Smoking cessation in Secondary Care

Review 1 (Component 5)

Review of effects of nicotine in secondary care

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November 2021: NICE guidelines PH45 (June 2013) and PH48 (November 2013) have been updated and replaced by NG209. The recommendations labelled [2013] or [2013, amended 2021] in the updated guideline were based on these evidence reviews. See www.nice.org.uk/guidance/NG209 for all the current recommendations and evidence reviews.

Glossary

Adverse event	Any adverse change in health or side effect that is documented in a study. This may or may not be considered related to the study medication (see also serious adverse event)
Akathisia	A syndrome that is characterized by a feeling of being unable to sit still or need to move around. This often manifests as a rocking motion when sitting or standing, and crossing and uncrossing legs when sitting, for example. Akathisia is a side effect of anti-psychotic drugs
Aminophylline	A drug that used for the treatment of respiratory disease such as asthma. It acts to dilate the airways making breathing easier.
Area under the Curve (AUC)	This is a term used in pharmacokinetics and represents the area under the curve of blood drug concentration over time. The AUC is a measure of drug bioavailability.
Bioavailability	This is the amount of a drug that appears in the blood after a dose of the drug is taken.
Clearance	Refers to the clearance of a drug from the body (usually via the kidneys)
C_{max}	The maximum blood concentration of a drug reached after a drug is taken.
Cryptorchidism	Absence of one or both testes from the scrotum
Delirium	This is an acute confusional state that is caused by physical and mental illness. It is usually temporary and reversible.
Myocardial infarction	This is more commonly known as a heart attack and it occurs when the heart muscle is deprived of oxygen and muscle cells die.
Nicotine	Nicotine is an alkaloid that is found in the leaves of the tobacco plant. It is present in tobacco smoke and absorbed quickly into the blood. It exerts its main effect in the brain. Nicotine is primarily responsible for tobacco dependence
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.
Pharmacogenetics	This is the study of variations in genes that give rise to difference responses to drugs
Pharmacokinetics	The study of the fate of drugs when they are taken into the body. This includes absorption, distribution and excretion.
Serious adverse event	This is an adverse event with serious consequence (i.e. results in death or disability, is life-threatening, requires hospitalisation).

$t_{1/2}$	The half-life of a drug. This is the time it takes for blood concentration of the drug to halve.
Theophylline	A drug that used for the treatment of respiratory disease such as asthma. It acts to dilate the airways making breathing easier.
T_{max}	The time it takes for the maximum (Cmax) blood concentration of a drug to be reached.
Warfarin	An anti-coagulant drug (used to thin the blood) that is used in people with atrial fibrillation and those with artificial heart valves

List of abbreviations

ABS	Agitated Behaviour Scale
AE	Adverse event
BAS	Barnes Akathisia Scale
BDI	Becks Depression Inventory
BP	Blood pressure
Bpm	Beats per minute
BPRS	Brief psychiatric rating scale
BSI	Brief Symptom Inventory
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CBF	Cutaneous blood flow
CBT	Cognitive behavioural therapy
Cmax	Maximum plasma concentration
CO	Carbon monoxide
COPD	Chronic obstructive airways disease
CPD	Cigarettes per day
CVD	Cardiovascular disease
ECG	Electrocardiogram
EDD	Estimated date of delivery
FFA	Free fatty acids
FHR	Fetal heart rate
HAM-D	Hamilton depression rating scale
HR	Heart rate
hr	Hour
ICU	Intensive care unit
INR	International normalised ratio
L	Litre

LBW	Low birth weight
MAP	Mean arterial pressure
ug	Microgram
mg	Milligram
MGA	Mean gestational age
MI	Myocardial infarction
min	Minute
ml	Millilitre
ng	Nanogram
OR	Odds ratio
PANSS	Positive and Negative Symptom Scale
PD	Parkinson's Disease
POMS	Profile of Mood States
PONV	Post-operative nausea and vomiting
PRN	Pro re nata – a Latin phrase used to describe the administration of drugs as needed
PTSD	Post traumatic stress disorder
RCT	Randomised controlled trial
RR	Relative risk
SAE	Serious adverse event
SAH	Sub-arachnoid haemorrhage
SANS	Scale for assessment of negative symptoms
SF-12	12-item short form health survey
STAI	State Trait Anxiety Inventory
Tmax	Time to maximum plasma concentration
YBOCS	Yale-Brown Obsessive-Compulsive Scale

EXECUTIVE SUMMARY

INTRODUCTION

Each year thousands of smokers are admitted to hospitals in the United Kingdom (UK). UK hospitals are now smoke-free, with patients unable to smoke in buildings and in many cases on the hospital grounds. Nicotine replacement therapy (NRT) is usually prescribed for those who need it.

There exist concerns regarding the safety of NRT use in some groups of patients such as cardiac patients and pregnant women. There are also concerns regarding the acute effects of tobacco withdrawal on patients in Intensive Care Units (ICU), and the effects of tobacco abstinence on metabolism of several commonly used medications. Finally, there are concerns about the impact of tobacco abstinence on smokers with mental health illness. These issues are important in considering clinical recommendations regarding stopping smoking and using NRT.

The aim of this review is to assess effects of NRT and of acute nicotine withdrawal on the mental and physical health of people using secondary care and maternity services. The review does not cover health effects of smoking or efficacy of NRT.

METHOD

A comprehensive literature search was conducted using a search strategy developed to capture literature relating to (1) the review population, (2) nicotine use, (3) tobacco use and cessation of tobacco use, and (4) use of medications and any interactions.

The following limitations were applied to the database searches (1) studies published from 1980[1] to December 2011, (2) human studies, and (3) studies published in English.

A total of 19 databases were searched, including AMED, ASSIA, British Nursing Index, and CINAHL. Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Current Contents, EMBASE, Medline, PsycINFO, Sociological Abstracts, and Web of Knowledge (Science and Social Science Citation Indexes). Websites were also searched for relevant information.

A total of 10,466 records were screened, 442 papers were selected for further review, and 286 of these contained relevant information and are included in the review.

The literature has been organised into three Chapters covering the three populations of interest:

Chapter 1: Hospital patients with physical illness

Chapter 2: Mental health services users

Chapter 3: Pregnant women.

[1] Some papers with a publication date prior to 1980 have been included on request of the PGD

Within the chapters, sections have been created to summarise data related to individual sub-topics addressing concrete clinical issues. Evidence statements have been provided for each section. Data did not allow for any meta-analyses to be undertaken.

FINDINGS AND EVIDENCE STATEMENTS

CHAPTER 1: EFFECTS OF NICOTINE AND OF ACUTE TOBACCO WITHDRAWAL IN HOSPITALISED PATIENTS

We identified 101 studies seeking to determine the health effects of nicotine, primarily nicotine delivered via NRT, and the effects of abstinence from tobacco on hospitalised smokers. We present the findings in 3 parts, with further sub-divisions into sections. Part 1 concerns cardiac patients; Part 2 concerns intensive care unit (ICU) and surgery patients; and Part 3 concerns all other hospital patients.

PART 1: EFFECTS OF NICOTINE IN PATIENTS WITH CARDIOVASCULAR DISEASE

Next to pregnant women, patients with cardiovascular disease (CVD) are considered the group of health service users most sensitive of any potential harm from NRT. There are also concerns about the effect of stopping smoking on metabolism of some CVD drugs.

This part includes 3 sections. Section 1 covers acute effects of nicotine on the cardiovascular system; Section 2 is covering effects of NRT used over extended period of time for smoking cessation; and Section 3 covers the effects of smoking and of tobacco abstinence on CVD medications.

Section 1: Studies of acute effects of NRT

In laboratory studies involving several different NRT formulations, acute effects of NRT on cardiovascular parameters were weaker than effects of smoking. Where participants smoked and used NRT during the same time period, NRT use did not contribute any additional negative effects. No signal of risk that would require further investigation has emerged.

ES 1.1.1 There is strong evidence that the acute effects of NRT on cardiovascular function are significantly smaller than smoking (Benowitz et al. 1993, RCT, [+]; Gembala 2006, non-randomised CT, [+]; Keeley 1996, RCT, [+]; Mahmarian 1997, prospective cohort, [+])

ES 1.1.2 There is moderate evidence that NRT has no acute adverse effect on cardiovascular function in patients with stable CVD (Nitenberg 1999, controlled trial, [+]; Tanus-Santos 2001, controlled cross-over trial, [+])

Section 2: Studies of effects of NRT used to stop smoking

No randomised trial comparing NRT and placebo, or cohort study comparing users of NRT with other groups, found any signal of risk in terms of adverse events, changes in CVD, MI or stroke.

Four case studies reported cardiac events occurring in smokers using NRT. All four concern patches that are the only NRT product, which media linked to cardiac events. A very large

number of cardiac incidents occur daily and they will coincide with practically any activity and medication, but of course a rare causal effect cannot be ruled out.

A systematic review which included studies reporting cardiovascular events following NRT or placebo use in healthy populations concluded that NRT does not cause adverse cardiovascular events in healthy users.

Overall, there is no evidence suggesting that NRT use is unsafe for people with CVD.

ES 1.1.3 There is strong evidence that use of NRT does not lead to adverse events when used in patients with stable CVD (Joseph et al 1996, RCT [++]; The Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease 1994, RCT, [++]; Tzivoni et al 1998, RCT [+]; Marsh et al (2005, RCT [+]; Hubbard et al. 2005, Retrospective cohort [+]; Kimmel et al 2001, Case control [+]; Meine et al 2005, Case control [+]; Willmer and Bell 2003, retrospective audit, [-])

ES 1.1.4 There is strong evidence that use of NRT in the general population is not associated with an increased risk of cardiac events (Greenland et al 1998, systematic review, [++]; Hubbard et al. 2005, Retrospective cohort [+]; Allen et al. 1994, RCT [++]) or stroke (Greenland et al 1998, systematic review, [++]; Hubbard et al. 2005, Retrospective cohort [+]).

ES 1.1.5 There is moderate evidence that NRT does not cause any serious adverse events in patients with unstable CVD (Kimmel et al 2001, Case control [+]; Meine et al 2005, case control study [+]; Willmer and Bell 2003, retrospective audit, [-]).

Section 3: Effects of stopping smoking on patients' wellbeing and on CVD medications

Among patients hospitalised for MI or CABG surgery, long-term stress levels decreased in those who stopped smoking, but remained unchanged in smokers.

Stopping smoking may lead to some 12% increase in plasma levels of warfarin. Monitoring of warfarin levels when there is a change in smoking status is recommended.

ES 1.1.6 There is moderate evidence that in smokers with CVD who stop smoking successfully long-term levels of stress decrease rather than increase (Hajek et al. 2010, prospective cohort, [+])

ES 1.1.7 There is moderate evidence that smokers may require higher doses of warfarin to achieve an INR in therapeutic range (seven studies found this: Aquilante et al. 2006, prospective cohort, [+]; Gage et al. 2008, prospective cohort, [+]; Lee et al. 2005, prospective cohort, [+]; Lenzini et al. 2008, prospective cohort, [+]; Millican et al. 2007, prospective cohort, [+]; Mungall et al 1985, retrospective cohort, [+]) Pamboukian et al. 2008, retrospective cohort, [+]), but four studies found no difference between requirements in smokers vs. non-smokers (Mitchell et al. 1972, retrospective cohort, [+]; The University of Illinois at Chicago 1999, case control, [+]; Weiner et al. 1984, retrospective cohort, [+]; Whitley et al. 2007, retrospective cohort, [+])

ES 1.1.8 There is moderate evidence that stopping smoking can lead to an increase in the systemic level of warfarin, with an associated increase in INR (Bachmann et al 1979, prospective cohort, [+]; Kuykendall 2004, case study, [-]; Evans et al (2005, case study, [-])

PART 2: EFFECTS OF NICOTINE AND EFFECTS OF STOPPING SMOKING ON PATIENTS ADMITTED TO ICU OR UNDERGOING SURGERY

Regarding the impact of acute changes in nicotine and smoke intake on surgery outcomes, we found 29 studies that are presented in three sections. Section 1 concerns perioperative outcome; Section 2 concerns the risk of delirium; and Section 3 covers the effects of nicotine and tobacco withdrawal on the perception of pain.

Section 1: Effects of nicotine on perioperative outcomes

Given the number of possible acute effects of both tobacco abstinence and nicotine intake on a number of surgery and ICU outcomes, the literature we identified is limited. It consists primarily of cohort studies that pose problems with interpreting the results because there were normally a number of differences between patients who were and who were not given the patches. Different studies also concerned different populations and different outcomes.

ES 1.2.1 There is mixed evidence regarding the safety of NRT use in critically ill patients. Two studies found an increased risk of mortality associated with NRT use in ICU and bypass surgery patients (Lee et al 2007, retrospective cohort, [+]; Paciullo et al 2009, retrospective cohort, [+]). Three studies found no increased risk of unfavourable outcomes (Panos et al 2010, retrospective cohort, [+]; Carandang et al 2011, retrospective cohort, [+]; Cartin-Ceba et al 2011, prospective cohort [+]). One study found an increased risk of pulmonary complications and seizures but lower risk of mortality in NRT users (Seder et al 2011, retrospective cohort [+]).

ES 1.2.2 There is moderate evidence that the adverse effects on bone healing and post-surgical complications are not due to nicotine (W-Dahl and Toksvig-Larsen 2007, prospective cohort study [+])

ES 1.2.3 There is weak evidence to suggest that nicotine patches should be removed prior to micro vascular reconstructive surgery to limit any possible vasoconstrictive effects of nicotine and surgery using vasopressin injections (Jagadeesan et al. 2007, case study, [-]; Groundine & Morley (1996, case study, [-])

ES 1.2.4 There is strong evidence that smokers who abstain from smoking 10 hours prior to surgery need smaller doses of atracurium for maintenance of anaesthesia than those who smoke up to a few hours before surgery or wear nicotine patches (Puura et al. 1998, RCT [++])

ES 1.2.5 There is strong evidence that chewing nicotine gum prior to surgery is not associated with an increased gastric fluid volume (Soreide et al. 1995, RCT, [++])

Section 2: Effects of smoking, tobacco withdrawal, and NRT on the risk of delirium

A number of hospitals give NRT patches automatically to smokers undergoing surgery and to those admitted to ICUs. Such smokers normally do not ask for NRT and are not bothered by

the need to smoke. They are usually not consulted about receiving the patches. The practice is in place due to a perception that smokers are more likely to suffer from delirium and that NRT may reduce the risk.

The available literature suggests that the practice has no sound evidence base. It should be suspended until randomised trials of effects of NRT on surgery and ICU outcomes provide evidence that this is beneficial rather than irrelevant or harmful.

ES 1.2.6 There is moderate evidence that abstinence from smoking does not increase the risk of delirium. (Four studies found no link: Dubois et al 2001, prospective cohort, [+]; Nicholson et al. 2006, retrospective cohort, [-]; Ouimet et al. 2007, prospective cohort, [+]; Van Rompaey 2009, prospective cohort, [-], while two studies reported a link but did not control for possible confounders: Miyazaki et al. 2011, retrospective cohort, [+]; Lucidarme et al. 2010, prospective cohort, [-])

ES 1.2.7 There is weak evidence that application of NRT is associated with an increased risk of delirium (Cartin-Ceba et al 2011, prospective cohort [-]; Seder et al 2011, retrospective cohort [+]).

Section 3: Stopping smoking and perception of pain

There is some evidence that nicotine may act as an analgesic. This raises a concern that in the context of acute care, stopping smoking may have a negative effect on pain perception and patient comfort. The available evidence suggests that NRT may reduce post-operative pain in non-smokers but definitive trials are needed. Stopping smoking have no long-term effect on pain ratings but the acute effects are not known.

ES 1.2.8 There is good evidence that NRT alleviates post-operative pain in **non-smokers** (Flood and Daniel 2004, RCT, [+]; Habib et al. 2008, RCT, [+]; Hong et al. 2008, RCT, [+]; Yagoubian et al. 2011, RCT, [+])

ES 1.2.9 There is moderate evidence that NRT does not alleviate post-operative pain in **smokers** (Olson et al. 2009, RCT, [-]; Turan et al. 2008, RCT, [+])

ES 1.2.10 There is moderate evidence that in the long-term, smoking cessation has no effect on perception of pain in general population (Shi et al. 2011, retrospective cohort, [+])

PART 3: EFFECTS OF NICOTINE AND EFFECTS OF STOPPING SMOKING IN NON-CARDIAC AND NON-SURGICAL HOSPITAL PATIENTS

This part covers a mixture of studies concerning several topics. It is divided into 3 sections. Section 1 covers studies addressing safety of NRT in non-cardiac patients and effects of smoking ban; Section 2 concerns effects of nicotine and smoking on some medications; and Section 3 concerns the special case of ulcerative colitis.

Section 1a: Safety of NRT in hospital patients

This diverse group of studies did not identify any further risks of NRT use.

ES 1.3.1 There is strong evidence that the use of NRT in medically stable patients is not associated with an increased risk of adverse events (Lewis et al 1998, RCT, [+]; Molyneux et al 2003, RCT, [+]; Murray et al 1996, RCT, [++]; Murray et al 2009, prospective cohort, [+], Wagena et al. 2003, general review, [+])

ES 1.3.2 There is moderate evidence that renal disease can impair nicotine clearance (Molander et al 2000, prospective cohort, [+]; Whiss et al. 2000, prospective cohort, [+])

ES 1.3.3 There is moderate evidence that nicotine use in patients with renal disease does not adversely affect platelet function (Whiss et al. 2000, prospective cohort, [+])

ES 1.3.4 There is moderate evidence that nicotine has little effect on insulin secretion (Epifano et al. 1992, randomized cross-over study, [+]; Axelsson et al. 2001, randomized cross-over study, [+])

ES 1.3.5 There is moderate evidence that medicinal nicotine is associated with insulin resistance, although significantly less so than smoking (Epifano et al. 1992, randomized cross-over study, [+]; Axelsson et al. 2001, randomized cross-over study, [+])

Section 1b: Effects of smoking ban on hospital patients

Most smokers hospitalised in smoke-free hospitals experience some degree of tobacco withdrawal symptoms, but this is mostly mild and only a minority find abstinence in this setting difficult.

ES 1.3.6 There is moderate evidence that smokers who cannot smoke in hospital can experience some tobacco withdrawal symptoms (Rigotti et al 2000, prospective cohort, [+]; Zabaneh 1994, case study [-]; Carmel 2007, case study, [-]; Gallagher 1998, case study, [-]; Rosin et al 2001, case study, [-])

Section 2: Effects of tobacco withdrawal on theophylline, aminophylline, and insulin

Smoking and stopping smoking have an effect on the metabolism of a number of medicines. Theophylline levels are sensitive to smoking and abstinence and aminophylline levels are influenced even by passive smoking. In patients who change their smoking status, doses of these drugs need to be monitored and adjusted. There are inconsistent data regarding the effect of smoking on the absorption of subcutaneous insulin.

ES 1.3.7 There is moderate evidence that theophylline levels are sensitive to smoking and abstinence (Lee et al 1987, quasi-experimental, [+]; Rao 1996, case study, [-]) and aminophylline levels are influenced even by second hand smoke (Mayo et al. 2001, case control study, [+]). One study, Eldon et al. 1987 (cross-over trial, [+]), showed no effect of a 36-hour period of abstinence on serum theophylline levels.

ES 1.3.8 There is moderate evidence that nicotine does not influence theophylline levels (Lee et al 1987, quasi-experimental, [+])

ES 1.3.9 There are inconsistent data regarding the interaction between subcutaneous insulin and smoking (Klemp et al. 1982, quasi-experimental, [+]; Muhlhauser et al. 1984, quasi-experimental, [+])

Section 3: effects of smoking and smoking cessation on ulcerative colitis

Ulcerative colitis (UC) is an inflammatory disease of the colon, which is seen primarily in non-smokers and ex-smokers. Nicotine seems to be beneficial for UC, and stopping nicotine intake may lead to worsening of the disease.

ES 1.3.10 There is strong evidence that NRT can have positive effects on ulcerative colitis (Guslandi et al 1998, RCT, [+]; Guslandi et al 2002, RCT, [+]; Ingram 2005, RCT, [+]; Pullan et al 1994, RCT, [+]; Sandborn 1997, RCT, [+]; Thomas et al 1996, RCT, [+]; McGarth et al. 2009, systematic review [++]; Nikfar et al. 2010, systematic review [+])

ES 1.3.11 There is moderate evidence that smokers with ulcerative colitis experience worsening of their symptoms when they stop smoking (Bastida et al, review (+), Beaugerie et al 2001, retrospective cohort, [-]; Green et al 1998, retrospective cohort, [-]; Wahed et al. 2011, retrospective cohort, [-])

CHAPTER 2: EFFECTS OF NICOTINE USE AND EFFECTS OF TOBACCO WITHDRAWAL IN PATIENTS WITH MENTAL ILLNESS

The main hypothesis for why smoking rates are exceptionally high in people with mental health illness is that they smoke to alleviate some of the symptoms associated with their illness. The concern is therefore that when such patients stop smoking, either of their own accord or because they are forced to abstain, their functioning may deteriorate. There is also a specific concern that concurrent stopping smoking may undermine the efficacy of treatments for patients with alcohol and drug addictions. Finally, smoking affects the speed with which a number of psychiatric drugs are metabolised and stopping smoking may lead to an increase in drug side effects.

In this chapter we review literature concerning the effects of abstinence and of stop-smoking treatments on psychiatric symptoms and psychiatric medications, and also the literature on the effects of smoking cessation on treatment outcome of other drug dependencies.

We identified 92 relevant papers. The material is organised into the following Parts:

1. Effects of tobacco abstinence and effects of stop-smoking medications on mental health
2. Effects of tobacco abstinence on psychiatric medications
3. Effects of smoking cessation on the outcome of other substance abuse treatment;
4. Effects of smoke free policy on behaviour and psychiatric symptoms of psychiatric in-patients.

PART 1: EFFECTS OF SMOKING CESSATION AND EFFECTS OF NRT ON MENTAL HEALTH OF PSYCHIATRIC PATIENTS

Enforced abstinence from smoking can induce acute discomfort, but in the small self-selected group of patients who manage to achieve longer-term abstinence, no deterioration

of mental health was observed. Bupropion promotes smoking cessation and may have positive effects on mood.

ES 2.1 There is strong evidence that PTSD patients who manage to stop smoking do not experience any worsening of their condition (McFall et al 2005, RCT [+]; McFall et al 2010, RCT [++])

ES 2.2 There is good evidence that in patients with schizophrenia, overnight abstinence from smoking can increase negative symptoms (Smith et al 2002, cross over trial, [++])

ES 2.3 There is moderate evidence that short (7 days) smoking abstinence does not lead to cognitive deterioration but may slow down psychomotor speed (Evins et al 2005a and 2005b, RCT [+])

ES 2.4 There is weak to moderate evidence that patches may decrease agitation in smokers with schizophrenia with acute symptoms admitted to non-smoking wards but increase involuntary movements (Allen et al 2011, RCT [+], Dalack et al 1999, RCT [+])

ES 2.5 There is strong evidence that treatment with bupropion for smoking cessation does not lead to any deterioration in mental health (Tsoi et al 2010a, systematic review [+]; Tsoi et al 2010b, systematic review [+]; Banham & Gilbody 2010, systematic review [+]; Evins et al 2001, RCT [+]; Evins et al 2005a and 2005b, RCT [+]; Evins et al 2007, RCT [+]; Fatima et al 2005, cross over trial, [+]; George et al 2002, RCT [+]; George et al 2008, RCT [+]).

ES 2.6 There is moderate evidence that treatment with bupropion may lead to improved mood and reduction in akathisia (Evins et al 2001, Evins et al 2007, RCT [+]; RCT [+]; George et al 2002, RCT [+])

ES 2.7 There is strong evidence that receiving smoking cessation interventions (which is not the same as stopping smoking, which very few of the recipients of such interventions achieve) does not adversely affect mental health (Allen et al 2011, RCT [+]; Baker et al 2006, RCT [+]; Evins et al 2001, RCT [+]; Evins et al 2005a and 2005b, RCT [+]; Evins et al 2007, RCT [+]; Fatima et al 2005, cross over trial, [+]; Gallagher et al 2007, RCT [+]; George et al 2000, RCT [+]; George et al 2002, RCT [+]; George et al 2008, RCT [+]; Williams et al 2010, RCT [+]).

ES 2.8 There is good evidence that among patients with schizophrenia or schizoaffective disorder, those who manage to stop smoking do not experience any worsening in their condition (Evins et al 2007, RCT [+]; Gallagher et al 2007, RCT [+]; Williams et al 2010, RCT [+])

ES 2.9 There is moderate evidence that mood improves in depressed smokers who manage to stop smoking compared to those who fail in their quit attempt (Blalock et al 2008, prospective cohort [+]; Thorsteinsson et al 2001, RCT [+])

PART 2: EFFECTS OF STOPPING SMOKING ON PSYCHIATRIC MEDICATION

Several common psychiatric medications are metabolised faster by smokers than by non-smokers. The corollary of this finding is that in stable patients on well-tolerated medication doses, stopping smoking is likely to increase systemic levels of these drugs and needs to be accompanied by dose adjustments. We found no data on whether NRT mitigates the effects of stopping smoking on increasing systemic levels of these medications, but it is unlikely to do so.

ES 2.10 There is strong evidence that clozapine and olanzapine are metabolised much faster by smokers, and stopping smoking can increase their systemic levels (Derenne & Baldessarini 2005, case study, [-]; Dettling et al. 2000, prospective cohort [+]; Diaz et al 2005, randomised non-controlled trial, [+]; Haring et al. 1989 retrospective cohort [+]; Haslemo et al 2006, prospective cohort [+]; Meyer 2001, case control study [+]; Ozdemir et al 2001, prospective cohort [+]; Pettitt et al. 2009, case study, [-]; Rostami-Hodjegan et al. 2004, retrospective cohort [+]; Sandson et al. 2007, case study, [-]; Seppala et al. 1999, prospective cohort [+]; van der Weide et al. 2003, retrospective cohort, [+]; Wenzel-Seifert et al 2011, retrospective cohort [+]; Wetzel et al. 1998, prospective cohort [+]; Callaghan et al. 1999, prospective cohort [+]; Carrillo et al. 2003, prospective cohort [+]; Gex-Fabry et al 2003, retrospective cohort [+]; Skogh 2002, retrospective cohort [+]; Wu et al. 2008, prospective cohort [+]). Although two studies found no significant effects of smoking on serum clozapine levels (Hasegawa et al. 1993, prospective cohort [+]; Palego et al. 2002, prospective cohort [+]).

ES 2.11 There is moderate evidence that haloperidol is metabolised faster by smokers than by non-smokers (Jann et al. 1986, prospective cohort [+]; Miller et al. 1990, prospective cohort [+]; Perry et al. 1993, retrospective cohort [+] found a difference, Fukunda 2000, retrospective cohort [+]) found no difference)

ES 2.12 There is moderate evidence that chlorpromazine is metabolised faster by smokers than by non-smokers (Chetty et al. 1994, retrospective cohort [+]; Pantuck et al 1982, prospective cohort, [+]; Stimmel and Falloon (1983, case study [-])

ES 2.13 There is moderate evidence that fluphenazine, perphenazine and thioridazine are metabolised faster by smokers than by non-smokers (Ereshefsky et al 1985, retrospective cohort [+]; Jin et al 2010, prospective cohort [+]; Berecz et al 2003, prospective cohort [+])

ES 2.14 There is weak evidence that methadone levels increase following a reduction in smoking (Wahawisan et al 2011, case study, [-]).

ES 2.15 There is moderate evidence that smoking does not affect the metabolism of triazolam, diazepam or midazolam (Ochs et al. 1987, prospective cohort [+]; Otani et al. 1997, prospective cohort [+]; Ochs et al. 1985, prospective cohort [+]).

ES 2.16 There is inconsistent evidence regarding the effect of smoking on alprazolam. One study showed that smoking was associated with increased clearance (Hossain et al. 1997, prospective cohort [+]). Another found that smoking had no effect on any pharmacokinetic parameters (Otani et al. 1997, prospective cohort [+]).

ES 2.17 There is weak evidence that smoking increases the metabolism of desmethyldiazepam when given orally (Norman et al. 1981, prospective cohort [+]), but not intravenously (Ochs et al. 1986, prospective cohort [+]).

ES 2.18 There is weak evidence that smoking has no effect on the clearance of carbamazepine (Martin et al. 1991, retrospective cohort, [+])

ES 2.19 There is moderate evidence that the metabolism of quetiapine (an atypical antipsychotic) is unaffected by tobacco smoke (DeVane & Nemeroff 2001, review [+]).

ES 2.20 There is weak evidence that smoking increases metabolism of two selective serotonin reuptake inhibitors duloxetine (Fric et al. 2008, retrospective cohort [+]) and fluvoxamine (Spigset et al. 1995, prospective cohort [+]).

ES 2.21 There is weak evidence that smoking has no effect on the metabolism of thiothixene (Ereshesfsky et al. 1991, retrospective cohort, [+]).

ES 2.22 There is weak evidence that smoking is associated with lower plasma levels of clomipramine (John et al. 1980, prospective cohort, [+]) and imipramine (Perel et al. 1976, retrospective cohort, [+]).

ES 2.23 There is inconsistent evidence regarding the effect of smoking on amitriptyline and nortriptyline. Two studies showed smoking was associated with lower plasma levels of these drugs (Linnoila et al. (1981, prospective cohort, [+]; Perry et al. 1986, prospective cohort, [+]) and three studies found no effect of smoking on pharmacokinetic parameters (Norman et al. 1977, prospective cohort, [+]; Rickels et al. 1983, prospective cohort, [+]; Ziegler & Biggs 1977, prospective cohort, [+]).

ES 2.24 There is weak evidence that smoking has no effect on the metabolism of zotepine (Kondo et al. 1996, prospective cohort [+]).

ES 2.25 There is moderate evidence that the metabolism of zuclopenthixol (an antipsychotic drug) is unaffected by tobacco smoke (Jaanson et al. 2002, prospective cohort [+]; Jorgensen et al. 1985, prospective cohort [+]).

PART 3: EFFECTS OF SMOKING CESSATION INTERVENTIONS ON THE USE OF OTHER SUBSTANCES

The question of whether people undergoing drug and alcohol treatments should be encouraged to stop smoking at the same time has no generally accepted answer at the moment. There are concerns that removing one source of gratification may make the others more precious, or that self-control is a limited resource and that refraining from one desired activity may undermine self-control in other areas. On the other hand, some drug and alcohol advisors emphasise the importance of a fresh start free of all addictive substances and many tobacco control specialists promote smoking cessation as a priority in any setting.

A number of studies show that the provision of stop-smoking treatments does not undermine concurrent treatments for alcohol and drug dependence. However, the majority of these studies analysed only the effects of treatment allocation, and the large majority of smokers did not manage to stop smoking. The questions of whether actual stopping smoking helps with or undermines drug and alcohol sobriety, and whether concurrent or sequential treatments yield better results, have not been fully answered so far and await future trials. (This does not concern methadone maintenance treatment, where in stable patients stopping smoking has no negative effects).

ES 2.25 There is strong evidence that receiving smoking cessation treatment (as opposed to actually stopping smoking) does not undermine concurrent treatments for other drug addictions (Brown et al 2001, RCT [+]; Burling et al 2001, RCT [+]; Campbell et al 1995, prospective cohort, [+]; Cooney et al 2007, RCT [+]; Cooney et al 2009, RCT [+]; Dunn et al 2009, prospective cohort [+]; Grant et al 2007, RCT [+]; Haug et al 2004, RCT, [+]; Kalman et al 2001, RCT [+]; Okoli et al 2010, general review [+]; Prochaska et al 2004, systematic review, [+]; Reid et al. 2008, RCT [+]; Richter et al 2005, prospective cohort, [-]; Shoptaw et al 2002, RCT [+])

ES 2.26 There is good evidence that in alcoholics, smoking deprivation does not increase cue-induced urge to drink (Cooney et al 2003, randomised cross over trial [++])

ES 2.27 There is good evidence that abstinence from smoking does not undermine opioid maintenance treatment in successfully maintained patients (Campbell et al 1995, prospective cohort, [-]; Dunn et al 2009, prospective cohort [+]; Haug et al 2004, RCT, [+]; Okoli et al 2010, general review [+]; Richter et al 2005, prospective cohort, [-]; Shoptaw et al 2002, RCT [+])

ES 2.28 There is moderate evidence that being unable to smoke during treatment reduces the efficacy of inpatient treatment for cocaine dependence (Joseph et al 1993b, retrospective cohort [+])

ES 2.29 There is good evidence that being unable to smoke during treatment encourages successful smoking cessation later (Joseph et al 1990, prospective cohort [+]; Joseph 1993a, prospective cohort [+]; Joseph et al 2004, RCT [+])

ES 2.30 There is weak evidence that smoking cessation treatment may assist with abstinence from opiates (Shoptaw et al 2002, RCT [+]), although a small prospective cohort study showed no beneficial effect (Shoptaw et al 1996, prospective cohort, [-]).

ES 2.31 There is weak evidence that smoking cessation is associated with abstinence from alcohol at long-term follow-up (Grant et al 2007, RCT [+]).

PART 4: EFFECTS OF SMOKE-FREE POLICY ON BEHAVIOUR AND SYMPTOMS IN PSYCHIATRIC IN-PATIENTS

Smoking bans generate a significant increase in patients' weight and in systemic levels of clozapine and probably other drugs. Otherwise the reviewed papers provide mixed information, with some studies reporting some negative impact on symptoms and behaviour (mostly only during the initial implementation), some finding no adverse effects, and some reporting positive effects.

ES 2.31 There is mixed evidence regarding the effect of smokefree policy on behaviour and symptoms in inpatients with mental illness. Five studies found some signs of worsening functioning within a few weeks of the ban (Cole et al 2010, retrospective cohort [+]; Cormac et al 2010, prospective cohort [+]; Harris et al 2007, retrospective cohort [+]; Ryabik et al 1994, prospective cohort [+]; Velasco et al 1996, retrospective cohort [+]). Three studies found no change after smoking ban (Resnick & Bosworth 1989, retrospective cohort [+]; Shetty et al 2010, retrospective cohort [+]; Voci et al 2010, retrospective cohort [+]) and four studies found improvements in disruptive behaviours (Hempel et al 2002, retrospective cohort [+]; Hollen et al 2010, retrospective cohort [+]; Smith et al 1999, prospective cohort [+]; Quin et al 2000, prospective cohort [+])

ES 2.32 There is moderate evidence that total smoking bans generated a significant weight gain (Harris et al 2007, retrospective cohort [+]; Hempel et al 2002, retrospective cohort [+])

ES 2.33 There is good evidence showing that total smoking bans lead to increased systemic levels of clozapine and a need to lower its dosing (Meyer 2001, case control study [+]; Cormac et al 2010, prospective cohort [+]; Shetty et al 2010, retrospective cohort [+])

CHAPTER 3: SAFETY OF NICOTINE REPLACEMENT IN PREGNANCY

The available evidence suggests that NRT is safer than smoking, although probably not entirely safe. There are currently no safety reasons to withhold NRT from pregnant women who are unable to stop smoking without it. However, given the 'probably not entirely safe' verdict and the question marks about NRT efficacy in this population, there is a strong rationale for examining safety and efficacy of varenicline in pregnant smokers.

ES 3.1 There is strong evidence that in some conditions nicotine patches can deliver as much nicotine as smoking, but have overall smaller effects on foetal haemodynamics (Hackman et al. 1999, prospective cohort [-]; Ogburn et al. 1999, prospective cohort [+]; Schroeder et al. 2002, prospective cohort [+]; Oncken et al. 1997, randomised cross-over trial [+]; Wright et al. 1997, prospective cohort [+])

ES 3.2 There is strong evidence that oral NRT products deliver less nicotine than smoking and have smaller or no effect on foetal haemodynamics (Lehtovirta et al 1983, non-randomised trial [-]; Lindbald & Marsal 1987, randomised cross-over trial [+]; Lindbald et al. 1988, randomised cross-over trial [+]; Oncken et al. 1996, RCT [+]; Oncken et al. 2009, RCT [+])

ES 3.3 There is strong evidence that nicotine clearance is increased during pregnancy (Dempsey et al. 2002, experimental study [++])

ES 3.4 There is moderate evidence that there is minimal systemic uptake of nicotine in breast milk by the breastfed infant (Ilett et al. 2003, prospective cohort [+])

ES 3.5 No trial so far has identified any adverse pregnancy outcomes linked to NRT (Coleman et al. 2012 RCT [++]; Hegaard et al. 2003, RCT [+]; Hotham et al. 2006, RCT [-]; Kapur et al 2001, RCT [-]; Oncken et al. 2008, RCT [+]; Pollack et al. 2007, RCT [+]; Wisborg et al. 2000, RCT [+]; Lassen et al 2010, retrospective cohort [+]; Strandberg-Larsen et al. 2008, retrospective cohort [+])

ES 3.6 There is inconsistent evidence regarding positive effects of NRT on birth weight. Two studies found this (Wisborg et al. 2000, RCT [+]; Oncken et al. 2008, RCT [+]) but four studies found no effect (Gaither et al. 2009, retrospective cohort [-]; Lassen et al 2010, retrospective cohort [+]; Pollack et al. 2007, RCT [+]; Hegaard et al. 2003, RCT [+]).

ES 3.7 There is weak evidence that babies born to mothers who used NRT during pregnancy have an increased risk of musculoskeletal abnormalities compared to babies born to non-smokers (Morales-Suarez-Varela et al. 2006, retrospective cohort [+]). The prevalence of musculoskeletal malformations was higher in children of NRT users (14/250, 5.6%) compared to non-smokers (1242/55,915, 2.2%), RPR=2.6, (CI: 1.53-4.52). When only major musculoskeletal malformations were considered, there was no significant difference (2.4% vs. 1.2%, RPR=2.05 (95% CI: 0.91–4.63). The findings are difficult to interpret because no comparison was made between NRT users and smokers not using NRT and the numbers of NRT users are so small. Data from high quality study (Coleman et al. 2012 [RCT ++]) failed to show any association between NRT use and congenital abnormalities.

ES 3.8 There is moderate evidence that babies born to mothers who used NRT during pregnancy had an increased risk of cryptorchidism compared to babies born to non-smokers (Damgaard et al. 2008, prospective cohort [+]). Smoking was not found to be a risk factor.

However the study does not provide a comparison between smokers who did and smokers who did not use NRT, so the effects of smoking cannot be differentiated from any effects of NRT.

DISCUSSION, GAPS AND RESEARCH RECOMMENDATIONS

The review concerned two main clinically relevant issues. The first is whether there are any populations or circumstances where NRT use may be unsafe; and the second is whether there are any populations or circumstances where acute tobacco abstinence may be unsafe.

Regarding the safety of NRT, the review did not identify any safety concerns related to its use for stopping smoking in cardiac patients or in any other group of secondary care users. No concerns were raised about NRT safety in mental health service users either, although it may not be effective in this population. Regarding pregnancy, any risks associated with NRT use are much smaller than those associated with smoking, and may be clinically negligible. Nevertheless, given uncertainty about NRT efficacy in pregnant smokers and the possibility that it is not totally harmless, there is a need for research into the safety and efficacy of other treatments such as varenicline.

The review identified one area of NRT use that does raise concerns. It seems that in some hospitals it became a common practice to put NRT patches on ICU and surgery patients deemed to present a risk of delirium. There is little evidence that tobacco deprivation contributes to delirium. There is also no evidence that NRT patches help and there is some evidence that they may be harmful in several ways, although some of these the finding are likely to be due to patient selection. No controlled trial has examined this issue. This represents a gap in evidence that would be relatively easy to fill.

Regarding effects of acute tobacco abstinence, this may affect comfort of some hospitalised patients, and it increases systemic levels of a number of medications. This is of particular relevance to patients hospitalised in psychiatric hospitals. E.g. patients on olanzapine are likely to experience a significant weight gain and increased risk of diabetes due to their medications. When hospitalised and prevented from smoking, they are at risk of further weight gain due to tobacco withdrawal and some additional weight gain and other, potentially serious, adverse effects from an increase in systemic olanzapine levels. A recommendation should be considered for routine lowering of dosing in all smokers on these medications admitted to smoke-free wards.

There is one relevant area where more evidence is needed, concerning the timing of quit attempts in people undergoing treatment for drug and alcohol dependence. It is currently not known whether stopping smoking during such treatments facilitates or undermines drug and alcohol sobriety or has no effect on it.

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METHODOLOGY

RATIONALE FOR THIS REVIEW

Each year thousands of smokers are admitted to secondary care settings in the United Kingdom (UK) for treatment of smoking related diseases. For many of these people the admission and the illness represents a prompt for stopping smoking, and brings them into contact with health care professionals who can help. Even for smokers who are not ready to quit, assistance may be required to help them abstain whilst in a smokefree environment.

Nicotine replacement therapy (NRT) is the most commonly used smoking cessation treatment in the secondary care setting, where it is effective in alleviating the symptoms of tobacco withdrawal and increases the chances of long-term abstinence (Stead, Perera et al. 2008). Traditionally NRT has been used only for smoking cessation, but more recently its use has been extended to assist smoking reduction and temporary abstinence and this further increased its usefulness.

Although NRT has a good safety profile, there remains some concern about the safety of nicotine, especially in groups such as pregnant women and patients with cardiovascular disease. These concerns are common both among smokers and among healthcare professionals. One concern is the incorrect belief that nicotine is the main component in tobacco smoke responsible for illness. Many smokers believe that NRT products are just as likely as cigarettes to cause smoking related disease (Bansal, Cummings et al. 2004; Shiffman, Ferguson et al. 2008). There is general agreement among experts that it is not nicotine that causes the adverse health effects associated with smoking. However health risks associated with nicotine cannot be ruled out completely. There are some data that suggest that nicotine might have adverse effects in pregnancy (Bruin, Gerstein et al. 2010) and other concerns focus on the cardiovascular system.

Abstinence from smoking can result in adverse effects such as those associated with tobacco withdrawal (e.g. irritability and depression) and changes in plasma levels of some medications. Smoking tobacco causes induction of the liver enzyme cytochrome P450 (CYP1A1, CYP1A2) (Zevin and Benowitz 1999). This is mainly the effect of the polycyclic aromatic hydrocarbons present in tobacco smoke. CYP1A2 is responsible for the breakdown of several medications (e.g. clozapine) and medications metabolised by this enzyme will be metabolised faster in smokers than in non-smokers. On a person's cessation of smoking these enzymes return to a normal level of activity that can result in a change in metabolism of several medications. Subsequent dosage adjustments may be necessary to avoid over-medication.

Smokers with mental health illness are of particular interest in this context. They often use medicines that are affected by smoking and may cause dangerous side effects in users who decide to or are forced to abstain from smoking. There is also a fairly widespread belief that their mental health may also be affected by the use and withdrawal of tobacco and/or nicotine.

In summary, the issues above concern three main groups of smokers: Those hospitalised with physical illness, smokers hospitalised with mental illness, and pregnant smokers. We review the available evidence concerning these three groups in three separate chapters.

Aim

The aim of this review is to ascertain the effects of nicotine intake or changes in levels of nicotine intake including nicotine from tobacco, on the mental and physical health of people using secondary care services; and on pregnant women and the foetus. We shall cover these effects separately for smokers hospitalised with physical illness, smokers with mental illness, and pregnant smokers.

Research questions

This review aims to answer the following three questions posed by NICE:

Question 1: What are the effects of nicotine intake, or changes in levels of nicotine intake, on the mental and physical health of people using secondary care services who are on medication?

Question 2: What are the effects of tobacco consumption, or changes in tobacco consumption, on the mental and physical health of people using secondary care services who are on medication?

Question 3: What are the effects of nicotine intake, or changes in levels of nicotine intake, on the mental and physical health of people using secondary care services?

Structure of this review

We have structured this review in a pragmatic and logical way that addresses the three main populations: (1) users of general secondary care services, (2) mental health service users and (3) pregnant women. This is because each of these three groups generates clinically important questions concerning nicotine use and tobacco withdrawal, which are specific to them and not relevant to the other two groups. Each population with its set of relevant issues is covered in a separate Chapter.

The key topics covered in this review are safety of medicinal nicotine and of nicotine deprivation in hospital patients (both in those who are medically stable and acutely unwell), the effects of smoking status on medications, the effects of nicotine deprivation on psychiatric symptoms in mental health service users, and the safety of medicinal nicotine in pregnancy.

Groups that are covered in this review

This review includes evidence from studies of the following people of all ages who use tobacco (smoked or smokeless):

- Patients and users of acute and maternity services, including those who are in the process of being referred to hospital or have recently been discharged;
- Patients and users of secondary care mental health services, including those who are in the process of being referred to or have recently been discharged from:

- Child, adolescent, adult and older people mental health services; and
- Inpatient, residential and long-term care for severe mental illness in hospitals, psychiatric and specialist units and secure hospitals.

ISSUES NOT COVERED IN THIS REVIEW

This review does not consider evidence relating to long-term effects of tobacco use and of stopping smoking on health. This is a very broad area outside the scope of this review that focuses on safety issues related to acute abstinence and to use of NRT.

The review also does not cover the efficacy of NRT in alleviating tobacco withdrawal and in helping smokers quit. This is covered in review 2.

SEARCH METHODOLOGY

The evidence base for this review was sourced from reviews and trials published between 1980[2] and December 2011 in the English language. The searchable databases included ASSIA, MEDLINE, Cochrane Central Register of Controlled Trials, CINAHL and PsychINFO (a full list of the databases searched is included in the review protocol in Appendix 1). Several websites were also searched for relevant data these included NHS Centre for Smoking Cessation and Treatment, Action on Smoking and Health (ASH), Treat tobacco.net and WHO Tobacco Free Initiative (a full list of websites searched is 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 main search strategy combined terms relevant to capture evidence on the effects of nicotine use, or withdrawal in secondary care patients.

The search strategy was developed to capture all relevant data for the review (see appendix 1 for search terms used).

The following studies were considered for the review:

- Quantitative studies (both experimental and observational studies, including case studies);
- Qualitative studies;
- Systematic reviews, reviews, reviews of reviews; and
- Information that addresses the review questions.

