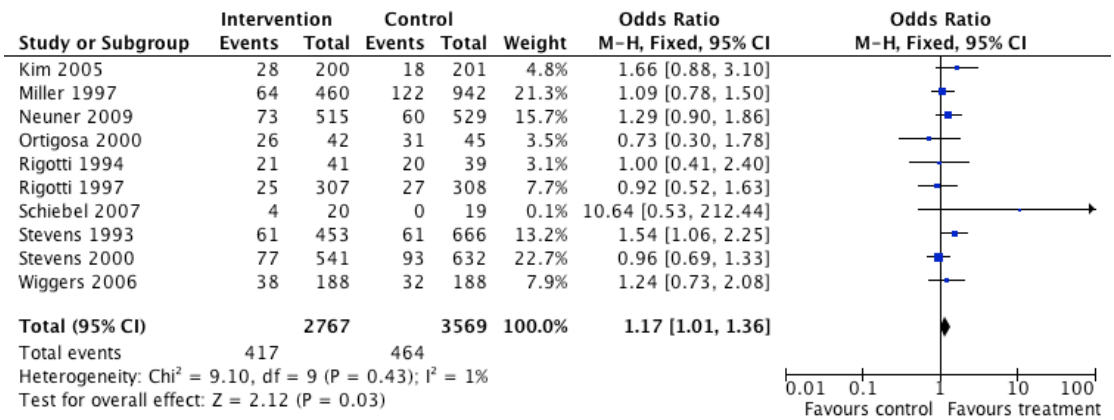
Three studies (Brandt et al 1997 [RCT +]; Hennrikus, et al 2005 [RCT +]; Papadakis et al 2011 [RCT +]) reported on the effects of one-off brief interventions (short advice and booklets) with no follow-up. The results were homogenous and show no additional effect of such interventions compared to usual care (OR=1.26; 95% CI:0.89-1.78).

Figure 3 - Efficacy of intervention to non-surgical patients - Intensity 2 (One or more contacts in hospital lasting in total > 15 minutes, no follow-up support)



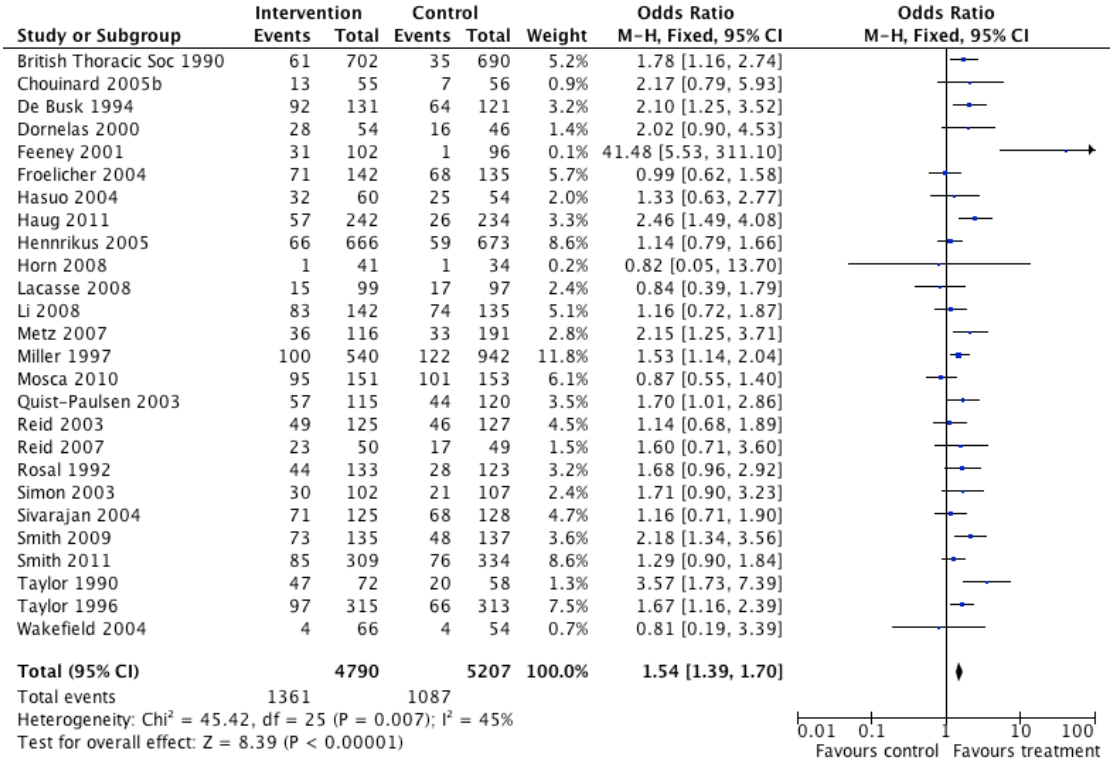
The results from six studies (Chouinard et al 2005 [RCT ++]; Hajek et al 2002 [RCT ++]; Molyneux et al 2003 [RCT ++]; Nagle et al 2005 [RCT +]; Pederson et al 1991 [RCT +]; Pelletier et al 1998 [RCT -]) which reported slightly more intensive interventions in hospital (a longer counselling session or two plus booklets) with no further follow up were similar, showing no effect of such interventions (OR=1.04; 95%CI: 0.83-1.31). The results were again homogenous.

Figure 4 - Efficacy of intervention to non-surgical patients - Intensity 3 (Any hospital contact plus follow-up <=1 month)



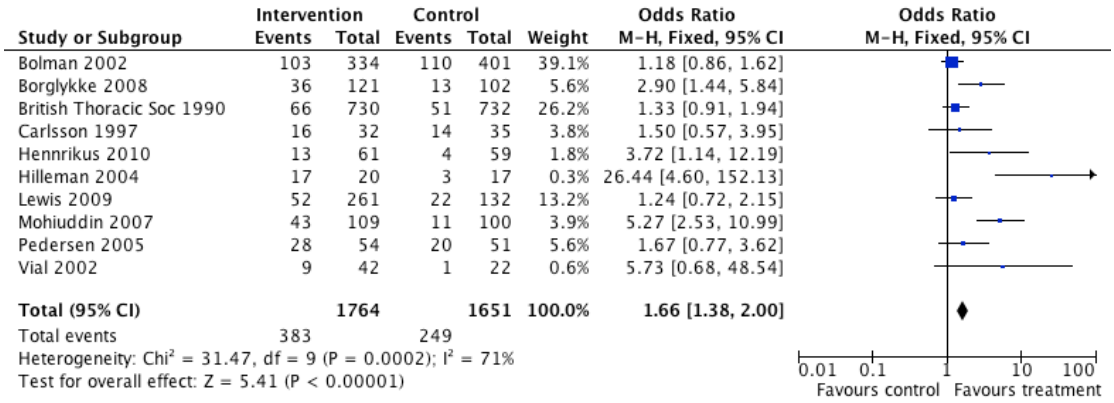
Ten studies (Kim et al 2005 [RCT +]; Miller et al 1997 [RCT +]; Neuner et al 2009 [RCT -]; Ortigosa et al 2000 [RCT +]; Rigotti et al 1994 [RCT ++]; Rigotti et al 1997 [RCT +]; Schiebel et al 2007 [RCT -]; Stevens et al 1993 [RCT -]; Stevens et al 2000 [RCT -]; Wiggers et al 2006 [RCT +]) provided telephone support post-discharge for up to 4 weeks. This generated a marginally significant effect overall (OR=1.17; 95% CI: 1.01-1.36), but there was no effect when only studies which validated self-reported abstinence were included (see below). The studies were homogenous. Only one study (Stevens et al 1993, [RCT -]) yielded a significant result. If there is an effect, it is likely to be small.

Figure 5 - Efficacy of intervention to non-surgical patients - Intensity 4



The largest number of trials (26) included telephone follow-ups for over 4 weeks (British Thoracic Society B 1990 [RCT ++]; Chouinard et al 2005 [RCT ++]; De Busk et al 1994 [RCT ++]; Dornelas et al 2000 [RCT +]; Feeney et al 2001 [RCT ++]; Froelicher et al 2004 [RCT +]; Haug et al 2011 [RCT -]; Hasuo et al 2004 [RCT +]; Hennrikus et al 2005 [RCT +]; Horn et al 2008 [RCT -]; Lacasse et al 2007 [RCT -]; Li et al 2008 [RCT -]; Metz et al 2007 [RCT -]; Miller et al 1997 [RCT +]; Mosca et al 2010 [RCT +]; Quist-Paulsen et al 2003 [RCT +]; Reid et al 2003 [RCT +]; Reid et al 2007 [RCT -]; Rosal 1992 [RCT ++]; Simon et al 2003 [RCT +]; Sivarajan et al 2004 [RCT -]; Smith et al 2009 [RCT -]; Smith et al 2011 [RCT +]; Taylor et al 1990 [RCT +]; Taylor et al 1996 [RCT +]; Wakefield et al 2004 [RCT ++]). Such interventions were effective (OR=1.54; 95%CI: 1.39-1.70). The studies were heterogeneous, with two outliers (Feeney et al 2001, [RCT ++]; Taylor et al 1996, [RCT +]). Removing them reduced the heterogeneity (p=0.06) with the result remaining significant (OR=1.48, 1.33-1.64).

Figure 6 - Efficacy of intervention to non-surgical patients - Intensity 5 (Any hospital contact plus follow-up >1 month including at least one face-to-face session)



Ten studies included at least one post-discharge face-to-face contact (Bolman et al 2002 [RCT -]; Borglykke et al 2008 [RCT +]; British Thoracic Society A 1990 [RCT ++]; Carlsson et al 1997 [RCT -]; Hennrikus et al 2010 [RCT +]; Hilleman et al 2004 [RCT ++]; Lewis et al 2009 [RCT +]; Mohiuddin et al 2007 [RCT ++]; Pedersen et al 2005 [RCT -]; Vial et al 2002 [RCT-]). They differed widely in the number of sessions and the nature of support provided. There were also substantial differences in the nature of the control interventions, which ranged from minimal to Intensity 5. There was an overall significant effect (OR=1.66; 95%CI: 1.38-2.00), but the studies were heterogeneous. Removing the two outliers, which both provided intensive face-to-face treatment over extended periods of time (Hilleman et al 2004, [RCT ++]; Mohiuddin et al 2007, [RCT ++]) reduced heterogeneity (p=0.19). The overall effect was reduced as well but it remained significant (OR=1.45, 1.19-1.76).

Overall we found that only interventions of Intensity 4 and 5, which provide support to smokers over a period longer than 4 weeks showed efficacy.

Validated studies by intensity of intervention

We next re-ran the five analyses including only studies, which validated self-reported abstinence.

Figure 7 – Validated by intensity of intervention in non-surgical patients - Intensity 1

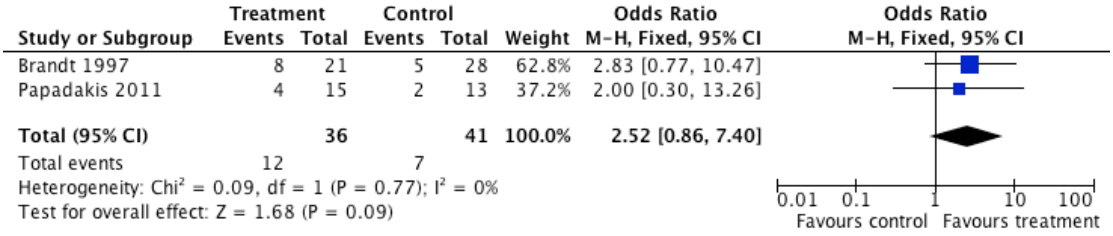


Figure 8 – Validated by intensity of intervention in non-surgical patients - Intensity 2

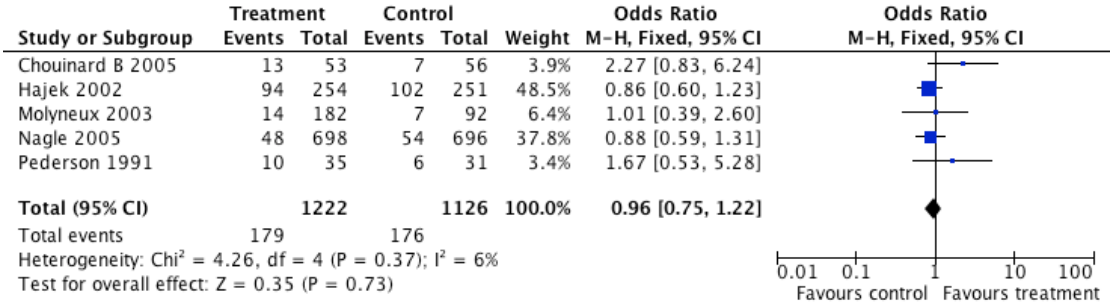


Figure 9 – Validated by intensity of intervention in non-surgical patients - Intensity 3

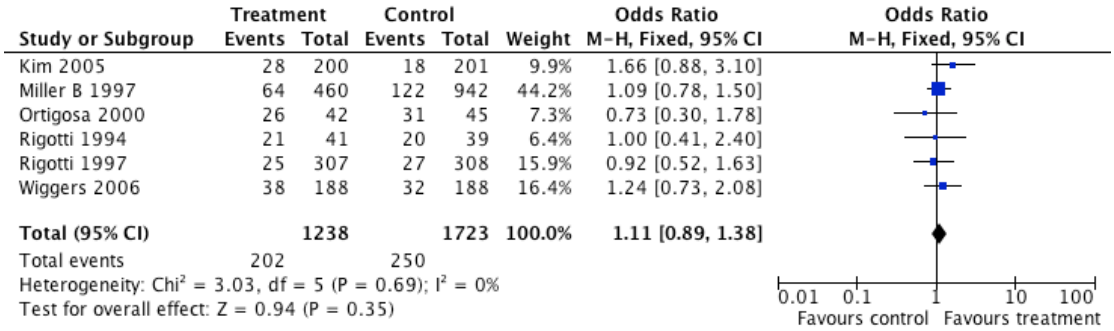


Figure 10 – Validated by intensity of intervention in non-surgical patients - Intensity 4

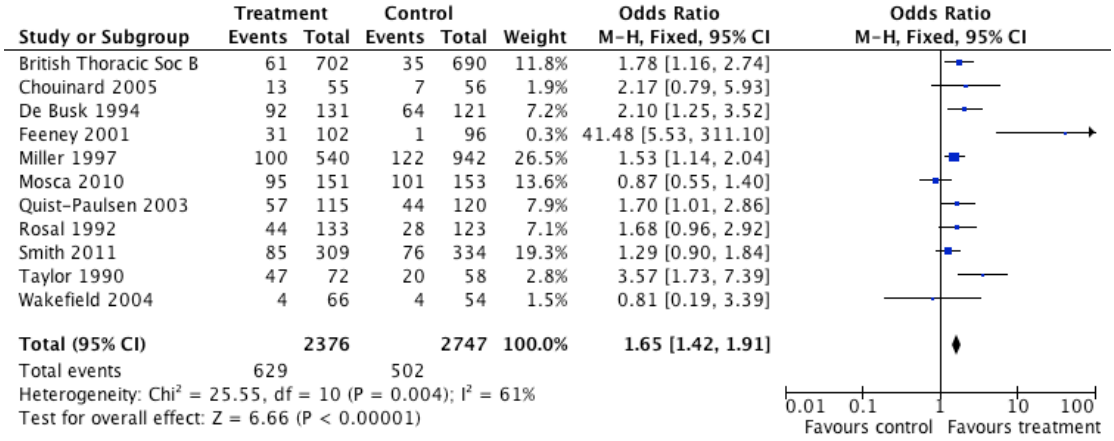
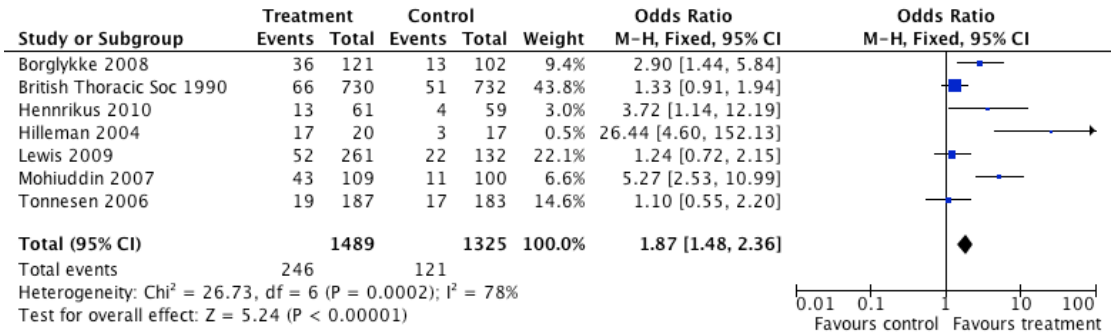


Figure 11 – Validated by intensity of intervention in non-surgical patients - Intensity 5



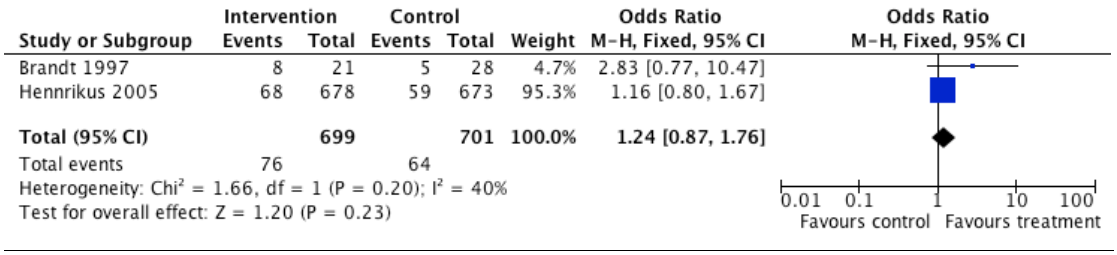
The results remain unaltered, showing a lack of efficacy for low intensity interventions, and significant effects of interventions providing follow-up support for the duration longer than four-weeks. They thus agree with the finding of Rigotti et al. (2007 [Systematic Review ++]).

Use of medications

The next key question, not addressed in the previous meta-analyses, concerns the role of stop smoking medications. Some of the interventions examined in these studies included medications and some did not. The analyses presented above do not clarify whether significant effects can be achieved without medications, and whether the finding of differential effectiveness of interventions of different intensity is confounded by more intensive interventions being more likely to include pharmacotherapy. Clarifying this issue has obvious implications for recommended practice and for intervention costs.

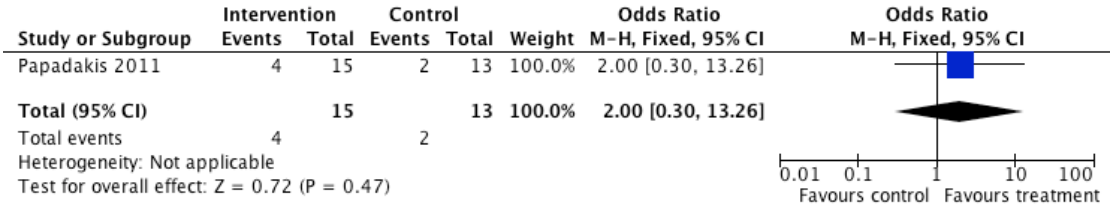
We divided studies of each intensity into those, which included medications and those that did not. The relevant meta-analyses are presented below. Medication was mostly NRT.

Figure 12 - Intensity 1 – behavioural support only



Two studies (Brandt et al 1997 [RCT +]; Hennrikus et al 2005 [RCT +]) included behavioural support only and this showed no effect on abstinence (OR=1.24; 95%CI: 0.87-1.76).

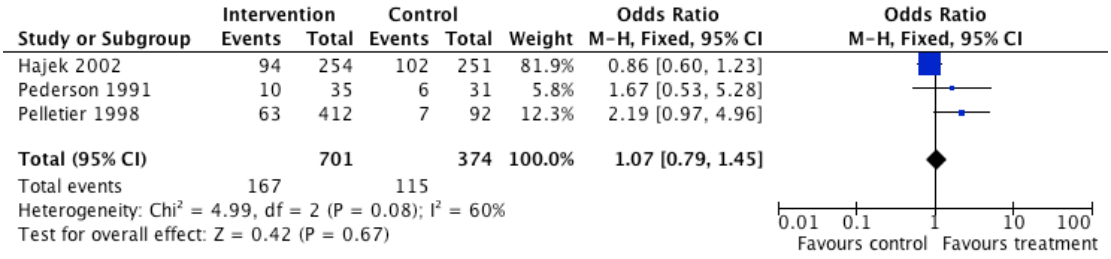
Figure 13 - Intensity 1 – behavioural support plus medications



One study (Hennrikus, et al 2005 [RCT +]) included medications. The study allowed a choice of NRT, bupropion or varenicline. At this level of support, such interventions were not effective (OR=2.00; 95%CI: 0.30-13.26).

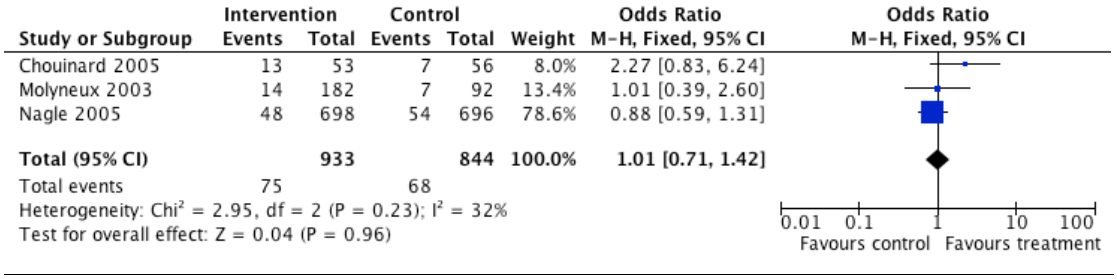
Intensity 1 interventions are ineffective with or without medications.

Figure 14 - Intensity 2 – behavioural support only



Three studies (Hajek et al 2002 [RCT ++]; Pederson et al 1991 [RCT +]; Pelletier et al 1998 [RCT -]) included behavioural support only and pooled data show that this was not effective (OR=1.07; 95%CI: 0.79-1.45).

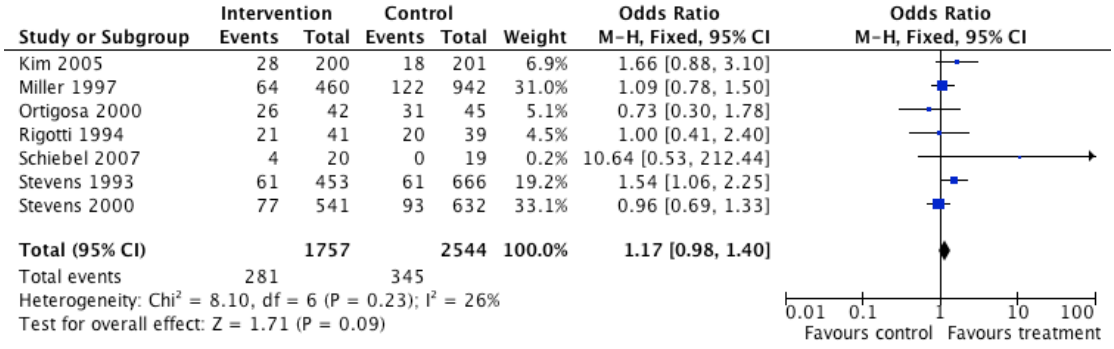
Figure 15 - Intensity 2 – behavioural support plus medications



Three studies (Chouinard et al 2005 [RCT ++]; Molyneux et al 2003 [RCT ++]; Nagle et al 2005 [RCT +]) included NRT. At this level of support, such interventions were not effective (OR=1.01; 95%CI: 0.71-1.42).

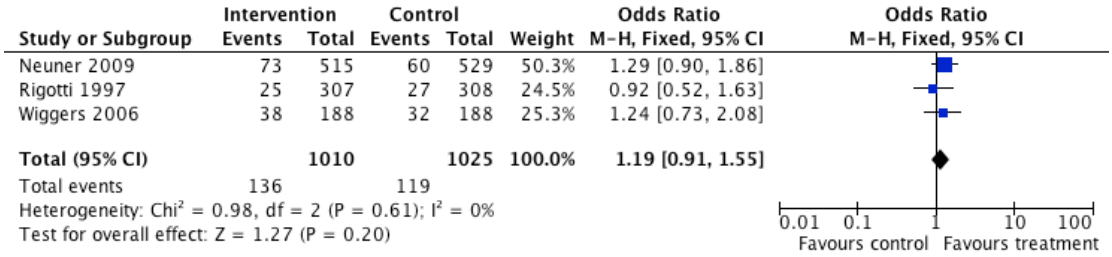
Intensity 2 interventions are ineffective with or without medications.

Figure 16 - Intensity 3 – behavioural support only



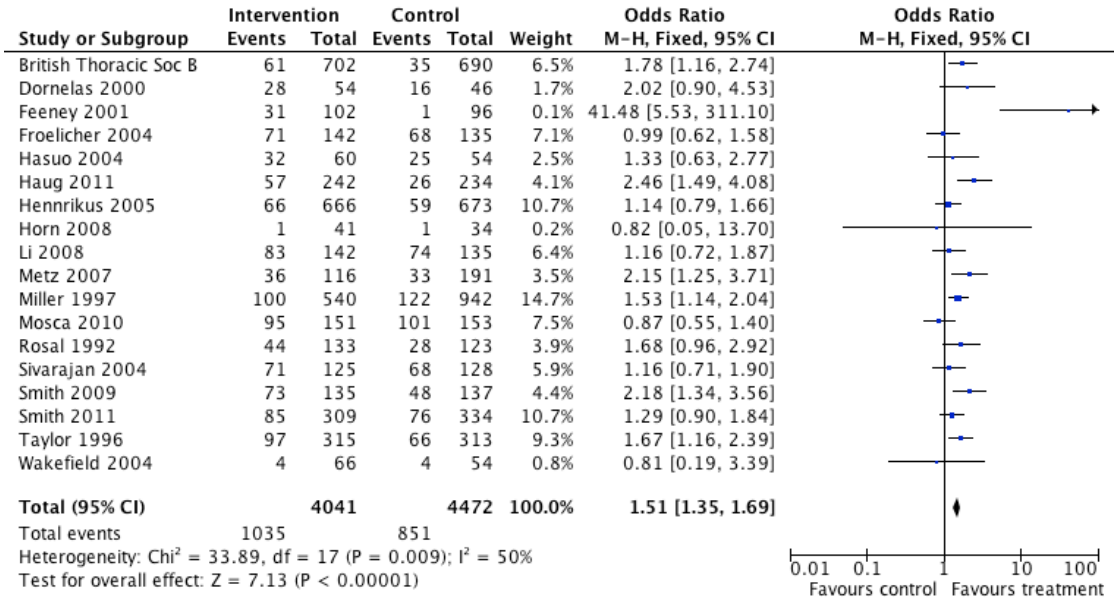
Seven studies (Kim et al 2005 [RCT +]; Miller et al 1997 [RCT +]; Ortigosa et al 2000 [RCT +]; Rigotti et al 1997 [RCT +]; Schiebel et al 2007 [RCT -]; Stevens et al 1993 [RCT -]; Stevens et al 2000 [RCT -]) included behavioural support only and pooled data show that this was not effective (OR=1.17; 95%CI: 0.98-1.40).

Figure 17 - Intensity 3 – behavioural support plus medications



Three studies (Neuner et al 2009 [RCT -]; Rigotti et al 1997 [RCT +]; Wiggers et al 2006 [RCT +]) used NRT. At this level of support, such interventions were not effective (OR=1.19; 95%CI: 0.91-1.55). Intensity 3 interventions are ineffective with or without medications. The results are homogenous.

Figure 18 - Intensity 4 – behavioural support only

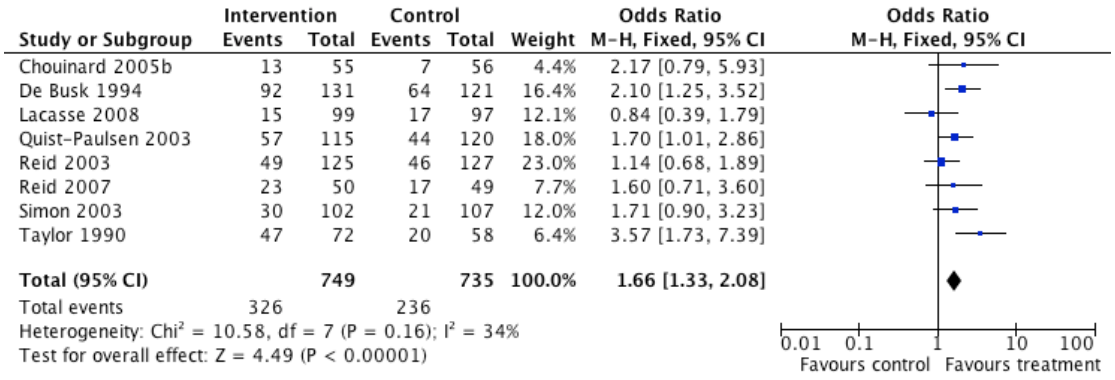


Eighteen studies (British Thoracic Society B 1990 [RCT ++]; Dornelas et al 2000 [RCT +]; Feeney et al 2001 [RCT ++]; Froelicher et al 2004 [RCT +]; Hasuo et al 2004 [RCT +]; Haug et al 2011 [RCT -]; Hennrikus et al 2005 [RCT +]; Horn et al

2008 [RCT -]; Li et al 2008 [RCT -]; Metz et al 2007 [RCT -]; Miller et al 1997 [RCT +]; Mosca et al 2010 [RCT +]; Rosal et al 1992 [RCT ++]; Sivarajan et al 2004 [RCT -]; Smith et al 2009 [RCT -; Smith et al 2011 [RCT +]; Taylor et al 1996 [RCT +]; Wakefield et al 2004 [RCT ++])) included behavioural support only and pooled data show this level of support was effective (OR=1.51; 95%CI: 1.35-1.69).

The results of the pooled behaviour support only studies were heterogeneous. Removing the outlier (Feeny et al. 2001) reduces heterogeneity (0.10) and remained significant (OR=1.43, 1.26-1.61).

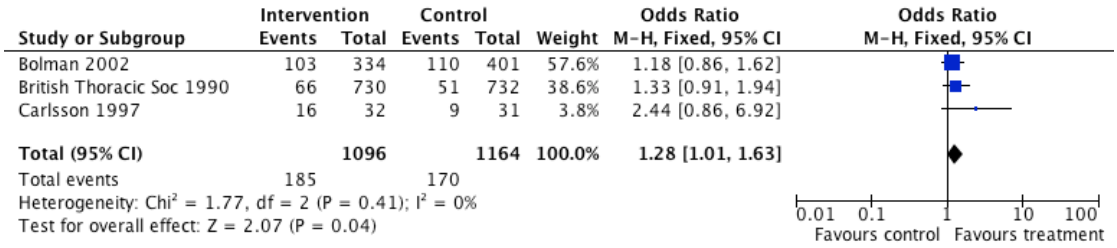
Figure 19 - Intensity 4 – behavioural support plus medications



Eight studies (Chouinard et al 2005b [RCT ++]; De Busk et al 1994 [RCT ++]; Lacasse et al 2008 [RCT -]; Quist-Paulsen et al 2003 [RCT +]; Reid et al 2003 [RCT +]; Reid et al 2007 [RCT -]; Simon et al 2003 [RCT +]; Taylor et al 1990 [RCT +]) included medications. All studies used NRT, but Chouinard et al 2005 included bupropion as well. At this level of support, such interventions were effective (OR=1.66; 95%CI: 1.33-2.08).