[2] Some papers with a publication date prior to 1980, recommended by the NICE PDG, have been included post-database search

SEARCH RESULTS

Searches of the databases returned 21,400 records. After duplicates were removed a total of 10,466 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 to check accuracy. Of the total number of abstracts 192 (1.8%) required review from a third member of the project team as to whether they should be included in the review. A total of 442 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 the appendix 2, along with a brief reason for exclusion. Each of the included studies was rated ('++', '+' or '-' – see Table 1) to indicate its quality. Data from included studies were extracted into evidence tables. The quality of the included trials and reviews was assessed using criteria outlined in NICE guidance.

Table 1: Quality assessment ratings

++	All or most of the checklist criteria have been fulfilled; where they have not been fulfilled the conclusions are very unlikely to alter.
+	Some of the checklist criteria have been fulfilled, where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter.
–	Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

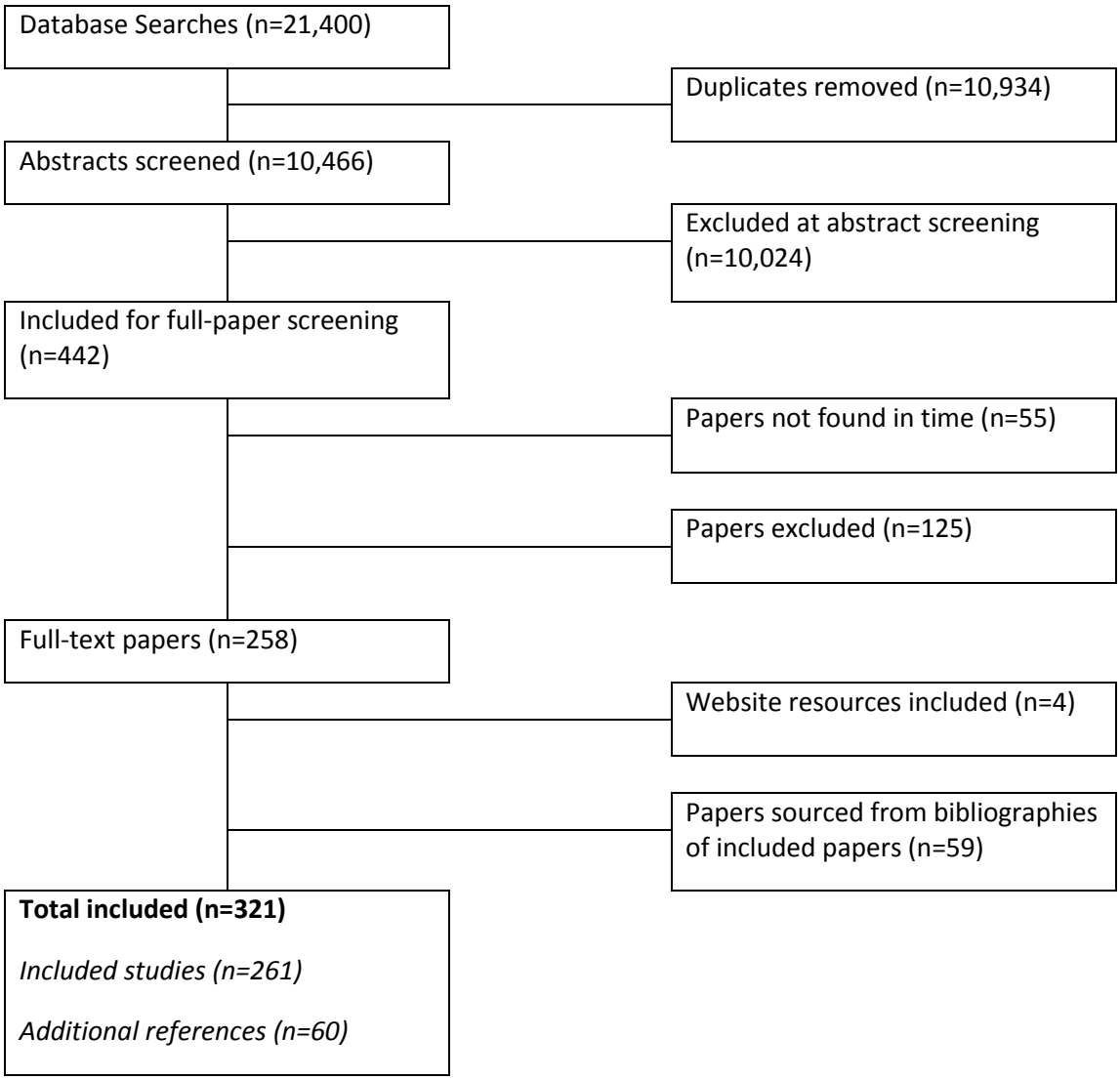
Regarding individual studies, studies with serious methodological problems and most case studies were marked as -, well conducted RCTs with representative samples were marked as ++, and the remaining studies were marked as +.

EVIDENCE STATEMENTS

Evidence statements used in this review contain a descriptor, strength, and direction of the evidence. The strength of evidence was classified as:

- No evidence
- Inconsistent evidence (studies with contradictory results)
- Weak evidence (one or more studies but none scores [+] for quality)
- Moderate evidence (one or more studies, where at least one scores [+] for quality and the results are consistent).
- Strong evidence (two or more studies, where at least two score a [+] for quality; or at least one study which scores (++) for quality, and the results are consistent)

Figure 1: Flow diagram for papers



CHAPTER ONE

Effects of nicotine and of acute tobacco withdrawal in hospitalised patients

Introduction

We identified 101 studies seeking to determine the health effects of nicotine, primarily nicotine delivered via NRT, and the effects of abstinence from tobacco on hospitalised smokers. Patients with mental health illness are covered in Chapter 2.

We organised the material addressing one or more aspects of this wide and varied field into the parts and sections structure to allow consideration of manageable volumes of evidence concerning distinct clinical issues.

1. Part 1 concerns cardiac patients
2. Part 2 concerns intensive care unit (ICU) and surgery patients
3. Part 3 concerns all other hospital patients

A brief interpretative summary of findings is provided at the end of each section, and evaluation and evidence statements are at the end of the Chapter.

Part 1: Effects of nicotine in patients with cardiovascular disease

Next to pregnant women, patients with cardiovascular disease (CVD) are considered the group of health service users most sensitive of any potential harm from NRT. There are also concerns about the effect of stopping smoking on metabolism of some CVD drugs.

This part includes 3 sections. Section 1 covers acute effects of nicotine on the cardiovascular system; Section 2 is covering effects of NRT used over extended period of time for smoking cessation; and Section 3 covers the effects of smoking and of tobacco abstinence on CVD medications.

Section 1: Studies of acute effects of NRT

We found eight experimental studies examining acute effects of NRT on the cardiovascular system.

Table 2 summarises the studies included in this section.

Table 2: Summary of studies included in part 1 section 1

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Benowitz et al (1993)	Randomised placebo controlled cross-over trial	USA 12 male smokers allocated to three 5-day treatment blocks (smoking 22 cpd, 21mg patch, and placebo patch).	Urine concentration of thromboxane B2 (TXB2), blood samples and platelet aggregation.	Smoking was associated with significantly greater excretion of TXB2, higher levels of plasma fibrinogen.	Quality +
Gembala et al (2006)	Non-randomised controlled trial	USA 27 healthy subjects allocated to smoking a single cigarette or to chew a piece of 4mg gum after overnight abstinence.	Left ventricular diastolic function assessed on an echocardiogram.	Only cigarette smoking was associated with acute, but non-significant, changes in LV diastolic function.	Quality +
Goldsmith et al (1989)	Prospective cohort study	USA 11 patients (2 smokers) with congestive heart failure and 8 healthy subjects (1 smoker) chewed a piece of 2mg gum over an hour.	Heart rate (HR), mean arterial pressure (MAP), plasma noradrenaline (NA) and nicotine.	Healthy subjects showed a significant increase in HR and plasma NA after 45 minutes. Heart failure patients showed no significant change in plasma NA.	Quality -
Kelley et al (1996)	Randomised placebo controlled trial	USA 19 smoking patients referred for evaluation of chest pain used nicotine nasal spray (n=14) or placebo spray (n=5) after smoking a single cigarette.	Coronary cineangiography and plasma nicotine levels.	Only smoking the first cigarette was associated with increased heart rate and a change in coronary artery diameter.	Quality +
Leja et al (2007)	Randomised placebo controlled trial	USA 55 smokers with coronary artery disease (CAD) received 21mg patch or placebo whilst smoking for a week, and then trying to abstain for 3 weeks.	Myocardial perfusion defect measured after an exercise test, blood nicotine levels and CO in expired breath.	No significant differences were seen in total perfusion defect between patch and placebo.	Quality +
Mahmarian et al (1997)	Prospective cohort	USA 40 patients with CAD were given 14mg patches for 3 days and then 21mg patches for 3 days, and asked to stop smoking.	Changes in perfusion defect and time to ST segment depression on ECG. CO in expired breath and serum nicotine and cotinine levels.	In patients using patches showed the total perfusion defect size decreased (improved) from baseline and time to ST depression significantly increased (improved) from baseline.	Quality +
Nitenberg et al (1999)	Controlled trial	France 17 ex-smokers undergoing diagnostic coronary angioplasty. A cold-pressor test given without and with chewing 4mg nicotine gum for 30 minutes.	Diastolic and systolic aortic blood pressures and cross sectional area of normal and stenosed coronary arteries.	Cold pressor test increased blood pressures and decreased cross-sectional area of both normal and diseased arteries; the gum had no additional effect.	Quality +
Tanus-Santos et al (2001)	Single blind, placebo controlled	Brazil 9 healthy non-smoking controls, 10 normotensive	MAP, heart rate, plasma TXB2 levels were measured.	The patch caused a significant increase in MAP in normotensive smokers	Quality +

	cross over trial	smokers, and 10 hypertensive smokers. Admitted to a research unit on 2 different days and randomised to 21mg patch or placebo.		and controls. No significant changes seen in the hypertensive smokers.	

Benowitz et al. (1993, RCT, [+]) studied 12 healthy male smokers admitted to a research ward for a total of 16 days and allocated to three 5-day treatment blocks. The treatment blocks were to smoke 22 cigarettes per day, to wear a 21mg patch or to wear a placebo patch. At 24-hours, AUC values for nicotine concentrations were 451+/- 62 ng/ml in the smoking condition and 357+/- 30 ng/ml on the patch (NS). Smoking was associated with significantly greater excretion of TXB2 and higher levels of plasma fibrinogen than both nicotine and placebo patch, and the patches did not differ. Nicotine does not appear to cause an increase in platelet activation and fibrinogen. Although this study did not examine the effects of patches in people with CVD, the results suggest that any risk associated with patch use is outweighed by the risks of continued smoking.

Gembala (2006, non-randomised CT, [+]) studied 27 healthy subjects (most were ex-smokers) self-assigned to smoking a single cigarette or to chewing a piece of 4mg nicotine chewing gum after overnight abstinence from smoking. Prior to smoking or gum use participants had an echocardiogram, which was repeated immediately after smoking and 15 minutes after administration of the gum. All subjects had normal LV diastolic function. Cigarette smoking was associated with acute changes in LV diastolic function that were in the direction of impaired relaxation (although this was not clinically significant). Gum use had no effect on LV diastolic function.

Goldsmith (1989, prospective cohort, [-]) recruited 8 healthy subjects (1 smoker), and 11 patients with congestive heart failure (2 smokers) to examine the effects of chewing 2mg nicotine gum for an hour. Healthy subjects showed a significant increase in HR and plasma noradrenaline at 45 minutes ($p<0.01$). Heart failure patients showed a non-significant change in heart rate and plasma NA. Both groups showed a small rise in mean arterial pressure, but this was only significant in the heart failure group at 45 minutes after gum use (increased from 85 +/-10 mmHg to 91+/-13 mmHg, $p<0.05$). The results are difficult to interpret because the majority of subjects were non-smokers.

Keeley (1996, RCT, [+]) randomised 19 smokers referred for cardiac catheterisation to receive either the nicotine nasal spray (N=14) or placebo nasal spray (N=5). After overnight abstinence participants smoked a cigarette. A 20-minute 'washout period' was allowed before the procedures were repeated with the nasal spray. Another cigarette was smoked 5 minutes after the nasal spray was used. Coronary cineangiography and plasma nicotine levels were taken at baseline and 5 minutes after each cigarette and nasal spray. Smoking the first cigarette, but not nicotine spray or second cigarette, increased heart rate. Smoking resulted in a significant increase in blood nicotine (4 +/- 2 to 18 +/- ng/ml, $p<0.0001$). The increase in blood nicotine after use of the nasal spray did not reach significance (9 +/- 2 to 15 +/- 2). Smoking the first cigarette was the only condition associated with a significant change (-5% +/- 2, $p=0.009$) in coronary artery diameter. The spray seems to have delivered little nicotine, but a 5-minute post-use interval may have been too short. With this proviso, the results can be interpreted as showing that using nicotine spray while smoking did not generate any safety concerns in CVD patients.

Leja (2007, RCT, [+]) randomised 55 smokers with coronary artery disease to either 21mg or placebo patch whilst continuing to smoke for a week. Patch use was associated with a significant increase in blood nicotine levels (p=0.01) and a decrease in CO (p=0.02) at week 1. No significant differences were seen in total perfusion defect between nicotine patch and placebo patch groups (25+/-16 to 23 +/- 15 for patch and 21 +/- 10 to 17 +/- 10 for placebo, p=0.37).

Mahmarian (1997, prospective cohort, [+]) studied 40 patients with CAD who were given 14mg patches for 3 days and then 21mg patches for a further 3 days. Whilst wearing patches patients were asked to stop smoking. Carbon monoxide levels and cigarette consumption both showed significant decrease from baseline, whilst nicotine levels increased (15.8 +/- 8.3 to 24.2 +/- 12.0 to 30.4 +/- 10.8 ng/ml), p<0.001. Time to ST depression significantly increased from baseline (352 +/- 132 s) when on the 14mg patch (436 +/- 121 s) and 21mg patch (417 +/- 133 s), p<0.01. Total perfusion defect size decreased from baseline (17.5% +/- 10.6) on 14mg (12.6 +/- 10.1) and 21 mg patches (11.8 +/- 9.9), p<0.001. These were beneficial effects, most likely due to smoking reduction.

Nitenberg (1999, controlled trial, [+]) investigated 17 ex-smokers undergoing diagnostic coronary angioplasty. A baseline coronary arteriography was undertaken followed by a cold pressor test (sympathetic stimulation). The same procedure was undertaken after the patient had chewed one piece of 4mg nicotine gum for 30 minutes. The cold pressor test increased blood pressure; however the gum had no additional effect. No significant changes were observed in heart rate (HR) in either condition. The cold pressor test resulted in a significant decrease in cross-sectional area of both normal and diseased arteries (p<0.0001). The gum had no additional effect.

Tanus-Santos (2001, controlled cross-over trial, [-]) studied 9 healthy, non-smoking controls, 10 normotensive smokers, and 10 hypertensive smokers. Participants were admitted to a research unit on 2 different days and randomised to 21mg or placebo patch. There was a significant (p<0.05) increase in mean arterial pressure (MAP) and HR and in plasma thromboxane B2 levels in the non-smokers control group, 30-60 minutes after applying the patch. There was also a significant increase in MAP in the normotensive smokers from 2-4 hours after application of the patch. There were no significant changes in the hypertensive smokers.

INTERPRETATION

In laboratory studies involving several different NRT formulations (4 studies of patches, 3 of oral NRT and 1 study of nicotine nasal spray), acute effects of NRT on cardiovascular parameters were weaker than effects of smoking. Where participants smoked and used NRT during the same time period, NRT use did not contribute any additional negative effects. No signal of risk that would require further investigation has emerged.

SECTION 2: STUDIES OF EFFECTS OF NRT USED TO STOP SMOKING

Given the NRT is often used routinely with cardiac patients, and a number of NRT trials were conducted in this population, there is now a volume of data relevant for considering safety of such 'real life' use of NRT over an extended period of time.

We found five experimental studies, one systematic review, four observational studies, and four case studies. They are summarised in Table 3.

Table 3: Summary of studies included in part 1 section 2

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Allen et al (1994)	Randomised placebo controlled trial	USA 935 healthy smokers given patches 21mg, 14mg, 7mg, or 0mg for 6 weeks.	BP, HR, weight, and fasting total cholesterol, HDL-C, LDL-C and triglycerides.	Abstainers (n=432) in all groups had a significant decease in HR, systolic BP, and LDL-C, and increased HDL-C.	Quality ++ Healthy population
Dacosta et al (1993)	Case study	France 34-year-old male smoker (20-40 cpd for 14 years).	Developed chest pain when using a 21mg patch during a quit attempt.	Diagnosed with acute myocardial infarctions (MI).	Quality -
Greenland et al (1998)	Systematic review	Data from 35 clinical trials of 5501 subjects receiving nicotine patch and 3752 subjects receiving placebo patch	Adverse events associated with patch use	Patch use showed no statistically significant increase in risk of CV AEs compared with placebo.	Quality ++ Healthy population
Hubbard et al (2005)	Retrospective cohort study	UK 33,247 smokers that had used NRT identified from a UK general practice database.	Incidence of myocardial infarction, stroke and mortality 56 days before and after using NRT	861 patients had a MI and 506 had a stroke. No link to NRT	Quality +
Joseph et al (1996)	Randomised double blind placebo controlled trial	USA 584 outpatients with CVD given 10-week course of 21mg nicotine patch or placebo	CO validated abstinence and adverse events	Significantly more SAEs in the placebo group. Quit rates higher in the nicotine group.	Quality ++
Kimmel et al (2001)	Case control study	USA 653 current or recent (smoking within the last year) smokers admitted with first MI. Controls were smokers without MI interviewed via telephone.	Patch use within 1 week of hospital admission (cases) or telephone interview (controls)	No association between patch use and MI. Smoking concurrently with patches did not increase risk compared with smoking alone.	Quality + Few smokers reported using a patch
Marsh et al (2005)	Randomised open label trial	USA 901 patients with heart disease given 4mg lozenge or 4mg	Adverse events	SAEs were similar in the lozenge and gum groups.	Quality +

		gum.			
Meine et al (2005)	Case control study	USA 991 hospitalised patients with unstable angina undergoing cardiac catheterisation. Nicotine patch users (n=187) were matched with non-patch users (n=187)	7-day, 30-day and 1-year mortality.	No differences between patch users and non-patch users in deaths at any time point	Quality +
Ottervanger et al (1995)	Case study	Netherlands 39-year-old man, smoking 50-100 cigarettes per day, suffered acute MI 20 days after starting a patch.		Exercise stress test and coronary angiogram several weeks after discharge was normal.	Quality -
Ropchan et al (1997)	Case study	Canada 33-year-old women. Quit smoking using nicotine patches. Developed chest pain after 3 days.	Pain resolved when patch removed and returned when reapplied	Subsequently found to have a dissected aortic aneurism.	Quality -
Tzivoni et al (1998)	Double blind randomised placebo controlled trial	Switzerland 106 patients with CAD given 2-week course of 21mg nicotine patch or placebo	ECG monitoring and exercise testing.	No difference in ischemic episodes.	Quality +
Warner and Little (1994)	Case study	USA 47-year-old male smoker, history of inferior AMI. Stopped smoking on nicotine patch.	After a week smoked one cigarette while on patch, developed chest pain	Diagnosed with n MI caused by subtotal occlusion of the proximal left anterior descending artery.	Quality -
Willmer and Bell (2003)	Retrospective audit	UK 42 patients, post acute MI, enrolling in a smoking cessation service. 76% used NRT.	Adverse events and abstinence (CO validated) at 12 month follow-up	No reported adverse events and 64% self-reported (CO validated) abstinence at 12 months.	Quality -
Working Group for Study of Transdermal Nicotine in Patients with CAD (1994)	Randomised double blind placebo controlled trial	USA 156 patients with stable CAD given nicotine patch (14mg/24hrs) or placebo.	Self reported cardiac symptoms; ECG, BP and HR. Blood samples for chemistry, haematology, nicotine and cotinine.	No differences in angina attacks, ECG or blood results.	Quality ++

EXPERIMENTAL STUDIES

The first study reported here concerned healthy subjects, but it is included because of its specific focus on cardiovascular effects of NRT.

Allen et al. (1994, RCT [++]) randomised 935 healthy smokers (without CVD) to use one of four different nicotine patch strengths (21mg, 14mg, 7mg, 0mg) for 6 weeks to investigate the effects of abstinence and nicotine use on risk factors for CVD. 432 participants achieved abstinence and 254 continued to smoke. Abstainers in all groups experienced a decrease in heart rate, systolic blood pressure, and LDL, and an increase in HDL and triglycerides. There was a greater weight gain and decrease in heart rate on placebo than on 21mg patch.

Joseph et al (1996, RCT [++]) randomised 584 outpatients with CVD (40% had a history of myocardial infarction) to a 10-week course of 21mg nicotine (N=294) or placebo patch (N=290). The following serious adverse events were reported in the nicotine and placebo group: Death 1 vs. 6; AMI 0 vs. 1; Cardiac arrest 1 vs. 1; Admission for worsening angina 7 vs. 10; Admission for arrhythmia 5 vs. 3; Admission for congestive heart failure 2 vs. 2. At the end of treatment a total of 16 in the nicotine group (5.4%) vs. 23 in the placebo group (7.9%), (p=0.23) had reported a serious adverse event (SAE). There was no significant difference in reporting of secondary endpoint SAEs: 35 (11.9%) vs. 28 (9.7%), p=0.37. If SAEs are only considered in abstainers then total SAEs in the nicotine vs. placebo group were 19 (6%) and 9 (3%), significance levels were not reported. Abstinence rates at 14 weeks were significantly higher in the nicotine group (21%) versus the placebo group (9%), p=0.001. The results indicate good safety profile of NRT in CVD patients.

Marsh et al (2005, RCT [+]) randomly allocated 901 patients with cardiovascular disease or diabetes to a 12 weeks course of 4mg lozenge (N=447) or 4mg gum (N=454). SAEs were similar in the lozenge (11/447) and gum (13/454) groups. There was no difference in the proportion of AEs by amount and duration of product use. The majority of patients (>60%) had no change in their condition over the course of the study. Less than 5% reported a worsening of their CV condition with the remainder showing an improvement. Overall gum and lozenge were well tolerated and AEs were similar in type and frequency to those seen in smokers without CV illness.

Tzivoni et al (1998, RCT [+]) randomised 106 patients with coronary artery disease to receive a 2-week course of 21mg nicotine patch (N=52) or placebo patch (N=54). No differences were seen in the number of patients with at least one ischemic episode between nicotine and placebo groups after patch was started (13 vs. 16) and at 2 weeks (16 vs. 12). Two patients in the patch group had worsening angina compared to one in the placebo group. There were also no significant changes from baseline in exercise testing between the groups.

Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease (1994, RCT [++]) randomised 156 smokers with stable coronary artery disease (CAD) to nicotine patch (14mg/24hrs) (N=77), or placebo patch (N=79). Patients needing more help had the option of increasing the patch doses to 21mg. Four-week abstinence rates were higher in the nicotine patch group (36% vs. 22% p<0.05). The rates of withdrawal from the study due to adverse events did not differ between the groups (3 in the patch group and 8 in the placebo group, p=0.13). There was no significant difference in the number of patients reporting angina attacks, in ECG findings, blood chemistry or haematology.

OBSERVATIONAL STUDIES

Hubbard et al. (2005, Retrospective cohort [+]) identified 33,247 smokers prescribed NRT from a UK general practice database. 861 had an MI and 506 had a stroke. There was a progressive increase in the incidence of first MI incidence in the 56 days before the first NRT prescription (IR=5.55, CI 4.42-6.98), but no increase in the 56 days after starting NRT (IR=1.27, CI 0.82-1.97). The results were similar for second MI and for stroke. There were 960 deaths during 2.6 years after starting NRT, with no evidence of increased mortality in the 56 days after NRT prescription (IR=0.86, CI 0.60-1.23). The study shows on a very large sample that NRT does not cause AMI and stroke.

Kimmel et al (2001, Case control [+]) studied 653 current or recent smokers admitted to hospital with their first MI and a control group of 2,990 smokers without any history of AMI recruited via random dialling. Data on MI patients' patch use within 1 week of admission was collected from patient charts. Telephone interviews were used to collect data from the control group. In the MI group vs. no MI group, 3/653 and 30/2990 respectively, reported using a nicotine patch. There was no significant association between patch use and MI (OR=0.46, 95%CI:0. 09-1.47). The results remain the same when baseline characteristics were included as potential confounders. Smoking concurrently with patches did not increase the risk of an MI compared with smoking alone (OR=0.83 95%CI: 0.09-3.81, p=1.0).

Meine et al (2005, Case control [+]) followed up patients who were admitted for unstable angina and who underwent cardiac catheterisation (N=991) identified from a hospital database. Patch use (n=194) was ascertained from pharmacy records. Propensity matching was used to match individuals from the NRT group with the non-NRT participants, generating a cohort of 187 NRT users and 187 non-NRT users. There were no significant differences between NRT and non-NRT groups in the number of deaths at 7 days (1 vs. 0), 30 days (3 vs. 2) or 1 year (10 vs. 9). Additionally there were no differences in the numbers needing coronary artery bypass surgery (26 vs. 37) or coronary angioplasty (79 vs. 94).

Willmer and Bell (2003, retrospective audit, [-]) audited 42 patients with a diagnosis of myocardial infarction approached whilst enrolling in a smoking cessation service. 32 used NRT, mostly patch (n=31). 27 (64%) were CO validated as being abstinent at 12 months. There were no adverse events.

CASE STUDIES

Dacosta et al (1993, case study, [-]) reported the case of a 34 year old smoker using 21mg patch to stop smoking. Several hours after applying the patch he felt unwell with chest pain. This occurred throughout the day and then disappeared. He continued to smoke intermittently whilst on the patches. The pain returned two weeks into patch treatment and the diagnosis of a latero-apical infarction was made. He was subsequently found to have a thrombus of the left anterior descending artery.

Ropchan et al (1997, case study, [-]) reported a case of a 33-year-old female smoker who made a quit attempt using a 20mg patch and after three days developed chest pain. The patch was removed and the pain resolved. After two weeks she reapplied the patch on two mornings as part of another quit attempt and the pain returned on the second day of patch use. She was subsequently found to have a dissected aortic aneurism.

Ottervanger et al (1995, case study, [-]) reported the case of a 39-year-old man, who was smoking 50-100 cigarettes per day. The man suffered an AMI, 20 days after starting the patch treatment. A cardiac catheterisation had occurred two years earlier (attributed to a post traumatic injury) but he showed no evidence of coronary artery disease. ECG on

admission to hospital showed acute transmural inferior MI. Exercise stress test and coronary angiogram conducted several weeks after discharge all showed normal results.

Warner and Little (1994, case study, [-]) reported on a 47 year old male smoker with a history of an MI using a 21mg nicotine patch to stop smoking. After a week he smoked one cigarette while still using the patch, and developed chest pain. He was diagnosed with an MI caused by subtotal occlusion of the proximal left anterior descending artery.

SYSTEMATIC REVIEWS AND OTHER REVIEWS

Greenland et al (1998 systematic review [++]) analysed data from 35 trials of 5501 subjects receiving nicotine patches and 3752 subjects receiving placebo patches. These were not trials of hospital patients or patients with cardiac disease, but the review is relevant for our topic because it collated all adverse events associated with nicotine and placebo patch use, including cardiovascular outcomes. Patch use was associated with no increased risk of CV events compared with placebo patch use. Individual findings were as follows for patch vs. placebo: MI 3/360 vs. 3/362; stroke 1/354 vs. 2/357; tachycardia 2/239 vs. 0/238; palpitations 2/446 vs. 8/451; angina 1/239 vs. 1/238; arrhythmia 11/406 vs. 9/441; hypertension 8/354 vs. 5/357.

Ten papers provided general reviews (not summarised in the tables) of the effects of nicotine replacement therapy in patients with cardiovascular disease (Joseph 1996; Benowitz & Gourlay 1997; Pisinger et al 1999; Balfour et al 2000; McRobbie & Hajek 2001; Joseph & Fu 2003; Ford & Zlabek 2005; Ludvig et al 2005; Galen et al 2011; Pipe et al 2011). All agree that the benefits outweigh any risks

INTERPRETATION

Most studies focused on nicotine patches. Among the various NRT products, patches provide the highest nicotine levels and in the 24-hour form, they can provide nicotine overnight and occasionally in excess of smoking levels. Of the eight studies examining the acute effects if NRT, four studied the effects of patches, three studied oral and one nicotine nasal spray. The nasal spray is a product that provides the most rapid increase in blood nicotine levels and so might be assumed to result in a greater effect on cardiovascular parameters. However smoking the first cigarette, but not nicotine spray or second cigarette, increased heart rate suggesting that using nicotine spray even while smoking does not generate any safety concerns in CVD patients.

In studies following smokers with CVD using NRT (the majority were patch studies) or placebo for a protracted period of time, there were no differences in adverse events or changes in CVD between patients on NRT and patients on placebo. No randomised trial found any signal of risk. This provides the best available evidence on safety of NRT in this patient group.

Three cohort studies found no link between NRT use, MI and stroke.

Four case studies report cardiac events occurring in smokers using NRT. It is worth noting that all four concern patches rather than any of the short acting NRT products. Patches are the only NRT product that media linked to cardiac events. A very large number of cardiac incidents occur daily and they will coincide with practically any activity and medication.

Randomised trials found no difference between cardiac events on patches and on placebo, but of course a rare causal effect cannot be ruled out.

A systematic review, which included studies reporting cardiovascular events following NRT or placebo use in healthy populations, which were outside the brief of this review, showed that NRT does not cause adverse cardiovascular events in healthy users. A number of commentaries agree that benefits of NRT outweigh any risks.

Overall, there is no evidence suggesting that NRT use is unsafe for people with CVD. Of course it cannot be said that NRT is 'safe', but data evidence shows that its use is associated with less risk than the risks associated with smoking.

Section 3: Effects of stopping smoking on patients' wellbeing and on CVD Medications

We found one study of the aftermath of stopping smoking in patients with MI on their stress levels and 17 studies and reviews of the interactions between smoking and warfarin, an anti-coagulant that is used to prevent thrombosis and embolism in people with atrial fibrillation and artificial heart valves. Table 4 summarises 18 papers included in Section 3.

Table 4: Summary of studies included in section 3

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Hajek et al (2010)	Prospective cohort study	UK 469 smokers hospitalised after MI or bypass surgery given stop smoking advice or usual care	Ratings of perceived stress were measured at baseline and 1-year follow-up	At 1 year stress was reduced among abstainers compared with continued smokers.	Quality +
Aquilante et al (2006)	Prospective cohort study	USA 350 patients who were stable on warfarin	Warfarin dose, smoking history.	Current smoking was associated with a higher prescribed warfarin dose	Quality +
Backman et al (1979)	Prospective cohort study	USA 9 smokers given warfarin for 2 weeks whilst smoking and 2 weeks abstaining	Steady-state plasma levels of warfarin, clearances, half-life, and prothrombin times,	13% increase in plasma warfarin concentration and 13% decrease in clearance. No effect on prothrombin time	Quality +
Evans et al (2005)	Case study	Canada 58-year-old smoker on a stable dose of warfarin admitted to hospital with bacterial meningitis.	Quit smoking on discharge, his INR was 2.0 and he continued on his usual warfarin dose.	Two months after discharge INR increased to 5.5 (outside therapeutic range). Dose was decreased and INR stabilised.	Quality -
Gage et al (2008)	Prospective cohort study	USA 1015 patients on warfarin.	Warfarin dose, smoking history.	Smoking status was an independent predictor of smoking status, with smokers requiring a 10% increase in dose compared to non-smokers	Quality +

Holbrook et al (2005)	Systematic review	Effect of smoking and smoking cessation on warfarin		No evidence of an effect, but limited high quality data	Quality +
Kuykendall (2004)	Case study	USA 34-year-old male smokeless tobacco user with a history of MI and stroke.	Taking warfarin, but it was difficult to achieve a therapeutic INR	In an effort to achieve a therapeutic INR he was asked to stop his tobacco use and in 6 days his INR increased from 1.1 to 2.3.	Quality -
Lee et al (2005)	Prospective cohort study	Hong Kong 63 participants using warfarin (9 smokers).	Stable warfarin requirement	Smoking affected stable warfarin requirements	Quality +
Lenzini et al (2008)	Prospective cohort study	USA Studied 2 algorithms for warfarin dosing in 179 (genetic algorithm) and 233 (clinical algorithm) joint replacement patients	Therapeutic warfarin dose variation.	Current smokers required 14% and 7% increase in warfarin dose using the genetic and clinical algorithms respectively.	Quality +
McGriff-Lee et al (2005)	Retrospective cohort study	USA 350 ambulatory care patients on long-term warfarin and followed in a cardiology clinic	INR within the therapeutic range, smoking history.	Current smoking was not an independent predictor of INR.	Quality +
Millican et al (2007)	Prospective cohort study	USA 92 patients undergoing hip or knee joint surgery	Warfarin dose, smoking history.	Smokers require a 20% increase in dose compared to non-smokers.	Quality +
Mitchell et al (1972)	Retrospective cohort study	USA 230 people (86 non-smokers, 97 light smokers and 47 heavy smokers) on stable warfarin doses.	Mean warfarin dose.	Mean warfarin dose marginally higher in smokers but the difference was not significant.	Quality +
Mungall et al (1985)	Retrospective cohort study	USA Measured warfarin levels in 613 blood samples from 32 adult hospitalized patients and 131 adult outpatients.	Plasma warfarin levels, smoking history.	Compared to non-smokers, smokers had an increased (10%) clearance of warfarin	Quality +
Nathisuwan et al (2011)	Systematic review of 13 studies	Effects of smoking and smoking cessation on warfarin	Percentage change and actual change in warfarin dose	In a meta-analysis of 3 studies, smoking was associated with 12% increase in warfarin dosage	Quality +
Pamboukain et al (2008)	Retrospective cohort study	USA 80 patients with heart failure taking warfarin	INR within the therapeutic range, smoking history.	Tobacco use was associated with a lower INR.	Quality +
The university of Illinois at Chicago (1999)	Case control study	USA 18 smokers and 35 non-smokers receiving a stable dose of warfarin for at least one month	Warfarin pharmacokinetics	There were no significant differences in warfarin pharmacokinetics	Quality +

Weiner et al (1984)	Retrospective cohort study	USA 174 patients (117 non-smokers and 57 smokers) after valve replacement surgery.	Maintenance dose of warfarin	No difference between smokers and non-smokers in daily warfarin dose	Quality +
Whitley et al (2007)	Retrospective cohort study	USA 131 patients attending an internal medicine clinic	Warfarin dose, smoking history.	No effect of tobacco use on warfarin dose	Quality +

Stopping smoking can generate acute discomfort and many smokers also perceive smoking as a helpful strategy for coping with stress. This can create worries about the effects of smoking cessation on patient's wellbeing, especially in CVD patients trying to reduce their levels of stress.

We found one study assessing changes in stress levels in CVD patients who stopped smoking.

Hajek et al. (2010, prospective cohort, [+]) studied 469 smokers hospitalised after a Myocardial Infarction (MI) or after undergoing bypass surgery who received either a brief stop smoking intervention or usual care. Perceived stress was rated at baseline and at 1-year follow-up. At 1-year, ratings of stress were significantly lower among abstainers (N=194) whose stress levels decreased from baseline compared with those who continued to smoke (N=275) whose stress levels did not change. The effect remained significant when other variables were controlled for ($p=0.003$), and in a multivariate analysis including all predictors of abstinence ($p<0.01$).

Stopping smoking can also affect the metabolism of certain drugs. Considerable attention was given to the effects of stopping smoking on levels of warfarin; a widely used anti-coagulant that requires close monitoring to ensure the dose is safe and effective.

We found two relevant systematic reviews. **Holbrook et al (2005, systematic review [+])** reviewed drug and food interactions with warfarin. Most studies were of poor quality. The authors concluded that tobacco use had only a non-clinical effect. **Nathisuwan et al (2011, systematic review [+])** included data published since the Holbrook (2005) review. The authors included 13 studies in their final analyses. Six studies showed no association between smoking and warfarin levels and seven did. The 13 studies are summarised below.

Aquilante et al. (2006, prospective cohort, [+]) assessed the effects of common genetic polymorphisms in 350 patients who were on stable warfarin doses. Data were also collected on other factors. Current smoking was associated with a higher prescribed warfarin dose ($p = 0.0009$).

Bachmann et al (1979, prospective cohort, [+]) studied the effects of smoking and then smoking cessation on plasma warfarin in 9 smokers. A 13% increase in plasma warfarin concentration and a 13% decrease in clearance was observed during smoking cessation. There was no change in prothrombin time.

Gage et al. (2008, prospective cohort, [+]) sought to develop and validate a pharmacogenetic algorithm to aid better dosing of warfarin. Smoking status was an independent predictor of warfarin dose, with smokers receiving a higher prescribed dose (10%) than non-smokers.

Lee et al. (2005, prospective cohort, [+]) examined stable warfarin requirements in 63 Chinese patients using warfarin for at least 3 months. Nine were current smokers. Smoking affected stable warfarin requirements (p=0.001).

Lenzini et al. (2008, prospective cohort, [+]) studied cohorts of 179 and 233 patients undergoing hip or knee joint replacement surgery. 14% and 17% were smokers. The authors' genetic algorithm explained 70% of the therapeutic dose variation, compared to 48% in the clinical algorithm group. Current smokers required 13.7% and 7.4% increase in warfarin dose using the genetic and clinical algorithms respectively. Algorithms are available online at www.warfarindosing.org

McGriff-Lee (2005, retrospective cohort, [+]) looked for predictors of non-therapeutic International Normalized Ratio (INR) in 350 ambulatory care patients on long-term warfarin therapy. Tobacco use was not an independent predictor.

Millican et al. (2007, prospective cohort, [+]) used data from 92 patients undergoing hip or knee joint replacement surgery and on warfarin to develop and algorithm to guide warfarin dosing. Smokers required a 20% increase in dose.

Mitchell et al. (1972, retrospective cohort, [+]) found that smokers were maintained on a higher dose compared to non-smokers, but the difference was not significant.

Mungall et al (1985, retrospective cohort, [+]) analyzed the effects of demographic variables on warfarin plasma concentrations in 163 patients. Smoking resulted in a 10% increase in warfarin clearance.

Pamboukian et al. (2008, retrospective cohort, [+]) studied 80 patients with heart failure taking warfarin. Tobacco use was associated with a lower INR.

The University of Illinois at Chicago (1999, case control, [+]) report compared 18 smokers and 35 non-smokers, who were on a stable warfarin dose for at least a month, in warfarin pharmacokinetics (PK) There were no significant differences in any PK parameters.

Weiner et al. (1984, retrospective cohort, [+]) studied 174 patients undergoing cardiac valve replacement. There was no difference between smokers and nonsmokers in their daily warfarin maintenance dose.

Whitley et al. (2007, retrospective cohort, [+]) looked at predictors of warfarin dose in 131 patients. The results showed no significant effect of tobacco use.

Three of these studies were included in a meta-analysis looking at the percentage difference in warfarin dose between smokers and non-smokers (Millican, Lenzini et al. 2007; Gage, Eby et al. 2008; Lenzini, Grice et al. 2008). This showed a 12% increase (95%CI: 7-17%; p<0.001) in warfarin dosing to smokers. Three studies were included in a meta-analysis to assess the additional milligrams of warfarin dose needed in smokers, compared to non-smokers (Lee, You et al. 2005; Aquilante, Langaee et al. 2006; Whitley, Fermo et al. 2007). This showed a non-significant increase in warfarin dosage of 2.26mg (95% CI: -2.53-7.04) in smokers.

A sensitivity analysis of multivariate studies that included pharmacogenomics factors was also undertaken. Authors were able to convert data from 1 study that reported increased dose to % increase so that data from 4 studies could be included in the meta-analysis. The analysis showed a 13% increase in dose required in smokers (95%CI: 9-18).

We found two relevant case studies

Kuykendall (2004, case study, [-]) describes a case of a 34-year-old male with a history of four myocardial infarctions and ischaemic strokes. He was prescribed warfarin, but it was difficult to achieve a therapeutic INR level. He was a smokeless tobacco user. In an effort to achieve a therapeutic INR he was asked to stop his tobacco use and in 6 days his INR increased from 1.1 to 2.3.

Evans et al (2005, case study, [-]) report on a case of a 58-year-old man on a stable dose of warfarin, admitted to hospital with bacterial meningitis. He was a smoker but after this admission he decided to quit. His INR on discharge was 2.0, two months after discharge his INR had increased to 5.5 (outside the therapeutic range). His warfarin dose was decreased and his INR stabilised.

The British National Formulary (BNF) does not provide any advice on warfarin dosage adjustments in relation to smoking or smoking cessation. However the summary of product characteristics for warfarin (available online at http://www.medicines.org.uk/EMC/) states that smoking cessation "may exaggerate the effect of warfarin tablets, and necessitate a reduction of dosage" (Goldshield Group Limited 2010).

INTERPRETATION

Stopping smoking is likely to lead to some 12% increase in plasma levels of warfarin. This could be more in individual cases. Monitoring of warfarin levels when there is a change in smoking status is recommended.

EVIDENCE STATEMENTS 1.1: EFFECTS OF NICOTINE IN PATIENTS WITH CVD

STUDIES EXAMINING ACUTE EFFECTS OF NRT ON THE CARDIOVASCULAR SYSTEM

In laboratory studies involving several different NRT formulations, acute effects of NRT on cardiovascular parameters were weaker than effects of smoking. Where participants smoked and used NRT during the same time period, NRT use did not contribute any additional negative effects. No signal of risk that would require further investigation has emerged.

ES 1.1.1 There is strong evidence that the acute effects of NRT on cardiovascular function are significantly smaller than smoking (Benowitz et al. 1993, RCT, [+]; Gembala 2006, non-randomised CT, [+]; Keeley 1996, RCT, [+]; Mahmarian 1997, prospective cohort, [+])

ES 1.1.2 There is moderate evidence that NRT has no acute adverse effect on cardiovascular function in patients with stable CVD (Nitenberg 1999, controlled trial, [+]; Tanus-Santos 2001, controlled cross-over trial, [+])

STUDIES EXAMINING THE EFFECTS OF NRT WHEN USED TO STOP SMOKING

No randomised trial comparing NRT and placebo, or cohort study comparing users of NRT with other groups, found any signal of risk in terms of adverse events, changes in CVD, MI or stroke. Most studies identified in this systematic review used nicotine patches. Only one experimental study looked at nicotine nasal spray and four investigated the effects of oral NRT (mostly nicotine gum), however the conclusions from these studies are not different from those examining the effects of patches. These data provide good evidence of the low risk of NRT in CVD patients.

Four case studies reported cardiac events occurring in smokers using NRT. All four concern patches, which are the only NRT product that media linked to cardiac events. A very large number of cardiac incidents occur daily and they will coincide with practically any activity and medication, but of course a rare causal effect cannot be ruled out.

A systematic reviews which included studies reporting cardiovascular events following NRT or placebo use in healthy populations concluded that NRT does not cause adverse cardiovascular events in healthy users.

A number of commentaries agree that benefits of NRT outweigh any risks.

Overall, there is no evidence suggesting that NRT use is associated with an increased risk of cardiovascular adverse events in people with CVD.

ES 1.1.3 There is strong evidence that use of NRT does not lead to adverse events when used in patients with stable CVD (Joseph et al 1996, RCT [++]; The Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease 1994, RCT, [++]; Tzivoni et al 1998, RCT [+]; Marsh et al (2005, RCT [+]; Hubbard et al. 2005, Retrospective cohort [+]; Kimmel et al 2001, Case control [+]; Meine et al 2005, Case control [+]; Willmer and Bell 2003, retrospective audit, [-])

ES 1.1.4 There is strong evidence that use of NRT in the general population is not associated with an increased risk of cardiac events (Greenland et al 1998, systematic review, [++]; Hubbard et al. 2005, Retrospective cohort [+]; Allen et al. 1994, RCT [++]) or stroke (Greenland et al 1998, systematic review, [++]; Hubbard et al. 2005, Retrospective cohort [+]).

ES 1.1.5 There is moderate evidence that NRT does not cause any serious adverse events in patients with unstable CVD (Kimmel et al 2001, Case control [+]; Meine et al 2005, case control study [+]; Willmer and Bell 2003, retrospective audit, [-]).

EFFECTS OF STOPPING SMOKING ON PATIENTS' WELLBEING AND ON CVD MEDICATIONS

Among patients hospitalised for MI or CABG surgery, long-term stress levels decreased in those who stopped smoking, but remained unchanged in smokers.

Stopping smoking is likely to lead to some 12% increase in plasma levels of warfarin. Monitoring of warfarin levels when there is a change in smoking status is recommended.

ES 1.1.6 There is moderate evidence that in smokers with CVD who stop smoking successfully long-term levels of stress decrease rather than increase (Hajek et al. 2010, prospective cohort, [+])

ES 1.1.7 There is moderate evidence that smokers may require higher doses of warfarin to achieve an INR in therapeutic range (Aquilante et al. 2006, prospective cohort, [+]; Gage et al. 2008, prospective cohort, [+]; Lee et al. 2005, prospective cohort, [+]; Lenzini et al. 2008, prospective cohort, [+]; Millican et al. 2007, prospective cohort, [+]; Mungall et al 1985, retrospective cohort, [+]) Pamboukian et al. 2008, retrospective cohort, [+]), but four studies found no difference between requirements in smokers vs. non-smokers (Mitchell et al. 1972, retrospective cohort, [+]; The University of Illinois at Chicago 1999, case control, [+]; Weiner et al. 1984, retrospective cohort, [+]; Whitley et al. 2007, retrospective cohort, [+])

ES 1.1.8 There is moderate evidence that stopping smoking can lead to an increase in the systemic level of warfarin, with an associated increase in INR (Bachmann et al 1979, prospective cohort, [+]; Kuykendall 2004, case study, [-]; Evans et al (2005, case study, [-])

PART 2: EFFECTS OF NICOTINE AND EFFECTS OF STOPPING SMOKING ON PATIENTS ADMITTED TO ICU OR UNDERGOING SURGERY

Regarding the impact of acute changes in nicotine and smoke intake on surgery outcomes, there exist two contradictory concerns. One is that stopping smoking shortly before surgery may increase the risk of post-operative complications, and the other that nicotine from NRT can impair wound healing and post-operative recovery.