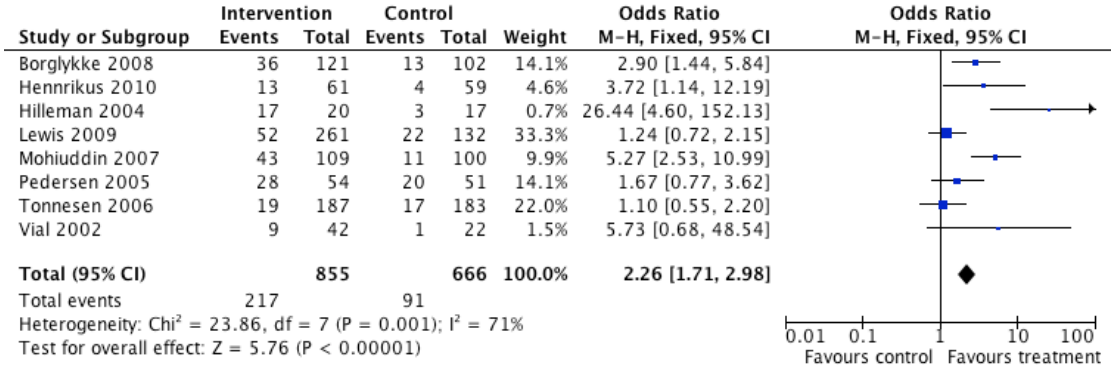
Intensity 4 interventions are effective without medications and their efficacy further increases when medications are added.

Figure 20 - Intensity 5 – behavioural support only



Three studies (Bolman et al 2002 [RCT +]; British Thoracic Society A 1990 [RCT ++]; Carlsson et al 1997 [RCT -]) included behavioural support only and pooled data showed borderline efficacy (OR=1.28; 95%CI: 1.01-1.63).

Figure 21 - Intensity 5 – behavioural support plus medications



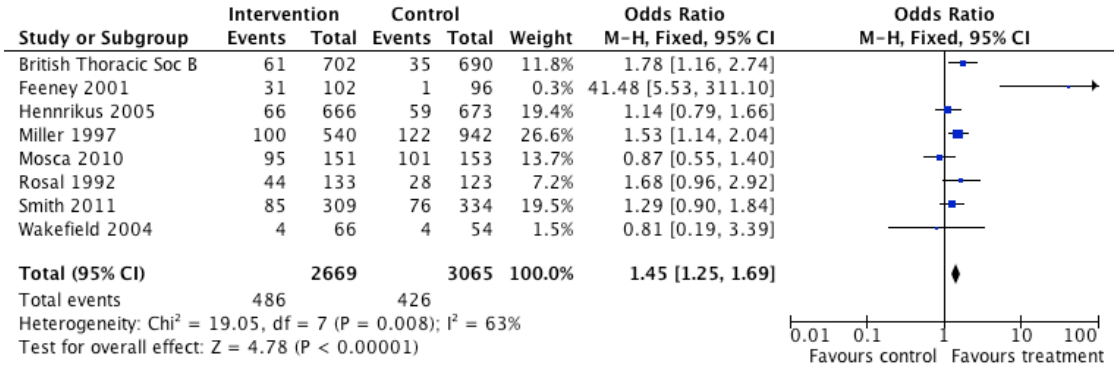
Eight studies (Borglykke et al 2008 [RCT +]; Hennrikus et al 2010 [RCT +]; Hilleman et al 2004 [RCT ++]; Lewis et al 2009 [RCT +]; Mohiuddin et al 2007 [RCT ++]; Pedersen et al 2005 [RCT -]; Tonnesen et al 2006 [RCT ++]; Vial et al 2002 [RCT -]) included medications. At this level of support, such interventions were effective (OR=2.26; 95%CI: 1.71-2.98). All studies used NRT, Mohiuddin et al 2007

[RCT ++] included bupropion as well and Hennrikus et al 2010 [RCT +] provided a choice of NRT, bupropion or varenicline.

Intensity 5 interventions without medications showed borderline effects, but with medications included, such interventions have good efficacy.

We next re-ran intensity 4 & 5 analyses including only studies which validated self-reported abstinence.

Figure 22 - Intensity 4 – behavioural support only – validated



The results of the pooled validated behaviour support only studies were heterogeneous. Removing the outlier (Feeny et al. 2001 [RCT ++]) reduces heterogeneity (p=0.28) with the result remaining significant (OR=1.35, 1.15-1.57).

Figure 23 - Intensity 4 –behavioural support plus medications – validated

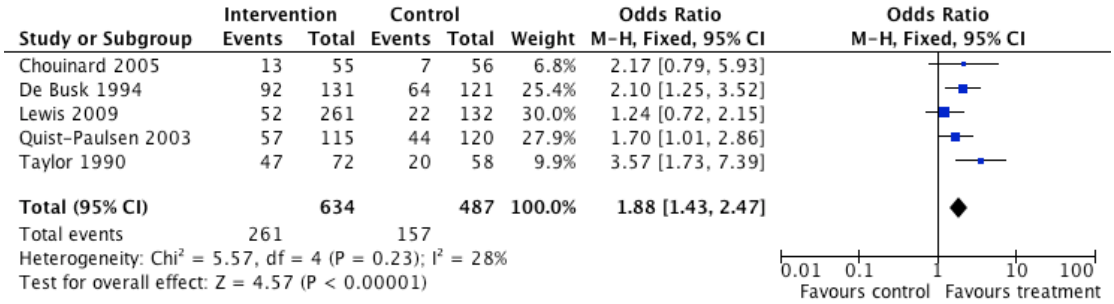


Figure 24 - Intensity 5 – behavioural support only – validated

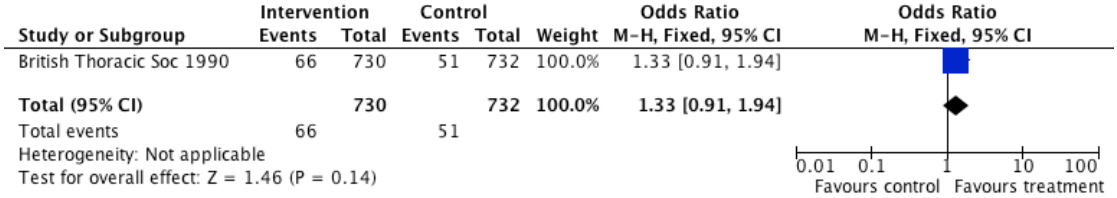
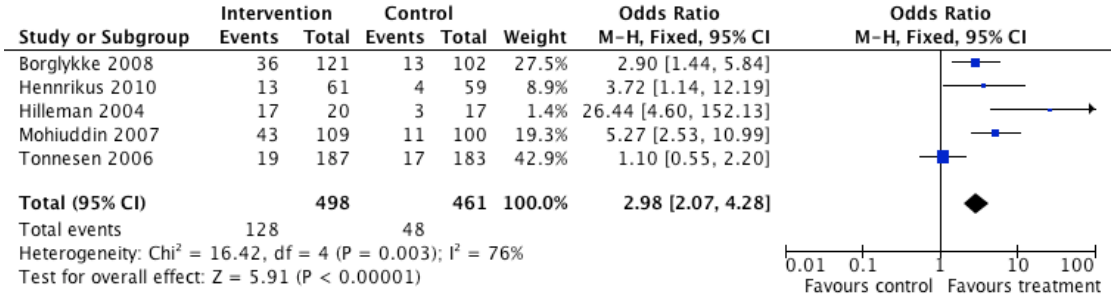


Figure 25 - Intensity 5 – behavioural support plus medications – validated



The results of the pooled validated behaviour support plus medications studies were heterogeneous. Removing the outlier (Tonnesen et al. 2006 [RCT ++]) reduces heterogeneity (p=0.13) with the result remaining significant (OR=4.39, 2.81-6.84).

The analyses including validated studies only show good efficacy of intensive interventions accompanied by medications, especially when support is provided face-to-face.

Low intensity interventions were ineffective with or without medications. Interventions of Intensity 4 and 5 showed uncertain or modest efficacy without medications and good efficacy when medications were included. The analysis of studies, which validated self-reported abstinence, replicated these findings.

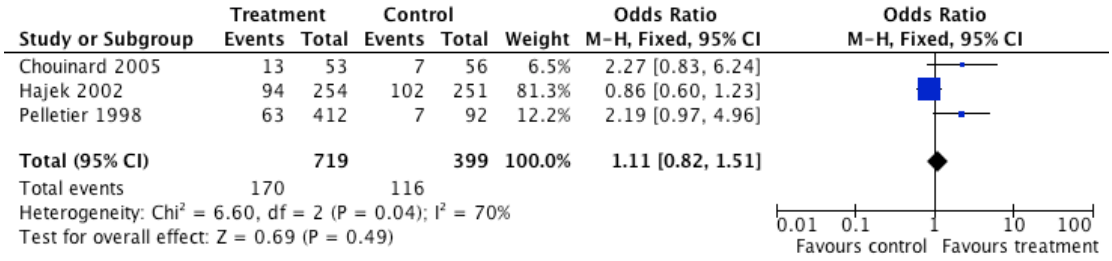
2) Patient groups

There is little reason to expect that stop-smoking interventions targeting dependent smokers motivated to quit will differ in efficacy depending on smokers' physical illness. However, we analysed separately the interventions for the main groups of hospital patients.

Patients with cardiovascular disease

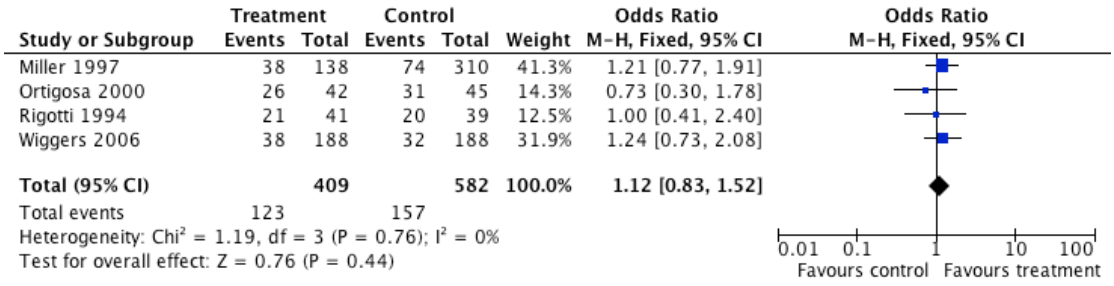
Intensity 1: There were no such studies

Figure 26 – Patients with cardiovascular disease - Intensity 2



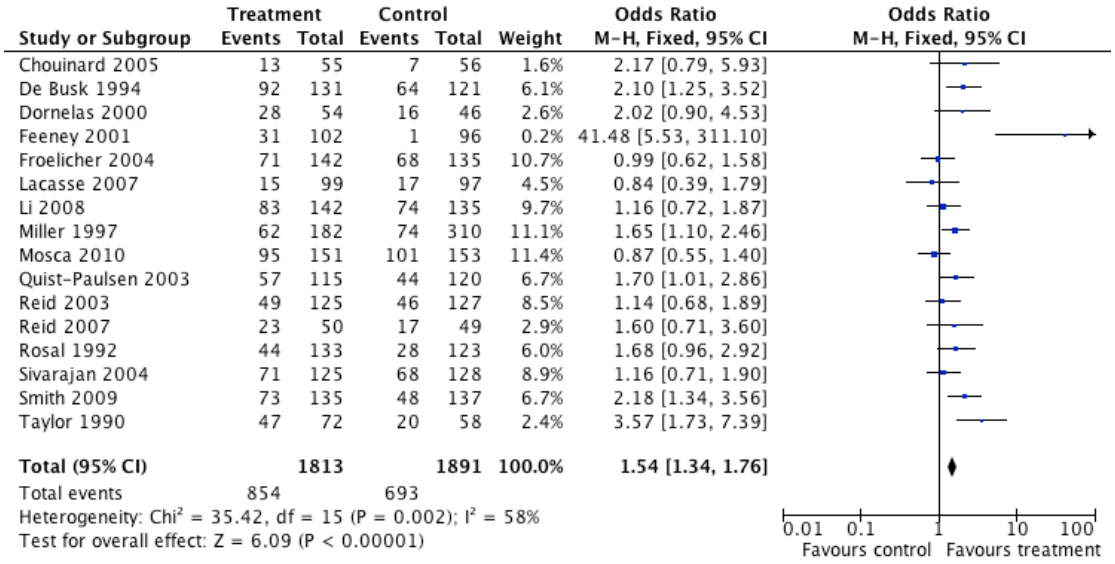
Pooled results from 3 studies (Chouinard et al 2005 [RCT ++]; Hajek et al 2002 [RCT ++]; Pelletier et al 1998 [RCT -]) showed no effect of this intensity (OR=1.11; 95%CI: 0.82-1.51).

Figure 27 – Patients with cardiovascular disease - Intensity 3



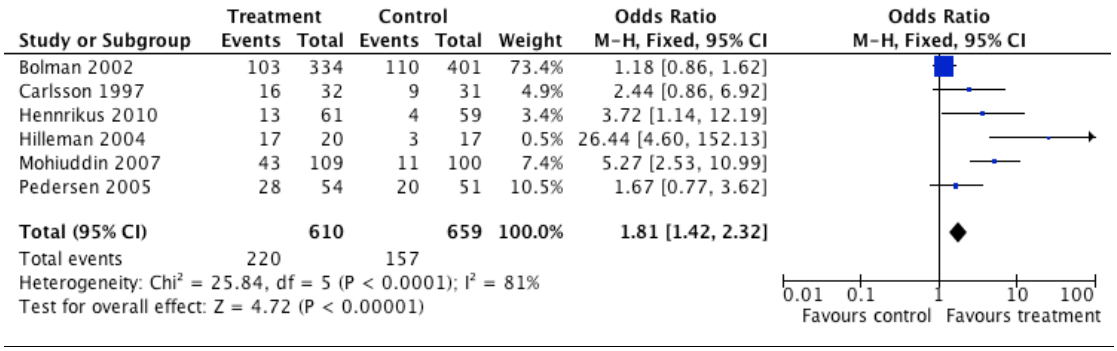
Pooled results from 4 studies (Miller et al 1997 [RCT +]; Ortigosa et al 2000 [RCT +]; Rigotti et al 1997 [RCT +]; Wiggers et al 2006 [RCT +]) showed no effect of this intensity (OR=1.12; 95%CI: 0.83-1.52).

Figure 28 – Patients with cardiovascular disease - Intensity 4



Pooled results from 16 studies (Chouinard et al 2005 [RCT ++]; De Busk et al 1994 [RCT ++]; Dornelas et al 2000 [RCT +]; Feeney et al 2001 [RCT ++]; Froelicher et al 2004 [RCT +]; Lacasse et al 2007 [RCT -]; Li et al 2008 [RCT -]; Miller et al 1997 [RCT +]; Mosca et al 2010 [RCT +]; Quist-Paulsen et al 2003 [RCT +]; Reid et al 2003 [RCT +]; Reid et al 2007 [RCT -]; Rosal et al 1992 [RCT ++]; Sivarajan et al 2004 [RCT -]; Smith et al 2011 [RCT +]; Taylor et al 1990 [RCT +]) showed that this level of intensity is effective in patients with CVD (OR=1.54; 95%CI: 1.34-1.79).

Figure 29 – Patients with cardiovascular disease - Intensity 5

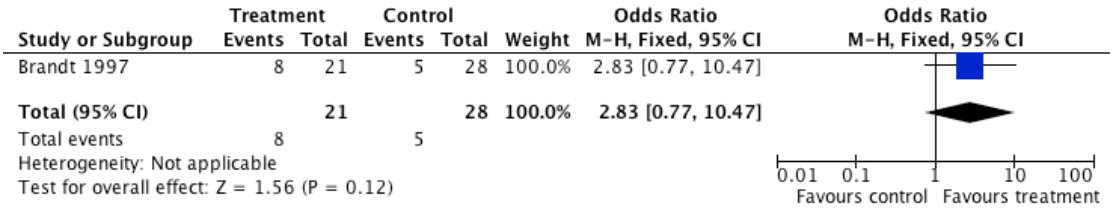


Pooled results from 6 studies (Bolman et al 2002 [RCT -]; Carlsson et al 1997 [RCT -]; Hennrikus et al 2010 [RCT +]; Hilleman et al 2004 [RCT ++]; Mohiuddin et al 2007 [RCT ++]; Pedersen et al 2005 [RCT -]) showed that this level of intensity is effective in patients with CVD (OR=1.81; 95%CI: 1.42-2.32).

The results are the same as for all patient groups together, showing lack of efficacy for low intensity interventions, and significant effects of interventions providing support over periods longer than four weeks.

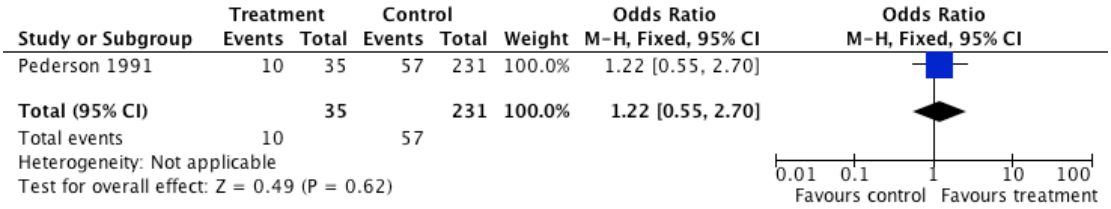
Patients with respiratory disease

Figure 30 – Patients with respiratory disease - Intensity 1



There was only one study offering this intensity of treatment (Brandt et al 1997 [RCT +]) that showed no significant effect (OR=2.83; 95%CI: 0.77-10.47).

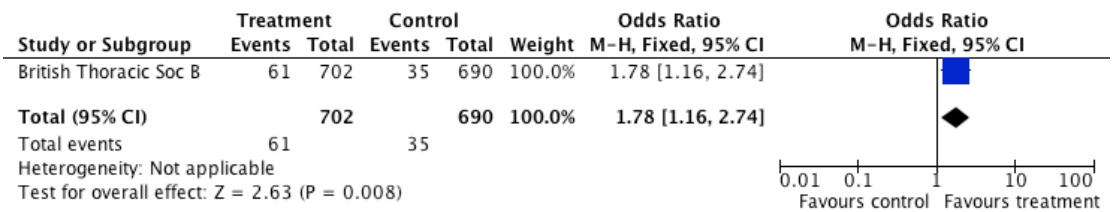
Figure 31 – Patients with respiratory disease - Intensity 2



Similarly one study offering this intensity of treatment (Pederson et al 1991 [RCT +]) showed no significant effect (OR=1.22; 95%CI: 0.55-2.70).

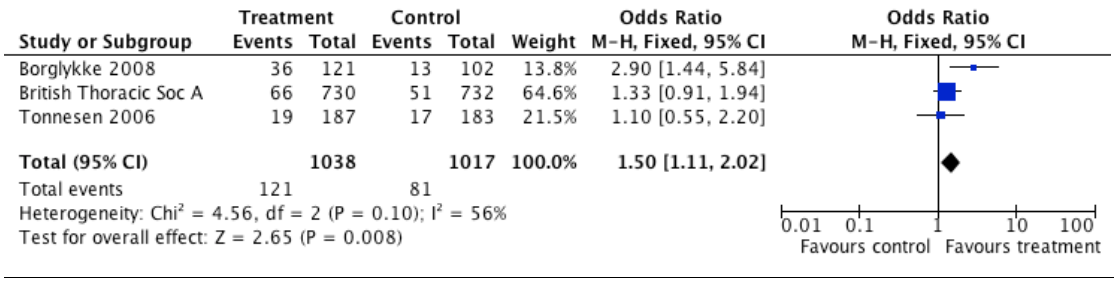
Intensity 3: No studies were available

Figure 32 – Patients with respiratory disease - Intensity 4



Pooled results from 1 study (British Thoracic Society B 1990 [RCT ++]) showed no effect of this intensity in patients with respiratory illness (OR=1.78; 95%CI: 1.16-2.74).

Figure 33 – Patients with respiratory disease - Intensity 5



Pooled results from 3 studies (Borglykke et al 2008 [RCT +]; British Thoracic Society A 1990 [RCT ++]; Tonnesen et al 2006 [RCT ++]; showed that this level of intensity is effective in patients with respiratory illness (OR=1.50; 95%CI: 1.11-2.02).

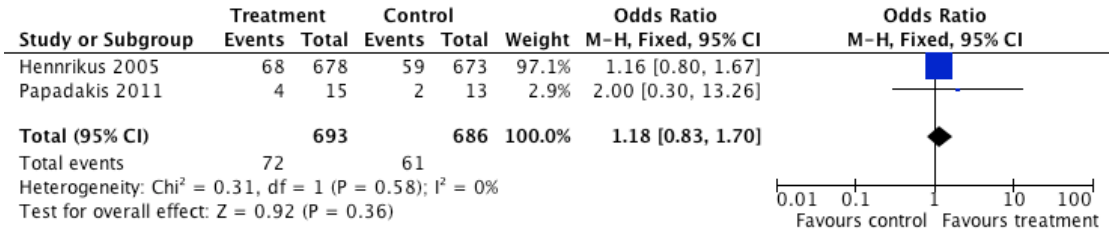
The results are similar to those from other patient groups, showing lack of efficacy for low intensity interventions, and better effects of more intensive interventions, although in this group of studies, only interventions with extended face-to-face support achieved a significant effect.

Patients with cancer

There was only one study focusing on cancer patients. This was Intensity 4 with no medications and showed no intervention effect (Wakefield et al 2004, [RCT ++]).

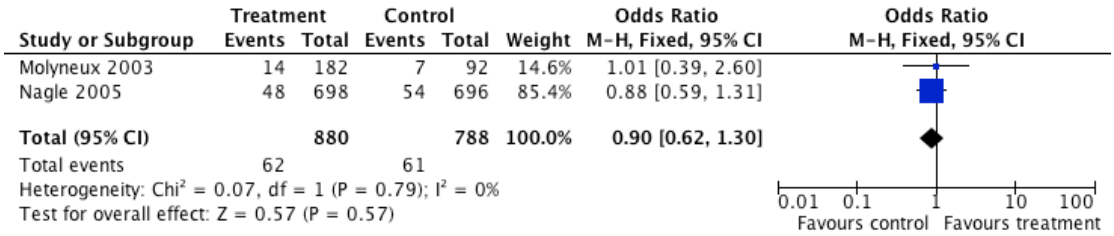
Unselected/other hospital patients

Figure 34 – Patients with cancer - Intensity 1



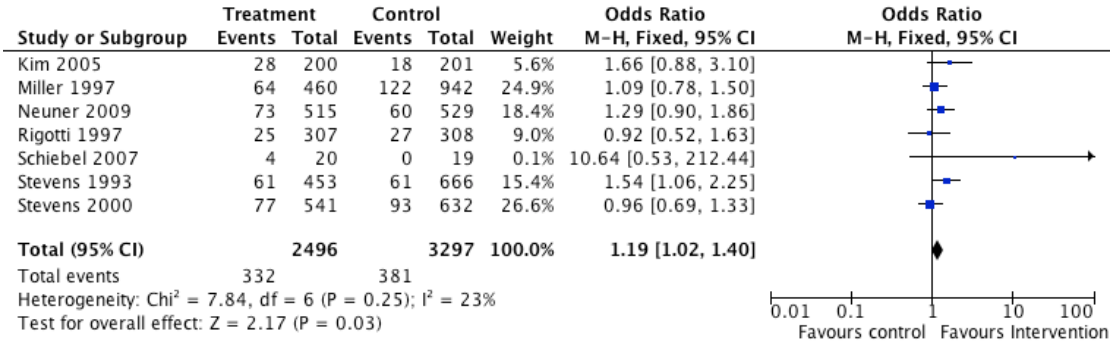
Pooled results from 2 studies (Hennrikus, et al 2005 [RCT +]; Papadakis et al 2011 [RCT +]) showed no effect (OR=1.18; 95%CI: 0.83-1.70).

Figure 35 – Patients with cancer - Intensity 2



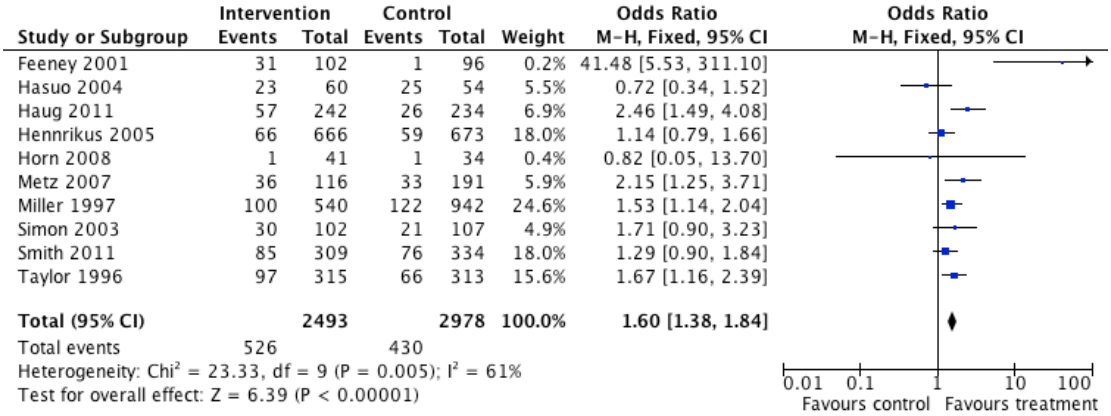
Results from two studies (Molyneux et al 2003 [RCT ++]; Nagle et al 2005 [RCT +]) showed no effect (OR=0.90; 95%CI: 0.62-1.30).

Figure 36 – Patients with cancer - Intensity 3



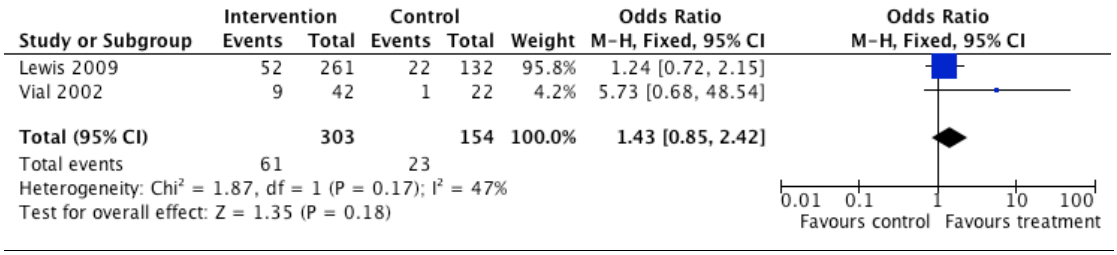
Pooled results from 7 studies (Kim et al 2005 [RCT +]; Miller et al 1997 [RCT +]; Neuner et al 2009 [RCT -]; Rigotti et al 1997 [RCT +]; Schiebel et al 2007 [RCT -]; Stevens et al 1993 [RCT -]; Stevens et al 2000 [RCT -]) showed a modest improvement in abstinence rates (OR=1.19; 95%CI: 1.02-1.40).

Figure 37 – Patients with cancer - Intensity 4



Pooled results from 10 studies (Feeney et al 2001 [RCT ++]; Hasuo et al 2004 [RCT +]; Haug et al 2011 [RCT -]; Hennrikus et al 2005 [RCT +]; Horn et al 2008 [RCT -]; Metz et al 2007 [RCT -]; Miller et al 1997 [RCT +]; Simon et al 2003 [RCT +]; Smith et al 2011 [RCT +]; Taylor et al 1996 [RCT +]) showed a positive effect (OR=1.60; 95%CI: 1.38-1.84).

Figure 38 – Patients with cancer - Intensity 5



Pooled results from 2 studies (Lewis et al 2009 [RCT +]; Vial et al 2002 [RCT-]) failed to show a significant effect (OR=1.43; 95%CI: 0.85-2.42).

The results show lack of efficacy for low intensity interventions and significant effects of Intensity 4 interventions, though the results of the two Intensity 5 interventions did not reach significance (Lewis et al 2009 [RCT +]; Vial et al 2002 [RCT -]).

3) Patients receiving intervention after hospital discharge

Three trials evaluated interventions delivered after hospital discharge (i.e. patients did not receive any intervention whilst in hospital). We are including them because they target hospital patients and hospitals could in theory refer patients to such programmes. One trial (Carruthers et al 2005 [RCT +]) included NRT.

Figure 39 – Intervention received after hospital discharge - Intensity 1

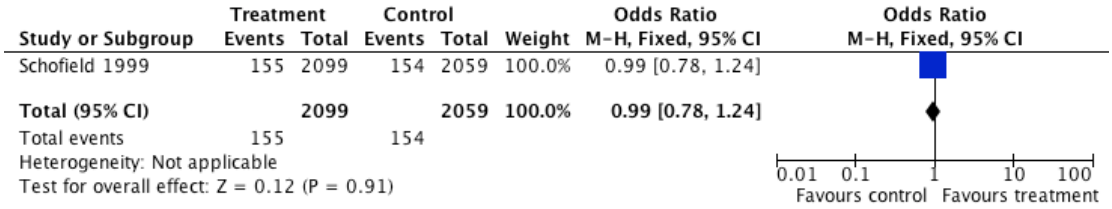
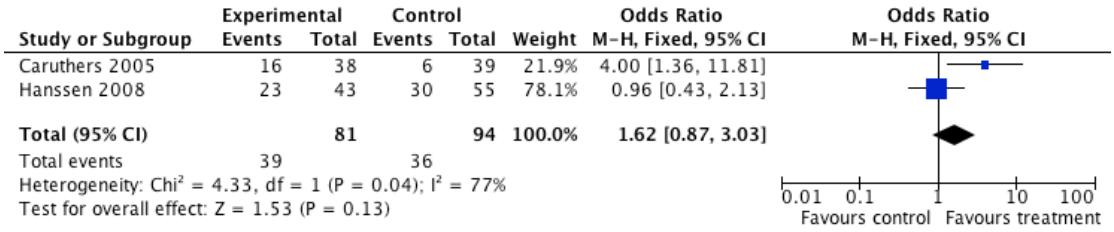


Figure 40 – Intervention received after hospital discharge - Intensity 4



Only one study evaluating the efficacy of extended support accompanied by NRT showed a significant effect (Carruthers et al 2005 [RCT +]).

Conclusions

The overall picture emerges showing that brief interventions with users of acute care are not effective, even if they include medications. Regarding interventions providing support for over 4 weeks, interventions with face-to-face support seem to achieve better results than interventions relying on phone calls, but without the addition of

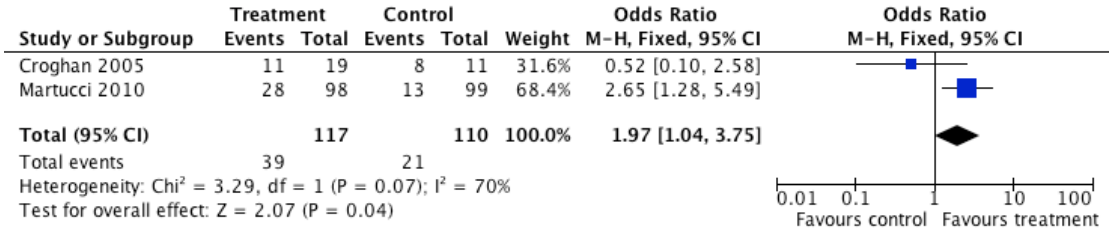
medications, any effects are modest. The inclusion of medications strongly enhances efficacy of these treatments.

4) Efficacy of interventions delivered to surgery patients

Six trials evaluated interventions initiated prior to surgery. With one exception (Croghan et al 2005 [RCT +]), all trials included NRT.

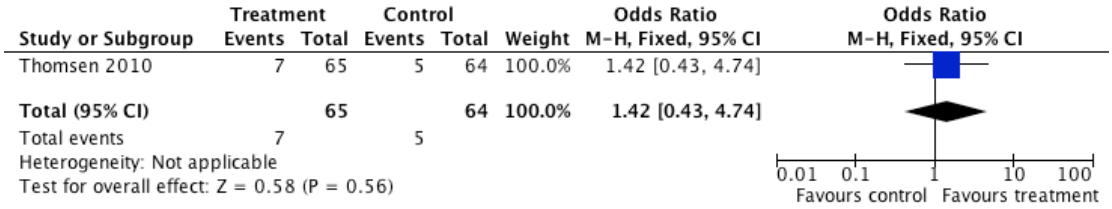
Intensity 1: There were no such trials

Figure 41 – Interventions delivered to surgery patients - Intensity 2



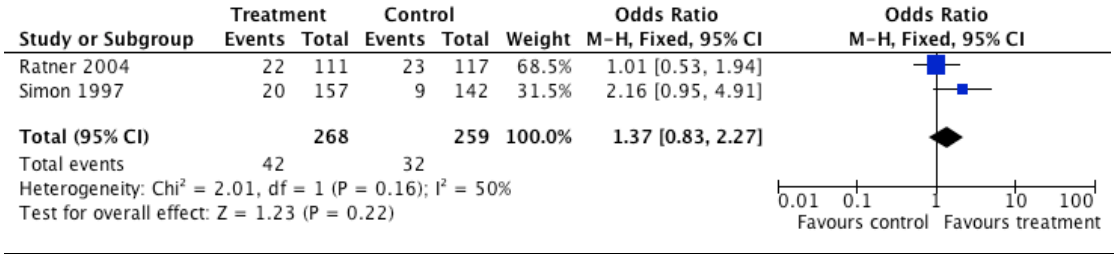
Two trials (Croghan et al 2005 [RCT +]; Martucci et al 2010 [RCT +]) found mixed effects but the pooled result reached statistical significance (OR=1.97; 95% CI:1.04-3.75).

Figure 42 – Interventions delivered to surgery patients - Intensity 3



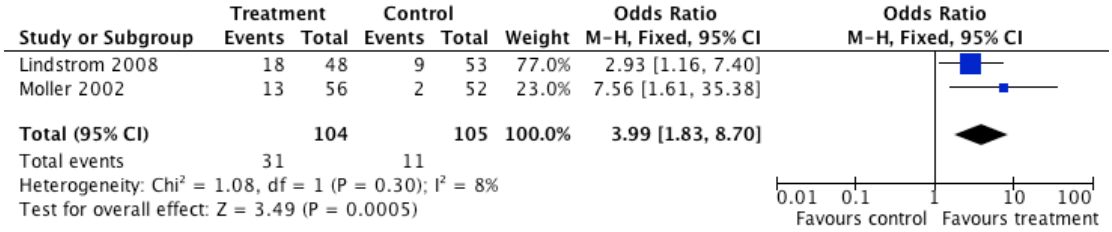
One study (Thomsen et al 2010a [RCT +]) showed no effect (OR=1.42; 95% CI: 0.43-4.74).

Figure 43 – Interventions delivered to surgery patients - Intensity 4



Two studies (Ratner et al 2004 [RCT +]; Simon et al. 1997 [RCT +]) showed no effect (OR=1.37; 95% CI:0.83-2.27).

Figure 44 – Interventions delivered to surgery patients - Intensity 5

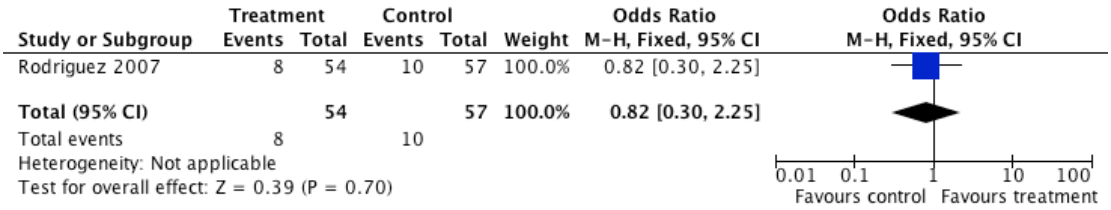


Two studies (Lindstrom et al 2008 [RCT ++]; Moller et al 2002 [RCT ++]) showed a significant effect (OR=3.99; 95%CI: 1.83-8.70).

Of the two studies examining level 2 intensity interventions, one was positive (Croghan et al 2005 [RCT +]) and one was negative (Martucci et al 2010 [RCT +]). As the larger study was positive, the pooled results reach statistical significance. Both studies of Intensity 5 interventions provided face-to-face contact and NRT. Both showed good efficacy.

One trial [Rodriquez et al 2007 [RCT -]) evaluated effects of one session of stop-smoking messages delivered under deep sedation.

Figure 45 – Intervention delivered under deep sedation



The intervention had no effect.

Conclusions

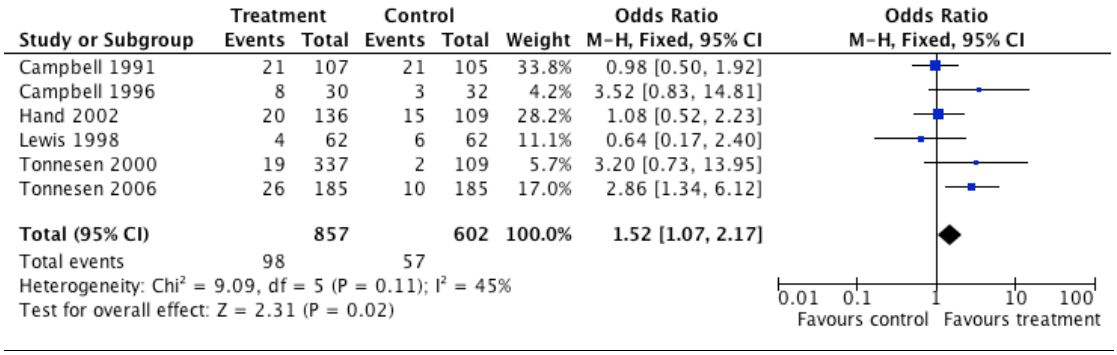
Brief interventions initiated prior to surgery lack efficacy even if accompanied by NRT. Face-to-face support lasting for over 4 weeks accompanied by NRT is effective. Stop-smoking messages delivered under sedation are not effective.

5) Efficacy of pharmacological interventions with hospital patients

In this section, we cover trials which evaluated medications by comparing study arms with the same intensity of behavioural support which only differed in whether they received active medications or not.

Six trials compared NRT treatment accompanied by behavioural support with the same support delivered with placebo or with no medication. The intensity of behavioural support was 4 or 5 in all trials.

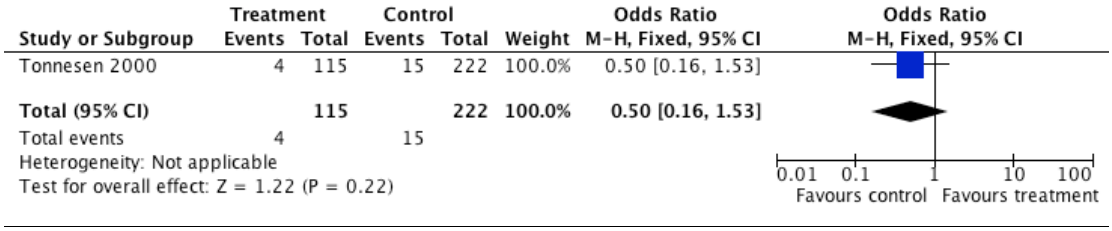
Figure 46 – NRT intervention - Intensity 4 or 5



Six trials (Campbell et al 1991 [RCT ++]; Campbell et al 1996 [RCT ++]; Hand et al 2002 [RCT ++]; Lewis et al 1998 [RCT +]; Tonnesen et al 2000 [RCT ++]; Tonnesen et al 2006 [RCT ++]) compared NRT accompanied by behavioural support (intensity 4 or 5 in all studies) with the same support delivered with placebo or with no medication. NRT was effective (OR=1.52; 95%CI: 1.07-2.17).

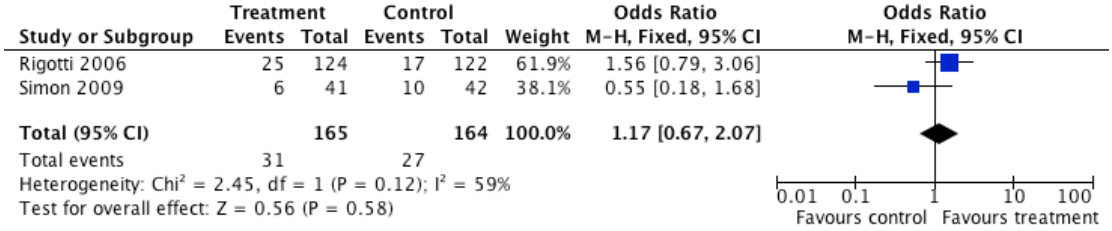
In this group of studies, NRT was effective.

Figure 47 – NRT and inhalator - Intensity 4



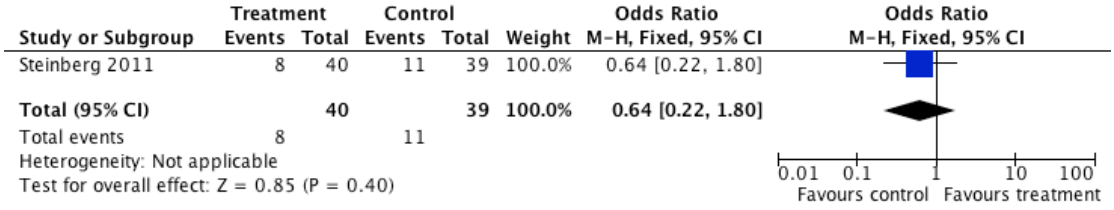
One trial (Tonnesen et al 2000 [RCT ++]) compared patch and inhaler alone with the two medications combined. The results showed that single NRTs were as effective as their combination (OR=0.50; 95% CI: 0.16-1.53).

Figure 48 – Bupropion - Intensity 4



Two trials (Rigotti et al 2006 [RCT ++]; Simon et al 2009 [RCT +]) compared bupropion and placebo. Both trials relied on telephone calls and neither offered any post-quit face-to-face support. The trials did not show the intervention to be effective (OR=1.17; 95%CI:0.67-2.07).

Figure 49 – Varenicline - Intensity 5



One small placebo controlled trial (Steinberg et al 2011 [RCT +]) evaluated varenicline accompanied by brief counselling session/sessions (it is not clear if there was one or more, but it was attended by 16 participants only). The trial did not find the treatment effective (OR=0.64; 95%CI: 0.22-1.80).

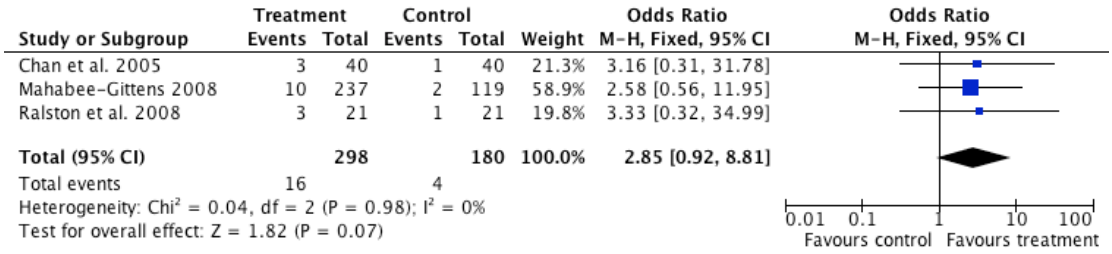
Conclusions

NRT accompanied by behavioural support extended over four weeks is effective. A combination of patches and inhaler was not more effective than each medication on its own. Bupropion and varenicline provided without on-going face-to-face support lack efficacy.

6) Efficacy of intervention with patients' relatives

Three trials evaluated interventions with parents of children hospitalised on paediatric wards. Two used one-off advice with a phone reminder (Chan et al 2005 [RCT -]) or fax referral to Quitline (Mahabee-Gittens et al 2008 [RCT -]) and one used >30 minutes of counselling and access to NRT for some participants (Ralston et al 2008 [RCT -], Intensity 2). This group of studies had shorter follow-ups (Chan 2005 - one month, Mahabee-Gittens 2008 - 3 months, Ralston 2008 - 6 months).

Figure 50 – Interventions with patients relatives - Intensity 1 or 2



The interventions overall lacked efficacy despite a short follow-up. This is relevant because intervention effects often dissipate over time.

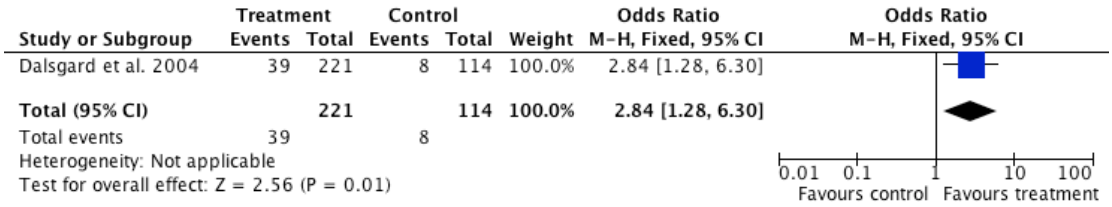
Conclusions

Brief interventions (Intensity 1 and 2) with parents of hospitalised children lack efficacy.

7) Efficacy of intervention with hospital staff

We found only one study evaluating an intervention with hospital employees. It was a high-quality placebo controlled trial of bupropion with Intensity 5 support.

Figure 51 – Interventions with hospital staff - Intensity 5



The trial showed bupropion with regular face-to-face support to be an effective treatment for hospital employees.

Conclusions

Bupropion accompanied by intensive support is an effective treatment for hospital employees.

Systematic reviews

We found two relevant Cochrane reviews. We discussed the Rigotti (2007 [systematic review, ++]) review earlier. Our conclusions in the areas covered by Rigotti (2007) are similar. The same applies to the review by Thomsen (2010b [systematic review, ++]) concerning surgery patients.

We identified 11 other reviews, listed below. We rated their quality as ++ for systematic reviews showing awareness of key methodological features of stop-smoking studies, + for reviews which were less systematic and/or did not take into account the key quality aspects of included studies, and – for reviews which were selective and/or posed methodological problems. All relevant and eligible studies included in these reviews are also included in our review.

Table 3 – Summary of systematic reviews

Author	Aim	No of studies	Findings	Quality
Aziz et al. 2009	Effectiveness of smoking cessation intervention in hospitalised patients with cardiovascular disease	11	Significantly higher abstinence rates in patients receiving intervention in hospital continued post discharge for at least 3 months alongside NRT compared to usual care	+
Barth et al. 2008	Effectiveness of behavioural interventions, telephone support and self-help	16	Positive effects of interventions on abstinence after 6 to 12 months	+

	interventions in people with coronary heart disease (CHD)			
Mistiaen et al. 2006	Effectiveness of follow –up telephone calls in the first month after discharge (not smoking specific)	33	Inconclusive evidence about the effectiveness of telephone FU	++
Munafo et al. 2001	Effectiveness of interventions for hospitalised patients	15	High intensity behavioral support of at least 1 month of follow up contact is effective	++
Nayan et al. 2011	Smoking cessation interventions and rates of smoking in cancer patients	8	No significant difference between interventions and usual care	++
Rice et al. 2008	Effectiveness of nurse-delivered smoking cessation intervention	42	Slightly increased rate of quitting	++
Rice et al. 2009	Effectiveness of nurse-delivered smoking cessation intervention – updated from Rice 2008	34	Interventions of high and low intensity provided by a nurse generated an increased rate of quitting	++
Rigotti et al. 2008	Effectiveness of hospital interventions initiated during hospital stay	33	Counselling initiated during hospitalization with follow up of at least 1 month increased long term smoking cessation	++

Van der Meer 2001	Effectiveness of smoking cessation interventions in people with COPD	5	Interventions including medications were effective	++
Wagena 2004	Effectiveness of behavioural interventions for people with COPD	5	Intensive behavioral support + NRT increased abstinence rates. Bupropion did not increase abstinence rates.	++
Wiggers 2003	Effectiveness of smoking cessation interventions in cardiovascular patients	12	No evidence of effectiveness for pharmacotherapy, self help materials, group, individual or telephone counselling. Limited evidence for doctor or nurse delivered advice	+

Discussion

A large number of studies have been included in this review, which evaluated a range of stop-smoking interventions trying to use the window of opportunity that a hospital admission provides. It is worth noting at this stage, that there are some problems in generalising the results of the majority of these studies to the UK setting.

The NHS is now far ahead in terms of the care available for smokers compared to most other countries, in that stop smoking medications are provided free of charge and there is also free access to the NHS-SSS who provide specialist multi session face-to-face counselling (Croghan 2011). Most of the existing trials were conducted in environments and with methods, which were much less favourable to successful smoking cessation than the current UK routine practice. Nevertheless, the existing literature is extensive and it does provide some useful pointers, which can contribute to guidelines on how best to support such smokers. We now discuss our findings in the context of the **intensity of the intervention, patient groups, pharmacotherapy, patient relatives,** and **hospital staff**.

Intervention intensity

We defined the intensity of an intervention based on the description provided in the Rigotti (2007) hospital review. We further expanded their single definition of follow up, to include 2 levels of intervention intensity that looked at the impact of face-to-face and no face-to-face contact post discharge. We initially considered whether using a definition based on the intensity levels described in Rigotti's (2007) paper was adequate for the purpose of looking at this extensive body of literature. Using intensity based on length of contact is a useful and practical way of analysing this

data, particularly when the focus of nationwide recommendations is often cost effectiveness of the services being implemented. Being able to show that an intervention is successful in the long term by providing a post discharge follow-up service via telephone calls weekly would be more cost effective, for example, than using HCPs in the community to schedule appointments and see patients in practice.

However, there are things worth considering that are not covered by this definition. One of the main criticisms of our current definition is that we use the term 'brief advice' to describe a contact but this is not fully defined. What do we mean by 'brief advice'? In one study this could be simply identifying a smoker and asking if they would like to quit whereas in another study this could be smoking status checked, asked if they want to quit, medication dispensed and advice given, and include more tailored individual support and advice. Within this body of research there are many different methods used to provide smoking cessation advice; interactive voice follow up systems (e.g. Reid 2007); self- help booklets (e.g. Molyneux et al. 2003); cognitive Behavioural treatment (CBT) (e.g. Metz et al. 2007); motivational treatment (MT) (e.g. Metz et al. 2007); audio workbooks (e.g. Horn et al. 2008). There would be clear justification for using methodology and different behaviour change techniques as a definition to look at the effectiveness of smoking cessation interventions across the studies rather than our current definition of frequency and duration of support.

However, as the focus of this review was to look at recommendations for the provision of smoking cessation services in UK services, where the delivery of support is defined by NICE guidelines (NICE 2008), the use of looking at the intensity of the service provision rather than the content was deemed as the best definition for the

purpose of looking at results across this large body of global research. To consider the evidence in terms of the content of the service provided (e.g. CBT, MT) would also be of interest for future research in this area.

The results of the systematic review by definition of the intensity of the smoking cessation intervention are presented in the following passages.

Intensity 1 – 3

Advice by doctors and nurses during hospitalisation, possibly repeated and reinforced during the hospital stay and accompanied by leaflets, is by far the simplest and least expensive option, which could be provided routinely on a large scale. Unfortunately, we found no evidence that such interventions work. Dealing with a population of hospital smokers who may have received strong encouragement to stop smoking on a number of previous occasions but continue to smoke despite high motivation to stop as a result of illness suggests a high level of dependence and a need for more intensive treatment. The provision of a single contact from a HCP in hospital (with or without take-home materials) is not effective with this population.

Intensity 4

The next level of intervention, which still requires modest resources, is to reinforce the in-hospital intervention by telephone calls over the first few weeks after discharge. This too was not shown to be effective.

Intensity 5

The next level of intervention, which requires more extensive resources, is to reinforce in-hospital intervention with face-to-face contact post discharge. This

approach was also found to be effective and is in-line with the findings by Rigotti (2007), who concluded that for interventions with hospital patients to be effective, an extended support and stop smoking medication should provided for at least 4 weeks.

The results compared studies that gave at least one post discharge face-to-face follow up visit (Intensity 5) was similar to the effect of support provided over telephone with no face-to-face contact (Intensity 4) in non-surgical patients. It appears that it in this case it is the duration of the follow-ups that is important rather than the mode in which it is delivered. However, one thing that was not assessed was who provided the follow up sessions. We were unable to assess systematically assess any effects of the background of the person providing the advice in hospital and after discharge. This was due mostly to the limited description provided in the methods section of these studies. In practice, the provision of post-discharge support would be more cost efficient if provided via telephone.

Our results also found that support alone without medications has only uncertain effects but it has good efficacy when provided in combination with smoking cessation medications. This finding could be explained simply as the result of use of a medication during a quit attempt and would put into question whether the provision of behavioural support, above that of providing information on the use of the medication, is effective in this situation. The difficulty we have with this large data set, which was commented on earlier, is that the content of the behavioural support is not always outlined in sufficient detail. This is an important consideration for future reviews, to untangle whether there is any difference seen in different behavioural support approaches when provision of medication is included.

In summary, based on our definition of intensity, for smoking cessation interventions with hospital patients to be effective, an extended support and stop smoking medication provided for over 4 weeks seem necessary.

Patient groups

There is no a-priori reason to expect that smokers with different diagnoses would react differently to different interventions. However, it could be argued that those admitted with generic reasons compared with those admitted for reasons attributed to smoking (e.g. coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD)), may differ in their dependence and therefore require different levels of input in order to successfully quit. In order to look at this more closely we extracted the studies that provided data on patients with ***cardiovascular disease, respiratory disease***, and ***general patient*** samples separately.

Our results broadly confirm the main findings; that the more intensive the follow up the more effective the intervention for smoking cessation was longer term.

We further looked at the intensity of interventions in a population of patients undergoing surgery. The results showed that only Intensity 5 interventions (extended face-to-face support post discharge) accompanied by medications were effective with these patients. No effect was seen in this population when solely using telephone follow-up only post-discharge. There were only 2 studies for both intensity 4 and 5 analyses so both results need to be evaluated with some caution. However, it may be the case that those undergoing surgery respond better if they are seen face-to-face to discuss smoking cessation. This could be for a number of reasons including: they may

be visiting the hospital/GP after discharge and may expect the same level of interaction for smoking cessation treatment. Additionally, those who have not quit pre-operatively, even with the advice of their surgeon, may have a higher level of dependence, which requires more intense support. Post-operative patients may need more support than general admissions, although this is unlikely but due to the limited data available this is an area that needs to be investigated further when more research is available.

Pharmacotherapy

Single NRT products

We next looked at trials, which evaluated medications by comparing study arms with the same intensity of behavioural support, which only differed in whether they received active or placebo medications. We found that NRT accompanied by intensive behavioural support extended over a period of four weeks was effective. Provision of NRT without behavioural support was not effective.

Combination NRT products

One trial looked at the effectiveness of a combination of patches and the inhaler compared with each medication on its own (Tonnesen et al 2000 [RCT ++]). There was no significant difference found between using a combination or a single product. Previous research has shown an advantage of combination treatment over single NRT product use (RR 1.35, 95% CI: 1.11-1.63) (Stead et al. 2008). The explanation as to why combination use was not superior to single use may be due to the particular products used for this study. Oral nicotine products are popular among smokers but compared with the nicotine patch, they take a lot of effort from the user to get

adequate nicotine delivery and to avoid under dosing (Killen, Fortmann, Newman & Varady 1990). As a result many smokers only use the inhalator sporadically when in combination with a patch. As there was only one study looking at combination therapy use in this setting then more data is required before concluding that combination is no more effective than single NRT products in hospital patients. We know from previous research that in general population's combination therapy is more successful (Stead et al. 2008). We see no reason why this would not also be the case in hospitalised patients.

Bupropion and varenicline

When looking at bupropion and varenicline, we found that without on-going face-to-face support that the medications lacked efficacy. This would support the current protocol in clinical practice where this medication is only available on prescription and usually only provided in combination with support from GPs or the NHS-SSS. Previous research into NRT has shown it to be ineffective without support (Stead et al. 2008). It is likely that this is also the case with both bupropion and varenicline.

To summarise, NRT accompanied by extended multi-session support lasting over 4 weeks is effective in the acute services setting. A few small trials evaluated bupropion and varenicline accompanied by minimal support and did not find such treatments effective. NRT is known to be ineffective without support and follow-up and this is probably true for other stop-smoking medications as well.

Patient relatives

Only 3 trials were available to evaluate the effect of smoking cessation interventions with parents of hospitalised children on paediatric wards. We found that brief

interventions with parents of hospitalised children did not show efficacy. Approaching parents at a time when they are likely distracted and distressed at their child being hospitalised does not appear to be the optimal time to provide them with smoking cessation support. This does not mean it is not a time to discuss it with parents but it may be more effective if the offer of treatment is provided at discharge rather than during the child's hospital stay.

Hospital staff

Only one study was found that evaluated an intervention with hospital employees. The results found that using bupropion alongside regular face-to-face support was an effective treatment for hospital staff. This study is extremely important, as one issue that is debated frequently is the rights of hospital staff who smoke and how they do that when they work at a smoke-free hospital. Provision of treatment has been proposed whether for temporary abstinence during work hours or for cessation, like the above example. Setting up pathways for smoking staff is an important issue that needs to be addressed, evidence that medication and support with this population can work would offer some assurance to employers that this would be a worthwhile initiative to implement.

Grey literature

Unfortunately due to the large number of papers found in this review it was not possible to cover the grey literature in this expansive field of research. However, this would be an important thing to do next as the current review only focused on RCTs. Further exploration of the grey literature would lead to more understanding on the content needed for the provision of behavioural support, the importance of the

background of the provider and highlight some of the more practical barriers and facilitators for implementing smoking cessation interventions in the populations of interest

Next steps

Current practice

The NHS practice currently involves interventions at bedside accompanied by medications and/or referrals to the NHS-SSS for treatment after discharge, which combines extended face-to-face support with smoking cessation medications. The reviewed evidence confirms that this is likely to be the optimal approach. The high cost of such approach is mitigated by the fact that the NHS provides centrally funded stop-smoking services, which are proactively recruiting smokers and have ample capacity to accept such referrals and to treat them without further costs and without any delays.

The UK is now well ahead of the existing research in this area, compared to most countries where front line staff cannot refer smokers to specialists and so are trained to provide treatment themselves. Referral for smoking cessation treatment post-discharge is essential. This review demonstrates that hospital based smoking cessation interventions of any kind are ineffective unless they include multi-session follow-up of 4 weeks or more post-discharge. Routine front line staff cannot take on the role of specialist advisors and organise extended support over a number of consultations set up just for this purpose. Even if they did, and such activities were given priority over their primary purpose, training tens of thousands of doctors and nurses in specialist interventions and supervising and monitoring them would be impractical.

Since the establishment of the NHS-SSS, the task of front line staff in the UK is to motivate smokers to quit and refer them on, rather than to take on the role of stop-smoking advisors. Training in the UK for HCPs or implementing automated prompts

can thus focus exclusively on motivating and referring smokers. There is evidence that a brief training (40 minutes) is effective in increasing referrals from UK GPs (McRobbie et al. 2008). There is no reason to expect that the same approach would not work in secondary care.

Apart from organisational, financial, and time constraints, we are aware of two other barriers to a routine implementation of training within acute care, which are not captured in the current literature. The notes below are only anecdotal, but they may be informative.

As a legacy from past initiatives, many PCTs continue to try to train front line staff in smoking cessation interventions they are asked to provide themselves. Some others try to focus on the core tasks of motivating smokers and referring them on, but cannot resist including a host of marginal topics and making the training events unnecessarily long and demanding (e.g. half-day long). This makes such events expensive and poorly attended, without improving the chance that they will increase referrals more than a simple straightforward instruction. We estimate that less than 40 minutes of training should be sufficient as per the findings from McRobbie et al. (2008), especially if the hospital organisation is willing to include this as a part of compulsory induction of all new staff, and monitor the rates of referrals for smoking cessation treatment and provide feedback to staff who under-perform.

Another barrier to implementing such a brief and practicable approach is that there exists no clear template for what such training should involve. Perhaps the UK Centre for Tobacco Control Studies (UKCTCS), which includes specialists with direct

experience of smoking cessation interventions in acute care can be commissioned to develop a simple and straightforward training content which would be easy to disseminate. One possible hurdle to such a plan is the lack of consistency in the way different SSS operate.

Conclusion

The NHS practice for hospitalised smokers currently involves interventions at bedside accompanied by medications and/or referrals to specialist stop-smoking services for treatment after discharge, which combines extended face-to-face support with smoking cessation medications. The reviewed evidence confirms that this is likely to be the optimal approach.

There seems to be a number of barriers to providing help to smokers in secondary care. For instance there is a widespread concern that stopping smoking shortly before surgery may have negative effects on surgery outcomes, hospital electronic records are often inflexible and make recording of patient smoking status difficult and staff do not see addressing smoking as a part of their core duties. There is a need to systematically review not just the efficacy of stop smoking interventions, which are usually evaluated in a somewhat rarefied research setting but also the barriers and facilitators of stop smoking activities in acute and maternity settings. There is a scope to systematically increase referrals and access to smoking cessation services in acute hospital settings, which such a review could facilitate. The authors of this review are currently undertaking such a review to look at the facilitators and barriers to implementing stop smoking interventions in acute and maternity settings. This review will be part of the guidance published along with this review in 2013 by NICE.

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Table 4 – Glossary for part 4

Abstinence	Throughout this review we refer to abstinence from smoking as abstinence. Rates of abstinence are also presented. See point prevalence abstinence, continuous abstinence, sustained abstinence and CO-validated abstinence.
Biochemically validated	Self-reported abstinence rates are often validated, or confirmed, by biochemical tests. These tests include measurement of CO in expired breath and cotinine in saliva, blood, and urine.
Bupropion	Bupropion or Zyban ™ is an atypical antidepressant that is also effective in helping people to stop smoking. In the UK it is only licensed as a smoking cessation aid
CO-validated abstinence	Measurement of carbon monoxide in expired breath is commonly used to validate self-reported abstinence. A cut-off of 10 ppm is routinely used, so if someone reports they have not smoked and have a CO reading of less than 10ppm then they would be considered to be a CO-validated abstainer.
Continuous abstinence	This measures continuous abstinence from smoking, either not a single puff or a small number of slips allowed (e.g. less than 5 cigarettes in total), from a pre-determined time point (e.g. Quit Date) to all follow-up points. Continuous abstinence rates are typically lower than point prevalence abstinence rates, but more likely to give a more accurate assessment of the effect of an intervention.
Nicotine replacement therapy	Nicotine replacement therapy is a licensed medicinal product to aid smoking cessation, smoking reduction and temporary abstinence. There are seven different formats: patch, gum, lozenge, sublingual tablet, nasal spray, mouth spray and inhalator.
Point prevalence abstinence	This measures abstinence from smoking at a particular time. 7-day point prevalence (i.e. not smoking at all over the past 7 days) is a commonly used measure.
Varenicline	Varenicline or Champix ™ is a nicotine analogue that was developed specifically to help people stop smoking. It acts primarily to reduce the severity of tobacco withdrawal symptoms thus making quitting easier.