An influential paper by Warner (1989) initiated the first concern. There now exists a volume of empirical literature on this topic, which we recently reviewed (Myers et al. 2011). The systematic review and meta-analysis found no increase in risk associated with stopping smoking. Warner's paper was largely cited as a reason for why smoking cessation interventions should not be instigated prior to surgery (i.e. as a barrier) and so this topic will be covered in Review 3.

The second concern involves specifically nicotine and the relevant evidence is reviewed below.

The studies are presented in three sections.

1. Section 1 concerns perioperative outcomes
2. Section 2 concerns ICU outcomes
3. Section 3 concerns effects of tobacco withdrawal and NRT on the risk of delirium
4. Section 3 covers the effects of nicotine and tobacco withdrawal on the perception of pain

SECTION 1: EFFECTS OF NICOTINE ON PERIOPERATIVE OUTCOMES

We identified 8 studies with relevant information, summarised in Table 5. They concern effects of nicotine patches on perioperative outcomes, effects of nicotine versus other constituents of tobacco smoke on bone healing, and some other effects with unclear implications.

Table 5: Summary of studies included in part 2 section 1

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Czarenetzki et al (2011)	Randomised controlled trial	Switzerland Non-smokers receiving GA for surgery (N=90) given patches or placebo 1 hour before surgery.	Post-operative nausea and vomiting (PONV).	More insomnia in the first post-operative night in the nicotine group.	Quality + Patches induce nausea in non-smokers
Groundine & Morley (1996)	Case report	USA Smoker on patch having laser treatment for cervical dysplasia	Hypotension and bradycardia.	Suggests NRT in combination with vasopressin caused the symptom	Quality -
Jagadeesan et al (2007)	Case report	UK Smoker undergoing surgery for a tumour excision,	Vascular spasm.	Suggests NRT may have contributed to vascular spasms.	Quality -

		wearing a nicotine patch.			
Paciullo et al (2009)	Retrospective cohort	USA 2057 patients with CABG surgery. 90 used nicotine patches post-operatively. 67 were randomly selected and matched to a sample of smokers not using NRT.	Hospital mortality	In the matched sample 3 NRT users died compared to none of non-users. The difference was significant when other variables entered.	Quality +
Puura et al (1998)	Randomised controlled trial	Finland 100 minor surgery patients on nicotine or placebo patch pre-surgery. Group 3 on placebo, smoked up to 1-3 hours pre- surgery	Atracurium (ATR) induced neuromuscular block	Abstinence from smoking without patch (but not with patch) increases duration of ATR neuromuscular block	Quality ++ RCT
Soreide et al (1995)	Randomised controlled trial	Norway 44 smokers having gynaecologic laparoscopy given gum or no gum before surgery.	Gastric fluid volume and acidity.	No differences between the groups. Gum associated with less dry mouth, thirst and irritability.	Quality ++
Usuki et al (1998)	Cohort study	Japan 86 volunteers (25 smokers) given 2mg nicotine gum or ordinary gum.	Skin temperature and cutaneous blood flow (CBF).	Elevation in skin temperature and CBF on NRT.	Quality - Non-randomised, methods and results unclear
W-Dahl & Toksvig-Larsen (2007)	Prospective cohort study	Sweden 175 patients having tibial osteotomy, 41 smokers, 21 oral snuff users and 113 non-smokers.	Time in external fixation and post-operative complications.	Smokers needed longer fixation and had more complications, no difference between snus users and non-smokers.	Quality +

Two case studies suggest possible reasons for removing NRT patches prior to surgery.

Jagadeesan et al. (2007, case study, [-]) reported occasional episodes of intra-operative vascular spasm in a patient undergoing tumour excision while wearing a nicotine patch. The spasms were benign and their link with the patches speculative, but the authors recommend removing patches before surgery, particularly before microvascular reconstructive surgery.

Groundine & Morley (1996, case study, [-]) reported severe hypotension and bradycardia during gynaecological surgery in a patient who received a paracervical injection of vasopressin. The patient was wearing nicotine patch and the authors propose that the complication may have been caused by a synergism of vasoconstrictive properties of nicotine and vasopressin. They suggest nicotine patches should be removed 24h before surgery if exposure to vasopressin is anticipated.

One cohort studies examined safety of patches administered to post-coronary artery bypass surgery.

Paciullo et al (2009, retrospective cohort, [+]) studied 2057 patients (579 smokers and 1478 non-smokers) who underwent coronary artery bypass grafting. Ninety patients used nicotine patches post-operatively. 67 smokers using NRT were randomly selected from the 90 and matched for pack year history and APACHE II (Acute Physiology and Chronic Health Evaluation 2) score to a sample of smokers. Three patients using NRT died during their hospital stay, versus none in the non-NRT group (p=0.08). In the next step, all smokers using

NRT post-operatively, smokers not using NRT, and non-smokers were compared in hospital mortality. No significant difference in mortality was seen between the NRT (3%), non-NRT (1%), and non-smokers (2%) groups. However, when differences in age and baseline atrial fibrillation were controlled for, NRT users had a significantly increased risk compared to non-NRT users (OR=6.06; CI: 1.65-22.21).

One study suggests that patches during surgery reduce the need for atracurium maintenance.

Puura et al. (1998, RCT [++]) studied atracurium-induced neuromuscular block (NB) in non-smokers (N=20) and in smokers abstaining for at least 10 hours prior to surgery who were randomised to receive 21mg patches (N=30), placebo patches (N=30) or were allowed to smoke 1-3 hours before anaesthesia (N=20). The placebo group experienced a significantly longer duration of the block ($p<0.05$) and needed smaller maintenance dose of atracurium ($p<0.001$) than all the other groups. Curiously, the authors avoid discussing practical implications (which seem to be that unaided abstinence is preferable to NRT in this particular respect).

A good quality study suggests that constituents of tobacco smoke other than nicotine are responsible for slow bone healing.

W-Dahl and Toksvig-Larsen (2007, prospective cohort study [+]) compared post-surgery bone healing in 41 smokers, 21 users of oral snuff (which contains nicotine but no combustion products), and 113 non-smokers undergoing high tibial osteotomy. Smokers needed longer time in external fixation than the other two groups ($p=0.03$) and had a much higher risk of developing complications (RR=6.1, CI: 1.2-36.4), with no difference between snus users and non-smokers (delayed healing 0% vs. 9%, NS, and complications 5% vs. 22%, NS, for snus users and non-smokers)

We identified three other studies, which have some, albeit mainly indirect relevance to the considerations of the safety of nicotine use in surgery patients.

Soreide et al. (1995, RCT, [++]) studied the effects of chewing nicotine chewing gum compared to no chewing on the morning before gynaecologic surgery on gastric fluid volume and acidity during surgery in 44 smokers. The two groups showed no difference, but the gum was associated with a reduction in dryness of the mouth ($p=0.001$), thirst ($p=0.03$) and irritability ($p=0.03$).

In a curious study, **Czarnetzki et al. (2011, RCT, [+])** gave 90 non-smokers nicotine or placebo nicotine patches (24h, 17.5 mg) one hour before surgery. This was to see if nicotine alleviates post-operative nausea and vomiting (PONV). There was no effect, though it is possible that the patches alleviated PONV but induced nicotine nausea at the same time so the effects cancelled each other. Nicotine patches impaired sleep during the first post-operative night ($p=0.01$).

Usuki et al. (1998, cohort study, [-]) observed anecdotally that (presumably non-smoking) volunteers' hands became sweaty and warm after using nicotine gum. To verify this observation, they gave nicotine and/or ordinary chewing gum to 86 volunteers (23 were

smokers) and measured their cutaneous blood flow (CBF) and skin temperature. 64% of volunteers recorded increased CBF and 74% increased temperature after using NRT. This may mitigate concerns about vasoconstricting effects of NRT, but the study statistics and controls are unclear.

INTERPRETATION

Given the number of possible acute effects of both abstinence and nicotine intake on a number of perioperative outcomes, the literature we identified is limited.

NRT patches were associated with an increased mortality in one cohort study.

Compared to no nicotine provisions, patches and smoking increase the need for atracurium maintenance of anaesthesia.

There is evidence that the adverse effects of smoking on bone healing are not due to nicotine, which provides further reassurance regarding the use of NRT.

A single case study reports on possible vasospasm in a patient wearing a nicotine patch whilst undergoing microvascular surgery. The spasms were benign and their link with the patches speculative, but the authors recommend removing patches before surgery, particularly before microvascular reconstructive surgery. Given that there is no evidence to suggest that patch use in the perioperative period is benefit then removing patches prior to surgery is reasonable. However the need for post-operative NRT use should be considered. Any risks of using NRT are outweighed by the risks associated with smoking.

Section 2: Effects of nicotine in Patients Requiring Intensive Care

We identified 5 studies with relevant information concerning the effects of nicotine (all studies investigated the effect of nicotine patches) in patients requiring intensive care (see Table 6). We also include Paciullo et al (2009) again as patients undergoing CABG require intensive care post-operatively.

Table 6: Summary of studies included in part 2 section 2

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Carandang et al (2011)	Retrospective cohort study	USA 1486 patients with subarachnoid haemorrhage (SAH) admitted to neuro-ICU. Of 352 smokers 87 used NRT patch.	Clinical and angiographic vasospasm, Glasgow Coma Outcome Score (GOS) on discharge.	NRT users had less vasospasm and shorter length of hospital stay than smokers not using patch.	Quality +
Cartin-Ceba et al (2011)	Prospective cohort study	USA 2441 consecutive ICU patients. 174 of 330 smokers used NRT within 24 hours of admission	Hospital and ICU mortality, length of ICU and hospital stay	NRT use not associated with an increased risk of mortality.	Quality +
Lee et al (2007)	Retrospective cohort study	USA Of 6735 admissions to a medical ICU, 90 patients who received NRT were matched with 90 smokers not on NRT.	Hospital mortality, 28-day ICU and mechanical ventilator-free days	More deaths among smokers on NRT than among other smokers (20% vs. 7%, p<0.01)	Quality +
Paciullo et al (2009)	Retrospective cohort	USA 2057 patients with CABG surgery. 90 used nicotine patches post-operatively. 67 were randomly selected and matched to a sample of smokers not using NRT.	Hospital mortality	In the matched sample 3 NRT users died compared to none of non-users. The difference was significant when other variables entered.	Quality +
Panos et al (2010)	Retrospective cohort study	USA 340 patients admitted to a neurosurgery ICU; 114 were smokers who received 21mg nicotine patch; 113 were smokers who did not receive NRT; and 113 non-smokers.	Unfavourable hospital discharge (UHD) disposition, angiographic documented vasospasm.	No difference in UHD, or vasospasm (when controlling for the presence of SAH) between NRT users vs. non-users. NRT users had significantly longer hospital stay.	Quality +
Seder et al (2011)	Retrospective cohort study	USA 234 smokers with SAH admitted to a neuro-ICU. 128 patients received 21mg patch and 106 did not.	Diagnosis of delirium	NRT users had more pneumonia, delirium, pulmonary oedema and seizures but lower death rate at 3 months.	Quality +

Carandang et al (2011, retrospective cohort, [+]) reported on 352 smokers admitted to a neuro-intensive care unit (neuro-ICU) for treatment of subarachnoid haemorrhage (SAH), 87

of whom were treated with a nicotine patch (doses ranged between 7-21mg). A matched non-NRT control group was formed of 171 smokers. NRT users had less severe clinical disease. Mortality was not significantly different between the NRT and non-NRT groups (2% vs. 7%; p-value not reported). The NRT group had a lower proportion of clinical vasospasm (20% vs. 33%, p=0.026) and more patients with a better scores on Glasgow Coma Scale Score (82% vs. 63%, p=0.005). In multivariate analysis, adjusting for the aneurysm grade, NRT group had less clinical vasospasm (OR=0.45, CI: 0.23-0.88, p=0.019). There was no difference in angiographic vasospasm. NRT users had significantly shorter length of stay (17.4 vs. 21.5 days, p=0.0168).

Cartin-Ceba et al (2011, prospective cohort [+]) studied 330 critically ill smokers admitted to intensive care. NRT (21mg patch) was started within 24 hours of admission in 174 of these smokers; the remaining 156 did not receive NRT. There were no significant differences between the groups in hospital mortality, length of hospital stay, or 28-day mechanical ventilator free days. Adjusting for baseline differences, NRT use was not related to hospital mortality (OR=1.4 CI: 0.5-3.9, p=0.51).

Lee et al (2007, retrospective cohort, [+]) screened 6,735 admissions to a medical ICU, to find that NRT was provided to 115 smokers. After excluding patients with missing data and those who started NRT after 24hours of admission, 90 patients were included in the NRT group and matched with 90 control patients who smoked. Baseline characteristic differed only on ethnicity (p=0.03). There were more hospital deaths among NRT users (20% vs. 7%, p=0.0085). When adjusted for severity of disease NRT remained an independent risk factor for hospital mortality (Odds Ratio = 24.6 95%CI: 3.6-167.6, p=0.001).

Paciullo et al (2009, retrospective cohort, [+]) has been summarised above, but to recap the study reports on outcomes of 67 patients who underwent CABG surgery and used nicotine patches post-operatively matched with a sample of smokers. Three patients using NRT died during their hospital stay, versus none in the non-NRT group (p=0.08). The study also compared in hospital mortality between all smokers using NRT post-operatively, with smokers not using NRT, and non-smokers. No significant difference in mortality was seen between the NRT (3%), non-NRT (1%), and non-smokers (2%) groups. However, when differences in age and baseline atrial fibrillation were controlled for, NRT users had a significantly increased risk compared to non-NRT users (OR=6.06; CI: 1.65-22.21).

Panos et al (2010, retrospective cohort, [+]) studied a cohort of 340 patients admitted to a neuro-ICU. There were 114 smokers who received 21mg nicotine patch, 113 were smokers who did not receive NRT; and 113 non-smokers. Smokers who used NRT, compared to smokers who did not, were significantly more likely to have a diagnosis of SAH (49% vs. 28%, p<0.001), and smoked more packs per day (1 vs. 0.7, p=0.04). There was no difference in unfavourable discharge outcomes between smokers using NRT, compared to those who did not (42% vs. 33%, p=0.17). Smokers using NRT had significantly longer hospital stays (13 vs. 9.7 days, 0=0.014) and were more likely to have angiographic documented vasospasm (20% vs. 11%, p=0.016), although the difference in the latter lost significance when data were adjusted for presence of SAH.

Seder et al (2011, retrospective cohort [+]) report on 234 smokers with SAH admitted to a neuro-ICU; 128 received NRT (21mg patch) and 106 did not. NRT users were more likely to be heavier smokers (p<0.001) and drinkers (p=0.01), have diabetes (p=0.006), and have cerebral oedema on admission (p<0.001). A higher proportion of NRT users suffered pneumonia (29% vs. 17%, p=0.037), pulmonary oedema (24% vs. 9%, p=0.004), delirium (19% vs. 7%, p=0.006), and seizures (9% vs. 2%, p=0.024), compared to non-NRT users. However death at 3-months was lower among NRT users (7% vs. 17%, p=0.02). In

multivariate analysis NRT use remained associated with a lower risk of death (OR=0.12, CI 0.04-0.37, p < 0.001).

INTERPRETATION

Given the number of possible acute effects of both abstinence and nicotine intake on a number of ICU outcomes, the literature we identified is limited.

The reviewed studies suggest that patches are often provided to acutely ill patients admitted to ICU who are unlikely to request such help or to suffer from tobacco withdrawal. We examine the rationale and evidence for this in the next section.

NRT patches were associated with an increased mortality in one of the five cohort studies. However patch use was also associated with a longer hospital stay, less vasospasm, and no effect in other studies. The results are difficult to integrate as there were a number of differences between patients who were and who were not given the patches and different studies concerned different population and outcome measures.

SECTION 3: EFFECTS OF SMOKING, TOBACCO WITHDRAWAL, AND NRT ON THE RISK OF DELIRIUM

A number of hospitals give NRT patches automatically to smokers undergoing surgery and to those admitted to ICUs. Such smokers normally do not ask for NRT and are not bothered by the need to smoke. They are usually not consulted about receiving the patches. The practice seems to be in place due to a perception that smokers are more likely to suffer from delirium, which can lead to removal of intubation and other disruption, and that NRT alleviates the risk.

We identified 9 papers with relevant content. These are summarised in Table 7.

Table 7: Summary of studies included in part 2 section 3

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Cartin-Ceba et al (2011)	Prospective cohort study	USA 2441 consecutive patients admitted to ICU. Of current smokers (n=330) 174 used NRT within 24 hours of admission; 156 did not.	Delirium control and agitation control.	NRT users were more likely to be confused and need physical restraint than non-NRT users.	Quality - No control for baseline differences in delirium analyses
Dubois et al (2001)	Prospective cohort study	Canada 216 ICU patients admitted for at least 24 hours	Diagnosis of delirium	Smoking at least 20 cpd linked to increased risk of delirium in univariate, but not multivariate analysis	Quality +
Lucidarme et al (2010)	Prospective cohort study	France 144 ICU patients (44 smokers) requiring	Presence of agitation or delirium, number	Smokers more likely to have agitation or delirium, higher rates	Quality - No control for baseline

		mechanical ventilation for > 48 hours. No patients received NRT.	of ventilator free days, total doses of sedatives and analgesics.	of accidental removal of tubes and catheters, more sedation and physical restraints.	differences in delirium analyses
Miyazaki et al (2011)	Retrospective cohort study	Japan 685 patients' (178 smoked) records reviewed after CABG surgery	Diagnosis of post-operative delirium	Smoking was a significant predictor of delirium in multivariate analysis (p=0.048)	Quality +
Mayer et al (2001)	Case studies	5 case studies of the development of delirium in patients who smoke with brain injury admitted to ICU		Each shows an improvement when treated with a 21mg nicotine patch.	Quality -
Nicholson & Rolfson (2006)	Retrospective cohort study	Canada 163 elderly patients, orthopaedic hip replacement.	Diagnosis of post-operative delirium	Smoking status was not associated with delirium.	Quality - No control for baseline differences
Ouimet et al (2007)	Prospective cohort study	Canada 820 ICU patients admitted for at least 24 hours	Diagnosis of delirium	Smoking was a significant predictor of delirium in univariate (p=0.0123) but not multivariate analysis.	Quality +
Seder et al (2011)	Retrospective cohort study	USA 234 smokers with SAH admitted to a neuro-ICU. 128 patients received 21mg patch and 106 did not.	Diagnosis of delirium	NRT users had more pneumonia, delirium, pulmonary oedema and seizures but lower death rate at 3 months.	Quality +
Van Rompaey et al (2009)	Prospective cohort study	Belgium Consecutive patients (N=523; 131 were smokers) admitted to an ICU.	Diagnosis of delirium.	Smoking status not related to delirium.	Quality – No control for baseline differences in delirium analyses

We identified six studies assessing the link between smoking status and delirium.

Dubois et al (2001, prospective cohort, [+]) studied 216 patients admitted to an ICU for more than 24 hours. Delirium developed in the majority of patients (78%) in the first 36 hours of admission. Univariate analysis showed that smoking a minimum of 20 cigarettes a day prior to admission was associated with an increased risk of delirium (OR=2.2 95% CI: 1.07-4.51). In the multivariate analysis being a heavy smoker prior to admission was not a significant predictor of delirium (OR=2.2 95%CI 0.94-4.94). Compared to non-delirious patients, those with delirium were more likely to remove of catheters (p=0.003) and extubate (p=0.02) themselves. Delirium was not associated with an increased risk of mortality or longer hospital stay.

Lucidarme et al. (2010, prospective cohort, [-]) studied 144 patients (44 smokers) admitted to an ICU who required mechanical ventilation for > 48 hours. Smokers were more likely to develop agitation or delirium (64% vs. 32%, p=0.0005) and spend more days with agitation (1.54 vs. 0, p=0.0006). They were also significantly more likely to have higher rates of accidental removal of tubes and catheters, and required more sedation and physical restraints. After adjustment of baseline differences, smoking remained a significant

predictor of agitation (OR=3.13, CI: 1.45-6.74) but not of delirium. Matching of cases and controls was possible for 62 patients (31 in each group). The proportion of patients who had at least one event of agitation was 80% vs. 42%, p=0.004.

Miyazaki et al. (2011, retrospective cohort, [+]) reviewed the clinical records of 685 patients following coronary artery bypass surgery. Post-operative delirium was seen in 118 patients. Smoking was not a significant predictor of delirium in univariate analysis but it was a significant predictor in multivariate analysis (OR=1.65, 95%CI: 1.00-2.72, p=0.048).

Nicholson et al. (2006, retrospective cohort, [-]) studied patients over the age of 75 who were undergoing orthopaedic hip replacement surgery to see if tobacco withdrawal increased post-operative delirium. Only 7.4% of all patients included in the study were smokers. Smoking status was not associated with delirium (p=.54).

Ouimet et al. (2007, prospective cohort, [+]) assessed the risk factors for delirium in a sample 820 consecutive patients admitted to ICU for more than 24 hours. Delirium was assessed in a sample of 764 patients (56 were comatose for > 5days). 243 patients were diagnosed with delirium. Being a current smoker was a significant risk factor for delirium (p=0.0123) in univariate analysis, but it was no longer a significant predictor in the multivariate analysis.

Van Rompaey (2009, prospective cohort, [-]) studied patients admitted to ICUs at four hospitals who were then screened for delirium. 131 were daily smokers and 366 were non-smokers. Delirium was recorded in 33/131 (25%) of smokers and 120/366 (31%) of non-smokers. Daily smokers represented 22% of patients who had delirium and 27% of those who did not. Smokers who reported smoking over 10 cigarettes per day were represented more among the group who had delirium (48%) then among those who did not (31%). Smoking did not feature as a predictor of delirium in a multivariate model including a range of variables, but the results are difficult to follow.

Two studies examined the link between NRT and delirium in ICU and post-surgery patients.

Cartin-Ceba et al (2011, prospective cohort [-]) studied 330 critically ill smokers admitted to intensive care. NRT (21mg patch) was started within 24 hours of admission in 174 of these smokers; the remaining 156 did not receive NRT. There were no significant differences between the groups in hospital mortality, length of hospital stay, or 28-day mechanical ventilator free days. Adjusting for baseline differences, NRT use was not related to hospital mortality (OR=1.4 CI: 0.5-3.9, p=0.51). NRT patients, compared with those not receiving NRT, were more likely to be confused (23% vs. 13.1%, p<0.001) and needed to be physically restrained (38% vs. 19.5%, p<0.001). The authors' note that it is more likely that patients were administered NRT because of confusion and agitation, as opposed to NRT causing this.

Seder et al (2011, retrospective cohort [+]) report on 234 smokers with SAH admitted to a neuro-ICU; 128 received NRT (21mg patch) and 106 did not. NRT users were more likely to be heavier smokers (p<0.001) and drinkers (p=0.01), have diabetes (p=0.006), and have cerebral oedema on admission (p<0.001). A higher proportion of NRT users suffered pneumonia (29% vs. 17%, p=0.037), pulmonary oedema (24% vs. 9%, p=0.004), delirium (19% vs. 7%, p=0.006), and seizures (9% vs. 2%, p=0.024), compared to non-NRT users. However death at 3-months was lower among NRT users (7% vs. 17%, p=0.02). In multivariate analysis NRT use remained associated with a lower risk of death (OR=0.12, CI 0.04-0.37, p < 0.001).

We identified one relevant case study

Mayer (2001, case study [-]) presented 5 cases of delirium in smokers admitted to intensive care with brain injuries which showed an improvement when treated with a 21mg nicotine patch.

Two general reviews included some consideration of NRT use in the ICU setting to manage tobacco withdrawal.

Fronterta (2011, selective review [-]) supports such use of NRT, quoting Mayer (2001) and Lucidarme et al. (2010) as evidence of tobacco withdrawal causing disruption within the ICU setting.

Honisett (2001, review [+]) recommends further research into whether ICU patients do get tobacco withdrawal symptoms whilst sedated and whether NRT help.

INTERPRETATION

Smoking status was not consistently related to the risk of delirium in cohort studies. Four cohort studies found no link, while two studies not controlling for other variables did. Two observational studies found more rather than less delirium in ICU smokers on patches, but it is likely that high-risk patients were more likely to be given the medication. Case studies suggest that delirium may be alleviated by NRT, but it is also possible that the episodes subsided spontaneously.

No controlled trial has examined the effects of patches on delirium or any other ICU or surgery outcome.

The practice of putting patches on smokers undergoing major surgery or admitted to ICU to prevent delirium appears to have no sound evidence base. Two studies suggest that such practice may increase mortality and no study suggests that it helps.

The practice should be suspended until trials of effects of NRT on surgery and ICU outcomes provide evidence that this is beneficial rather than irrelevant or harmful.

SECTION 4: STOPPING SMOKING AND PERCEPTION OF PAIN

INTRODUCTION

Nicotine has acute analgesic properties (Jamner 1998) and there is some evidence from animal studies that nicotine withdrawal is associated with increased sensitivity to pain stimuli (Anderson et al. 2004; Biala et al. 2005). Many smokers also view smoking as a coping tool for stress in general and for pain in particular (Hajek et al. 2010, Hooten et al. 2011), and may be worried that smoking deprivation may have a negative effect on their capacity to cope with pain. There is some evidence that it is difficult for smokers with chronic pain to achieve abstinence from smoking (Fishbain et al 2008, Hooten et al 2009).

There is thus a concern that in the context of acute care, stopping smoking may have a negative effect on pain perception and patient comfort. Such concern may represent one of the barriers to stop-smoking interventions.

We identified six studies (summarised in Table 8) looking at analgesic effects of nicotine in patients undergoing surgery.

Table 8: Summary of studies included in part 2 section 4 [A]

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Flood and Daniel (2004)	Randomized controlled trial	USA 20 female non-smokers undergoing myomectomy or hysterectomy used nicotine nasal spray or placebo post-operatively	Post-operative pain scores and dose of patient controlled analgesia (PCA)	Nasal spray, compared with placebo lowered pain scores and reduced the need to PCA	Quality +
Habib et al (2008)	Randomized controlled trial	USA 90 non-smokers undergoing radical prostatectomy used 7mg nicotine patch or placebo 30-60 min before anaesthesia	Post-operative pain scores and use of morphine post-operatively	No difference in pain scores but patients using nicotine patches used less morphine.	Quality +
Hong et al (2008)	Randomized controlled trial	USA 40 non-smokers having pelvic or abdominal surgery used placebo, 5, 10, or 15 mg patches	Post-operative pain scores	Patch use resulted in lower pain scores for the first ($p<0.01$) and for the next 4 days at home ($p<0.05$).	Quality +
Olson et al (2009)	Randomized controlled trial	USA 28 smokers having abdominal or pelvic surgery used 0, 5, 10 or 15 mg patches.	Post-operative pain scores	No effect of the nicotine dose and no overall effect.	Quality – Small sample
Turan et al (2008)	Randomized controlled trial	USA 97 hysterectomy patients (60% were smokers) used 21mg	Post-operative pain scores, analgesic use, time to return to work	No effect on pain, analgesics use or time to return to work. More nicotine	Quality +

		nicotine patches or placebo to 1 hour before and for 2 days after surgery.		group ready for discharge at 48 hours (p<0.001) and 72 hours (p<0.04).	
Yagoubian et al. (2011)	Randomized controlled trial	20 non-smokers having third molar surgery given nicotine nasal spray (3mg) and placebo during 2 visits	Post-operative pain scores and analgesic use	Spray associated with less pain during 5 days after surgery. No effect on analgesia use.	Quality +

[A] Effects of nicotine on post-surgery pain

Flood and Daniel (2004, RCT, [+]) found that in 20 female non-smokers undergoing myectomy or hysterectomy, nicotine nasal spray (3mg) administered at the completion of surgery, lowered pain scores (p<0.001) and reduced the dose of patient-controlled analgesia (PCA) for 60 min after surgery (p<0.05), compared with placebo treatment. Pain scores were significantly lower for a full 24 h after nicotine dosing (p<0.01).

Habib et al. (2008, RCT, [+]) gave 7mg or placebo patches 30–60 min before surgery to 90 non-smokers undergoing prostatectomy. Patches were left in place for 24 h. There was no effect on pain score, but patients on nicotine used significantly less morphine at 24 h (p<0.01), and plasma nicotine concentrations were negatively correlated with morphine consumption (P<0.01). There was more nausea in the nicotine-treated group (p<0.05).

Hong et al. (2008, RCT, [+]) gave placebo, 5, 10, or 15 mg/16 h nicotine patches to 40 non-smokers undergoing pelvic or abdominal surgery. This resulted in lower pain scores for the first hour after surgery (p<0.01) and then for the next 4 days at home (p<0.05).

Olson et al. (2009, RCT, [-]) gave 0, 5, 10 or 15 mg 16-hour patches to smokers undergoing abdominal or pelvic surgery. There were 6-8 participants in each group. There was no effect of the dose and no overall effect, but merging the three nicotine arms produced a group with a higher pain score over the first hour after surgery compared to the placebo group (p<0.01), while the placebo group had higher diastolic blood pressure in the first hour (11 mm Hg, p<0.01). There were no other significant effects over any other time period on any variable.

Turan et al. (2008, RCT, [+]) gave 21mg nicotine patches or placebo to 97 hysterectomy patients (60% were smokers) 1 hour before and for 2 days after surgery. This had no significant effect on pain ratings or analgesics use or the time to return to work (19 days). There was no difference between the responses of smokers and non-smokes on these variables. However, more patients in the nicotine group were ready for discharge at 48 hours (p<0.001) and 72 hours (p<0.04). These outcomes are not reported separately for smokers and non-smokers.

Yagoubian et al. (2011, RCT, [+]) administered nicotine nasal spray (3mg) and placebo to 20 non-smokers undergoing third molar surgery during two visits. Nicotine treatment was associated with a decrease it post-operative pain reported during 5 days after the surgery. The effect was very strong in the first day after surgery where pain scores were almost halved. The use of pain tablets (hydrocodone/ acetaminophen) was not affected.

INTERPRETATION

Given that most studies had only small samples, the fairly consistent finding of a significant effect suggests that the nicotine-induced analgesia is a genuine phenomenon that should be evaluated in more definitive trials. The Habib et al. (2008) finding of an objectively measured dose response between blood nicotine concentrations and self-administered analgesics provides an indication of a true biological effect.

The results seem consistent in the four studies of non-smokers but not in the two studies that included smokers. This tallies with the hypothesis that the prolonged effect of a single dose of nicotine observed in some studies may be a result of a lack of desentization of nACh receptors at very low concentrations (Benowitz 2008), which is more likely to arise in non-smokers who lack tolerance to nicotine effects. Other explanations of the effect include potential synergy with an opioid, and inhibition of inflammation (Habib et al 2008, Benowitz 2008), which can again be expected to be more pronounced in people 'naïve' to nicotine than in regular users.

The evidence above may have some tentative bearing on the hypothesis that in smokers, nicotine deprivation may heighten post-surgery pain (i.e. if nicotine reduces post-surgery pain, it is possible that its removal in habitual users increases it), but the reduction seems to apply to non-smokers rather than to smokers. It can also possibly provide an indirect argument for providing nicotine replacement to smokers undergoing surgery. However, such assumptions require empirical verification.

Olson et al. included smokers in their study, but the study was too small to detect any realistic effects, and further diluted by graded nicotine exposure and by combining experimental groups with very different response profiles. The lack of studies looking at the effect of NRT on post-surgery pain in acutely deprived smokers represents a gap in evidence, which would be relatively easy to fill.

[B] EFFECTS OF STOPPING SMOKING ON POST-SURGERY PAIN

We found no studies addressing this issue, but identified one study (summarised in Table 9) with an indirect relevance to the topic.

Table 9: Summary of studies included in part 2 section 3 [B]

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Shi et al (2011)	Retrospective cohort	USA 4,695 smokers	Self reported pain scores	Stopping smoking had no effect on pain occurrence, pain worsening, or on resolution or improvement of pain	Quality +

Shi et al. (2011, retrospective cohort, [+]) report the results of biennial surveys of a nationally representative US sample of older smokers taking place from 1992 through 2006. In 4,695 50-60 years old smokers reporting no pain or mild pain at enrolment, stopping smoking had no effect on pain occurrence (OR=1.04, 0.92,1.17) or pain worsening (OR=0.95, 0.84,1.08). In 1,118 smokers who reported moderate to severe pain at enrolment, stopping

smoking had no effect on resolution (OR=0.97, 0.82-1.15) or improvement (OR=0.87, 0.70-1.08) of self-reported pain.

INTERPRETATION

The study provides a reassurance regarding long-term effects of stopping smoking on pain perception. However, it does not address the effects of acute nicotine deprivation on post-surgery patients. It would be difficult to randomise smokers to a condition that allows smoking shortly after surgery, and such arrangement would also not be available in the smoke-free NHS. The relevant question however could be answered relatively easily by studies discussed at the end of the previous section, i.e. by a placebo controlled trial of the effects of NRT on post-surgery pain ratings and analgesics use in smokers.

EVIDENCE STATEMENTS 1.2

EFFECTS OF NRT IN PATIENTS REQUIRING INTENSIVE CARE

Given the number of possible acute effects of both abstinence and nicotine intake on a number of ICU outcomes, the literature we identified is limited and the results are difficult to integrate as there were a number of differences between patients who were and who were not given the patches and different studies concerned different population and outcome measures.

ES 1.2.1 There is mixed evidence regarding the safety of NRT use in critically ill patients. Two studies found an increased risk of mortality associated with NRT use in ICU and bypass surgery patients (Lee et al 2007, retrospective cohort, [+]; Paciullo et al 2009, retrospective cohort, [+]). Three studies found no increased risk of unfavourable outcomes (Panos et al 2010, retrospective cohort, [+]; Carandang et al 2011, retrospective cohort, [+]; Cartin-Ceba et al 2011, prospective cohort [+]). One study found an increased risk of pulmonary complications and seizures but lower risk of mortality in NRT users (Seder et al 2011, retrospective cohort [+]).

EFFECTS OF NRT IN PATIENTS UNDERGOING SURGERY

ES 1.2.2 There is moderate evidence that the adverse effects on bone healing and post-surgical complications are not due to nicotine (W-Dahl and Toksvig-Larsen 2007, prospective cohort study [+])

ES 1.2.3 There is weak evidence to suggest that nicotine patches should be removed prior to micro vascular reconstructive surgery to limit any possible vasoconstrictive effects of nicotine and surgery using vasopressin injections (Jagadeesan et al. 2007, case study, [-]; Groundine & Morley (1996, case study, [-])

ES 1.2.4 There is strong evidence that smokers who abstain from smoking 10 hours prior to surgery need smaller doses of atracurium for maintenance of anaesthesia than those who smoke up to a few hours before surgery or wear nicotine patches (Puura et al. 1998, RCT [++])

ES 1.2.5 There is strong evidence that chewing nicotine gum prior to surgery is not associated with an increased gastric fluid volume (Soreide et al. 1995, RCT, [++])

EFFECTS OF TOBACCO WITHDRAWAL AND NRT ON RISK OF DELIRIUM

The practice of putting patches on smokers undergoing major surgery or admitted to ICU to prevent delirium appears to have no sound evidence base. Two studies reported above suggest that such practice may increase mortality and no study suggests that it helps. The practice should be suspended until randomised trials of effects of NRT on surgery and ICU outcomes provide evidence that this is beneficial rather than irrelevant or harmful.

ES 1.2.6 There is moderate evidence that abstinence from smoking does not increase the risk of delirium. (Four studies found no link: Dubois et al 2001, prospective cohort, [+]; Nicholson et al. 2006, retrospective cohort, [-]; Ouimet et al. 2007, prospective cohort, [+]; Van Rompaey 2009, prospective cohort, [-], while two studies reported a link but did not control for possible confounders: Miyazaki et al. 2011, retrospective cohort, [+]; Lucidarme et al. 2010, prospective cohort, [-])

ES 1.2.7 There is weak evidence that application of NRT is associated with an increased risk of delirium (Cartin-Ceba et al 2011, prospective cohort [-]; Seder et al 2011, retrospective cohort [+]).

EFFECTS OF NRT AND SMOKING CESSATION ON PAIN

NRT may reduces post-operative pain in non-smokers but definitive trials are needed. Stopping smoking have no long-term effect on pain ratings but the acute effects are not known.

ES 1.2.8 There is good evidence that NRT alleviates post-operative pain in non-smokers (Flood and Daniel 2004, RCT, [+]; Habib et al. 2008, RCT, [+]; Hong et al. 2008, RCT, [+]; Yagoubian et al. 2011, RCT, [+])

ES 1.2.9 There is moderate evidence that NRT does not alleviate post-operative pain in smokers undergoing surgery (Olson et al. 2009, RCT, [-]; Turan et al. 2008, RCT, [+])

ES 1.2.10 There is moderate evidence that in the long-term, smoking cessation has no effect on perception of pain in general population (Shi et al. 2011, retrospective cohort, [+])

PART 3: EFFECTS OF NICOTINE AND EFFECTS OF STOPPING SMOKING IN NON-CARDIAC AND NON-SURGICAL HOSPITAL PATIENTS

This part covers a mixture of studies concerning several disparate topics. It is divided into 3 sections.

1. Section 1 covers studies addressing safety of NRT in non-cardiac patients and effects of smoking ban
2. Section 2 concerns effects of nicotine and smoking on medications
3. Section 3 concerns the special case of ulcerative colitis.

SECTION 1: SAFETY OF NRT IN HOSPITAL PATIENTS

Thirteen studies provided some information relevant for considering the safety of NRT when used over a period of time for smoking cessation. They are summarised in Table 10.

Table 10: Summary of studies included in part 3 section 1

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Axelsson et al (2001)	Randomised placebo cross over trial	Sweden 6 patients with type-2 diabetes matched to 6 health subjects. Two sessions, infusion of nicotine or saline.	Serum glucose, free insulin and free fatty acids (FFA) were measured.	No differences in serum insulin or glucose. Nicotine increased FFA in both groups.	Quality - Smoking status unknown
Carmel and Sheitman (2007)	Case studies	USA Two patients with dementia and agitation, 7mg nicotine patch given to one and 21mg to other.		Nicotine patch alleviated agitation in both patients.	Quality -
Epifano et al (1992)	Randomised placebo cross over trial	Italy 12 patients with type 2 diabetes; 1) smoking 1 cigarette per hour; 2) 21mg patch; 3) placebo patch - all after overnight abstinence.	Insulin secretion and insulin action. Blood glucose levels.	After smoking, hepatic glucose production suppressed less by insulin than patch than placebo. Smoking associated with lower stimulation of glucose utilisation than patch than placebo.	Quality +
Gallagher (1998)	Case studies	Canada Two smokers with terminal cancer developed delirium whilst in palliative care		Delirium resolved when NRT was provided.	Quality -
Lewis et al (1998)	Randomised controlled trial	UK 185 hospital in-patients given (1) brief quit advice (2) counselling plus 22mg patch (3) counselling plus placebo.	Abstinence (CO validated) and information on AEs.	No effect on abstinence adverse events. No SAEs were reported.	Quality +
Molander	Prospective	Sweden	Levels of nicotine	Degree of renal	Quality +

et al (2000)	cohort	15 patients with chronic renal failure and nine healthy subjects given an intravenous infusion of nicotine over 10 minutes.	and cotinine in plasma, urine, and peritoneal dialysate; nicotine PK	impairment linked to nicotine clearance. Severe renal impairment lowers renal and non-renal clearance.	
Molyneux et al (2003)	Randomised controlled trial	UK 274 hospitalised smokers given usual care, counselling alone, or counselling plus NRT.	Abstinence rates and adverse events.	There were 3 deaths and 30 other SAEs. No differences between groups.	Quality +
Murray et al (1996)	Randomised controlled trial	USA 5,887 patients with early stage COPD given 2mg gum or usual care.	Hospitalisations, adverse effects of gum use	Gum use not linked to fatal or non-fatal cardiovascular events or hospitalisation.	Quality ++
Murray et al. (2009)	Randomised controlled trial	USA 3,320 from above study followed up for 7.5 years	Surveillance for cancers	Smoking during the study predicted cancer but NRT use did not	Quality +
Rigotti et al (2000)	Prospective cohort study	USA 650 smokers taking part in RCT smoking cessation programme. During the study the hospital adopted a smoke-free policy	Nicotine withdrawal symptoms	89% reported at least one symptom in the first 24-48 hours of admission. 29% reported that it was difficult or very difficult to abstain.	Quality +
Rosin et al (2001)	Case study	USA Four cases of patient with dementia and agitation; 2 former smokers, 2 non-smokers	Occurrence of agitation	All patients were given 7mg patch. Agitation decreased. One patient showed deterioration when patch removed.	Quality -
Roth et al (2002)	Case study	A 58-year-old man experienced exacerbation of asthma after using nicotine nasal spray.		The authors suggest a causal relationship.	Quality -
Whiss et al. (2000)	Prospective cohort	Sweden 10 smokers and 4 wet snuff users, 7 patients with renal failure and 7 healthy subjects. Received IV infusion of nicotine after 36 hours of abstinence form tobacco.	Blood samples for nicotine and platelet analysis taken before and after, and again 2 hours after the nicotine infusion.	Plasma concentrations of nicotine over time were not different between groups. No differences in platelet function.	Quality +
Wagena et al. (2003)	General review	Summarised the findings of the Lung Health Study on the safety of NRT		Concluded that NRT increases abstinence rates when used in smokers with COPD and has a good safety profile	Quality +
Zabaneh et al (1995)	Case study	USA 36-year-old smoker admitted with acute cholecystitis.	Denied permission to smoke but smoked anyway.	His cigarette, combined with oxygen therapy, caused his bed to catch fire and he suffered second-degree burns.	Quality -

Lewis et al (1998, RCT, [+]) randomised 185 hospital inpatients (non-cardiac) to one of three groups: (1) brief quitting advice from a physician (N=61); (2) counselling plus 22mg patch (N=62); or (3) counselling plus placebo patch (N=62). There were no significant differences in

point abstinence or AE rates between the patch and placebo groups. No serious adverse events (SAEs) were reported.

Molyneux et al (2003, RCT, [+]) randomised 274 inpatients to usual care (N=92), counselling alone (N=91), or counselling plus NRT (N=91). A choice of 5 NRT products was offered to the smokers (patch, gum, inhalator, tablet or spray). Eighty-nine adverse events (AEs) were reported in 65 patients. There were no significant differences in the number of AEs between treatment groups.

Murray et al (1996, RCT, [++]) report on safety of nicotine gum use in participants of the Lung Health Study. Participants, diagnosed with early stage COPD, were randomised to a smoking cessation intervention, which included the use of 2mg nicotine gum (N=3,923), or usual care (N=1,964). Patients had the option of using the gum for the duration of the study period (5 years). Using gum long-term did not predict any fatal or non-fatal cardiovascular events, nor was it associated with hospitalisation. There was also no risk associated with concomitant gum use and smoking.

Murray et al (2009, cohort follow-up [+]) compared Lung Health Study patients who did (N=1986) and did not (N=1,329) use nicotine chewing gum in incidence of cancer over 7.5 years. Smoking status during the study was a significant predictor of lung cancer, but use of NRT had no effect.

In a general review **Wagena et al. (2003, general review, +)** summarised the findings of the Lung Health Study on the safety of NRT and concluded that NRT increases abstinence rates when used in smokers with COPD and has a good safety profile.

Two studies concerned the effect of renal impairment on nicotine clearance

Molander et al (2000, prospective cohort, [+]) recruited 15 patients with chronic renal failure and 9 healthy subjects. Eighteen of the patients smoked cigarettes and six used wet snuff. Each participant was given an intravenous infusion of nicotine (0.028 mg/kg) over a 10-minute period. There was a significant correlation between the degree of renal impairment and total nicotine clearance. Patients with severe renal impairment had lower renal and non-renal clearance of nicotine. Conversely these patients also showed highest area under the curve (AUC) 64.3 +/- 43.9 ng.h/ml compared with 23.5 +/- 6.8 ng.h/ml in healthy subjects.

Whiss et al. (2000, prospective cohort, [+]) enrolled 7 patients with renal failure and 7 health subjects to examine the effect of nicotine on platelet function. All participants were tobacco users (10 cigarette smokers, and 4 wet snuff users) who were asked to abstain from tobacco use for 36 hours prior to receiving an IV infusion of nicotine (0.028 mg/kg over 10 minutes). Blood samples for platelet analysis were taken immediately before and after, and again 2 hours after the nicotine infusion. Blood samples for nicotine and cotinine analysis were also collected. Plasma concentrations of nicotine over time were not statistically different between groups. Cotinine levels however were significantly higher ($p<0.05$) at all time points in patients with renal failure. Nicotine caused increased platelet responsiveness in both groups, with no significant differences in platelet function between groups.

Two studies examined the effect of nicotine on insulin secretion and its actions.

Axelsson et al. (2001, randomized cross-over study, [+]) studied 6 patients with type 2 diabetes and 6 healthy subjects matched for sex, age and BMI. They were given either an infusion of nicotine or saline in two experimental sessions. Smoking status of the participants was not reported. There were no significant differences in plasma levels of insulin or glucose under the two conditions. The levels of free fatty acids (FFA) were significantly higher during the nicotine infusion compared to saline ($p<0.01$). Insulin sensitivity was lower in the diabetics compared to controls during both sessions. In the patients with diabetes the nicotine infusion was associated with lower insulin sensitivity than seen with the saline infusion.

Epifano et al. (1992, randomized cross-over study, [+]) randomly allocated 12 smokers with type 2 diabetes to participate in each of 3 conditions (smoking one cigarette per hour; abstaining using a 21mg patch; and abstaining using a placebo patch) after overnight abstinence. Each study condition was undertaken over 2 days, with 5 days between them. The patch and smoking did not affect insulin secretion any differently than placebo. Hepatic glucose production was suppressed less by high insulin after smoking than by the patch ($p<0.05$). In turn the patch suppressed glucose production less than placebo ($p<0.05$). Similarly, smoking was associated with significantly lower stimulation of glucose utilisation compared to the patch, which in turn produced lower stimulation of glucose stimulation than placebo ($p<0.05$ for both comparisons). Smoking (and to a significantly lesser extent the patches) affect insulin resistance, but not insulin secretion.

One case study reported on a potential risk of nasal spray use in asthma.