PART 3 – PROFESSIONAL PRACTICE

In part 3 of the portfolio, 2 case studies are presented; which reflect on my professional practice whilst on the Doctorate in Health Psychology (post-chartered "Top-up") degree.

Summary of Part 3

Case study 1 (2 sections)

The first case study follows the theme of treatments for smoking cessation and provides a clinician and patient perspective on current practices.

There are two sections to the first case study. ***Section 1*** of the professional practice chapter highlights the clinician view of current practices in combining smoking cessation medications; the section reviews the experience of clinician use of combination nicotine replacement therapy (NRT), which is a licensed and evidence-based medication option. The clinician views were taken after a lecture I presented at the "Stop Smoking Live" conference in London in December 2010. The case study highlights the extent to which combination NRT is recommended in current practice, barriers to use for the clinician and client and provides a reflection on my own experience of presenting at an educational symposium.

For the second patient perspective case study for this chapter (***section 2***), clients attending the Tobacco Dependence Research Unit (TDRU) smokers' clinic in East London, who were using a combination of varenicline and NRT during their quit attempt, were approached and asked if they were willing to discuss why they had chosen these mediations and what benefit (if any) it gave them. The National Institute

for Health and Clinical Excellence (NICE 2008) guidelines currently do not advocate the combination of varenicline and NRT as there is a lack of evidence on its efficacy. Anecdotally, however, we are aware that clients will take it upon themselves to use the medications in combination and report that this is useful in helping them to stop. This piece of work gives some background into how clients attending an NHS-SSS clinic find the experience of using a combination treatment of varenicline and NRT.

Case study 2

The second case study is a reflection on my current clinical practice, giving some insight into my day-to-day role at the TDRU. I reflect on some of the key issues when conducting research and some of the things I have learnt over the last few years during my involvement in research. An example of a trial I have been involved in is also discussed.

Chapter 1 - Case study 1 – using combination treatment in practice

Section 1 - Health Professional views on combination NRT

Introduction

It is standard practice in the UK to offer pharmaceutical treatments to help smokers who are trying to quit. Use of stop smoking medications is offered at the initiation of a quit attempt in order to help alleviate withdrawal symptoms that are experienced post cessation. In the UK patients have access to NRT, bupropion (Zyban) and varenicline (Champix) (NICE 2008). All are proven methods for increasing successful quitting (Cahill, Stead & Lancaster 2012, Hughes, Stead & Lancaster 2007, Stead, Perera, Bullen, Mant & Lancaster 2008).

There are extensive data showing the efficacy of NRT (Stead et al. 2008). The use of NRT products during a quit attempt approximately double the chances of long-term abstinence compared with placebo (Stead et al. 2008). There is evidence to show that use of combination NRT (e.g. using a nicotine patch in combination with another nicotine product such as the nicotine gum) is more beneficial during a quit attempt than using a single product alone (Stead et al. 2008).

The advice to routinely prescribe NRT products in combination is included in the NICE (2008) guidelines for treating nicotine dependence. However, despite evidence-based recommendations for this treatment option there are still clinical issues arising within local NHS stop smoking services (NHS-SSS), which limit and often prevent clients receiving combination NRT.

The following case study is a reflection on a presentation given on combination treatment at a London conference to health care professionals (HCPs) involved in treating smokers in the UK. The case study discusses some of the issues raised by UK HCPs treating smokers.

"Stop Smoking Live" conference 2010

In 2010 I was invited by GlaxoSmithKline (GSK) to be the key speaker at an educational symposium on the use of combination NRT products at a national conference called "Stop Smoking Live". This was a London-based conference at the Islington Business Design Centre, which was held on 10 December 2010. GSK are a worldwide leading company who manufacture NRT products.

My supervisor, Dr Hayden McRobbie had suggested that, given my experience in working with smokers and my extensive knowledge of NRT, I would be an appropriate presenter for this session. The presentation's focus was on the effectiveness, use and practical issues of using combination NRT. As part of my on-going role as a Health Psychologist working within the NHS-SSS, it was an excellent opportunity to discuss current medication options for smokers with other clinicians in the field.

The brief given by GSK was to present and discuss the issues around the use of combination NRT in NHS-SSS and to increase knowledge around the evidence on combination NRT. The intention was to increase confidence among HCPs when using combination NRT in clinical practice.

In preparation for the presentation I reviewed all the current literature on combination treatment and also reflected on my current clinical practice in order to inform the sessions content.

Background

Personal perspective – current clinical practice

I have worked as a Research Health Psychologist at the TDRU, Queen Mary's School of Medicine and Dentistry (QMUL), University of London for the last 7 years. The TDRU delivers smoking cessation support (provided by specialist advisors) alongside stop smoking medications, across 2 boroughs in London (City & Hackney and Tower Hamlets). The service provides intense withdrawal-oriented therapy (Hajek 1989) over seven weeks to patients that indicate they would like to stop smoking. In order to successfully help people to stop smoking, the aim of the sessions are to enhance motivation to quit, increase self-efficacy, to understand the role of habits, to discuss coping skills, cue sensitivity, individual patterns of smoking and to ultimately endorse behaviour change. Objective measures of self-reported smoking status are routinely measured by carbon monoxide (CO) monitors.

Pharmaceutical treatments are also discussed, NRT and non-nicotine medications (bupropion and varenicline) are offered as part of standard treatment. As per current NICE guidelines (2008), patients who choose to use NRT are offered the option of using more than one NRT product to use in combination during their quit attempt. However, since January 2013, due to recent changes to the structure of the Primary Care Trusts (PCTs), financial cuts to the service have been implemented. This has resulted in combination treatment no longer being offered to patients accessing the

TDRU. At the time of the presentation development for the "Stop Smoking Live" conference, the TDRU offered combination treatment to every smoker using NRT.

What do we know about combination NRT?

In a 2008 Cochrane review on the effectiveness of combination NRT (Stead et al. 2008), six studies were identified that compared combination NRT versus single NRT use (see Table 1 for study summaries). Pooling of the six trials comparing combination treatment with single NRT showed an advantage of combination use at 6 month follow up (RR 1.35, 95% CI: 1.11-1.63). Only one of the trials (Blondal, Olafsdottir, Gustavsson & Westin 1999), comparing nasal spray and patch with patch alone, showed a significantly higher rate of sustained abstinence at one year with combined NRT.

Table 1 – Summary of studies included in Stead et al (2008) Cochrane review on NRT

Study	Products	RR	95% CI
Kornitzer, Boutsen, Dramaix, Thijs, & Gustavsson 1995	Patch + gum vs. patch	1.43	0.83-2.46
Puska, Korhonen, Vartiainen, Urjanheimo, Gustavsson & Westin 1995	Patch + gum vs. gum	1.38	0.88-2.17
Blondal et al. 1999	Nasal spray + patch vs. patch	2.48	1.37-4.49
Bohadana, Rasmussen & Martinet 2000	Patch + inhalator vs. inhalator	1.39	0.89-2.17
Tonnesen & Mikkelsen 2000	Patch + inhalator vs. either product	0.51	0.17-1.52
Croghan, Sloan, Croghan, Novotny, Hurt & Dekrey 2003	Patch + nasal spray vs. nasal spray vs patch	1.23	0.85-1.78

Since the release of the Cochrane review two further studies have been published.

Piper, Smith, Schlam, Fiore, Jorenby, Fraser & Baker (2009) conducted a study using monotherapy (single product), combination NRT (patch and lozenge) and bupropion versus placebo. The results found that all treatments showed a significant effect compared to placebo. Only patch and lozenge combination was found to be better than monotherapy (OR, 1.35, 95% CI: 1.01-1.79).

A 2009 study (Cooney, Cooney, Perry, Carbone, Cohen, Steinberg, Pilkey, Sevarino, Onken & Litt 2009) used combination nicotine patch plus either active or placebo nicotine gum in alcohol dependent smokers in an outpatient setting. At 1 year follow up the patch plus active gum group had higher rates of validated prolonged smoking cessation rates compared to the placebo gum group (13% versus 0%). As the results of this study cannot easily be generalised due to the specific population of dependent drinkers that it included, only the Cochrane review (Stead 2008) and study by Piper et al. (2009) were used in the development of the slides for the "Stop Smoking Live" presentation (see Appendix 1).

Presentation preparation

Conference calls with GSK

As part of the preparation for the presentation I was contacted by GSK on 2 occasions. They arranged conference calls several weeks before the stop smoking live event in order to discuss the content and development of the presentation and the logistics for the day. This was the first time I had been involved in this process before a presentation; it was very useful to confirm that the ideas I wanted to present were in line with the aims GSK had for the session.

Feedback questionnaire

A feedback questionnaire had been designed by GSK to be given to delegates to complete after the presentation. The feedback questionnaires were placed on each seat by the GSK team at the beginning of the lecture. At the end of the session a request was made at the end for people to complete the questionnaire and to hand in on their way out of the lecture theatre (for details of questions see Appendix 2). The main purpose of the feedback questionnaire was to see how useful the topic of combination treatment was for the audience and also to gauge what is currently happening across services in the UK.

Participants

A total of 462 delegates attended the "Stop Smoking Live" conference and of those, 300 (64%) attended the educational symposium on combination therapy for smoking cessation. Forty of those who attended (13%), completed the feedback questionnaire

and returned them at the end of the session. The summary of the feedback provided by the delegates is discussed below.

Background of delegates

The majority of those who attended the session and completed the feedback questionnaire were smoking cessation advisors (N=27, 68%), with a small number of pharmacists (N=2, 5%), practice nurses (N=3, 8%) and a further 8 attendees (20%) were health care professionals such as health psychologists, PCT public health consultants, healthcare assistants and those from a commercial background.

The knowledge of the audience varied with 28% (N=11) of the delegates rating their knowledge of combination NRT before the presentation as very good, while 50% (N=20) said that their knowledge was good.

Knowledge improvement

Nearly all of the delegates (N= 39, 97%) found the session useful/very useful. Thirty-two (80%) delegates felt that they had learnt something new from the presentation.

Applying combination treatment in practice

Nearly 70% (N=28) of the delegates said they would increase their use of combination therapy after the presentation, with 30% (N=12) saying they would stay as they were. Over 80% (N=32) of the delegates said they would be discussing the information from the presentation with colleagues and would use the information from the presentation at work.

Speaker evaluation

Thirty-four (85%) delegates found the speaker to be very knowledgeable on the subject of combination treatment and 93% (N=37) felt that the speaker encouraged participation. The following comments were included in the open text section of the questionnaire.

'Very interesting talk.'

'I found this session very good. I learnt a few things that I didn't know.'

'Very good session.'

Over 80% (N=33) of the delegates agreed that there was a good mix of theory and real-life experience included in the presentation.

Reflection on the presentation

Accepting the offer of presenting at "Stop Smoking Live"

This was the first time I have ever been asked to be present at an educational symposium. Before agreeing to do the presentation I discussed the presentation with my supervisor, who is a very experienced presenter. He was able to advise me about what I should expect with regards to the work that would be involved in the development of the presentation and we also discussed the amount of input GSK would have. After the discussion with my supervisor I accepted the invitation to present, as it was a good opportunity for my professional development; presenting in front of a large audience, knowledge development on combination treatment as well as understanding from the audience what the current UK situation is with regards to combination NRT prescribing.

Feedback

Only forty delegates (13%) completed the feedback questionnaire after the presentation. This seemed like a disappointingly low return rate which I discussed this with the GSK team after the session. The number appeared to be consistent with previous events they had had experience of running. On reflection, I should have spoken about the feedback questionnaire at both the beginning and end of the presentation in order to re-iterate the importance of getting their feedback for the development of future presentations on the topic rather than just mentioning at the end of the discussion, when everyone was ready to leave.

As the sponsors provided lunch at the session, it may help to increase the number of people completing the feedback questionnaires by handing out a lunch box on condition that the questionnaire is completed and handed in.

It would be good practice to aim to have at least half of the delegates providing feedback and to use different methods to see how this rate can be increased rather than accepting that low numbers will return the questionnaires.

The feedback questionnaire that was given to the delegates was developed by GSK. I had no input into the development of the feedback questionnaire, which on reflection would have been an interesting exercise. I could have included more clinician focused questions for the purposes of my own professional development, for example, details on how they treat smokers (groups, one to one sessions) and how they prescribe combination treatment. For future presentations I will take more time to consider the content of the feedback, which on reflection is as important as the presentation itself.

Discussion and feedback from the presentation

There were several discussions that took place after the presentation which were very informative about the current practices and issues facing UK clinicians working with smokers.

Financial constraints on prescribing

During the presentation several discussions were raised. One of the key topics was the financial barrier of providing combination treatment.

Financial cuts are affecting the NHS-SSS and unfortunately this affects if and what stop smoking medications are provided. The current NICE guidelines (2008) ask that anyone treating smokers to '*consider offering a combination of nicotine patches and another form of NRT (such as gum, inhalator, lozenge or nasal spray) to people who show a high level of dependence on nicotine or who have found single forms of NRT inadequate in the past'*. However, in practice it appears this is not the case in some NHS-SSS, as many delegates after the presentation raised the issue of not being able to provide both combination NRT or varenicline due to financial constraints.

One of the reported reasons some NHS-SSS do not provide varenicline, is because the course of treatment is more expensive than using a single NRT product (e.g. 12 week course; varenicline £327.60, 4mg gum £218.88). Currently, it is the decision of each NHS-SSS and individual GP prescribers to adjust their prescribing based on their budget and they decide if and who can receive smoking cessation medications. Although this practice is seen as standard I think there is scope here for discussion with NICE and the NHS-SSS about the current prescribing practice across the

country, in order to improve the provision of medications for smokers in the UK. The most effective medications should be offered to all smokers attending the NHS-SSS as per NICE guidelines (2008). It should not be as a result of a postcode lottery.

As a result of financial restrictions, many NHS-SSS now only prescribe one form of NRT, while advising patients to purchase a second form of NRT themselves. This can be met with a negative response. Cost of NRT has been mentioned in the literature, as one of the main barriers to patients not being able to access and use stop smoking medications (Foulds, Hughes, Hyland, Le Houezec, McNeill, Melvin, Okuyemi, Shiffman, Wassum, Williams & Zeller 2009). In my own clinical experience, asking people to pay for their own medications usually means they will fail to get the medications you recommend or only use them for a short period of time. Offering stop smoking medications on prescription is important in order to increase access to effective medications, especially to those on a low income.

In preparation for this presentation I had been thinking about my own experience as a clinician and the protocols that are in place at my place of work. Whereby I am able to provide treatment to anyone interested in using combination NRT, as part of a quit attempt. I had not experienced any restrictions on what pharmacotherapy I could offer patients, so in hindsight I had not considered this issue fully. On reflection I should have researched thoroughly what practice is common in other NHS-SSS as it appears for a large majority due to financial saints they can be very restricted not just in prescribing combination treatment but also how long they are able to provide the medication. Since the presentation was delivered this is also the same scenario as we now have at the TDRU.

This hot topic aroused some debate among delegates but was not something included in the feedback questionnaire. Asking the delegates why combination treatment was not offered as standard would have been extremely informative to clearer picture of what is happening across the UK.

High-dose NRT

Another issue that was discussed regards protocols for the use of combination and high doses of nicotine. Multiple NRT products i.e. two or three patches are being used in practice and some delegates felt there was a need for guidance on this approach. In addition, some delegates would have liked to have more discussion about using dual oral NRT. This was not something I had prepared for and could only give anecdotal information from my experience of prescribing multiple products i.e. 2 patches. The most typical smoker that would be given this form of treatment at the TDRU are highly dependent smokers, often those who also have mental health illnesses and who find it particularly challenging to quit. My colleague commonly prescribes in this way and after the presentation I discussed with her some plans to write up a protocol for use of high dose NRT alongside some of our findings.

Despite only 40 of the 300 delegates providing feedback, the discussion during the session provided some good insight into the varied experience across the country when using combination NRT.

The delegates agreed on the feedback form that there was a good mix of theory and real-life experience in the presentation. I think this reflects the relevance of the presentation to UK clinicians. The briefing sessions that were held by GSK before the presentation helped me to focus on the content and enabled me to facilitate the

practical discussion. The contact GSK had with me regarding the development of the presentation also conveyed how important the presentation was to GSK and that I had a key role to play. This was the first time I had been involved in an educational symposium and so the importance of being prepared and confident in my knowledge on the subject was incredibly important. I found that taking time to review all the literature as well as discussion among colleagues helped me to prepare for the presentation and I will use this approach for future presentations.

It was encouraging to learn that as a result of the presentation, a large number of the delegates would increase their practice of combination NRT. I think this reflects the importance of my role as a practicing Health Psychologist, being able to communicate both evidence and practical clinical experience, which can lead to a change and/or improvement in clinical practice.

The experience improved my confidence in speaking to large numbers of clinicians. I felt that talking about my own experience alongside the evidence behind combination treatment really helped me to feel more at ease when presenting.

Summary and next steps

UK combination therapy use

The majority of those attending on the day had a good knowledge of using combination treatment in practice so it was positive to see that 80% (N=33) of the participants had learnt something new from the session. It was also encouraging to hear that a high percentage of those who attended would increase practice of combination treatment.

This case study highlights that there is currently a high proportion of people advising the use of combination treatment NRT. However, routine practice of combination treatment has been reduced due to financial barriers. Limited knowledge was also seen as a barrier in recommending combination treatment. This highlights the importance of clinicians attending practice-based lectures and conferences. I know from previous experience that it is often very useful to discuss barriers and facilitators in the provision of NHS-SSS among colleagues, as it often is the way to find solutions to these issues. Conferences can act as a forum for aiding discussion among clinicians in the field.

On reflection, acknowledging the importance of being involved in the development of any feedback questionnaire was a useful lesson to learn. Consideration for how best to get the majority of the delegates to complete them is as important as the development of the presentation content. As a health professional my presenting skills will not be improved without feedback from other HCPs. Feedback is also important in order to

understand what issues are affecting NHS-SSS and to use this to also guide future presentations on the topic of combination NRT treatment.

I enjoyed the experience of presenting at the "Stop Smoking Live" conference. If the opportunity arises to be involved in any future conferences I shall strive to make presentations both practical as well as evidence based.

Section 2 - Patient perspective of combination varenicline and NRT use

Introduction

Nicotine replacement therapy (NRT) is the most widely used medicine for smoking cessation (Stead et al. 2008). There are extensive data showing the efficacy of NRT (Stead et al. 2008). Using more than one NRT product as part of a stop smoking attempt is something that is commonly used in practice and is recommended by UK national guidelines (NICE 2008) as an effective treatment option.

In the UK, smokers also have the option of using non-nicotine treatment options when attempting to stop smoking, these include bupropion and varenicline. Varenicline is a popular medication choice due to its limited contraindications (Pfizer Limited 2011), which means the majority of smokers, even those with other illnesses and medication use, can be recommended the product. Varenicline also has very few side effects that are associated with its use (Pfizer Limited 2011). The adverse event most commonly reported is nausea (28.6%) (Pfizer Limited 2011). In the majority of cases nausea occurs early in the treatment period, is mild to moderate in severity and seldom resulted in discontinuation (Pfizer Limited 2011).

Varenicline is a partial nicotinic agonist which acts on α4β2 nicotinic receptors (Cahill et al. 2012). It is presumed to alleviate withdrawal discomfort, but also diminishes rewarding effects of cigarettes (Cahill et al. 2012). Varenicline has been shown to increase the success of quitting and some evidence shows a slightly higher

success rate when compared to bupropion but the results are slightly less clear for its increased efficacy compared to NRT (Cahill et al. 2012).

Unlike NRT research, which shows an increased effectiveness when using more than one nicotine product (Stead et al. 2008), the use of a combination of varenicline and NRT treatment have not yet been experimentally evaluated. An increasing number of clients request and are using a combination of varenicline and NRT products, despite there being no evidence to show that this combination has any benefit above and beyond using either product on its own. At the TDRU, our approach is that we do not put people off combining products but we are clear that we do not know if it is better than using only varenicline or NRT on its own. However, from clinical experience it is common for people to self medicate and "top up" their varenicline use with other NRT products (which can easily be obtained over the counter and without a prescription) and report feeling a benefit from doing so.

The other reported reason for using an NRT product when using varenicline, is that smokers miss the sensory and behavioural cues associated with smoking (e.g., the sensory effects of smoke in the mouth and throat and the action of puffing on a cigarette). Sensory and behavioural cues appear to provide additional reinforcement of smoking behaviour (Rose 2008), which is often missed when attempting to stop smoking. So for someone using varenicline, use of an oral NRT product may help to compensate for the reduced sensory cues associated with stopping smoking and should in theory improve cessation rates.

Part 1 of this portfolio outlines the first randomised trial on the effectiveness of using a combination of a nicotine patch and varenicline, which found no increased efficacy when using the products in combination. This case study aims to give a qualitative reflection on smokers attending the TDRU Smokers' Clinic, who were using a combination of both varenicilne and NRT, without given instruction to do so. The case studies aim was to explore the reasons why they chose to use both products, despite not being advised to do so and whether they found any benefit from it. Clients were also asked to discuss if they had any concerns whilst using the combination of medications.

Method

The researcher developed a structured questionnaire. The questions included were guided from experience of working with smokers using combination treatment (see Appendix 3). Questions were written in order to allow participants to expand on the topic rather than eliciting a yes/no response. The questions aimed to establish the reasons for using combination treatment, where they got the medications from, frequency and duration of use and their thoughts on how useful combination treatment was.

Participants

Participants were recruited opportunistically and approached if they were using combination treatment and would consent to answering some questions. Two clients who were attending treatment sessions at the TDRU Smokers' Clinic, who were highlighted as using combination varenicline and NRT, consented to take part. All data was collected anonymously, no demographic details were collected other than specific questions on their use of combination treatment and their smoking history. Both participants were using varenicline (1mg BID as per standard protocol) but with an added oral product. Neither of the participants had ever used a varenicline and NRT combination in previous quit attempts.

1) Case study – Mr Inhalator

Mr Inhalator reported smoking 15 hand rolled cigarettes per day and had been smoking since the age of 11. His FTND score was 4 (low tobacco dependence rating) and it was his first visit to the NHS-SSS. Mr Inhalator had used nicotine patch and inhalator in a previous quit attempt. He had tried to quit smoking 2-3 times in the last 5 years and his last quit attempt was in the last 3 months. He reported stress as the main thing that led to relapse on the previous quit attempt.

Mr Inhalator had reported a slip back to smoking, 4 weeks into the quit attempt. The inhalator had been bought to avoid full relapse back to smoking. He reported hearing another member in the smokers group discussing use of a combination of varenicline and an inhalator, which is why he felt it was ok for him to use the same combination. Using both the varenicline and inhalator was discussed with his clinician who said it was fine to use.

Mr Inhalator reported that the inhalator would only work if he had a slip and saw the inhalator more of a last option before smoking. The inhalator was being used 2-4 times per day, mainly after meals. Mr Inhalator reported that he would complete the 12-week course of varenicline and that the inhalator would be used during this time if needed.

Mr Inhalator reported no side effects from using combination varenicline and inhalator and had no concerns about using the medication combination.

2) Case study – Mr Lozenge

Mr Lozenge reported smoking 20 cigarettes per day and had been smoking since the age of 16. His FTND score could not be calculated due to missing data. It was his first visit to the NHS-SSS.

Mr Lozenge had used nicotine lozenges in the past and had some at home (left over from a previous quit attempt). He had found the TQD hard and so used the lozenges to "get through the day". He started using the lozenges from day 7 of the quit attempt and its use was situation dependent (the participant reported increased use when drinking). He reported that the benefit of using the lozenges was that it was "something to do".

Mr Lozenge was asked how long he would use the medications for; he said he would use the lozenges for the foreseeable future (at least a further 3 months if not longer) and was going to use varenicline for the full course of treatment (12 weeks).

His clinician had agreed to it being used and the general message seemed to be "whatever works for you".

Mr Lozenge reported no side effects from using combination varenicline and lozenge and had no concerns about using the medication combination.

Summary and reflection on the findings of the case studies

Part 1 of this portfolio, was the first randomised study of using a combination of both varenicline and nicotine patches versus varenicline alone in smokers seeking help to stop smoking. The results found no difference in efficacy between the two treatment options. The aim of these brief case studies was to look at patients' perspectives and to reflect on the current thinking about combination of varenicline and NRT, in attendees at the TDRU Smokers' Clinic.

The 2 participants that were interviewed for this case study were both using an oral NRT product (inhalator and lozenge) alongside varenicline. The medication choice described by the two participants was one made by them without the guidance of a clinician, who in practice is not currently able to recommend and prescribe NRT and varenicline in combination. Both participants gave different reasons for using the product they chose; hearing about another smokers experience with the product and having the product at home after a previous quit attempt.

Both smokers reported that they found the combination beneficial which contradicts the main findings in ***part 1,*** which reported no difference in efficacy when using combination NRT and varenicline**.** It could be argued that use of the short-acting oral NRT formulations such as the ones used by the two participants interviewed, which can be used opportunistically, could be more effective than a nicotine patch. This is possible, but any gains in better efficacy of short-acting NRT products are usually undermined by the fact that they are less user-friendly and generate much lower adherence than patches. Nevertheless, this is something that should be considered.

Anecdotally, it is unusual for someone to report use of a nicotine patch in combination with varenicline. So from a patient perspective using a patch "top-up" product does not typically have the same appeal as an oral product. There could be several reasons for this.

There are other underlying mechanisms of smoking that are not addressed when using varenicline on its own (i.e. sensory and environmental cues) which may be something that needs to be addressed for some smokers to be able to succeed in stopping smoking (Rose 2008).

Most smokers report that the first few weeks of a quit attempt are the hardest to get through. Cravings to smoke are typically more frequent and intense in the early stages of quitting, so risk of relapse is high (Hughes, Kelly & Naud 2004). Use of NRT whilst using varenicline may in theory act as a distraction when cravings are difficult to control, as was the case with Mr Lozenge.

It would be interesting to see if those who choose to use a combination of NRT and varenicline would be identified as more sensitive to sensory and environmental cues than those who use varenicline on its own.

For some patients, having a 'back up' treatment option when experiencing increased urges and cravings early into a quit attempt is important. This is supported by the views of the participants about their use of combination varenicline and NRT. It is interesting to hear that Mr Inhalator viewed the NRT as important in case of having a slip. It seems having the products does not indicate then need for regular use, for these

participants it was having the product there in case they experience an increase in cravings to smoke that they have something to use. This appears to help the smoker to feel more in control when cravings do occur and is a way then can delay relapsing to smoking.

It was interesting that in this case study, both participants chose an oral NRT as opposed to a patch. I think that practically, the oral products seem more useful to the patients as they can be used as and when desired.

Regarding the safety of combination use of NRT and varenicline, a single pre-marketing study has previously shown that smokers using varenicline and a transdermal patch for 12 days reported a higher incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue than smokers who used NRT alone (Pfizer Limited 2011). However, these symptoms may have been due to varenicline use, as opposed to combined use of varenicline and NRT. Post-marketing data suggests that combined use of varenicline and NRT is well tolerated (Ebbert 2009).

It was encouraging to see that no negative effects from combining the two treatment options were reported by the 2 participants that were interviewed; this is also supported by the results found from ***section 1***.

Conclusion

Combination varenicline and NRT is currently being used by smokers during attempts to stop smoking, despite there being no current guidelines to implement this treatment regimen. The results of ***Part 1*** of this portfolio found no efficacy for using nicotine patches and varenicline above using varenicline alone. Once these results are published and are available for clinicians to guide patient treatment, it is thought that patients will continue to use this combination treatment option as for many it is used to compensate for the reduce sensory aspects associated with being a smoker that some smokers find harder than others to deal with when initially trying to stop smoking.

Adopting a qualitative approach to this topic could be very interesting, especially in the light that combination treatment may not be more effective than using a single product. The current case studies targeted people who were regularly using a combination, so it would be presumed that these people would be the people reporting a benefit. It would be important to interview people who had started using a combination but stopped and to find out the reasons why they stopped.

To conclude, it is thought that the occasional practice of combining varenicline and NRT will continue for the few smokers that find it useful. As there are no safety implications of using combination varenicline and NRT, smokers may continue its use if they find it of benefit.

Chapter 2 - Case study 2 – Reflection on clinical practice

Summary of clinical practice

Working for an NHS-SSS has been a great experience for developing my clinical and academic skills. As I came into my job straight from university I had no experience of providing behaviour change interventions, which was initially extremely daunting. However, I was encouraged by my supervisor to attend training days and courses and I soon found my confidence improving both when dealing with other HCPs and also with my patients.

Having a role, which sees me as part of QMUL, the NHS and the PCT has led me to meet a variety of HCPs and students and has enabled me to have many different opportunities within all these service providers.

I have worked at the TDRU as the clinic administrator, hospital inpatient stop smoking advisor, as a research health psychologist and now my role is as a research fellow; managing several trials within the unit. I am regularly involved in teaching and have examiner experience involving the medical students of QMUL.

After nearly 7 years in the unit, my role is now primarily in research which has been a very steep learning curve for me. I am involved in grant applications for funding studies (details can be found in the preface), study protocol development, in addition to the day-to-day running of research conducted in the unit. We currently have 5 studies running in both smoking cessation and weight management; in which I

supervise the research leads for each project. This role is extremely demanding and requires regular reflection and knowledge development.

Reflection on research practice

Over the last 2 years, my supervised practice on the DPsych course has really helped me to focus on my role and to develop systems for ensuring all my work is kept to a high professional standard.

In order to reflect on my practice during the supervised period of my DPsych, I will discuss some of the practical considerations and issues that are faced on a daily basis when involved in clinical research and how protocols have been implemented to ensure Good Clinical Practice (GCP) is followed. This case study also highlights key skills my job entails and a discussion of some of the practicalities that are involved in research in an academic setting. These issues are also discussed in the context of a study I have been involved in to reflect my current and on-going practice.

Background to GCP regulations

GCP is a term used to identify the components of Schedules 1 and 2 of the Medicines for Human Use (Clinical Trials) Regulations 2004. Table 2 describes 13 principles and 3 conditions, which define lawful conduct when carrying out research into medicinal products. GCP is a major part of the overall Research Governance Framework for Health and Social Care.

Table 2 – GCP guidelines

- Clinical trials shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with good clinical practice and the requirements of these regulations.
- Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- The rights, safety and well-being of the trial subjects are the most important considerations and shall prevail over interests of science and society.
- The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the clinical trial.
- Clinical trials shall be scientifically sound, and described in a clear, detailed protocol.
- A trial shall be conducted in compliance with the protocol and has a favourable opinion from an ethics committee.
- The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of an qualified dentist.
- Each individual involved in conducting a trial shall be qualified by education, training, and experience to perform his or her respective task(s).
- Subject to the other provisions of this schedule relating to consent, freely given informed consent shall be obtained from every subject prior to clinical trial participation.
- All clinical trial information shall be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
- The confidentiality of records that could identify subjects shall be protected, respecting the privacy and confidentiality rules in accordance with the requirements of the Data Protection Act 1998 and the law relating to confidentiality.
- Investigational medicinal products used in the trial shall be
  a) manufactured or imported, and handled and stored, in accordance with the

principles and guidelines of good manufacturing practice, and b) used in accordance with the approved protocol.