Roth et al (2002, case study, [-]) describes a case of a 58-year-old man who experienced exacerbation of his asthma and required hospitalisation for 48 hours, after using nicotine nasal spray.

One study and four case studies concern the effects of smoke-free hospital environment on smokers.

Carmel (2007, case study, -) reports on 2 smokers with severe dementia who developed agitation. Both were treated with a nicotine patch that alleviated agitation.

Gallagher (1998, case study, [-]) reports on 2 cases of patients with terminal cancer who were formally heavy smokers. They both developed delirium whilst in palliative care which resolved when NRT was provided.

Rigotti et al (2000, prospective cohort, [+]) studied a cohort of 650 patients who participated in a RCT of an inpatient smoking cessation programme. During the study the hospital adopted a smoke-free policy meaning that smoking was restricted to outside. The majority of the participants (89%) reported at least one tobacco withdrawal symptom in the first 24-48 hours after admission. Over half (57%) found it easy to abstain in hospital, 29% reported that it was difficult or very difficult. Only 17% reported smoking whilst in hospital. Greater ratings of craving ($p<0.001$), and restlessness ($p=0.011$) were associated with smoking whilst hospitalised.

Rosin et al (2001, case study, [-]) report on four patients (2 former smokers, 2 non-smokers) with dementia who developed agitation while in a smokefree hospital. All patients were treated with a 7mg patch with subsequent decreases in agitation. One case showed deterioration in clinical state when the patch was removed.

Zabaneh (1994, case study [-]) reported a case of a 36-year old man who smoked and was admitted to hospital with acute cholecystitis. A day after admission he became irritable, anxious and restless. He was denied permission to smoke but smoked anyway. His cigarette, combined with his oxygen therapy, caused his bed to catch fire and he suffered second-degree burns.

INTERPRETATION

This diverse group of studies did not identify any further risks of NRT use. Most smokers hospitalised in smoke-free hospitals experience some degree of tobacco withdrawal symptoms, but this is mostly mild and only a minority finds abstinence in this setting difficult.

SECTION 2: EFFECTS OF TOBACCO WITHDRAWAL ON THEOPHYLLINE, AMINOPHYLLINE, AND INSULIN

Smoking and stopping smoking have an effect on the metabolism of a number of medicines.

Our literature search found three studies concerning theophylline and aminophylline (theophylline ethylenediamine) as well as a case report of theophylline toxicity following smoking cessation. We also identified two studies concerning insulin. These studies are summarised in Table 11.

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Table 11: Summary of studies included in part 3 section 2

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Eldon et al. 1987	Cross-over trial	USA. 12 healthy male smokers randomly allocated to a 36-hour period of abstinence or smoking. After the first 24 hours they were administered an aminophylline infusion.	Theophylline plasma concentration	No significant differences in plasma theophylline levels between the two conditions.	Quality +
Lee et al (1987)	Quasi-experimental	USA (research lab setting) 14 healthy smokers in 2 conditions. Group 1 (n=7): days 1-7 smoking, days 8-14 abstaining, days 15-22 smoking. Theophylline	Theophylline plasma concentration, clearance (CL) and half life	CL significantly reduced and half life significantly increased during abstinence In both groups	Quality +

		infusion on days 7, 14 and 22. Group 2 (n=7) same procedure, but 4mg gum on abstaining days.			
Mayo et al (2001)	Case control	Canada 31 children receiving IV aminophylline, with smoking parents. Age and gender matched control group (n=31) without smoke exposure.	Duration of hospital stay and steady state plasma concentration of aminophylline	Hospitalisation was longer and plasma concentration lower in case vs. control.	Quality +
Rao (1996)	Case study	USA 65-year-old woman with emphysema on oral theophylline. Stopped smoking for 9 months, admitted with weakness, nausea and vomiting.		Congestive heart failure, later seizures. Serum theophylline level was 45.2 ug/ml (therapeutic range 10-20 ug/ml)	Quality -
Muhlhauser et al (1984)	Randomised cross-over trial	West Germany 8 healthy smokers given 2 types of insulin with and without smoking after overnight abstinence.	Serum insulin (mU/L)	No differences in serum insulin	Quality +
Klemp et al (1982)	Quasi experimental	Denmark 9 diabetic smokers, abstained overnight, given iodine-labelled insulin before and after smoking	Disappearance (half time) of iodine-labelled insulin	113% decreased absorption of insulin during smoking	Quality +

THEOPHYLLINE AND AMINOPHYLLINE

Eldon et al. (1987, cross-over trial, [+]) recruited 12 healthy male smokers who were randomly allocated to a 36 hour period of abstinence or smoking. After the first 24 hours they were administered an aminophylline infusion and had blood samples collected over a 12 hour period. They participated in the other condition a week later. There were no significant differences in plasma theophylline levels between the two conditions.

Lee et al (1987, quasi-experimental, [+]) allocated 14 healthy smokers to two conditions. Group 1 (n=7): day 1-7 smoking, day 8-14 abstaining, and days 15-22 smoking. Theophylline infusion was given on days 7, 14 and 22. Group 2 followed the same procedure, but chewed 4mg gum (1 piece/hr) on abstaining days. In Group 1, clearance was reduced by 38% ($p<0.001$) and half-life of theophylline was increased by 36% ($p<0.05$) during abstinence. In Group 2, clearance decreased and half-life increased by 32% ($p<0.05$) and 40% ($p<0.05$) respectively. The authors recommend that in smokers who stop smoking, theophylline dose should be reduced by a quarter to a third. The results suggest that this is not due to nicotine.

Mayo (2001, case control study, [+]) studied 31 children aged 1 to 9 receiving IV aminophylline for 48 hours who had smoking parents. A matched control group of 31 children had no second hand smoke exposure. Mean duration of hospitalisation case vs. Control was 4.4 vs. 2.9 days ($p<0.05$). Steady state plasma concentration of aminophylline in cases versus controls was 55.3 vs. 73.2 umol/L ($p<0.0001$). CL in cases vs. control was 1.36 vs. 0.90 ($p<0.00001$).

Rao (1996, case study, [-]) described a case of a 65 year old woman with emphysema, taking sustained released theophylline (200mg twice daily). She had stopped smoking 9 months ago and was admitted with weakness, nausea and vomiting. She had congestive heart failure and later developed seizures. Her serum theophylline level of 45.2 ug/ml (therapeutic range is 10-20 ug/ml) was considered the cause.

INSULIN

Klemp et al. (1982, quasi-experimental, [-]) gave 9 diabetic smokers iodine-labelled insulin after overnight abstinence. Ninety minutes later they were allowed to smoke a cigarette. Half time measured 30 mins before smoking was 158 +/- 22 mins. In the period during smoking half time increased to 336 +/- 97 mins ($p<0.05$) representing a 113% decrease in insulin absorption. In the first 30 minutes after smoking the half-life was still significantly higher than at baseline, 207 +/- 29 mins ($p<0.05$).

Muhlhauser et al. (1984, quasi-experimental, [-]) randomly allocated 8 healthy male smokers to 4 conditions over 10 days after overnight abstinence from smoking: (1) Neutral insulin with smoking; (2) Neutral insulin without smoking; (3) Mixtard insulin with smoking; and (4) Mixtard insulin without smoking. During the smoking conditions subjects smoked one cigarette 2.5 minutes before and one cigarette 5 minutes after insulin injection. There were no significant differences in serum insulin concentrations between smoking and non-smoking conditions.

INTERPRETATION

Two experimental studies of theophylline use in healthy subjects report conflicting results. However the study that found no difference examined changes over a very short period of abstinence. The remaining data suggest that theophylline levels are sensitive to smoking and abstinence, with increase clearance and decreased half-life following smoking cessation. Aminophylline levels are influenced even by passive smoking. In patients who change their smoking status, doses of these drugs need to be monitored and adjusted. The changes are caused by chemicals in cigarette smoke other than nicotine.

Two small studies of insulin from 1980's examined only acute effects of smoking and they report conflicting results.

SECTION 3: EFFECTS OF SMOKING AND SMOKING CESSATION ON ULCERATIVE COLITIS

Ulcerative colitis (UC) is an inflammatory disease of the colon, which is seen primarily in non-smokers and ex-smokers. Smoking seems to be beneficial for UC, possibly because nicotine might reduce the expression of cytokines that promote inflammation.

Our literature search identified 12 relevant studies, summarised in Table 12.

Table 12: Summary of studies included in part 2 section 3

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Bastida et al. (2011)	General review	General review of the association of smoking and smoking cessation with UC		Smoking cessation patients with UC may cause worsening of symptoms	Quality +
Beaugerie et al (2001)	Retrospective cohort	France 32 patients who quit smoking at some time following their diagnosis of UC	Signs and symptoms of UC	Smoking cessation was associated with a flare up of the disease ($p<0.01$) and longer duration of medical treatment ($p<0.01$).	Quality -
Green et al (1998)	Retrospective cohort	UK 51 patients (all current smokers) with verified ulcerative colitis, which had developed when they were either non-smokers or ex-smokers.	Review of development of UC and control of disease whilst smoking	19 report developing UC within two years of smoking cessation. Most (n=28) believed that smoking improved symptoms associated with UC.	Quality -
Guslandi et al (1998)	Randomised controlled trial	Italy 38 patients in remission of UC (no current smokers) randomised to a 5-week course of 15mg nicotine patch (n=21) or oral prednisone.	Signs and symptoms of UC The first 15 patients with remission followed up for further 6 months.	UC relapse less common in patch group (20%) vs. the prednisone group (60%), p=0.027. No difference in remission (15/21 vs. 15/17) at end of treatment.	Quality +
Guslandi et al (2002)	Randomised controlled trial	Italy 30 UC patients, who were non-smokers maintained on a mesalamine 4g enema, to 15mg nicotine patch or oral mesalamine for 4 weeks	Clinical remission	Remission was greater in patch users (12/15; 80%) than those on mesalamine (5/15; 33%), p=0.027.	Quality +
Ingram (2005)	Randomised controlled trial	UK 104 patients with UC to a 6-week treatment course of 6mg nicotine or placebo enemas, in addition to their standard UC therapy.	Clinical remission	No difference in clinical remissions was observed between the groups (p=0.55).	Quality +
McGarth et al (2009)	Systematic review	Included 5 of 9 RCTs assessing the effects of nicotine patches for	Clinical or sigmoidoscopic remission,	Showed a significant benefit of patches compared to placebo in clinical remission.	Quality ++

		induction of remission of UC.	adverse events		
Nickfar et al (2011)	Systematic review	Investigated the effect of nicotine preparations in the treatment of active UC.	Clinical remission	No difference in efficacy NRT in achieving clinical remission of UC compared to placebo or corticosteroids.	Quality +
Pullan et al (1994)	Randomised controlled trial	UK 72 patients with UC to a 6-week course of 15-25mg patch (n=35) or placebo (n=37).	Clinical remission	More patients in the patch group (17/35) than in the placebo group (9/37) had complete remission (p=0.03).	Quality +
Sandborn (1997)	Randomised controlled trial	USA 64 non-smoking UC patients to a 4-week course of 22mg patches (n=31) or placebo (n=33).	Clinical improvement and remission	More patients on patch showed improvement (p = 0.007). No difference in remission rates.	Quality +
Thomas et al (1996)	Randomised controlled trial	UK 61 patients with active UC randomized to 6-weeks treatment with nicotine patch (15-25 mg/day) or oral prednisolone.	Sigmoidoscopic remission	More patients in the prednisolone group achieved full remission p<0.05	Quality +
Wahed et al. (2011)	Retrospective cohort	UK 73 UC patients (9 smokers)	Beneficial effects of smoking on their disease	Only 21% were aware of the beneficial effects of smoking on their disease, and the knowledge was not related to smoking status.	Quality -

We found 6 randomised trials of NRT in patients with UC.

Guslandi et al (1998, RCT, [+]) randomised 38 patients in remission of UC, none of whom were current smokers, to a 5-week course of 15mg nicotine patch (n=21) or oral prednisone. The first consecutive 15 patients with signs of remission were followed up for a further 6 months. Relapses of UC were significantly less common in the patch group (20%) vs. the prednisone group (60%), p=0.027. There was no significant difference between the groups in remission (15/21 vs. 15/17) at the end of treatment.

Guslandi et al (2002, RCT, [+]) randomised 30 UC patients, who were non-smokers maintained on a mesalamine 4g enema, to 15mg nicotine patch or oral mesalamine for 4 weeks. Remission was greater in patch users (12/15; 80%) than those on mesalamine (5/15; 33%), p=0.027.

Ingram (2005, RCT, [+]) randomised 104 patients with UC to a 6-week treatment course of 6mg nicotine or placebo enemas, in addition to their standard UC therapy. No difference in clinical remissions was observed between the groups (14 of 52 receiving nicotine vs. 14 of 43 receiving placebo, p=0.55).

Pullan et al (1994, RCT, [+]) randomised 72 patients with UC to a 6 week course of 15-25mg patch (n=35) or placebo (n=37). At the end of the study period more patients in the patch group (17/35) than in the placebo group (9/37) had complete remission (p=0.03).

Sandborn (1997, RCT, [+]) randomised 64 non-smoking UC patients to a 4-week course of 22mg patches (n=31) or placebo (n=33). A higher proportion of patients in the patch group

(12/31) showed clinical improvement than patients using placebo (3/33), p = 0.007. There was no significant difference in remission rates (2/31 vs. 0/33).

Thomas et al (1996, RCT, [+]) compared the effects of nicotine patch (15-25 mh/day) with oral prednisolone in a RCT in 61 patients with active UC. Both treatments were used for 6 weeks. Significantly more patients in the prednisolone group (14/31) achieved full remission compared to those in the nicotine group (6/30), p<0.05.

We found two reviews of these RCTs. A Cochrane Review **(McGarth et al. 2009, [++])** included five RCTs in a meta-analysis. Pooling the results of the two placebo controlled trials showed a significant benefit of nicotine patches compared to placebo in clinical remission (OR=2.56, CI: 1.02-6.45). Three trials compared patches with standard therapy, showing no significant difference in outcomes (OR=0.90, CI: 0.12-6.94). Patients treated with NRT were more likely to withdraw from treatment than those using placebo or standard treatment (OR=5.82, CI: 1.66-20.47).

Nikfar et al. (2010, [+]) conducted a systematic review and meta-analysis and included 5 randomised controlled trials; four were included in the Cochrane review (Pullan et al 1994; Thomas et al 1996; Sandborn et al 1997; Guslandi & Tittobello 1998) and one additional trial that investigated the use of a nicotine enema (Ingram et al 2005). The meta-analyses found no effect of nicotine compared to placebo, on clinical remission (relative risk = 1.40, 95%CI:0. 63-3.12), but it also found no difference between the effects of NRT and corticosteroids (RR=0.74, 95%CI: 0.5-1.09).

We found four other publications relevant for the topic.

In a general review of the topic **Bastida et al. (2011, general review, +)** concluded that smoking cessation in a patient with UC may cause worsening of symptoms and that such patients should receive information regarding the risks of continued smoking versus those associated with stopping. In the authors' opinion, given the increasing number of available treatments for exacerbations of UC and the risks of continuing to smoke, patients with UC should be advised and assisted to stop.

Beaugerie et al (2001, retrospective cohort, [-]) reported on 32 patients who quit smoking at some time following their diagnosis of UC. Smoking cessation was associated with a flare-up of the disease (p<0.01) and patients who quit were more likely to require medical treatment for longer (p<0.01). There was no difference in the risk of needing colectomy.

Green et al (1998, retrospective cohort, [-]) collected data from a cohort of 51 UC patients who were smokers. Their disease had developed when they were either non-smokers or ex-smokers. Nineteen reported developing UC within two years of stopping smoking. Most (N=28) believed that smoking improved their symptoms.

Wahed et al. (2011, retrospective cohort, [-]) reported that in a sample of 73 UC patients (of which 9 were smokers), only 21% were aware of the beneficial effects of smoking on their disease, and the knowledge was not related to smoking status.

INTERPRETATION

Nicotine patches, but not nicotine enema, have a positive effect on ulcerative colitis. Nicotine treatment however is not more effective than standard treatment and causes more

side effects in non-smokers. Ulcerative colitis sufferers who smoke can expect worsening of their symptoms if they stop smoking.

Evidence Statements 1.3

Safety of NRT in medically stable patients

This diverse group of studies did not identify any further risks of NRT use.

ES 1.3.1 There is strong evidence that the use of NRT in medically stable patients is not associated with an increased risk of adverse events (Lewis et al 1998, RCT, [+]; Molyneux et al 2003, RCT, [+]; Murray et al 1996, RCT, [++]; Murray et al 2009, prospective cohort, [+], Wagena et al. 2003, general review, [+])

ES 1.3.2 There is moderate evidence that renal disease can impair nicotine clearance (Molander et al 2000, prospective cohort, [+]; Whiss et al. 2000, prospective cohort, [+])

ES 1.3.3 There is moderate evidence that nicotine use in patients with renal disease does not adversely affect platelet function (Whiss et al. 2000, prospective cohort, [+])

ES 1.3.4 There is moderate evidence that nicotine has little effect on insulin secretion (Epifano et al. 1992, randomized cross-over study, [+]; Axelsson et al. 2001, randomized cross-over study, [+])

ES 1.3.5 There is moderate evidence that medicinal nicotine is associated with insulin resistance, although significantly less so than smoking (Epifano et al. 1992, randomized cross-over study, [+]; Axelsson et al. 2001, randomized cross-over study, [+])

Effect of smoking abstinence on hospitalised smokers

Most smokers hospitalised in smoke-free hospitals experience some degree of tobacco withdrawal symptoms, but this is mostly mild and only a minority find abstinence in this setting difficult.

ES 1.3.6 There is moderate evidence that smokers who cannot smoke in hospital can experience some tobacco withdrawal symptoms (Rigotti et al 2000, prospective cohort, [+]; Zabaneh 1994, case study [-]; Carmel 2007, case study, [-]; Gallagher 1998, case study, [-]; Rosin et al 2001, case study, [-])

Effects of tobacco withdrawal and nicotine on theophylline and aminophylline

Theophylline levels are sensitive to smoking and abstinence and aminophylline levels are influenced even by passive smoking. In patients who change their smoking status, doses of these drugs need to be monitored and adjusted.

ES 1.3.7 There is moderate evidence that theophylline levels are sensitive to smoking and abstinence (Lee et al 1987, quasi-experimental, [+]; Rao 1996, case study, [-]) and aminophylline levels are influenced even by second hand smoke (Mayo et al. 2001, case control study, [+]). One study, Eldon et al. 1987 (cross-over trial, [+]), showed no effect of a 36-hour period of abstinence on serum theophylline levels.

ES 1.3.8 There is moderate evidence that nicotine does not influence theophylline levels (Lee et al 1987, quasi-experimental, [+])

EFFECTS OF TOBACCO WITHDRAWAL AND NICOTINE ON SUB-CUTANEOUS INSULIN

There are inconsistent data regarding the effect of smoking on the absorption of insulin, and no data regarding the effect of NRT on insulin absorption.

ES 1.3.9 There are inconsistent data regarding the interaction between subcutaneous insulin and smoking (Klemp et al. 1982, quasi-experimental, [+]; Muhlhauser et al. 1984, quasi-experimental, [+])

EFFECTS OF TOBACCO WITHDRAWAL AND NICOTINE ON ULCERATIVE COLITIS

Effects of nicotine on ulcerative colitis

ES 1.3.10 There is strong evidence that NRT can have positive effects on ulcerative colitis (Guslandi et al 1998, RCT, [+]; Guslandi et al 2002, RCT, [+]; Ingram 2005, RCT, [+]; Pullan et al 1994, RCT, [+]; Sandborn 1997, RCT, [+]; Thomas et al 1996, RCT, [+]; McGarth et al. 2009, systematic review [++]; Nikfar et al. 2010, systematic review [+])

Effects of smoking cessation on ulcerative colitis

ES 1.3.11 There is moderate evidence that smokers with ulcerative colitis experience worsening of their symptoms when they stop smoking (Bastida et al, review (+), Beaugerie et al 2001, retrospective cohort, [-]; Green et al 1998, retrospective cohort, [-]; Wahed et al. 2011, retrospective cohort, [-])

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CHAPTER 2

Effects of nicotine use and effects of tobacco withdrawal in patients with mental illness

INTRODUCTION

The main hypothesis for why smoking rates are exceptionally high in people with mental health illness is that they smoke to alleviate some of the symptoms associated with their illness (Aubin et al 2012). The concern is therefore that when such patients stop smoking, either of their own accord or because they are forced to abstain, their functioning may deteriorate (Aubin 2009; Hughes 1993).

There is also a specific concern that concurrent stopping smoking may undermine the efficacy of treatments for patients with alcohol and drug addictions.

Finally, smoking affects the speed with which a number of psychiatric drugs are metabolised and stopping smoking may lead to an increase in drug side effects (Kroon 2007).

Below we present data from 92 studies concerning the effects of abstinence and of stop-smoking treatments on psychiatric symptoms and psychiatric medications, and also on the effects of smoking cessation on treatment outcome of other drug dependencies. The material is organised into the following sections:

1. Section 1: Effects of tobacco abstinence and effects of stop-smoking medications on mental health
2. Section 2: Effects of tobacco abstinence on psychiatric medications
3. Section 3: Effects of smoking cessation on the outcome of other substance abuse treatment;
4. Section 4: Effects of smoke free policy on behaviour and psychiatric symptoms of psychiatric in-patients.

A brief interpretative summary of findings is provided at the end of each section, and evaluation and evidence statements are at the end of the Chapter.

SECTION 1: EFFECTS OF SMOKING CESSATION AND EFFECTS OF NRT ON PSYCHIATRIC SYMPTOMS

We found literature concerning the impact of stopping smoking on several conditions, including post-traumatic stress disorder, schizophrenia, and depression. We review the studies concerning these three conditions separately, and cover systematic reviews of the topic at the end. Twenty-nine studies covered in Part 1 are presented in Table 13 below.

Table 13: Summary of studies included in Chapter 2 Section 1

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes

Allen et al (2011)	Randomised double blind placebo controlled trial	USA 40 smokers with high agitation on admission to a psychiatric ward, received nicotine patch or placebo.	Agitated Behaviour Scale (ABS), Overt Aggression Scale, + and - Symptom Scale (PANSS); at baseline, 4 and 24 hrs.	ABS score decreased over 24h in both groups. PANSS excited component score decreased more in patch group.	Quality +
Baker et al (2006)	Randomised controlled trial	Australia 298 psychiatric outpatients with non-acute illness given patch or usual care.	Abstinence, change in symptoms measured with BDI, BPRS, STAI, SF-12	No changes in BPRS scores. SF-12 and BDI scores lower than baseline in the intervention group at all time points.	Quality + No comparison of quitters vs. smokers
Banham & Gilbody (2010)	Systematic Review	Included 9 papers, from 8 RCTs examining the efficacy of smoking cessation interventions for people with severe mental health illness	Abstinence from smoking and data regarding psychiatric symptoms were also extracted	Psychiatric symptoms were largely not different between intervention and control groups	Quality + Does not analyse effects of abstinence
Benazzi & Mazzoli (1994)	Case study	Italy 40-year old man with a history of psychotic illness		Presented with psychosis following smoking cessation	Quality -
Blalock et al (2008)	Prospective cohort study	USA 21 depressed smokers on patch + behavioural counselling or mood management counselling	Abstinence (CO validated) and PANSS and BDI to measure psychiatric symptoms	9 patients quit and showed significant improvement in the PANSS positive symptoms score and BDI	Quality + (- in terms of study design, but + in terms of usefulness of data)
Bock et al (1996)	Case studies	USA Three women who developed significant depression following smoking cessation			Quality -
Dalak et al (1999)	Randomised double blind cross over study	USA 10 smokers with schizophrenia given 22mg or placebo patch over 2-days. They could smoke ad lib. 5-day wash out	Blood nicotine levels, CO, psychiatric symptoms, withdrawal symptoms	Patch use reduced CO by 15%. No effect on psychiatric symptoms.	Quality +
Evins et al (2001)	Randomised controlled trial	USA 18 outpatients with schizophrenia used either bupropion or placebo with a 12-week group CBT intervention	Abstinence and change in psychiatric symptoms	BPRS scores decreased on bupropion and increased on placebo. Depressive symptoms improved on bupropion.	Quality +
Evins et al (2005a and 2005b) 2 papers related to the same study	Randomised controlled trial	USA 53 smokers with schizophrenia. 12-week CBT plus bupropion or placebo.	Abstinence and change in psychiatric symptoms. 2005b reports on tests of cognitive functioning.	Greater reductions in PANSS depressive and cognitive subscales in bupropion group. No deterioration on cognitive measures.	Quality +
Evins et al (2007)	Randomised placebo	USA 51 smokers with	Abstinence (CO validated) and	No effect on abstinence or psychiatric symptoms	Quality +

	controlled trial	schizophrenia on nicotine patch and allocated to 12-week bupropion or placebo	psychiatric symptoms		
Fatima et al (2005)	Randomised cross over trial	10 outpatients with schizophrenia or schizoaffective disorder given bupropion or placebo for 21 days	Abstinence (CO validated) and psychiatric symptoms	A non-significant reduction in CO levels, no effect on psychiatric symptoms	Quality +
Gallagher et al (2007)	Randomised controlled trial	USA 181 patients with schizophrenia and other severe illnesses. Contingent reinforcement (CR), CR plus NRT; or self-quitting.	CO validated abstinence and psychiatric symptoms (Brief Symptom Inventory BSI. Followed up at 36 weeks	No effect on abstinence or BSI.	Quality +
George (2000)	Randomised controlled trial	USA 45 smokers with schizophrenia, nicotine patches plus group treatment programme (GTP) for patients with schizophrenia or standard GTP.	Abstinence rates and psychiatric symptoms measured by AIMS, BDI, PANSS, and WEPS	No effect on abstinence. Patients in the specialist GTP had lower PANSS negative symptom scores.	Quality +
George et al (2002)	Randomised placebo controlled trial	USA 32 patients with schizophrenia or schizoaffective disorder received bupropion or placebo	Abstinence (CO validated) at 6-months. Psychiatric symptoms: PANSS, BDI, AIMS, WEPS.	Abstinence higher in bupropion group. No effect on positive PANSS score, but decreases in negative symptoms greater on bupropion	Quality +
George et al (2008)	Randomised controlled trial	USA 58 outpatients with schizophrenia or schizoaffective disorder received 10 week bupropion + patch, or placebo + patch	Abstinence (CO validated) and psychiatric symptoms (PANSS and BDI)	Significant effect on abstinence. No effects of abstinence on psychiatric symptoms.	Quality +
Hill & Chang (2007)	Case series	USA 9 psychiatric outpatients in group-based CBT or group based CBT plus NRT	BDI at baseline and monthly for 3 months	No effect on cigarette consumption or BDI	Quality -
Jenkusky 1993	Case study	USA 27-year-old woman with schizoaffective disorder admitted with anxiety, agitation and nausea		Wore a nicotine patch whilst smoking	Quality -
Lundberg et al (2004)	Case studies	USA 5 patients with obsessive-compulsive disorder treated with NRT gum for 8 weeks	Yale-Brown Obsessive-Compulsive Scale (YBOCS)	4 patients showed improvement, 3 reported mild side effects of the gum	Quality -
McFall et al (2005)	Randomised controlled	USA 66 smokers with PTSD	Abstinence (CO validated), PTSD	No changes in symptoms and no differences	Quality +

	trial	received intervention by PTSD physicians or referral to smoking cessation clinic	checklist and Becks Depression Inventory (BDI) at 6 and 9 months	between smokers and abstainers	
McFall et al (2010)	Randomised controlled trial	USA 943 smokers with PTSD received intervention by PTSD physicians or referral to smoking cessation clinic	Abstinence (CO validated); PTSD symptoms; depressive symptoms	Abstinence rates higher in intervention group. At 18 months reductions in PTSD and depressive symptoms in both groups.	Quality ++
Moadel et al (1999)	Case study	USA 62-year-old man with depression and anxiety and bladder cancer. Smoked a pack of cigarettes a day.	He required regular cystoscopy and before each procedure he would get very anxious.	He was provided with a 14 mg patch to wear on the day of the procedure and was less anxious	Quality -
Scharf 2009	Case studies	Canada 3 psychiatric inpatients, heavy smokers		Successfully helped to stop smoking with 21mg nicotine patches	Quality -
Smith et al (2002)	Randomised cross over study	USA 30 patients with schizophrenia: (1) high nicotine cigarettes (2) denicotinized cigarettes (3) active nasal spray (4) placebo nasal spray, all after overnight abstinence	Psychiatric symptoms PANSS, SANS	Negative symptom scores raised after overnight abstinence and decreased after smoking either type of cigarette	Quality ++
Thorsteinsson et al (2001)	Randomised controlled trial	USA 38 patients with a history of major depressive disorder on patch or placebo for 2-weeks. Followed by all on placebo for 8 days.	HAM-D, BDI, Profile of Mood States (POMS) and tobacco withdrawal symptoms.	Mood rating decreased over time for abstainers. Placebo users had greater decrease in POMS scores	Quality +
Tsoi et al (2010)	Systematic Reviews	Included 21 RCTs of smoking cessation or reduction in smokers with schizophrenia or schizoaffective disorder	Abstinence rates (Russell standard), changes in psychiatric symptoms and adverse events	No significant differences in positive or negative symptoms or depressive symptoms.	Quality + No comparison of abstainers vs. smokers
Weiner et al (2011)	Randomised controlled trial	USA 9 patients with schizophrenia were received varenicline or placebo for 12 weeks.	Abstinence (CO validated) and changes in psychiatric symptoms (BPRS).	No difference between groups	Quality - Tiny sample
Williams et al (2004)	Case studies	USA 12 patients with schizophrenia using nicotine nasal spray		1 patient could not tolerate spray, most used maximum dose without problems	Quality -
Williams et al (2010)	Randomised controlled trial	USA 87 patients with schizophrenia in high or low intensity treatment for 6 months	Abstinence (CO validated) and psychiatric symptoms (BDI, PANSS)	No difference in BDI or PANSS by treatment group or by abstinence	Quality +

Patients with Post Traumatic Stress Disorder

McFall et al (2005, RCT [+]) randomised 66 patients with Post-traumatic Stress Disorder (PTSD) to a smoking cessation intervention delivered by PTSD physicians (N=33) or a referral to a smoking cessation clinic (N=33). The latter group was meant to act as the control. Overall there were no significant changes in PTSD checklist scores or Becks Depression Inventory (BDI) from baseline to 6 and 9 months follow-up, and no difference between smokers and abstainers.

McFall et al (2010, RCT [++]) randomised 943 PTSD smokers to a smoking cessation intervention, including stop-smoking medications, delivered by PTSD physicians (N=472) or a referral to a smoking cessation clinic (N=471). Twelve month abstinence rates were higher in the physician-delivered treatment group (8.9%) versus the control (4.5%), OR=2.26 (CI: 1.30-3.91). At 18 months both abstainers (n=63) and smokers (n=880) showed significant reductions in severity of PTSD and depressive symptoms. Only the change in depressive symptoms was significantly different between the groups with non-quitters worsening slightly (p=0.03). The proportion of people with SAEs did not differ between abstainers (41%) and smokers (47%, p=0.39). Only a fraction of these (2%) were considered potentially related to the study, the breakdown for abstainers and smokers is not provided.

Patients with schizophrenia or schizoaffective disorder

Allen et al (2011, RCT [+]) randomised 40 patients with acute schizophrenia with a significant level of agitation hospitalised in a smoke-free hospital to 21mg nicotine (n=20) or placebo patches (n=20). Agitation score, Overt Aggression Scale, Positive and Negative Symptoms Scale (PANSS) excited component subscale, and Richmond Agitation-Sedation Scale were administered at baseline, 4 and 24 hours later. The ABS score decreased in all patients over 24 hours (p=0.055). The decrease in PANSS score was greater in the patch vs. placebo group (p=0.01). There were no significant differences on the other scales.

Baker et al (2006, RCT [+]) randomised 298 psychiatric outpatients with non-acute illness to motivational interviewing plus 21mg patch or usual care. The intervention had no effect on smoking status. The mental health component SF-12 (p<0.001) and BDI (p<0.001) scores were significantly lower than baseline in both groups at all time points with no differences between groups. Changes by smoking status were not reported.

Dalack et al (1999, RCT [+]) studied 19 outpatients in a cross over trial. Following one day of ad libitum smoking they were randomised to 3 days of abstinence (spent at a research centre) wearing 22mg nicotine patch or placebo. There were no significant differences in numerous measures between the conditions. Repeated measures ANOVA showed an interaction between Abnormal Involuntary Movement Score (AIMS), patch type and day of abstinence. AIMS score differed significantly between patch groups at day 2 (p<0.02). Scores decreased during placebo use and increased during patch use.

Evins et al (2001, RCT [+]) recruited 18 outpatients with schizophrenia to a 12-week group-based smoking cessation intervention where they were randomized to receive either bupropion (n=9) or placebo (n=9). *Brief Psychiatric Rating Scale (BPRS)* scores decreased in bupropion users and increased in placebo users (p=0.03) over the treatment period. A similar change was seen in the Hamilton Depression Rating Scale (*HAM*-D) scores (p<0.01), showing an improvement in depressive symptoms among bupropion users. The placebo

group showed worsening depressive symptoms, although this was only significant at week 14 (p=0.002). No data are provided on the change in symptoms by smoking status.

Evins et al (2005a and 2005b, RCT [+]) randomised 53 patients to a 12-week group CBT intervention and either bupropion (n=25) or placebo (n=28). Abstinence rates were higher in the bupropion group at the end of treatment (4/25 vs. 0/28, p = 0.043). The bupropion group had greater reductions in the PANSS depressive (p=0.017) and cognitive (p=0.029) subscales that the placebo group. Nine patients achieved abstinence for 7-days and this was associated with better recall compared to those who continued to smoke (p=0.038). There was no deterioration on any cognitive measures, although there was a slowing of motor speed, as measured by finger tapping (p=0.003).

Evins et al (2007, RCT [+]) randomly allocated 51 patients with schizophrenia who wanted to quit smoking, to a 12-week course of bupropion (n=25) or placebo (n=26) in addition to CBT and nicotine patch. Barnes Akathisia Scale (BAS) scores were significantly improved in the intervention group (p=0.005). Otherwise the intervention had no effect on abstinence, and there were no differences in symptom scores between abstainers and smokers or between medication groups. There were no serious adverse events (SAEs) reported.

Fatima et al (2005, cross over trial, [+]) enrolled 10 patients into a randomised cross-over trial to use bupropion or placebo for 21 days. Patients were not instructed to quit. Bupropion use led to a non-significant reduction in carbon monoxide levels. There were no significant changes in numerous measures of psychiatric symptoms by treatment group.

Gallagher et al (2007, RCT [+]) randomly allocated 181 patients with schizophrenia and other severe mental health illnesses to (1) contingent reinforcement (CR); (2) CR plus NRT; (3) self quitting. All groups received treatment for 16 weeks and were followed up at 36 weeks. No significant difference in abstinence rates was seen between the groups, and there was no significant change in Brief Symptom Inventory (BSI) over time within and between groups. The results were similar for abstainers versus smokers (data not reported).

George et al (2000, RCT [+]) randomly allocated 45 patients to a specialized group treatment programme (GTP) (n=28) or a standard GTP (n=17). All patients received nicotine patches. The intervention had no effect on abstinence rates, but GTP was associated with lower PANSS negative symptom scores (p<0.05). Data are not presented by smoking cessation outcome.

George et al (2002, RCT [+]) randomised 32 patients with schizophrenia or schizoaffective disorder to a 10-week course of bupropion (n=16) or placebo (n=16). Abstinence rates were higher in the bupropion group (8/16) compared with placebo (2/16), p<0.05. There were no differences in positive PANSS score, but there was a decrease in negative symptoms in the bupropion group (p<0.05). There were no significant changes in the other scales. The authors do not report on change in symptoms by smoking status.

George et al (2008, RCT [+]) randomised 58 outpatients with schizophrenia or schizoaffective disorder to a 10 week course of bupropion + patch (n=29) or placebo + patch (n=29). There was a difference in abstinence rates between the intervention (8/29) and control (1/29) groups, OR=10.67, (CI: 1.24-91.98). There were no effects of abstinence on psychiatric symptoms. Three patients (1 using bupropion and 2 using placebo) had a psychotic breakdown.

Smith et al (2002, cross over trial, [++]) crossed-over 30 in-patients into (1) high nicotine cigarette (1.9mg) (2) denicotinized cigarette (0.1mg) (3) active nasal spray (NS), and (4) placebo nasal spray after overnight abstinence. Data were collected before and after

patients smoked 2 cigarettes or used NS. The negative symptoms scores were significantly raised, compared with baseline smoking, after overnight abstinence. Smoking either type of cigarette resulted in a decrease in all of the negative symptom measures ($p<0.006$). However the high nicotine cigarette produced a greater decrease in some of them than the denicotinised cigarette. Active NS increased scores in tests of verbal memory compared with placebo ($p<0.05$). Neither NS had any other effects.

Weiner et al (2011, RCT [-]) randomised 9 patients to varenicline (n=4) or placebo (n=5) for 12 weeks. Varenicline users had marginally higher activation score than placebo users ($p=0.06$). There were no serious adverse events reported.

Williams et al (2010, RCT [+]) randomly allocated 87 smokers with schizophrenia or schizoaffective disorder to 24 smoking cessation sessions over 6 months (N=45) or 9 sessions only (N=42). This had no effect on 6-month abstinence rates (7/45 vs. 8/42, $p=0.78$) or scores of BDI or PANSS (p-values>0.4). Abstinence status had no effect on psychiatric scores either.

CASE STUDIES

Benazzi & Mazzoli (1994, case study [-]) describe a 40-year old man with a history of psychotic illness who presented with psychosis following smoking cessation.

Jenkusky (1993, case study [-]) reports on a 27-year-old woman with schizoaffective disorder who was admitted to a psychiatric service with anxiety and agitation. She also complained of nausea. She was subsequently found to be wearing a nicotine patch and concurrently smoking.

Scharf (2009, case study [-]) presents three cases of psychiatric in-patients who were successfully treated with 21mg patches.

Williams et al (2004, case study [-]) report on 12 patients with schizophrenia who used nicotine nasal spray to hep them quit smoking. Only one patient could not tolerate this treatment and most (n=9) used it at its maximum dose without any adverse effects.

PATIENTS WITH DEPRESSIVE DISORDER

Blalock et al (2008, prospective cohort [+]), in a non-randomised trial, allocated 21 smokers with current depressive disorders to behavioural counselling (n=9) or mood management counselling (n=12). Both groups received 21mg nicotine patches. Nine patients achieved prolonged abstinence and showed an improvement from baseline in the PANSS positive symptoms score ($p=0.003$) and BDI ($p=0.008$).

Thorsteinsson et al (2001, RCT [+]) randomised 38 patients with a history of major depressive disorder, not currently treated, to 21mg/24 hr. patch (n=18) or placebo (n=20) for a 2-week treatment period. Change in psychiatric symptoms data are only presented for 24 abstainers (13 patients relapsed and 1 patient in the placebo group developed depression and was withdrawn). Mood improved over time in both groups. Only the POMS scores showed a difference between groups, with the placebo group showing a greater improvement ($p<0.05$).

CASE STUDIES

Bock et al (1996, case study [-]) report three case studies, all women, who developed significant depression following smoking cessation.

Hill & Chang (2007, case study [-]) report on 9 patients attending a psychiatric outpatient clinic and receiving CBT smoking cessation treatment (n=6) or CBT plus NRT (n=3). Patients in both groups reported reducing their cigarette consumption. Their BDI scores deceased over time, although these changes were not statistically significant.

Lundberg et al (2004, case study [-]) describe five cases of patients with obsessive-compulsive disorder who were treated with nicotine chewing gum for 8 weeks. Four patients showed an improvement in their illness, as measured on the Yale-Brown Obsessive-Compulsive Scale (YBOCS). Three patients reported mild side effects of the gum.

Moadel et al (1999, case study [-]) present a case of a 62 year old male smoker with depression and anxiety who required regular cystoscopy for bladder cancer and who would get very anxious before each procedure. When he was provided with a 14 mg patch to wear on the day of the procedure, he was less anxious.

SYSTEMATIC REVIEWS

Tsoi et al (2010a, systematic review [+]) reviewed 21 RCTs of smoking cessation or reduction in smokers with schizophrenia or schizoaffective disorder. Nine of these trials were relevant to this review and are presented above. The others reported smoking cessation outcomes only. The review focused on the efficacy of stop-smoking interventions rather than on the impact of stopping smoking on mental health status.

Tsoi et al (2010b, systematic review [+]) reviewed 7 studies of bupropion for smoking cessation or reduction. Only 5 could be included in the meta-analysis, the other two (Weiner et al, 2007 and Li et al., 2009) provide abstracts only. The included five trials, described above, showed a marginal effect of bupropion on abstinence at 6-months (Risk Ratio=2.78, CI: 1.02-7.58). Mental state outcomes (positive, negative, and depressive symptoms) from 3 studies could be pooled and compared between bupropion groups and controls. There were no differences in positive, negative, or depressive symptoms. No studies reported seizures. Symptoms such as dry mouth were more frequently reported in the bupropion groups ($p<0.05$). Mental health outcomes in smokers and abstainers were not compared.

Banham & Gilbody (2010, systematic review [+]) reviewed data from 9 papers, including 8 RCTs, examining the efficacy of smoking cessation interventions for people with severe mental health illness. Psychiatric symptoms did not differ greatly between the intervention and control groups, although data could not be pooled for meta-analyses and no comparison between smokers and abstainers is provided.

INTERPRETATION

Most of the experimental studies reviewed above had methodological problems, including small sample sizes, large numbers of measures, and unclear outcomes. Most of the smoking cessation trials generated very few abstainers and had insufficient power to detect other than large effects. Studies usually only analysed differences between the randomized groups. As most patients across the randomized conditions continued to smoke, such comparisons

were not examining changes in mental health due to abstinence. Some studies however produced interpretable findings.

Regarding PTSD, stopping smoking seems to generate no deterioration of the condition.

Regarding schizophrenia, abstinence from smoking can induce some discomfort acutely and possibly increase agitation. There are a few case reports of smoking cessation coinciding with deterioration in mental health. However, no evidence emerged from experimental studies that stopping smoking leads to the worsening of mental health status in patients who achieve longer-term abstinence. This needs to be considered as a tentative conclusion, as only a few studies analysed such outcomes and these had only small samples of abstainers. It is possible that patients who experienced negative effects of abstinence returned to smoking. Nevertheless, it is reassuring that in the small proportion of patients who do manage to achieve abstinence, no deterioration of mental health was observed.

Regarding depression, there is some evidence that mood improves in patients who manage to stop smoking compared to those who fail in their quit attempt and continue to smoke.

Nicotine patches may decrease agitation in acutely ill smokers hospitalised in smoke-free hospitals, though one study suggested that they may increase involuntary movements, and another reported better mood improvements in successful quitters who used placebo compared to nicotine patches. It should be noted however that anti-psychotic drugs can cause involuntary movements, and it is possible that the effect noted in this one study may be due to the increase in plasma levels of these drugs following smoking cessation.

SECTION 2: EFFECTS OF STOPPING SMOKING ON PSYCHIATRIC MEDICATION

Smoking and stopping smoking have an effect on the metabolism of a number of psychiatric drugs. Below we review the existing literature on the effects of smoking and stopping smoking on benzodiazepines, carbamazepine, chlorpromazine, clozapine, fluphenazine, haloperidol, methadone, olanzapine, perphenazine, quetiapine, selective serotonin reuptake inhibitors (SSRIs), thioridazine, thiothixene, tricyclic antidepressants, zotepine and zuclopenthixol. Experimental studies are presented first, followed by observational and case studies. The review includes 59 studies summarised in Table 14.

Table 14: Summary of studies included in Chapter 2 Section 2

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Arnoldi and Repking (2011)	Case study	USA 73-year-old Caucasian woman taking olanzapine. Pervious heavy smoker.	Stopped smoking, was diagnosed with Parkinson's Disease (PD).	Diagnosis of drug induced parkinsonism made. Olanzapine stopped and PD symptoms reduced	Quality -
Berecz et al (2003)	Prospective cohort study	Spain 76 patients (58 smokers) with chronic psychiatric disorders and on a stable dose of thioridazine.	Plasma concentrations of thioridazine and its metabolites	Compared to non-smokers, smokers had significantly lower levels of thioridazine and its metabolites.	Quality +
Bondolfi et al (2005)	Case studies	Switzerland (1) 51-year-old man on clozapine + fluvoxamine. His blood clozapine level was 230 ng/ml. (2) 33-year-old woman recently started on clozapine 250mg/day and increased to 550 mg/day.	Two weeks after stopping smoking complained of severe sedation and fatigue. Abstained for 16 days.	Clozapine levels checked 8-month later and found to be 667 ng/ml. Blood clozapine concentration of 3005 ng/ml.	Quality +
Brownlowe et al (2008)	Case study	USA 64-year-old woman with schizoaffective disorder, on long-term clozapine. Admitted with uro-sepsis. She was also found to have myocarditis.	Smoked a pack of cigarettes per day up until a few days before admission to hospital when she quit completely.	Her serum clozapine level elevated and this was subsequently stopped.	Quality -
Callaghan et al (1999)	Prospective cohort study	USA 9 healthy smokers and 30 non-smoker) received a single oral dose of olanzapine (5, 10, 15mg)	Pharmacokinetic parameters of olanzapine	Compared to non-smokers, smokers had a significantly higher clearance of olanzapine (p=0.03).	Quality +
Carrillo et al (2003)	Prospective cohort study	Spain 17 (8 smokers) inpatients After 15 days on olanzapine C:D ratio calculated and assessment enzyme activity using debrisoquine and caffeine	Blood olanzapine levels 12-14 hours post dose. Examined the	Mean dose higher in smokers (10mg/day), compared to non-smokers (7.5mg/day). Caffeine indices showed smokers had higher CYP1A2 activity	Quality +

Chetty et al (1994)	Retrospective cohort study	South Africa 31 patients with schizophrenia	Plasma chlorpromazine levels	Clearance was higher in smokers (175 L/hr) than non-smokers (127 L/hr)	Quality +
Derenne & Baldessarini (2005)	Case study	USA Woman with chronic psycho-affective illness maintained on clozapine (450 mg/day) who, following smoking cessation, developed worsening clozapine-related side effects.		Her mean total drug level/dose increased from 2.25 ± 0.54 ng/ml/mg/day whilst smoking to 4.65 ± 0.82 ng/ml/mg/day after she quit.	Quality -
Dettling et al. 2000	Prospective cohort study	Germany 34 people (25 smokers) with schizophrenia using clozapine.	Plasma clozapine concentrations	Smokers had lower dose-corrected clozapine levels than non-smokers (0.6 ± 0.3 ng/ml per mg vs. 1.2 ± 0.7 ng/ml per mg, p=0.001).	Quality +
DeVane and Nemeroff (2001)	Review	Summary of data from clinical trials of quetiapine (an atypically antipsychotic)		Metabolism of this drug is not influenced by smoking.	Quality +
Diaz et al (2005)	Randomised trial	Colombia 47 patients randomised to 3 doses of clozapine	Plasma clozapine levels	Significant variability in plasma levels in heavy vs. light smokers on 100mg/day dose, but not at higher doses.	Quality +
Ereshefsky (1985)	Retrospective cohort study	USA Included 40 psychiatric inpatients (18 smokers) treated with fluphenazine	Dosage, plasma concentration and clearance	Smokers on a higher dose of intramuscular fluphenazine, and had lower plasma levels with oral dosing	Quality +
Ereshesfsky et al. (1991)	Retrospective cohort study	USA 42 patients undergoing routine thiothixene therapeutic drug monitoring.	Daily thiothixene dose, plasma thiothixene levels	No significant difference between smokers and non smokers in plasma levelss (1.33 ± 1.40 vs. 1.24 ± 1.63 ng/ml) or daily dose (32.4 ± 17.5 vs. 25.0 ± 22.9 mg/day).	Quality +
Fric et al. (2008)	Retrospective cohort study	Germany 28 people with depression, 8 of who smoked.	Daily dose and steady-state levels of duloxetine	Smokers, compared to non-smokers had a lower mean plasma duloxetine concentration (24.3 ± 18.8 vs. 67.8 ± 87.5 ng/ml) and higher daily dose (90.5 ± 16.0 vs. 84 ± 25.8 mg).	Quality +
Fukunda (2000)	Retrospective cohort study	Japan 102 inpatients (46 smokers) on haloperidol	Haloperidol level over dose ratio calculated	No difference between smokers and non-smokers	Quality +
Gex-Fabry (2003)	Retrospective cohort study	Switzerland Data collected from 250 people with mental health illness.	Plasma olanzapine concentration	Olanzapine levels were significantly reduced in smokers.	Quality +
Haring (1989)	Retrospective	Austria	Trough blood	Average plasma clozapine	Quality +

	cohort study	148 psychiatric patients receiving clozapine. 81 were smokers.	samples taken for determination of plasma clozapine levels	concentrations in smokers were significantly higher than non-smokers.	
Hasegawa et al. (1993)	Prospective cohort study	USA 59 people with treatment-resistant schizophrenia taking clozapine.	Plasma clozapine concentrations	Clozapine concentrations did not differ between smokers and non-smokers.	Quality +
Haslemo (2006)	Prospective cohort study	Norway 73 patients with schizophrenia (59 smokers). 33 and 40 on long-term clozapine and olanzapine	Drug plasma concentration	Smokers receiving higher doses, but no differences in plasma levels	Quality +
Hossain et al. (1997)	Prospective cohort study	USA Examined PK parameters of alprazolam in 17 healthy adults (8 smokers).	PK parameters	Smoking was associated with a 100% increase in alprazolam clearance (7.5 L/h for smokers vs. 3.77 L/hr for non-smokers, $p<0.05$).	Quality +
Jaanson et al. (2002)	Prospective cohort study	Estonia 52 patients (15 smokers) with schizophrenia receiving zuclopenthixol. The main aim of the study was to determine the impact of the CYP2D6 polymorphism on steady-state zuclopenthixol levels.	Serum concentrations of zuclopenthixol	Overall, smokers had significantly ($p=0.049$) lower mean C/D ratios (0.029 nmol/L) than non-smokers (0.037 nmol/L). In homozygous extensive metabolisers there was no significant difference in C/D ratio (smokers vs. non-smokers (0.029 vs. 0.033 nmol/L, $p=0.36$)	Quality +
Jain et al (2008)	Case studies	USA 47-year-old patient with schizophrenia stabilised on clozapine for 11 years. A 21-year-old smoker admitted with acute psychotic mania. Stabilised on olanzapine.	She quit smoking and complained of extreme fatigue and tiredness.	She had plasma clozapine level of 1083 ng/ml! The dose was subsequently reduced. On a weekend pass become manic again after smoking 4-packs of cigarettes	Quality -
Jann et al (1986)	Prospective cohort study	West Germany 23 smokers and 27 non-smokers	Plasma concentrations and clearance of haloperidol	Smokers were found to have lower plasma concentrations than non-smokers ($p<0.05$)	Quality +
Jin (2010)	Prospective cohort study	USA (multicentre) 156 Patients with schizophrenia (smokers=52) using perphenazine.	Plasma levels of perphenazine and PK variables	Race and smoking status had a significant effect on clearance.	Quality +
John et al. (1980)	Prospective cohort study	UK Examined effects of age, cigarette smoking and oral contraceptives on plasma clomipramine	Plasma clomipramine concentrations	Smokers had lower mean blood levels (29.0 ± 3.0 ng/ml) than non-smokers (60.0 ± 15.3 ng/ml). No difference in levels of the	Quality +

		concentrations.		main clomipramine metabolite between groups.	
Jorgensen et al. (1985)	Prospective cohort study	Denmark 20 patients with schizophrenia receiving zuclopenthixol	serum concentrations of zuclopenthixol	Smoking status had no effect on serum drug concentration.	Quality +
Kondo et al. 1996	Prospective cohort study	Japan Examined pharmacokinetics of zotepine and its interaction with diazepam in 14 healthy men (8 smokers, 6 non-smokers).	PK parameters of zotepine	Smoking status had no effect on any PK parameters.	Quality +
Linnoila et al. (1981)	Prospective cohort study	USA 88 depressed inpatients, 16 of whom smoked.	Steady-state plasma amitriptyline and/or nortriptyline levels	Plasma concentrations of amitriptyline + nortriptyline were significantly ($p<0.05$) lower in smokers (73.4 ± 13.7 ng/ml) vs. non-smokers (107.3 ± 31.5 ng/ml). Nortriptyline alone (smokers: 39.9 ± 18.5 ng/ml; non-smokers: 69.4 ± 18.0; $p<0.05$).	Quality +
Martin et al. (1991)	Retrospective cohort study	USA 45 adults with mental health illness taking carbamazepine.	Clearance of carbamazepine	Smoking status had no significant effect on clearance.	Quality +
Meyer (2001)	Before-After case control study	USA 11 long-term patients with schizophrenia receiving stable clozapine doses for at least 30 days.	Changes in clozapine levels after total smoking ban.	Mean plasma clozapine levels pre-ban were significantly lower than post-ban.	Quality +
Miller et al. (1990)	Prospective cohort study	20 healthy volunteers, 10 of who were smokers received a single dose (20mg) of haloperidol	Plasma concentrations of haloperidol	The elimination half-life was significantly shorter in smokers, compared to non-smokers	Quality +
Norman et al. (1977)	Prospective cohort study	Australia 22 smokers and 31 non-smokers.	Steady state plasma nortriptyline levels	No significant difference was found between the groups (smokers: 191.2 ± 141.3 ng/ml; non-smokers: 169.3 ± 92.4 ng/ml).	Quality +
Norman et al. (1981)	Prospective cohort study	Australia Examined PK parameters of oral desmethyldiazepam in 12 healthy male volunteers, half of who smoked.	PK parameters	Compared to non-smokers, smokers had a shorter elimination half-life (54.7 ± 17.7 vs. 29.8 ± 9.9 hours, $p<0.05$) and lower maximum plasma concentrations (413 ± 106 ng/ml vs. 245 ± 50 ng/ml, $p<0.05$).	Quality +
Ochs et al.	Prospective	Germany	PK parameters	Smoking status had no	Quality +

(1985)	cohort study	Examined PK parameters of IV diazepam, midazolam and lorazepam in 20 healthy adults half of whom smoked.		significant effect on any PK parameters for diazepam and midazolam. A 19% decrease ($p<0.05$) in elimination half-life of lorazepam was seen in smokers (13.3 ± 0.7 hours) compared to non-smokers (16.4 ± 1.2).	
Ochs et al. (1986)	Prospective cohort study	Germany Examined PK parameters of IV desmethyldiazepam in 19 healthy adult volunteers (8 were smokers).	PK parameters	Smoking status had no effect on any PK parameters of IV desmethyldiazepam.	Quality +
Ochs et al. (1987)	Prospective cohort study	Germany Examined PK parameters of triazolam in 24 healthy male volunteers, half of who smoked daily.	PK parameters	Smoking status had no effect on any PK parameters.	Quality +
Otani et al. 1997	Prospective cohort study	Japan Examined PK parameters of triazolam and alprazolam in 10 healthy male volunteers.	PK parameters	Smoking status had no effect on any PK parameters.	Quality +
Ozdemir et al (2001)	Prospective cohort study	Canada 18 patients with schizophrenia treated with clozapine	Plasma clozapine levels	Non-smokers have a significantly higher plasma clozapine level than smokers	Quality +
Palego et al. (2002)	Prospective cohort study	Italy 50 patients (22 smokers) taking clozapine.	Plasma clozapine concentrations	Clozapine levels were lower among smokers compared with non-smokers (57.4 vs. 86.4 ng/ml/mg/day/kg). Difference not statistically significant.	Quality +
Pantuck et al (1982)	Prospective cohort study	USA 17 health men (8 smokers, 9 non-smokers), prescribed 75 mg chlorpromazine	Plasma chlorpromazine levels	Mean peak plasma concentration was 24% lower in smokers	Quality +
Perel et al. (1976)	Retrospective cohort study	USA 26 patients with unipolar affective illness.	Plasma concentration of imipramine	Mean plasma concentration of imipramine was significantly lower ($p<0.05$) in smokers (160 ng/ml) compared to non-smokers (290 ng/ml).	Quality +
Perry et al. (1993)	Retrospective cohort study	24 smoking and 16 non-smoking patients with schizophrenia who were stable on oral doses of between 10 -70 mg/day	Plasma concentrations of haloperidol	At doses below 0.5 mg/kg/day, non-smokers had higher plasma levels. At doses above 0.5 mg/kg/day they did not differ from non-smokers.	Quality +
Perry et al.	Prospective	USA	Steady-state	Mean normalised total	Quality +

1986	cohort study	9 smokers and 15 non-smokers.	plasma nortriptyline concentration and other pharmacokinetic parameters	nortriptyline concentration was significantly lower in smokers (118 ± 33 ng/ml) compared with non-smokers (158 ± 35 ng/ml).	
Pettitt et al. (2009)	Case study	New Zealand Studied changes in serum clozapine concentrations in six mental health inpatients following the implementation of smokefree policy.		At 4-weeks post-cessation the mean increase in serum clozapine was 2.09 times baseline. Five clients required a dosage adjustment.	Quality -
Rickels et al. (1983)	Prospective cohort study	USA 74 outpatients with depression	Plasma amitriptyline levels at 2 and 6 weeks after starting treatment.	No significant correlation with tobacco use was found.	Quality +
Rostami-Hodjegan et al. (2004)	Retrospective cohort study	UK 3782 patients taking clozapine. Smoking was recorded in 53% of males and 44% of females.	Plasma clozapine levels	Mean plasma clozapine concentration was significantly lower in smokers compared with non-smokers (393 vs. 553 ng/ml, p<0.001).	Quality +
Sandson et al. (2007)	Case study	USA Smoker with schizophrenia who was started and stabilised on clozapine (500mg/day) whilst on a smokefree mental health unit. On discharge he started smoking again and experienced a deterioration of his psychiatric symptoms.		The clozapine level on readmission was low. He required 900 mg/day to achieve therapeutic clozapine levels whilst smoking.	Quality -
Seppala et al. 1999	Prospective cohort study	Finland 44 patients with schizophrenia taking clozapine. 34 smokers.	Plasma clozapine concentrations	Smokers had lower mean clozapine concentrations compared with non-smokers (184 ± 97 vs. 298 ± 127 nmol/L per mg/kg, p=0.021).	Quality +
Skogh (1999)	Case study	38-year-old patient with schizophrenia, maintained on a daily dose of 700-725 mg of clozapine. Admitted to hospital unconscious, and developed seizures.		Stopped smoking 14 days earlier. Plasma clozapine not reported, but dose was reduced to 500 mg/day.	Quality -
Skogh (2002)	Retrospective cohort study	Sweden 194 Swedish patients (69 smokers) taking oral olanzapine	Plasma olanzapine concentration, Concentration: Dose ratio	Smokers had lower concentrations and lower prescribed dose. C/D ratio was also lower in smokers.	Quality +
Spigset et al.	Prospective	Sweden	PK parameters	Smokers had significantly	Quality +

(1995)	cohort study	Examined PK parameters of a single dose of oral fluvoxamine in 24 healthy adult volunteers (12 were smokers).		(p=0.012) lower maximum plasma drug concentration (39.1 ± 17.3 nmol/L) compared with non-smokers (57.7 ± 21.5 nmol/L).	
Stimmel and Falloon (1983)	Case study	25-year-old man with schizophrenia treated with chlorpromazine.		Smoking cessation was accompanied by an increase in medication side effects, and increased chlorpromazine levels.	Quality -
van der Weide et al. (2003)	Retrospective cohort study	Netherlands 80 people with schizophrenia on long-term clozapine.	Serum clozapine concentration and dose	The C/D ratio was on average 2.5 times lower in smokers than non-smokers, and smokers required a significantly ($p<0.01$) higher maintenance dose (382 mg/day) than non-smokers (197 mg/day).	Quality +
Wahawisan et al (2011)	Case study	46-year-old man admitted to intensive care with symptoms of methadone toxicity	Had been on stable methadone dose for 4 months	Had reduced cigarette consumption from pack to half a pack/day over the past month.	Quality -
Wenzel-Seifert et al (2011)	Retrospective cohort study	Germany Analysed data from therapeutic monitoring programmes (N's not reported)	Routine drug concentrations, demographic data, weight, height and smoking status	Smoking increased clearance of clozapine in men and women by 49% and 63%, increased olanzapine clearance by 83% and 53%.	Quality +
Wetzel et al (1998)	Prospective cohort study	USA 30 patients on clozapine and later added fluvoxamine or paroxetine (SSRIs)	Plasma clozapine levels	32% lower serum levels in smokers.	Quality +
Wu et al (2008)	Prospective cohort study	Taiwan 27 patients with schizophrenia; 9 non-smokers, 9 light smokers (<5 cpd), 9 heavy smokers).	Levels of olanzapine after 10mg oral dose.	Maximum plasma concentration was lower in heavy smokers compared to non-smokers ($p<0.001$).	Quality +
Ziegler & Biggs 1977	Prospective cohort study	USA Patients with depression treated with amitriptyline (n=35) or nortriptyline (n=30).	Serum drug levels	No statistically significant difference in mean drug levels between smokers and non-smokers in amitriptyline users (68.1 vs. 77.9 ng/ml) or nortriptyline users (95.7 vs. 86.3 ng/ml).	Quality +
Zullino et al (2002)	Case study	Switzerland Case 1: 37-year-old smoker with schizophrenia smoker also smoking cannabis given	1 month post quit both tobacco and cannabis agitated and confused	Blood clozapine (3.5 months after quitting) 1328 ng/ml. Dose reduced and symptoms resolved	Quality -

		clozapine 700mg/day. Case 2: 25-year-old smoker with bipolar disorder treated with olanzapine 30mg/day.	Reduced smoking from 40 to 10 cpd, Parkinson's 4 days later.	Olanzapine dose was reduced to 20mg/day and symptoms disappeared.	

Benzodiazepines

Hossain et al. (1997, prospective cohort [+]) examined PK parameters of alprazolam in 17 healthy adults (8 smokers). Smoking was associated with a 100% increase in alprazolam clearance (7.5 L/h for smokers vs. 3.77 L/hr for non-smokers, $p<0.05$).

Norman et al. (1981, prospective cohort [+]) examined PK parameters of oral desmethyldiazepam (the main metabolite of clorazepate) in 12 healthy male volunteers, half of who smoked. Compared to non-smokers, smokers had a shorter elimination half-life (54.7 ± 17.7 vs. 29.8 ± 9.9 hours, $p<0.05$) and lower maximum plasma concentrations (413 ± 106 ng/ml vs. 245 ± 50 ng/ml, $p<0.05$). Clinically, the subjective sedative effect was less in smokers than non-smokers.

Ochs et al. (1985, prospective cohort [+]) examined PK parameters of diazepam, midazolam and lorazepam, given intravenously, in 20 healthy adults half of whom smoked. Smoking status had no significant effect on any PK parameters for diazepam and midazolam. However for lorazepam a 19% decrease ($p<0.05$) in elimination half-life was seen in smokers (13.3 ± 0.7 hours) compared to non-smokers (16.4 ± 1.2).

Ochs et al. (1986, prospective cohort [+]) examined PK parameters of intravenous desmethyldiazepam (the main metabolite of clorazepate) in 19 healthy adult volunteers (8 were smokers). Smoking status had no effect on any PK parameters of intravenous desmethyldiazepam.

Ochs et al. (1987, prospective cohort [+]) examined PK parameters of triazolam in 24 healthy male volunteers, half of who smoked daily. Smoking status had no effect on any PK parameters.

Otani et al. (1997, prospective cohort [+]) examined PK parameters of triazolam and alprazolam in 10 healthy male volunteers. Smoking status had no effect on any PK parameters.

Carbamazepine

Carbamazepine is an anticonvulsant medication, but is indicated in the treatment of a number of other illnesses including prophylaxis of bipolar disorder unresponsive to lithium and acute alcohol withdrawal (BNF). Martin et al. (1991, retrospective cohort, [+]) measured clearance of carbamazepine in 45 adults with mental health illness. Smoking status had no significant effect on clearance.

Chlorpromazine

Chetty et al. (1994, retrospective cohort [+]) analysed plasma chlorpromazine levels among 31 patients with schizophrenia. Clearance was higher among smokers (175 L/hr) compared to non-smokers (127 L/hr).

Pantuck et al (1982, prospective cohort, [+]) report on a cohort of 17 healthy participants (8 smokers and 9 non-smokers) prescribed 75mg of chlorpromazine. Mean peak plasma concentration was 24% lower in smokers (5.4 +/- 1.9 ng/ml) than non-smokers (7.1 +/- 0.9 ng/ml) although this difference was not significant.

Stimmel and Falloon (1983, case study [-]) report a case of a 25-year-old man with schizophrenia treated with chlorpromazine. Smoking cessation was accompanied by an increase in medication side effects, and the patient was found to have increased chlorpromazine levels.

Clozapine

Dettling et al. (2000, prospective cohort [+]) measured plasma clozapine concentrations in 34 people with schizophrenia. Smokers (n=25) had significantly lower dose-corrected clozapine concentrations than non-smokers (0.6 ± 0.3 ng/ml per mg vs. 1.2 ± 0.7 ng/ml per mg, p=0.001).

Diaz et al (2005, randomised non-controlled trial, [+]) randomized 47 patients to three daily doses of clozapine (100mg, 300mg and 600mg). For heavy smokers (30 or more cigarettes per day), compared to non-heavy smokers, there was significant variability in plasma concentrations (p=0.03) when receiving the 100mg/day dose. At higher doses there was no significant difference.

Haring et al. (1989 retrospective cohort [+]) examined trough clozapine levels 148 psychiatric patients, 81 of whom were smokers. Average plasma clozapine concentrations in smokers were 82% that of non-smokers, p<0.022.

Hasegawa et al. (1993, prospective cohort [+]) measured plasma clozapine concentrations in 59 people with treatment-resistant schizophrenia. Clozapine concentrations did not differ between smokers and non-smokers.

Haslemo et al (2006, prospective cohort [+]) assessed plasma concentrations of clozapine (N=33) or olanzapine (N=40) in patients with schizophrenia using the medications for at least 18 months. Fifty-nine were smokers, 14 were non-smokers. Smokers were receiving higher doses of medication, but not significantly higher. The plasma concentration of clozapine was higher in non-smokers (2,063 nmol/l) compared with smokers (1,370 nmol/l), although the difference did not reach statistical significance (p=0.06). C/D ratio was significantly greater in non-smokers (6.0) compared with smokers (2.8; p=0.004).

Meyer (2001, case control study [+]) studied clozapine levels in 11 patients with schizophrenia before and after a complete smoking ban in a psychiatric hospital (Meyer 2001). Mean plasma clozapine concentrations pre ban was 550+/-160 ng/ml, rising to 993+/-713 ng/ml post-ban, an 80% increase (p<0.034). One patient who had plasma concentration of 3066 ng/ml post ban (261% increase from baseline) suffered aspiration pneumonia.

Ozdemir et al (2001, prospective cohort [+]) monitored 18 patients with schizophrenia treated with clozapine. Non-smokers have a significantly higher plasma clozapine level than smokers (3.2 fold difference, $p<0.05$).

Palego et al. (2002, prospective cohort [+]) measured plasma clozapine concentrations in 50 patients (22 smokers). Clozapine levels were lower among smokers compared with non-smokers (57.4 vs. 86.4 ng/ml/mg/day/kg) although the difference was not statistically significant.

Rostami-Hodjegan et al. (2004, retrospective cohort [+]) measure plasma clozapine levels in blood samples from 3782 patients. Smoking was recorded in 53% of males and 44% of females. Mean plasma clozapine concentration was significantly lower in smokers compared with non-smokers (393 vs. 553 ng/ml, $p<0.001$).

Seppala et al. (1999, prospective cohort [+]) measured plasma clozapine concentrations in 44 patients with schizophrenia. Smokers (n=34) had significantly lower mean clozapine concentrations compared with non-smokers (184 ± 97 vs. 298 ± 127 nmol/L per mg/kg, $p=0.021$).

van der Weide et al. (2003, retrospective cohort, [+]) measured serum clozapine concentration and dose in 80 people with schizophrenia who were on long-term clozapine. The C/D ratio was on average 2.5 times lower in smokers than non-smokers, and smokers required a significantly ($p<0.01$) higher maintenance dose (382 mg/day) than non-smokers (197 mg/day).

Wenzel-Seifert et al (2011, retrospective cohort [+]) report on drug concentrations of clozapine and olanzapine collected routinely as part of a therapeutic drug monitoring programme and the relationship with sex and smoking status. Smoking increased clearance of clozapine in men and women by 49% and 63%. Smoking increases olanzapine clearance by 83% and 53% in men and women respectively. The authors recommend that the dose of clozapine and olanzapine needs to be reduced by approximately 35% when people stop smoking. A reduction in cigarette consumption does not require dosage adjustment.

Wetzel et al. (1998, prospective cohort [+]) treated 30 patients with clozapine and later added fluvoxamine or paroxetine (SSRIs) to investigate the effects on serum clozapine levels. When only on clozapine, differences in serum levels were observed between smokers and non-smokers, with 32% lower serum levels in smokers.

Eight case studies document the risk of increase in clozapine levels in patients who stop smoking.

Bondolfi et al (2005, case study [-]) presented two cases. A 51-year-old man on clozapine 400 mg/day plus fluvoxamine 50 mg/day had blood clozapine level 230 ng/ml prior to stopping smoking. Two weeks after stopping smoking he complained of severe sedation and fatigue. Clozapine levels 8-month later were 667 ng/ml. A 33 year old woman started on clozapine 250mg/day. After 2 days of treatment she was transferred from the psychiatric unit to a surgical ward where she was unable to smoke for 16 days. Her clozapine dose was increased to 450 mg/day. She was transferred back to the psychiatric unit where her dose was further increased to 550 mg/day. Her blood clozapine concentration was 3005 ng/ml.

Brownlowe et al (2008, case study [-]) described a case of a 64-year-old woman with schizoaffective disorder, on long-term clozapine. She was admitted with uro-sepsis and

treated with ciprofloxacin. Whilst in hospital she was also diagnosed with myocarditis and an elevated level of clozapine. Ciprofloxacin is known to interact with clozapine, and the authors conclude that smoking cessation contributed to the elevation in serum clozapine.

Derenne & Baldessarini (2005, case study, [-]) report a woman with chronic psycho-affective illness maintained on clozapine (450 mg/day) who, following smoking cessation, developed worsening clozapine-related side effects. Her mean total drug level/dose increased from 2.25 ± 0.54 ng/ml/mg/day whilst smoking to 4.65 ± 0.82 ng/ml/mg/day after she quit.

Jain et al (2008, case study [-]) reported on a 47-year-old woman with schizophrenia stabilised on clozapine (750mg day) for 11 years. One month after stopping smoking, she complained of hypersalivation, extreme fatigue and daytime sleepiness. She was found to have a plasma clozapine level of 1083 ng/ml. Her clozapine dose was subsequently reduced. The paper also reports on a 21-year-old male smoker admitted to hospital with acute psychotic mania. He was stabilised on olanzapine but during a weekend at home he become manic again, which was thought to be due to the fact that he had smoked heavily, thus reducing the olanzapine cover.

Pettitt et al. (2009, case study, [-]) studied changes in serum clozapine concentrations in six mental health inpatients following the implementation of smokefree policy. At 4-weeks post-cessation the mean increase in serum clozapine was 2.09 times baseline. Five clients required a dosage adjustment.

Sandson et al. (2007, case study, [-]) report on a smoker with schizophrenia who was started and stabilised on clozapine (500mg/day) whilst on a smokefree mental health unit. On discharge he started smoking again and experienced a deterioration of his psychiatric symptoms. The clozapine level on readmission was low. He required 900 mg/day to achieve therapeutic clozapine levels whilst smoking.

Skogh (1999, case study [-]) reports on a 38 year old man with a history of schizophrenia, maintained on a high daily dose of 700-725 mg of clozapine. His trough plasma concentration on this dose was only 197 ng/ml. He was admitted to hospital in an unconscious state, and developed seizures. After he was stabilised he reported stopping smoking 14 days prior to admission. Plasma clozapine concentration was not reported, but he had a dose reduction in clozapine to 500 mg/day. Six months later his trough plasma concentration was 334 ng/ml and so his dose was further reduced to 425mg/day, which gave a trough level of 187 ng/ml.

Zullino et al (2002, case study [-]) reports on a 37-year-old man with schizophrenia treated with clozapine (700mg/day), who had smoked tobacco since adolescence. He was also a daily cannabis smoker. One month after stopping smoking both tobacco and cannabis he became increasingly agitated and confused over a 2 month period. His blood clozapine level (3.5 months after quitting) was 1328 ng/ml. His clozapine dose was reduced and within a week his adverse symptoms disappeared

Fluphenazine

Ereshefsky et al (1985, retrospective cohort [+]) studied 40 psychiatric inpatients treated with fluphenazine (18 oral, 22 intramuscular). Smokers were on a significantly higher dose of intramuscular (IM) fluphenazine than non-smokers (48.28 mg/day vs. 28.34 mg/day, $p<0.02$). There was no difference in oral dosage between smokers and non-smokers, but plasma concentration was significantly lower in smokers vs. non-smokers in this group (0.89 ng/ml vs. 1.83 ng/ml, $p<0.05$). Clearance of fluphenazine was significantly greater in smokers taking

oral fluphenazine (16.72 vs. 9.99 l/min, p<0.005) and IM fluphenazine (7.37 vs. 3.16 l/min, p<0.005)

Haloperidol

Fukuda (2000, retrospective cohort [+]) examined haloperidol level over dose ratio in a cohort of 102 long-term psychiatric patients (46 smokers and 56 non-smokers). There was no significant difference between smokers and non-smokers (57.2+/-21.1 ng.ml and 60.9+/-29.0 mg/ml, respectively).

Jann et al. (1986, prospective cohort [+]) assessed plasma concentrations and clearance of haloperidol in 23 smokers and 27 non-smokers. Smokers were found to have lower plasma concentrations than non-smokers (p<0.05) and marginally greater clearance (p=0.052).

Miller et al. (1990, prospective cohort [+]) studied gave a single dose (20mg) of haloperidol to 20 people, 10 of who were smokers. The elimination half-life was significantly shorter in smokers, compared to non-smokers.

Perry et al. (1993, retrospective cohort [+]) compared plasma concentrations of haloperidol in 24 smoking and 16 non-smoking patients with schizophrenia who were stable on oral doses of between 10 and 70 mg/day. At doses below 0.5 mg/kg/day, non-smokers had higher plasma concentrations. However at doses above 0.5 mg/kg/day there was no difference between smokers and non-smokers.

Methadone

Wahawisan et al (2011, case study, [-]) reported on a 46-year-old man admitted to intensive care with symptoms of methadone toxicity. He had smoked a pack of cigarettes per day for 33 years, and had been commenced on methadone treatment 4-months prior to admission for back pain. Over the previous month he had halved his cigarette consumption. The authors recommend that patients who are maintained on methadone and stop smoking should be monitored for signs of methadone toxicity.

Olanzapine

Callaghan et al. (1999, prospective cohort [+]) report on a data held on file by Eli Lilly and Company from a single dose olanzapine pharmacokinetic study that recruited 39 healthy volunteers (19 smokers and 30 non-smokers). Compared to non-smokers, smokers had a significantly higher clearance of olanzapine (p=0.03).

Carrillo et al. (2003, prospective cohort [+]) examined the concentration to dose ratio in 17 inpatients (8 were smokers) after 15 days on the drug. Smokers were on 10mg/day, and non-smokers on 7.5mg/day (p<0.01). Caffeine indices in non-smokers and smokers were 17+/-8 and 101+/-44 (mean diff = -84, CI -115 - -52, p<0.0001), showing that smokers had much higher CYP1A2 activity. CYP1A2 activity in smokers of <5 cigarettes per day was similar to non-smokers. There was a five-fold decrease in plasma concentration in smokers of 5 or more cigarettes per day compared to non-smokers (concentration: dose [C/D] ratio 7.9+/-2.6 vs. 1.56+/-1.1 ng/ml, p<0.001).

Gex-Fabry et al (2003, retrospective cohort [+]) assessed plasma concentrations in 250 patients of whom 70 were smokers. Smokers had a significantly reduced (12%) plasma olanzapine concentration compared to non-smokers (expected value =0.88; CI: 0.77-1.00; p=0.046).

Haslemo et al. (2006, prospective cohort [+]) in the study reported above showed that the plasma concentration of olanzapine was greater in non-smokers (210 nmol/l) compared with smokers (126 nmol/l; p=0.004), although the difference did not reach statistical significance (p=0.06). The C/D ratio was significantly higher in non-smokers (6.1) compared with smokers (12.8; p=0.001).

Skogh (2002, retrospective cohort [+]) analysed data from 194 patients taking oral olanzapine. Smokers (n=69) had a significantly lower plasma olanzapine concentrations (60 nmol/l) than non smokers (n=73) (92 nmol/l, p<0.001). They also had a significantly lower prescribed dose (10mg vs.12.5mg p<0.05). C/D ratio was substantially lower among smokers (4.0 vs. 9.2 nmol/l/mg, p<0.001)

Wu et al. (2008, prospective cohort [+]) studied the pharmacokinetics of a 10 mg oral dose of olanzapine in 27 male Taiwanese inpatients with schizophrenia. Nine were non-smokers, 9 light smokers (<5 cigarettes per day) and 9 heavy smokers. Maximum plasma concentration was significantly lower in heavy smokers compared to non-smokers (p<0.001). Adjusting for body weight heavy smokers had a significantly lower plasma concentration that non-smokers (p<0.001) and light smokers (p<0.05).

A case report documents an increase in olanzapine levels after stopping smoking (see also Jain et al. 2008 included in clozapine case studies).

We found two case reports of olanzapine induced Parkinson's disease following smoking cessation (**Arnoldi and Repking 2011, case study [-])**, and smoking reduction **(Zullion et al 2002, case study [-])** but no plasma levels were reported.

Perphenazine

Jin et al (2010, prospective cohort [+]) examined the interaction between smoking and perphenazine in 156 patients with schizophrenia. 104 patients were current smokers. Both race and smoking status had a significant effect on clearance of perphenazine. The highest rate of clearance was observed in smoking African Americans (AA) (833.90 L/h) compared with a rate of 444.23 L/h in non-Smoking non-AA (p<0.001). Similar differences were observed for mean daily drug dose (mg) for smokers versus non-smokers (25.33 vs. 21.62; p<0.05).

Quetiapine

DeVane and Nemeroff (2001, Review, [+]) report that data from clinical trials of quetiapine (an atypically antipsychotic) show that smoking does not influence the metabolism of this drug. Values of apparent oral clearance in 30 non-smoking patients with psychosis was not statistically difference different to clearance in 94 patients who smoked.

Selective Serotonin Reuptake Inhibitors

Fric et al. (2008, retrospective cohort [+]) measured steady-state levels of duloxetine in 28 people with depression, 8 of who smoked. The mean plasma duloxetine concentration was significantly lower in smokers (24.3 ± 18.8 ng/ml), compared with non-smokers (67.8 ± 87.5 ng/ml). Smokers, compared to non smokers were taking a higher daily dose (90.5 ± 16 vs. 84 ± 25.8 mg).

Spigset et al. (1995, prospective cohort [+]) examined PK parameters of a single dose of oral fluvoxamine in 24 healthy adult volunteers (12 were smokers). Smokers had significantly ($p=0.012$) lower maximum plasma drug concentration (39.1 ± 17.3 nmol/L) compared with non-smokers (57.7 ± 21.5 nmol/L). The elimination half-life did not differ between groups.

Thioridazine

Berecz et al (2003, prospective cohort [+]) examined the difference in plasma concentrations of thioridazine and its metabolites in a cohort of 76 patients (58 smokers and 18 non smokers) on a stable dose of thioridazine. Compared to non-smokers, smokers had significantly lower levels of thioridazine (4.0 vs. 7.4, $p<0.001$) and its metabolites.

Thiothixene

Ereshesfsky et al. (1991, retrospective cohort, [+]) measured plasma thiothixene levels in 42 patients undergoing routine therapeutic drug monitoring. Overall, there was no significant difference between levels in smokers (1.33 ± 1.40 ng/ml) versus non-smokers (1.24 ± 1.63 ng/ml).

Tricyclic antidepressants

John et al. (1980, prospective cohort, [+]) examined the effects of age, cigarette smoking and oral contraceptives on plasma clomipramine concentrations. Smokers had lower mean blood clomipramine levels (29.0 ± 3.0 ng/ml) than non-smokers (60.0 ± 15.3 ng/ml). However, there was no difference in levels of the main clomipramine metabolite between groups. People who smoked 15 or more cigarettes per day were noted to tolerate the daily dose (75mg) better than non-smokers.

Linnoila et al. (1981, prospective cohort, [+]) examined steady-state plasma amitriptyline and/or nortriptyline levels in 88 depressed inpatients (16 smokers). Plasma concentrations of amitriptyline + nortriptyline were significantly ($p<0.05$) lower in smokers (73.4 ± 13.7 ng/ml) compared to non-smokers (107.3 ± 31.5 ng/ml). The same pattern was also observed for nortriptyline alone (smokers: 39.9 ± 18.5 ng/ml; non-smokers: 69.4 ± 18.0; $p<0.05$).

Norman et al. (1977, prospective cohort, [+]) examined steady state plasma nortriptyline levels in 22 smokers and 31 non-smokers. No significant difference was found between the groups (smokers: 191.2 ± 141.3 ng/ml; non-smokers: 169.3 ± 92.4 ng/ml).

Perel et al. (1976, retrospective cohort, [+]) assessed plasma concentration of imipramine in 26 patients with unipolar affective illness. Mean plasma concentration of imipramine was significantly lower ($p<0.05$) in smokers (160 ng/ml) compared to non-smokers (290 ng/ml).

Perry et al. (1986, prospective cohort, [+]) determined steady-state plasma nortriptyline concentration and other pharmacokinetic parameters in 9 smokers and 15 non-smokers. Mean normalised total nortriptyline concentration was significantly lower in smokers (118 ± 33 ng/ml) compared with non-smokers (158 ± 35 ng/ml).

Rickels et al. (1983, prospective cohort, [+]) measured plasma amitriptyline levels in 74 outpatients with depression at 2 and 6 weeks after starting treatment. No significant correlation with tobacco use was found.

Ziegler & Biggs (1977, prospective cohort, [+]) measured serum drug levels in patients with depression treated with amitriptyline (n=35) or nortriptyline (n=30). There was no statistically significant difference in mean drug levels between smokers and non-smokers in amitriptyline users (68.1 vs. 77.9 ng/ml) or nortriptyline users (95.7 vs. 86.3 ng/ml).

Zotepine

Kondo et al. (1996, prospective cohort [+]) examined pharmacokinetics of zotepine and its interaction with diazepam in 14 healthy men (8 smokers, 6 non-smokers). Smoking status had no effect on any PK parameters.

Zuclopenthixol

Jaanson et al. (2002, prospective cohort [+]) measured serum concentrations of zuclopenthixol in 52 patients (15 smokers) with schizophrenia. The main aim of the study was to determine the impact of the CYP2D6 polymorphism on steady-state zuclopenthixol levels. Most patients (n=35) were homozygous extensive metabolisers, 13 were heterozygous and 4 were poor metabolisers. Overall, smokers had significantly (p=0.049) lower mean C/D ratios (0.029 nmol/L) than non-smokers (0.037 nmol/L). However, 87% of smokers were homozygous extensive metabolisers, which confound the results. When considering only the group of homozygous extensive metabolisers there was no significant difference in C/D ratio between smokers and non-smokers (0.029 vs. 0.033 nmol/L, p=0.36).

Jorgensen et al. (1985, prospective cohort [+]) measured serum concentrations of zuclopenthixol in 20 patients with schizophrenia. Smoking status had no effect on serum drug concentration.

Reviews

We did not find any systematic reviews, but identified seven reviews discussing relevant literature (de Leon 2004; Montalto & Farid 1997; Zevin and Benowitz 1999; Desai et al 2001; Kroon 2007; Schaffer 2009; and Murray 2010). All these reviews identify medications sensitive to smoking, and recommend monitoring of their systemic levels if there is a change in smoking status.

INTERPRETATION

Most of the reviewed medications seem to be metabolised faster by smokers than by non-smokers. The corollary of this finding is that in stable patients on well-tolerated medication

doses, stopping smoking is likely to increase systemic levels of these drugs and needs to be accompanied by dose adjustments.

The effect seems particularly striking with clozapine and olanzapine. Haslemo et al (2006) make an important point that because smoking prevalence is high in psychiatric patients, the dosing recommendations were established in smoking populations. Non-smokers thus may be at risk of over-medication and AE if put on the standard dose. The authors suggest that in non-smokers, the standard starting dose should be reduced by 50%. de Leon (2004, general review) estimates that a correction factor of 1.5 should be applied for estimating changes in blood levels of clozapine and olanzapine. This means, for example, if a patient on taking clozapine stops smoking their plasma clozapine levels could increase by a factor of 1.5 within 2-4 weeks. However, this is only an approximation.

Regarding dose response to smoking levels, smoking above 4 cigarettes per day seems sufficient to induce CYP1A2. In regular smokers, self-reported cigarettes per day provide little further information.

We found no data on whether NRT mitigates the effects of stopping smoking on increasing systemic levels of these medications.

SECTION 3: EFFECTS OF SMOKING CESSATION INTERVENTIONS ON THE USE OF OTHER SUBSTANCES

The question of whether people undergoing drug and alcohol treatments should be encouraged to stop smoking at the same time has no generally accepted answer at the moment. There are concerns that removing one source of gratification may make the others more precious, or that self-control is a limited resource and that refraining from one desired activity may undermine self-control in other areas (Richter et al. 2002, Baumeister and Tierney, 2011). On the other hand, some drug and alcohol advisors emphasise the importance of a fresh start free of all addictive substances and many tobacco control specialists promote smoking cessation as a priority in any setting.

Below we review literature bearing on the question of whether stopping smoking during drug and alcohol treatment enhances or undermines drug and alcohol sobriety. We identified 20 studies relevant for this topic. These are summarised in Table 15.

Table 15: Summary of studies included in Chapter 2 Section 3

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Brown et al (2001)	Randomised controlled trial	191 adolescent smokers hospitalised with substance abuse given motivational interviewing (N=116) or brief advice (N=75) to stop smoking	Participants were followed up for 1 year	Smoking cessation outcomes were not reported but the context suggests that the intervention had no effect. It had no effect on substance use either.	Quality +
Burling et al (2001)	Randomised controlled trial	USA 150 smokers at a veterans residential rehabilitation programme randomised to usual care (UC), multicomponent smoking treatment (MST) or MST + "generalised training" for both cessation and relapse prevention skills to drug and alcohol use (MST + G).	Smoking status and breath alcohol and urine tests measured at 1, 3, 6 and 12 months.	Continuous drug and alcohol abstinence rate that was significantly higher in the MST vs. MST+G condition (40% versus 20%; p<0.05), but neither condition differed from UC (33%). Smoking abstinence rates were higher in the MST and MST + G compared to UC (12% vs. 10% vs. 0%; p=<0.05).	Quality +
Campbell et al (1995)	Prospective cohort study	66 smokers undergoing smoking cessation treatment at an outpatient and residential drug treatment centre. Half were heroin addicts.	Smoking status at end of treatment (16 weeks) and urges to use drugs of abuse between quit day and day 4.	19/66 reported significantly less urges for drug use (p=0.045), and 9/66 reported increased urges (0=0.02). 7 clients abstinent at end of treatment, and 3 reported drug use in the past week.	Quality +
Cooney et al (2003)	Randomised cross over	USA 40 alcoholics assessed at	Self-reported urges to smoke and drink	Alcohol cue exposure led to increase in urge to	Quality ++

		baseline and had cue exposure to alcohol after 34 hours of not smoking and cue exposure after smoking.		drink that was similar when patients smoked as normal or abstained.	
Cooney et al (2007)	Randomised controlled trial	USA 118 alcohol dependent smokers received a brief or intensive smoking cessation counselling	Smoking abstinence and proportion of days of heavy drinking (PDH) in 30 days prior to 6-month follow-up.	Neither smoking nor alcohol abstinence at 6 months was significantly different between brief and intensive interventions.	Quality +
Cooney et al (2009)	Randomised controlled trial	USA 96 outpatient smokers with a diagnosis of alcohol dependence given 21mg patch + 2mg gum or placebo gum.	Smoking abstinence (CO validated) and validated abstinence from alcohol.	Patch and active gum users more likely abstinent from tobacco and alcohol at 12 months, but only tobacco significant.	Quality +
Dunn et al (2009)	Prospective cohort study	USA 28 smokers enrolled in opioid maintenance treatment given 2-weeks stop-smoking treatment	Daily urine and breath sampling for illicit drug use plus another sampling 30 days after the target quit day	12 abstained, 16 did not. Abstainers and non-abstainers had 99% and 96% samples negative for all illicit drugs.	Quality +
Grant et al (2007)	Randomised controlled trial	USA 58 people undergoing treatment for substance use disorder received nicotine patch + 300mg bupropion/day (n=30) or nicotine patch + placebo bupropion (n=28) and behavioural support.	Smoking status (7-day point prevalence) and alcohol use (no use in last 30 days) were measured at 6-month follow-up	Smoking cessation rates for bupropion and placebo groups were 17% vs. 29% (p=0.35). Rates of abstinence from alcohol use were greater in quitters (13/13) than continued smokers (17/27), p=0.016.	Quality +
Haug et al (2004)	Randomised controlled trial	63 pregnant opioid dependent smokers given motivational therapy (n=30) or usual care (n=33).	Smoking abstinence and test for illicit drug use at 10-weeks	No difference in smoking abstinence rates or illicit drug use	Quality +
Joseph (1993a)	Prospective cohort study	USA 319 patients from Joseph et al (1990) contacted by phone 1-year after discharge. Split into pre and post smoking ban groups.	Improvement in chemical dependency and smoking status	Self-reported abstinence for smoking was higher in the post-ban group than the pre-ban group.	Quality +
Joseph et al (1990)	Prospective cohort study	USA 445 inpatients in a substance abuse programme pre smoking ban and 457 post smoking ban	Surveys on admission and discharge.	Post-ban a greater proportion of smokers abstained for at least a week, reported not smoking regularly and planned to quit smoking.	Quality +
Joseph et al (1993b)	Retrospective cohort study	USA 314 drug and alcohol patients hospitalised before and after unit moved to new premises	154 patients hospitalised post-smoking ban compared with 160 hospitalised pre-	No difference in drug or alcohol use recovery, but when non-responders included as treatment failures, recovery in	Quality +

		where smoking was not permitted in-doors.	smoking ban	cocaine users was lower in the post-ban group	
Joseph et al (2004)	Randomised controlled trial	USA 499 smokers in treatment for alcohol dependence given concurrent (during treatment) or delayed (6 months later) stop-smoking intervention	Alcohol use and abstinence from tobacco (CO validated)	No effect on smoking or alcohol use	Quality +
Kalman et al (2001)	Randomised controlled trial	USA 36 male smokers from an inpatient veteran substance abuse treatment programme randomised to smoking cessation 2 weeks (concurrent treatment) or 6 weeks (delayed treatment) after admission.	Number of drinks per day and percent days of alcohol use were recorded for the 90 days previous to admission and the 20-week period after admission.	No significant difference was in smoking quit rates between groups ($p=0.74$). Number if people with alcohol relapse in the delayed ($n=6$) vs. concurrent ($n=3$) groups ($p<0.07$).	Quality +
Okoli et al (2010)	Review (not systematic)	8 studies of stopping smoking in patients on methadone maintenance, five assessed drug use outcomes		Concluded that smoking cessation treatment does not worsen substance abuse.	Quality +
Prochaska et al (2004)	Systematic Review	Included 19 studies that investigated smoking cessation interventions in patients in substance misuse treatment or recovery.	Smoking cessation and substance use outcomes at the end of treatment, long-term follow-up and substance use outcomes.	Smoking cessation interventions increased abstinence rates at the end of treatment and no effect on other substance use at the end of treatment	Quality +
Reid et al. (2008)	Randomised controlled trial	225 smokers in drug and alcohol maintenance and treatment programmes given stop-smoking treatment or usual care	Smoking cessation at 26 weeks. Retention in substance abuse treatment, abstinence from and craving for primary substance of abuse	Quit rates were 0% in the control group and about 10% in SC. No difference in retention in substance treatment, abstinence or craving for primary substance	Quality +
Richter et al (2005)	Prospective cohort study	28 smokers from methadone clinic treated with bupropion, nicotine gum and motivational interviewing	Smoking abstinence at 6-months, illicit drug use.	14% achieved 6-month smoking abstinence. No change in illicit drug use.	Quality –
Shoptaw et al (1996)	Prospective cohort study	17 smokers on methadone maintenance, 4-weeks contingency management (CM) for smoking cessation	Thrice weekly breath test for CO and urine tests for illicit drug use.	None managed to stop smoking and 16/17 used illicit opiates and 10/17 used cocaine at least once during the study.	Quality –
Shoptaw et al	Randomised controlled trial	175 smokers on methadone maintenance received 12 weeks patch	Thrice weekly breath test for CO and urine tests for illicit drug	Smoking abstinence was a significant predictor of opiate abstinence	Quality +

(2002)		only, relapse prevention (RPI) + patch, CM + patch + RPI or CM + patch.	use.	(p=0.0002) and cocaine abstinence (p<0.0001).	