- Systems with procedures that assure the quality of every aspect of the trial shall be implemented.

The importance of these guidelines is crucial to the successful running of a clinical research project. Below is a discussion of some of the steps and issues to consider when conducting clinical trials in an academic setting.

Associated requirements

One of the key things to understand in research is who does what in the process of gaining approval. This can often be very challenging, especially with regular document and process change within departments. The first experience I had with this process was when I went on the GCP training course, run by Barts and the London and QMUL's Research and Development (R&D) department. The complexities of all the processes can be quite overwhelming, with several different research bodies being involved in the process of gaining approval to do research; National Research Ethics Service (NRES), local ethics, Medicines and Healthcare Products Regulatory Agency (MHRA) and R&D.

Over the last few years I have found that the most important relationship is with the local R&D department. Having good working relationships with the team means that queries can be answered quickly and it also is reassuring to know that there are people on hand to help with queries throughout the process of gaining approval for research. It is important to keep up to date with any changes in documentation and legislation. I have found that regularly visiting the websites for all the key bodies involved keeps

me up to date with the information we need to know to run our studies in line with UK standards.

Approval from all the relevant research bodies is needed before commencing a research project, although giving approval to start a project is not their only role. They maintain contact throughout the trial and it is important to know at what stage they need to be involved. If any substantial changes (e.g. a change to the statistical plan of the project) happen to the project whilst it is being conducted then this will need to be approved by R&D and NRES. For example, we recently had to send a substantial amendment document to relevant bodies in order to change the number of participants we were going to recruit, in the first instance R&D will approve this.

The MHRA require an annual report, this includes the number of adverse events that have occurred as well as the number of participants recruited and a summary of the project. All of the study bodies will be informed when the study is closed by the site and once all the data is analysed, a summary of the results will be sent to all involved to officially close the project.

To summarise, there is regular contact needed with many research bodies throughout the running of a research project, which requires planning. It is key to be aware of what needs to be sent and when, as this is a legal obligation of the Principal Investigator on behalf of the project sponsor.

Protocol development

Protocol development is one of the most importance aspects of research, which can sometimes be underestimated. Having a research protocol that is detailed and methodical ensures good working practice and really can act as the researcher's 'bible' should any issues come up. Getting as much feedback and review from different parties is important to ensure you have a robust protocol that covers all the key aspects of the research proposed. One important issue to consider is when there are multiple researchers simultaneously working on the same protocol, as it very easy to lose track of new amendments. In my experience the key is to have someone overseeing the process to ensure version control.

Trial Master file (TMF)

In order to keep all documentation mentioned above in order, a Trial Master File (TMF) is maintained for the duration of the study. The TMF should tell the 'story' of the research project from start to finish. The TMF contains all approved documents and the most current versions of all the study documents e.g. study questionnaires, informed consent form and protocol. It should reflect any changes made to the study and it should be clearly documented if there are any deviations from the protocol. One of the most important things is to keep it current, which means reviewing it regularly. All communication (email, faxes, letters) should be included in the TMF from study staff, funders and the sponsor alongside any communication with the main approval bodies (R&D, NRES and MHRA).

Standard Operating Procedures (SOPs)

Within the TMF, Standard Operating Procedures (SOPs) are outlined at the start of the study, which work simply as the working protocol for the study. The SOPs give

details, for example, about deviation protocols, managing data, regular auditing of clinic practice and data collection. The SOPs that are used within the department are a mixture of QMUL wide guidelines along with some that have been developed at the unit for our specific studies. These documents are essential for the running of a successful study as they provide clear guidelines for any major challenges that the team may face in the process of running the study.

Database management

Having come into the post from my masters I had very little knowledge of legal, ethical and professional standards. As part of my role as the inpatient advisor I was required to manage an SPSS database. As I had used SPSS during my time at university, I was familiar with how it worked but I had not been involved in implementing any SOPs for entering and analysing data.

The importance of database management and audit is essential when conducting research. It is important to know that once the database is finally shut down ready for analysis that the data entry is accurate. Over the last few studies I have implemented SOPs to help deal with errors, for example, applying limiters to questions which prevent any outliers being entered. We have also put in place SOPs for auditing the data throughout the data entry period. We usually work from a Microsoft Access database, which gets exported to a Microsoft Excel to then finally be exported to SPSS (version 18) for analysis. At the excel stage an independent member of staff not involved in the study will pick 10% of the CRFs to input. This is then compared to the original data entry and errors are highlighted. Data will only be exported once the team is confident that the data is accurate.

Data protection

The Data Protection Act (1998) was developed to protect the confidentiality of personal data stored on living individuals. Personal data is defined as data, which relates to a living individual who can be identified from those data. It is a legal duty to abide by the Data Protection Act. Its eight defining principles are that data should be;

- Fairly and Lawfully processed
- Processed for specified purposes
- Adequate, relevant and not excessive
- Accurate
- Not kept for longer that necessary
- Processed in accordance with the data subjects rights
- Secure from unauthorised access or alteration
- Not transferred to countries without adequate data protection controls

The security of the database at the TDRU is one of our main priorities. Data is stored in a locked room, on a stand-alone computer with 2 password-protected screens. Having no internet link on the computer increases the security of the database. Many of the changes I have implemented were as a result of extensive conversations with QMUL IT services, as well as with R&D. All databases and study computers within the unit are now in-line with both QMUL and MHRA regulations.

Auditing

I have learnt that the safety and interests of patient information and confidentiality of data is one of the most important issues to consider. Systems need to be regularly monitored so that clinic procedures can be audited without any problems. This is an

issue I had not even considered until attending the GCP training course in which they discussed the regularity with which the university is audited. In October 2008 a trial in which I was involved was audited and the procedures we had in place passed all the auditors criteria. On reflection, this was as a result of on-going efforts to keep the TMF up to date.

The trials I have been involved in have opened my eyes to the amount of paperwork that is involved in research and its importance in conducting clinical trails correctly. It is important to be up-to-date with all documents including staff CVs and training courses such as the GCP training.. I have learnt that for legal reasons documentation for a trial must be up-to-date and be easily accessible for review.

Dealing with clinical issues

Reflecting on when issues have arisen concerning the service, I have tried to use opportunities such as appraisals to address these matters. As I have progressed in my career, the importance of immediate action when issues or concerns are raised about the service has become very evident. I feel my confidence when approaching senior colleagues has risen since starting my training. I now enjoy discussing patient and service issues with my manager and other colleagues rather than shying away from concerns, which I think is a reflection of my confidence as a practicing Health Psychologist.

Care Quality Commission (CQC)

After several years of being involved in the processes of conducting research, I was asked by the head of R&D at QMUL to apply and represent our unit as a Care Quality

Commission (CQC) manager. CQC is the government body that regulates, inspects and reviews the quality of patient care across clinical care settings. There are a total of 5 CQC managers within QMUL. Having research experience has helped me to focus on the important organizational aspects involved in running the smokers' clinic. Implementing SOPs to deal with patient care at the smokers' clinic is very similar to the process of SOP development for research. This is an extremely important role that I now have and it comes with some responsibility. However, I believe my training and organisational skills with regards to research has increased my confidence in being able to implement clear pathways for ensuring patient care is our priority in a clinical care setting as well as a research unit.

In order to reflect on some of the above points in practice, I have outlined a recent study I was involved in and some of the issues that occurred and how they were dealt with.

Example of a recent study - Varenicline treatment for four weeks prior to quitting smoking reduces ad-lib smoking and increases smoking cessation rates

In 2009 I was asked to co-ordinate and manage a Randomised Control Trial (RCT) using a new treatment regime for the stop smoking medication, varenicline. The current treatment schedule is to commence the medication one week before the patient stops smoking. Participants who were involved in the study were asked to instead, take the medication for 4 weeks before quitting to see if the increased period of medication reduced cigarette satisfaction and improved chances of quitting.

Recruitment for the trial began in July 2009. We aimed to recruit and randomise 100 participants. The study consisted of telephone screening, followed by a first visit to the clinic to be screened for eligibility and consented. If a participant was eligible then they were asked to start taking varenicline in anticipation of quitting 4 weeks later. Participants were asked to smoke ad-lib until the quit day. All participants recruited for the study attended the smokers' clinic on a weekly basis for a total of 7 weeks as per usual NHS-SSS protocol.

This was not the first time I had managed a clinical trial but it was the first time I had full control over the protocol and procedural logistics for the trial. Previously, the studies I had been involved in were supervised by data monitoring companies that were recruited to oversee the running of the trial on behalf of the funder.

Several members of staff were recruited for the study; it was important that the staff involved understood their responsibilities and I ensured that all members of staff were properly trained. This involved role-plays of sessions and printed protocols of responsibility for each person. It was key to ensure people were doing appropriate jobs that worked with their strengths. For example, I used several members of staff that had previous trial experience in more complex areas of the study. More junior members of the team were involved in telephone screening and day-to-day management of the trial paperwork.

Another important aspect that needed to be considered was to ensure all participants were up to date with training courses required to take part in the study. The university was contacted and everyone involved attended a GCP training course before the trial began.

Recruitment

Participants were recruited via an advertisement in 2 London wide papers; The Metro and Evening Standard. Participants were screened over the phone for eligibility to be invited to the screening/baseline session. I then developed a telephone-screening questionnaire, which was to be completed by the delegated clinicians for each participant that called. In order to unify the procedures for this a simplified script covering the main points of the protocol was developed for their use during the calls. I also trained everyone involved on the simplified protocol for the screening. I found conducting role-plays was a very useful way of highlighting any areas that needed improvement and we were then able to discuss these as a team.

Auditing

The JRO at QMUL audited the clinic site, which included my storing of confidential information. This allowed us the opportunity to review our procedure. The auditor had very few criticisms with regard to the running of the study, which was extremely positive. All documents were up to date, including the temperature logs and staff documentation.

General Issues

We had several participants who experienced a Serious Adverse Events (SAEs), this is defined as any unknown medical occurrence that at any dose results in:

1. Death
2. is life-threatening
3. requires hospitalisation or prolongation of existing hospitalisation
4. results in persistent or significant disability/incapability, or
5. is a congenital anomaly/birth defect

It was important that I knew how to identify these but also how to report them and to who. It highlighted the importance of knowing who to contact when experiencing these problems. I felt it was part of GCP to email for confirmation of my actions and also to keep a concise log of all communications regarding the trial.

One of the major issues we had concerned the labelling of the commercial supply of the medications. We had to contract a company to do this for us but we had to spend a lot of time researching the options available to us. We also needed to go through several layers of approval before we could contract the company, which again added delays. The start of the project was substantially delayed as a result of this process.

With the next project I was involved in, this process was started months before it was needed to ensure that we started recruitment on time.

Learning

I have learnt several things as a result of this experience that I hope to address in any future study management.

I have learnt that it is important to delegate work and not to put too much pressure on myself. At the start of the study I wanted to do everything because I wanted to be involved and also because I knew that I had to check that things were being done correctly. However, this is not a practical way to manage a study. I am now confident that mistakes can be minimised if staff are well trained and that they know you are available to discuss any issues/problems.

Continued reflection and discussion with all members of the team is essential to the smooth running of any trial. Initially meetings would be arranged ad hoc but the importance of discussing project progress is crucial. I now book regular weekly meetings with key members of staff. I find this is useful to keep me up to speed with the project but also ensures that the researchers are able to discuss any problems they are experiencing with me and also to share good practice.

SUMMARY

To summarise I have had several years of experience working in an academic research setting. This case study was presented to discuss some of the many obstacles that are faced by researchers when conducting research. My role as a practicing health psychologist is to continue to use my training and research experience to conduct new and important pieces of research within my areas of expertise in order to help inform and try to improve smoking cessation services and treatment outcome. I hope to continue to further develop my skills in both research and clinical practice.

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APPENDICIES FOR PART 1

Appendix 1 – Advertisements

Advertisements version 1.0 25 May 2010

SMOKERS WANTED

A new approach to stopping smoking is being tested at Barts and The London Medical School.

For information please call:

[redacted]

Smokers Wanted

Barts and The London School of Medicine is testing a new approach to help smokers quit.

If you would like to take part call:

[redacted]

for more information

Appendix 2 – Telephone Screening Questions

We need to ask a few questions about you and your health to make sure that this study is suitable for you. Is this ok?	Y N	If **no**, excluded
Are you 18 years or older?	Y N	If **no**, excluded
Do you have severe kidney disease?	Y N	If **yes**, excluded
Have you ever had an allergic reaction to champix?	Y N	If **yes**, exclude
Have you ever had an allergic reaction to Nicotine Patches?	Y N	If **yes**, exclude
Are you currently receiving treatment for any psychiatric illness such as depression or schizophrenia?	Y N	If **yes**, exclude
If female, are you breast-feeding, pregnant or planning to become pregnant within the next 3 months?	Y N N/A	If **yes**, exclude
Have you taken part in any clinical trials within the last 3 months or do you intend to participate in another clinical trial at the same time as this trial?	Y N	If **less than 3 months,** exclude

Eligible: Y☐ No ☐

If eligible:

Name:

Address:

Phone number home/work

Mobile number

Email:

Where did you see this advertised?

Date of appointment for Baseline visit:

Time of Baseline visit:

Appointment letter sent: Yes No

Appendix 3 – Telephone screening script

Hello, Tobacco Dependence Research Unit.

Thank you for calling us. Let me explain what this is about. There are two main medications proven to help smokers quit. Varenicline (Champix) and nicotine replacement treatments such as patch and gum. Smokers normally have to choose one or the other. However, some people found it most effective to use both and we are now trying to find out if using Champix and patch together is better than using Champix alone.

If you are eligible and willing to take part, you will receive our standard state-of-the art treatment at our research clinic with specialist support and Champix, taken for up to 12 weeks. In addition, you will be allocated by a computer to use a nicotine patch or a placebo (dummy) patch from your quit day for 4 weeks.

All treatment will be free of charge and will be provided at the clinic so you will not have to go to a chemist.

If interested, you will be invited to a screening session on Saturday 7th or Sunday 8th May to be seen by the study doctor. This will take some 20 minutes and takes place at the Royal London Hospital opposite the tube station in Whitechapel. You will then attend 7 weekly sessions at the smoker's clinic. Each participant will be given an option of coming to the smokers on either a Tuesday or Wednesday evening (5.30-6.30 and 6.30-7.30 will be available). The clinics will start on 10th and 11th May (the Tuesday and Wednesday after the weekend screening).

If this is of interest, can I ask you a few question to see if you are eligible to take part in the trial

Ask questions and fill in the telephone screening form.

If not suitable at any point: Unfortunately this means that you cannot take part in this study. However, you are still able to attend our clinic and take part in the standard treatment programme. If you would like to do this, I will get someone to call you and make an appointment for you later today or tomorrow.

Write NOT ELIGIBLE on the form, and if interest in the local Clinics, write address and telephone contact, and pass on to XXXX. If out of area give them the national number, they can direct them to their local service [redacted]

If eligible: Great, thank you, you are eligible for the initial visit. Before I give you a slot for the screening session, let me warn you that on the weekend of 7-8 May, the underground service will be suspended, Is this OK? We will send you detailed information in the post about how you can get to us.

If OK, allocate a slot and note this on the form.

If you give me your address and phone number I will send you the confirmation and study details. (The phone number is needed if there are any last minute changes). We will also be including some questionnaires, if you could fill these in before your visit it will save time during your visit.

Put contact details on the form, fill in the appointment letter, write address on the envelope and seal it.

Appendix 4 – Patient information sheet

INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

Effects of a combination of varenicline and transdermal nicotine patch on post-quitting urges to smoke

We invite you to take part in a research study which we think may be important. The information that follows tells you what will happen if you take part and what the risks might be. Whether or not you do take part is entirely your choice. Please ask any questions you want to about the research and we will try our best to answer them.

The Study

Varenicline (Champix) and Nicotine Replacement Therapy (NRT) are effective treatments for helping people to quit smoking. Smokers will usually choose to use either Varenicline or NRT alone, but some people have reported finding it beneficial to use both medications. We are trying to find out if using Varenicline and a Nicotine Patch is better than using Varenicline alone.

This study has been developed by researchers at Barts and The London, Queen Mary's School of Medicine and Dentistry. It is funded by Pfizer (who make Champix) and has been approved by the local ethical committee.

What will happen to you if you take part?

If you are eligible and willing to take part in the study there will be only small differences from the normal treatment that smokers receive at our clinic.

The main difference is that whilst using Varenicline you will be randomly allocated (by chance) to use a 15mg/16hr nicotine patch or a placebo patch (dummy patch) from your quit day for a total of 4 weeks. Neither your advisor nor yourself will know which patch you have received. Varenicline will be continued for a total of 12 weeks after the quit day (this is standard treatment).

The visits and phone calls that need to be made are outlined in the table below.

If you are included in the study there will be a couple of things that you will be asked to do that is not usually required with the standard stop smoking clinic. For this study we will ask you to attend one extra visit to the clinic 12 weeks after the target quit day (8 visits compared to the usual 7) and we will call you once, 24 hours after the target quit day. You will be asked to fill in a brief questionnaire on both of these occasions.

Study outline

Session 1	2 weeks before quit day	At this first ***visit*** to the Smokers' Clinic we will describe the study and go through this information sheet. You will then have the opportunity to ask any questions. We will then ask you to sign a consent form to show that you have agreed to take part. You will then complete a short questionnaire to tell us about your smoking and mood. We will also measure the amount of carbon monoxide (CO) in your breath. You will be given an appointment time to attend the clinic the following week.
Session 2	1 week before quit day	At this second ***visit*** to the Smokers' Clinic we will ask you to complete a short questionnaire. We will also record the number of cigarettes that you are smoking per day and measure the amount of CO in your breath. You will be given a week's supply of Varenicline to start using. We will also help you prepare for your Quit Day the next week.
Session 3	QUIT DAY	You will ***visit*** the Smokers' Clinic and we will ask you to complete some short questionnaires to measure any withdrawal symptoms. We will also record the number of cigarettes that you are smoking per day and we will measure the amount of CO in your breath. You will be given another supply of Varenicline and you will be given a nicotine patch to start using. We will provide you with some counselling to help you get through the first week.
Session 4	24 hours after quit day	We will ***call*** you 24 hours after your quit day to see how you are getting on. We will provide you with some support and assess your level of craving for cigarettes and other withdrawal symptoms.
Sessions 5-7	1-3 weeks after the quit day	At each of these sessions you will ***visit*** the Smokers' Clinic and we will ask if you have smoked or not, measure the amount of CO in your breath and ask whether you are experiencing withdrawal symptoms. Medication will be given to you at each session. We will provide you with support on a weekly basis to assist you in your quit attempt.
Session 8	4 weeks after the quit day	At this session we will ask you to stop using the Nicotine patches but will ask you to continue using Varenicline. After this session we will not formally contact you again until you have finished the course of treatment (8 weeks later). Of course you should feel able to contact us during this time if you have any questions or concerns.
Session 9	12 weeks after quit day	We will ask you to attend one final ***visit*** to see how you are after finishing the medication and how you are managing with not smoking. We will ask if you have smoked or not, measure the amount of CO in your breath and ask whether you are experiencing withdrawal symptoms. Advice will be given on how to stay stopped or try to quit again if you have not been able to stop.

Who Can Take Part

Like all medicines, the ones approved for use to stop smoking can have side effects and people with certain medical conditions are more likely to experience these than others. As in our routine care, we will check your medical history and only allow you to take part in the study if it is safe for you to use varenicline.

You will not be able to take part if you

- You are under 18 years of age
- Are pregnant or breastfeeding
- Have severe kidney disease
- Have a current psychiatric illness
- Are unable to fill in questionnaires in English
- You have an allergy to varenicline
- You have an allergy to Nicotine Patches
- Are planning to conceive during the study period
- Are currently involved in another clinical trial

Data Protection

If you agree to take part, we will ask you to complete the standard clinic questionnaire and some short additional questionnaires required for this study. We will not request any medical information about you from your doctor. All information will be kept confidential, just as is normal for smokers attending the clinic. We will inform your GP, with your consent, that you are taking part in this study.

Only the study staff will have access to this data. The results of the study will be presented to the smoking cessation experts and may be printed in medical journals. However this will not include any information which could identify you.

Risks/Side Effects

Varenicline is used in routine clinical treatment. It can have a number of side effects; the most common of these is nausea. Mostly this is mild/moderate and usually gets less over time. Other side effect may include abdominal pain, abnormal dreams, constipation, dry mouth, indigestion, flatulence (gas), flu syndrome, headache, increased appetite, insomnia (sleeplessness), irritability, drowsiness, altered taste, trouble concentrating, and vomiting.

More recently there have been reports of depression and suicidal thoughts in people taking varenicline. However this may not be due to the medicine. Advice from agencies that monitor medicines recommend that people taking varenicline should be informed about this possible adverse effect and monitored. We will be seeing you on a weekly basis and you will be asked to report any low mood.

Nicotine patches are also used commonly in routine clinical treatment. The most common side effect is for the patches to irritate the skin. Other side effects such as nausea, dizziness and headaches have been reported.

Your study doctor will check you carefully before you start treatment and during the study to make sure that you are able to take these medications.

Medication

Varenicline and Nicotine/Placebo Patches will be supplied at the smokers' clinic free of charge. Pfizer is donating the Varenicline and Johnson & Johnson will be providing the patches.

Your Rights

Participation in this study is entirely voluntary. You are free to decide not to be in this trial or to drop out at any time. If you decide not to be in the study, or drop out, this will not put at risk you ordinary medical care. All records relating to the study will be kept strictly confidential.

What happens if you are worried or if there is an emergency?

You will be able to contact Katie Myers at the Smokers' Clinic to discuss your concerns and/or get help. The phone number is [redacted] or email [redacted]. Outside office hours you can call [redacted].

The chief investigator in this study is [redacted]

We believe that this study is safe and do not expect you to suffer any harm or injury because of your participation in it. However, *Queen Mary and Westfield College, University of London* has agreed that if your health does suffer as a result of your being in the study then you will be compensated. In such a situation, you will not have to prove that the harm or injury which affects you is anyone's fault. If you are not happy with any proposed compensation, you may have to pursue your claim through legal action.

If you have a complaint please contact [redacted]

Email: [redacted]

If you wish to ask any further questions, or you have entered the study and are unsure about something, then please do not hesitate to contact Katie Myers, telephone [redacted]

We would like to thank you for your interest in this study, even if you decide not to take part.

Appendix 5 – Invitation to participate

Queen Mary
University of London

Dear

Re: "Effects of a combination of varenicline and transdermal nicotine patch on post-quitting urges to smoke"

Thank you very much for your interest in taking part in this study.

Please find enclosed some information about it (see Participant Information Sheet). We will go through this with you in more detail when you come to see us at your first appointment on:

_____at _____at the Royal London Hospital Smokers' Clinic. We have enclosed a map to help you find us.

We would also be most grateful if you could complete the short questionnaire enclosed. This is our standard Smokers' Clinic Questionnaire that gives us information about you, your current health and your smoking.

In case you decide not to take part or cannot come for your appointment, please do let us know so we can allocate your slot to someone else (the phone number and e-mail address are below)

If you have any questions or concerns regarding taking part in this study please do not hesitate to contact me on 020 7882 8230 or by e-mail on k.myers@qmul.ac.uk

Yours sincerely,

Miss Katie Myers

Study Manager

Appendix 6 – Smokers clinic questionnaire

CLIENT TREAT NO: 201 _ : _ _ _ _

Smokers Clinic Questionnaire

Please complete this form and bring it to your first appointment. If you have any problems with the questions, please don't worry or be put off coming. We will help you if necessary. The information collected is strictly confidential, for use by Trust staff. Some items, e.g. age, sex, ethnicity, are required by the Department of Health to monitor the service we provide. Other items, including those obtained from all sessions and follow-ups, will be used by the clinic to guide your treatment, and may be used in research on smoking. No names or information that might identify you will be used in any reports, only figures from many smokers together. The information will be stored in accordance with the Data Protection Act and you have the right to review it, or withdraw your permission for us to use it. Your participation in this work is voluntary and your treatment at the clinic will not be affected if you refuse. Please discuss any concerns you may have regarding this information with the clinic staff. Signing below indicates that you have read this notice and agree to your information being used in this way.

Signature _____ **Date** _____

Please write where you see the lines. Circle the word which applies to you

Your name: _____ **Are you?** 1 **Male** 2 **Female** (***circle ONE only***)

Your date of Birth: _____ **Your age?** _____ **years**

Your address: _____

_____ **Post Code:** _____

Home tel no: _____ **Work tel no:** _____

Mobile tel no: _____ **Email:** _____

Person to contact if we cannot reach you: _____ **Tel No:** _____

Name/Address of your GP: _____

_____ **Post Code:** _____ **Tel No:** _____

1. **Are you?** 1 **Married** 2 **Divorced** 3 **Separated** 4 **Widowed** 5 **Single (never married)** (***circle ONE***)

2. **Do you live?** 1 **With your spouse/partner** 2 **Family/friends** 3 **On your own** 4 **Hostel/residential home** (***circle ONE***)

3. **Are you? (** ***circle ONE*** **)**

1 **Working in a routine or manual occupation**

2 **Working in an intermediate occupation**

3 **Working in a managerial or professional occupation**

4 **Unemployed / not working for a year or more**

5 **Full time student**

6 **Retired**

7 **Sick / Disabled / Unable to return to work**

8 **Home carer (unpaid)**

9 **None of these**

4. **What is your most recent or current occupation?** _____

5. **Which qualifications do you have?** 1 **None** 2 **GCSE/CSE** 3 **A-Level** 4 **Diploma/HND** 5 **Degree** 6 **Other_____**

6. **Are you entitled to free prescriptions?** 1 **Yes** 2 **No** (***circle one***)

7. **Which of these best describes your ethnic origin?** (***circle ONE category below***)

1 **WHITE - British** 2 **WHITE - Irish** 3 **WHITE - other background**

4 **MIXED - White and Black Caribbean** 5 **MIXED - White and Black African** 6 **MIXED - White and Black Asian**

7 **MIXED - other background** 8 **ASIAN / Asian British - Indian** 9 **ASIAN / Asian British - Pakistani**

10 **ASIAN / Asian British - Bangladeshi** 11 **ASIAN or Asian British - other** 12 **BLACK or Black British - Caribbean**

13 **BLACK or Black British - Africa** 14 **BLACK or Black British - other** 15 **CHINESE**

16 **TURKISH or KURDISH** 17 **Another ethnic group: _____** 18 **Don't wish to answer**

Questions about your smoking

8. **How many cigarettes do you usually smoke each day?** _____ (***write a SINGLE average number***)

9. **How many of these are hand-rolled cigarettes?** _____ (***write a single average number***)

10. **How soon after waking up do you usually smoke?** (***circle one***)

3 **Within 5 mins** 2 **6 to 30 mins** 1 **31 to 60 mins** 0 **After 1 hour**

11. **Do you find it difficult not to smoke in places where smoking is not allowed?** 1 **Yes** 0 **No** (***circle one***)

12. **Do you smoke more in the first hours after waking up than during the rest of the day?** 1 **Yes** 0 **No** (***circle one***)

13. **Which cigarette would you hate most to give up?** 1 **The first of the morning** 0 **Another one** (***circle one***)

14. **Do you smoke if you are so ill that you are in bed most of the day?** 1 **Yes** 0 **No** (***circle one***)

15. **How often do you wake up at night and smoke?** ***(circle one)***

1 **Never** 2 **Less than once a month** 3 **1 or 2 times a month** 4 **1 or 2 times a week** 5 **Most nights**

16. **How old were you when you first started smoking regularly?** _____ **years old**

17. **Do you smoke mainly to cope or because you enjoy it?** (***circle one***)

1 **Mainly to cope** 2 **Mainly because I enjoy it** 3 **About the same**

18. **Does your spouse or partner smoke?** 1 **Yes** 2 **No** 3 **No spouse/partner** (***circle one***)

19. **How many times have you tried to stop smoking in the last 5 years?** **** **(*circle one*)**

1 **Not at all** 2 **Once** 3 **2 or 3 times** 4 **4 or 5 times** 5 **More than 5 times**

20. **What is the longest time you've succeeded in giving up smoking in the last 5 years?** **** **(*circle one*)**

1 **Few hours** 2 **1 day** 3 **2 -3 days** 4 **4 -7 days** 5 **1-3 weeks** 6 **1-3 months** 7 **More than 3 months** 8 **Not tried**

21. **How long ago was your last serious attempt to stop?** **(*circle one*)**

1 **1 - 3 weeks** 2 **1 - 6 months** 3 **More than 6 months** 4 **More than a year** 5 **Never tried before**

22. **What was the ONE MAIN THING that led you back to smoking last time?** **(*circle JUST ONE reason below*)**

1 **Never stopped before** 2 **Got too miserable** 3 **Craved too much** 4 **Put on too much weight** 5 **Got too bad-tempered**

6 **Got too stressed** 7 **Thought I could smoke and stop easily** 8 **Cannabis smoking** 9 **Getting drunk** 10 **Something else**

23. **If you have tried to stop smoking before, which of these was more difficult to cope with?** **(*circle one*)**

1 **That something was constantly missing and that I could not function normally without smoking**

2 **That I could not smoke at those special moments when smoking was really enjoyable and made me feel good**

3 **Both were equally difficult**

24. **If you try stopping smoking now with clinic help, how confident are you of succeeding?** **(*circle one number below*)**

Not at all confident **1 2 3 4 5 6 7 8 9 10** *Totally confident*

25. **How determined are you to stop for good in the next few weeks?** **(*circle one*)**

1 **Not sure** 2 **Fairly determined** 3 **Very determined** 4 **Totally determined**

26. **How recently has your GP advised you to stop?** 1 **In the last year** 2 **More than a year ago** 3 **Never** **(*circle one*)**

27. **What is your ONE MAIN REASON for wanting to stop now?** **(*circle JUST the most important ONE*)**

1 **To save money** 2 **To stop being addicted** 3 **To protect my health** 4 **To please others** 5 **It's anti-social** 6 **Another reason**

28. **Which of these medicines have you tried before to help you stop?** **(*circle ALL THE ONES you have ever tried*)**

(a) **None** 0 (b) **Nicotine Gum** 1 (c) **Nicotine Inhalator** 2 (d) **Nicotine Patch** 3 (e) **Nicotine Microtab** 4

(f) **Zyban** 5 (g) **Nicotine Lozenge** 6 (h) **Nicotine Nasal Spray** 7 (i) **Champix (Varenicline)** 8 (j) (j) **Nicotine Minis** 9

29. **Have you ever suffered any unpleasant reactions to any of the above medications?** (a) 1 **Yes** 2 **No**

If yes,

(b) **Which medication?** _____

(c) **What reaction?** _____

30. **Which of these methods have you tried before to help you stop? (*circle all the ones you have tried*)**

(a) **None** 0 (b) **Hypnosis** 1 (c) **Help-lines** 2 (d) **Books/videos** 3 (e) **Counselling** 4 (f) **Herbal cigarettes** 5

(g) **Acupuncture** 6 (h) **Alan Carr** 7 (i) **NicoBloc** 8 (j) **Nicobrevin** 9 (k) **Stoppers** 10 (x) **Other** 11 _____

31. **How did you hear about this smokers' clinic? (*circle one*)**

1 **Told about it by a GP** 2 **Hospital doctor** 3 **Nurse** 4 **Friend or family member** 5 **Telephone Help-line** 6 **Advert** 7

Newspaper/magazine 8 **A leaflet or poster (** 8a **where? _____)** 9 **Street recruitment** 10 **Another way**

32. **Have you been to this Smokers' Clinic before?** (a) 1 **Yes** 2 **No** (b) **If Yes, which year was it?** _____

Questions about your health

What is your weight _____kg What is your height _____cm

33. **How many times have you been to your GP about your health in the last year?**

1 **Not at all** 2 **1 or 2 times** 3 **3 or 4 times** 4 **5 to 10 times** 5 **More than 10 times** **(*circle one*)**

34. **Do you regularly use cannabis?** 1 **No** 2 **Yes, with tobacco** 3 **Yes, but not with tobacco** **(*circle one*)**

35. **How many units of alcohol do you drink during a typical WEEK? _____ units** *

(one unit = glass of wine / half pint of beer / single spirit)

36. **If you are female, are you?** 1 **Pregnant** 2 **Trying to conceive** 3 **Breast Feeding** 4 **None of these** *

Please turn over and complete the last page

If join the clinic programme, you may be prescribed a medicine to help. Some medicines can be harmful for some people, so we ask everyone to complete the medical checklist below. If you don't understand some of the questions, a therapist at the clinic will help you.