Brown et al (2001, RCT [+]) randomised 191 adolescent smokers hospitalised with substance abuse to motivational interviewing (MI, N=116) or brief advice (BA, N=75) for smoking cessation. Participants were followed up for 1 year. Smoking cessation outcomes were not reported but the context suggests that the intervention had no effect. It had no effect on substance use either.

Burling et al (2001, RCT [+]) randomised 150 smokers at a veterans residential rehabilitation programme to receive usual care (UC), multicomponent smoking treatment (MST) or MST + "generalised training" for both cessation and relapse prevention skills to drug and alcohol use (MST + G). Breath alcohol and urine tests were taken at 1, 3, 6 and 12 months. The MST condition had a continuous drug and alcohol abstinence rate that was significantly higher than the MST+G condition (40% versus 20% at 12 month FU; p<0.05), neither condition differed from UC. Smoking abstinence rates were higher in the MST and MST + G compared to UC condition (12% vs. 10% vs. 0%; p=<0.05).

Campbell et al (1995, prospective cohort, [+]) report on urges to use drugs of abuse in 66 clients receiving smoking cessation treatment (16 weeks duration). Urge to use drugs of abuse were measured at quit date (baseline) and day 4. Most participants (19/66) reported less urges to use drugs on day 4 than at baseline (p=0.045). However 9/66 reported a significant increase in urges (p=0.02). Urges by smoking status are not reported.

Cooney et al (2003, randomised cross over trial [++]) studied 40 alcohol dependent smokers who took part in three conditions in which they rated their urges to smoke and urges to drink alcohol: (1) baseline (2) cue exposure to alcohol after 34 hours of smoking deprivation and (3) cue exposure after normal smoking. Alcohol cue exposure was associated with an increase in urge to drink that was similar when patients smoked as normal or abstained.

Cooney et al (2007, RCT [+]) randomised 118 alcohol dependent smokers to a brief smoking cessation counselling session (n=63) or an intensive intervention (n=55) including 8-weeks of nicotine patches. There was no difference between the groups in either smoking abstinence at 6 months (1/63 vs. 4/55) or in abstinence from alcohol (30/63 vs. 27/55).

Cooney et al (2009, RCT [+]) randomised 96 outpatient alcoholics to 21mg patch + 2mg gum (n=45) or 21mg patch + placebo gum (n=55). Patch and active gum generated a higher abstinence rate at 12 months (13%) than patch and placebo gum (0%) (p<0.01). 90-day alcohol abstinence rates were somewhat higher in the active gum group (43%) compared with placebo gum (32%) but the difference was not significant.

Dunn et al (2009, prospective cohort [+]) provided 2-weeks stop-smoking treatment (with daily urine and breath sampling plus another sampling 30 days after the target quit day) to 28 smokers enrolled in opioid maintenance treatment. There were 12 abstainers with confirmation of abstinence in >90% of biochemical verifications and 16 non-abstainers. Assays were conducted for presence of opioids, cannabis, cocaine, benzodiazepines, and other substances. Abstainers and non-abstainers had 99% and 96% samples negative for all illicit drugs.

Grant et al (2007; RCT, [+]) randomised 58 people undergoing treatment for alcohol use disorder to receive nicotine patch + 300mg bupropion/day (n=30) or nicotine patch + placebo bupropion (n=28) and behavioural support to aid smoking cessation. Smoking

cessation rates (self-reported 7-day point prevalence) at 6-months were not significantly different between bupropion and placebo groups (17% vs. 29%, p=0.35). At 6-month follow-up there was no differences in alcohol abstinence rates (no use in last 30 days) by treatment group. However, 6-month alcohol abstinence rates were greater in those abstinent from smoking at 6 months (13/13) compared to those who were smoking (17/27), p=0.016.

Haug et al (2004; RCT, [+]) randomised 63 pregnant opioid dependent smokers to motivational enhancement therapy (n=30) or usual care (n=33) to help them quit. Women were followed up at 10-weeks and smoking abstinence (CO validated) and illicit drug use (detected in urine samples) was measured. No significant difference in tobacco abstinence rates was found (p-value not reported). No significant differences in illicit drug use were found between reported between motivational enhancement therapy and usual care groups. Positive tests for marijuana, cocaine, and opioids were seen in 6%, 26% and 28% or women respectively. 45% of women had positive test for either cocaine of opioids (45%).

Joseph et al (1990, prospective cohort [+]) compared data from 445 patients admitted to an inpatient substance abuse programme pre smoking ban and 457 post smoking ban. (The ban allowed smoking outside hospital buildings). Questionnaires were completed by 91% and 65% of pre and post-ban patients respectively. In the post-ban sample, a greater proportion of smokers abstained for at least a week (41% vs. 9%. P<0.001), reported not smoking regularly (58% vs. 19%, p<0.001), and planned to quit smoking (42% vs. 32%, p<0.001). There was no difference in the proportion of patients who thought that quitting would threaten sobriety (32% vs. 28%, p=0.22).

Joseph (1993a, prospective cohort [+]) followed up the study above (Joseph et al. 1990) by contacting 319 patients by telephone about 1-year after discharge. 156 were treated in an inpatient substance abuse programme before the hospital implemented a smoking ban and 163 were treated after the ban (the ban allowed smoking outside hospital buildings). There was no difference in the proportion of patients who claimed to have an improvement in their chemical dependence (97% vs. 89%, p=0.15). Self-reported abstinence from smoking was higher in the post-ban group (11%) than the pre-ban group (3%), p<0.05.

Joseph et al (1993b, retrospective cohort [-]) reported on patients hospitalised before and after a drug and alcohol treatment unit moved to new premises where smoking was not permitted in-doors. Data from 154 patients hospitalised post- smoking ban who responded to follow-up (out of 168) were compared with data from 160 responders hospitalised pre-smoking ban (out of 176). The two groups did not differ in drug or alcohol use recovery, although when non-responders were included as treatment failures, the recovery rate of cocaine users was lower in the post-ban group (71% recovered in the pre-ban group vs. 40% in the post-ban group, p<0.05).

Joseph et al (2004, RCT [+]) randomised 499 smokers in treatment for alcohol dependence to a concurrent (during treatment, n=251) or delayed (6 months later, n=248) smoking cessation intervention. There was no significant difference in self-reported 7-day tobacco abstinence rates at 18 months (9% in both groups). There was also no difference in the primary measure of alcohol abstinence (41% in the concurrent group vs. 48% in the delayed group, p=0.14). When using a softer measure of alcohol abstinence, a significant difference appeared (48% vs. 60%, p=0.01). The time to first use of alcohol was also significantly shorter in the concurrent group than in the delayed group (p=0.025). Given that the stop-smoking treatment did not affect smoking rates, any impact on alcohol use would seem to be due to factors other than nicotine deprivation.

Kalman et al (2001, RCT [+]) randomised 36 male smokers from an inpatient veteran substance abuse treatment programme to begin smoking cessation 2 weeks (concurrent treatment) or six weeks (delayed treatment) after admission. Number of drinks per day and percent days of alcohol use were recorded for the 90 days previous to admission and the 20-week period after admission. At the 20-week follow up more people in the delayed condition (n=6) compared to the concurrent condition relapsed back to alcohol (n=3), however this was not significant ($p<0.07$). No significant difference was seen in smoking abstinence rates between concurrent (n=3) and delayed (8%) treatment conditions ($p=0.74$).

Reid et al. (2008, RCT [+]) randomised 225 smokers in drug and alcohol maintenance and treatment programmes to smoking cessation treatment to accompany their usual treatment (SC) or the usual treatment only (control). Quit rates were 0% in the control group and about 10% in SC. The two groups did not differ in rates of retention in substance abuse treatment, abstinence from primary substance of abuse, or craving for primary substance of abuse.

Richter et al (2005, prospective cohort, [-]) recruited 28 patients who smoke from a methadone clinic and followed them up for 6-months following the start of smoking cessation treatment. They received a 7 week course of bupropion along with 12-weeks of nicotine gum and six sessions of motivational interviewing. The 6-month CO validated abstinence rate was 14%. There was no significant change in the group as a whole in the proportion of patients using illicit drugs.

Shoptaw et al (1996, prospective cohort, [-]) recruited 17 outpatients who smoke on methadone maintenance, to participate in a 4-weeks contingency management study for smoking cessation. Thrice weekly breath test for CO and urine tests for illicit drug use were undertaken. Although none managed to stop smoking completely during the study, 4 patients managed 3 or more consecutive days of abstinence. Nearly all (16/17) used illicit opiates and 10/17 used cocaine at least once during the study. However those able to abstain for even a few days was significantly less likely to use cocaine ($p<0.01$). There was no significant association between smoking cessation and illicit opiate use.

Shoptaw et al (2002, RCT [+]) randomised 175 outpatients who smoke and on methadone maintenance to 12 weeks treatment with (1) patch only, (2) a relapse prevention intervention (RPI) + patch, (3) contingency management (CM) + patch + RPI or (4) CM + patch. Thrice weekly breath test for CO and urine tests for illicit drug use during treatment and once at 6 and 12-month follow-up. Overall, smoking abstinence was a significant predictor of opiate abstinence ($p=0.0002$) and cocaine abstinence ($p<0.0001$). Individuals receiving the RPI, compared to the other interventions, were more likely to be abstinent from opiates ($p<0.0001$).

The results of these additional studies tally with the findings of the systematic review and do not raise any additional concerns.

Systematic reviews

Prochaska et al (2004, systematic review, [+]) reviewed 19 RCTs that investigated smoking cessation interventions in patients in substance misuse treatment or recovery. Smoking cessation interventions increased tobacco abstinence rates at the end of treatment (7-day abstinence rates 12% vs. 3% in control groups, RR=2.03 CI: 1.21-3.39) but not at long-term follow-up (7% vs. 6%). Regarding the decreased use of other substances, there was no difference between smoking cessation intervention and control groups at the end of treatment (RR=1.10, CI:0.93-1.29), but a significant positive effect at longer term follow-up

(37% vs. 31%, RR=1.25, CI:1.07-1.46). As this is the opposite of the impact the interventions had on smoking, the finding awaits explanation. The review provides no comparison of later drug outcomes between patients who initially stopped smoking versus those who continued to smoke.

Kodl et al (2006, general review, [+]) considered some issues of concurrent or sequential smoking cessation in patients treated for alcohol problems. The authors point out that in studies reviewed by Prochaska et al (2004) very few smokers stopped smoking, and conclude that alcohol-dependent smokers prefer sequential treatment; and that simultaneous treatment can negatively impact alcohol use outcomes, although the literature is not conclusive.

Okoli et al (2010, general review [+]) conducted a review of the literature on smoking cessation interventions in patients on methadone maintenance. The authors identified eight studies, five of which assessed drug use outcomes (Campbell et al 1995; Haugh et al 2004; Richter et al 2005; Shoptaw et al 1996; Shoptaw et al 2002). The conclusion drawn was that smoking cessation treatment does not worsen substance abuse.

INTERPRETATION

Randomised controlled trials of stop-smoking interventions show that the provision of such treatments does not undermine concurrent treatments for alcohol and opiate dependence. However, a more pertinent question of whether abstinence from smoking (as opposed to being in a group offered a stop-smoking treatment) undermines such treatments is not answered well by these studies. This is because the majority analysed only the effects of treatment allocation, and the large majority of smokers did not manage to stop smoking.

Other types of studies provide better information on whether abstinence from tobacco has a positive, negative, or no impact on ability to abstain from other substances. One study showed that the urge to drink following a cue exposure was not affected by tobacco abstinence acutely. One small RCT showed that people who reported not smoking at 6-months were more likely to have better alcohol outcomes that those who were smoking. Three studies compared treatment outcomes before and after hospitals became smoke-free. One of these provides a tentative suggestion that tobacco withdrawal may have a negative effect on treatment for cocaine dependence, but otherwise there were no negative outcomes, and the bans encouraged more smokers to quit. One study comparing objectively measured substance use in maintenance patients who did and did not stop smoking found no effect of tobacco abstinence, though this was a group in very solid remission with drug abstinence rates of almost 100%. Reassuringly, the majority of patients in substance abuse treatments did not think that stopping smoking would threaten their sobriety.

The questions of whether stopping smoking helps with or undermines drug and alcohol sobriety, and whether concurrent or sequential treatments yield better results, have not been fully answered so far and await future trials.

SECTION 4: EFFECTS OF SMOKE-FREE POLICY ON PSYCHIATRIC SYMPTOMS

There is a concern that banning smoking on psychiatric wards may have negative effects on patients' wellbeing and symptoms. We found 16 relevant studies addressing this issue. These are summarised in Table 16.

Table 16: Summary of studies included in Chapter 2 Section 4

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Cole et al (2010)	Retrospective cohort study	USA Patients on olanzapine or clozapine before and after smoking ban.	Psychiatric symptoms (BPRS) and Global Assessment of Functioning (GAF)	Decrease in GAF, i.e. worsening of symptoms. Increase in PRN medication in the first few months, decrease thereafter.	Quality +
Cormac et al (2009)	Retrospective cohort study	UK 48 smokers before and after a smoking ban	Doses and plasma levels of clozapine	A 25% increase in clozapine levels >1000 mcg/ml after the ban	Quality +
Cormac et al (2010)	Retrospective cohort study	UK 289 patients (217 smokers) admitted to psychiatric institution over 8-month period.	Incidents, changes in medications and use of NRT from medication charts over 4-month pre and post ban.	No effect on self-harm, verbal abuse, physical aggression and damage to property. Decrease in medication dosing post-ban.	Quality +
El-Guebaly et al (2002)	Review (not systematic)	Literature on smoking bans in mental health and addiction settings.		7 studies that report on effects of total smoking bans. Six reported on change in behaviour.	Quality -
Greenman & McClellan (1991)	Case study	USA 4 patients adversely affected by a total smoking ban.		Considerable staff time spent assessing patients' ability to leave the unit to smoke.	Quality -
Harris et al (2007)	Retrospective cohort study	Canada 119 patients 1-year before and after smoke-free policy.	Physical health, psychiatric symptoms and disruptive behaviours from clinical records.	Post ban smokers less likely to be in a good mood. An increase in plasma clozapine levels and subsequent decrease in dose.	Quality +
Hempel et al (2002)	Retrospective cohort study	USA 140 patients at maximum-security hospital for at least 4 weeks before and after ban.	Disruptive behaviours, medication for agitation, weight gain.	Reduction in disruptive behaviour in moderate and heavy smokers.	Quality +
Hollen et al (2010)	Retrospective cohort study	70 psychiatric hospitals at two time points.	Smoking as precursor to seclusion, smoking related health conditions,	Smokefree policy linked to reduction in smoking as a precursor to seclusion, smoking related health	Quality +

			coercion or threats, elopements and fires.	conditions and coercion or threats	
Meyer (2001)	Before-After case control study	USA 11 patients with schizophrenia receiving stable clozapine doses for at least 30 days.	Changes in clozapine levels after a smoking ban.	Levels were lower pre-ban compared to post-ban.	Quality +
Quin et al (2000)	Prospective cohort study	USA Acts of aggression over one month before and after smoking ban.	Overt Aggression Scale	There was a reduction in verbal and physical acts of aggression	Quality +
Resnick & Bosworth (1989)	Retrospective cohort study	USA 30 consecutive charts from a month before and a month after ban on acute ward	Chart reviews.	No change in drug doses, PRN medications, episodes of seclusion or restraint or discharges against medical advice.	Quality +
Ryabik et al (1994)	Prospective cohort study	USA 194 admissions to a locked psychiatric unit 6 weeks before and after ban.	Security calls per shift, seclusions and restraints, assaults, PRN medications for agitation, NRT gum use, discharges against medical advice.	Few changes	Quality +
Shetty et al (2010)	Retrospective cohort study	UK 56 patient records, resident 3 months before and after, and again 12 months after the ban on smoking on hospital grounds.	Smoking rates, incidents of smoking related aggression, use of tranquillising medicine, serum clozapine levels and use of NRT	Reduction in incidents and aggression post-ban. 23 smokers on clozapine had increased concentrations, 4 needed dose reduction.	Quality +
Smith et al (1999)	Prospective cohort study	USA 60 patients, 44 smokers admitted to inpatient unit with enforced smokefree policy	BPRS	Mean BPRS scores decreased over 3 days in both smokers and non-smokers.	Quality +
Velasco et al (1996)	Retrospective cohort study	USA 289 patients on a psychiatric unit immediately after the ban and again 2-years later.	Patient records reviewed for calls for security assistance, assaults, PRN use of medication	Increase in verbal assaults and prescribing of PRN medications for anxiety immediately after the ban. Not observed two years later.	Quality +
Voci et al (2010)	Retrospective cohort study	Canada Staff views on change in patient behaviour at 2-7 (n=481) and 31-33 months (n=500)	Staff perceptions and emergency calls before and after ban	More withdrawal symptoms after ban but no change in emergency calls	Quality +

		post ban			

We did not find any systematic reviews of this topic.

El-Guebaly et al (2002, review [-]) reviewed several studies of smoking bans in mental health and addiction settings. Six studies reported on changes in patients' behaviour. Five of these studies (Resnick & Bosworth 1989, Haller et al 1996, Velasco et al 1996, Smith et al 1999, and Quit et al 2000) are described below together with a number of other studies not included in this review. One report (Dingman et al 1988, which according to El-Guebaly et al. found no negative effects of the ban on patient behaviour) could not be obtained and has no abstract.

The majority of the studies described below compare data from hospital records before and after the implementation of a smoke-free policy. Three such reports concerning hospitals treating patients with addictions (Joseph et al. 1990, 1993a, 1993b) were reviewed in Part 3.

Cole et al (2010, retrospective cohort [+]) studied 26 psychiatric patients on olanzapine or clozapine hospitalised before and after implementation of a smoking ban. The authors describe the implementation of a smoke-free environment, but some patients were still able to obtain contraband cigarettes. Psychiatric symptoms (BPRS) and Global Assessment of Functioning (GAF) scores were collected. Patients showed a significant decrease in GAF (39.0 vs. 36.5, $p<0.001$) indicating a worsening of psychiatric symptoms post-ban. There was a significant increase in PRN medication use ($p<0.001$) in the first few months following the ban, but this decreased in the reminder of the year. Other changes were not significant.

Cormac et al (2010, prospective cohort [+]) audited data from 289 patients (217 smokers) admitted to a psychiatric institution over an 8-month period (4-months pre and 4-months post smoking ban). The facility was a secure unit and a total ban was enforced. Among smokers there were no significant differences in pre vs. post ban incidence of self-harm (61 vs. 61), verbal abuse (95 vs. 85) physical aggression (22 vs. 30) and damage to property (2 vs. 2; total count 180 vs. 178). Data were also collected in the first week of the 4 months pre ban and the last week of the 4-months post ban. The results showed a significant increase in incidents (158 pre-ban vs. 198 post ban, $p=0.01$). There was a significant decrease in the mean dose of antipsychotics post-ban (64.06, vs. 61.16, $p=0.025$). No significant changes were seen in the need for PRN medications.

Greenman & McClellan (1991, case study [-]) report on four patients who were adversely affected by a total smoking ban in a secure mental health unit. Two cases involved patients being transferred to facilities where they could smoke. Considerable staff time was spent assessing patients' ability to leave the unit to smoke.

Harris et al (2007, retrospective cohort [+]) studied 119 psychiatric patients in a maximum-security unit and in an open ward. Across the wards, compared to the year before the implementation of a total smoking ban, post ban smokers were less likely to be in a good mood. They also gained approximately 5 kg of weight. Smokers showed a significant increase in plasma clozapine levels and a subsequent decrease in daily clozapine dose. In the open wards, there was a significant increase in aggression towards staff. There were almost no adverse reactions in patients in the maximum-security unit.

Hempel et al (2002, retrospective cohort [+]) reported on 140 patients staying in a maximum-security psychiatric hospital for at least four weeks before and after the

implementation of total smoking ban. There was no significant change in disruptive behaviour among non-smokers and light smokers. A significant reduction in disruptive behaviour was seen in moderate (49% decrease, p=0.025) and heavy smokers (49% decease, p=0.007). Similar patterns were seen in reduction of sick calls (calls for assessment of physical illness) after the implementation of the smoke-free policy, with moderate (54% reduction, p=0.038) and heavy smokers (61% reduction, p=0.008) showing significant changes. Instances of verbal aggression decreased in light (0.39-0.30, ns), moderate (0.72-0.36, p=0.056) and heavy (0.34-0.11, p=0.034) smokers. All groups gained 7-8 pounds of weight post-ban.

Hollen et al (2010, retrospective cohort [+]) collected data from 70 psychiatric hospitals at two time points (2006 and 2008). All hospitals allowed smoking in 2006, but 28 (40%) banned smoking in hospital (including outside areas, and applied to all staff, patients and visitors) by 2008. In hospitals that had implemented smoke-free policy there was a significant reduction (pre vs. post) in reporting smoking as a precursor to seclusion (9 vs. 1, p=0.021), smoking related health conditions (21 vs. 5, p=0.001) and coercion or threats incidents (14 vs. 2, p<0.001). There were no significant changes in the numbers of hospitals reporting elopements or fires. The only significant change in hospitals that still allowed smoking was a reduction in coercion and threats incidents (22 vs. 10, p=0.04).

Resnick & Bosworth (1989, retrospective cohort [+]) reviewed 30 consecutive charts of patients on an acute locked psychiatric ward from a month before and a month after implementation of a smoke-free policy (total smoking ban). There were no significant changes in antipsychotic drug doses, PRN (as required) psychotropic medications dispensed, episodes of seclusion or restraint or discharges against medical advice.

Ryabik et al (1994, prospective cohort [+]) collected data from 194 admissions to a locked psychiatric unit for 6 weeks before and after the implementation of smoke-free policy. However, despite a total smoking ban within the unit, patients could smoke during out of hospital activities. The following outcomes are presented as number of events per 100 patients per week (pre vs. post smoking ban): security calls (4.5 vs. 4.3, ns); seclusions and restraints (8.7 vs. 11.0, ns); verbal assaults (9.5 vs. 29.5, p=0.075); physical assaults (1.5 vs. 2.8, ns); number of PRN medications for agitation (12.8 vs. 27.5, p<0.05); pieces of nicotine gum dispensed (6.2 vs. 38.8, p<0.01); and discharges against medical advice (0.17 vs. 0.50, ns).

Shetty et al (2010, retrospective cohort [+]) reviewed records of 56 hospitalised patients, 3 months before and after, and again 12 months after the introduction of a total smoking ban in hospital buildings and grounds. 50 patients were smokers. 27 of them used NRT following policy implementation. The number of incidents of verbal aggression 3-months pre and 3-months post ban was 29 vs. 16 (p=0.9), physical aggression 20 vs. 11 (p=0.6); there was no significant change in the use of tranquillisers.

Smith et al (1999, prospective cohort [+]) followed up 60 patients (44 smokers) admitted to an secure inpatient psychiatric unit with an enforced smoke-free policy. Mean BPRS scores decreased over 3 days in both smokers (31.8, 29.4, 28.0) and non-smokers (33.8, 32.7, 32.9). The change in scores between day 1 and 3 was significant in smokers (p<0.001), but not non-smokers. The change in score of the hostility item of the BPRS between days 1 and 2 decreased in smokers (p=0.001), and showed a small, but non-significant increase in non-smokers. 10 smokers used nicotine gum, but most used it only once or twice.

Quin et al (2000, prospective cohort [+]) recorded patients' acts of aggression (using the Overt Aggression Scale) over one month before and after the implementation of smoke-free

policy (no use of tobacco in any part of the hospital campus). There were 1184 verbal acts of aggression before and 656 after the policy was introduced (45% decrease, p<0.01). Similarly there was a decrease in physical acts of aggression (266 before vs. 133 after, 50% decrease, p<0.01)

Velasco et al (1996, retrospective cohort [+]) assessed behaviour in 289 patients on a psychiatric unit immediately after the implementation of a smoke-free policy and again 2-years later. There was a significant increase in verbal assaults and prescribing of PRN medications for anxiety immediately after the ban. However this was not observed two years later.

Voci et al (2010, retrospective cohort [+]) surveyed staff at a large mental health and addiction teaching hospital on their views towards smokefree policy and change in patient behaviour at 2-7 (n=481) and 31-33 months (n=500) post implementation of an indoor smokefree policy (patients could still smoke outside). An objective measure, number of emergency codes called before and after implementation, was also used. The only significant change over time was an increase in agreement that patients were experiencing more withdrawal symptoms after implementation of the smokefree policy (p<0.001). There was no significant change in the emergency codes called during the year before and after the smokefree policy.

We found three reports of the effects of smoking bans on plasma clozapine levels.

Meyer (2001, case control study [+]) studied clozapine levels in 11 patients with schizophrenia before and after a complete smoking ban in a psychiatric hospital (Meyer 2001). Mean plasma clozapine concentrations pre ban was 550+/-160 ng/ml, rising to 993+/-713 ng/ml post-ban, an 80% increase (p<0.034). One patient who had plasma concentration of 3066 ng/ml post ban (261% increase from baseline) suffered aspiration pneumonia.

Cormac et al (2010, retrospective cohort [+]) studied records of 48 smokers before and after a hospital smokefree policy was implemented. Before the ban 2/48 (4.2%) patients had a clozapine level >1000 mcg/ml and mean plasma clozapine concentration was 500 mcg/ml. After the ban 14/48 (29.2%) patients had a clozapine level >1000 mcg/ml and mean plasma clozapine concentration was 900 mcg/ml (p=0.0005).

Shetty et al (2010, retrospective cohort [+]) shows that in 23 smokers on clozapine, there was a significant increase in plasma clozapine concentrations post ban (p=0.0006) and four patients required a dose reduction. At 12 months post policy implementation there was no record of aggression related to nicotine withdrawal.

INTERPRETATION

The reviewed papers provide mixed information, with some studies reporting some negative impact on patient symptoms and behaviour (mostly only during the initial implementation), some finding no adverse effects, and a few studies reporting positive effects. The coverage and enforcement of the smokefree policy, that were not always well described within the studies, may influence the patient outcomes of smoking bans. Partial bans, where smoking is allowed on grounds, or on outings, may result in different outcomes than total smoking bans that prohibit smoking in buildings and on hospital grounds.

It is unknown if negative symptoms experienced by patients who are unable to smoke are secondary to tobacco withdrawal or changes in blood drug levels.

The bans generated an increase in patients' weight, and an increase in systemic levels of clozapine. The striking finding in some studies of patients being more subdued after the ban than before the ban may have been the result of increased sedation due to elevated systemic levels of medication in smokers now unable to smoke.

As the ban on smoking in psychiatric institutions has been implemented across the NHS, the issue is largely academic, though the findings may be relevant for considerations of further bans of smoking also on hospital grounds.

EVIDENCE STATEMENTS

EFFECTS OF SMOKING CESSATION ON PSYCHIATRIC SYMPTOMS

Most of the experimental studies reviewed above had methodological problems but some studies produced interpretable findings. Enforced abstinence from smoking can induce acute discomfort, but in the small self-selected group of patients who manage to achieve longer-term abstinence, no deterioration of mental health was observed. Bupropion promotes smoking cessation and may have positive effects on mood, but the evidence for positive effects of NRT is weaker.

ES 2.1 There is strong evidence that PTSD patients who manage to stop smoking do not experience any worsening of their condition (McFall et al 2005, RCT [+]; McFall et al 2010, RCT [++])

ES 2.2 There is good evidence that in patients with schizophrenia, overnight abstinence from smoking can increase negative symptoms (Smith et al 2002, cross over trial, [++])

ES 2.3 There is moderate evidence that short (7 days) smoking abstinence does not lead to cognitive deterioration but may slow down psychomotor speed (Evins et al 2005a and 2005b, RCT [+])

ES 2.4 There is weak to moderate evidence that patches may decrease agitation in smokers with schizophrenia with acute symptoms admitted to non-smoking wards but increase involuntary movements (Allen et al 2011, RCT [+], Dalack et al 1999, RCT [+])

ES 2.5 There is strong evidence that treatment with bupropion for smoking cessation does not lead to any deterioration in mental health (Tsoi et al 2010a, systematic review [+]; Tsoi et al 2010b, systematic review [+]; Banham & Gilbody 2010, systematic review [+]; Evins et al 2001, RCT [+]; Evins et al 2005a and 2005b, RCT [+]; Evins et al 2007, RCT [+]; Fatima et al 2005, cross over trial, [+]; George et al 2002, RCT [+]; George et al 2008, RCT [+]).

ES 2.6 There is moderate evidence that treatment with bupropion may lead to improved mood and reduction in akathisia (Evins et al 2001, Evins et al 2007, RCT [+]; RCT [+]; George et al 2002, RCT [+])

ES 2.7 There is strong evidence that receiving smoking cessation interventions does not adversely affect mental health (Allen et al 2011, RCT [+]; Baker et al 2006, RCT [+]; Evins et al 2001, RCT [+]; Evins et al 2005a and 2005b, RCT [+]; Evins et al 2007, RCT [+]; Fatima et al

2005, cross over trial, [+]; Gallagher et al 2007, RCT [+]; George et al 2000, RCT [+]; George et al 2002, RCT [+]; George et al 2008, RCT [+]; Williams et al 2010, RCT [+]).

ES 2.8 There is good evidence that among patients with schizophrenia or schizoaffective disorder, those who manage to stop smoking do not experience any worsening in their condition (Evins et al 2007, RCT [+]; Gallagher et al 2007, RCT [+]; Williams et al 2010, RCT [+])

ES 2.9 There is moderate evidence that mood improves in depressed smokers who manage to stop smoking compared to those who fail in their quit attempt (Blalock et al 2008, prospective cohort [+]; Thorsteinsson et al 2001, RCT [+])

EFFECTS OF STOPPING SMOKING ON PSYCHIATRIC MEDICATION

All the reviewed medications seem to be metabolised faster by smokers than by non-smokers. The corollary of this finding is that in stable patients on well-tolerated medication doses, stopping smoking is likely to increase systemic levels of these drugs and needs to be accompanied by dose adjustments. We found no data on whether NRT mitigates the effects of stopping smoking on increasing systemic levels of these medications, but it is unlikely to do so.

ES 2.10 There is strong evidence that clozapine and olanzapine are metabolised much faster by smokers, and stopping smoking can increase their systemic levels (Derenne & Baldessarini 2005, case study, [-]; Dettling et al. 2000, prospective cohort [+]; Diaz et al 2005, randomised non-controlled trial, [+]; Haring et al. 1989 retrospective cohort [+]; Haslemo et al 2006, prospective cohort [+]; Meyer 2001, case control study [+]; Ozdemir et al 2001, prospective cohort [+]; Pettitt et al. 2009, case study, [-]; Rostami-Hodjegan et al. 2004, retrospective cohort [+]; Sandson et al. 2007, case study, [-]; Seppala et al. 1999, prospective cohort [+]; van der Weide et al. 2003, retrospective cohort, [+]; Wenzel-Seifert et al 2011, retrospective cohort [+]; Wetzel et al. 1998, prospective cohort [+]; Callaghan et al. 1999, prospective cohort [+]; Carrillo et al. 2003, prospective cohort [+]; Gex-Fabry et al 2003, retrospective cohort [+]; Skogh 2002, retrospective cohort [+]; Wu et al. 2008, prospective cohort [+]). Although two studies found no significant effects of smoking on serum clozapine levels (Hasegawa et al. 1993, prospective cohort [+]; Palego et al. 2002, prospective cohort [+]).

ES 2.11 There is moderate evidence that haloperidol is metabolised faster by smokers than by non-smokers (Jann et al. 1986, prospective cohort [+]; Miller et al. 1990, prospective cohort [+]; Perry et al. 1993, retrospective cohort [+] found a difference, Fukunda 2000, retrospective cohort [+]) found no difference)

ES 2.12 There is moderate evidence that chlorpromazine is metabolised faster by smokers than by non-smokers (Chetty et al. 1994, retrospective cohort [+]; Pantuck et al 1982, prospective cohort, [+]; Stimmel and Falloon (1983, case study [-])

ES 2.13 There is moderate evidence that fluphenazine, perphenazine and thioridazine are metabolised faster by smokers than by non-smokers (Ereshefsky et al 1985, retrospective cohort [+]; Jin et al 2010, prospective cohort [+]; Berecz et al 2003, prospective cohort [+])

ES 2.14 There is weak evidence that methadone levels increase following a reduction in smoking (Wahawisan et al 2011, case study, [-]).

ES 2.15 There is moderate evidence that smoking does not affect the metabolism of triazolam, diazepam or midazolam (Ochs et al. 1987, prospective cohort [+]; Otani et al. 1997, prospective cohort [+]; Ochs et al. 1985, prospective cohort [+]).

ES 2.16 There is inconsistent evidence regarding the effect of smoking on alprazolam. One study showed that smoking was associated with increased clearance (Hossain et al. 1997, prospective cohort [+]). Another found that smoking had no effect on any pharmacokinetic parameters (Otani et al. 1997, prospective cohort [+]).

ES 2.17 There is weak evidence that smoking increases the metabolism of desmethyldiazepam when given orally (Norman et al. 1981, prospective cohort [+]), but not intravenously (Ochs et al. 1986, prospective cohort [+]).

ES 2.18 There is weak evidence that smoking has no effect on the clearance of carbamazepine (Martin et al. 1991, retrospective cohort, [+])

ES 2.19 There is moderate evidence that the metabolism of quetiapine (an atypical antipsychotic) is unaffected by tobacco smoke (DeVane & Nemeroff 2001, review [+]).

ES 2.20 There is weak evidence that smoking increases metabolism of two selective serotonin reuptake inhibitors duloxetine (Fric et al. 2008, retrospective cohort [+]) and fluvoxamine (Spigset et al. 1995, prospective cohort [+]).

ES 2.21 There is weak evidence that smoking has no effect on the metabolism of thiothixene (Ereshesfsky et al. 1991, retrospective cohort, [+]).

ES 2.22 There is weak evidence that smoking is associated with lower plasma levels of clomipramine (John et al. 1980, prospective cohort, [+]) and imipramine (Perel et al. 1976, retrospective cohort, [+]).

ES 2.23 There is inconsistent evidence regarding the effect of smoking on amitriptyline and nortriptyline. Two studies showed smoking was associated with lower plasma levels of these drugs (Linnoila et al. (1981, prospective cohort, [+]; Perry et al. 1986, prospective cohort, [+]) and three studies found no effect of smoking on pharmacokinetic parameters (Norman et al. 1977, prospective cohort, [+]; Rickels et al. 1983, prospective cohort, [+]; Ziegler & Biggs 1977, prospective cohort, [+]).

ES 2.24 There is weak evidence that smoking has no effect on the metabolism of zotepine (Kondo et al. 1996, prospective cohort [+]).

ES 2.25 There is moderate evidence that the metabolism of zuclopenthixol (an antipsychotic drug) is unaffected by tobacco smoke (Jaanson et al. 2002, prospective cohort [+]; Jorgensen et al. 1985, prospective cohort [+]).

EFFECTS OF STOPPING SMOKING ON THE USE OF OTHER SUBSTANCES

A number of studies show that the provision of stop-smoking treatments does not undermine concurrent treatments for alcohol and drug dependence. However, the majority of studies analysed only the effects of treatment allocation, and the large majority of smokers did not manage to stop smoking. The questions of whether actual stopping smoking helps with or undermines drug and alcohol sobriety, and whether concurrent or sequential treatments yield better results, have not been fully answered so far and await future trials.

ES 2.25 There is strong evidence that receiving smoking cessation treatment (as opposed to actually stopping smoking) does not undermine concurrent treatments for other drug addictions (Brown et al 2001, RCT [+]; Burling et al 2001, RCT [+]; Campbell et al 1995, prospective cohort, [+]; Cooney et al 2007, RCT [+]; Cooney et al 2009, RCT [+]; Dunn et al 2009, prospective cohort [+]; Grant et al 2007, RCT [+]; Haug et al 2004, RCT, [+]; Kalman et al 2001, RCT [+]; Okoli et al 2010, general review [+]; Prochaska et al 2004, systematic review, [+]; Reid et al. 2008, RCT [+]; Richter et al 2005, prospective cohort, [-]; Shoptaw et al 2002, RCT [+])

ES 2.26 There is good evidence that in alcoholics, smoking deprivation does not increase cue-induced urge to drink (Cooney et al 2003, randomised cross over trial [++])

ES 2.27 There is good evidence that abstinence from smoking does not undermine opioid maintenance treatment in successfully maintained patients (Campbell et al 1995, prospective cohort, [-]; Dunn et al 2009, prospective cohort [+]; Haug et al 2004, RCT, [+]; Okoli et al 2010, general review [+]; Richter et al 2005, prospective cohort, [-]; Shoptaw et al 2002, RCT [+])

ES 2.28 There is moderate evidence that being unable to smoke during treatment reduces the efficacy of inpatient treatment for cocaine dependence (Joseph et al 1993b, retrospective cohort [+])

ES 2.29 There is good evidence that being unable to smoke during treatment encourages successful smoking cessation later (Joseph et al 1990, prospective cohort [+]; Joseph 1993a, prospective cohort [+]; Joseph et al 2004, RCT [+])

ES 2.30 There is weak evidence that smoking cessation treatment may assist with abstinence from opiates (Shoptaw et al 2002, RCT [+]), although a small prospective cohort study showed no beneficial effect (Shoptaw et al 1996, prospective cohort, [-]).

ES 2.31 There is weak evidence that smoking cessation is associated with abstinence from alcohol at long-term follow-up (Grant et al 2007, RCT [+]).

EFFECTS OF SMOKE-FREE POLICY ON PSYCHIATRIC SYMPTOMS

Smoking bans generate a significant increase in patients' weight and in systemic levels of clozapine and probably other drugs as well. Otherwise the reviewed papers provide mixed information, with some studies reporting some negative impact on patient symptoms and behaviour (mostly only during the initial implementation), some finding no adverse effects, and some reporting positive effects.

ES 2.31 There is mixed evidence regarding the effect of smokefree policy on behaviour and symptoms in inpatients with mental illness. Five studies found some signs of worsening functioning within a few weeks of the ban (Cole et al 2010, retrospective cohort [+]; Cormac et al 2010, prospective cohort [+]; Harris et al 2007, retrospective cohort [+]; Ryabik et al 1994, prospective cohort [+]; Velasco et al 1996, retrospective cohort [+]). Three studies found no change after smoking ban (Resnick & Bosworth 1989, retrospective cohort [+]; Shetty et al 2010, retrospective cohort [+]; Voci et al 2010, retrospective cohort [+]) and four studies found improvements in disruptive behaviours (Hempel et al 2002, retrospective

cohort [+]; Hollen et al 2010, retrospective cohort [+]; Smith et al 1999, prospective cohort [+]; Quin et al 2000, prospective cohort [+])

ES 2.32 There is moderate evidence that total smoking bans generated a significant weight gain (Harris et al 2007, retrospective cohort [+]; Hempel et al 2002, retrospective cohort [+])

ES 2.33 There is good evidence showing that total smoking bans lead to increased systemic levels of clozapine and a need to lower its dosing (Meyer 2001, case control study [+]; Cormac et al 2010, prospective cohort [+]; Shetty et al 2010, retrospective cohort [+])

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CHAPTER 3

Safety of nicotine replacement use in pregnancy

INTRODUCTION

Smoking in pregnancy carries a number of risks. The majority of these are associated with non-nicotine components of tobacco smoke including carbon monoxide and heavy metals. However nicotine is also associated with risks to the foetus and pregnancy.

Most experts agree that it is best for women to avoid any form of nicotine throughout pregnancy. However most pregnant smokers in the UK continue to smoke throughout pregnancy (Hajek, West et al. 2001). For pregnant women who are having difficulty abstaining from smoking, a question arises whether NRT may provide a lower risk option than smoking.

There is an associated question of whether NRT is effective in pregnant smokers. This is covered in Review 2, which provides a systematic review of the relevant literature and meta-analysis. Here we focus on the issues of nicotine safety.

Below we present data from 27 studies that seek to determine the health effects of NRT on the foetus and newborn children. We divided the literature into experimental studies, epidemiological studies, systematic reviews, and opinion pieces. A brief interpretative summary of findings is provided at the end of each section, and evaluation and evidence statements are at the end of the Chapter.

Table 17: Summary of studies included in Chapter 3

Paper	Study Details	Population & Setting	Outcomes	Results	Quality & Notes
Coleman et al (2010)	Systematic review	5 RCTs of NRT (3 placebo-controlled, 2 non-placebo controlled)	Abstinence rates, birth outcomes adherence and side effects.	No difference in adverse pregnancy outcomes, trends for better outcomes in NRT groups.	Quality ++
Coleman et al (2012)	Randomised controlled trial	UK 1050 pregnant women assigned to 8 weeks of 15mg/16 hour patches or placebo	Abstinence rates, birth outcomes adherence and side effects.	No difference in adverse pregnancy outcomes, but active patch users were more likely to have caesarean section	Quality ++
Damgaard et al (2008)	Prospective cohort study	Finland and Denmark Pregnant women (n=4957) completed health questionnaires in 1st trimester.	Questionnaires included smoking status and use of NRT. 2,496 boys examined for cryptorchidism.	Smoking not a risk factor for cryptorchidism. Boys of NRT users regardless of smoking status had increased risk compared to never smokers.	Quality +
Dempsey et al (2002)	Prospective experimental study	USA 10 pregnant women received infusions of deuterium-labelled nicotine and cotinine	Blood and urine measurements	Increase in clearance of nicotine and cotinine during pregnancy, compared with the post partum period.	Quality ++

		during and after pregnancy after overnight abstinence from smoking.			
Gaither et al (2009)	Retrospective cohort study	USA 5716 women from monthly random sampling using birth certificates mailed questionnaires.	Self-reported if a healthcare professional recommended NRT, preterm birth and low birth weight (LBW)	225 were recommended or prescribed NRT. Those recommended NRT were more likely to have LBW or preterm baby than non-smokers.	Quality -
Hackman et al (1999) Pilot study for Kapur et al (2001)	Prospective cohort study	Canada 7 pregnant women who smoke were given 15mg/16 hour patches to use daily for a week	Serum and salivary nicotine and cotinine	Mean serum cotinine significantly decreased from baseline smoking levels.	Quality -
Hegaard et al (2003)	Quasi-randomised controlled trial	Denmark 647 pregnant smokers received counselling + 15mg/16 hr patch and/or 2mg gum for 11 weeks or usual care	Abstinence (salivary cotinine) and birth weight	Abstinence rates higher in NRT group. No differences in birth weight.	Quality +
Hegaard et al (2004)	Case control study	See Hegaard et al (2003) 75 women in the intervention group that used NRT matched with 2 comparable controls from control group.	Incidence of pregnancy related complications	No difference between the groups in number of pre-term births. No foetal deaths.	Quality +
Hotham (2006)	Randomised controlled trial	Australia 40 pregnant women received counselling or counselling plus 15mg/16hr nicotine patches for 12 weeks.	Abstinence (CO validated), adverse events	Abstinence in 3/20 vs. 0/20 of the intervention and control groups. Only 5 participants used patches for 12 weeks. No serious AEs reported.	Quality – Small sample for an outcome study
Ilett et al (2003)	Prospective cohort study	Australia 15 lactating women stopped smoking using nicotine patches (21mg for 6 weeks, 14mg for 2 weeks, 7 mg for 2 weeks).	Abstinence (CO validated); milk intake over 24hr whilst smoking and on patches; nicotine and cotinine in milk and plasma	Infant milk intake similar across conditions. Milk nicotine similar with smoking and 21mg patch. 14mg and 7mg produced lower concentrations than smoking.	Quality +
Kapur (2001)	Randomised controlled trial	Canada 30 pregnant smokers given 16h nicotine or placebo patch for 12 weeks.	Smoking status, adverse events	No effect on stopping smoking. One woman, on placebo, reported rapid and forceful foetal movements 3 hours after quitting smoking.	Quality - Small sample for an outcome study
Lassen et al (2010)	Retrospective cohort study	Denmark 72,761 women interviewed by phone at 16 and 31 weeks gestation.	NRT use and smoking status from interviews, birth outcome data from national registry.	1,828 women reported NRT use during 27 weeks of pregnancy. No effect on birth weight.	Quality +
Lehtovirta et al (1983)	Non randomised trial	Finland 31 pregnant women (8 current smokers, 23 ex-	Foetal heart rate variability, maternal blood pressure and	Gum associated with a transient decrease in the interval index of FHR	Quality – Mix of smokers

		smokers) chewed 2mg nicotine gum for 20 minutes or smoked a herbal cigarette	HR.	variability. Maternal BP and HR increased during chewing gum and smoking.	and ex-smokers
Lindbald & Marsal (1987)	RCT cross-over	Sweden 20 pregnant smokers, after overnight abstinence chewed 4mg gum or placebo	Maternal and foetal hameodynamics and blood samples	Increase in maternal HR and BP on gum, but no changes in FHR, aortic or umbilical venous blood flow.	Quality +
Lindbald et al (1988)	RCT cross-over	Sweden 24 pregnant smokers. Group 1 on normal cigarette (NC) , two NCs, 1 herbal cigarette (HC), and 2 HCs. Group 2 on 4mg gum (4G) followed by placebo gum (PG), b) 2 PGs in sequence and c) 2 4Gs in sequence.	Blood nicotine and catecholamine, maternal HR and BP and FHR and foetal blood flow.	Smoking and 4Gs increased maternal HR and BP. FHR increased after NCs, but not after 2 4Gs. A similar pattern in foetal aortic blood flow. Umbilical vein blood flow increased after NC smoking only.	Quality +
Lumley et al (2009)	Systematic review	72 RCTs of smoking cessation in pregnancy. 5 trials assessed efficacy of NRT, and 3 reported birth outcomes.	Smoking status, birth weight; pre-term birth	No difference in birth weight, number of low birth weight babies or preterm births.	Quality ++
Morales-Suarez-Varela et al (2006)	Retrospective cohort study	Denmark 76,768 women with singleton births. 250 reported using NRT, 20,603 women reported smoking, and 56,165 were non-smokers.	NRT use and smoking status from interviews, birth outcome data from national registry.	Congenital malformations did not differ between smokers and non-smokers. Higher prevalence in children of non-smoking NRT users compared to non-smokers	Quality +
Gobur et al (1999)	Prospective cohort study	USA 8-week course of 22mg/24 hour patch in 21 pregnant smokers	Blood nicotine and cotinine, FHR, biophysical profile. Doppler flow on days 1 and 4.	Nicotine and continue concentrations with patch not different from smoking. Morning FHR when smoking higher than on patch.	Quality +
Oncken et al (1996)	Randomised controlled trial	USA 29 pregnant smokers either continued smoking or abstained and used at least 6 pieces of 2mg nicotine gum per day for 5 days.	Blood nicotine and cotinine concentration, maternal and foetal haemodynamic parameters.	Significant reductions were seen in nicotine and cotinine levels in the gum group. Changes in haemodynamic parameters were greatest during smoking.	Quality +
Oncken et al (1997)	Randomised crossover study	USA 23 women used a 21mg patch or smoked ad lib for 8 hours after overnight abstinence. Crossed over after a week.	Blood samples of nicotine and cotinine concentrations, maternal BP and HR and FHR.	No significant differences seen in blood nicotine or cotinine levels between groups. There was a non-significant loss in FHR reactivity between the 2 groups.	Quality +
Oncken et al (2008)	Randomised controlled trial	USA 194 pregnant smokers on 6 weeks nicotine 2mg gum or placebo	Abstinence at 32-35 weeks gestation, birth weight, adverse events	No difference in abstinence rates. Babies born to mother using NRT were heavier. No overall difference in SAEs.	Quality +

Oncken et al (2009)	Randomised controlled trial	USA 21 pregnant women after overnight abstinence smoked, then on nicotine nasal spray + placebo patch or placebo spray + 15mg/16hr patch or placebo spray + placebo patch.	FHR, nicotine and cotinine concentrations	Blood nicotine higher with smoking than with NRT. FHR decreased on day 5 in placebo group and increased on NRT, but this treatment by time interaction did not reach significance.	Quality +
Pollack et al (2007)	Randomised controlled trial	USA 181 pregnant smokers received CBT alone or CBT + NRT for 6 weeks. NRT: choice of 16 hr patch, 2mg gum or 2mg lozenge	Abstinence (validated with salivary cotinine) and SAEs	Abstinence rates higher on NRT. No difference in birth weight, gestational age or SAEs.	Quality +
Schroeder et al (2002)	Prospective cohort study	See Ogburn et al (1999)	AEs related to patch use, pregnancy outcomes, maternal and cord nicotine and cotinine at delivery	AEs were mild and typical of patch treatment. No differences in nicotine or cotinine when smoking vs. using patches.	Quality +
Strandberg-Larsen et al (2008)	Retrospective cohort study	Denmark 87,032 women assessed for relationship between NRT use and stillbirth.	NRT use and smoking status from interviews, birth outcome data from national registry.	1,927 women used NRT. No association with stillbirth, even in women who smoked and used NRT concurrently.	Quality +
Wisborg et al (2000)	Randomised controlled trial	Denmark 250 pregnant women on placebo or nicotine patches 15mg/16hr for 11 weeks.	Abstinence and birth weight	No difference in abstinence rates. Birth weight higher on NRT.	Quality +
Wright et al (1997)	Prospective cohort study	USA 6 pregnant women admitted to inpatient unit where they could not smoke for 21 hours. 11 hours after admission given 21 mg patch.	Salivary, cotinine, maternal and foetal haemodynamic measurements.	No differences in foetal wellbeing on patch. After 8 hours on patch salivary nicotine similar to baseline.	Quality +

EXPERIMENTAL STUDIES

We found 12 studies that investigated the haemodynamic effects of NRT and/or nicotine delivery achieved with NRT. Coleman et al (2012, RCT [++]) was not captured by our literature search as it was published in 2012, but as it is the largest RCT to date is important to include in this review.

Coleman et al. (2012, RCT [++]) randomised 1050 pregnant smokers (12-24 weeks gestation) to 8 weeks of nicotine (15mg/16hr) or placebo patch with one face-to-face midwife counselling session at enrolment followed by 3 telephone counselling calls. There was no significant difference in salivary cotinine validated abstinence rates at delivery (9.4% vs. 7.6% in nicotine and placebo groups, respectively). There were no significant differences between

the groups (NRT vs. placebo) in rates of miscarriage (0.6% vs. 0.4%), still birth (1% vs. 0.4%), preterm birth (7.9% vs. 8.7%), low birth weight (11% vs. 8.3%), congenital abnormalities (1.8% vs. 2.5%) or NICU admissions (6.5% vs. 6.8%). NRT users were however more likely to have a caesarean section compared to placebo users (20.7% vs. 15.3%, OR=1.45 95%CI: 1.05-2.01). The authors concluded that this was likely to be a chance finding.

Dempsey et al. (2002, experimental study [++]) gave 10 pregnant smokers infusions of deuterium-labelled nicotine and cotinine during and after pregnancy after overnight abstinence from smoking. There was a significant increase in total clearance of nicotine (60% increase) and cotinine (140% increase) in pregnancy, compared with the post partum period, and a 54% increase in clearance of nicotine via its metabolism to cotinine. Mean plasma cotinine concentration during smoking in pregnancy was 119 ng/ml (SD=75), compared to 202 ng/ml (SD=77) postpartum ($p<0.05$).

Hackman et al. (1999, prospective cohort [-]) recruited 7 pregnant women to stop smoking and use 15mg/16 hr patches daily for a week. After one week, mean serum cotinine decreased from 247.6 (SD=96.9) to 163.7 ng/ml (SD=72.9), p=0.003.

Ilett et al. (2003, prospective cohort [+]) assessed the exposure to nicotine in infants of 15 lactating women who stopped smoking using nicotine patches. Measures were taken whilst mothers were smoking and when they stopped and wore the patches of decreasing strength. Nicotine concentrations in milk were not different between smoking and 21mg patch, but the 14mg and 7mg were associated with significantly lower concentrations of nicotine in milk than smoking ($p<0.05$). The total nicotine equivalents consumed by the infant were similar in the smoking and 21mg patch conditions, but significantly less ($p<0.05$) when women were using the 14 and 7mg patches. Blood samples were taken in 9 infants during the time mothers were using the 21mg patch. Nicotine could not be detected in any of these samples. Mean cotinine concentration was much lower than that seen in mothers (22 vs. 175 mcg).

Lehtovirta et al (1983, non-randomised trial [-]) allocated 31 pregnant smokers to chew a piece of 2mg nicotine gum for 20 minutes (N=15) or to smoke a nicotine-free herbal cigarettes for 5 minutes (N=15). Eight women were current smokers. Nicotine gum was associated with a significant transient decrease in the interval index of FHR variability. Maternal BP and HR increased transiently during chewing gum and smoking. The herbal cigarette had no influence on FHR variability.

Lindbald & Marsal (1987, randomised cross-over trial [+]) randomised 20 pregnant smokers to chew a piece of 4mg or placebo gum for 30 minutes after overnight abstinence. There was a significant increase in maternal heart rate and blood pressure following use of the gum, but no significant changes in foetal heart rate, aortic or umbilical venous blood flow.

Lindbald et al. (1988, randomised cross-over trial [+]) allocated 24 pregnant smokers to two groups. Group 1 (n=12) tested 4 smoking conditions after overnight abstinence a) one standard cigarette, b) two standard cigarettes one after the other, c) one herbal cigarette, and d) two herbal cigarettes. Group 2 (n=12) was randomly allocated to 3 conditions a) 4mg gum followed by placebo gum, b) two placebo gums in sequence and c) two 4mg gums in sequence. Both smoking and active gum increased maternal HR and BP. FHR increased significantly after standard cigarette, but the increase was not significant after two pieces of gum. A similar pattern was seen with an increase in foetal aortic blood flow. Umbilical vein blood flow increased after a standard cigarette, the other conditions had no significant

effects. Chewing one piece of gum resulted in maternal plasma levels of 12.4 ng/ml and although maternal HR and BP increased, foetal haemodynamics remained unaffected.

Ogburn et al. (1999, prospective cohort [+]) and **Schroeder et al. (2002, prospective cohort [+])**, report the same study of an 8-week course of 22mg/24 hr patch in 21 pregnant smokers. The patch was initiated during a 4-day inpatient stay. Blood nicotine levels when smoking vs. day 4 of patch treatment were 14.4 vs. 11.8 (Ogburn et al. 1999). A significant difference in morning foetal heart rate was found between smoking (142 bpm) and patch treatment (136 bmp), p=0.017. There were no differences in systolic/diastolic ratio in the umbilical artery measured on Doppler ultrasound. Adverse events were mild and typical of patch treatment (Schroeder et al. 2002). Seven women discontinued treatment because of AEs (5=rash; 1=nausea; 1=dizziness). There were 21 live births. Three suffered severe morbidity, but none were considered related to NRT.

Oncken et al. (1996, RCT [+]) randomised 29 pregnant smokers to continue smoking (n=10) or abstain and chew at least 6 pieces (and up to 30) of 2mg nicotine gum per day for 5 days (n=19). Most (15/19) women using gum managed to abstain for 5 days, and chewed 8 pieces of gum/day, on average. Significant reductions were seen in nicotine and cotinine plasma concentrations in the gum group. The changes in blood nicotine concentration were significantly greater following smoking (6.7 ng/ml to 19.7 ng/ml) compared to chewing a piece of gum (3.3 ng/ml to 5.7 ng/ml), p<0.01. The changes in haemodynamic parameters were greater in those who smoked compared to chewed gum, although none of these differences were statistically significant.

Oncken et al. (1997, randomised cross-over trial [+]) compared the effects of smoking for 8 hours with an 8-hour application of a 21mg nicotine patch in 23 pregnant smokers. Participants were crossed over to the two conditions. Blood samples were taken at baseline, then 2,3,4,6, and 8 hours after starting patch treatment. Area under the curve (AUC) plasma nicotine/time for smoking vs. patch was 89 vs. 93 ng-hr/ml, p=0.77. Mean maximum nicotine plasma concentration (Cmax) for smoking and patch were 19.7 ng/ml (SD=8.09) vs. 16.0 ng/ml (SD=3.5) and time to maximum concentration (Tmax) 5.0 hrs. (SD=2.4) vs. 3.2 hrs. (SD=1.7). There was a non-significant loss in FHR reactivity in 5/8 tracings after patch use vs. 1/6 after smoking.

Oncken et al. (2009, RCT [+]) studied 21 pregnant smokers. They smoked as normal after overnight abstinence and were then randomly assigned to one of the following groups 1) nicotine nasal spray (NNS) + placebo patch; 2) placebo spray + 15mg/16hr patch; 3) placebo spray + placebo patch. Women were instructed to start these products on their quit date. The baselines measures were repeated on day 5. Blood nicotine levels were significantly higher with smoking than with nasal spray, patch and placebo use (p=0.002). Maternal HR showed a significantly greater decrease from baseline in placebo and nasal spray users than patch users (p=0.021). FHR treatment by time interaction did not reach significance (p=0.052).

Wright et al. (1997, prospective cohort [+]) admitted 6 pregnant smokers to an inpatient unit where they could not smoke for 21 hours. After overnight abstinence (11 hours after admission) they were provided with a 21 mg nicotine patch to wear for 6 hours. Maternal and foetal haemodynamic measurements were taken at baseline, prior to patch use and 2 and 6 hours after the patch was applied. No measurable differences in foetal or maternal wellbeing were reported following application of the patch. Eight hours after patch application salivary nicotine concentration was similar to baseline.

We found 6 randomised controlled trials providing data on safety of NRT when used for smoking cessation.

Hegaard et al. (2003, RCT [+]) randomised 647 pregnant smokers to counselling (N=327) (9 session over 14 weeks) + NRT (15mg/16 hour patch and/or 2mg gum for up to 11 weeks), or control group (N=320) (single session with midwife). Abstinence in the 37th week of pregnancy (validated with salivary cotinine < 30ng/ml) was 7% (n=23) and 2.2% (n=7) for intervention and control groups, respectively (p=0.004). There was no significant difference in mean birth weight between the groups (3401g vs. 3433, p=0.6) or the proportion of LBW babies (3.6% vs. 3.0%, p=0.7).

Hegaard et al. (2004, case control [+]) reported further safety data from the same trial. A small subsample of women on NRT provided saliva samples at baseline and at least 1-week after starting and using NRT. The cotinine concentrations (ng/ml) whilst smoking versus using NRT were as follows: Gum users (n=6) 132 (SD=95) vs. 35 (SD=28) (CI:-6-200); patch users (n=7) 173 (SD=41) vs. 70 (SD=33), (CI:60-146); and combination NRT users (n=5) 246 (SD=91) vs. 105 (SD=51), (CI:47-236). There were no foetal deaths. The proportion of pre-term births (NRT users vs. controls), was 4/75 vs. 5/150 (p=0.5) and small for gestational age babies 5/75 vs. 11/150 (p=1.0).

Hotham et al. (2006, RCT [-]) randomised 40 pregnant smokers to brief counselling (N=20) or counselling plus the offer of 15mg/16hr nicotine patches for 12 weeks (N=20). Abstinence was achieved in 3/20 vs. 0/20 of the intervention and control groups respectively (significance not reported). Only five women used patches for 12 weeks. Five women in the NRT arm reported minor adverse effects (rash, 'dead arm', 'ill, flat and nauseous', increased morning sickness, depression following abstinence) but no ill effects on pregnancy were noted.

Kapur et al (2001, RCT [-]) allocated 30 pregnant smokers to 16hr nicotine patch or placebo for 12 weeks. There were four counselling sessions. There was no significant difference in abstinence rates at the end of treatment between the nicotine group (4/17) and placebo group (0/13), p=0.11. One woman, receiving a placebo patch, reported rapid and forceful foetal movements 3 hours after quitting smoking. These subsided within 20 minutes of returning to smoking. Subsequent to this adverse event the trial was stopped prematurely (it intended to recruit 20 women to each group).

Oncken et al. (2008, RCT [+]) randomised 194 pregnant smokers to either nicotine or placebo chewing gum for 6 weeks. Gum use was low (3 pieces/day in both groups). There was no difference in abstinence rates, but the nicotine gum group smoked less cigarettes per day (p<.05) and had lower urinary cotinine levels (p<.05). Importantly, babies born to mother using NRT were significantly heavier (3287g vs. 2950g, p<0.01) and had greater gestational age (p<.05). A breakdown of SAEs in the nicotine vs. placebo groups were as follows: preterm birth (7/97 vs. 16/87 p=0.027); Low Birth Weight [LBW] (2/97 vs. 16/87 p<0.001); spontaneous abortion (2/97 vs. 0/87 p=0.5); foetal death in utero (2/97 vs. 1/87 p=0.54); newborn death (2/97 vs. 1/87 p=0.60); maternal hospitalisation (9/97 vs. 8/87 p=0.90); and NICU admission (7/97 vs. 11/87 p=0.20).

Pollack et al. (2007, RCT [+]) randomised 181 pregnant smokers to 6 sessions of CBT alone (N=59) or CBT + NRT (N=122). The NRT group had a choice of 16-hour patch, 2mg gum or 2mg lozenge for 6 weeks. The study aimed to recruit 300 women, but it was stopped prematurely at interim analysis because an ill-informed study monitoring group thought that the results (which were showing a strong effect) indicated lack of efficacy. Validated abstinence rates (nicotine vs. placebo) at 7 weeks post randomisation were 18% vs. 3%

(p=0.006), and at 38 weeks 14% vs. 2% (p=0.01). There were no significant differences in birth weight, SAE, or any indicators of negative birth outcomes.

Wisborg et al. (2000, RCT [+]) randomised 250 pregnant smokers to 11 weeks of nicotine or placebo patch with 3 counselling sessions. There was no significant difference in salivary cotinine validated abstinence rates 4 weeks before EDD (28% vs. 25% p=0.52 in nicotine and placebo groups, respectively). However, women allocated to nicotine patch had significantly heavier babies (3457g vs. 3721g , CI: 35-336). There was no difference in the proportions of LBW or preterm births.

INTERPRETATION

The results from studies of the acute effects of NRT on the foetus are reassuring. In some laboratory trials, patches delivered similar amounts of nicotine as smoking, but the effects on foetus were mostly less and never more than the effects of smoking.

In women using NRT over a prolonged period of time, and in those using oral NRT products, NRT delivered substantially less nicotine than smoking. In randomised studies comparing the effects of standard doses of NRT with placebo in pregnant smokers using the drug throughout pregnancy, no adverse effects on pregnancy outcomes emerged. Two studies reported better birth weights in NRT groups compared to placebo groups.

Pregnancy seems to speed up elimination of nicotine by over 50%. That means that if the NRT dosing is to reach standard levels considered helpful, it should be increased considerably above the dosing used with people who are not pregnant.

Breast-fed infants of mothers on NRT have negligible systemic nicotine absorption.

Overall, the existing experimental literature suggests that NRT use in pregnancy is associated with lower risk than smoking. Only large studies with long follow-up can determine whether it is totally safe. The largest randomised trial of nicotine patches in pregnancy (Coleman et al 2012 [RCT ++]) did not find any adverse effects of NRT use in pregnancy, including congenital abnormalities. However Coleman and colleagues recommend some caution be applied to the interpretation of these findings due to the low rates of adherence to treatment and to the fact that a larger sample would be needed to comprehensively assess safety.

OBSERVATIONAL STUDIES

We identified 5 cohort studies comparing pregnancy outcomes in NRT users with other groups.

Damgaard et al. (2008, prospective cohort [+]) studied risk factors associated with cryptorchidism in 4957 pregnant women. The participants completed health questionnaires late in the 1st trimester. Boys (n=2,496) were examined at birth and 3-months. 128 boys were confirmed as cryptorcid. Smoking was not a risk factor. However children of NRT users (n=40) regardless of smoking status had a marginally increased risk (OR=3.04, 95%CI:1.00-9.27), compared to never smokers (adjusted for country, social class, birth weight, stress, alcohol and caffeine intake). The study does not provide a comparison between smokers who did and smokers who did not use NRT, so the effects of smoking cannot be differentiated from any effects of NRT.

Gaither et al. (2009, retrospective cohort [-]) used data from a programme which provides monthly random sampling using birth certificate data and mails questionnaires to women asking about maternal behaviours and birth outcomes. Regarding NRT use, women were asked to report whether a healthcare professional prescribed or recommended the use of NRT (this did not necessarily mean they used it). Data from 5,716 women were included, 225 of whom were smokers recommended or prescribed NRT and 637 were smokers not recommended or prescribed NRT. The odds ratio (adjusted for age, marital status, ethnicity and education) for LBW in the NRT group vs. non-smokers was 1.95 (95%CI:1.10-3.46) and for preterm birth, OR=2.05 (95%CI:1.14-3.63). The authors also looked at risk in smokers vs. non-smokers, finding a non-significantly increased risk of LBW (OR=1.36, 95% CI: 0.98-1.97). There was no analysis comparing smokers who were recommended/prescribed NRT and smokers not recommended/prescribed NRT. This makes the findings difficult to interpret.

Three papers report data from a Danish national birth cohort.

Lassen et al (2010, retrospective cohort [+]) analysed data from 72,761 women of whom 1,828 reported NRT use during pregnancy. 56% used gum, 30% patches, 27% used inhalers, and 10% used more than one product for a median period of 2 weeks. The proportion of preterm births in smokers using NRT vs. smokers not using NRT was 4.1% and 3.9% respectively. There was no significant relationship between the duration of NRT use and birth weight. Combination NRT was associated with a non-significant decrease in birth weight (b= -10.73g per week of NRT use, 95% CI:-26.51-5.05).

Morales-Suarez-Varela et al. (2006, retrospective cohort [+]) explored NRT use during the first trimester and congenital malformations. 76,768 women who had singleton births answered questions in the first 12 weeks of pregnancy. 26.8% (N=20,603) reported smoking during the first 12 weeks. Of the 56,165 woman who had not smoked in this period, 250 reported using NRT (patches, gum and inhalers). Congenital malformation data were obtained from the Hospital Medical Birth Registry. Children born to smokers did not differ in prevalence of congenital malformations compared to the children of non-smokers. Children born to ex-smokers who used NRT had a higher prevalence of congenital malformations (19/250, 7.6%) than non-smokers (2719/55,987, 4.9%), Relative Prevalence Rate Ratio (RPR)=1.6 (CI: 1.01-2.58). The group of non-smokers may have included some ex-smokers but the large majority are likely to be women who never smoked. The prevalence of malformations in smokers was 871/16812 (5.2%). The prevalence of musculoskeletal malformations was higher in children of NRT users (14/250, 5.6%) compared to non-smokers (1242/55,915, 2.2%), RPR=2.6, (CI: 1.53-4.52). When only major congenital malformations were considered, there was no significant difference (4.4% vs. 3.9%, RPR=1.13, CI: 0.62-2.07), with similar findings for major musculoskeletal malformations (2.4% vs. 1.2%, RPR=2.05 (95% CI: 0.91–4.63). The findings are difficult to interpret because no comparison was made between NRT users and smokers and quitters not using NRT and the number of NRT users is small.

Strandberg-Larsen et al. (2008, retrospective cohort [+]) assessed the relationship between NRT use and stillbirth. The sample consisted of 87,032 women enrolled between 1996 and 2002. Two per cent (N=1,927) of women reported using NRT. Over half of NRT users (N=1,091) reported to be current smokers, with the remaining 836 having quit. There were 8 stillbirths reported in NRT users, in 3 women who had quit smoking (3.6%) and in 5 who had not (4.6%). There was no significant difference in the risk of stillbirths in NRT users vs. non-users (adjusted Hazard Ratio [HR]=0.57, CI: 0.28-1.16). Nor was there any increased risk in the small sample of women who used NRT and smoked concurrently (adjusted HR = 0.83,

CI:0.34-2.00). Compared to non-smokers, smoking increased the risk of stillbirth (≤ 10 cpd: HR=1.36, CI:1.05-1.76); > 10 cpd: HR=1.94, CI:1.36-2.77).

INTERPRETATION

Given that smoking provides greater exposure to nicotine than NRT, the biological plausibility of any negative NRT effects above the effects of smoking is low.

Two national cohort studies showed no effect of NRT on still birth or premature birth.

One national cohort study found more congenital malformations in users of NRT than in non-smokers and another study found a marginally higher risk of cryptorchidism in NRT users compared to non-smokers. However, neither of these studies reported the more relevant comparison with smokers not using NRT. A high quality randomised controlled trial found no difference in congenital abnormalities in babies born to women who used nicotine patches compared to women using placebo patches.

Overall, NRT in pregnant women is safer than smoking. However data from observational studies suggest that it is probably not entirely safe. It would appear that varenicline, which has no known teratogenic effects and is more effective than NRT, should be a better option for pregnant smokers. No study has examined its efficacy and safety in this population so far. This represents a gap in knowledge.

SYSTEMATIC REVIEWS

Coleman et al. (2010, systematic review ++) conducted a systematic review and meta-analysis of the efficacy and safety of NRT in pregnancy. The authors searched literature up to August 2009 and included only RCTs. Five studies were included (all have been described above). There were no significant differences in pregnancy outcomes, though several trends favoured NRT groups. Given that only a small minority of women used NRT as recommended (most use little NRT or none), the finding is encouraging. NRT vs. control groups: Mean birth weigh: difference=158g, CI:-53.13-369.52; Preterm birth: RR=0.78 (CI:0.39-1.56), perinatal mortality: RR=0.70 , CI:0.14-3.60, post-randomisation foetal deaths RR=0.88 CI:0.30-2.56, NICU admissions RR=0.92 CI: 0.35-2.43, miscarriage and spontaneous abortion RR=1.04 95% CI:0.20-5.43. Low birth weight data could not be pooled because of heterogeneity, however pooling the data from the two placebo controlled trials (Wisborg et al. 2000 and Oncken et al. 2008) showed a lower proportion of LBW babies was observed in the NRT arms (RR=0.22, CI:0.07-0.72).

Lumley et al. (2009, systematic review ++) conducted the Cochrane Review of interventions promoting smoking cessation during pregnancy. The review included 72 RCTs. Only three of these studies, described above (Hegaard et al 2003; Pollack et al 2007; Wisborg et al 2000), concerned NRT trials that reported birth outcomes. Pooling their data showed no significant difference between the arms in birth weight, proportion of low birth weight babies, or preterm birth (OR=0.97, CI 0.61 to 1.53).

INTERPRETATION

The two reviews conclude that no experimental data are available to suggest that NRT poses risks in pregnancy. There is some evidence that NRT use improves birth weight. Such an effect could be mediated by reduction in smoking.

OTHER REVIEWS AND GUIDELINES

We found 28 non-systematic reviews of the effects of nicotine and the use nicotine replacement therapy in pregnancy. Most (n=20) recommend that NRT be considered in pregnancy for those women who have been unable to quit unaided (Benowitz 1991, Oncken 1996, Oncken et al 1998, Scalrea and Koren 1998, Benowitz et al 2000, McElhatton et al 2000, Bald et al 2000, Dempsey and Benowitz 2001, Koren 2001, Chan and Koren 2003, Fan 2003, Oncken and Kranzler 2003, Benowitz and Dempsey 2004, Rayburn and Bogenschutz 2004, Smith et al 2006, Coleman 2007, Coleman 2008, USDHHS 2008, American College of Obstetricians 2010, Treatobacco.net 2010, Clark and Nakad 2011). The advice to use NRT is based on animal data, the experimental data presented above, and on the low likelihood that NRT can cause any adverse effects over and above smoking.

The most widely used of these reviews is by Benowitz and Dempsey (2004). Its recommendations are similar to what other newer positive reviews recommend, i.e. that NRT be used in combination with behavioural support; the minimum effective dose should be used; the delivery system should be suitable for the individual's need; if a patch is preferred then 16 hour patch is recommended; and NRT should be started as early in the pregnancy as possible.

Two reviews did not provide recommendations (Wickstrom 2007, Oncken and Kranzler 2009) and six recommend that NRT should not be used in pregnancy (Slotkin 1998, Ginzel et al 2007, Pauly and Slotkin 2008, Slotkin 2008, Maritz 2009, Bruin et al 2010). Those who advise against using NRT (e.g. Pauly and Slotkin, 2008), argue that NRT efficacy in pregnant smokers is unproven, and that it is not known whether its use results in better outcomes than smoking. They suggest that other agents such as bupropion, varenicline or cytisine may be preferable and should be studied in this context.

Regarding UK recommendations, NICE public Health Guidance 26 (2010), 'How to stop smoking in pregnancy and following childbirth' concluded that there is insufficient evidence to show that NRT is effective in helping pregnant smokers quit and that there are insufficient data to confirm that NRT is safe to use in pregnant women. Subsequent recommendations were that (1) the risks and benefits of NRT use should be discussed with pregnant women who smoke; (2) NRT should only be used if smoking cessation without NRT has failed; (3) only prescribe NRT, in two week supplies, for use once women have stopped smoking; and (4) advise pregnant women to remove patches before going to bed.

CONCLUSIONS

In laboratory studies examining acute effects of NRT on the foetus, patches delivered similar amounts of nicotine as smoking, but the effects on foetus were mostly less and never more than the effects of smoking. Oral NRT products delivered substantially less nicotine than smoking and had only limited or no effects on the foetus.

In trials of NRT where women were able to use the drug throughout pregnancy, no adverse effects on pregnancy outcomes emerged.

Apart from experimental studies, which provide the cleanest evidence, some data were also provided by cohort studies. These are weaker as any associations can have a common cause or be related to external variables. E.g. women who opt to use NRT are likely to differ from women who do not on many variables including health concerns, degree of tobacco dependence, etc., and some of these differences could be related to pregnancy outcomes.

NRT use was not associated with stillbirth or low birth weight, but one study found more congenital malformations in NRT users than in non-smokers and another study found more cryptorchidism in NRT users than in non-smokers. With no comparison between NRT users and smokers presented, the results are difficult to interpret.

Two systematic reviews of this literature identified no risk of NRT for pregnancy. One review reported that NRT might help to reduce the incidence of LBW. Other reviews, opinion pieces and guidelines generally suggest that pregnant women should avoid nicotine, but if unable to stop smoking unaided, NRT should be considered. In such cases, overnight dosing should be avoided. A minority of the reviews advises against NRT use until there is better evidence that it is safe and that its use leads to outcomes that are more favourable than smoking.

Overall, the existing experimental literature did not identify any clear risks associated with NRT use in pregnancy compared to continuing smoking. This is consistent with the theoretical expectation that is unlikely that nicotine alone would pose more risk than the same drug delivered in the smoke form in higher doses together with a large number of other chemicals with known detrimental effects.

EVIDENCE STATEMENTS

The writers of this review interpret the available evidence as showing that NRT is safer than smoking, although probably not entirely safe. There are currently no safety reasons to withhold NRT from pregnant women who are unable to stop smoking without it. However, given the 'probably not entirely safe' verdict and the question marks about NRT efficacy, there would appear to be a strong rationale to examine safety and efficacy of varenicline in this population.

ES 3.1 There is strong evidence that in some conditions nicotine patches can deliver as much nicotine as smoking, but have overall smaller effects on foetal haemodynamics (Hackman et al. 1999, prospective cohort [-]; Ogburn et al. 1999, prospective cohort [+]; Schroeder et al. 2002, prospective cohort [+]; Oncken et al. 1997, randomised cross-over trial [+]; Wright et al. 1997, prospective cohort [+])

ES 3.2 There is strong evidence that oral NRT products deliver less nicotine than smoking and have smaller or no effect on foetal haemodynamics (Lehtovirta et al 1983, non-randomised trial [-]; Lindbald & Marsal 1987, randomised cross-over trial [+]; Lindbald et al. 1988, randomised cross-over trial [+]; Oncken et al. 1996, RCT [+]; Oncken et al. 2009, RCT [+])

ES 3.3 There is strong evidence that nicotine clearance is increased during pregnancy (Dempsey et al. 2002, experimental study [++])

ES 3.4 There is moderate evidence that there is minimal systemic uptake of nicotine in breast milk by the breastfed infant (Ilett et al. 2003, prospective cohort [+])

ES 3.5 No trial so far has identified any adverse pregnancy outcomes linked to NRT (Coleman et al. 2012 RCT [++]; Hegaard et al. 2003, RCT [+]; Hotham et al. 2006, RCT [-]; Kapur et al 2001, RCT [-]; Oncken et al. 2008, RCT [+]; Pollack et al. 2007, RCT [+]; Wisborg et al. 2000, RCT [+]; Lassen et al 2010, retrospective cohort [+]; Strandberg-Larsen et al. 2008, retrospective cohort [+])

ES 3.6 There is inconsistent evidence regarding positive effects of NRT on birth weight. Two studies found this (Wisborg et al. 2000, RCT [+]; Oncken et al. 2008, RCT [+]) but four studies found no effect (Gaither et al. 2009, retrospective cohort [-]; Lassen et al 2010, retrospective cohort [+]; Pollack et al. 2007, RCT [+]; Hegaard et al. 2003, RCT [+]).

ES 3.7 There is weak evidence that babies born to mothers who used NRT during pregnancy have an increased risk of musculoskeletal abnormalities compared to babies born to non-smokers (Morales-Suarez-Varela et al. 2006, retrospective cohort [+]). The prevalence of musculoskeletal malformations was higher in children of NRT users (14/250, 5.6%) compared to non-smokers (1242/55,915, 2.2%), RPR=2.6, (CI: 1.53-4.52). When only major musculoskeletal malformations were considered, there was no significant difference (2.4% vs. 1.2%, RPR=2.05 (95% CI: 0.91–4.63). The findings are difficult to interpret because no comparison was made between NRT users and smokers not using NRT and the numbers of NRT users are so small. Data from high quality study (Coleman et al. 2012 [RCT ++]) failed to show any association between NRT use and congenial abnormalities.

ES 3.8 There is moderate evidence that babies born to mothers who used NRT during pregnancy had an increased risk of cryptorchidism compared to babies born to non-smokers (Damgaard et al. 2008, prospective cohort [+]). Smoking was not found to be a risk factor. However the study does not provide a comparison between smokers who did and smokers who did not use NRT, so the effects of smoking cannot be differentiated from any effects of NRT.

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DISCUSSION, GAPS AND RESEARCH RECOMMENDATIONS

The review concerned two main clinically relevant issues. The first is whether there are any populations or circumstances where NRT use may be unsafe; and the second is whether there are any populations or circumstances where acute tobacco abstinence may be unsafe.

Regarding the safety of NRT, the review did not identify any safety concerns related to its use for stopping smoking in cardiac patients or in any other group of secondary care users. No concerns were raised about NRT safety in mental health service users either, although it may not be effective in this population. Regarding pregnancy, any risks associated with NRT use are much smaller than those associated with smoking, and may be clinically negligible. Nevertheless, given uncertainty about NRT efficacy in pregnant smokers and the possibility that it is not totally harmless, there is a need for research into the safety and efficacy of other treatments such as varenicline.

The review identified one area of NRT use that does raise concerns. It seems that in some hospitals it became a common practice to put NRT patches on ICU and surgery patients deemed to present a risk of delirium. There is little evidence that tobacco deprivation contributes to delirium. There is also no evidence that NRT patches help and there is some evidence that they may be harmful in several ways, although some of these findings are likely to be due to patient selection. No controlled trial has examined this issue. This represents a gap in evidence that would be relatively easy to fill.

Regarding effects of acute tobacco abstinence, this may affect comfort of some hospitalised patients, and it increases systemic levels of a number of medications. This is of particular relevance to patients hospitalised in psychiatric hospitals. E.g. patients on olanzapine are likely to experience a significant weight gain and increased risk of diabetes due to their medications. When hospitalised and prevented from smoking, they are at risk of further weight gain due to tobacco withdrawal and some additional weight gain and other, potentially serious, adverse effects from an increase in systemic olanzapine levels. A recommendation should be considered for routine lowering of dosing in all smokers on these medications admitted to smoke-free wards. Some studies of the effect of smokefree policies on patient behaviour noted that NRT was made available to patients but none reported on the effects of NRT on patient behaviour and symptoms. Another research need is to investigate the effect of NRT, compared to an adequate control, on level of discomfort and psychiatric symptoms in smokers with mental health illness in smokefree environments.

There is one relevant area where more evidence is needed, concerning the timing of quit attempts in people undergoing treatment for drug and alcohol dependence. It is currently not known whether stopping smoking during such treatments facilitates or undermines drug and alcohol sobriety or has no effect on it.

Appendices

APPENDIX 1 - REVIEW PROTOCOL

Review Protocol

Smoking cessation in Secondary Care

Review 1 (Component 5)

Review of effects of nicotine in secondary care

Hayden McRobbie

Katie Myers

Peter Hajek

Final Version

22 December 2011

Overview of project

The National Institute for Health and Clinical Excellence (NICE) has been asked by the Department of Health to develop two separate pieces of complementary guidance on:

- 'Smoking cessation in secondary care: acute and maternity services'
- 'Smoking cessation in secondary care: mental health services'.

The guidance will address smokefree policies and smoking cessation and make recommendations on approaches to help secondary care commissioners, professionals and managers (including patients and service users and their family or carers, visitors and staff) in hospitals and other acute, maternity or mental healthcare settings (including emergency care, planned specialist medical care or surgery, and maternity care provided in hospitals, outpatient clinics, community outreach and rural units, as well as intensive services in psychiatric units and secure hospitals).

There are five components of work associated with the guidance development:

1. Smoking cessation in acute and obstetric services: one review of effectiveness and one review of barriers and facilitators (reviews 2 & 3).
2. Smoking cessation in mental health services: one review of effectiveness and one review of barriers and facilitators (reviews 4 & 5).
3. Smokefree strategies and interventions in secondary care settings: one review of effectiveness and one review of barriers and facilitators (reviews 6 & 7).
4. An economic analysis (cost effectiveness review and economic model)
5. Review of effects of nicotine in secondary care (review 1)

The CPHE has commissioned the National Centre for Smoking Cessation and Training (NCSCT) to deliver four of these components (1,2,3 and 5).

This review protocol sets out the process for Component Five - Review of effects of nicotine in secondary care, referred to as Review 1.

The aim of this review is to ascertain the effects of nicotine in patients using secondary care services. Specifically this review seeks to ascertain:

a) the effects of nicotine intake, or changes in levels of nicotine intake, on the mental and physical health of patients and service users who are on medication and receiving support from secondary care health services
b) the effects of tobacco consumption, or changes in tobacco consumption, on the mental and physical health of patients who are on medication and receiving support from secondary care health services
c) the effects of nicotine intake, or changes in levels of nicotine intake, on the mental and physical health of patients and users of secondary care health services

1.1 The Review Team

The review will be led by Dr McRobbie (Project Team Leader) who has 12 years experience of working in tobacco control and smoking cessation research. He has led a NICE systematic review (see McRobbie et al 2006(McRobbie, Hajek et al. 2006)) and is an author of two Cochrane Systematic Reviews(Whittaker, Borland et al. 2009; Barnes, Dong et al. 2010) and one recent systematic review investigating the effects of pre-operative smoking cessation on peri-operative outcome.(Myers, Hajek et al. 2011) Dr McRobbie was also the lead author of the literature review for the New Zealand Smoking Cessation Guidelines.(Ministry of Health 2008)

Ms Myers will assist Dr McRobbie with this review. Katie Myers has lead a NICE review of Relapse Prevention Interventions in pregnancy(Myers, West et al. 2009) and was the lead author on the pre-operative smoking cessation systematic review.(Myers, Hajek et al. 2011)

Professor Hajek will provide advice and mentoring for our Project Team and will contribute to the final report. He has a long history of working with NICE and extensive experience in systematic reviews.(Hajek and Stead 2006; McRobbie, Hajek et al. 2006; Hajek, Stead et al. 2009; Myers, West et al. 2009; Parsons, Shraim et al. 2009; Myers, Hajek et al. 2011)

Nigel Chee will provide expert project management support to the Project Team given the tight timeframes for this Component. He is an experienced manager with experience in managing large and complex health research, strategy, and policy and implementation projects. He will primarily focus on driving the process for the project to ensure timelines are met and will also manage the relationships between the key stakeholders (including the Project Team, Independent Information Specialist, collaborators, NCSCT and NICE).

1.1.1 Independent Information Specialist

In addition to the skills and experience of the Project Team an independent information specialist (Ms Claire Stansfield) from the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre) will provide advice on the search strategy and the approach to undertaking the literature search. Ms. Stansfield has extensive expertise in methods for identifying research for systematic reviews, is familiar with the syntax requirements of the databases used in NICE systematic reviews, and is a member of the Cochrane Collaboration's Information Retrieval Methods Group.

1.1.2 Collaborators

This review will also involve several other collaborators (listed below) who are leading components 2 and 3. The rationale for involving these wider collaborators is that we believe there are significant overlaps between the four components. Although each component “stands alone”, we believe that working as a broader collective team will enable synergies across the work to be completed. The wider team is multi-disciplinary consisting of health and clinical psychologists, clinicians, research nurses, epidemiologists and medical statisticians and covers a wide range of specialist technical expertise including mental health care, secondary care and tobacco control research.

- Professor Ann McNeill (University of Nottingham);
- Dr Jo Leonardi-Bee (University of Nottingham);
- Dr Rachael Murray (University of Nottingham);
- Dr Elena Ratschen (University of Nottingham);
- Professor Sarah Lewis (University of Nottingham);
- Ms Kathryn Angus (University of Stirling); and

- Mr Douglas Eadie (University of Stirling).

1.2 The review process

This review will involve the following steps, which are described further within this protocol.

1) Searching and retrieval of relevant evidence/studies as outlined in the search protocol and strategy (see Appendix 1)
2) Selecting relevant evidence/studies using appropriate title/abstract screening checklists (see Appendix 3). Titles/abstracts will be screened independently by two reviewers.
3) Retrieval of full papers assessed to be potentially relevant following title/abstract screening.
4) Full papers will be screened independently by two reviewers and quality assessed using the NICE quality appraisal checklists (see Appendices 4-6).
5) Data will be extracted from each paper and entered into data extraction tables (see Appendices 7 & 8).
6) Data will be collated and presented in evidence tables, narrative summaries, summary tables, graphical presentation, and meta-analysis where appropriate. Sensitivity analyses related to inequality measures will be carried out, where possible.
7) Evidence statements and applicability statements will be formulated.

1.3 Project deliverables

At the completion of this process the review team will

1 Submit a **1st draft of the review** to the NICE Team by 27 January 2012
2 Undertake any amendments to the draft following NICE comments and provide a revised draft (**2nd draft**) by 20 February 2012
3 Present the review findings to the PDG meeting on 7 March 2012
4 Undertake any amendments to the reviews following comment from the PDG and summit a **3rd draft by** 21 March 2012
5 Provision of written contributions and technical support during and after the completion of the reviews, as required during the development of the public health programme guidance. This will include:
   - Supporting the NICE Team in responding to any stakeholder comments on the reviews during the consultation on the draft guidance (consultation is currently planned for 5th April to 5th June 2013).
   - Attendance at PDG meetings as required (dates for these meetings are outlined in Annex 2).
6 Submit the **final review** following public consultation, by 31 July 2012

Background

Each year thousands of smokers are admitted to secondary care settings in the United Kingdom (UK) for treatment of smoking related diseases. For many of these people the admission and the illness represents a good motivator to stop, and brings them into contact with health care professionals who can help. Even for those people who are not ready to quit assistance may be required to help them abstain whilst in a smokefree environment.

Nicotine replacement therapy (NRT) is the most commonly used smoking cessation treatment in the secondary care setting,(NHS Centre for Smoking Cessation and Training 2011) and is effective at alleviating the symptoms of tobacco withdrawal and increases the chances of long-term abstinence.(Stead, Perera et al. 2008) There are currently seven products available on the worldwide market (patch, gum, lozenge, sublingual tablet, inhaler, nasal spray, and mouth spray). Traditionally NRT has been used primarily for smoking cessation but more recently its use has been extended to assist smoking reduction, temporary abstinence and use in combination with other NRT products.

Although NRT has a good safety profile there remains some concern about the safety of nicotine among smokers and healthcare professionals. One concern is the incorrect belief that nicotine is the main component in tobacco smoke responsible for smoking-related disease. Published data show that smokers believe that NRT products are just as likely as cigarettes to cause smoking related disease.(Bansal, Cummings et al. 2004; Shiffman, Ferguson et al. 2008) There is general agreement among experts that it is not nicotine that causes the adverse health effects associated with smoking. However health risks associated with nicotine cannot be ruled out completely. There are some data that suggest that nicotine might have adverse effects in pregnancy(Bruin, Gerstein et al. 2010) and that it might be involved in steps that increase the likelihood of some cells becoming cancerous although there is no evidence that nicotine induces cancer.(Thunnissen 2009) Other concerns focus on the adverse effects of nicotine on wound healing and the cardiovascular system.

Abstinence from smoking can result in adverse effects such as those associated with tobacco withdrawal (e.g. irritability and depression) and changes in plasma levels of some medications.(Zevin and Benowitz 1999; Hughes 2007) Smoking tobacco causes induction of the liver enzyme cytochrome P450 (CYP1A1, CYP1A2).(Zevin and Benowitz 1999) This is mainly the effect of the polycyclic aromatic hydrocarbons present in tobacco smoke. CYP1A2 is responsible for the breakdown of several medications (e.g. clozapine) and medications metabolised by this enzyme will be metabolised faster in smokers than in non-smokers. On a person's cessation of smoking these enzymes return to a normal level of activity which can result in a change in metabolism of several medications and subsequent dosage adjustments are often required.(Zevin and Benowitz 1999) These issues are relevant to many patients in secondary care settings but are pertinent important for patients with mental health illness.

Patients with mental health illness are of particular interest in the review. Not only are they more likely to be using medicines that are affected by the compounds in tobacco smoke, but there health may also be affected by the use and withdrawal of tobacco and/or nicotine. One of the hypotheses for why people with mental health illness may smoke more is that it may alleviate some psychiatric symptoms.(Glassman 1993) However, there is some evidence to suggest that smoking cessation improves some psychiatric symptoms such as anxiety and stress,(West and Hajek 1997; McNeill 2002) depressive symptoms,(Kahler, Brown et al. 2002) and lead to a general improvement in mental health.(Mino, Shigemi et al. 2000) Smoking may also reduce the side effects of some neuroleptic medications.(Lawn and

Pols 2005) It is also reported that nicotine may improve cognitive function.(Lawn and Pols 2005)

Aim

The aim of this review is to ascertain the effects of nicotine intake or changes in levels of nicotine intake including nicotine from tobacco, on the mental and physical health of people using secondary care services.

Scope

This review will be informed by the two scope documents:

1. Smoking cessation: acute and maternity services http://guidance.nice.org.uk/PHG/Wave23/22/Scope/pdf/English
2. Smoking cessation: mental health services http://guidance.nice.org.uk/PHG/Wave23/36/Scope/pdf/English

4.1 Groups that will be covered

This review will include evidence from studies of the following people of all ages who use tobacco (smoked or smokeless):

- Patients and users of acute and maternity services, including those who are in the process of being referred to hospital or have recently been discharged;
- Patients and users of secondary care mental health services, including those who are in the process of being referred to or have recently been discharged from:
  - Child, adolescent, adult and older people mental health services; and
  - Inpatient, residential and long-term care for severe mental illness in hospitals, psychiatric and specialist units and secure hospitals.