Have you EVER suffered from these illnesses?			**&**	**Do you take any medicines for these illnesses?**		
(*circle one*)				**(*circle one*) Name of any medicine you are taking**		
37. **Heart disease or condition?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
38. **Cancer?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
39. **Bronchitis?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
40. **High blood pressure?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
41. **Emphysema or lung disease**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
42. **Asthma?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
43. **Alcohol problems?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
44. **Drug problems?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
45. **Depression?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
46. **Any form of psychosis?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
47. **Skin allergies or eczema?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
48. **Nasal problems or nose bleeds?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
49. **Bi-polar (high-low) depression?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	*
50. **A stroke?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	*
51. **An eating disorder?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	*
52. **Liver or kidney disease?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	*
53. **A brain tumour?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	*
54. **A head injury?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	*
55. **Fits or seizures or epilepsy?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	*
56. **Diabetes?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	*

Other CURRENT illness not listed above :	**Name of other medicines / tablets / injections not listed above:**
57.	
58.	
59.	

Please check that you have included ALL the medicines you are currently taking somewhere above

60. **To my knowledge the information I have given above is correct. Signed:**_____

Thank you very much. Please remember to bring this form with you to the clinic

Appendix 7 – Consent form

Effects of a combination of varenicline and transdermal nicotine patch on post-quitting urges to smoke - Informed Consent Form

Investigator: Dr Al-Rehan Abdul Aziz Dhanji

Participant Name: Participant Number:

	Please initial each line
I confirm that I have read (or someone else has read to me) and I understand the Participant Information Sheet (Version 1.1) dated 14 Dec 2010 for the above study.	
I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand that my participation is voluntary (my choice) and that I am free to withdraw at any time without giving reason, without my medical care or legal rights being affected.	
I understand that all information collected will be in accordance to the Data Protection Act of 1998.	
I agree to my GP being informed of my participation in the study	
I agree to take part in the above study	

I understand that the research data collected during the study may be looked at by other individuals from the research team, sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.

_____	_____	_____
Participant Name (please print)	Signature of Participant	Date
_____	_____	_____
Name of person taking consent	Signature	Date

Appendix 8 – GP letter

[Insert Date]

[Insert GP Name and Address]

Dear Dr [GP Name],

Re: Patient participation in a smoking cessation study "Effects of a combination of varenicline and transdermal nicotine patch on post-quitting urges to smoke"

This is to inform you that your patient

[insert patient details]

has volunteered to take part in the above-mentioned study. We have included a brief summary of the study on the reverse of this letter.

If you have any questions or concerns regarding your patient taking part in this study please do not hesitate to contact me.

Kind regards

Yours sincerely,

Miss Katie Myers

Research Health Psychologist

Study Summary

Varenicline and nicotine replacement therapy (NRT) are both effective smoking cessation treatment. Anecdotally smokers who are finding their quit attempt difficult have reported benefit from adding NRT to varenicline. Using varenicline in combination with NRT may reduce craving and increase quitting.

This study will recruit 120 smokers and randomly allocate them to take varenicline + 15mg/16hr patch or varenicline + 15mg/16hr placebo patch. All participants will receive standard NHS Stop Smoking Service support. Urges to smoke, and other withdrawal symptoms, experienced during the study period will be compared between groups to see if this combination therapy may be useful.

Appendix 9 – Clinical record form (CRF)

PARTICIPANT Treatment Number:			
PARTICIPANT INITIALS:			

CLINICAL RECORD FORM

CONVICT STUDY

STUDY STAFF USE ONLY:

Session 1 (Screening session)

Date:			/			/	**2**	**0**	**1**	
Group Clinic/Number										

Inclusion/Exclusion Criteria

Excluded if answers YES to any of the below questions:

	No	**Yes**
Aged < 18	☐	☐
Pregnant or breastfeeding	☐	☐
End-stage renal disease	☐	☐
Current psychiatric illness	☐	☐
Previous allergic reaction to varenicline or patch	☐	☐
Females only:		
Not using contraception/planning pregnancy	☐	☐

Eligible to take part **Yes** ☐ **No** ☐

Documents completed (please tick when completed)

Consent form ☐

Assigned to group clinic (please add detail above) ☐

Study staff initials | | |

Please help us monitor your progress by completing this page

About how many cigarettes did you smoke <u>per day</u> in the last week? _____ (write one number)

Please show for each of the items how you have been feeling over the <u>past week</u>
(circle the ONE which best applies to you on each line)

Depressed	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Irritable	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Restless	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Hungry	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Poor concentration	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Slept worse than usual	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*

Carbon monoxide reading ☐☐ **ppm**

Weight _____ kg Scale ☐ Number

Session 2 (Preparation session)

Please help us monitor your progress by completing this page

Date: _____

About how many cigarettes did you smoke <u>per day</u> in the last week? _____ (write one number)

Please show for each of the items how you have been feeling over the <u>past week</u>
(circle the ONE which best applies to you on each line)

Depressed	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Irritable	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Restless	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Hungry	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Poor concentration	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Slept worse than usual	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*

Carbon monoxide reading | | | **ppm**

STUDY STAFF USE ONLY:

Champix starter pack dispensed ☐

Session 3 (Target Quit Date - TQD)

Please help us monitor your progress by completing this page

Date: _____

About how many cigarettes did you smoke <u>per day</u> in the last week? _____ (write one number)

Please show for each of the items how you have been feeling over the <u>past week</u>
(circle the ONE which best applies to you on each line)

Depressed	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Irritable	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Restless	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Hungry	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Poor concentration	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Slept worse than usual	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Nausea	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*

Have you found your urges to smoke stronger or weaker than usual in the last week? (circle one below)

Much stronger	*Slightly stronger*	*Same as before*	*Slightly weaker*	*Much weaker*

Have you found cigarettes more or less enjoyable than usual in the last week? (circle one below)

Much more enjoyable	*Slightly more enjoyable*	*Same as before*	*Slightly less enjoyable*	*Much less enjoyable*

On how many days did you use your tablets over the past week? _____

If you didn't take your tablets what was the one main reason for not taking it?

Forgot	*Too unpleasant*	*Didn't need it*	*It wasn't helping*	*Other (please specify)* _____

Have you experienced any unpleasant effects from the tablets in the last week?

☐ **No**
☐ **Yes - please list these on the ADVERSE EVENTS PAGE**

STUDY STAFF USE ONLY:

Carbon monoxide reading ☐☐ **ppm**

Randomisation code ☐☐☐☐

Patches dispensed ☐

GP letter sent and copy in file ☐

Study staff initials ☐☐

STUDY STAFF USE ONLY:

Phone call 1 (24 hour phone call)

Date: _____

Have you smoked any cigarettes in the last 24 hours? YES NO
(circle one)

If YES, how many cigarettes did you smoke?

Just a few puffs *Between 1 and 5 cigarettes* *More than 5 cigarettes*

Please show for each of the items how you have been feeling over the <u>past 24 hours</u>

(circle the ONE which best applies to you on each line)

Depressed	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Irritable	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Restless	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Hungry	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Poor concentration	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Slept worse than usual	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Nausea	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*

How much of the time have you felt the urge to smoke in the past 24 hours?
(circle one below)

Not at all	*A little of the time*	*Some of the time*	*A lot of the time*	*Almost all the time*	*All the time*

How strong have these urges been? (circle one below)

No urges	*Slight*	*Moderate*	*Strong*	*Very strong*	*Extremely*

Champix Use

Did you take your tablet this morning?

☐ **Yes**
☐ **No**

If you didn't take your tablet what was the one main reason for not taking it?

Forgot	*Too unpleasant*	*Didn't need it*	*It wasn't helping*	*Other (please specify)* _____

Nicotine Patch Use

Did you put on the patch this morning?

☐ **Yes**
☐ **No**

If you didn't use the patch what was the one main reason for this?

Forgot	*Too unpleasant*	*Didn't need it*	*It wasn't helping*	*Other (please specify)* _____

Have you experienced any unpleasant effects from the tablets or patches in the last 24 hours?

☐ **No**
☐ **Yes - please ask participants for details and list these on the ADVERSE EVENTS PAGE**

Session 4 5 6 7

Please help us monitor your progress by completing this page

Date: _____

Have you smoked any cigarettes since your last visit? YES NO
(circle one)

If YES, how many cigarettes did you smoke?

Just a few puffs *Between 1 and 5 cigarettes* *More than 5 cigarettes*

Please show for each of the items how you have been feeling over the <u>past week</u>

(circle the ONE which best applies to you on each line)

Depressed	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Irritable	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Restless	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Hungry	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Poor concentration	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Slept worse than usual	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Nausea	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*

How much of the time have you felt the urge to smoke in the last week? (circle one below)

Not at all	*A little of the time*	*Some of the time*	*A lot of the time*	*Almost all the time*	*All the time*

How strong have these urges been? (circle one below)

No urges	*Slight*	*Moderate*	*Strong*	*Very strong*	*Extremely strong*

Champix Use

On how many days did you use the tablets over the past week? _____

How many tablets did you use, on average per day? (please circle) 1 2

If you didn't take your tablet every day what was the one main reason for not taking it?

Forgot	*Too unpleasant*	*Didn't need it*	*It wasn't helping*	*Other (please specify)* _____

Nictone Patch Use

On how many days did you use patches over the past week? _____

If you didn't use your patches every day what was the one main reason for not using them?

Forgot	*Too unpleasant*	*Didn't need it*	*It wasn't helping*	*Other (please specify)* _____

Have you experienced any unpleasant effects from the tablets or patches since your last visit?

☐ **No**
☐ **Yes - please list these on the ADVERSE EVENTS PAGE**

STUDY STAFF USE ONLY:

Carbon monoxide reading ☐☐ **ppm**

Champix dispensed ☐

Session 8 (12 week follow up)

Please help us monitor your progress by completing this form

Date: _____

Have you smoked any cigarettes since your last visit? YES NO
(circle one)

If YES, how many cigarettes did you smoke?

Just a few puffs *Between 1 and 5 cigarettes* *More than 5 cigarettes*

Please show for each of the items how you have been feeling over the <u>past week</u>

(circle the ONE which best applies to you on each line)

Depressed	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Irritable	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Restless	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Hungry	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Poor concentration	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Slept worse than usual	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*
Nausea	*Not at all*	*Slightly*	*Somewhat*	*Very*	*Extremely*

How much of the time have you felt the urge to smoke in the last week? (circle one below)

Not at all	*A little of the time*	*Some of the time*	*A lot of the time*	*Almost all the time*	*All the time*

How strong have these urges been? (circle one below)

No urges	*Slight*	*Moderate*	*Strong*	*Very strong*	*Extremely strong*

Champix Use

On how many days did you use the tablets over the past week? _____

How many tablets did you use, on average per day? (please circle) 1 2

If you didn't take your the tablets every day what was the one main reason for not taking them?

Forgot	*Too unpleasant*	*Didn't need it*	*It wasn't helping*	*Other (please specify)* _____

Nictone Patch Use

On how many days did you use patches over the past week_____

If you didn't use your patches every day what was the one main reason for not taking it?

Forgot	*Too unpleasant*	*Didn't need it*	*It wasn't helping*	*Other (please specify)* _____

Have you experienced any unpleasant effects from the tablets or patches since your last visit?

☐ **No**
☐ **Yes - please list these on the ADVERSE EVENTS PAGE**

STUDY STAFF USE ONLY:

Carbon monoxide reading | | | **ppm**

Date of last Champix dose: _____

Adverse Events Page

List each effect below	**Date side effect started**	**Date side effect finished** ***(leave blank if still ongoing)***	**Study staff use only**
			Severity: ☐ Mild ☐ Moderate ☐ Severe **Related to study medication?** ☐ Yes ☐ No ☐ Unknown **If yes,** which IMP? **Patch** ☐ **Champix** ☐ **Serious?** ☐ Yes ☐ No **Action taken:** ☐ None ☐ Dose reduction☐ Stopped medication ☐ Withdrawn from study
			Severity: ☐ Mild ☐ Moderate ☐ Severe **Related to study medication?** ☐ Yes ☐ No ☐ Unknown **If yes,** which IMP? **Patch** ☐ **Champix** ☐ **Serious?** ☐ Yes ☐ No **Action taken:** ☐ None ☐ Dose reduction☐ Stopped medication ☐ Withdrawn from study

Final /Early termination

Subject Summary

Subject completed study YES ☐ NO ☐

Subject withdrawn before randomisation YES ☐ NO ☐

Subject was withdrawn during active treatment period YES ☐ NO ☐

Date subject withdrawn (dd-mm-yyyy) _____

Date of last dose (dd-mm-yyyy) _____

Reason for withdrawal

Adverse event YES ☐ NO ☐

Subject died YES ☐ NO ☐

Protocol violation YES ☐ NO ☐

Lost to follow-up YES ☐ NO ☐

Did not meet entrance criteria YES ☐ NO ☐

Subject no longer willing to participate YES ☐ NO ☐

Withdraw due to pregnancy YES ☐ NO ☐

Study terminated by sponsor YES ☐ NO ☐

Other YES ☐ NO ☐

Specify _____

Investigator's declaration

_____

I have reviewed this subject's data and confirm that, to the best of my knowledge, it accurately reflects the study information obtained from the subject.

Investigator Signature: _____

Date (dd-mm-yyyy) _____

Appendix 10 – Protocol for CONVICT study

Barts and The London NHS Trust

Barts and The London School of Medicine and Dentistry

It is a requirement of Good Clinical Practice (GCP) and the Research Governance Framework for Health & Social Care 2005, that all research projects have a scientifically sound and ethically valid protocol.

The protocol is the starting point of any high quality research and all research studies must be conducted according to the protocol. A protocol provides written evidence for the necessity and feasibility of a study, as well as giving a detailed plan of investigation.

This document is to be submitted for approval to a Research Ethics Committee and the Competent Authority (MHRA). This allows the regulatory, ethical and peer review processes to validate the scientific and ethical considerations of the study. The guidance detailed below is for Clinical Trials of Investigational Medicinal Products (CTIMPs).

Red border or text – Mandatory text – not be changed or removed

Blue border or text – further details to be inserted in line with the comments attached

Yellow border or text – if applicable to this study, further details to be inserted

Purple border or text – further information to be inserted by the statistician

The front page of the Protocol requires the full study title along with the EudraCT number for that protocol.

The protocol must be versioned and dated with the date of finalisation of the version.

(If there are any subsequent changes made to the protocol, both the version number and finalisation date should be updated accordingly.)

TITLE OF THE PROTOCOL:

Effects of a combination of varenicline and transdermal nicotine patch on post-quitting urges to smoke

Short title/Acronym: Combination of NRT and varenicline to increase cessation of tobacco (CONVICT Study)

Sponsor: Queen Mary University of London

Representative of the Sponsor:

[redacted]

REC reference: 10/H0709/85

EudraCT reference: 2010-022334-92

Clinical Trial Registration No: NCT01184664

Version control

Version	Date	Comments
Version 1.0	**25 May 2010**	
Version 1.1	**14 Dec 2010**	**Updated and approved by Ethics Committee**

STUDY SUMMARY/SYNOPSIS

TITLE	Effects of a combination of varenicline and transdermal nicotine patch on post-quitting urges to smoke
SHORT TITLE	Combination of NRT and varenicline to increase cessation of tobacco (CONVICT study)
Protocol Version Number and Date	Version 1.1 (14 Dec 2010)
Methodology	Randomised double blind placebo controlled trial
Study Duration	1-year
Study Centre	Single centre: Tobacco Dependence Research and Treatment Unit
Objectives	***Primary objective:*** To determine if combining NRT and varenicline provides better withdrawal and craving relief in the first week of abstinence than varenicline alone. ***Secondary objective:*** To determine the effect of combination NRT and varenicline use on ratings of urges in the first 24 hours of abstinence, short-term abstinence rates and withdrawal symptoms during the first 4-weeks of abstinence; client ratings of treatments; and adverse effects of combined NRT and varenicline use.
Phase of the Trial	Phase IV
Number of Subjects/Patients	120 smokers who want to quit
Main Inclusion Criteria	Smokers seeking treatment, aged 18 and over, consenting to take part in the trial
Statistical Methodology and Analysis	Differences between the varenicline with NRT and varenicline with placebo arms will be assessed using analysis of variance for continuously distributed endpoints and using chi-square tests for categorical endpoints. The relationship between pre-quit variables and post-quit endpoints will be assessed using regression modelling. The primary analysis will include only those who attended the first weekly treatment session and provided an MPPS score. Randomised patients lost to follow-up will be classified as non-abstainers in all analyses.

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EudraVIGILANCE	European Union Drug Regulating Authorities Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISRCTN	International Standard Randomised Controlled Trial Number
JRO	Joint Research and Development Office
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator

QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

Introduction

1.1 Background

Nicotine replacement therapy (NRT) is the most widely used medicine for smoking cessation. Almost 70% of NHS-SSS patients used NRT last year in 2009 (The Health and Social Care Information Centre, 2009). There are extensive data showing the efficacy of NRT (Stead et al., 2008a) however despite its good track record people who use NRT still have a less than 20% chance of quitting for a year or more.

Varenicline is a partial nicotinic agonist which acts on alpha4 beta2 nicotinic receptors. It is presumed to alleviate withdrawal discomort, but also to diminish rewarding effects of cigarettes. In studies evaluating its efficacy, patients who lapsed and smoked after the target quit date were asked to rate their experience. Compared to patients on placebo, bupropion and nicotine patch, those on varenicline derived less satisfaction from their cigarettes (West et al., 2008, Jorenby et al., 2006, Gonzales et al., 2006, Aubin et al., 2008).

Combining varenicline and NRT may in theory improve withdrawal relief; help to extinguish smoking rewards and lower the risk of lapses translating into relapse, and/or NRT may reduce some withdrawal symptoms which are less sensitive to varenicline and vice versa. There are smokers who report no reaction to one of the treatments who may be sensitive to the other and the combination may be of particular benefit to this group.

Such hypotheses have not been experimentally evaluated. One cohort report from an in-patient smoking cessation facility found no difference between NRT plus varenicline combination and NRT plus bupropion (Ebbert et al., 2009). As there was no 'NRT only' or 'varenicline only' group, the results are difficult to interpret, but the report reinforces the need to conduct a randomised 'proof-of-concept' study before launching into a large outcome trial.

Regarding the safety of combination use of NRT and varenicline a single pre-marketing study showed that smokers using varenicline and transdermal patch for 12 days reported a higher incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue than smokers who used NRT alone (Pfizer Limited, 2009). However these symptoms may have been due to varenicline use, as opposed to combined use of varenincline and NRT. Post-marketing data suggests that combined use of varenicline and NRT is well tolerated (Ebbert et al., 2009).

This is a proposal to examine whether combining NRT and varenicline provides better withdrawal and craving relief than varenicline alone, in a sample of 120 smokers who want to quit, short-term post-quitting urges to smoke and withdrawal severity.

1.2 Investigational Medicinal Product - VARENICLINE

Sections 1.2 – 1.5 are taken from the Summary of Product Characteristics for varenicline.

Varenicline binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist - a compound that has both agonist activity, with lower intrinsic efficacy than nicotine, and antagonist activities in the presence of nicotine.

1.2.1 Preclinical Data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, fertility and embryo-foetal development. In male rats dosed for 2 years with varenicline, there was a dose-related increase in the incidence of hibernoma (tumour of the brown fat). In the offspring of pregnant rats treated with varenicline there were decreases in fertility and increases in the auditory startle response. These effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Nonclinical data indicate varenicline has reinforcing properties albeit with lower potency than nicotine. In clinical studies in humans, varenicline showed low abuse potential.

1.2.2 Clinical Data

The efficacy of CHAMPIX in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 nicotinic receptor where its binding produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity).

1.2.3 Rationale and Risks/Benefits

Smoking cessation with or without treatment is associated with various symptoms. For example, dysphoric or depressed mood; insomnia, irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain have been reported in patients attempting to stop smoking. No attempt has been made in either the design or the analysis of the CHAMPIX studies to distinguish between adverse events associated with study drug treatment or those possibly associated with nicotine withdrawal.

Clinical trials included approximately 4,000 patients treated with CHAMPIX for up to 1 year (average exposure 84 days). In general, when adverse reactions occurred, onset was in the first week of therapy; severity was generally mild to moderate and there were no differences by age, race or gender with regard to the incidence of adverse reactions.

In patients treated with the recommended dose of 1mg BID following an initial titration period the adverse event most commonly reported was nausea (28.6%). In the majority of cases nausea occurred early in the treatment period, was mild to moderate in severity and seldom resulted in discontinuation.

The treatment discontinuation rate due to adverse events was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse events in varenicline treated patients were as follows: nausea (2.7% vs. 0.6% for placebo), headache (0.6% vs. 1.0% for placebo), insomnia (1.3% vs. 1.2% for placebo), and abnormal dreams (0.2% vs. 0.2% for placebo).

1.3 Investigational Medicinal Product – NICOTINE TRANSDERMAL PATCH

Sections 1.2 – 1.5 are taken from the Summary of Product Characteristics for Nicorette® 15mg transdermal patch

Nicotine has no therapeutic uses except as replacement therapy for the relief of abstinence symptoms in nicotine-dependent smokers. Owing to its many actions, the overall effects of nicotine are complex. A wide variety of stimulant and depressant effects are observed that involve the central and peripheral nervous, cardiovascular, endocrine, gastro-intestinal and skeletal motor systems. Nicotine acts on specific binding sites or receptors throughout the nervous system.

1.3.1 Preclinical Data

Preclinical data indicate that nicotine is neither mutagenic nor genotoxic.

1.3.2 Clinical Data

Nicorette Patch is indicated for the relief of nicotine withdrawal symptoms as an aid to smoking cessation in adults and children over 12 years of age. It is also indicated in pregnant and lactating women.

No clinically relevant interactions between nicotine replacement therapy and other drugs has definitely been established. However nicotine may possibly enhance the haemodynamic effects of adenosine i.e. increase in blood pressure and heart rate and also increase pain response (angina-pectoris type chest pain) provoked by adenosine administration.

1.3.3 Rationale and Risks/Benefits

There are no risks in using nicotine replacement therapy in people who smoke as it provide only nicotine that smokers would have other received from tobacco. Nicorette Patch may cause adverse reactions similar to those associated with nicotine given by other means, including smoking, and these are mainly dose-dependent. At recommended doses Nicorette Patch has not been found to cause any serious adverse effects. Excessive use of Nicorette Patch by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches. About 20% of Nicorette patch users experience mild local skin reactions, during the first weeks of treatment. In some patients the skin reactions may become more severe eg skin blistering or a burning sensation or may be more generalized.

2. Trial Objectives and Design

2.1 Trial Objectives

Primary Objective

The principal question this project plans to answer is does using a combination of varenicline and NRT reduce post-quitting urges to smoke more than varenicline alone.

Secondary Objectives

In addition to change in urges to smoke this study will determine if combined use of varenicline and NRT:

Affects severity of withdrawal symptoms over 4-weeks after quitting

Affects 4-week and 12-week abstinence rates

Is associated with an increase in adverse effects

Primary Endpoint

Ratings of urges to smoke one week after the target quit date assessed by Mood and Physical Symptoms Scale [MPSS] (West and Hajek, 2004).

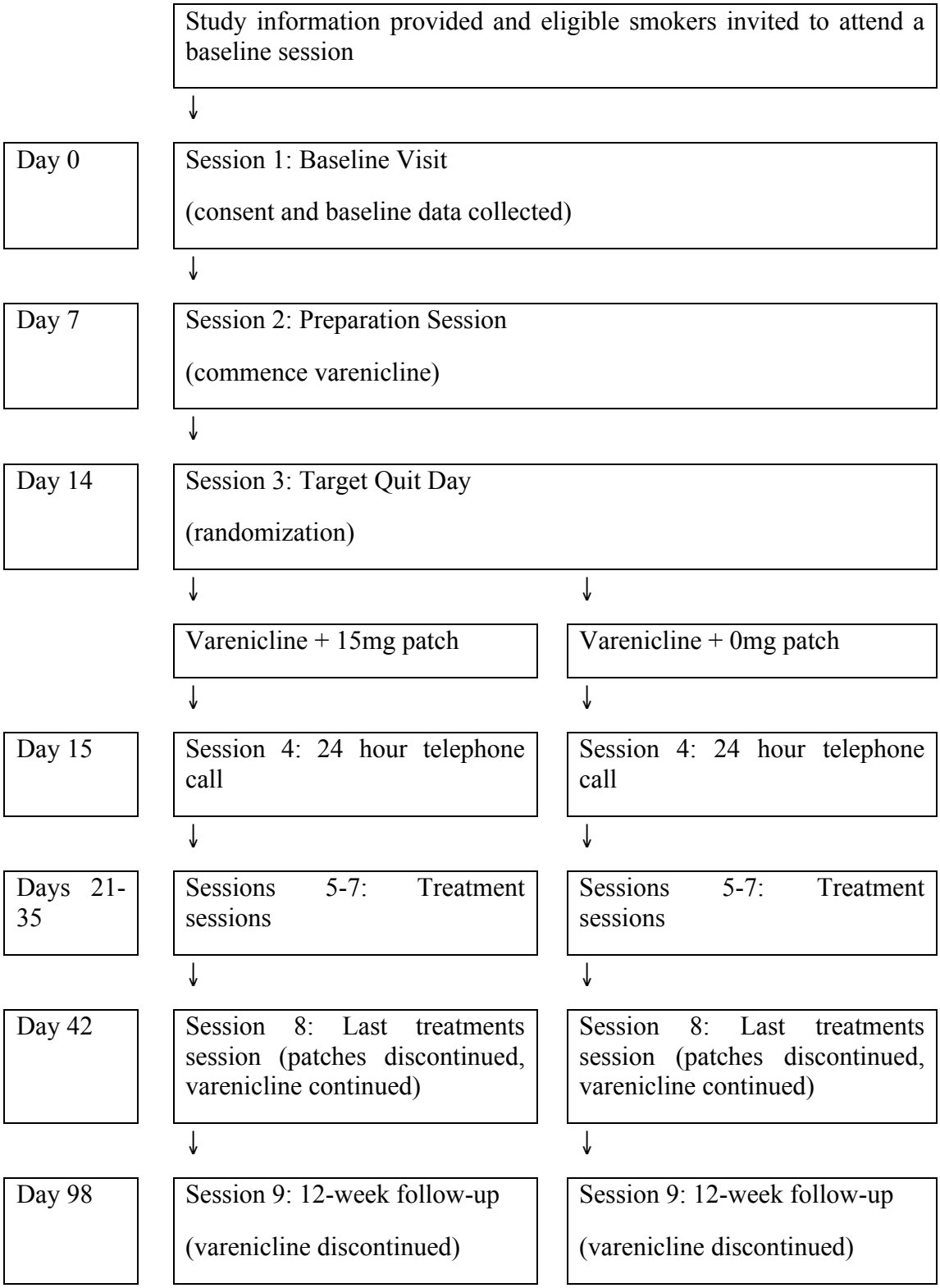
Secondary Endpoints

Ratings of urges to smoke 24 hours after target quit date, change in MPSS scores of urges to smoke and tobacco withdrawal symptoms throughout the first four weeks of abstinence; client ratings of treatments; adverse events profile; abstinence rates at 4-weeks and 3-months.

2.2 Trial Design

This is a randomised double blind placebo-controlled trial. Participants will be randomised to using varenicline plus nicotine 15mg/16hr transdermal patch or varenicline plus placebo 15mg/16hr patch. Varenicline will be used in the standard way (commenced 1-week prior to quitting and continued for 12 weeks). The patches will be started on the quit day and be used for 4-weeks.

2.3 Study Scheme Diagram



3. Subject Selection

3.1 Number of Subjects and Subject Selection

A total of 120 smokers who want to quit will be recuited for this study

Participants would be recruited by advertising in London Newspapers including the Evening Standard, Metro, and local papers. Callers would be mailed study information and baseline questionnaire and invited to attend a baseline session several days later.

Prior to randomisation all particpants will provide written informed consent.

The expected duration of participation in this study is 14 weeks (2 weeks prior to and 12 weeks after the target quit date).

3.2 Inclusion Criteria

Smokers seeking treatment, aged 18 and over, consenting to take part in the trial.

3.3 Exclusion Criteria

Current psychiatric illness, pregnant or breastfeeding, end-stage renal disease, previous allergic reaction to varenicline or patch, females planning to conceive during the study period, unable to fill in the questionnaire in English, currently involved or intends to be involved in another research project.

3.4 Criteria for Premature Withdrawal

(1) The participant withdraws his/her consent to participate

(2) Withdrawal events

These are events leading to withdrawal from the trial although participants will continue to be followed with the same schedule of clinic visits. The following events are grounds for withdrawal from the study:

Acute myocardial infarction, angina pectoris, or other serious medical condition

A major psychiatric disorder which impedes compliance with trial protocol

Pregnancy

A serious adverse drug event (defined as any untoward medical occurrence that at any dose results in death, in significant or permanent disability or incapacity, is life-threatening, requires hospitalisation or prolongs hospitalisation). In the event of a serious adverse drug event the investigator will notify the appropriate ethical committee and sponsor within 48 hours of becoming aware of the event

4. Investigational Medicinal Product

4.1 List and definition of each IMP, including placebos

Test condition

Standard dose of varenicline (Champix™) 1 mg bid combined with Nicorette® 15mg patch

Reference condition

Standard dose of varenicline (Champix™) 1 mg bid combined with Nicorette® 0mg (placebo) patch

4.2 Formulation of IMP

Varenicline (Champix™) Film-coated tablet

0.5 mg film-coated tablets (commercial supply): White, capsular-shaped, biconvex tablets debossed with "Pfizer" on one side and "CHX 0.5" on the other side. Each film-coated tablet contains 0.5 mg of varenicline (as tartrate).

1 mg film-coated tablets (commercial supply): Light blue, capsular-shaped, biconvex tablets debossed with "Pfizer" on one side and "CHX 1.0" on the other side. Each film-coated tablet contains 1 mg of varenicline (as tartrate).