4.2 Activities / interventions that will be covered

This review will address the effects of nicotine use, or withdrawal in secondary care patients. This will include

- Interventions that help people stop smoking
- Intervention that help people temporarily abstain
- Interventions that enforce abstinence from smoking
- Smoked tobacco products
- Smokeless tobacco products
- Nicotine replacement therapy (NRT)
  - Gum
  - Transdermal patches
  - Lozenges
  - Sublingual tablets
  - Inhalator/inhaler
  - Nasal spray
  - Mouth spray

4.3 Activities / interventions that will not be covered

This review will not consider evidence relating to the adverse effects of tobacco use on general health or the health benefits of quitting in secondary care patients.

PICO table to summarise the review scope

Population

This review will include evidence from studies of the following people of all ages who use tobacco (smoked or smokeless):

- Patients and users of acute and maternity services, including those who are in the process of being referred to hospital or have recently been discharged;
- Patients and users of secondary care mental health services, including those who are in the process of being referred to or have recently been discharged from:
  - Child, adolescent, adult and older people mental health services; and
  - Inpatient, residential and long-term care for severe mental illness in hospitals, psychiatric and specialist units and secure hospitals.

Intervention/Activity

This review will address the effects of nicotine use or withdrawal, and delivered via tobacco or pharmaceutical products, in secondary care patients. This will include

- Interventions that help people stop smoking
- Intervention that help people temporarily abstain
- Interventions that enforce abstinence from smoking
- Smoked tobacco products
- Smokeless tobacco products
- Nicotine replacement therapy (NRT)
  - Gum
  - Transdermal patches
  - Lozenges
  - Sublingual tablets
  - Inhalator/inhaler
  - Nasal spray
  - Mouth spray

Comparison

Data from placebo controlled NRT trials

No intervention – data from studies of people who smoke

Data from studies of ex-smokers or never smokers

Data from studies of smoking restrictions and bans

Outcomes

The following factors and outcomes will be considered:

- Any (adverse or favourable) effects of nicotine and specific risks for secondary care patients; (note that this will not extend to the health risks associated with smoking)
- Any (adverse or favourable) effects of nicotine withdrawal for secondary care patients;
- Effects (adverse or favourable) of nicotine from NRT and nicotine withdrawal on drug interactions, specific risks and the frequency at which they occur;
- Interactions of nicotine and medication use in secondary care;
- Any effects on pharmacotherapeutic management.

It is known that the polyaromatic hydrocarbons contained within tobacco smoke also affects the metabolism of some medications therefore outcomes regarding the interactions of tobacco use and tobacco cessation will be considered.

4.4 Research questions

This review will answer the following three questions:

Question 1: What are the effects of nicotine intake, or changes in levels of nicotine intake, on the mental and physical health of people using secondary care services who are on medication?

Question 2: What are the effects of tobacco consumption, or changes in tobacco consumption, on the mental and physical health of people using secondary care services who are on medication?

Question 3: What are the effects of nicotine intake, or changes in levels of nicotine intake, on the mental and physical health of people using secondary care services?

Literature search protocol

5.1. Aims

The aim of this review is to answer three of the key questions in the final scopes for the two separate pieces of complementary guidance:

1. What are the effects of nicotine intake, or changes in levels of nicotine intake, on the mental and physical health of people using secondary care services who are on medication?
2. What are the effects of tobacco consumption, or changes in tobacco consumption, on the mental and physical health of people using secondary care services who are on medication?
3. What are the effects of nicotine intake, or changes in levels of nicotine intake, on the mental and physical health of people using secondary care services?

5.2 Search approach

This review will use a systematic approach to identify literature of the highest quality available that provides information on:

a) the effects of nicotine intake, or changes in levels of nicotine intake, on the mental and physical health of patients and service users who are on medication and receiving support from secondary care health services
b) the effects of tobacco consumption, or changes in tobacco consumption, on the mental and physical health of patients who are on medication and receiving support from secondary care health services
c) the effects of nicotine intake, or changes in levels of nicotine intake, on the mental and physical health of patients and users of secondary care health services

The review will also attempt to draw out any specific issues for different groups. For example it will be important to examine the effects of nicotine use and withdrawal on people with mental health illness.

5.3 Search questions

The key search questions are as follows:

- What are the effects of nicotine use on mental and physical health of the patients?
- What are the effects of nicotine withdrawal on mental and physical health of the patients?
- What are the effects of nicotine use and withdrawal on medications and required doses?
- What are the effects of tobacco use on the mental health of patients?
- What are the effects of tobacco use and withdrawal on medications and required doses?
- What are the effects of tobacco withdrawal on mental and physical health of the patients?

5.4 Developing the search strategy

The main search strategy has been developed to capture the following:

(1) Review population

This includes patients using secondary healthcare services. The review will all also capture the sub-population of people using medications. The following search terms will be used

Hospitalization/; Outpatients/; Outpatient clinics, Hospital/; Inpatients/ Child, Hopsitalized/; Adolescent, Hospitalised/; Hospital units/; Emergency medical services/; Emergency services, Psychiatric/; Pregnant women/; Obstetrics/; Obstetrics and gynaecology department, hospital/; Mental health services/ Patient admission/; inpatient*; outpatient*; patient*; rehabilitation; psychiatric; "day centres"; "day centers"; "day units"; "day centre"; "day center"; "day unit"; residential; "long term care"; "long-term care"; psychiatric; "mental health"; "emergency services"; "specialised care"; "special care"; "specialized care"; readmitted; "re-admitted" pregnancy/maternal medicine*; antenatal clinic.

(2) Nicotine use

Nicotine agonists/ Nicotine/ nicotine

(3) Tobacco use and cessation of tobacco use

Tobacco use cessation/; Tobacco use disorder/; Tobacco, smokeless/; Smoking cessation/; Smoking/; Tobacco/; Tobacco; cigar*; "hand-roll"; handroll*; "hand-rolls"; "hand-rolled"; bidi; bidis; beedi; beedis; rolie; rolies; paan; gutkha; snuff; betel; smoking cessation; stop* smoking; withdraw*; smoking quit*; smoking; reduce smoking; abstain smoking; temporary abstinence

(4) Use of medications and interactions

Prescription drugs/; Drug therapy/; Drug interactions/; Psychotropic drugs/; pharmacology; drugs; drug; prescribed; therapy; prescription; treatment; prescribed; therapy; therapeutic; prescription; treatment; "therapeutic drug"; "therapeutic drugs"; "drug interaction"; "drug interactions"; pharmacotherapy; adverse adj3 (event* or experience* or effect); side effect; drug therap*; pharmacolog*

5.4.1 Search strategy

The search strategy for Medline is shown in Appendix 1.

A systematic search of the grey literature will not be undertaken but hand searching of bibliographies of systematic reviews the meet the inclusion criteria will be carried out to ensure that relevant data are included in this review.

To supplement the search for evidence NICE may issue a call for evidence from registered stakeholders. Relevant evidence will be included in this review

5.4.2 Equality and Diversity

The search strategy will be inclusive and aims to capture a broad range of evidence across all ethnic and disadvantaged groups.

5.5 Electronic resources

5.5.1 Databases

The following list includes the electronic databases that will be searched

- 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' reviews' and Health Technology Assessment (HTA) database in the CRD database)
- Current Contents
- EMBASE
- 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

5.5.2 Websites

The following list includes the websites that will be searched

- 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

5.5.3 Other sources

- Medicines and Healthcare products regulatory agency (MHRA) http://www.mhra.gov.uk/index.htm
- US Food and Drug Administration (FDA) http://www.fda.gov/
- Drug Information Online http://www.drugs.com/
- Electronic Medicines Compendium (eMC) http://www.medicines.org.uk/emc/
- National electronic library for medicines http://www.nelm.nhs.uk/en/
- UK Medicines Information http://www.ukmi.nhs.uk/default.asp

5.6 Restrictions

The following inclusion and exclusion criteria will be applied to the searches.

5.6.1 Inclusion Criteria

The following will be included:

- Studies published from 1980 to the most recent available at the time if the search
- Contain information that addresses the review questions.
- Published in English

5.6.2 Exclusion Criteria

The following will be excluded:

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

Gathering the evidence.

The search strategy will be translated for use, and then run on each of the various databases and websites.

6.1 Documenting the search process

At the completing of searching each database the following steps will be undertaken:

1. Results from the database searches will be downloaded into 'Endnote'. Items which cannot be downloaded into bibliographic software will be recorded in a Word document
2. A word document containing the search strategies for each resource searched will be created. Each strategy will include audit information, as shown in appendix 2.
3. A final de-duplicated 'Reference manager database'.

Reference details for any studies which may be of relevance to the contractors who will be undertaking components 1 (Acute & Maternity reviews), component 2 (Mental Health reviews), component 3 (smokefree reviews) or component 4 (Cost effectiveness review and economic analysis) will be recorded in EndNote and provided to the NICE Team to pass these files onto the relevant contractors.

Reviewing the evidence

Reviewing of the scientific evidence will involve the following five steps:

1) Select the relevant evidence.
2) Assess its quality.
3) Extract, synthesise and present it.
4) Derive evidence statements.
5) Assess its applicability.

Studies will be selected on the basis of relevance to the scope of this review and consideration will given to:

- Relevance to the PICO table described above
- The hierarchy of evidence
- Availability of evidence – if high quality evidence is not available then we will use the best available evidence.

7.1 Selecting the relevant evidence

7.1.1 Title/ abstract screening

All titles and abstracts obtained from the search will be independently screened by two members of our Project Team (Dr McRobbie and Ms Myers) using a screening checklist (a sample screening checklist is outlined in Appendix 3). Where there is disagreement the full paper will be obtained and resolved by discussion with the third member of our Project Team, Professor Hajek.

The following studies will be considered:

- Quantitative studies (both experimental and observational studies);
- Qualitative studies;
- Systematic reviews, reviews, reviews of reviews; and
- Information that addresses the review questions.

7.1.2 Full-paper screening

Full papers will be obtained for those abstracts that meet the criteria for inclusion and will be independently screened for inclusion by Dr McRobbie and Ms Myers. Any disagreement will be resolved with our third reviewer, Professor Hajek. The composite inter-rater reliability scores will be reported and the selection process will be summarised in a flow diagram. Each study excluded at the full-paper screening stage will be listed in the appendix of the review, along with the reason for its exclusion.

7.2 Assessment of study quality

The internal and external validity of studies will be assessed using quality appraisal checklists. The checklist for quantitative studies is provided in appendix 4, and that for qualitative studies in appendix 5. Reviews will be assessed using the checklist in appendix 6.

Each paper will be graded, by the lead reviewer (Dr McRobbie), using the rating scale summarised below. Quality of this process will be assessed by appraising 10% of papers by a second appraiser (Ms Myers) to check accuracy. Any disagreement will be resolved by a third appraiser (Professor Hajek). The composite inter-rater reliability scores will be reported. This approach was utilised in previous NICE systematic reviews completed by members of this review team.(McRobbie, Hajek et al. 2006; Myers, West et al. 2009)

7.2.1 Internal validity

The review team will use the checklists to ascertain if potential sources of bias have been minimised and to determine if its conclusions are open to any degree of doubt. Each study should be rated ('++', '+' or '-') to indicate its quality, where:

- ++ All or most of the checklist criteria have been fulfilled; where they have not been fulfilled the conclusions are very unlikely to alter.
- + Some of the checklist criteria have been fulfilled, where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter.
- – Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

The reasons for the quality rating will be documented in the appraisal checklist.

7.2.2 External validity

The external validity of studies will be assessed by determining the extent to which the findings for the study population are generalisable to the whole 'source population'. A rating of EV++, EV+, or EV- will be applied to indicate the degree of quality.

7.3 data extraction and synthesis

7.3.1 Data extraction

A narrative summary and evidence table will be completed for each selected study. Data will be extracted into the evidence tables and will document data regarding the: aim; objectives; setting; target population; intervention (e.g. use of nicotine replacement products); outcomes; and assessment. The template that will be used for the evidence table is shown in Appendix 7, and is based on the recommendations of the NICE CPHE Methods Manual.(National Institute for Clinical Excellence 2009) For quantitative studies exact p-values (whether or not significant) and confidence Intervals, where available, will be reported. Separate evidence tables will be produced to summarise the evidence related to each review question.

For qualitative data, analysis of the themes will be presented in the evidence tables along with a brief narrative of the paper – see Appendix 8.

7.3.2 Data synthesis

Findings from the review will be grouped into sections that will answer each review question. Subsections will be created to summarise data related to particular sub-topics. Evidence statements will be provided for each subsection. Where data allows, meta-analyses will be undertaken. Qualitative data will be themed and summarised.

7.3.2.1 Meta-analyses

Meta-analyses will be conducted using RevMan software. A fixed effect model will be used, except in situations where there is statistical heterogeneity where a random effects model will be used. Forest plots will be presented for all meta-analyses.

7.3.2.1 Narrative summaries

Narrative summaries will be provided for included studies. These will include a brief description of the study design, methodology, population, setting, and outcomes.

7.4 Evidence statements

The proposed evidence statements to be used in this evidence review will follow NICE recommendations. Statements will contain a descriptor, strength, and direction (positive or negative) of the evidence. Quality ratings of studies will be used to formulate the strength. The overall strength will be summarised using the following:

- No evidence
- Weak evidence
- Moderate evidence
- Strong evidence
- Inconsistent evidence

Evidence statements will also be developed from qualitative data. These will summarise the quality, context and key findings, and state the degree of concurrence between studies.

7.5 Applicability statements

The degree of applicability of the evidence, summarised in each evidence statement in this review, to the UK setting will be assessed. For each study included the reviewers will assess characteristics of the population, setting, intervention and outcomes studied. An applicability statement, showing the applicability of the evidence to the UK setting will be formulated and presented after each evidence statement using the following terms:

- directly applicable
- partially applicable
- not applicable.

7.5.1 Issues related to Inequalities

Any issues related to inequalities that appear in the literature will be flagged and summarised in a separate section of the final report.

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Appendix 1: Search strategy for Medline

MEDLINE strategy

No.	Database	Search term	Hits
1	MEDLINE	nicotine.ti,ab	25887
2	MEDLINE	NICOTINIC AGONISTS/ OR NICOTINE/	21319
3	MEDLINE	1 OR 2	31267
4	MEDLINE	PRESCRIPTION DRUGS/	1583
5	MEDLINE	pharmacology.sh	32243
6	MEDLINE	exp DRUG THERAPY/	971760
7	MEDLINE	exp DRUG INTERACTIONS/	132358
8	MEDLINE	exp PSYCHOTROPIC DRUGS/	305096
9	MEDLINE	"drug therapy".sh	33169
10	MEDLINE	((drug adj2 prescrib*) OR (drug adj2 therapy) OR (drug adj2 therapeutic) OR (drug adj2 prescription) OR (drug adj2 treatment) OR (drugs adj2 prescrib*) OR (drugs adj2 therapy) OR (drugs adj4 therapeutic) OR (drugs adj2 prescription) OR (drugs adj2 treatment) OR (drug adj2 therapies)).ti,ab	85156
11	MEDLINE	(medicines OR medication OR medicament OR medicaments OR medications).ti,ab	180623
12	MEDLINE	Pharmacotherapy.ti,ab	15780
13	MEDLINE	((adverse adj3 event) OR (adverse adj3 experience) OR (adverse adj3 experiences) OR (adverse adj3 effect) OR "side effect" OR "side effects" OR (adverse adj3 effects) OR (adverse adj3 events)).ti,ab	300409
14	MEDLINE	SUBSTANCE WITHDRAWAL SYNDROME/	18188
15	MEDLINE	"TOBACCO USE CESSATION"/ OR "TOBACCO USE DISORDER"/ OR TOBACCO, SMOKELESS/	9275
16	MEDLINE	SMOKING CESSATION/	17086
17	MEDLINE	SMOKING/	107311
18	MEDLINE	(tobacco OR cigar* OR "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).ti,ab	94406

No.		Database	Search term	Hits
19	☐	MEDLINE	(((smoking adj2 cessation) OR (stop smoking) OR (stopped smoking) OR (stopping smoking) OR (smoking adj3 quit) OR (smoking adj3 quitting) OR (smoking adj3 abstain) OR (smoking adj3 abstinence) OR (smoking adj3 withdrawal) OR (smoking adj3 reduction) OR (smoking adj3 restriction) OR (smoking adj3 restrict) OR (smoking adj3 reduce) OR (smoking adj3 abstaining) OR (smoking adj3 withdraw) OR "temporary abstinence")).ti,ab	20516
20	☐	MEDLINE	TOBACCO/	20769
21	☐	MEDLINE	15 OR 16 OR 17 OR 18 OR 19 OR 20	172181
22	☐	MEDLINE	(inpatient* OR outpatient*).ti,ab	134860
23	☐	MEDLINE	exp HOSPITALIZATION/	136755
24	☐	MEDLINE	exp OUTPATIENTS/	7185
25	☐	MEDLINE	exp INPATIENTS/	10316
26	☐	MEDLINE	"out-patient".ti,ab	7789
27	☐	MEDLINE	CHILD, HOSPITALIZED/ OR ADOLESCENT, HOSPITALIZED/	5777
28	☐	MEDLINE	(hospitalised OR hospitalized).ti,ab	59690
29	☐	MEDLINE	("in-patient" OR "in-patients" OR "out-patients").ti,ab	968878
30	☐	MEDLINE	((day adj2 patients) OR (day adj2 patient)).ti,ab	9231
31	☐	MEDLINE	"ill patients".ti,ab	20702
32	☐	MEDLINE	PATIENT ADMISSION/	16409
33	☐	MEDLINE	PREGNANT WOMEN/	4564
34	☐	MEDLINE	PREGNANCY/ OR PREGNANCY IN ADOLESCENCE/	647893
35	☐	MEDLINE	"acutely ill".ti,ab	2598
36	☐	MEDLINE	(primip* OR primigravid*).ti,ab	9636
37	☐	MEDLINE	22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36	1878735
38	☐	MEDLINE	"secondary care".ti,ab	2578
39	☐	MEDLINE	"secondary health".ti,ab	367
40	☐	MEDLINE	discharged.ti,ab	35970
41	☐	MEDLINE	(referred OR referral).ti,ab	147118
42	☐	MEDLINE	(emergency OR emergencies OR admitted OR admissions OR admission).ti,ab	319133

No.	Database	Search term	Hits
43	MEDLINE	exp HOSPITALS/	183727
44	MEDLINE	HOSPITAL UNITS/	8132
45	MEDLINE	exp HOSPITAL UNITS/	67581
46	MEDLINE	EMERGENCY MEDICAL SERVICES/	27979
47	MEDLINE	EMERGENCY SERVICES, PSYCHIATRIC/ OR exp EMERGENCY SERVICE, HOSPITAL/	42596
48	MEDLINE	exp OUTPATIENT CLINICS, HOSPITAL/	15023
49	MEDLINE	(re-admission OR readmission).ti,ab	6236
50	MEDLINE	discharge.ti,ab	98623
51	MEDLINE	exp MATERNAL HEALTH SERVICES/	28931
52	MEDLINE	OBSTETRICS/	14433
53	MEDLINE	OBSTETRICS AND GYNECOLOGY DEPARTMENT, HOSPITAL/	2242
54	MEDLINE	((rehabilitation OR psychiatric OR (day adj3 centres) OR (day adj3 centers) OR (day adj3 units) OR (day adj3 centre) OR (day adj3 center) OR (day adj3 unit) OR residential OR "long term care" OR "long-term care" OR psychiatric OR "mental health" OR "emergency services" OR "specialised care" OR "special care" OR "specialized care" OR readmitted OR "re-admitted")).ti,ab	294067
55	MEDLINE	((day adj2 care)).ti,ab	6110
56	MEDLINE	DAY CARE/	4484
57	MEDLINE	MENTAL HEALTH SERVICES/	22852
58	MEDLINE	((accident adj3 unit) OR (accident adj3 department) OR (emergency ADJ unit) OR (emergency ADJ department) OR (surgical ward) OR (surgical wards) OR (surgery adj2 unit) OR (surgery adj2 department) OR (surgery adj2 departments) OR (acute adj2 unit) OR (acute adj2 department) OR (acute adj2 units) OR (acute adj2 departments) OR (accident adj3 units) OR (accident adj3 departments) OR (emergency ADJ units) OR (emergency ADJ departments) OR (surgery adj2 units) 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").ti,ab	59804
59	MEDLINE	(postdischarge OR "post discharge" OR referrals OR inhospital).ti,ab	15821

No.		Database	Search term	Hits
60	☐	MEDLINE	(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 "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 "matenity healthcare" OR "obstetric healthcare" OR "prenatal healthcare" OR "antenatal healthcare" OR "perinatal healthcare" OR "maternal care" OR "maternal service" OR "maternal services").ti,ab	286096
62	☐	MEDLINE	((patient adj2 surgery) OR (patients adj2 surgery)).ti,ab	45407
63	☐	MEDLINE	(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 "obstetric healthcare" OR "prenatal healthcare" OR "antenatal healthcare" OR "perinatal healthcare" OR "maternal care" OR "maternal service" OR "maternal services" OR "obstetric services").ti,ab	286115
65	☐	MEDLINE	38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 63	1337813
66	☐	MEDLINE	(hospital OR hospitals).af	2522490
67	☐	MEDLINE	65 OR 66	3278615
68	☐	MEDLINE	(smoker* OR (tobacco adj3 user) OR (tobacco adj3 users) OR (cigar* adj3 user) OR (cigar* adj3 users)).ti,ab	51690
69	☐	MEDLINE	(patient OR patients).ti,ab	3967960
70	☐	MEDLINE	PATIENTS/	14572

No.	Database	Search term	Hits
71	MEDLINE	69 OR 70	3973162
72	MEDLINE	67 AND 71	1441140
73	MEDLINE	67 AND 68	13617
74	MEDLINE	72 OR 73	1448071
75	MEDLINE	ANIMALS/ AND HUMANS/	1321543
76	MEDLINE	ANIMALS/	4951979
77	MEDLINE	pharmacol*.ti,ab	211996
78	MEDLINE	((favourabl* adj3 effect*)).ti,ab	3315
79	MEDLINE	((favorabl* adj3 effect*)).ti,ab	5700
80	MEDLINE	((favorabl* adj3 event*) OR (favourabl* adj3 event*) OR (favorabl* adj3 experience) OR (favourabl* adj3 experiences)).ti,ab	675
81	MEDLINE	((adverse adj2 reaction) OR (adverse adj2 reactions) OR (adversely adj2 react)).ti,ab	27801
82	MEDLINE	((drug adj3 interact*) OR (drugs adj3 interact*)).ti,ab	24996
83	MEDLINE	patient.ti OR patients.ti	1102082
84	MEDLINE	(dosage OR dose OR doses).ti,ab	968019
85	MEDLINE	(reaction* OR inhibit OR inhibitor* OR inhibits OR impair* OR interact*).ti,ab	2720463
86	MEDLINE	(adversely adj2 react*).ti,ab	93
88	MEDLINE	((patient adj9 nicotine) OR (patients adj9 nicotine)).ti,ab	943
90	MEDLINE	(drug ADJ therap*).ti,ab	28553
91	MEDLINE	4 OR 6 OR 8 OR 9 OR 10 OR 11 OR 12 OR 84 OR 90	2119326
92	MEDLINE	7 OR 14 OR 82	164213
93	MEDLINE	((undesirabl* ADJ effect) OR (undesirabl* ADJ effects)).ti,ab	1769
94	MEDLINE	5 OR 13 OR 77 OR 78 OR 79 OR 80 OR 81 OR 85 OR 86 OR 93	3120930
95	MEDLINE	91 AND 94	598459
96	MEDLINE	92 OR 95	717858
97	MEDLINE	3 AND 96	5852
98	MEDLINE	76 NOT 75	3630436
99	MEDLINE	97 NOT 98	3113
103	MEDLINE	64 OR 83	2527076

No.	Database	Search term	Hits
106	MEDLINE	21 AND 72 AND 96	819
107	MEDLINE	73 AND 96	829
109	MEDLINE	102 OR 105 OR 106 OR 107 [Limit to: Publication Year 1990-Current]	2572
111	MEDLINE	((64 OR 73 OR 72 OR 83) AND 3)	4626
112	MEDLINE	111 OR 88	4932
113	MEDLINE	112 NOT 98	4272
114	MEDLINE	(((pregnant adj3 women) OR (pregnant adj3 mothers) OR (pregnant adj3 adolescents))).ti,ab	54166
115	MEDLINE	5 OR 7 OR 14 OR 77 OR 82	393883
116	MEDLINE	95 OR 115	876108
117	MEDLINE	3 AND 116	7383
118	MEDLINE	117 NOT 98	4016
120	MEDLINE	118 [Limit to: Publication Year 1980-Current]	3686
121	MEDLINE	99 [Limit to: Publication Year 1980-Current]	2973
122	MEDLINE	120 NOT 121 [Limit to: Publication Year 1980-Current]	713
123	MEDLINE	37 OR 62 OR 114 OR 83	2517618
124	MEDLINE	21 AND 123	26496
125	MEDLINE	21 AND 72	13492
126	MEDLINE	73 OR 102 OR 124 OR 125 [Limit to: Publication Year 1990-Current]	35131
127	MEDLINE	126 AND 116 [Limit to: Publication Year 1990-Current]	2951
128	MEDLINE	127 NOT 98 [Limit to: Publication Year 1990-Current]	2878
129	MEDLINE	(123 OR 72 OR 73)	3257143
130	MEDLINE	3 AND 129	4593
131	MEDLINE	88 OR 130	4899
132	MEDLINE	131 NOT 98	4254
133	MEDLINE	132 [Limit to: Publication Year 1980-Current]	4118
138	MEDLINE	((patients adj9 cigar*) OR (patients adj9 tobacco*) OR (patients adj9 smok*) OR (patient adj9 cigar*) OR (patient adj9 tobacco*) OR (patient adj9 smok*)).ti,ab	18988
139	MEDLINE	124 OR 125 OR 73 OR 138	49579
140	MEDLINE	139 AND 118	816

No.	Database	Search term	Hits
141	MEDLINE	139 AND 116	3337
142	MEDLINE	141 NOT 98	3257
143	MEDLINE	142 [Limit to: Publication Year 1980-Current]	3214
144	MEDLINE	120 OR 133 [Limit to: Publication Year 1980-Current]	6886

Appendix 2: Audit information that will accompany each database and website search

Database name	
Search date	
Database host *(name of host or environment in which the database was searched)*	
Coverage dates	
Name of searcher	
Search strategy checked by	
Number of records retrieved	
Name of EndNote library	
Number of records loaded into EndNote library	
Reference numbers of records in EndNote library *(range of unique reference numbers assigned to the records by EndNote)*	
Number of records after deduplication in EndNote library	

Appendix 3: Title/Abstract Screening Checklist

1	Does the paper report on effects (adverse or favourable) of nicotine replacement therapy OR the effects (adverse or favourable) of abstinence from tobacco?*	Yes – go to next question	No – exclude
2	Does the paper address /include the relevant population?*	Yes – go to next question	No – exclude
3	Include in full text screening?	Yes	

*Where the assessor is unsure about a paper then the abstract will be discussed among all reviewers and a final decision made.

Appendix 4: Quality appraisal checklist for quantitative studies

Study identification:		
Study design:		
Assessed by:		
Section 1: Population		
• Is the source population or source area well described? • Was the country (e.g. developed or nondeveloped, type of health care system), setting (primary schools, community centres etc.), location (urban, rural), population demographics etc. adequately described?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	Comments:
• Is the eligible population or area representative of the source population or area? • Was the recruitment of individuals/clusters/areas well defined (e.g. advertisement, birth register)? • Was the eligible population representative of the source? Were important	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
☐ Do the selected participants or areas represent the eligible population or area? ☐ Was the method of selection of participants from the eligible population well described? ☐ What % of selected individuals/clusters agreed to participate? Were there any sources of bias? ☐ Were the in-/exclusion criteria explicit and appropriate?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
Section 2: Method of Allocation to intervention (or comparison)		
• Allocation to intervention (or comparison). • How was selection bias minimised? • Was allocation to exposure and comparison randomised? • Was it truly random ++ or pseudo-randomised + (e.g. consecutive admissions)? • If not randomised, was significant confounding likely (-) or not (+)? • If a cross-over, was order of intervention randomised?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Were interventions (and comparisons) well described and appropriate? • Were intervention/s & comparison/s described in sufficient detail (i.e. enough for study to be replicated)? • Was comparison/s appropriate (e.g. usual practice rather than no intervention)?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Was the allocation concealed? • Could the person(s) determining allocation of participants/clusters to intervention or comparison groups have influenced the allocation? • Adequate allocation concealment (++) would include centralised allocation or computerised allocation systems.	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Were participants and/or investigators blind to exposure and comparison? • Were participants AND investigators – those delivering and/or assessing the intervention kept blind to intervention allocation?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	

• Was the exposure to the intervention and comparison adequate? • Is reduced exposure to intervention or control related to the intervention (e.g. adverse effects leading to reduced compliance) or fidelity of implementation (e.g. reduced adherence to protocol)? • Was lack of exposure sufficient to cause important bias?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Was contamination acceptably low? • Did any in the comparison group receive the intervention or vice versa? • If so, was it sufficient to cause important bias? • If a cross-over trial, was there a sufficient wash-out period between interventions?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Were other interventions similar in both groups? • Did either group receive additional interventions or have services provided in a different manner? • Were the groups treated equally by researchers or other professionals? • Was this sufficient to cause important bias?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Were all participants accounted for at study conclusion? • Were those lost-to-follow-up (i.e. dropped or lost pre-/during/post-intervention) acceptably low (i.e. typically <20%)? • Did the proportion dropped differ by group? For example, were drop-outs related to the adverse effects of the intervention?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Did the setting reflect usual UK practice? • Did the setting in which the intervention or comparison was delivered differ significantly from usual practice in the UK? • For example, did participants receive intervention (or comparison) condition in a hospital rather than a community-based setting?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Did the intervention or control comparison reflect usual UK practice? • Did the intervention or comparison differ significantly from usual practice in the UK? • For example, did participants receive intervention (or comparison) delivered by specialists rather than GPs? Were participants monitored more closely?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
Section 3: Outcomes		
• Were outcome measures reliable? • Were outcome measures subjective or objective (e.g. biochemically validated nicotine levels ++ vs self-reported smoking -). • How reliable were outcome measures (e.g. inter- or intra-rater reliability scores)? • Was there any indication that measures had been validated (e.g. validated against a gold standard measure or assessed for content validity)	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Were all outcome measurements complete? • Were all/most study participants who met the defined study outcome definitions likely to have been identified?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Were all important outcomes assessed? • Were all important benefits and harms assessed? Was it possible to determine the overall balance of benefits and harms of the intervention versus comparison?	☐ ++ ☐ + ☐ - ☐ NR	

	☐ NA	
• Were outcomes relevant? • Where surrogate outcome measures were used, did they measure what they set out to measure?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Were there similar follow-up times in exposure and comparison groups?	☐ ++ ☐ + ☐ - ☐ NR NA	
• Was follow-up time meaningful? • Was follow-up long enough to assess longterm benefits/harms? • Was it too long, e.g. participants lost to follow-up?	☐ ++ ☐ + ☐ - ☐ NR NA	
Section 4: Analyses		
• Were exposure and comparison groups similar at baseline? If not, were these adjusted? • Were there any differences between groups in important confounders at baseline? • If so, were these adjusted for in the analyses (e.g. multivariate analyses or stratification). • Were there likely to be any residual differences of relevance?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Was Intention to treat (ITT) analysis conducted? • Were all participants (including those that dropped out or did not fully complete the intervention course) analysed in the groups (i.e. intervention or comparison) to which they were originally allocated?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Was the study sufficiently powered to detect an intervention effect (if one exists)? • Is a power calculation presented? If not, what is the expected effect size? Is the sample size adequate?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Were the estimates of effect size given or calculable? • Were effect estimates (e.g. relative risks, absolute risks) given or possible to calculate?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Were the analytical methods appropriate? • Were important differences in follow-up time and likely confounders adjusted for? • If a cluster design, were analyses of sample size (and power), and effect size performed on clusters (and not individuals)? • Were subgroup analyses pre-specified?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Was the precision of intervention effects given or calculable? Were they meaningful? • Were confidence intervals and/or p-values for effect estimates given or possible to calculate? • Were CI's wide or were they sufficiently precise to aid decision-making? • If precision is lacking, is this because the study is under-powered?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	

Section 5: Summary		
• Are the study results internally valid (i.e. unbiased)? • How well did the study minimise sources of bias (i.e. adjusting for potential confounders)? • Were there significant flaws in the study design?	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
• Are the findings generalisable to the source population (i.e. externally valid)? • Are there sufficient details given about the study to determine if the findings are generalisable to the source population? • Consider: participants, interventions and comparisons, outcomes,	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	
Overall assessment	☐ ++ ☐ + ☐ - ☐ NR ☐ NA	

Appendix 5: Quality appraisal checklist for qualitative studies

Study identification		
Checklist completed by:		
Theoretical approach		
• Is a qualitative approach • appropriate?	☐ Appropriate ☐ Inappropriate ☐ Not sure	Comments:
• Is the study clear in what it seeks to do?	☐ Clear ☐ Unclear ☐ Mixed	
Study Design		
• How defensible/rigorous is the research design/methodology?	☐ Defensible ☐ Indefensible ☐ Not sure	
Data collection		
• How well was the data collection carried out?	☐ Appropriately ☐ Inappropriately ☐ Not sure/ inadequately reported	
Trustworthiness		
• Is the role of the researcher clearly described? • Does the paper describe how the research was explained and presented to the participants?	☐ Clearly described ☐ Unclear ☐ Not described	
• Is the context clearly described? • Were observations made in a sufficient variety of circumstances? • Was context bias considered	☐ Clear ☐ Unclear ☐ Not sure	
• Were the methods reliable? • Do the methods investigate what they claim to?	☐ Reliable ☐ Unreliable ☐ Not sure	
Analysis		
• Is the data analysis sufficiently rigorous? • How systematic is the analysis, is the • procedure reliable/dependable? • Is it clear how the themes and concepts • were derived from the data?	☐ Rigorous ☐ Not rigorous ☐ Not sure/ not reported	
• Is the data 'rich'?	☐ Rich ☐ Poor ☐ Not sure/ not reported	
• Is the analysis reliable?	☐ Reliable ☐ Unreliable ☐ Not sure/ not reported	

• Are the findings convincing?	☐ Convincing ☐ Not ☐ Convincing ☐ Not sure	
• Are the findings relevant to the aims of the study?	☐ Relevant ☐ Irrelevant ☐ Partially ☐ Relevant	
Conclusions		
• Does this enhance understanding of the research topic? • Are the implications of the research clearly defined? • Is there adequate discussion of any limitations encountered?	☐ Adequate ☐ Inadequate ☐ Not sure	
Ethics		
• How clear and coherent is the reporting of ethics? • Was the study approved	☐ Appropriate ☐ Inappropriate ☐ Not sure/ not reported	
Overall Assessment		
As far as can be ascertained from the paper, how well was the study conducted?	☐ ++ ☐ + ☐ -	

Appendix 6: Review screening form

Study identification	
Checklist completed by**:**	
In a well-conducted systematic review:	In this review this criterion is met: (Circle one option for each question)
Does the review address an appropriate and clearly-focused question that is relevant to one or more of the guidance topic's key research question/s?	Yes No Unclear
Does the review include the types of study/s relevant to the key research question/s?	Yes No Unclear
Is the literature search sufficiently rigorous to identify all the relevant studies?	Yes No Unclear
Is the study quality of included studies appropriately assessed and reported?	Yes No Unclear
Is an adequate description of the analytical methodology used included, and are the methods used appropriate to the question?	Yes No Unclear
Overall Quality	Comments

Appendix 7: Data extraction form/Evidence Table for Quantitative studies

Study details	**Population and setting**	**Method of allocation to intervention/control**	**Outcomes and methods of analysis**	**Results**	**Notes**
Authors	Source populations	Method of allocation	Primary outcome	Primary outcome	Limitations identified by author
Year		Intervention description	Secondary outcomes	Secondary outcomes	Limitations identified by review team
Citation					
Aim of Study	Eligible population	Control/comparison			
Study design		Sample size	Follow-up periods	Attrition details	Evidence gaps
Quality score	Selected population	Any baseline differences?			
External validity		Study sufficient powered?	Method of analysis		Source of funding

Appendix 8: Data extraction form/Evidence Table for Qualitative studies

Authors	What was the research question?	What population were the sample recruited from:	Brief description of method and process of analysis:	Limitations identified by author
Year		How were they recruited:		
Citation	What theoretical approach does the study take (if specified):	How many participants were recruited:	Key themes relevant to this review:	Limitations identified by review team
	How were the data collected:	Were there specific exclusion criteria		Evidence gaps
Quality score		Were there specific inclusion criteria:		Source of funding

APPENDIX 2 – EXCLUDED PAPERS

Table 18: Full text papers relevant to chapter 1 that were excluded

Paper (n=55)	Reason
Afessa et al (2010)	Editorial on Lucidarme
Armstrong et al (2011)	Did not report on the effects of changes in nicotine or tobacco
Baron (1996)	Did not report on the effects of changes in nicotine or tobacco
Bernstein et al (2011)	Did not report on the effects of changes in nicotine or tobacco
Bize et al (2006)	Did not report on the effects of changes in nicotine or tobacco
Bock et al (2008)	Did not report on the effects of changes in nicotine or tobacco
Borowitz et al (2008)	Did not report on the effects of changes in nicotine or tobacco
Braganza 2008	Did not report on the effects of changes in nicotine or tobacco
Browman et al (2008)	Reported on outcomes of radiotherapy in smokers vs. non-smokers. Not clear if related to changes in nicotine or tobacco
Campbell et al (1996)	Did not report on the effects of changes in nicotine or tobacco
Chen et al (2010)	Did not report on the effects of changes in nicotine or tobacco
Cropley et al (2008)	Did not report on the effects of changes in nicotine or tobacco
Eissenberg et al (2010)	Did not report on the effects of changes in nicotine or tobacco
Emmons et al (2000)	Did not report on the effects of changes in nicotine or tobacco
Feeney et al (2001)	Did not report on the effects of changes in nicotine or tobacco
Fiore et al (2000)	Did not report on the effects of changes in nicotine or tobacco
Freund et al (2009)	Did not report on the effects of changes in nicotine or tobacco
Gadomski et al (2010)	Did not report on the effects of changes in nicotine or tobacco
Gadomski et al. (2011)	Did not report on the effects of changes in nicotine or tobacco
Gothe et al (1985)	Did not report on the effects of changes in nicotine or tobacco
Gourlay (1994)	Did not report on the effects of changes in nicotine or tobacco
Gratziou (2009)	Did not report on the effects of changes in nicotine or tobacco
Hall (2007)	Did not report on the effects of changes in nicotine or tobacco
Hand et al (2002)	Did not report on the effects of changes in nicotine or tobacco
Hawkshaw et al (2005)	Did not report on the effects of changes in nicotine or tobacco
Hayes et al (2010)	Did not report on the effects of changes in nicotine or tobacco
Hays (2000)	Did not report on the effects of changes in nicotine or tobacco
Hunsballe et al (2001)	Population was not relevant (non smoking teenagers and adults with enuresis)
John et al (2009)	Did not report on the effects of changes in nicotine or tobacco
Labbate et al (1992)	Did not report on the effects of changes in nicotine or tobacco
McKee et al (2003)	Did not report on the effects of changes in nicotine or tobacco
Molyneux (2004)	Did not report on the effects of changes in nicotine or tobacco
Molyneux et al (2001)	Covered in molyneux 2003
Munafo et al (2001)	Did not report on the effects of changes in nicotine or tobacco
Ohare (1993)	Did not report on the effects of changes in nicotine or tobacco
Padula & Willey (1993)	Reports on tobacco withdrawal in 17 smokers in CCU, but no usable data.
Pbert (2006)	Did not report on the effects of changes in nicotine or tobacco
Pine & Hatterer (1994)	Did not report on the effects of changes in nicotine or tobacco
Quist-Paulsen et al (2005)	Did not report on the effects of changes in nicotine or tobacco
Reid et al (2003)	Did not report on the effects of changes in nicotine or tobacco
Reid et al (2010)	Did not report on the effects of changes in nicotine or tobacco
Reid et al (2011)	Did not report on the effects of changes in nicotine or tobacco
Rigotti et al (1999)	Did not report on the effects of changes in nicotine or tobacco
Rigotti et al (2006)	Did not report on the effects of changes in nicotine or tobacco
Rigotti et al (2007)	Did not report on the effects of changes in nicotine or tobacco
Rigotti et al (2008)	Did not report on the effects of changes in nicotine or tobacco
Rigotti et al (2009)	Did not report on the effects of changes in nicotine or tobacco

Simon et al (2003)	Did not report on the effects of changes in nicotine or tobacco
Stead & Lancaster (2005)	Did not report on the effects of changes in nicotine or tobacco
Strassmann et al (2009)	Did not report on the effects of changes in nicotine or tobacco
Unkle et al (2011)	Editorial on Cartin Ceba (2011)
Van der Klauw et al (1996)	Reports on a case study of vasculitis in a patch user
Weiss (1996)	Discusses symptoms of nicotine overdose only
Wiggers et al (2003)	Did not report on the effects of changes in nicotine or tobacco
Wolfenden et al (2008)	Did not report on the effects of changes in nicotine or tobacco

Table 19: Full text papers relevant to chapter 2 that were excluded

Paper (n=55)	Reason
Anonymous (2007)	No data regarding the effects of changes in nicotine
Anonymous (1996)	No data regarding the effects of changes in nicotine
Anonymous (2011)	No data regarding the effects of changes in nicotine
Banham et al (2008)	No data regarding the effects of changes in nicotine
Bersani et al (2011)	General review on clozapine, reports on Meyer (2001)
Brown et al (2003)	No data regarding the effects of changes in nicotine
Campion et al (2008b)	General review on smoking cessation only
Connors et al (1996)	Not population of interest
Dalack et al (1997)	No data regarding the effects of changes in nicotine
Dalack and Meador-Woodruff (1999)	No data regarding the effects of changes in nicotine
Dingman et al (1988)	Paper could not be obtained in time and has no abstract
El-Guebaly et al (2002)	Review of smoking cessation approaches only
Elkader et al. (2009)	No data regarding the effects of changes in nicotine
Elliott (2009).	No data regarding the effects of changes in nicotine
Els (2004)	No data regarding the effects of changes in nicotine
Etter et al (2008)	No data regarding the effects of changes in nicotine
Fagerstrom and Aubin (2009).	No data regarding the effects of changes in nicotine
Garti et al (2002)	No extractable data
Gehricke et al (2009)	Not population of interest
Gralnick (1988)	No data regarding the effects of changes in nicotine
Greenwood-Smith et al (2003)	No data regarding the effects of changes in nicotine
Hall et al (1993)	No data regarding the effects of changes in nicotine
Hall et al (1996)	No data regarding the effects of changes in nicotine
Hall et al (2006)	No data regarding the effects of changes in nicotine
Hartman et al (1991)	Reports on smoking cessation outcome only
Hayes et al (2010)	No data regarding the effects of changes in nicotine
Hughes (1987)	No data regarding the effects of changes in nicotine
Jochelson & Majrowski (2006)	No data regarding the effects of changes in nicotine
Julyan (2006)	No data regarding the effects of changes in nicotine
Kalman et al (2001)	No extractable data
Kalman et al (2011)	No data regarding the effects of changes in nicotine
Karam-Hage et al (2011)	No data regarding the effects of changes in nicotine
Keizer et al (2009)	No data regarding the effects of changes in nicotine
Kisely & Campbell (2008)	No data regarding the effects of changes in nicotine
Knadler et al (2011)	No data regarding the effects of changes in nicotine
Kroger et al (2005)	No data regarding the effects of changes in nicotine
Kumari & Postma (2005)	No data regarding the effects of changes in nicotine
Lawn & Pols (2003)	No data regarding the effects of changes in nicotine
Levin and Rezvani (2007)	No data regarding the effects of changes in nicotine
Levin et al. (1996)	No data regarding the effects of changes in nicotine
Matthews et al (2011)	No data regarding the effects of changes in nicotine

Nursing Standard (2009)	Editorial only
Prochaska et al (2004)	No data regarding the effects of changes in nicotine
Prochaska et al (2006)	Reports only on smoking cessation outcomes
Prochaska et al (2009)	No data regarding the effects of changes in nicotine
Punnoose & Belgamwar (2009)	No data regarding the effects of changes in nicotine
Saxon et al (1997)	No data regarding the effects of changes in nicotine
Scharf et al (2011)	Reposts on patterns of NRT prescribing only
Schwenger et al (2011)	No data regarding the effects of changes in nicotine
Strong et al (2004)	No data regarding the effects of changes in nicotine
Taylor et al (1993)	Reports on attitudes to a smoking ban only
Tidey et al (2008)	No data regarding the effects of changes in nicotine
Van Dongen et al (1999)	No data regarding the effects of changes in nicotine
Williams & Hughes (2003)	No data regarding the effects of changes in nicotine
Yeh and Lee (2009)	No data regarding the effects of changes in nicotine

Table 20: Full text papers relevant to chapter 3 that were excluded

Paper (n=15)	**Reason**
ACOG (2005)	Superseded by ACOG (2010)
Andersen and Olsen (2011)	Summarises Strandberg-Larsen (2008) and Lassen (2010)
Atkinson (2003)	Abstract of Hotham
Cesta et al (2008)	Presents animal data
Coleman (2005)	Opinion paper, information covered in Coleman 2008
Coleman et al (2007)	No relevant information on effects of changes in nicotine
DiTommaso (2002)	No relevant information on effects of changes in nicotine
Dwyer et al (2008)	Data from animal studies presented
Einarson and Riordan (2009)	No relevant information on effects of changes in nicotine
Fish et al (2009)	Covers data relating to adherence to NRT treatment provided in Pollack 2007
Koren (2002)	No relevant information on effects of changes in nicotine
Low (1997)	No relevant information on effects of changes in nicotine
Ogburn et al (2001)	Abstract containing data covered in Ogburn 1999 and Schroeder 2002
Oncken et al (2006)	Abstract only with no useable data
Rigotti et al (2008)	No relevant information on effects of changes in nicotine