Excipients: Core Tablet, Cellulose, Microcrystalline, Calcium Hydrogen Phosphate Anhydrous, Croscarmellose Sodium, Silica, Colloidal Anhydrous, Magnesium Stearate, Film Coating, Hypromellose, Titanium Dioxide (E171), Macrogols, Triacetin

Nicorette® 15mg/16 hour transdermal patch

Nicotine, 15mg released over 16 hours use. Each patch is 30 sq.cm, containing nicotine 0.83mg/sq.cm.

Excipients: Medium molecular weight polyisobutylene, Low molecular weight polyisobutylene, Polybutylene, Polyester non-woven backing film, Siliconised polyester release liner

Placebo 0mg/16 hour transdermal patch

The placebo patch is identical to the standard patch except that it contains no nicotine.

4.3 IMP Supply

Dispatch of study medications:

A commercial supply of varenicline, supplied by Pfizer, will come from the EU (residing in a warehouse in the UK).

Patches will be supplied by McNeil Products Limited within the EU.

Name and address of manufacturer of varenicline: Pfizer GmbH Werk Godecke, Mooswaldallee 1, Freiburg, D-79090, Germany

Manufacturer authorisation number: 25-5482/2-FR

Name and address of manufacturer of nicotine 15mg/16hr patches

McNeil Products Limited

Foundation Park

Roxborough Way

Maidenhead

Berkshire

SL6 3UG

UK

Manufacturer authorisation number: PL 15513/0177

Name and address company packaging study medication: Bilcare GCS (Europe) Ltd, Waller House, Elvicta Business Park, Crickhowell Powys, NP8 1DF

Manufacturer authorisation number: MA IMP 10284

4.4 Prescription of IMP

IMP will be supplied by study staff under the supervision of the study physician.

4.5 Preparation and Administration of IMP

The table below shows the study **treatment regimen**.

Day(s)	**7-13**	**14-42**	**43-98**
Session(s)	**2**	**3 - 8**	**9**
Varenicline dose	Days 1-3: 0.5mg o.d. Days 4-7: 0.5mg b.d.	1mg b.d	1mg b.d
Patch dose	Nil	15mg/16hr or 0mg/16hr o.d.	Nil

4.6 Packaging and Labelling of IMPs

A 4-week supply of patches (active or placebo) will be packaged into a single box. Computer generated randomisation codes will be affixed to each box. The medication boxes will be sorted in numerical order and will be dispensed sequentially at the study site.

4.7 Accountability/Receipt /Storage and Handling of IMP

All packaged medications will be shipped to the Pharmacy (The Royal London) where they will be securely stored until required for dispensing in the study. Medications will not be dispensed to participants by the pharmacy, as study visits will be after hours. Instead, the study manager will be responsible for collecting study medications from the pharmacy when required and transferred to storage on the study site (Tobacco Dependence Research and Treatment Unit) in a locked cabinet in a locked room. Room temperature will be monitored on a daily basis. Only the study manager will have access to study medicines.

4.8 Dispensing of IMP

All participants will receive a commercial starter pack of varenicline at session 2. They will receive a commercial continuation pack (56 1mg tablets) at session 4, and a further two continuation packs at session 8. Participants will be randomised to either active patch or placebo by randomisation codes that will be prepared by computer in advance. On arrival on session 3 participants will be sequentially allocated to a randomisation code. The study staff will retrieve the product corresponding to the relevant randomisation code.

IMP will be dispensed by the study manager at the clinic site under supervision of the study doctor. A dispensing log will be kept. Participants will be asked to return any unused medication each week. Quantities of returned medication will be counted to assess compliance with treatment.

4.9 IMP Stability

The IMPs are stable at room temperature.

4.10 Prior and Concomitant Therapies

Information on whether the participants are currently taking concomitant therapy will be gathered during the first session prior to randomisation. There are no known drug interactions with varenicline or nicotine replacement therapy.

4.11 Dose modification/reduction/ delay

Not applicable

4.12 Return/Recall or Destruction of IMP

Unused study medication will be returned to the Bilcare for destruction. Return of study drugs will be documented in the study files.

5. Study Procedures

5.1 Informed Consent Procedures

All participants for this study will be provided with a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the ethics committee. The formal consent of a participant, using the approved consent form, will be obtained before that participant is submitted to any study procedure. This consent form will be signed by the participant, and the investigator-designated research professional (in this case the study physician) obtaining the consent.

Before obtaining his/her consent, the investigator will inform each participant of the objectives, benefits, risks and requirements of the study, as well as the nature of the test medication. An information sheet drafted in simple language will be given to each participant. All participants will have at least 24 hours to consider if they wish to take part.

All participants will give their written informed consent before entering the study. The consent form will be dated and co-signed by the investigator-designated research professional and the patient. A copy of the consent form will be provided to the participant.

5.2 Screening Procedures

At the baseline session, study details will be discussed and informed consent collected. Participants will be screened for inclusion and exclusion criteria.

5.3 Randomisation Procedures

Participants will be randomised to either active patch or placebo patch by randomisation codes that will be prepared by computer in advance. On arrival on the quit day session (session 3) participants will be sequentially allocated to a randomisation code. The study staff will retrieve the product corresponding to the relevant randomisation code.

5.4 Schedule of Treatment for each visit

Session 1: Baseline Session

At baseline session study details would be discussed and informed consent collected. Participants would be screened for inclusion and exclusion criteria. They would have CO measured in expired breath (this will be measured at every session) and receive information on the preparation session to be held on the following week. All participants would be asked to smoke ad-lib until the target quit day (TQD) when they will be asked to stop smoking.

Session 2: Preparation session

This session would be one week prior to participant's TQD. They would receive advice and support regarding their quit attempt and start their preparation. All participants would be provided with a standard varenicline starter pack, which they will start on the next day.

Session 3: Target Quit Date Session

Participants would be randomised to receive a four-week supply of active (15mg/16hr) or placebo patches on this day. They would be instructed to start using these at this session. Standard behavioural support will be provided.

Session 4: 24-hour telephone call

Participants will be called 24 hours after their TQD. Occurrence and severity of urges to smoke and tobacco withdrawal symptoms will be measured. Information on any adverse events will also be collected. Brief behavioural support will also be provided.

Sessions 5-8: Weekly treatment sessions

Participants will be provided with behavioural support and medication. Patches will be provided until session 8. An 8-week supply of varenicline will be provided at session 8. The occurrence and severity of tobacco withdrawal symptoms and adverse events will be measured at each session. Information on any adverse events will also be collected. Satisfaction with the treatment will also be assessed via self-completed questionnaire at session 8.

Most treatment sessions will take place between the hours of 5 and 7 pm during weekdays.

Session 9: 12-week follow-up

Participants will be asked to attend a 12-week follow up visit to measure abstinence. The occurrence and severity of tobacco withdrawal symptoms and adverse events will be measured

5.5 Schedule of Assessment

Table 2: Study sessions									
DAY	0	7	14	15	21	28	35	42	98
Session number	1	2	3	Phone call 1	5	6	7	8	9
Measures/ procedures	Base-line visit	Wk 1 visit	Wk 0 TQD	24h call	Wk 1 visit	Wk 2 visit	Wk 3 visit	Wk 4 visit	Wk 12 visit
Informed consent	X								
Baseline questionnaire	X								
FTND	X								
CO	X	X	X		X	X	X	X	X
MPSS	X	X	X	X	X	X	X	X	X
Medication dispensed		X	X		X			X	
Weight	X	X	X		X	X	X	X	X
Smoking status/rate	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X

5.6 Measures

All proposed questionnaire measures are contained in the Baseline Smokers Clinic Questionnaire and Clinical Record Forms. These include the following:

Baseline questionnaire: Demographic details, health status, and smoking history.

Fagerstrom Test of Nicotine Dependence (FTND): Measure of dependence (Heatherton et al., 1991).

End-expired carbon monoxide reading: Collected using a Bedfont CO monitor

Mood and Physical Symptoms Scale (MPSS): Measure of severity of tobacco withdrawal symptoms (West and Hajek, 2004).

Smoking rate: Estimate of the average number of cigarettes smoked per day since the last visit

Smoking status: Any cigarettes smoked since last visit

Adverse events: Participants will be asked about the occurrence of any adverse events (AE's) at each contact.

Weight: Participants will have their weight taken at each session

5.7 End of Study Definition

The last participant completes 3-month (post TQD) follow-up.

5.8 Procedures for unblinding

In the event of an SAE the principal investigator will agree to the unblinding. The Principal Investigator is responsible for following the unblinding procedures when unblinding subjects from a trial and/or during study closeout. In instances when the PI needs to remain blinded, another member of the research team will be responsible for following these procedures.

The study statistician will hold the randomisation codes. A second responsible person, who is not a member of the study team, but located at the study site will hold the randomisation codes in a sealed envelope.

In the event of unblinding the standard operating procedure for unblinding will be followed. The unblinding will be recorded as a protocol violation.

All SAEs reported to the MHRA by the R&D office will be unblinded reports.

5.9 Subject Withdrawal

(1) The participant withdraws his/her consent to participate

(2) Withdrawal events

These are events leading to withdrawal from the trial although participants will continue to be followed with the same schedule of clinic visits. The following events are grounds for withdrawal from the study:

Acute myocardial infarction, angina pectoris, or other serious medical condition

A major psychiatric disorder which impedes compliance with trial protocol

Pregnancy

A serious adverse drug event (defined as any untoward medical occurrence that at any dose results in death, in significant or permanent disability or incapacity, is life-threatening, requires hospitalisation or prolongs hospitalisation). In the event of a serious adverse drug event the investigator will notify the appropriate ethical committee and sponsor within 48 hours of becoming aware of the event

5.10 Data Collection and Follow up for Withdrawn Subjects

If a participant is withdrawn from the study or withdraws consent to participate in the study part way through, attempts will be made to obtain permission to record at least adverse events and other data up to the end of the last visit. This will be done via phone calls to the participant and contact with the participant's general practitioner.

6. Laboratories

No laboratory services will be used in this study.

7. Pharmacovigilance

7.1 General Definitions

7.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of an Investigational Medicinal Product (IMP), **whether or not considered related to the IMP**.

7.1.2 Adverse Reaction (AR)

An AR is any untoward and unintended response in a subject to an Investigational Medicinal Product (IMP), which is related to any dose administered to that subject. All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

7.1.3 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An SAE fulfils at least one of the following criteria:

Is fatal – results in death (NOTE: death is an outcome, not an event)

Is life-threatening

Requires inpatient hospitalisation or prolongation of existing hospitalisation

Results in persistent or significant disability/incapacity

Is a congenital anomaly/birth defect

Serious Adverse Reaction (SAR)

An SAR is an adverse reaction that is classed as serious and which is consistent with the information about the medicinal product as set out in the Summary of Product Characteristics (SmPC) or Investigator's Brochure (IB) for that product.

7.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The definition of a SUSAR is any serious adverse event related to an IMP that is both suspected to be related to the IMP and unexpected. In this case the event is not outlined in the Summary of Product Characteristics (SmPC) or Investigator's Brochure (IB) for that product.

7.2 Investigators Assessment

7.2.1 Seriousness

The Chief/Principal Investigator responsible for the care of the patient, or in his absence an authorised medic within the research team, is responsible for assessing whether the event is serious according to the definitions given in section 7.1.

7.2.2 Causality

The Investigator must assess the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

7.2.3 Expectedness

The investigator must assess the expectedness of all SARs according to the definition given. If the SAR is unexpected, then it is a SUSAR.

7.2.4 Severity

The Investigator must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life

Moderate: Discomfort enough to affect/reduce normal activity

Severe: Complete inability to perform daily activities and lead a normal life

7.3 Notification and reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the CRF.

7.4 Notification and Reporting of Serious Adverse Events/SUSAR

7.4.1 All Serious Adverse Event (SAEs) will be recorded in the subjects' notes, the CRF, the sponsor SAE form and reported to the Joint Research and Development Office (JRO)/ IMP provider (if applicable) within 24 hours of the CI or PI or co-investigators becoming aware of the event. Nominated co-investigators will be authorised to sign the SAE forms in the absence of the CI at the co-ordinating site or the PI at the participating sites. Please ensure that the sponsor has been informed of these nominated co-investigators.

7.4.2 Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur during the trial will be reported to the JRO/ main REC/IMP provider (if applicable) within 24 hours of the CI or co-investigator becoming aware of the event. SUSARs should be reported to the sponsor (JRO Office) within 24 hours as the sponsor has a legal obligation to report this to the MHRA within 7 days (for fatal or life-threatening SUSARs) or 15 days for all other SUSARs. In the case of multicentre studies, the PI or the co-investigators at the participating site must inform the CI within 24 hours of the event. The CI or co-investigators at the co-ordinating site must inform the sponsor (JRO) immediately to allow reporting to the MHRA within the allocated timelines. The CI will need to complete the CIOMS form in conjunction with the sponsor SAE form to be sent to the MHRA by the sponsor. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug (or therapy) that this serious adverse event has been reported.

The original and any subsequent follow up of Serious Adverse Event Forms and CIOMS forms (where applicable), together with the fax confirmation sheet must be kept with the TMF at the study site.

7.5 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30. The measures should be taken immediately. In this instance, the approval of the Licensing Authority Approval prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor, Main Research Ethics Committee (via telephone) and the MHRA (via telephone for discussion with the medical assessor at the clinical trials unit) of this event **immediately**.

The CI has an obligation to inform both the MHRA and Main Ethics Committee **in writing within 3 days**, in the form of a substantial amendment. The sponsor (JRO) must be sent a copy of the correspondence with regards to this matter.

7.6 Annual Safety Reporting

The Annual Safety Reports (ASR) will be sent by the CI to the sponsor, the MREC and MHRA (the date of the anniversary is the date on the "notice of acceptance letter" from the MHRA) using the ASR

form. The CI will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial.

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the MREC "favourable opinion" letter from the MREC) and to the sponsor.

7.7 Procedures for reporting blinded SUSARs

In the case of a blinded study, it is recommended the treatment code for the patient is broken in the reporting of a SUSAR. However, the blind should be maintained, where possible and appropriate, for staff that are involved in data analysis and interpretation. It is the allocated responsibility of the CI by the sponsor for pharmacoviligance management and reporting. In this instance, an allocated unblinded individual (s), with no involvement in data management of the study should be responsible for the unblinding event. The unblinding of single cases by the PI/CI in the course of a clinical trial should only be performed if necessary for the safety of the trial subject.

It is recommended that in the case of a blinded study, the case is assessed for seriousness, expectedness and causal relationship as if it was the tested IMP that caused the reaction. If the case appears to be a SUSAR then it should be unblinded and the following considered:

If the administered product is the tested IMP, the case would be reported as a SUSAR to the MHRA/ appropriate Main Research Ethics Committee/IMP provider (if applicable) within the timelines outlined in section 7.4.2.

If the administered product is a comparator with a marketing authorisation, the adverse reaction should be reassessed for expectedness according to the study protocol. If the adverse reaction is unexpected then the SUSAR should be reported; otherwise it is an expected serious adverse reaction which still requires reporting to the sponsor/IMP provider (if applicable) within 24 hours.

7.8 Overview of the Safety Reporting Process/Pharmacoviligance responsibilities

The CI/PI has the overall pharmacovigilance oversight responsibility. The CI/PI has a duty to ensure that pharmacovigilance monitoring and reporting is conducted in accordance with the sponsor's requirements.

Please outline the process/organisation within the study team to ensure that all SAE/SUSAR reporting is conducted in accordance with the sponsor's timelines. Display this information within an organogram to be located in the appendices in section 15 to ensure that there is a clear and distinct reporting process outlined with the study members detailed within this process.

7.9 Pregnancy

If a patient becomes pregnant whilst involved in a CTIMP, it is not considered to be an SAE or an AE. However, it is an event that requires monitoring and follow up. If a patient, or his partner, becomes pregnant whilst enrolled in a CTIMP in which the foetus has been exposed to an investigational medicinal product, immediate reporting to the sponsor is required (within one working day of the PI/CI

becoming aware of the event) using a JRO pregnancy template form. The CI/PI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines. Please state whether the patient can continue on the study or whether the patient has to be prematurely withdrawn from the study here.

The PI/CI also must follow up the pregnancy until delivery as well as monitoring the development of the newborn for the appropriate time (please indicate for this IMP) after birth. Any events that occur during this time that could be considered to be a SAE must be reported to the sponsor in line with section 7.4.1, utilising the sponsor SAE reporting form.

8. Statistical Considerations

8.1 Primary Endpoint Efficacy Analysis

The primary endpoint is MPSS ratings of urges to smoke during the first week of abstinence. The difference between groups will be assessed using analysis of variance.

8.2 Secondary Endpoint Efficacy Analysis

Differences in validated abstinence rates over 12 weeks of abstinence will be assessed using chi-square tests.

8.3 Safety Endpoints

Type and frequency of adverse events will be reported. Frequency of adverse events between groups will be assessed using chi-square tests.

8.4 Sample Size

MPSS is a rating scale sensitive to tobacco withdrawal and to both pharmacological (West et al., 1990) and behavioural (McRobbie and Hajek, 2007) treatment effects. Effective treatments typically generate a difference in ratings over the first week of abstinence of at least 0.7 compared to control procedures, e.g. 1.8 (SD=1) compared to 2.5 (SD=1). As in this case the advantage of the combination over the first week of abstinence may be subtle and even a difference of 0.6 would be worth detecting, 45 participants would be needed in each group ($p<0.05$, 2-tailed test, power=0.80). Patient attrition between the TQD and Week 1 session is usually between 10% and 20%. The study would aim to randomise 120 participants.

8.5 Statistical Analysis

Differences between the varenicline with NRT and varenicline with placebo arms will be assessed using analysis of variance for continuously distributed endpoints and using chi-square tests for categorical endpoints. The relationship between pre-quit variables and post-quit endpoints will be assessed using regression modelling.

The primary analysis will include only those who attended the first weekly treatment session and provided an MPPS score. Randomised patients lost to follow-up will be classified as non-abstainers in all analyses.

9. Data Handling & Record Keeping

9.1 Confidentiality

Participants will be asked to complete the standard clinic questionnaire and the additional questionnaires required for this study. We will not request any medical information about participants from their other doctors (hospital or general practitioner). All information will be kept confidential, just as is normal for smokers attending the Stop Smoking clinic. We will inform participants' GPs, with their consent, of their participation in the study. Copies of all documents sent regarding the current study will be kept in the study master file.

Only study staff will have access to study data. All records relating to the study will be kept strictly confidential.

9.2 Study Documents

A signed protocol and any subsequent amendments

Current Summary of Product Characteristics/ Investigator's Brochure

Sponsor Self-Monitoring template for the trial team to complete on a regular basis as detailed by the Monitoring section

Current/Superseded Patient Information Sheets (as applicable)

Current/Superseded Consent Forms (as applicable)

Indemnity documentation from sponsor

Conditions of Sponsorship from sponsor

Conditional/Final R&D Approval

Signed site agreement

Ethics/MHRA submissions/approvals/correspondence

CVs of CI and site staff

UK regulations (GCP) course certificate of each of trial team

Laboratory accreditation letter, certification and normal ranges for all laboratories to be utilised in the study

Sample IMP labels

IMP accountability logs

Delegation log

Staff training log

Site signature log

Patient identification log

Screening log

Enrolment log

Monitoring visit log

Protocol training log

Correspondence relating to the trial

Communication Plan between the CI/PI and members of the study team

SAE reporting plan for the study

9.3 Case Report Form

The CRF was developed by Profesor Peter Hajek, Katie Myers and Dr Hayden McRobbie.

The elements of the CRF include:

Registration form (Standard Smokers Clinic Questionnaire)

Eligibility/exclusion criteria checklist

Visit details

Drug/dose, any dose reductions/delays

AEs page

End of study form

9.4 Record Retention and Archiving

During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 20 years. For trials involving BLT Trust patients, undertaken by Trust staff, or sponsored by BLT or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre which is based at 9 Prescot Street. Site files from other sites must be archived at that external site and cannot be stored at the Modern Records Centre.

9.5 Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and 2008, Trust and Research Office policies and procedures and any subsequent amendments.

9.6 Clinical Governance Issues

9.6.1 Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the Committee must be obtained and subsequently submitted to the JRO to obtain Final R&D approval.

9.7 Quality Control and Quality Assurance

9.7.1 Summary Monitoring Plan

This study will be subject to the Quality Control (QC)/Quality Assurance (QA) system of the Joint BLT/QMUL R&D Office (JRO).

The monitoring process is based on the Principal Investigator (PI) ensuring that the Study Manager completes a "Monitoring report" and sends it to the JRO for review. In addition, a routine check of the content, accuracy, and the completeness of data supplied by the PI to the JRO will be performed. This report will be reviewed by the JRO. Some of the data provided in the report will be entered into the R&D database. Any corrective/preventive actions will be followed up by the R&D Department. A number of reports will be selected; a staff member of the JRO will visit the trial team and verify the accuracy of the information entered.

9.7.2 Audit and Inspection

Auditing: Definition "A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

A study may be identified for audit by any method listed below:

1. A project may be identified via the risk assessment process.

2. An individual investigator or department may request an audit.

3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.

4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.

5. Projects may be randomly selected for audit by an external organisation (e.g. MHRA).

Internal audits will be conducted by a sponsor's representative

9.8 Serious Breaches in GCP or the Trial Protocol

The sponsor of the Clinical Trial is responsible for notifying the licensing authority in writing of any serious breach of:

The conditions and principles of GCP in connection with that trial; or

The protocol relating to the trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a 'serious breach', is a breach which is likely to effect to a significant degree:

The safety or physical or mental integrity of the subjects of the trials; or

The scientific value of the trial.

The CI is responsible for reporting any serious breaches to the sponsor (JRO) **within 24 hours**. The sponsor will notify and report to the MHRA within 7 working days of becoming aware of the serious breach.

9.9 Non-Compliance

(A noted systematic lack of both the CI and the study staff adhering to SOPs/protocol/ICH-GCP and UK regulations, which leads to prolonged collection of deviations, breaches or suspected fraud.)

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependant on the severity. If the actions are not dealt with accordingly, the JRO will agree an appropriate action, including an on-site audit.

10. Trial Committees

There will not be any data monitoring/steering/safety committees set up for this study

11. Publication Policy

Study data will be collected and held by the study investigators. Data analyses will be undertaken independently of the study funders.

A paper will be written for publication in a peer reviewed journal.

Appendix 11 – Ethics approval

NHS
National Research Ethics Service

[redacted]

Telephone: [redacted]
Facsimile:

17 December 2010

[redacted]

Dear Mr Abdul Aziz Dhanji

Study Title:	**Effects of a combination of varenicline and transdermal nicotine patch on post-quitting urges to smoke**
REC reference number:	**10/H0709/85**
Protocol number:	**qmul250510**
EudraCT number:	**2010-022334-92**

Thank you for your letter of 14 December 2010 responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The favourable opinion applies to the following research site(s):

Research Site	Principal Investigator / Local Collaborator
Tobacco Dependence Research Unit, Whitechapel, London, UK.	Mr Al-Rehan Abdul Aziz Dhanji

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to

the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Protocol	1.1	14 December 2010
Response to Request for Further Information		
Letter of invitation to participant	1	25 May 2010
GP/Consultant Information Sheets	1	25 May 2008
REC application	1	01 November 2010
Participant Information Sheet	1.1	14 December 2010
Questionnaire: smokers clinic questionnaire		
Advertisement		
Evidence of insurance or indemnity		
Investigator CV		
Participant Consent Form	1	25 May 2010
Covering Letter		14 December 2010
Letter from Sponsor		22 October 2010
Telephone Screening questions	1	25 May 2010
Summary of product characteristics		
Clinical Record Form	1.1	14 December 2010

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email [redacted]

10/H0709/85	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

[redacted]

Dr Jan Downer
Chair

Email: [redacted]

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Miss Katherine Myers*

Appendix 12 – MHRA approval

Safeguarding public health

MHRA

[redacted]

07/01/2011

Dear Dr Alrehan Abdulaziz Dhanji

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	22310/0005/001-0001
Eudract Number:	2010-022334-92
Product:	Varenicline (CHAMPIX)
Protocol number:	qmul250510

NOTICE OF ACCEPTANCE OF AMENDED REQUEST

I am writing to inform you that the Licensing Authority accepts your amended request for a clinical trial authorisation (CTA), received on 06/01/2011.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed; changes made as part of your amended request may need to be notified to the Ethics Committee.

Yours sincerely,

Clinical Trials Unit
MHRA

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
T 0203 080 6000 www.mhra.gov.uk

Appendix 13 - R&D sponsorship

School of Medicine and Dentistry

NHS Trust

FINAL R&D APPROVAL

[redacted]

[redacted]

Dear Dr. Dhanji

Tel: [redacted]
Fax: [redacted]

2nd February 2011

Protocol: CONVICT: Effects of a Combination of Varenicline and Transdermal Nicotine patch on Post-Quitting urges to smoke

ReDA Ref: 7434 QM

CSP:

REC Ref: 10/H0709/85

I am pleased to inform you that the Joint R&D Office for Barts and The London NHS Trust and Queen Mary, University of London, has approved the above referenced study and in so doing has ensured that there is appropriate indemnity cover against any negligence that may occur during the course of your project. Approved study documents are as follows:

Type	Version	Date
REC Approval		17.12.10
Protocol	v.1.1	14.12.10
Telephone screening Questions	v.1	25.5.10
Letter of Invitation to Participant	v.1	25.5.10
Participant Information Sheet	v.1.1	14.12.10
GP / Consultant Information Sheet	v.1	25.5.08
Participant Consent Form	v.1	25.5.10

Please note that all research within the NHS is subject to the Research Governance Framework for Health and Social Care, 2005. If you are unfamiliar with the standards contained in this document, or the BLT and QMUL policies that reinforce them, you can obtain details from the Joint R&D Office or go to:
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962

You must stay in touch with the Joint R&D Office during the course of the research project, in particular:

- If there is a change of Principal Investigator
- When the project finishes
- If amendments are made, whether substantial or non-substantial

This is necessary to ensure that your R&D Approval and indemnity cover remain valid. Should any Serious Adverse Events (SAEs) or untoward events occur it is **essential** that you inform the Sponsor within 24 hours. If patients or staff are involved in an incident, you should also follow the Trust Adverse Incident reporting procedure or contact the Risk Management Unit on [redacted]

We wish you all the best with your research, and if you need any help or assistance during its course, please do not hesitate to contact the Office.

Yours sincerely

[redacted]

Gerry Leonard, Head of Research Resources

cc to: Sponsor Organisation

Appendix 14 – Local ethics approval

NHS
National Research Ethics Service
North London REC 3
[redacted]
Telephone: [redacted]
Facsimile:

28 January 2011

[redacted]

Dear Mr Abdul Aziz Dhanji

Study title:	**Effects of a combination of varenicline and transdermal nicotine patch on post-quitting urges to smoke**
REC reference number:	**10/H0709/85**
SSA reference number:	**10/H0703/101**
Protocol number:	**qmul250510**
EudraCT number:	**2010-022334-92**

The REC gave a favourable ethical opinion to this study on 17th December 2011.

Notification(s) have been received from local assessor(s), following site-specific assessment. On behalf of the Committee, I am pleased to confirm the extension of the favourable opinion to the new site(s) and investigator(s) listed below:

Research Site	Principal Investigator / Local Collaborator
Tobacco Dependence Research Unit, Whitechapel, London, UK.	Mr Al-Rehan Abdul Aziz Dhanji

The favourable opinion is subject to management permission or approval being obtained from the host organisation prior to the start of the study at the site concerned.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

10/H0709/85 **Please quote this number on all correspondence**

Yours sincerely

[redacted]
Committee Co-ordinator

Email: [redacted]

Copy to: *Miss Katherine Myers*
Clinical Trials Unit, MHRA

APPENDICIES FOR PART 2

Appendix 1 - Databases used for the review

Electronic resources

- AMED (Allied and Complementary Medicine)
- ASSIA (Applied Social Science Index and Abstracts)
- British Nursing Index
- CINAHL (Cumulative Index of Nursing and Allied Health Literature)
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effectiveness (DARE; 'other reviews' and Health Technology Assesment (HTA) database in CRD database)
- Current Contents
- EMBASE
- EPPI Centre TRoPHI
- HMIC (or King's Fund catalogue and DH data)
- Medline
- UK Clinical Research Network Portfolio Database
- PsycINFO
- Sociological Abstracts
- Social Policy and Practice
- Web of Knowledge (Science and Social Science Citation Indexes)
- CDC Smoking & Health Resource Library database
- Specialist (public health) systematic review registers
    - EPPI Centre DoPHER
    - Health Evidence ca

Websites

- Smoke free http://smokefree.nhs.uk
- NHS Centre for Smoking Cessation and Training http://www.ncsct.co.uk/,
- Action on Smoking and Health (ASH) http://www.ash.org.uk
- Treat tobacco.net http://www.treatobacco.net/en/index.php
- Society for Research on Nicotine and Tobacco http://www.srnt.org
- International Union against Cancer http://www.uicc.org
- WHO Tobacco Free Initiative (TIF) http://www.who.int/tobacco/en
- International Tobacco Control Policy Evaluation Project http://www.itcproject.org
- Tobacco Harm Reduction http://www.tobaccoharmreduction.org/index.htm
- Current controlled trials www.controlled-trials.com
- Association for the treatment of tobacco use and dependence (ATTUD) www.attud.org
- National Institute on drug abuse- the science of drug abuse and addiction http://www.nida.nih.gov/nidahome.html
- NICE
- Public health observatories
- Scottish Government
- Welsh Assembly Government
- NHS Evidence
- Joseph Rowntree Foundation
- The Centre for Tobacco Control Research (University of Stirling)
- UK Centre for Tobacco Control Studies
- Tobacco Control Research Group (University of Bath)
- http://www.controlled–trials.com

Appendix 2 - Search terms

Example search strategy for Medline

Platform: EBSCO

Results: 6634

#	Query	Results
S1	MH ("TOBACCO USE CESSATION+")	18854
S2	(MH "Smoking Cessation")	16197
S3	(MH "Smoking/PC")	13139
S4	TI ("hand-roll" OR handroll* OR "hand-rolls" OR "hand-rolled" OR bidi OR bidis OR beedi OR beedis OR rolie OR rolies OR paan OR gutkha OR snuff OR betel OR cigar OR cigars)	1331
S5	AB ("hand-roll" OR handroll* OR "hand-rolls" OR "hand-rolled" OR bidi OR bidis OR beedi OR beedis OR rolie OR rolies OR paan OR gutkha OR snuff OR betel OR cigar OR cigars)	2629
S6	TI (quit* OR abstain* OR abstinence OR reduction OR restrict* OR reduce OR cessation)	119903
S7	AB (quit* OR abstain* OR abstinence OR reduction OR restrict* OR reduce OR cessation)	1167034
S8	TI ((stop N2 smoking) OR (stopping N2 smoking) OR (stopped N2 smoking) OR (stoppage N2 smoking))	526
S9	TI ((stop N2 cigarette) OR (stopping N2 cigarette) OR (stopped N2 cigarette) OR (stoppage N2 cigarette))	6
S10	AB ((stop N2 cigarette) OR (stopping N2 cigarette) OR (stopped N2 cigarette) OR (stoppage N2 cigarette))	63
S11	TI ((stop N2 cigarettes) OR (stopping N2 cigarettes) OR (stopped N2 cigarettes) OR (stoppage N2 cigarettes))	4
S12	AB ((stop N2 cigarettes) OR (stopping N2 cigarettes) OR (stopped N2 cigarettes) OR (stoppage N2 cigarettes))	39
S13	AB ((stop N2 tobacco) OR (stopping N2 tobacco) OR (stopped N2 tobacco) OR (stoppage N2 tobacco))	106
S14	TI ((stop N2 tobacco) OR (stopping N2 tobacco) OR (stopped N2 tobacco) OR (stoppage N2 tobacco))	28
S15	TI ((smoking N3 services) OR (smoking N3 service) OR (anti N1 smoking) OR (anti N1 tobacco))	531
S16	AB ((smoking N3 services) OR (smoking N3 service) OR (anti N1 smoking) OR (anti N1 tobacco))	1348
S17	AB ((smoking N2 prevent) OR (smoking N2 prevention) OR (smoking N2 preventing) OR (smoking N2 prevents) OR (tobacco N2 prevent) OR (tobacco N2 prevention) OR (tobacco N2 preventing) OR (tobacco N2 prevents) OR (cigarette# N2 prevent) OR (cigarette# N2 prevention) OR (cigarette# N2 preventing) OR (cigarette# N2 prevents) OR (smoker# N2 restrict#) OR (smoker# N2 restriction) OR (smoker# N2 restricted)	3480

	OR (cigarette# N2 restrict) OR (cigarette# N2 restricted) OR (cigarette# N2 restricts) OR (cigarette# N2 restricting) OR (cigarette# N2 restriction) OR (tobacco N2 restrict) OR (tobacco N2 restricted) OR (tobacco N2 restricts) OR (tobacco N2 restricting) OR (tobacco N2 restriction) OR (smoking N2 restrict) OR (smoking N2 restricted) OR (smoking N2 restricts) OR (smoking N2 restricting) OR (smoking N2 restriction)) OR TI ((smoking N2 prevent) OR (smoking N2 prevention) OR (smoking N2 preventing) OR (smoking N2 prevents) OR (tobacco N2 prevent) OR (tobacco N2 prevention) OR (tobacco N2 preventing) OR (tobacco N2 prevents) OR (cigarette# N2 prevent) OR (cigarette# N2 prevention) OR (cigarette# N2 preventing) OR (cigarette# N2 prevents) OR (smoker# N2 restrict#) OR (smoker# N2 restriction) OR (smoker# N2 restricted) OR (cigarette# N2 restrict) OR (cigarette# N2 restricted) OR (cigarette# N2 restricts) OR (cigarette# N2 restricting) OR (cigarette# N2 restriction) OR (tobacco N2 restrict) OR (tobacco N2 restricted) OR (tobacco N2 restricts) OR (tobacco N2 restricting) OR (tobacco N2 restriction) OR (smoking N2 restrict) OR (smoking N2 restricted) OR (smoking N2 restricts) OR (smoking N2 restricting) OR (smoking N2 restriction))	
S18	AB (temporary abstinence) OR TI (temporary abstinence)	34
S19	TI ((tobacco N2 quit) OR (tobacco N2 quitting) OR (tobacco N2 quitted) OR (tobacco N2 abstain) OR (tobacco N2 abstinence) OR (tobacco N2 reduction) OR (tobacco N2 reduces) OR (tobacco N2 reduce) OR (tobacco N2 abstaining))	269
S20	AB ((tobacco N2 quit) OR (tobacco N2 quitting) OR (tobacco N2 quitted) OR (tobacco N2 abstain) OR (tobacco N2 abstinence) OR (tobacco N2 reduction) OR (tobacco N2 reduces) OR (tobacco N2 reduce) OR (tobacco N2 abstaining))	1157
S21	TI ((smoking N2 quit) OR (smoking N2 quitting) OR (smoking N2 quitted) OR (smoking N2 abstain) OR (smoking N2 abstinence) OR (smoking N2 reduction) OR (smoking N2 reduces) OR (smoking N2 reduce) OR (smoking N2 abstaining))	1154
S22	AB ((smoking N2 quit) OR (smoking N2 quitting) OR (smoking N2 quitted) OR (smoking N2 abstain) OR (smoking N2 abstinence) OR (smoking N2 reduction) OR (smoking N2 reduces) OR (smoking N2 reduce) OR (smoking N2 abstaining))	6788
S23	TI ((cigarette N2 quit) OR (cigarette N2 quitting) OR (cigarette N2 quitted) OR (cigarette N2 abstain) OR (cigarette N2 abstinence) OR (cigarette N2 reduction) OR (cigarette N2 reduces) OR (cigarette N2 reduce) OR (cigarette N2 abstaining))	154
S24	AB ((cigarette N2 quit) OR (cigarette N2 quitting) OR (cigarette N2 quitted) OR (cigarette N2 abstain) OR (cigarette N2 abstinence) OR (cigarette N2 reduction) OR (cigarette N2 reduces) OR (cigarette N2 reduce) OR (cigarette N2 abstaining))	586
S25	TI ((cigarettes N2 quit) OR (cigarettes N2 quitting) OR (cigarettes N2 quitted) OR (cigarettes N2 abstain) OR (cigarettes N2 abstinence) OR (cigarettes N2 reduction) OR (cigarettes N2 reduces) OR (cigarettes N2 reduce) OR (cigarettes N2 abstaining))	30
S26	AB ((cigarettes N2 quit) OR (cigarettes N2 quitting) OR (cigarettes N2 quitted) OR (cigarettes N2 abstain) OR (cigarettes N2 abstinence) OR (cigarettes N2 reduction) OR (cigarettes N2 reduces) OR (cigarettes N2 reduce) OR (cigarettes N2 abstaining))	282
S27	TI ((smoking N2 cessation) OR (tobacco N2 cessation) OR (cigarettes N2 cessation) OR (cigarette N2 cessation))	6240
S28	AB ((smoking N2 cessation) OR (tobacco N2 cessation) OR (cigarettes N2 cessation) OR (cigarette N2 cessation))	12419
S29	TI ((smoker# N2 quit) OR (smoker# N2 quitting) OR (smoker# N2 quitted) OR (smoker# N2 abstain) OR (smoker# N2 abstaining) OR (smoker# N2 abstinence) OR (smoker# N2 reduction) OR (smoker# N2 reduce#) OR (smoker# N2 abstaining))	231
S30	AB ((smoker# N2 quit) OR (smoker# N2 quitting) OR (smoker# N2 quitted) OR (smoker# N2 abstain) OR (smoker# N2 abstaining) OR (smoker# N2 abstinence) OR (smoker# N2 reduction) OR (smoker# N2 reduce#) OR (smoker# N2 abstaining))	2118
S31	(S4 OR S5) AND (S6 OR S7)	530
S32	S1 or S2 or S3 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or	36889

	S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31	
S33	(MH "Patient Admission")	16145
S34	(MH "Hospitalization+")	133618
S35	(MH "Outpatients")	6928
S36	(MH "Inpatients")	10026
S37	(MH "Child, Hospitalized")	5455
S38	(MH "Adolescent, Hospitalized")	376
S39	(MH "Pregnant Women")	4529
S40	(MH "Patients")	14318
S41	TI (patient#)	1076780
S42	TI ((pregnant N3 teens) OR (pregnant N3 teenage#) OR (pregnant N3 teenager#) OR (pregnant N3 adolescent#) OR (pregnant N3 women) OR (pregnant N3 mothers))	13792
S43	AB ((pregnant N3 teens) OR (pregnant N3 teenage#) OR (pregnant N3 teenager#) OR (pregnant N3 adolescent#) OR (pregnant N3 women) OR (pregnant N3 mothers))	45618
S44	TI (inpatient# OR outpatient# OR "out patient" OR "out patients" OR "inhospital" OR (day N2 patient#) OR "ill patients" OR "acutely ill" OR primip* OR primigravid*)	40738
S45	AB (inpatient# OR outpatient# OR "out patient" OR "out patients" OR "inhospital" OR (day N2 patient#) OR "ill patients" OR "acutely ill" OR primip* OR primigravid*)	169326
S46	TI ((patient# N2 surgery) OR (patient# N2 operation) OR (patient# N2 discharge#) OR (patient# N2 readmission#) OR (patient# N2 postdischarge#) OR (patient# N2 emergency) OR (patient# N2 emergencies))	14963
S47	AB ((patient# N2 surgery) OR (patient# N2 operation) OR (patient# N2 discharge#) OR (patient# N2 readmission#) OR (patient# N2 postdischarge#) OR (patient# N2 emergency) OR (patient# N2 emergencies))	119288
S48	TI ((patient# N2 referral#) OR (patient# N2 referring) OR (patient# N2 admittance#) OR (patient# N2 admitting) OR (patient# N2 admission#) OR (patient# N2 readmittance) OR (patient# N2 readmitting) OR (patient# N2 readmission#) OR (patient# N2 postoperable) OR (patient# N2 postoperative) OR (patient# N2 refer) OR (patient# N2 refers) OR (patient# N2 admit) OR (patient# N2 admits))	4715
S49	AB ((patient# N2 referral#) OR (patient# N2 referring) OR (patient# N2 admittance#) OR (patient# N2 admitting) OR (patient# N2 admission#) OR (patient# N2 readmittance) OR (patient# N2 readmitting) OR (patient# N2 readmission#) OR (patient# N2 postoperable) OR (patient# N2 postoperative) OR (patient# N2 refer) OR (patient# N2 refers) OR (patient# N2 admit) OR (patient# N2 admits))	46690
S50	TI (maternity OR "maternal health" OR obstetrics OR "prenatal care" OR "prenatal services" OR "antenatal care" OR "antenatal services" OR "obstetric care" OR "obstetric services" OR "perinatal care" OR "prenatal clinic" OR "prenatal clinics" OR "prenatal health" OR "prenatal service" OR "antenatal clinic" OR "antenatal clinics" OR "antenatal service" OR "antenatal health" OR "obstetric clinic" OR "obstetric clinics" OR "obstetric service" OR "obstetric health" OR "perinatal clinic" OR "perinatal clinics" OR "perinatal service" OR "perinatal services" OR "perinatal health" OR pregnancy OR "maternity healthcare" OR "obstetric healthcare" OR "prenatal healthcare" OR "antenatal healthcare" OR "perinatal healthcare" OR "maternal care" OR "maternal service" OR "maternal services" OR hospitalised OR hospitalized OR "secondary care" OR "acute care" OR "secondary health service" OR "secondary health services" OR "acute health service" OR "acute health services" OR "acute setting" OR "acute settings" OR "acute service" OR "acute services")	157954
S51	AB (maternity OR "maternal health" OR obstetrics OR "prenatal care" OR "prenatal services" OR "antenatal care" OR "antenatal services" OR "obstetric care" OR	255290

	"obstetric services" OR "perinatal care" OR "prenatal clinic" OR "prenatal clinics" OR "prenatal health" OR "prenatal service" OR "antenatal clinic" OR "antenatal clinics" OR "antenatal service" OR "antenatel health" OR "obstetric clinic" OR "obstetric clinics" OR "obstetric service" OR "obstetric health" OR "perinatal clinic" OR "perinatal clinics" OR "perinatal service" OR "perinatal services" OR "perinatal health" OR pregnancy OR "maternity healthcare" OR "obstetric healthcare" OR "prenatal healthcare" OR "antenatal healthcare" OR "perinatal healthcare" OR "maternal care" OR "maternal service" OR "maternal services" OR hospitalised OR hospitalized OR "secondary care" OR "acute care" OR "secondary health service" OR "secondary health services" OR "acute health service" OR "acute health services" OR "acute setting" OR "acute settings" OR "acute service" OR "acute services")	
S52	TI ((acute W2 ward) OR (acute W2 wards) OR (general W2 ward) OR (general W2 wards) OR (stay W2 ward) OR (staying W2 ward) OR (stay W2 wards) OR (staying W2 wards))	677
S53	AB ((acute W2 ward) OR (acute W2 wards) OR (general W2 ward) OR (general W2 wards) OR (stay W2 ward) OR (staying W2 ward) OR (stay W2 wards) OR (staying W2 wards))	2962
S54	TI ((accident W3 unit) OR (accident W3 department) OR (emergency W1 unit) OR (emergency W1 department) OR (surgical W1 ward) OR (patient# N2 surgery) OR (surgery W2 unit) OR (surgery W2 department) OR (acute W2 unit) OR (acute W2 department))	23092
S55	AB ((accident W3 unit) OR (accident W3 department) OR (emergency W1 unit) OR (emergency W1 department) OR (patient# N2 surgery) OR (surgical W1 ward#) OR (surgery W2 unit) OR (surgery W2 department) OR (acute W2 unit) OR (acute W2 department))	108278
S56	TI (hospitals OR hospital OR (patient# N2 "post discharge"))	181415
S57	AB (hospitals OR hospital OR (patient# N2 "post discharge"))	493665
S58	(MH "Maternal Health Services+")	28351
S59	(MH "Obstetrics and Gynecology Department, Hospital")	2214
S60	(MH "Obstetrics")	14150
S61	(MH "Hospitals+")	180568
S62	(MH "Hospital Units+")	66597
S63	(MH "Outpatient Clinics, Hospital+")	14543
S64	(MH "Emergency Service, Hospital+")	40071
S65	(MH "Emergency Medical Services")	27584
S66	TI (("hospital staff") OR ("hospital personnel") OR (hospital W1 worker#) OR surgeon# OR gyne#cologist# OR obstetrician# OR midwiv* OR midwife)	25287
S67	AB (("hospital staff") OR ("hospital personnel") OR (hospital W1 worker#) OR surgeon# OR gyne#cologist# OR obstetrician# OR midwiv* OR midwife)	103541
S68	TI (hospital) OR AB (hospital)	533136
S69	TI (doctor# OR nurse# OR physician# OR clinician# OR pharmacist# OR health W1 worker# OR consultant# OR (medical W1 specialist#) OR (medical W1 officer#))	191646
S70	AB (doctor# OR nurse# OR physician# OR clinician# OR pharmacist# OR health W1 worker# OR consultant# OR (medical W1 specialist#) OR (medical W1 officer#))	412247
S71	S69 or S70	543647
S72	(S68 and S71)	67181
S73	AB (partnership# or "team work" or "teamwork" OR teamworking OR "team working" or cooperation or (cooperative W1 behavio#r) or "integration" or "integrative approach"	261508

	OR "integrative approaches" or collaborat* or interagenc* or multiagenc* or "inter-institutional" or "inter-institutionally" or "inter-professional" or "inter-departmental" or "inter-departmentally" or interinstitutional* or interprofessional or interdepartmental* or "interprofessional relations" or "interprofessional relationships" or (multidisciplin*) or "cross discipline" OR "cross disciplinary" or (interagency) OR linkage# OR "cross-discipline" OR "cross-disciplinary")	
S74	TI (partnership# or "team work" or "teamwork" OR teamworking OR "team working" or cooperation or (cooperative W1 behavio#r) or "integration" or "integrative approach" OR "integrative approaches" or collaborat* or interagenc* or multiagenc* or "inter-institutional" or "inter-institutionally" or "inter-professional" or "inter-departmental" or "inter-departmentally" or interinstitutional* or interprofessional or interdepartmental* or "interprofessional relations" or "interprofessional relationships" or (multidisciplin*) or "cross discipline" OR "cross disciplinary" or (interagency) OR linkage# OR "cross-discipline" OR "cross-disciplinary")	71666
S75	(S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S72 or S73 or S74)	2614599
S76	S75 AND S32	7304
S77	MH ("Humans") AND MH ("Animals")	1253188
S78	MH ("Animals")	4777882
S79	S78 NOT S77	3524694
S80	S76 NOT S79	6634

Notes:

= wildcard of 1 or 0 characters

* = truncation

N2 = words within 2 places of each other in any order

W2 = words within 2 places of each other in the order written in the text

Appendix 3 – Papers excluded from the hospital section (n=41)

(2007). "Inpatient smoking-cessation programs get the job done."	Article not relevant
(2008). "Treating patients who use tobacco."	Article not relevant
(2009). "Stop smoking hospitals pilots."	Newspaper article
(2010). "Thoracic surgeons can help patients stop smoking with a brief smoking cessation program."	Link to another paper - Kozower 2010
(2011). "Motivate patients to stop smoking."	Not RCT
Allen (1998)	Excluded by Rigotti
An (2008)	Not RCT
Bernstein (2011)	Only 3 month FU
Canga (2000)	Not included as not in right setting
Carson (2010)	Conference paper preliminary data only
Choo (2004)	Only 1 month FU data available
Dalton (1991)	Psychiatric setting
Fonteyn (2004)	Commentary on Quist-Paulsen 2003, exclude
Gies (2008)	Not RCT
Gritz (1991)	Describes trial and SS but no results
Hanssen (2007)	2008 paper includes longest time FU - 18 months
Holmes-Rovner(2008)	Cannot extract data
Jha (2005)	Review of Taylor
Joseph (1996)	Study methods - get full paper
Lacasse (2005)	Conference report on Lacasse 2007 study
Lisspers (1999)	Cannot extract data
Moller (2003)	Different question but related to Moller 2002
Mackay (2010)	Poster - not RCT
Maud-Christine (2005)	Chouinard paper - already included in Rigotti
Mohjuddin (2006)	Summary of Mohiuddin (2007)

Murray (2002)	Commentary on 2002 paper
Park (2011)	Non-randomised
Peterson (2004)	Not relevant setting
Reid (2011)	Conference report
Richman (2000)	3 month FU only
Stainislaw (1994)	Only 5 week FU
Tan (2011)	Not RCT
1994) "Nicotine replacement therapy for patients with coronary artery disease. Working Group for the Study of Transdermal Nicotine in Patients with Coronary artery disease."	Not acute services setting
Thorndike (2008)	Secondary analysis of Rigotti paper
Uzuner (2008)	Review 3
van Elderen-van Kemenade (1994)	No detail on number of baseline smokers
Vander Weg (2008)	Not relevant setting
Volpp (2006)	Not relevant setting
Wolfenden (2005)	No data - include in review 3
Wolfenden (2008)	Less than 12 month follow up, results not clear
Wong (2005)	No data/focus on smoking cessation

Appendix 4 – Papers unavailable for the hospital section (n=19)

(1994) "Nicotine replacement therapy for patients with coronary artery disease. Working Group for the Study of Transdermal Nicotine in Patients with Coronary artery disease."
(2010) "How one facility helps patients stop smoking."
(2011) "How one facility helps patients stop smoking."
Anders (2011)
Bock (2008)
Eisenberg (2011)
Glavas (2003)
Grandi (2011)
Kapur (2004)
Meysman (2010)
Murphy (1994)
Nett (1992)
Rigotti (1996)
Spencer (2004)
Strayer (2004)
Todd (1998)
Weissfeld (1991)
Wewers (1992)
Wewers (1993)

APPENDICIES FOR PART 3

Appendix 1 – “Stop smoking live” presentation

This presentation is sponsored by

GlaxoSmithKline
Consumer Healthcare

NCQ/C&W/SE/1010/02
November 2010

Optimising the use of Nicotine Replacement Therapy

Using Combination Therapy

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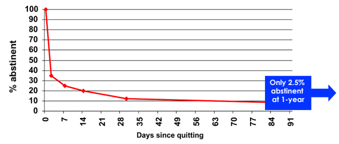
Quitting without support

- The majority of people who quit without support will relapse in the first week



Hughes et al. (2004) Shape of the relapse curve and long-term abstinence among untreated smokers, *Addiction*,**99** 29–38.

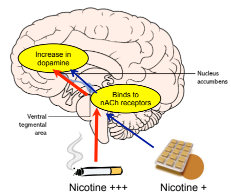
Tobacco Dependence

- A recognised disorder (DSM-IV)
- Requires treatment
- It is estimated that around half of all smokers will not be able to stop without some form of help

Nicotine Replacement Therapy

- Nicotine Replacement Therapy (NRT) products replace some of the nicotine from cigarette smoking to:
  - Eliminate various harmful elements from smoking
  - Satisfy the need for nicotine
  - Reduce nicotine dependence gradually and finally lead to being tobacco free and nicotine free

Mechanism of action

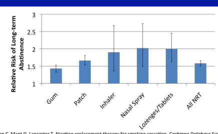


Replacing nicotine

- Reduces severity of withdrawal symptoms[1]
- Reduces urge to smoke[2]
- Delays weight gain[3]
- Reduces relapse[2]
- Approximately doubles success rates of long-term abstinence (regardless of type of support used)[1]

1. Stead, L. F., Perera, R., Bullen, C., Mant, D. & Lancaster, T. Nicotine replacement therapy for smoking cessation, *Cochrane Database Syst Rev*, CD000146. 2009
2. McEwen, A., Hajek, P., McRobbie, H. and West, R. *Manual of smoking cessation: A guide for counsellors and practitioners.* Oxford: Blackwell Publishing. 2006
3. Allen SS et al. Effect of nicotine replacement therapy on post-cessation weight gain and nutrient intake: a randomized controlled trial of postmenopausal female smokers. *Addict Behav*. 2005. Aug;30(7):1273-80.

NRT is effective



Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008(1)

- Despite its effectiveness people using NRT still have a <20% chance of quitting a year
- This may in part be due to
  - Incorrect use
  - Insufficient use

Under-dosing?

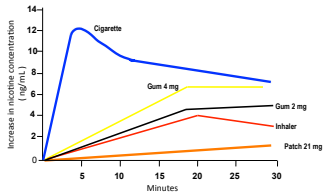
- NRT typically provides less than half the nicotine a smoker receives from their tobacco[1]
- Even with combination NRT treatment many smokers do not obtain blood nicotine levels comparable with their baseline smoking levels
  - In a trial of combined nicotine patch and inhalator, blood nicotine levels were only 60% of that achieved during ad lib smoking[2]

1. Johnstone E, Brown K, Saunders C, Roberts K, Drury M, Walton R, et al. Level of nicotine replacement during a quit-smoking attempt. *Nicotine Tob Res* 2004;6(2):377-9
2. Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med* 2000;160(20):3128-34

Cigarettes vs. Medication

- Cigarettes are the ideal delivery system for nicotine. They provide:
  - High levels of nicotine, sustained over the day
  - Acute increases in nicotine on demand
- No single NRT product can do this

Pharmacokinetics



Modified from Balfour DJ & Fagerström KO. *Pharmacol Ther* 1996; 72:51-81

In clinical practice

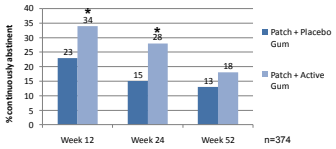
- "Can I recommend a patch and lozenge to be used at the same time?"
- "Is it safe for me to recommend combination therapy?"

Evidence for cessation

Study	Products	RR	95% CI
Kornitzer et al 1995	patch+gum vs. patch	1.43	0.83 - 2.46
Puska et al 1995	patch+gum vs. gum	1.38	0.88 - 2.17
Blondal et al 1999	nns+patch vs. patch	2.48	1.37 - 4.49
Bohadana et al 2000	patch+inh vs. inh	1.39	0.89 - 2.17
Tonnesen et al 2000	patch+inh vs. either	0.51	0.17 - 1.52
Croghan et al 2003	patch vs. spray vs. patch +spray	1.23	0.85 - 1.78

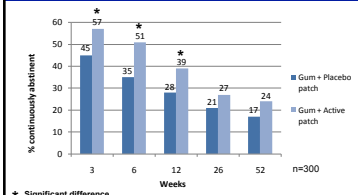
Stead, L. F., Perera, R., Bullen, C., Mant, D. & Lancaster, T. Nicotine replacement therapy for smoking cessation, *Cochrane Database Syst Rev*, CD000146. 2008

Patch + Gum



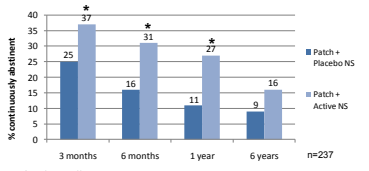
Kornitzer et al. *Prev Med* 1995.

Gum + Patch



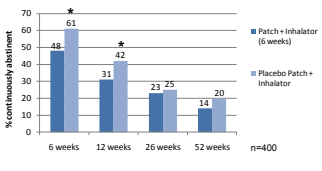
Puska et al. *Tobacco Control*, 1995

Patch + Nasal Spray



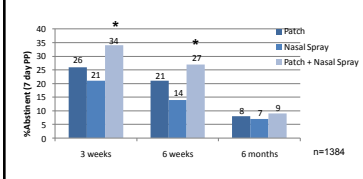
Blondal et al. *BMJ* 1999

Patch + Inhalator



Bohadana et al. *Arch. Int Med*, 2000 Dec

Patch *vs.* Nasal Spray *vs.* Combi



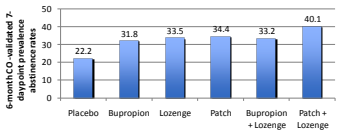
Croghan et al *NTR* 2003

Cochrane Review

- The six trials comparing combination with single NRT shows advantage of combination use
  - RR = 1.35 (95% CI: 1.11-1.63)

Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008(1)

A study of 'mono' and 'combi' treatment



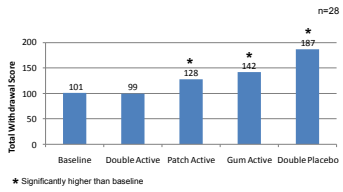
- All active treatments were significantly better than placebo
- Only patch + lozenge was better than monotherapy (p=0.04)

Ryan *et al. Arch Gen Psychiatry* 66 (1) 2009

Evidence for withdrawal relief

- Fagerstrom et al (1993)
  - Double-blind study
  - Assigned each smoker to 4 groups
    - 15mg/16hr patch + 2mg gum
    - 15mg/16hr patch + placebo gum
    - Placebo patch + 2mg gum
    - Placebo patch + placebo gum
  - Measured withdrawal ratings over 3 days

Total withdrawal scores



Fagerstrom *et al Psychopharmacology* 1993.

Safety of combination NRT use

- Incidence of adverse events with combination NRT is not significantly greater than that with single NRT used alone
- Data consistent with safety data showing favourable risk benefit of NRT over wide range of doses and situations
- Smokers capable of titrating their nicotine intake

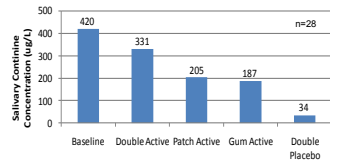
Risk of overdose

- Smokers have acquired tolerance to large amounts of nicotine
- The adverse effects of nicotine (nausea and vomiting) tend to limit overdose
- Nicotine undergoes first pass metabolism

Safety of combinations

- NRT usually provides nicotine:
  - in lower doses than smoking;
  - at a slower rate; and
  - without the large arterial-venous difference.
- Even the high doses used in studies is generally well tolerated

Salivary Cotinine



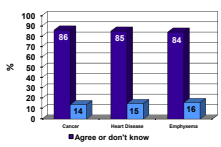
Fagerstrom *et al Psychopharmacology*, 1993

Public perception of NRT

- US national survey, 3,203 current and former smokers
  - 66% agreed that 'NRT is just as harmful as cigarettes' or were unsure if true
  - Less likely to use NRT and if used, used less and for shorter time
  - Public education is needed

Hoffman *et al. Addiction* 103, 1371–1376; 2008

Healthcare professionals perception of NRT



A cohort of NZ nurses were asked if nicotine is the MAIN product in tobacco smoke that causes cancer, heart disease, emphysema

Wong *et al* Smoking and Nurses in New Zealand. ASH-KAN Aotearoa: Assessment of smoking history, knowledge and attitudes of nurses in New Zealand. *ASH New Zealand*. 2009

In clinical practice

- Who would you recommend use combination NRT?
  - All smokers who want to quit?
  - Those who are highly dependent?
  - Those who have tried and failed on NRT in the past?
  - People with mental health illness?

In clinical practice

- What sort of combination would you recommend?
  - Combination 'on demand':
    - E.g. patch to provide a stable nicotine intake + intermittent on-demand use of single doses from oral NRT or nasal spray
  - Combination 'regular dosing':
    - E.g. patch + regular dosing of oral NRT or nasal spray
    - High daily nicotine concentration is achieved, and on-demand doses are still provided
    - Patch to provide a stable nicotine intake + intermittent on-demand use of single doses from oral NRT or nasal spray

Other advantages

- Some products provide more sensory stimulation than others
- Some products act faster than others
  - E.g. 4mg lozenges relieve craving within 5 minutes[1]; nasal spray also provides rapid relief
- On demand products allow help with breakthrough craving
  - E.g. Smokers are vulnerable to relapsing in the afternoon[2] (Ussher & West, 2003). An oral product may provide extra cover during this time

1. Duncan et al Efficacy of the nicotine lozenge in cue-provoked cravings. *44th Annual meeting of College on Problems on Drug Dependence*; San Juan, P.R. 2004
2. Ussher M & West R. Diurnal variations in first lapses to smoking for nicotine patch users. *Hum Psychopharmacol*. 2003 Jul;18(5):345-9.

Who can use NRT?

ALL SMOKERS OVER 12 CAN USE NRT

- Contraindications and **cautions** attached to NRT are **not warranted** (e.g. heart disease, age <18)
- In Dec 2005 the UK MHRA/CSM issued guidance on NRT
  - 12-18 year olds (up to 12 weeks)
  - Pregnancy on assessment, oral products, 16h patch if needed, not 24h patch
  - Breastfeeding, avoid patches if possible
  - CVD – acutely unwell patients only with medical supervision; stable disease OK to use
  - Can be used in people with diabetes
  - No drug interactions
  - Long-term use and NRT combinations are fine
- Further relaxation by MHRA & Commission on Human Medicines (CHM) in February 2010
  - A new element to the indication for NRT – "harm reduction" – was added, since it has become widely accepted that there are no circumstances in which it is safer to smoke than to use NRT

Medicines and Healthcare Products Regulatory Agency. *Report of the committee on safety of medicines working group on nicotine replacement therapy*. 2005
MHRA/CHM Drug Safety Update Feb 2010, vol 3 issue 7: 6

Conclusions

- NRT is effective in helping people to quit smoking
- NRT is generally well tolerated
- Combinations of NRT increase long-term abstinence rates
- Smokers should be routinely offered combination treatment if they are highly dependent or found single forms inadequate previously

Thank you

Appendix 2 – Feedback form

Question 1
What is your profession?
%
Question 2
Prior to attending this session please rate your knowledge of using NRT in combination
%
Question 3
After attending this session please rate your knowledge of using NRT in combination
%
Question 4
As a result of attending this session please indicate if you will now increase or decrease your recommendations of using NRT in combination for suitable patients?
%
Question 5
Following attendance at this session please indicate how useful you found it
%
Question 6
Please rate the following elements of the session from disagree (-) to agree (+)
The speaker was knowledgeable on the subject
%
There was a good balance of theory combined with real-life experience
%
The speaker engaged with the audience and encouraged participation
%
I learned something new by attending this session
%
I will use the information from this session in my work
%
I plan to discuss this information with my colleagues
%

Appendix 3 - Case study questions

- What products are you currently using?
- What made you combine NRT and Champix?
- At what point in your treatment did you begin to use a combination? E.g. from the beginning, from QD etc.
- Where did you get the NRT from? E.g. already had some, tesco, chemist etc.
- How often are using the NRT product?
- Do you feel any benefit from using a combination of products? If yes, what benefit do you get?
- Have you spoken to a HP/LSSS about combining the products?
- Have you had any side effects using a combination of champix and NRT?
- Did using a combination of NRT and champix ever concern you at any point?
- When do you think is the most important time to combine products
- How long do you feel you will need to use both medications for?/How long do you intend to use both products for?
- Have you ever combined NRT products before in previous quit attempts?